



# 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age

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## Summary

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**Background** The MINDACT trial showed excellent 5-year distant metastasis-free survival of 94·7% (95% CI 92·5–96·2) in patients with breast cancer of high clinical and low genomic risk who did not receive chemotherapy. We present long-term follow-up results together with an exploratory analysis by age.

**Methods** MINDACT was a multicentre, randomised, phase 3 trial done in 112 academic and community hospitals in nine European countries. Patients aged 18–70 years, with histologically confirmed primary invasive breast cancer (stage T1, T2, or operable T3) with up to three positive lymph nodes, no distant metastases, and a WHO performance status of 0–1 were enrolled and their genomic risk (using the MammaPrint 70-gene signature) and clinical risk (using a modified version of Adjuvant! Online) were determined. Patients with low clinical and low genomic risk results did not receive chemotherapy, and patients with high clinical and high genomic risk did receive chemotherapy (mostly anthracycline-based or taxane-based, or a combination thereof). Patients with discordant risk results (ie, patients with high clinical risk but low genomic risk, and those with low clinical risk but high genomic risk) were randomly assigned (1:1) to receive chemotherapy or not based on either the clinical risk or the genomic risk. Randomisation was done centrally and used a minimisation technique that was stratified by institution, risk group, and clinical-pathological characteristics. Treatment allocation was not masked. The primary endpoint was to test whether the distant metastasis-free survival rate at 5 years in patients with high clinical risk and low genomic risk not receiving chemotherapy had a lower boundary of the 95% CI above the predefined non-inferiority boundary of 92%. In the primary test population of patients with high clinical risk and low genomic risk who adhered to the treatment allocation of no chemotherapy and had no change in risk post-enrolment. Here, we present updated follow-up as well as an exploratory analysis of a potential age effect ( $\leq 50$  years vs  $> 50$  years) and an analysis by nodal status for patients with hormone receptor-positive and HER2-negative disease. These analyses were done in the intention-to-treat population. This study is registered with ClinicalTrials.gov, NCT00433589, and the European Clinical Trials database, EudraCT2005–002625–31. Recruitment is complete and further long-term follow-up is ongoing.

**Findings** Between Feb 8, 2007, and July 11, 2011, 6693 patients were enrolled. On Feb 26, 2020, median follow-up was 8·7 years (IQR 7·8–9·7). The updated 5-year distant metastasis-free survival rate for patients with high clinical risk and low genomic risk receiving no chemotherapy (primary test population, n=644) was 95·1% (95% CI 93·1–96·6), which is above the predefined non-inferiority boundary of 92%, supporting the previous analysis and proving MINDACT as a positive de-escalation trial. Patients with high clinical risk and low genomic risk were randomly assigned to receive chemotherapy (n=749) or not (n=748); this was the intention-to-treat population. The 8-year estimates for distant metastasis-free survival in the intention-to-treat population were 92·0% (95% CI 89·6–93·8) for chemotherapy versus 89·4% (86·8–91·5) for no chemotherapy (hazard ratio 0·66; 95% CI 0·48–0·92). An exploratory analysis confined to the subset of patients with hormone receptor-positive, HER2-negative disease (1358 [90·7%] of 1497 randomly assigned patients, of whom 676 received chemotherapy and 682 did not) shows different effects of chemotherapy administration on 8-year distant metastasis-free survival according to age: 93·6% (95% CI 89·3–96·3) with chemotherapy versus 88·6% (83·5–92·3) without chemotherapy in 464 women aged 50 years or younger (absolute difference 5·0 percentage points [SE 2·8, 95% CI −0·5 to 10·4]) and 90·2% (86·8–92·7) versus 90·0% (86·6–92·6) in 894 women older than 50 years (absolute difference 0·2 percentage points [2·1, −4·0 to 4·4]). The 8-year distant metastasis-free survival in the exploratory analysis by nodal status in these patients was 91·7% (95% CI 88·1–94·3) with chemotherapy and 89·2% (85·2–92·2) without chemotherapy in 699 node-negative patients (absolute difference 2·5 percentage points [SE 2·3, 95% CI −2·1 to 7·2]) and 91·2% (87·2–94·0) versus 89·9% (85·8–92·8) for 658 patients with one to three positive nodes (absolute difference 1·3 percentage points [2·4, −3·5 to 6·1]).

**Interpretation** With a more mature follow-up approaching 9 years, the 70-gene signature shows an intact ability of identifying among women with high clinical risk, a subgroup, namely patients with a low genomic risk, with an

excellent distant metastasis-free survival when treated with endocrine therapy alone. For these women the magnitude of the benefit from adding chemotherapy to endocrine therapy remains small (2·6 percentage points) and is not enhanced by nodal positivity. However, in an underpowered exploratory analysis this benefit appears to be age-dependent, as it is only seen in women younger than 50 years where it reaches a clinically relevant threshold of 5 percentage points. Although, possibly due to chemotherapy-induced ovarian function suppression, it should be part of informed, shared decision making. Further study is needed in younger women, who might need reinforced endocrine therapy to forego chemotherapy.

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## Introduction

Adjuvant systemic therapies, together with mammographic screening and improved locoregional treatment, have contributed to a decline in breast cancer mortality.<sup>1</sup> The introduction of effective cytotoxic agents and targeted drugs (eg, endocrine and anti-HER2 agents), given before and after surgery, has been instrumental in the eradication of micrometastases, but also has limitations: overtreatment of patients already cured by

locoregional therapy; short-term toxicities; emergence of chronic, long-term, and sometimes life-threatening side-effects; and financial toxicity.<sup>2–4</sup> Two multigene signatures, a 21-gene recurrence score (Oncotype DX, Exact Sciences, Madison, WI, USA) and a 70-gene prognosis signature (MammaPrint, Agendia, Amsterdam, Netherlands), have shown level 1 clinical utility to identify patients with preserved outcome when treated with adjuvant endocrine therapy and no chemotherapy,

## Research in context

### Evidence before this study

Breast cancer is conceivably a curable disease only when it is diagnosed early and treated effectively. Up until the early 2000s, oncologists relied on classical clinical and pathological variables for adjuvant chemotherapy decision making, but remained highly dissatisfied, especially for patients with lower risk node-negative disease, for whom integrating all the variables often resulted in a so-called grey zone and a high risk of overtreatment. No formal literature search was done on the topic of considerations for chemotherapy use before the initiation of the MINDACT trial, but a high unmet clinical need became apparent and was documented in the early 2000s, indicating that many patients with early-stage breast cancer were overtreated with chemotherapy. Considerable interest arose when two multigene expression signatures (a 70-gene signature and a 21-gene signature) were shown in retrospective studies to predict excellent clinical outcomes in node-negative disease untreated with chemotherapy for those identified with a low-risk prognostic signature. Along with TAILORx, MINDACT is one of the large, prospective clinical trials that showed the clinical utility of a gene expression signature as an aid to adjuvant chemotherapy decision making in early hormone receptor-positive HER2-negative breast cancer. TAILORx was restricted to a node-negative population without clinical risk stratification, whereas MINDACT included patients with zero to three positive lymph nodes and evaluated the 70-gene signature in the context of clinical risk stratification. In 2016, the first MINDACT results based on 5-year median follow-up confirmed its primary hypothesis: namely, an excellent prognosis at 5 years (eg, a distant metastasis-free survival of 94·7%) in women classified as at high clinical risk and low genomic risk untreated with chemotherapy. As a secondary aim, MINDACT also investigated,

through randomisation, the potential benefit of chemotherapy in this key patient subset: the 1·5 percentage points benefit seen at that time was of uncertain significance (hazard ratio 0·78; 95% CI 0·50–1·21) and not clinically relevant. Since hormone receptor-positive, HER2-negative breast cancer is characterised by a substantial proportion of late relapses (after 5 years), these outcomes should be revisited with a longer follow-up.

