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Standard Anthracycline Based Versus Docetaxel-Capecitabine in Early High Clinical and/or Genomic Risk Breast Cancer in the EORTC 10041/BIG 3-04 MINDACT Phase III Trial

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abstract

PURPOSE MINDACT demonstrated that 46% of patients with early breast cancer at high clinical but low genomic risk on the basis of MammaPrint may safely avoid adjuvant chemotherapy. A second random assignment (R-C) compared docetaxel-capecitabine with an anthracycline-based regimen.

PATIENTS AND METHODS R-C randomly assigned patients 1:1 between standard anthracycline-based regimens, with or without taxanes (control) and experimental docetaxel 75 mg/m^2 intravenously plus oral capecitabine 825 mg/m^2 two times per day for 14 days (DC) every 3 weeks for 6 cycles. The primary end point was disease-free survival (DFS). Secondary end points included overall survival and safety.

RESULTS Of 2,832 patients, 1,301 (45%) were randomly assigned, and 97% complied with R-C assignment. In the control arm, 29.6% only received taxanes (0.5% of N0 patients). DFS events (n = 148) were much less than required (n = 422) as a result of a lower-than-expected accrual and event rate. At 5 years of median follow-up, DFS was not different between DC (n = 652) and control (n = 649; 90.7% [95% CI, 88% to 92.8%] *v* 88.8% [95% CI, 85.9% to 91.1%]; hazard ratio [HR], 0.83 [95% CI, 0.60 to 1.15]; *P* = .26). Overall survival (HR, 0.91 [95% CI, 0.54 to 1.53]) and DFS in the clinical high and genomic high-risk subgroup (86.1% *v* 88.1%; HR, 0.83 [95% CI, 0.58 to 1.21]) were similar in both arms. DC led to more grade 1 neuropathy (27.1% *v* 11.2%) and more grade 2 hand/foot syndrome (28.5% *v* 3.3%) and diarrhea (13.7% *v* 5.8%). Serious cardiac events occurred in 9 patients (control, n = 4; DC, n = 5). Fifty-three patients developed second cancers (control, n = 32; DC, n = 21; leukemia: 2 *v* 1). Five treatment-related deaths occurred (control, 2 [0.3%]; DC, 3 [0.5%]).

CONCLUSION Although underpowered, this second randomization in MINDACT did not show any improvement in outcome or safety with the use of DC compared with anthracycline-based chemotherapy.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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Written on behalf of the MINDACT investigators and the TRANSBIG Consortium.

INTRODUCTION

As a result of improvements in early detection and treatment, nearly 80% of women diagnosed with breast cancer in high-income countries can expect long-term disease-free survival (DFS).[1] Corresponding with improved survival, awareness of treatment-associated toxicities has grown. There have been attempts to better identify patients who derive substantial benefits from medical interventions, as well as to develop less toxic interventions.[2] This especially concerns adjuvant chemotherapy, which has been associated with important short- and long-term adverse effects.[2] Although anthracycline-based chemotherapy regimens—in the 1990s, with the subsequent addition of taxanes in the late 2000s—have become standard in the adjuvant setting, the small magnitude of absolute benefit in some subgroups and associated risk-benefit ratio has been repeatedly questioned.[3] Of particular concern to patients with a medium rather than high risk of relapse are two possible long-term toxicities of anthracycline-based therapy: secondary leukemia and cardiac toxicity. The cumulative risk at 5 years of developing anthracycline-related leukemia or major cardiomyopathy is approximately 1% each for both doxorubicin and epirubicin.[2] Other than decreasing chemotherapy prescription through better prognostic assessments,[4,5] the use of alternative regimens

associated with less toxicity is another option to increase the individual risk-benefit ratio of adjuvant chemotherapy.

Capecitabine was of potential interest in this regard, given the promising preclinical and clinical data in the advanced breast cancer setting with its combination with docetaxel.[6]

The EORTC 10041/BIG 03-04 (MINDACT) study is an international, prospective, randomized phase III trial. It has first provided level 1A evidence regarding the clinical utility of the 70-gene signature (MammaPrint; Agendia, Irvine, CA) in addition to standard clinicopathologic criteria by which to select patients with early breast cancer for adjuvant chemotherapy.[4] MINDACT's second randomization aimed to evaluate whether an experimental docetaxel-capecitabine (DC) regimen was a more effective and less toxic alternative to a standard anthracycline-based regimen (control). The primary objective was DFS. Comparison of overall survival (OS) and safety between both arms were secondary objectives.

METHODS

Study design

The general design of the MINDACT trial has been previously described.[4] In summary, from 2007 to 2011, 6,693 patients with breast cancer with localized, fully resected, 0 to 3 node-positive breast adenocarcinoma were enrolled in the trial and underwent prognostic evaluation using both a standard clinicopathologic assessment and a genomic test. The 70-gene signature (MammaPrint) and a modified version of Adjuvant!Online (modified from 8.0, including human epidermal growth factor receptor 2 [HER2] status; http://www.adjuvantonline.com) were used to determine genomic and clinical risk, respectively. Patients with clinical high (c-high) and genomic high (g-high) risk tumors were to receive adjuvant chemotherapy, whereas those with both low clinical (c-low) and genomic (g-low) risk assessments were not. Patients with discordant results (c-high and g-low or c-low and g-high) were randomly assigned between the 2 risk assessment methods for chemotherapy decision. A second 1:1 randomization (R-C) was proposed to all patients who were allocated to receive chemotherapy between anthracycline-based regimens (control), with or without taxanes (standard regimen at the time the trial was conducted), and experimental docetaxel 75 mg/m^2 intravenously plus oral capecitabine 825 mg/m^2 two times per day for 14 days (DC) every 3 weeks for 6 cycles after surgery. The chemotherapy question was a randomized, two-arm, prospective, nonblinded, multicenter phase III study. Drug supply was provided by the manufacturers.

Trastuzumab was allowed and recommended for women with HER2-positive tumors upon approval and with availability for use in the adjuvant setting. Trastuzumab could be proposed either sequentially or concomitantly with chemotherapy, including in patients in the DC arm.

The European Organization for Research and Treatment of Cancer Protocol Review Committee and ethics committees of all participating 9 countries and 111 sites approved the study.

Patients

Eligible patients for accrual to MINDACT were women between age 18 and 70 years with histologically proven primary nonmetastatic (M0) invasive breast cancer (clinical T1, T2, or operable T3), initially lymph node negative only and, as of August 2009, with up to 3 positive axillary lymph nodes, and with a frozen tumor sample available. Patients were enrolled in the study from February 2007 to July 2011.