### Added value of this study

We present a planned updated analysis of MINDACT with a median follow-up of 8·7 years, to revisit all endpoints with more power. The updated MINDACT results, while confirming the trial's primary hypothesis in a 5-year timeframe, point to a slightly larger distant metastasis-free survival benefit from adjuvant chemotherapy at 8 years in women with a high clinical risk but a low genomic risk: absolute difference. In an exploratory analysis by age, no benefit of chemotherapy is seen in women older than 50 years, but a potentially clinically relevant benefit is seen in women aged 50 years or older.

### Implications of all the available evidence

The MINDACT trial shows excellent survival for women with high clinical risk and low genomic risk treated without chemotherapy at 5 years, a timeframe considered for chemotherapy cytotoxic benefit. Similarly to TAILORx, the updated results of MINDACT indicate that relying on the genomic signature to forego adjuvant chemotherapy is safer in older women with a high clinical risk than in younger women. The potential benefit of chemotherapy, given in addition to endocrine therapy, to younger women might be linked to chemotherapy-induced ovarian function suppression, although neither MINDACT nor TAILORx can confirm this hypothesis. These facts must be discussed in detail with every patient, as part of a shared decision-making process.

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through large, prospective phase 3 clinical trials TAILORx<sup>5</sup> and MINDACT.<sup>6</sup>

MINDACT (European Organisation for Research and Treatment of Cancer [EORTC] 10041, Breast International Group [BIG] 3–04) showed an excellent outcome at 5 years for women treated with endocrine therapy only, whose tumours were classified as clinically high risk (per standard clinical-pathological criteria) but were found to have a low-risk 70-gene signature (the key target group of the MINDACT trial). In these patients, 5-year distant metastasis-free survival was 94·7% (95% CI 92·5–96·2).<sup>6</sup>

Randomisation between relying on either the genomic risk or the clinical risk to decide the treatment strategy—a secondary endpoint of MINDACT—resulted in allocation to chemotherapy or not in the two discordant-risk groups (ie, patients with high clinical risk but low genomic risk, and those with low clinical risk but high genomic risk). However, the MINDACT trial was not powered for a reliable comparison of these two treatment strategies in 2016 at a 5-year median follow-up: at that time, a small distant metastasis-free survival advantage of 1·5 percentage points from chemotherapy could not be formally excluded in the target group of the trial.<sup>6</sup>

In this Article, we present updated results of MINDACT with a longer follow-up and a new exploratory analysis by age.

## Methods

### Study design and participants

The multicentre, phase 3, randomised MINDACT trial enrolled patients at 112 academic and community hospitals in nine European countries (appendix pp 3–6). The study design, patient eligibility, and logistics of the study have been described previously.<sup>6,7</sup> Patients were eligible to enrol if they were women aged 18–70 years with histologically confirmed unilateral primary non-metastatic (M0) invasive breast cancer (clinical stage T1 or T2 or operable T3) with zero to three positive axillary lymph nodes. In the initial study design, all patients had to have lymph node-negative disease, but on April 25, 2008, after new data were presented,<sup>8</sup> the protocol was revised to include patients with up to three positive axillary lymph nodes, who were enrolled as of Aug 25, 2008. Patients had to have a WHO performance status of 0–1, and adequate bone marrow reserve, renal function, and hepatic function. Exclusion criteria were pregnancy or breastfeeding at the time of diagnosis or randomisation. Patients should not have received neoadjuvant or adjuvant chemotherapy, endocrine therapy, or radiotherapy for the primary breast cancer before enrolling in this trial. No use of any investigational drug within 4 weeks of randomisation was allowed. Patients with concurrent or previous invasive cancer (other than breast cancer) within the preceding 5 years or any serious cardiac illness or medical condition were ineligible. All patients gave written informed consent. The ethics committees of all participating sites approved the study, which involved

collaboration of seven member groups of the BIG. The protocol is included in the appendix (pp 34–444).

### Randomisation and masking

The randomisation for treatment allocation described in this paper was only applicable to a subset of patients enrolled in the trial. Patients with discordant risk results at enrolment (ie, either high clinical risk and low genomic risk or low clinical risk and high genomic risk) were randomly assigned (1:1) to use their clinical or genomic result to guide treatment strategy and receive chemotherapy or to receive no chemotherapy as described previously.<sup>6</sup> The treatment randomisation used a minimisation technique stratified according to institution, risk group, hormone receptor status, nodal involvement, age, HER2 status, axillary treatment, and type of surgery (detailed information is provided in the appendix pp 8–9). All randomisations were open label (treatment allocation was not masked) and were done centrally, initially (from the start of the study in February, 2007) at the International Drug Development Institute (Louvain-la-Neuve, Belgium) and, as of January, 2010, at the EORTC (Brussels, Belgium).

### Procedures

The 70-gene signature<sup>9</sup> (MammaPrint) was used to determine genomic risk, and a modified version of Adjuvant! Online (modified from version 8.0 including HER2 status) to determine clinical risk.<sup>10</sup> Low clinical risk was defined in this study as a 10-year probability of breast cancer-specific survival without systemic therapy of more than 88% for women with oestrogen receptor-positive tumours and more than 92% for women with oestrogen receptor-negative tumours, to account for the 4 percentage point average absolute benefit of endocrine therapy for oestrogen receptor-positive tumours.<sup>1</sup> Details about the combinations of clinical-pathological criteria leading to the stratification of clinical risk according to Adjuvant! Online are provided in the appendix (p 10). In brief, clinical risk was defined as high for all node-positive patients, except if the tumour was grade 1 and had a diameter of 2 cm or smaller, while for node-negative patients, a grade 3 tumour with a diameter above 1 cm, a grade 2 tumour with a diameter above 2 cm, or a grade 1 tumour with a diameter above 3 cm were all considered high clinical risk.

The MINDACT protocol divided patients into four main groups on the basis of their clinical and genomic risk (appendix pp 8–9). All patients who had concordant clinical high risk and genomic high risk assessments were to receive adjuvant chemotherapy. All patients who were categorised as concordant low risk by both tests were not to receive adjuvant chemotherapy. Endocrine therapy was indicated for all patients with hormone receptor-positive tumours. Patients with discordant risk results at enrolment (ie, either clinical high risk and genomic low risk, or clinical low risk and genomic high

See Online for appendix

risk) were randomly assigned to use their clinical or genomic risk result to guide treatment strategy and receive chemotherapy or to receive no chemotherapy (eg, patients at high clinical risk and low genomic risk randomly assigned to follow the genomic risk received no chemotherapy). The investigator had to submit the eligibility checklist into the data capture system before the patient was enrolled and had therefore no knowledge of future treatment assignment. Once eligibility had been checked, a computerised system calculated the clinical risk and the genomic risk centrally, not at the site itself. The centralised computer system included both risk assessments to allocate treatment (as defined per protocol for patients with concordant risk or by random allocation for patients with discordant risks). All enrolled patients were further categorised according to their corrected risk after the adjustment of risk changes in genomic risk and incorrect reporting of clinical risk at enrolment. These assessments were done as part of the medical review process for eligibility after enrolment by the clinical research physician at EORTC, who would consult the study principal investigators in case of difficult issues. Another round of medical reviews was done at EORTC before the database lock at the time of analysis. Updates in either clinical or genomic risk were mostly made following updates in the diagnostic process at the local hospital, or an adjustment for genomic result, both reported to the trial sponsor. The investigator was informed about the clinical risk, the genomic risk, and the treatment decision outcome afterwards.

There were also two additional (optional) randomisations not reported here: a chemotherapy regimen randomisation (anthracycline-based chemotherapy *vs* docetaxel plus capecitabine)<sup>11</sup> in patients assigned to receive chemotherapy, either randomly because of discordant risk results or because of high-risk concordance of both tests, and an endocrine randomisation (tamoxifen followed by aromatase inhibitor *vs* aromatase inhibitor only) in patients with hormone receptor-positive breast cancer, to be published elsewhere. Details regarding the various therapy regimens of these randomisations are provided in the appendix (pp 8–9). For all other patients, the choice for the type of chemotherapy or endocrine therapy, or both, to be administered was decided by the treating physician, who followed the international and local guidelines effective during the conduct of this trial.

Follow-up visits (including disease assessments and laboratory monitoring) were done according to local standards, and follow-up data were submitted to EORTC. All adverse events and serious adverse events were reported or recorded (as per protocol: serious adverse events were part of the pharmacovigilance for all 6693 patients; other adverse events were only reported for patients who participated in any of the additional treatment randomisations for either chemotherapy or endocrine therapy, or both). All patients enrolled in the

trial were followed up for recurrence and survival, according to intention to treat, even in cases of major protocol violations or ineligibility.

### Outcomes

The primary endpoint of MINDACT was distant metastasis-free survival, defined as the time from enrolment until first distant metastatic recurrence or death from any cause. Secondary endpoints were: overall survival, disease-free survival, and distant metastasis-free interval. Overall survival was defined as the time from enrolment until death from any cause. Disease-free survival was defined as the time from enrolment until first disease progression (locoregional, distant relapse, ipsilateral or contralateral invasive breast cancer, ductal carcinoma in situ, or an invasive second primary cancer) or death from any cause. Distant metastasis-free interval was defined as the time from enrolment until first distant metastatic recurrence or death from breast cancer or unknown cause. Data for patients who had no event at the cutoff date were censored at the time of the last disease assessment for distant metastasis-free survival, disease-free survival, and distant metastasis-free interval endpoints and at the last follow-up date for overall survival. An overview of all endpoints with full definitions are provided in the appendix (p 13).

### Statistical analysis

The primary analysis tested the distant metastasis-free survival at 5 years in the primary test population of patients with high clinical risk and low genomic risk who were randomly assigned to use the genomic risk for the decision to forgo chemotherapy and who adhered to the treatment assignment of no chemotherapy. Patients with changes in clinical or genomic risk were excluded from the primary test population. The primary analysis was designed to test whether the lower boundary of the 95% CI for the rate of 5-year survival without distant metastasis would be 92% (ie, the non-inferiority boundary) or higher, at a one-sided significance level of 0.025. The sample size was modified during the trial enrolment (on May 31, 2011) from 6000 to 6600 patients, because the proportion of patients with both low clinical and low genomic risk was higher than originally projected. With 6600 patients accrued overall, the primary test population had an expected size of 672 patients. The primary test was first done in 2016 when two predefined conditions were met: the standard error for the rate of survival without distant metastasis at 5 years was 0.01 or less and at least 33% of patients in the primary test population had 5 years of follow-up. A two-sided 95% CI for the 5-year rate of survival without distant metastasis with the lower boundary of the 95% CI exceeding 92% was considered to indicate significance. Under these conditions, this test has 80% power to reject the null hypothesis if the true 5-year rate of survival without distant metastasis is 95%. In 2016, with

60% of patients followed for 5 years or longer, this analysis successfully showed that the lower boundary of the 95% CI for the 5-year distant metastasis-free survival was greater than 92% (ie, the predefined non-inferiority threshold).<sup>6</sup>

The protocol-defined data collection for the analysis of the endocrine randomisation allowed us to update the analyses with longer follow-up, which was supported by the independent data monitoring committee (appendix pp 445–94).

In addition, two planned secondary analyses are updated. In the first analysis, we evaluated the outcomes in the discordant-risk groups (on the basis of patients' risk at enrolment) according to whether they were assigned to chemotherapy or no chemotherapy (intention-to-treat population). In the intention-to-treat population, patients were analysed according to the randomised group, irrespective of adherence. Survival rates were estimated using the Kaplan-Meier method and hazard ratios (HRs) were estimated using Cox proportional hazard models adjusted for stratification factors used at randomisation except institution. The assumption of non-proportional hazards was assessed using the supremum test and it was found to hold (data not shown). In the second analysis, we evaluated distant metastasis-free survival in all patients according to whether the use of chemotherapy would be recommended by either clinical risk or genomic risk. To have an unbiased estimate for this analysis, data for patients in the discordant-risk groups were doubly weighted, because they were under-represented by a factor of two in the resulting sample. Both analyses are reported according to the risk category and treatment assignment at the time of enrolment. In analyses according to the four risk groups (the all patients population), results are reported according to the corrected risk group—ie, the post-enrolment risk assigned after updated assessments.<sup>6</sup>

The treatment randomisation analyses were repeated in the per-protocol population as a sensitivity analysis, which excluded patients who were ineligible, had a change in their clinical or genomic risk, or were non-adherent to the treatment assignment. A multivariate Cox proportional hazards model was used to determine the prognostic value of the 70-gene signature risk assessment on distant metastasis-free survival in all enrolled patients. Further details of the methods used are described in the appendix (p 33).

Exploratory analyses that were predefined prospectively in the statistical analysis plan for the updated 8·7-year analysis include analyses in the subgroup of patients with hormone receptor-positive and HER2-negative disease, by nodal status, and according to an approximate menopausal status defined by an age cutoff at 50 years. The trial has low power for comparison between chemotherapy and no chemotherapy groups; therefore, attention should go to the 95% CIs when interpreting the results. All analyses were done with the use of SAS, version 9.4.

This study is registered with ClinicalTrials.gov, NCT00433589; and the European Clinical Trials database, EudraCT2005–002625–31.

#### Role of the funding source

The study sponsor, EORTC, oversaw data management and statistics. The funders of this study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the paper for publication.

#### Results

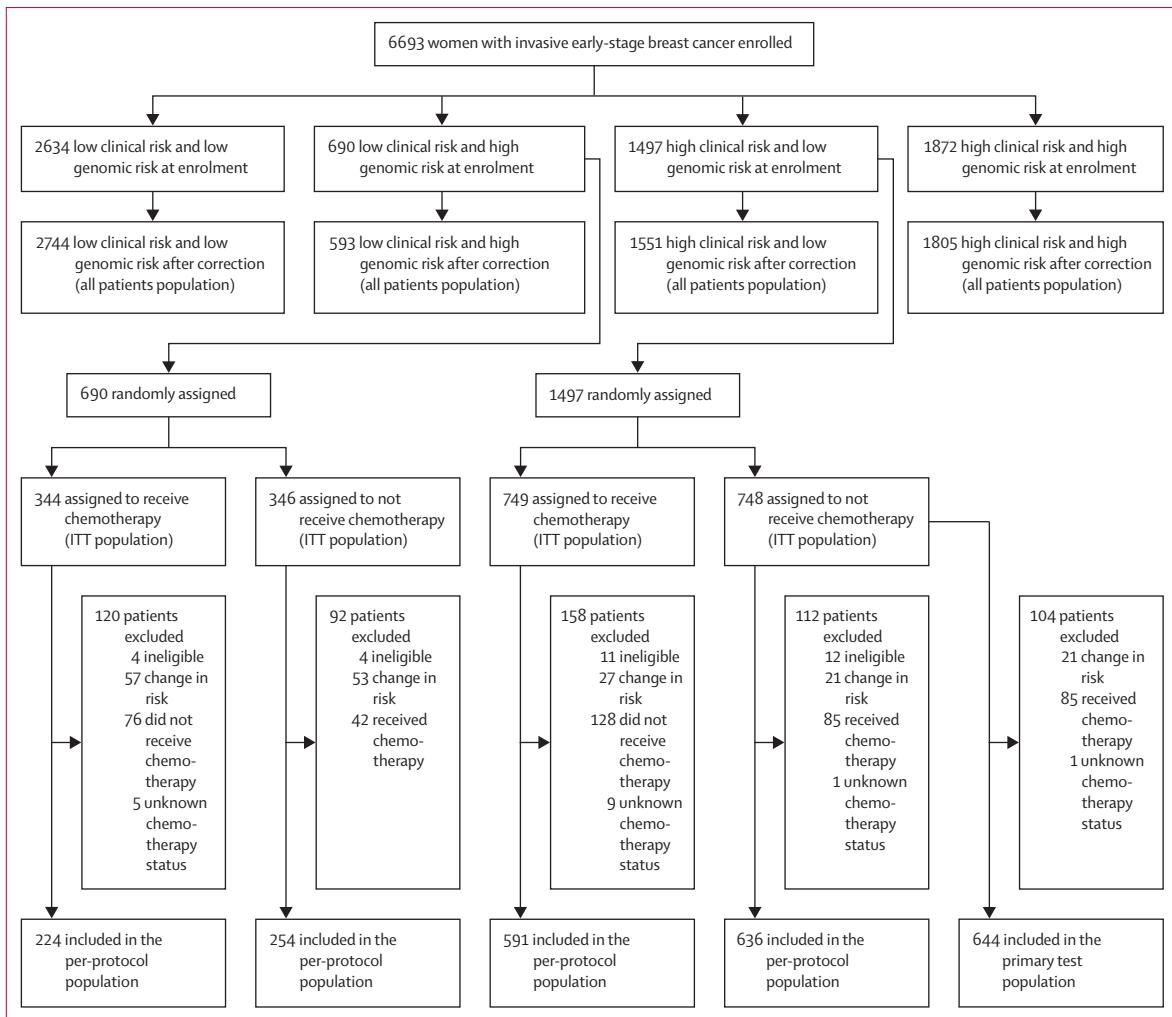
Between Feb 8, 2007, and July 11, 2011, 11288 patients were screened, of whom 6693 patients were enrolled (all patients population; figure 1). 75 (1·1%) of 6693 patients were found to be ineligible.