Patients were eligible for inclusion in the chemotherapy randomization (R-C) if they also met the following criteria: high risk of recurrence according to both clinicopathologic criteria and the 70-gene signature or high risk according to clinicopathologic criteria and a low risk according to the 70-gene signature, and randomly assigned (R-T) to use the clinicopathologic criteria for chemotherapy decision; or low risk according to clinicopathologic criteria and high risk according to the 70-gene signature, and randomly assigned (R-T) to use the 70-gene signature for chemotherapy decision. Women were also required to have WHO status 0 or 1, normal cardiac function, and to have signed the chemotherapy randomization-specific written informed consent. The interval between definitive surgery and the start of chemotherapy could not exceed 120 days.

Chemotherapy Randomization and Masking

All random assignments were performed centrally, first at the International Drug Development Institute and, as of 2010, at the European Organization for Research and Treatment of Cancer. For chemotherapy randomization (R-C), a minimization technique was used for random treatment allocation stratifying for institution, risk group (high risk genomic/low risk clinical *v* low risk genomic/high risk clinical *v* high risk genomic/high risk clinical), hormone receptor status (positive [estrogen receptor [ER] and/or progesterone receptor) *v* negative [both]), age (< 50 years *v* ≥ 50 years), HER2 (positive *v* negative *v* unknown at the time of R-C), method of axillary evaluation (sentinel lymph node only or dissection), and type of surgery (mastectomy or quadrantectomy/lumpectomy). If progesterone receptor was unknown, the patient was stratified to the hormone receptor–negative group if ER was negative and to the hormone receptor–positive group if ER was positive.

Treatment

Patients were randomly assigned 1:1 to standard anthracycline-based regimens, with or without taxanes (control arm) or experimental docetaxel 75 mg/m^2 intravenously plus oral capecitabine 825 mg/m^2 two times per day for 14 days (DC) every 3 weeks for 6 cycles after surgery. The anthracycline arm was different for patients with lymph node–negative disease and for patients with

lymph node–positive disease, as standard therapies were different for each subgroup at that time. Of node-negative patients, 99.5% received an anthracycline-based regimen without taxanes as per the current National and European guidelines at the time of the trial and including cyclophosphamide, doxorubicin, and fluorouracil (FAC, or CAF), cyclophosphamide, epirubicin, and fluorouracil (FEC), or 4 cycles of epirubicin followed by 4 cycles of cyclophosphamide, methotrexate, and fluorouracil (E-CMF; Appendix Table A1, online only). Of node-positive patients, 97.4% received a sequence of 3 cycles of cyclophosphamide, epirubicin (100 mg/m^2), and fluorouracil (FEC100) followed by 3 cycles of docetaxel.[7] Granulocyte-colony stimulating factor was prescribed according to local standards.

Outcomes

For all analyses related to R-C, time-to-event end points started at the date the sample was received at Agendia. For the primary end point (DFS) and secondary efficacy end points (distant metastases-free survival [DMFS] and OS) analyses, all randomly assigned patients were analyzed in the arm to which they were allocated by random assignment (intent to treat). Safety analyses, however, were conducted in all patients who were randomly assigned for R-C and who had started their allocated chemotherapy (at least one dose of the study drug(s), per protocol).

Events defining DFS included locoregional recurrence, distant (metastatic) recurrence, ipsilateral or contralateral invasive breast cancer, ductal carcinoma in situ, or a second primary invasive cancer. Patients who experienced multiple events within a 1-month time period were classified into the first applicable category according to the following priority list: distant metastasis, locoregional recurrence, new second primary cancer, or death from any cause. DFS was calculated as the time to either the date of disease recurrence or date of death. DMFS was calculated as the time to either the date of first distant metastatic recurrence or date of death. Patients who were found to be ineligible because of M1 status at baseline by medical review were censored at time 0. OS was calculated as the time to death from any cause. Patients with no event at the cutoff date for the final analysis were censored at the time of the last examination for DFS and DMFS and at the last follow-up date for OS. A sensitivity analysis of the primary end point (DFS) was conducted in the clinical-high risk/genomic-high risk group. Adverse events and laboratory abnormalities during chemotherapy were tabulated—worst National Cancer Institute Common Terminology Criteria for Adverse Events grade per patient—by treatment arm. National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 was used throughout the study. Events occurring on treatment plus 30 days are reported.

Statistical Analyses

Unadjusted hazard ratios (HRs) and corresponding 95% CIs were analyzed using a proportional hazard Cox regression model complemented with Kaplan-Meier curves. In the initial protocol, the primary comparison for R-C was powered at 80% to detect an HR of 0.76 (5-year DFS of 86% in the control arm *v* 89.2% in the experimental arm) at the 2-sided 5% level, requiring 422 DFS events to be observed. However, as a result of the insufficient number of patients randomly assigned to this part of the study, only 148 events were observed, corresponding to 38.5% power to detect the original alternative hypothesis (HR, 0.76). Comparisons for R-C were performed at the time of the primary trial's analysis, as planned. All statistical analyses were conducted using SAS version 4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics and Follow-Up

Among 2,832 patients who received chemotherapy within MINDACT, 1,301 (45.9%) were randomly assigned for the chemotherapy question (R-C). The main reason for not being included in R-C was chemotherapy administered outside of the trial on the basis of the physician's or patient's wishes. A consort diagram of the trial is shown in Figure 1. Among 1,301 randomly assigned patients, 787 (60.5%) were categorized to have a clinical-high and genomic-high risk (c-high/g-high), 351 (27.0%) a c-high/g-low, 137 (10.5%) a c-low/g-high, and 26 (2.0%) a c-low/g-low disease. In total, 649 patients were randomly assigned to the control arm and 652 to DC arm. The main patient characteristics were well balanced between the two arms (Table 1).

The cutoff date for the present analysis was March 1, 2016. Median follow-up is 5.0 years.

Treatments Received

The compliance rate for random assignment was 97.1% overall. Treatment received in each arm, as well as dose modifications or interruptions in both arms are shown in Table 2 and Appendix Table A1.

Primary End Point Analysis

Overall, 148 patients experienced a recurrence—there were 67 DFS events in the DC arm and 81 in the control arm. The majority of first recurrences were distant metastases (n = 66; 44.6%). Others were second primaries (n = 52; 35.1%) and local relapses (n = 22; 14.9%). Eight patients (5.4%) died without experiencing a relapse. At 5-year median follow-up, DFS was not significantly different between the DC arm (n = 652) and control arm (n = 649; 90.7% [95% CI, 88% to 92.8%] *v* 88.8% [95% CI, 85.9% to 91.15]; HR, 0.83 [95% CI, 0.60 to 1.15]; *P* = .26; Fig 2A). Models adjusted for stratification factors and those that were unadjusted led to the same results (data not shown). Figure 3 shows a forest plot of DFS in both arms by stratification factors. Of note, for the relevant clinical-high risk/genomic-high risk subgroup, DFS was also not different