A total of 2187 patients in the trial (intention-to-treat population) had discordant risk results: 1497 (22%) of 6693 patients had high clinical risk and low genomic risk, and 690 (10%) of 6693 patients had low clinical risk and high genomic risk. After correction these numbers were amended to 1551 patients at high clinical and low genomic risk and 593 at low clinical and high genomic risk (figure 1; corrected risk, all patients population). Table 1 presents the patient and tumour characteristics, adjuvant treatment characteristics, and the type of chemotherapy (in the large majority, chemotherapy was anthracycline-based or taxane-based, or a combination thereof), according to corrected risk for the two discordant-risk groups. The baseline characteristics of the patients according to corrected risk groups and treatment allocations are shown in the appendix (pp 11–12). Patients with high clinical risk and low genomic risk at enrolment were randomly assigned to receive chemotherapy (n=749) or not (n=748) (intention-to-treat population).

In the discordant-risk groups, overall adherence to the chemotherapy assignment was 86% (1852 of 2144). Among patients in the high clinical risk and low genomic risk group, the rate of adherence was 85% (676 of 791) in the chemotherapy group and 89% (677 of 760) in the no chemotherapy group. Among patients in the low clinical risk and high genomic risk group, the rates of adherence were 80% (239 of 297) in the chemotherapy group and 88% (260 of 296) in the no chemotherapy group.<sup>6</sup>

The cutoff date for the current analysis was Feb 26, 2020, at which time the median follow-up for disease assessment was 8·7 years (IQR 7·8–9·7). At this cutoff date, 908 (13·6%) of 6693 patients had been reported as lost to follow-up by their treating physician. In the primary test population, the percentage of patients with 5-year follow-up was now 91·9% (95% CI 89·5–93·7), and the standard error for the distant metastasis-free survival rate at 5 years was 0·0087.

The results of the primary analysis in patients who were at high clinical risk and low genomic risk as verified post-enrolment and did not receive adjuvant chemotherapy (primary test population, n=644) showed a 5-year



**Figure 1: Enrolment and risk groups included in the analysis**

The primary analysis was done in the primary test population. The treatment randomisation analyses for the groups with discordant clinical and genomic risks were done based on the risk at enrolment (ITT population). These analyses were repeated in the per-protocol population, which excluded patients who were ineligible, had a change in their clinical or genomic risk, or were non-adherent to their treatment assignment. Patients could have more than one reason for exclusion. ITT=intention-to-treat.

distant metastasis-free survival rate of 95·1% (95% CI 93·1–96·6), excluding the predefined non-inferiority threshold of 92%, and confirming the primary objective of the study (appendix p 14).

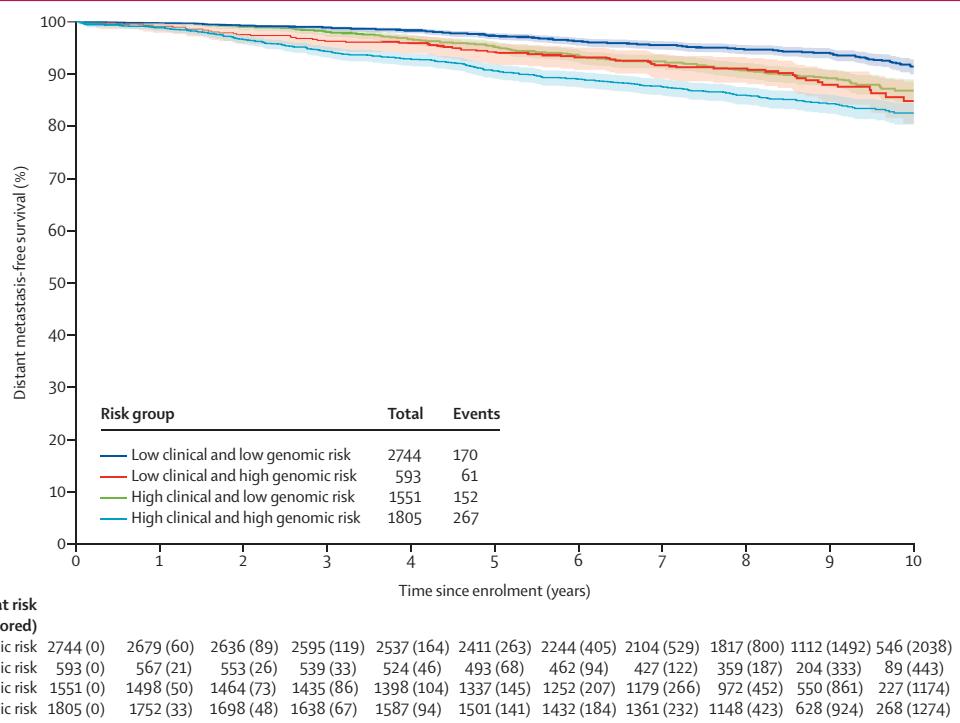
The following numbers of events have been reported in the MINDACT population of 6693 patients, with 70·4% (95% CI 69·2–71·5) of patients having a minimum follow-up of 8 years: there have been 458 deaths (262 in 2893 patients who were allocated to receive chemotherapy and 196 in 3800 patients who were not), 1166 disease-free survival events (564 in patients who were allocated to receive chemotherapy and 602 in patients who were not), and 650 distant metastasis-free survival events (362 in patients who were allocated to receive chemotherapy and 288 in patients who were not). Notably, a substantial proportion of patients have developed second primary cancers

(518 [44·4%] of all 1166 disease-free survival events: 12 [1·0%] leukaemia, 18 [1·5%] other haematological malignancies, 163 [14·0%] contralateral breast cancers, and 325 [27·9%] other solid tumours; 208 of 518 in patients who were allocated to receive chemotherapy and 310 of 518 in patients who were not) or have died from other causes than breast cancer or unknown cause (221 [48·3%] of all 458 deaths; 96 of 221 in patients who were allocated to receive chemotherapy and 125 of 221 in patients who were not). Of the 650 distant metastasis-free survival events, 447 (68·8%) represent distant metastases (275 of 447 in patients who were allocated to receive chemotherapy and 172 of 447 in patients who were not), and 203 (31·2%) correspond to deaths from any cause in the absence of a distant recurrence (87 of 203 in patients who were allocated to receive chemotherapy and 116 of 203 in patients who

	Discordant-risk groups		All patients (n=6693)
	Low clinical risk, high genomic risk (n=593)	High clinical risk, low genomic risk (n=1551)	
<b>Age, years</b>			
≤50	179 (30.2%)	535 (34.5%)	2226 (33.3%)
>50	414 (69.8%)	1016 (65.5%)	4467 (66.7%)
<b>Tumour size, cm</b>			
<1	198 (33.4%)	38 (2.5%)	920 (13.7%)
>1 to 2	384 (64.8%)	610 (39.3%)	3875 (57.9%)
>2 to 5	11 (1.9%)	845 (54.5%)	1819 (27.2%)
>5	0	58 (3.7%)	78 (1.2%)
Missing data	0	0	1 (0.0%)
<b>Tumour grade</b>			
1	92 (15.5%)	98 (6.3%)	1447 (21.6%)
2	415 (70.0%)	996 (64.2%)	3287 (49.1%)
3	83 (14.0%)	443 (28.6%)	1927 (28.8%)
Missing data	3 (0.5%)	14 (0.9%)	32 (0.5%)
<b>Lymph node status</b>			
Negative	578 (97.5%)	811 (52.3%)	5288 (79.0%)
Positive	..	..	..
1 node	10 (1.7%)	507 (32.7%)	942 (14.1%)
2–3 nodes	5 (0.8%)	226 (14.6%)	454 (6.8%)
≥4 nodes	0	6 (0.4%)	8 (0.1%)
Missing data	0	1 (0.1%)	1 (0.0%)
<b>Clinical-pathological subtype</b>			
Luminal HER2-negative (ER-positive, PR-positive, or both)	468 (78.9%)	1403 (90.5%)	5402 (80.7%)
Luminal HER2-positive (ER-positive, PR-positive, or both)	68 (11.5%)	115 (7.4%)	501 (7.5%)
Non-luminal HER2-positive (ER-negative, PR-negative)	5 (0.8%)	9 (0.5%)	137 (2.0%)
Triple negative (ER-negative, PR-negative, HER2-negative)	51 (8.6%)	20 (1.3%)	640 (9.6%)
Missing data	1 (0.2%)	4 (0.3%)	13 (0.2%)
<b>Adjuvant chemotherapy received</b>			
Yes	272 (45.9%)	753 (48.5%)	2820 (42.1%)
No	317 (53.4%)	789 (50.9%)	3838 (57.3%)
Unknown	4 (0.7%)	9 (0.6%)	35 (0.5%)
<b>Type of chemotherapy</b>			
Anthracycline-based	122/272 (44.9%)	297/753 (39.4%)	1140/2820 (40.4%)
Anthracycline and taxane-based	39/272 (14.3%)	181/753 (24.0%)	789/2820 (28.0%)
Taxane-based	71/272 (26.1%)	179/753 (23.8%)	697/2820 (24.7%)
CMF type	1/272 (0.4%)	4/753 (0.5%)	9/2820 (0.3%)
Other or missing	39/272 (14.3%)	92/753 (12.2%)	185/2820 (6.6%)
<b>Adjuvant trastuzumab received</b>			
Yes	39 (6.6%)	79 (5.1%)	427 (6.4%)
No	537 (90.5%)	1441 (92.9%)	6154 (91.9%)
Missing	17 (2.9%)	31 (2.0%)	112 (1.7%)
<b>Adjuvant endocrine therapy received</b>			
Yes	488 (82.3%)	1454 (93.7%)	5176 (77.3%)
No	88 (14.8%)	59 (3.8%)	1400 (20.9%)
Missing	17 (2.9%)	38 (2.5%)	117 (1.7%)

Data are n (%) or n/N (%). Percentages might not total 100 because of rounding. Shown are the treatment characteristics for the two discordant groups and summarised for all patients. ER=oestrogen receptor. PR=progesterone receptor. CMF=cyclophosphamide, methotrexate, and fluorouracil.

**Table 1: Patient, tumour, and adjuvant treatment characteristics and type of chemotherapy according to corrected risk for discordant-risk groups and all patients**



**Figure 2: Distant metastasis-free survival in the four risk groups**

The analysis included all enrolled patients, and the risk groups are based on corrected risk (all patients population). The time-to-event curves were estimated by means of the Kaplan-Meier method. The Kaplan-Meier curve is displayed until 10 years of follow-up due to the high level of censoring beyond this timepoint. Shading around curves shows 95% CIs.

were not). For all enrolled patients, the distant metastasis-free survival by risk group is presented in figure 2 (and rates of all endpoints and types of events are provided in the appendix p 15). Patients at low clinical and low genomic risk (2744 [41·0%] of 6693 patients who were recommended to receive endocrine therapy only) had excellent 5-year and 8-year survival rates for all endpoints. Whereas patients with high clinical and high genomic risk (1805 [27·0%] of 6693 patients, who were recommended to receive chemotherapy) had the worst 5-year and 8-year survival rates. The number of events for the discordant-risk groups by treatment allocation in the intention-to-treat population (one of the prespecified secondary analyses) are provided in table 2 and the appendix (pp 16–22) for all endpoints.

For the group of patients at high clinical risk and low genomic risk, all HRs (within wide CIs) indicate some risk reduction provided by chemotherapy, translating into a pointwise absolute difference for distant metastasis-free survival of 0·9 percentage points (SE 1·1, 95% CI –1·4 to 3·1) at 5 years and 2·6 percentage points (1·6, –0·5 to 5·7) at 8 years (table 2 and appendix p 16). For the group of patients at low clinical risk and high genomic risk, HRs also point to some risk reduction provided by chemotherapy, with a pointwise absolute difference for distant metastasis-free survival of

0·2 percentage points (SE 1·7, 95% CI –3·2 to 3·6) at 5 years and 1·5 percentage points (2·3, –2·9 to 5·9) at 8 years (table 2 and appendix p 16). There were no differences in overall survival in the group of patients at high clinical risk and low genomic risk with or without chemotherapy over the entire follow-up period (table 2 and appendix p 32). Outcome figures for the per-protocol analysis are provided in the appendix (p 17).

For the second prespecified secondary analysis we updated the estimated outcomes in all patients if the use of chemotherapy had been recommended by risk stratification into low or high risk on the basis of either clinical or genomic risk alone. At 8 years, the distant metastasis-free survival would have been 91·3% according to clinical risk and 90·9% according to genomic risk (appendix pp 23–24). These similar outcomes are achieved with a much lower use of chemotherapy according to the genomic risk strategy (a 46% reduction of chemotherapy use for clinical high-risk patients; appendix p 11).