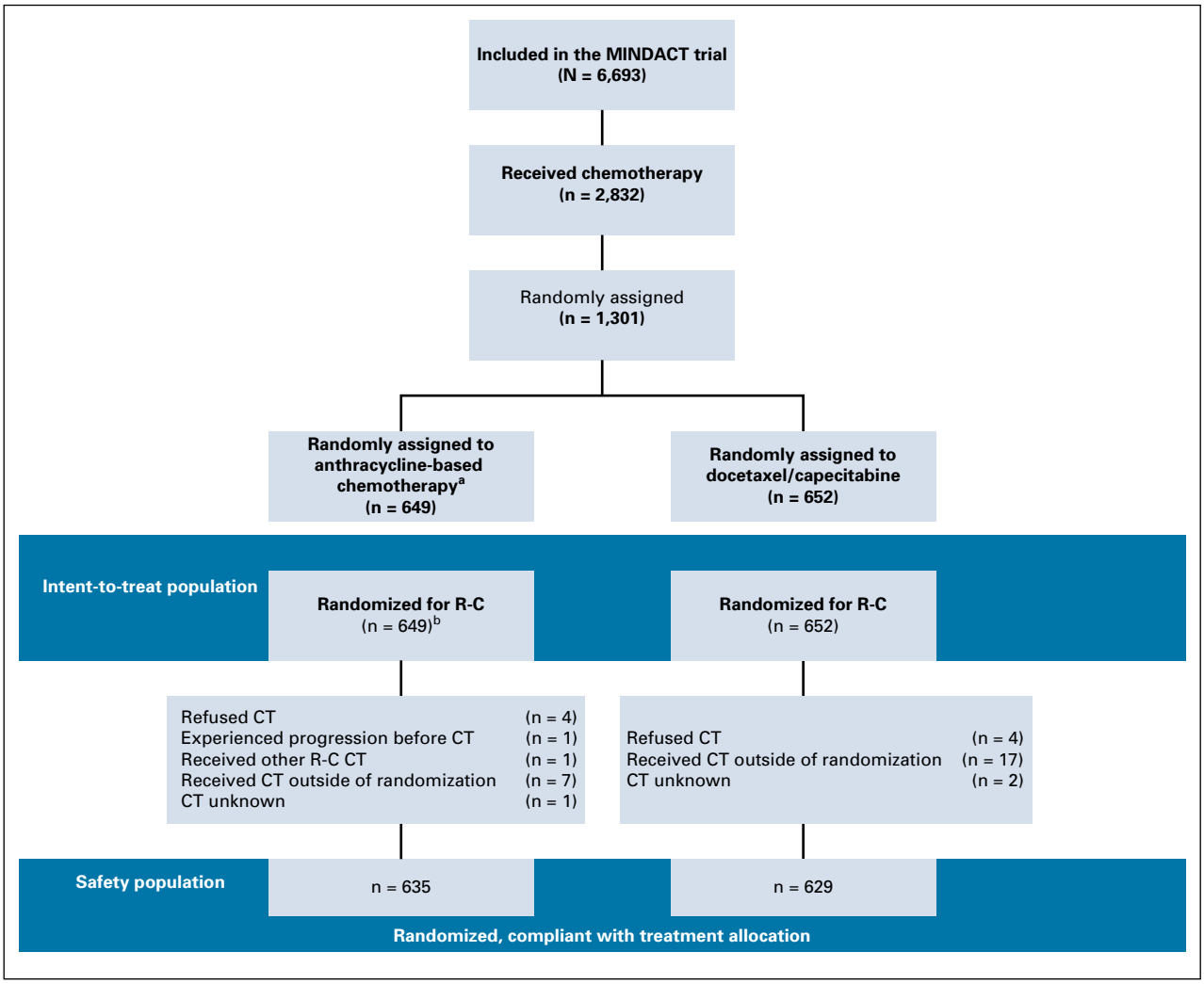

FIG 1. CONSORT diagram of randomization in the MINDACT study. ([a]) The control anthracycline arm was different for patients with LN0 breast cancer and for patients with lymph node (LN)–positive disease, as standard therapies were different for each subgroup at that time and evolved over time during the trial. For LN0 disease, anthracycline-based regimens without taxanes were used and included: cyclophosphamide, doxorubicin, and fluorouracil (FAC or CAF); cyclophosphamide, epirubicin, and fluorouracil (FEC); or 4 cycles of epirubicin followed by 4 cycles of cyclophosphamide, methotrexate, and fluorouracil. For LN-positive disease, the standard regimen was a sequence of 3 cycles of FEC 100 followed by 3 cycles of docetaxel. ([b]) One patient was found to be ineligible as a result of M1 status at baseline and was censored at time 0 in the analysis of disease-free survival and distant metastases–free survival end points.

between arms (5-years DFS DC: 88.1% [95% CI, 84.3% to 91.1%] *v* control: 86.1% [95% CI, 82.1% to 89.3%]; HR, 0.83 [95% CI, 0.58 to 1.21]).

Secondary Efficacy End Points

Seventy patients experienced a distant relapse—34 in the DC arm and 36 in the control arm—and 22 patients died without experiencing a distant relapse. Five-year DMFS was not significantly different between the two arms (DC: 94.4% [95% CI, 92.2% to 96%] *v* control: 93.5% [95% CI, 91.2% to 95.3%]; HR, 0.89 [95% CI, 0.59 to 1.34]; $P = .58$; Fig 2B). Fifty-seven deaths were reported at the time of the cutoff date—27 in the DC arm and 30 in the control arm. The main cause of death was progressive disease (36 patients; 63.2%). Similarly, 5-year OS was identical in both arms (DC: 96.3% [95% CI, 94.4% to 97.6%] *v* control: 96.2% [95% CI, 94.3% to 97.4%]; HR, 0.91 [95% CI, 0.54 to 1.53]; $P = .72$; Fig 2C). Appendix Figure A1 (online only) shows a forest plot of OS in both arms by stratification factors.

Safety

As shown in Table 3 and Appendix Table A2 (online only), the most common adverse events in DC compared with control were grade 2 hand/foot syndrome (3.3% in control *v* 28.5% in DC), grade 2 diarrhea (5.8% *v* 13.7%), and grade 1 peripheral neuropathy (11.2% *v* 27.1%). However, grade 2 anemia (14.2% in control *v* 5.1% in DC) and grade 4 neutropenia (24.6% *v* 20.5%) were slightly more frequent in the control arm. Serious cardiac events occurred in 9 patients overall, including 1 cardiac failure (control) and 1

TABLE 1. Patients Characteristics in the Chemotherapy Randomization Arms of MINDACT