One of the predefined exploratory analyses was to examine outcomes by nodal status in hormone receptor-positive, HER2-negative patients in the high clinical risk and low genomic risk group (1358 [90·7%] of 1497 patients in the intention-to-treat population), because these patients represent the main target population for using multigene predictors.<sup>12</sup> At 8 years, the distant metastasis-free survival

	Adjuvant chemotherapy*		No adjuvant chemotherapy*		Absolute difference, percentage points (SE; 95% CI) at 8 years	Hazard ratio (95% CI)†
	Events/patients	Survival estimate at 8 years, % (95% CI)	Events/patients	Survival estimate at 8 years, % (95% CI)		
<b>High clinical risk and low genomic risk</b>						
Distant metastasis-free survival	60/749	92.0% (89.6 to 93.8)	90/748	89.4% (86.8 to 91.5)	2.6 (1.6; -0.5 to 5.7)	0.66 (0.48 to 0.92)
Distant metastasis-free interval	50/749	93.1% (90.9 to 94.8)	75/748	90.7% (88.2 to 92.7)	2.4 (1.5; -0.5 to 5.4)	0.66 (0.46 to 0.95)
Disease-free survival	110/749	86.4% (83.5 to 88.8)	138/748	82.9% (79.8 to 85.6)	3.5 (2.0; -0.4 to 7.4)	0.79 (0.62 to 1.02)
Overall survival	37/749	95.7% (93.9 to 97.0)	53/748	94.3% (92.2 to 95.8)	1.4 (1.2; -0.9 to 3.8)	0.69 (0.45 to 1.05)
<b>Low clinical risk and high genomic risk</b>						
Distant metastasis-free survival	32/344	92.3% (88.7 to 94.8)	37/346	90.8% (86.9 to 93.6)	1.5 (2.3; -2.9 to 5.9)	0.85 (0.53 to 1.37)
Distant metastasis-free interval	21/344	95.4% (92.3 to 97.2)	30/346	92.4% (88.8 to 94.9)	2.9 (2.0; -0.9 to 6.8)	0.61 (0.34 to 1.07)
Disease-free survival	57/344	86.2% (81.7 to 89.6)	68/346	81.9% (77.1 to 85.9)	4.2 (3.0; -1.6 to 10.1)	0.79 (0.55 to 1.13)
Overall survival	23/344	93.8% (90.5 to 96.0)	26/346	93.0% (89.4 to 95.4)	0.9 (2.0; -3.1 to 4.8)	0.94 (0.54 to 1.67)

Data are n, survival estimate or hazard ratio (95% CI), or absolute difference (SE; 95% CI). Shown are the four major survival outcomes—distant metastasis-free survival, distant metastasis-free interval, disease-free survival, and overall survival—in the two discordant-risk groups at the time of enrolment (ie, patients with high clinical risk and low genomic risk or low clinical risk and high genomic risk), according to the randomised treatment (intention-to-treat population). \*Patients were randomly assigned to follow either the clinical or the genomic risk to receive chemotherapy (eg, patients at high clinical risk and low genomic risk randomly assigned to follow the genomic risk received no chemotherapy). †Hazard ratios for distant metastasis-free survival, distant metastasis-free interval, disease-free survival, and overall survival were calculated with use of a Cox proportional hazards model after adjustment for the factors used in stratification for randomisation of assignments. The reference group is no chemotherapy.

Table 2: Outcome for discordant-risk groups according to treatment strategy (intention-to-treat population)

rate for node-negative patients was 91.7% (95% CI 88.1–94.3) with chemotherapy ( $n=349$ ) and 89.2% (85.2–92.2) without chemotherapy ( $n=350$ ), representing an absolute difference of 2.5 percentage points (SE 2.3, 95% CI –2.1 to 7.2; HR 0.60; 95% CI 0.38–0.96; appendix pp 25–28). For patients with one to three positive lymph nodes, distant metastasis-free survival at 8 years was 91.2% (95% CI 87.2–94.0) with chemotherapy ( $n=326$ ) and 89.9% (85.8–92.8) without ( $n=332$ ), an absolute difference of 1.3 percentage points (SE 2.4, –3.5 to 6.1; HR 0.84; 95% CI 0.51–1.37; appendix pp 28–30), indicating a similar outcome regardless of nodal status.

Of note, in the group of patients with clinical high risk, genomic low risk status who had triple-negative breast cancer or HER2-positive breast cancer, who had been excluded from the above analysis, we observed in a post-hoc analysis distant metastasis-free survival events in one of nine patients with triple-negative breast cancer and seven of 56 patients with HER2-positive breast cancer who did not receive chemotherapy, but the small size of these subsets limits the interpretation.

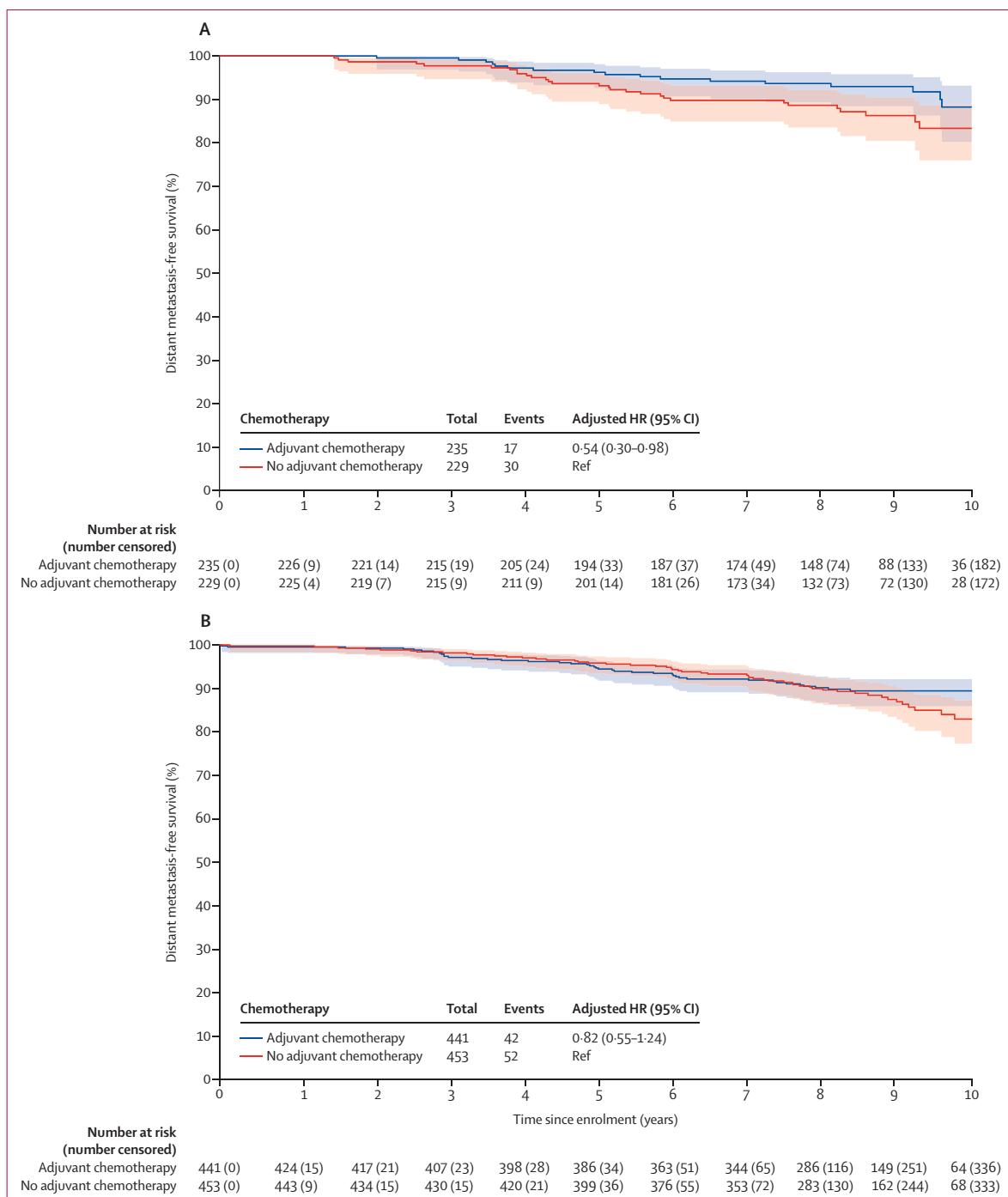
In an additional predefined exploratory analysis, we looked at distant metastasis-free survival with or without chemotherapy separately in hormone receptor-positive, HER2-negative women at high clinical risk and low genomic risk who were 50 years of age or younger versus in women older than 50 years, acknowledging the fact that chemotherapy might induce ovarian function suppression in premenopausal women, which represents an indirect additional therapy. In older women (aged >50 years), no chemotherapy benefit was seen at 8 years (distant metastasis-free survival 90.2% [95% CI 86.8–92.7] with chemotherapy [ $n=441$ ] vs 90.0% [86.6–92.6] without chemotherapy [ $n=453$ ]; absolute difference 0.2 percentage