Characteristic	Control Arm (n = 649)	DC Arm (n = 652)	Total (N = 1,301)
Age, years			
< 35	15.0 (2.3)	17.0 (2.6)	32.0 (2.5)
35-50	227.0 (35.0)	222.0 (34.0)	449.0 (34.5)
50-70	399.0 (61.5)	410.0 (62.9)	809.0 (62.2)
≥ 70	8.0 (1.2)	3.0 (0.5)	11.0 (0.8)
Corrected risk[a]			
cL/gL	12.0 (1.8)	14.0 (2.1)	26.0 (2.0)
cL/gH	70.0 (10.8)	67.0 (10.3)	137.0 (10.5)
cH/gL	175.0 (27.0)	176.0 (27.0)	351.0 (27.0)
cH/gH	392.0 (60.4)	395.0 (60.6)	787.0 (60.5)
Menopausal status			
Premenopausal	252.0 (38.8)	248.0 (38.0)	500.0 (38.4)
Postmenopausal	363.0 (55.9)	362.0 (55.5)	725.0 (55.7)
Not 1 or 2	34.0 (5.2)	42.0 (6.5)	76.0 (5.9)
Lymph node status			
Node negative	455.0 (70.1)	454.0 (69.6)	909.0 (69.9)
1-3 positive nodes	192.0 (29.6)	198.0 (30.3)	390.0 (29.0)
≥ 4 positive lymph nodes	2.0 (0.3)	0.0 (0.0)	2.0 (0.2)
Lymph node resection procedure			
Full axillary dissection	279.0 (43.0)	286.0 (43.9)	565.0 (43.4)
Sentinel lymph node sampling	370.0 (57.0)	366.0 (56.1)	736.0 (56.6)
Type of breast cancer surgery			
Breast conserving surgery	514.0 (79.2)	518.0 (79.4)	1,032.0 (79.3)
Mastectomy	135.0 (20.8)	134.0 (20.6)	269.0 (20.7)
Pathologic tumor size, cm			
≤ 1	37.0 (5.7)	36.0 (5.5)	73.0 (5.6)
1-2	332.0 (51.2)	320.0 (49.1)	652.0 (50.1)
2-5	269.0 (41.4)	282.0 (43.3)	551.0 (42.4)
> 5	11.0 (1.7)	14.0 (2.1)	25.0 (1.9)
Tumor grade			
1	33.0 (5.1)	27.0 (4.1)	60.0 (4.6)
2	256.0 (39.4)	253.0 (38.8)	509.0 (39.1)
3	358.0 (55.2)	369.0 (56.6)	727.0 (55.9)
Unknown	2.0 (0.3)	3.0 (0.5)	5.0 (0.4)
ER (local laboratory)			
Negative	160.0 (24.7)	169.0 (25.9)	329.0 (25.3)
Positive	489.0 (75.3)	483.0 (74.1)	972.0 (74.7)
PgR (local laboratory)			
Negative	232.0 (35.7)	237.0 (36.3)	469.0 (36.0)
Positive	413.0 (63.6)	411.0 (63.0)	824.0 (63.3)
Missing	4.0 (0.6)	4.0 (0.6)	8.0 (0.6)

(continued on following page)

TABLE 1. Patients Characteristics in the Chemotherapy Randomization Arms of MINDACT (continued)

Characteristic	Control Arm (n = 649)	DC Arm (n = 652)	Total (N = 1,301)
HER2 (local laboratory)			
Negative	584.0 (90.0)	594.0 (91.1)	1,178.0 (90.5)
Positive	64.0 (9.9)	55.0 (8.4)	119.0 (9.1)
Missing	1.0 (0.2)	3.0 (0.5)	4.0 (0.3)
Clinicopathologic subtype (local)			
Luminal HER2− (ER+ and/or PgR+, HER2-)	453.0 (69.8)	449.0 (68.9)	902.0 (69.3)
Luminal HER2+ (ER+ and/or PgR+, HER2+)	43.0 (6.6)	44.0 (6.7)	87.0 (6.7)
HER2+ (nonluminal) (ER−, PgR−, HER2+)	21.0 (3.2)	11.0 (1.7)	32.0 (2.5)
Triple negative (ER−, PgR−, HER2−)	131.0 (20.2)	144.0 (22.1)	275.0 (21.1)
Missing	1.0 (0.2)	4.0 (0.6)	5.0 (0.4)
Interval surgery to R-C			
≤ 8 weeks	515.0 (79.4)	529.0 (81.1)	1,044.0 (80.2)
8 weeks to 120 days	134.0 (20.6)	117.0 (17.9)	251.0 (19.3)
> 120 days	0.0 (0.0)	6.0 (0.9)	6.0 (0.5)

NOTE. Data are given as No. (%).

Abbreviations: cH, clinical high risk; cL, clinical low risk; ER, estrogen receptor; gH, genomic high risk; gL, genomic low risk; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; R-C, randomization.

[a]Corrected means that patients are classified according to their actual risk in case there was a change in either genomic or clinical risk postenrollment. For most patients, the corrected risk is identical to the risk recorded at enrollment.

cardiopulmonary arrest (DC). Fifty-three patients developed secondary cancers (Control, n = 32; DC, n = 21; leukemia: n = 2 in the control arm *v* 1 in the DC arm). Two toxic deaths related to chemotherapy were reported in the control arm (as a result of myelodysplastic syndrome and myocardial infarction) and 3 in the DC arm (1 cardiovascular arrest and 2 unspecified).

DISCUSSION

The present randomized phase III trial, nested within the large European MINDACT trial, did not demonstrate the superiority of a non–anthracycline-containing regimen over an anthracycline-based adjuvant chemotherapy in terms of 5-year DFS of patients with localized, high clinical and/or genomic risk breast cancer. Although the efficacy results seemed to be equivalent in both arms on all measurements, the current study's design precludes concluding a potential equivalence between both regimens as it was not powered to prove noninferiority. Furthermore, the safety profile of the DC combination was overall not better than that of anthracycline-based therapy. The most common adverse events for DC were hand/foot syndrome and diarrhea. Standard adverse events seemed to be manageable, with few dose reductions or treatment interruptions; however, major toxicities were also encountered, including 9 cardiac events and, more importantly, five toxic deaths, including 2 in the control arm (0.3%) and 3 in the DC arm (0.5%). Given the magnitude of the expected individual chemotherapy benefit even in categories currently considered high risk, such as the women included in the present trial,[4] this toxicity rate unfortunately seems to be barely acceptable and does not support a change of practice.

At the time this study was designed, anthracycline-based adjuvant regimens without taxanes remained the gold standard in node-negative disease. The benefits of adding taxanes to the previously established standard anthracycline-based chemotherapy regimens had been clearly demonstrated in patients with node-positive breast cancer.[3] Anthracyclines had long been associated with two major toxicities, namely long-term cardiac toxicity and secondary hematologic malignancies, both of which occurred in approximately 1% of treated women.[2] Efficient and less toxic anthracycline-free regimens had therefore been anticipated for years.[8] Results of the phase III trial of DC combination as first-line therapy in metastatic patients led to the hope that this regimen could be a safer and/or more effective replacement to anthracycline-based regimens.[6] Taxane use has meanwhile become widespread in the adjuvant setting on the basis of individual trial results and meta-analyses showing a consistent DFS benefit of approximately 4% to 5%, whatever the nodal status.[3] Taxanes are currently used as monotherapy, sequentially to anthracyclines; alternatively in combination with anthracyclines, with or without cyclophosphamide; or in some situations in combination with cyclophosphamide as an anthracycline-free regimen.[3,8] In patients with HER2-negative disease, the docetaxel-cyclophosphamide combination administered for 4 cycles has been identified as a potential standard regimen in intermediate-risk patients and as more efficient than 4 cycles of doxorubicin-cyclophosphamide (AC).[8] However, in high-risk patients, the same combination administered for 6 cycles

TABLE 2. Treatments Administered, and Dose and Treatment Adaptations in Both Arms (safety population)

Variable	Anthracycline/Taxane in Control Arm (n = 635)	Docetaxel/Capecitabine in DC Arm (n = 628)
Total No. of cycles	3,685.0	3,428.0
Median treatment duration, weeks	18.0	18.0
Median No. of cycles	6.0	6.0
1	1.0 (0.2)	6.0 (1.0)
2	3.0 (0.5)	5.0 (0.8)
3	5.0 (0.8)	3.0 (0.5)
4	8.0 (1.3)	7.0 (1.1)
5	20.0 (3.1)	29.0 (4.6)
6	590.0 (92.9)	573.0 (91.2)
7	2.0 (0.3)	4.0 (0.6)
8	5.0 (0.8)	1.0 (0.2)
9	1.0 (0.2)	0.0 (0.0)
Received anti-HER2 therapy (among HER2-positive cases)[a]	53.0/63.0 (84.3)	39.0/53.0 (72.2)
Chemotherapy regimen		
Anthracycline/cyclophosphamide ± FU only (AC/FAC/FEC regimens)	447.0 (70.4)	—
Sequential anthracycline-taxane regimen	188.0 (29.6)	—

	Anthracycline/Taxane in Control Arm (n = 3,685 cycles)	Docetaxel in DC Arm (n = 3,428 cycles)	Capecitabine in DC Arm (n = 3,428 cycles)
Treatment dose reduction			
No	3,602.0 (97.7)	3,295.0 (96.1)	3,017.0 (88.0)
Yes	82.0 (2.2)	133.0 (3.9)	411.0 (12.0)
Missing	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Reason for dose reduction	n = 82	n = 133	n = 411
Hematologic toxicity	23.0 (28.0)	14.0 (10.5)	15.0 (3.6)
Nonhematologic toxicity	41.0 (50.0)	103.0 (77.4)	333.0 (81.0)
Both	12.0 (14.6)	9.0 (6.8)	19.0 (4.6)
Non–drug related	6.0 (7.3)	6.0 (4.5)	40.0 (9.7)
Unknown	0.0 (0.0)	1.0 (0.8)	4.0 (1.0)
Treatment interrupted			
No	3,609.0 (99.8)	3,402.0 (99.2)	2,988.0 (87.2)
Yes	6.0 (0.2)	26.0 (0.8)	440.0 (12.8)
Yes and restart within this cycle	—	1.0 (0.0)	143.0 (4.2)
Stopped for the rest of the cycle	—	5.0 (0.1)	189.0 (5.5)
Drug definitively stopped	6.0 (0.2)	20.0 (0.6)	108.0 (3.2)
Missing	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)

NOTE. Data are given as No. (%) unless otherwise noted.

Abbreviations: AC, doxorubicin-cyclophosphamide; DC, docetaxel-capecitabine; FAC, cyclophosphamide, doxorubicin, and fluorouracil; FEC, cyclophosphamide, epirubicin, and fluorouracil; FU, fluorouracil; HER2, human epidermal growth factor receptor 2.

[a]Two patients had missing data for trastuzumab treatment.

and compared with standard sequential regimen produced mixed results, leaving the sequential regimen as standard.[9,10]

In parallel, several studies have explored the potential role of capecitabine as part of the treatment of early breast cancer. The current study is another part of this complex picture. Capecitabine generally increased treatment toxicity when added to standard therapies or when administered to elderly patients.[9,11-14] A recent meta-analysis demonstrated that in unselected patients, capecitabine did not influence DFS when added to standard regimens,