points, SE 2.1, 95% CI –4.0 to 4.4; adjusted HR 0.82, 95% CI 0.55–1.24; figure 3, appendix p 31). In younger women (aged ≤50 years), whose adjuvant endocrine therapy consisted mainly of tamoxifen (a luteinising hormone-releasing hormone [LHRH] analogue was administered to only 95 [21.3%] of 446 patients: 36 [16.2%] of 222 in the no chemotherapy group and 59 [26.4%] of 224 in the chemotherapy group), chemotherapy administration appeared to improve distant metastasis-free survival with an absolute difference of 5.0 percentage points (SE 2.8, 95% CI –0.5 to 10.4) in distant metastasis-free survival at 8 years [93.6% [95% CI 89.3–96.3] with chemotherapy [ $n=235$ ] vs 88.6% [83.5–92.3] without chemotherapy [ $n=229$ ]; adjusted HR 0.54 [95% CI 0.30–0.98]; figure 3, appendix p 31). These findings were consistent when this analysis was done in the per-protocol population (appendix p 31).

Finally, in the overall population, the 70-gene signature is confirmed to be significantly associated with distant metastasis-free survival after adjustment for chemotherapy, clinical risk, and patient and tumour characteristics in a multivariate analysis (HR 2.13, 95% CI 1.71–2.66, for patients at high genomic risk vs those at low genomic risk;  $p<0.0001$ ; appendix p 33).

## Discussion

These updated results from the MINDACT trial, at a median follow-up of 8.7 years, reveal that women with early-stage breast cancer who were at clinical high risk and genomic low risk for recurrence and who did not receive chemotherapy—the target population of the trial primary endpoint—continue to have an excellent 5-year distant metastasis-free survival of 95.1%. Thus, with 91.9% of patients followed up for a minimum of 5 years, the primary



**Figure 3:** Distant metastasis-free survival according to randomised treatment strategy in the clinical high-risk, genomic low-risk, hormone-receptor-positive, HER2-negative subgroup, by age

(A) Patients aged 50 years or younger and (B) patients aged older than 50 years. This analysis was done in the intention-to-treat population, which included patients who had discordant risk at the time of enrolment and who were analysed according to treatment strategy assignment. Time-to-event curves were estimated by means of the Kaplan-Meier method. Kaplan-Meier curve is displayed until 10 years of follow-up due to the high level of censoring beyond this timepoint. Shading around curves shows 95% CIs. HR=hazard ratio.

objective of the trial continues to be met, with a non-inferiority threshold greater than 92% (95% CI 93·1–96·6). For these high clinical risk and low genomic risk patients,

the secondary endpoint of the trial now shows a distant metastasis-free survival increase of 0·9 percentage points at 5 years and 2·6 percentage points at 8 years with

chemotherapy. Although these benefits remain of small magnitude on average, we also report here in an exploratory analysis a differential performance of the 70-gene signature according to age with this longer follow-up.

In 2016, we observed a 1·5 percentage points absolute benefit in distant metastasis-free survival from adjuvant chemotherapy in the MINDACT trial (HR 0·78, 95% CI 0·50–1·21), which was considered uncertain and very small in light of the potentially long-term, and sometimes irreversible, harmful effects of adjuvant chemotherapy.<sup>6</sup> With almost 4 additional years of follow-up and 650 distant metastasis-free survival events instead of 362, we have been able to re-evaluate the 2016 conclusions. Overall, the suggestion of a distant metastasis-free survival benefit from adjuvant chemotherapy, which was unclear in 2016, now seems to be more evident (HR 0·66, 95% CI 0·48–0·92) and in line with the proportion of risk reduction seen with adjuvant chemotherapy in the Early Breast Cancer Trialists' Collaborative Group meta-analysis.<sup>1</sup> However, with longer follow-up and with more mature data, the absolute increase in distant metastasis-free survival with chemotherapy at 5 years is reduced from 1·5 percentage points to 0·9 percentage points and remains small at 8 years (2·6 percentage points). Additionally, unlike in the meta-analyses where the differential effect of chemotherapy is primarily seen in the first 5 years after diagnosis, in MINDACT this difference starts only after 4 years. Notably, similar results were also observed in the lymph node-positive patients, which remained valid with longer follow-up. Overall survival outcomes did not differ in the group of patients with clinical high risk and genomic low risk with or without chemotherapy over the entire follow-up period.

With this longer follow-up, a potentially clinically relevant difference emerges in the hormone receptor-positive, HER2-negative patient population according to age. For patients with high clinical and low genomic risk who are older than 50 years, a consistent performance of the 70-gene signature to forego adjuvant chemotherapy is shown, with an absolute distant metastasis-free survival gain of just 0·2 percentage points, but in women aged 50 years or younger, an absolute distant metastasis-free survival benefit of 5·0 percentage points is seen at 8 years. It is important to acknowledge that this subgroup analysis was exploratory, limited to the 1358 women at high clinical and low genomic risk with hormone receptor-positive, HER2-negative tumours, and was driven by the interesting observation made by TAILORx investigators that in women 50 years old or younger with a midrange Oncotype-DX recurrence score and a high clinical risk as defined in MINDACT, the estimated distant recurrence at 9 years exceeded 10% if tamoxifen alone was given.<sup>13</sup> This so-called age effect is unlikely to be a chance finding because it shows striking similarities in the two largest prospective biomarker-driven trials in which only 16–20% of young women received an LHRH analogue in addition to tamoxifen<sup>13</sup> and it is seen in the

Early Breast Cancer Trialists' Collaborative Group meta-analysis of long-term outcomes in 100 000 women randomly assigned to receive adjuvant chemotherapy or not. The absolute benefits at 10 years in all breast cancer recurrences from adjuvant chemotherapy were three times as large for younger women (aged <50 years) than for older women (aged ≥50 years).<sup>1</sup>

What are the potential explanations for the enhanced chemotherapy effect in younger women? There are two possibilities: a greater cytotoxic effect of chemotherapy in younger women than in older women, or an indirect endocrine effect occurring through ovarian function suppression. The former potential mechanism is unlikely given that cytotoxicity from chemotherapy occurs in the first few years following its administration,<sup>1</sup> meaning that it is unlikely that this chemotherapy-related differential effect by age would emerge at longer follow-up. The latter mechanism (ovarian function suppression) is indirectly supported by the 9-year results of two trials: TAILORx<sup>13</sup> and SOFT.<sup>14</sup> In TAILORx, the chemotherapy benefit mentioned above was most evident at 45 years in premenopausal women and waned at younger and older ages and with menopause, which is consistent with an effect due to chemotherapy-induced premature menopause.<sup>13</sup> In SOFT,<sup>14</sup> a prospective trial investigating optimal adjuvant endocrine strategies in 3047 premenopausal women, it took 8 years to detect an advantage from the addition of ovarian function suppression to tamoxifen: the absolute 8-year improvements in disease-free survival and overall survival were 4·2 percentage points and 1·8 percentage points respectively.<sup>14</sup> Both the magnitude of the treatment effect and the pattern of recurrence (eg, after 5 years) reinforce the hypothesis of an indirect endocrine effect of chemotherapy in younger women, which has been previously advocated in 2009.<sup>15</sup> It cannot be assumed that chemotherapy could safely be replaced by ovarian function suppression: this uncertainty will need to be communicated to patients as part of informed shared decision making. For older women, a strong message from the mature results from MINDACT and TAILORx is that multigene signatures guiding omission of chemotherapy, in the presence of a high clinical risk, are robust decision aids.