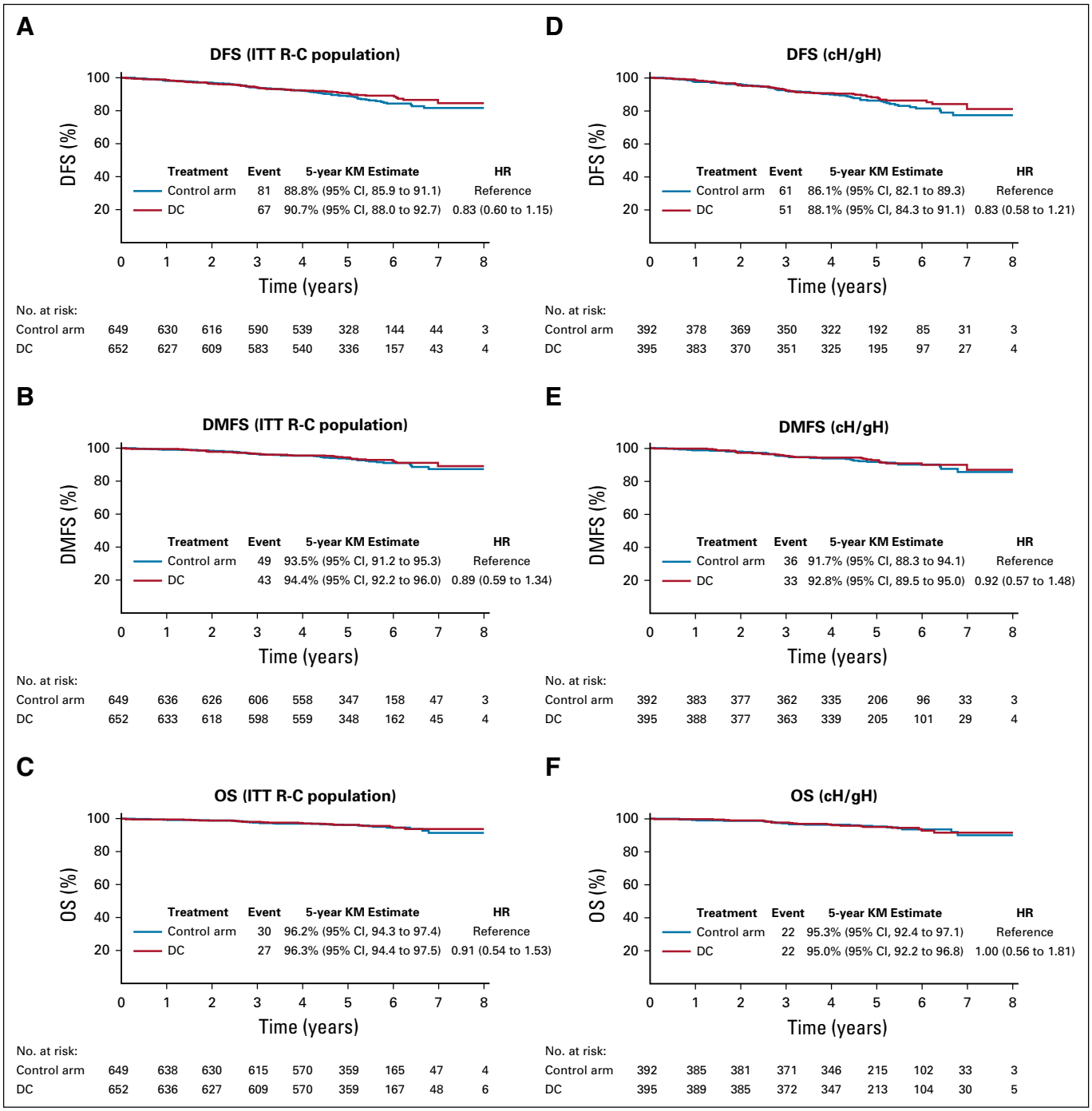

FIG 2. Efficacy end points in the chemotherapy randomization arms of MINDACT. (A) Disease-free survival (DFS; intent-to-treat [ITT] randomization [R-C] population). (B) Distant metastases–free survival (DMFS; ITT R-C population). (C) Overall survival (OS; ITT R-C population). (D) DFS (clinical-high risk [cH]/genomic-high risk [gH]). (E) DMFS (cH/gH). (F) OS (cH/gH). DC, docetaxel-capecitabine; HR, hazard ratio; KM, Kaplan-Meier.

except in exploratory subanalyses in patients with triple-negative breast cancer.[15] In the Create-X trial, administration of sequential capecitabine in patients with poor response to standard neoadjuvant therapy resulted in a DFS and OS benefit, mostly driven by patients with triple-negative breast cancer.[16] In TACT2, Cameron et al[17] concluded that capecitabine could be used in place of CMF without significant loss of efficacy and with improved quality of life. However, in the GEICAM/2003-10 study, capecitabine was inferior to docetaxel after anthracycline-cyclophosphamide.[18] The current study has a different design, with an attempt to insert capecitabine as an alternative to anthracyclines; however, it could not demonstrate any superiority in favor of the DC arm, whatever the subgroup, including the relevant clinical-high risk/genomic-high risk group.

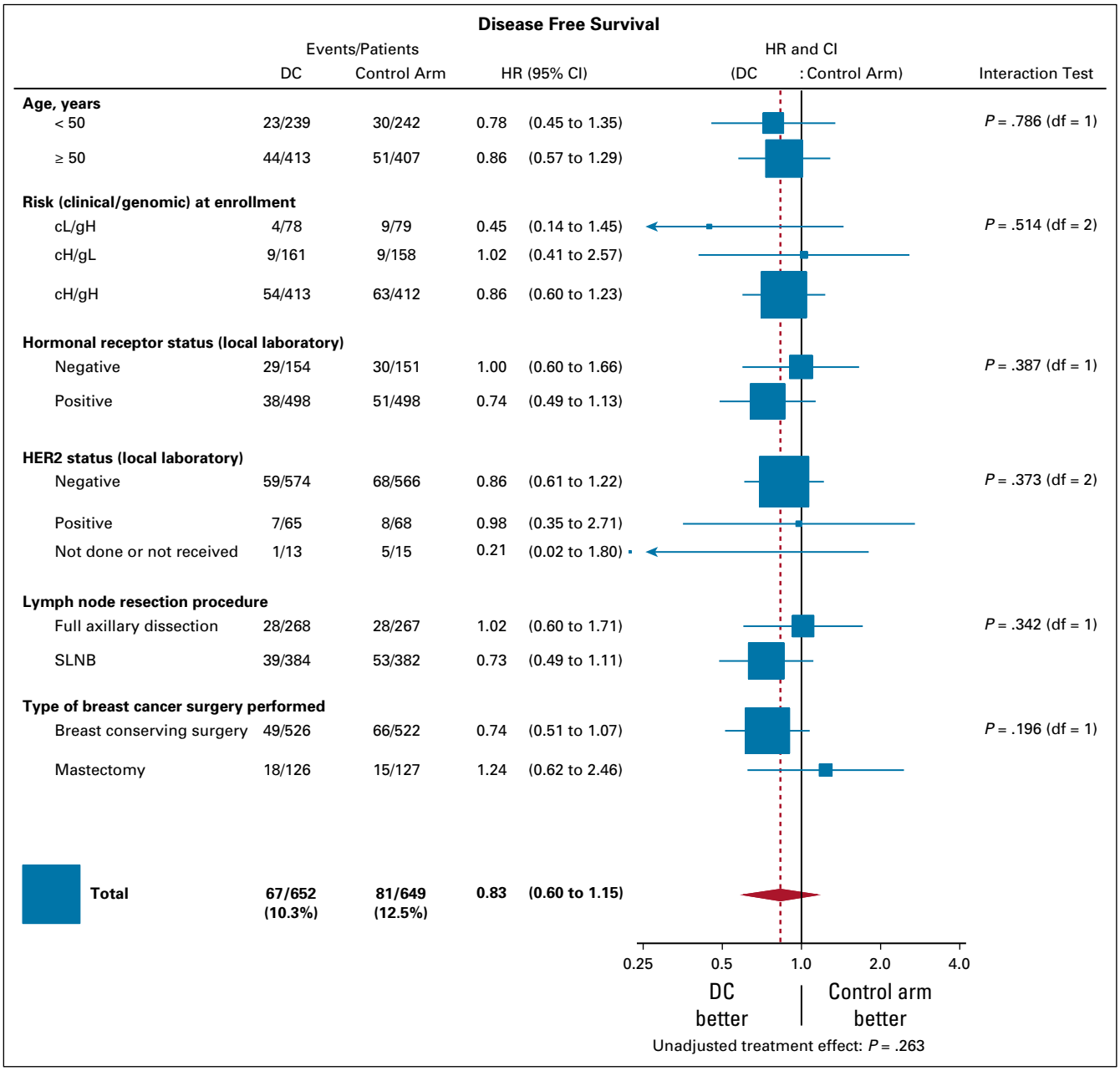

FIG 3. Forest plots of disease-free survival, by stratification factors. cH, clinical high risk; cL, clinical low risk; DC, docetaxel-capecitabine; gH, genomic high risk; gL, genomic low risk; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; SLNB, sentinel lymph node biopsy.

The current study has some limitations. The power to demonstrate a potential significant difference between arms was lower than expected, mainly because of a lower accrual rate than anticipated. Furthermore, patients' prognosis was remarkably good despite their classification as high risk, with DFS rates of 88.8% and 90.7% and DMFS rates of 93.5 and 94.4% at 5 years, respectively, in each arm. The potential to demonstrate the superiority of a given chemotherapy regimen in these conditions would therefore be low. The trial was designed as a superiority trial and would furthermore have even less power to demonstrate noninferiority. The regimen used in the control arm of the trial cannot be considered standard anymore—70% of patients did not receive taxanes. DC has therefore not been directly compared with the best current standards available, comprising sequential anthracycline-taxane or nonanthracycline regimens including taxanes, such as docetaxel-cyclophosphamide.[10] The population accrued was heterogeneous and consisted of patients with luminal and triple-negative (approximately 20% per arm) or HER2-positive (approximately 9% per arm) disease. An effect of the experimental therapy compared with the standard arm could therefore not be detected if limited to a tumor subset, such as the triple-negative subset, as suggested by other trials and discussed previously.[15,16]

TABLE 3. Adverse Events in Control and DC Arms (safety population, per patient, worse Common Terminology Criteria for Adverse Events version 3.0 grade, on treatment)

	Control Arm (n = 635)		DC Arm (n = 628)	
Adverse Event	**Grade 1-2**	**Grade ≥ 3**	**Grade 1-2**	**Grade ≥ 3**
Nausea	438.0 (69.0)	18.0 (2.8)	268.0 (42.7)	12.0 (1.9)
Vomiting	188.0 (29.6)	13.0 (2.0)	88.0 (14.0)	14.0 (2.2)
Fatigue	438.0 (69.0)	35.0 (5.5)	423.0 (67.4)	34.0 (5.5)
Neuropathy	88.0 (13.9)	4.0 (0.6)	252.0 (40.2)	26.0 (4.1)
Hand/foot syndrome	50.0 (7.9)	6.0 (0.9)	308.0 (49.0)	99.0 (15.8)
Neutropenia	74.0 (11.7)[a]	249.0 (39.2)	24.0 (3.8)[a]	180.0 (28.6)
Leukopenia	119.0 (18.7)[a]	139.0 (21.9)	87.0 (13.9)[a]	90.0 (14.3)
Thrombocytopenia	5.0 (0.8)[a]	4.0 (0.6)	2.0 (0.3)[a]	0.0 (0.0)
Anemia	90.0 (14.2)[a]	1.0 (0.2)	32.0 (5.1)[a]	0.0 (0.0)
Diarrhea	140.0 (22.0)	7.0 (1.1)	248.0 (39.5)	30.0 (4.8)
Constipation	180.0 (28.3)	5.0 (0.8)	146.0 (23.2)	0.0 (0.0)
Febrile neutropenia	0.0 (0.0)	65.0 (10.3)	0.0 (0.0)	44.0 (7.0)
Infection	127.0 (20.0)	39.0 (6.1)	122.0 (19.4)	33.0 (5.3)
Alopecia	390.0 (61.4)	0.0 (0.0)	354.0 (56.4)	0.0 (0.0)
Mucositis/stomatitis	291.0 (45.8)	12.0 (1.9)	300.0 (47.8)	20.0 (3.2)
Cough	62.0 (9.8)	0.0 (0.0)	39.0 (6.2)	1.0 (0.2)
Nail toxicity	66.0 (10.4)	2.0 (0.3)	238.0 (37.9)	60.0 (9.6)
Headache	101.0 (15.9)	1.0 (0.2)	44.0 (7)	1.0 (0.2)
Dry eye	107.0 (16.9)	1.0 (0.2)	148.0 (23.5)	1.0 (0.2)
Dry mouth	46.0 (7.2)	1.0 (0.2)	23.0 (3.7)	1.0 (0.2)
Dysgueusia	95.0 (15)	0.0 (0.0)	179.0 (28.5)	0.0 (0.0)-
SGPT increased	219.0 (34.5)	4.0 (0.6)	240.0 (38.2)	11 (1.8)
SGOT increased	164.0 (25.8)	1.0 (0.2)	201.0 (32.0)	5.0 (0.8)
Drug-related edema	34.0 (5.3)	2.0 (0.3)	112.0 (17.8)	2.0 (0.3)
Cardiac toxicity				
Ischemia/infarction	1.0 (0.2)	1.0 (0.2)	3.0 (0.5)	2.0 (0.3)
Hypertension	11.0 (1.7)	1.0 (0.2)	16.0 (2.5)	1.0 (0.2)
Hypotension	19.0 (3.0)	1.0 (0.2)	19.0 (3.0)	0.0 (0.0)
Left ventricular systolic dysfunction	1.0 (0.2)	0.0 (0.0)	1.0 (0.2)	0.0 (0.0)
Other	41.0 (6.4)	1.0 (0.2)	24.0 (3.9)	2.0 (0.4)
Toxic death		2.0 (0.3)		3.0 (0.5)

NOTE. Data are given as No. (%) unless otherwise noted.
Abbreviation: DC, docetaxel-capecitabine.
[a]Grade 2 only.

Regarding safety, standard administration of the drugs used have changed since then, such as prophylactic granulocyte-colony stimulating factor use, which was not mandatory in any arm of the trial.[19] Of note, such treatment would not be possible in the DC arm where capecitabine is administered during 14 days.[19] The trial was also not designed to provide detailed, longitudinal long-term safety data (such as for alopecia; Appendix Table A3, online only).

In conclusion, the adjuvant DC combination did not improve the outcome of high clinical and/or genomic risk patients included in the MINDACT study compared with anthracycline-based chemotherapy, including in the relevant clinical-high risk/genomic-high risk group. In addition, the safety profile does not favor this DC combination, which is therefore not recommended as a primary option in this setting but could be considered as an alternative if anthracyclines are contraindicated.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Standard Anthracycline Based Versus Docetaxel-Capecitabine in Early High Clinical and/or Genomic Risk Breast Cancer in the EORTC 10041/BIG 3-04 MINDACT Phase III Trial

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No other potential conflicts of interest were reported.