About half of the patients in the MINDACT trial (n=3337) had a low clinical risk defined by the prespecified clinical-pathological characteristics, mainly stage T1, grade 1 or 2, and node-negative tumours (appendix pp 11–12). The survival estimates for patients at low clinical risk but high genomic risk are, however, for all endpoints a few percentage points lower than for the clinical low-risk and genomic low-risk group. In this smaller subset of 690 patients (of whom 559 [81%] were hormone-receptor-positive, HER2-negative, intention-to-treat population) with clinical low-risk and genomic high-risk tumours randomly assigned to receive chemotherapy or not, a 1·5 percentage points improvement in distant metastasis-free survival is seen at 8 years with chemotherapy administration. Because this subset is enriched with small,

node-negative tumours of more aggressive subtypes, this estimated chemotherapy benefit of small magnitude is plausible. However, this analysis in this small subset of patients was considerably underpowered to determine the benefit of chemotherapy, and MINDACT is unlikely to provide a conclusive answer to the question of the clinical utility of the 70-gene signature in these women. Thus far, no genomic assay has been able to show a benefit from chemotherapy in an exclusively clinically low-risk group where the breast cancer-specific survival is already predicted to be more than 92% based on clinical assessment alone.

A limitation for the interpretation of this trial is the use of Adjuvant! Online as the clinical risk prediction tool, which as of 2016 is no longer available. However, for this reason, we provide details of how patients were stratified according to their clinical risk in MINDACT in the appendix (p 10). Due to the continuous improvement of clinical risk prediction models, with a better understanding of the combined value of clinical-pathological characteristics, fewer patients might be classified as clinically high risk today than there were during the conduct of the trial. Furthermore, a high-quality evaluation of oestrogen and progesterone receptor status, HER2, Ki67, and grade by an experienced breast pathologist could, for a proportion of the patients, be as good as a prognostic gene signature, but we believe that in a real-world setting such high-quality testing is often not available, thus highlighting the important role of gene signatures in routine clinical practice. Regarding the chemotherapy regimens used in this trial, a regimen of anthracyclines only would not be standard in the present era. However, all patients were treated as required according to the ongoing international recommendations during the conduct of this trial between 2007 and 2011. At that time, the addition of taxanes was not standard in the adjuvant treatment of breast cancer in Europe.<sup>16</sup> Furthermore, we do not believe that the regimens of anthracyclines alone were suboptimal, since even today the benefit of taxanes for the treatment of node-negative breast cancer is not fully clear; taxanes became the preferred standard more because of toxicity issues than for efficacy reasons.<sup>17</sup>

MINDACT confirms what has been learned in the past decade: namely that clinical and genomic risk assessments provide independent prognostic information and should both be integrated into treatment decisions about adjuvant chemotherapy in breast cancer.<sup>13,18</sup> MINDACT also shows that the inclusion of genomic information contributes to the much-needed personalised oncology component of clinical care and is a rich resource for further exploration on breast cancer full transcriptome data.<sup>19</sup>

In conclusion, the MammaPrint 70-gene signature shows clinical utility in women with invasive hormone-receptor-positive, HER2-negative breast cancer with up to three positive nodes considered at high clinical risk for developing metastases. If the signature's readout shows a

low genomic risk, it allows safe chemotherapy omission in women older than 50 years; in younger women, a potentially clinically relevant chemotherapy benefit of about 5 percentage points is observed at longer follow-up, which might be in part related to chemotherapy-induced ovarian function suppression.

#### Contributors

MP, FC, and EJTR were the study coordinators of the EORTC 10041, BIG 3–04 trial and made substantial contributions to the conception and design together with LJV and JB. For this manuscript, MP, LJV, CP, JMNLC, FC, and EJTR did the literature research. MP, SD, J-YP, PV, EB, SV, PAN, SC, TJS, GV, CS, ITR, SKü, GZ, AMT, EM, KZ, AP, BM, FC, and EJTR collected data. CP, with support for the tables from JMNLC, prepared figures and tables and did the statistical analyses. All authors had access to the data and vouch for its integrity and completeness. CP, JMNLC, and BM had access to and have verified the underlying raw data. MP, LJV, CP, JMNLC, SD, J-YP, PV, EB, SV, PAN, SC, TJS, GV, CS, ITR, SKü, GZ, AMT, EM, KZ, FH, DF, SKn, KT, JB, FC, and EJTR interpreted the data. All authors have contributed to the manuscript writing, reviewed draft and final versions of the manuscript before submission, given final approval for publication, and are accountable for all aspects of the work. The first and last authors (MP, LJV, CP, FC, and EJTR) had full access to all the data and had final responsibility for the decision to submit for publication.

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MP reports grants from Radius, Synthon, and Servier; grants and personal fees from AstraZeneca, Lilly, MSD (Merck Sharp & Dohme), Novartis, Odonate, Pfizer, Roche-Genentech, Menarini, and Immunomedics; personal fees from Camel-IDS, Debiopharm, Seattle Genetics, OncoLytic, and Immutep, all outside the submitted work. LJV reports personal fees and other (part-time employee, stock holder) from Agendia, during the conduct of the study. SD reports grants and non-financial support from Pfizer, AstraZeneca, and Roche Genentech; and grants from Novartis, Lilly, Puma, Myriad, Orion, Amgen, Sanofi, Genomic Health, GE, Servier, MSD, Bristol Myers Squibb (BMS), and Pierre Fabre, all outside the submitted work. J-YP reports grants, personal fees, and non-financial support from Roche; personal fees from Novartis, Genomic Health, Pfizer, and Lilly; and non-financial support from Sanofi, all outside the submitted work. PV reports personal fees from Novartis, Pfizer, MSD, and Lilly; personal fees and non-financial support from Roche; and other (speaker's fee) from AstraZeneca, all outside the submitted work. EB reports personal fees and other (travel and accommodation) from Pfizer and Roche; other (travel and accommodation) from Pierre Fabre, Novartis, and AstraZeneca; grants, personal fees, and other (travel and accommodation) from BMS; and personal fees from Samsung, TLC PharmaChem, Clinigen, Mylan, G1 Therapeutics, and Lilly, all outside the submitted work. GV reports personal fees from Roche Genentech, MSD Oncology, AstraZeneca, Daiichi Sankyo, and Menarini, all outside the submitted work. AMG reports that she is an employee of Agendia, the company that markets MammaPrint. SKü reports personal fees from Lilly, Roche, Genomic Health, Novartis, Amgen, Celgene, Daiichi Sankyo, AstraZeneca, Somatex, MSD, Pfizer, Puma Biotechnology, and PFM medical; and non-financial support from Roche and Daiichi Sankyo, all outside the submitted work. KZ reports other (participation in advisory board meeting, support for participation in international congress, support for organization of academic educational symposium) from AstraZeneca, Daiichi, Exact Science, Lilly, MSD, Mylan, Novartis, Pfizer, Roche, Pierre Fabre, and Vifor; and grant from Roche, all outside the submitted work. DF reports grants from European Commission Sixth Framework Programme, Breast Cancer Research Foundation, EBCC Breast Cancer Working Group, Susan G Komen for the Cure, Association le cancer du sein, parlons-en!, Prix Mois du Cancer du Sein, and Brussels BC Walk-Run/American Women's Club; grants and non-financial support from Novartis, F Hoffmann-La Roche, and Sanofi-Aventis; non-financial support from Agendia, during the conduct of the study; and grants from F Hoffmann-La Roche, AstraZeneca, Novartis, Pfizer, Servier, and Tesaro, outside the submitted work. KT is an employee (since Jan, 2018) of Merck Sharp & Dohme, a subsidiary of Merck & Co, outside the

submitted work. AP is an employee (since Sept, 2020) of AstraZeneca Pharma Poland, outside the submitted work. FC reports personal fees from Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Medscape, Merck Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Samsung Bioepis, Sanofi, Seattle Genetics, and Teva, all outside the submitted work. All other authors declare no competing interests.

#### Data sharing

For more on data request procedure see <https://www.eortc.org/data-sharing/>

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