APPENDIX

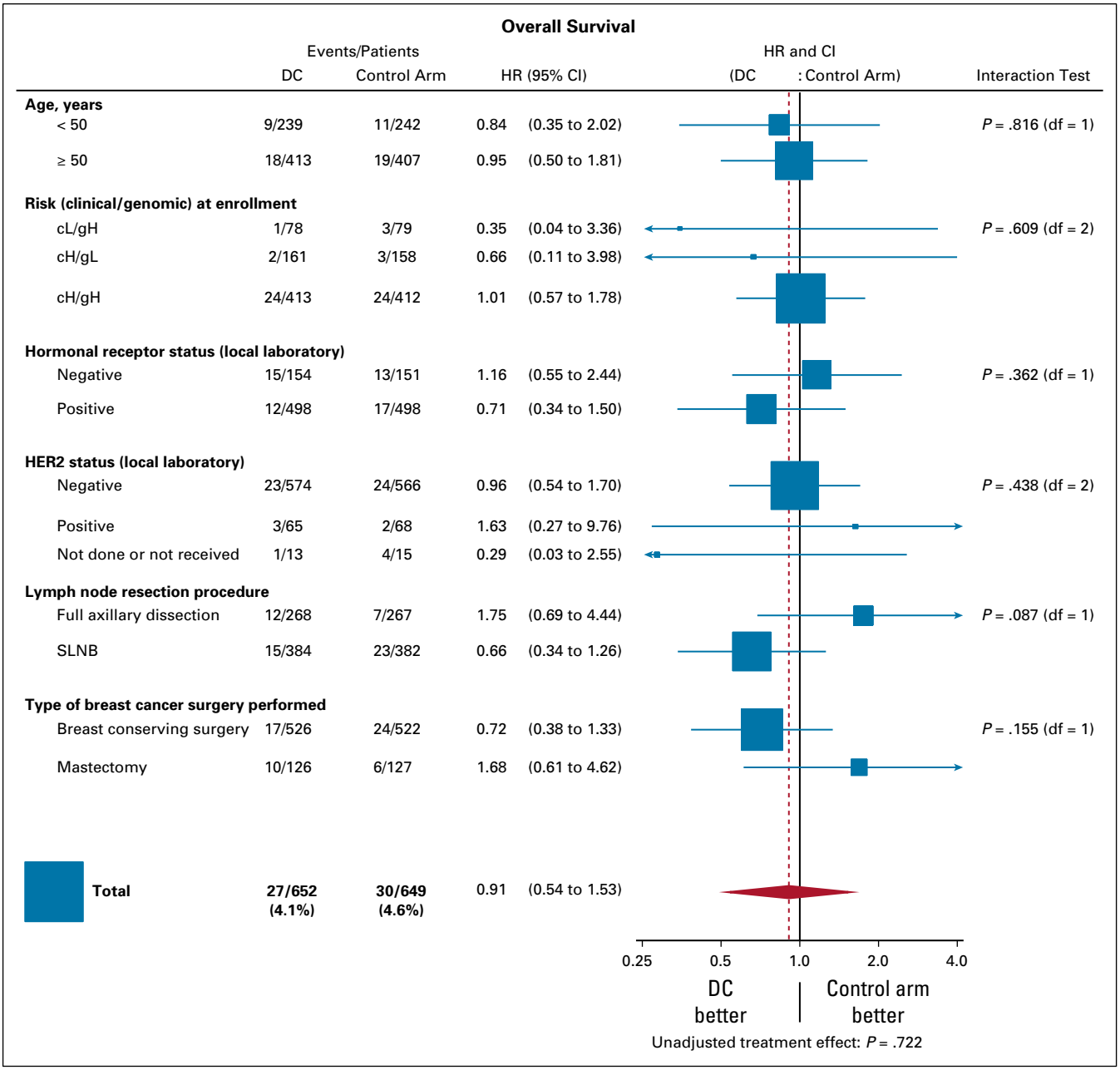

FIG A1. Forest plots of overall survival, by stratification factors, among patients randomly assigned between an anthracycline-based chemotherapy regimen (control) and docetaxel-capecitabine (DC). cH, clinical high risk; cL, clinical low risk; gH, genomic high risk; gL, genomic low risk; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; SLNB, sentinel lymph node biopsy.

TABLE A1. Chemotherapy Regimen Actually Received By Nodal Status Among Patients From the Control Arm

Chemotherapy Regimen By Nodal Status	LN Negative (%; n = 444)	LN Positive (%; n = 191)	Total (%; n = 635)
Anthracycline/cyclophosphamide ± FU only (AC/FAC/FEC regimens)	442.0 (99.5)	5.0 (2.6)	447.0 (70.4)
FEC 100	409.0 (92.1)	5.0 (2.6)	414.0 (65.2)
FAC	29.0 (6.5)	0.0 (0.0)	29.0 (4.6)
E-CMF	4.0 (0.9)	0.0 (0.0)	4.0 (0.6)
Sequential anthracycline-taxane regimen	2.0 (0.5)	186.0 (97.4)	188.0 (29.6)

Abbreviations: AC, doxorubicin-cyclophosphamide; E-CMF, 4 cycles of epirubicin followed by 4 cycles of cyclophosphamide, methotrexate, and fluorouracil; FAC, cyclophosphamide, doxorubicin, and fluorouracil; FEC, cyclophosphamide, epirubicin, and fluorouracil; FU, fluorouracil; LN, lymph node.

TABLE A2. Detailed Grading of Adverse Events in the Control and DC Arms (safety population, per patient, worse Common Terminology Criteria for Adverse Events version 3.0 grade, on treatment)

	Control Arm (n = 635)				DC Arm (n = 628)			
Adverse Event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Nausea	438.0 (69.0)	18.0 (2.8)	0.0 (0.0)	0.0 (0.0)	268.0 (42.7)	10.0 (1.6)	2.0 (0.3)	0.0 (0.0)
Vomiting	188.0 (29.6)	13.0 (2.0)	0.0 (0.0)	0.0 (0.0)	88.0 (14.0)	14.0 (2.2)	0.0 (0.0)	0.0 (0.0)
Fatigue	438.0 (69.0)	35.0 (5.5)	0.0 (0.0)	0.0 (0.0)	423.0 (67.4)	33.0 (5.3)	1.0 (0.2)	0.0 (0.0)
Neuropathy	88.0 (13.9)	4.0 (0.6)	0.0 (0.0)	0.0 (0.0)	252.0 (40.2)	26.0 (4.1)	0.0 (0.0)	0.0 (0.0)
Hand/foot syndrome	50.0 (7.9)	6 (0.9)	0.0 (0.0)	0.0 (0.0)	308.0 (49.0)	99.0 (15.8)	0.0 (0.0)	0.0 (0.0)
Neutropenia	74.0 (11.7)[a]	93.0 (14.6)	156.0 (24.6)	0.0 (0.0)	24.0 (3.8)[a]	51.0 (8.1)	129.0 (20.5)	0.0 (0.0)
Leukopenia	119.0 (18.7)[a]	92.0 (14.5)	47.0 (7.4)	0.0 (0.0)	87.0 (13.9)[a]	80.0 (12.7)	10.0 (1.6)	0.0 (0.0)
Thrombocytopenia	5.0 (0.8)[a]	2.0 (0.3)	2.0 (0.3)	0.0 (0.0)	2.0 (0.3)[a]	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Anemia	90.0 (14.2)[a]	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)	32.0 (5.1)[a]	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Diarrhea	140.0 (22.0)	7.0 (1.1)	0.0 (0.0)	0.0 (0.0)	248.0 (39.5)	29.0 (4.6)	1.0 (0.2)	0.0 (0.0)
Constipation	180.0 (28.3)	5.0 (0.8)	0.0 (0.0)	0.0 (0.0)	146.0 (23.2)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Febrile neutropenia	0.0 (0.0)	57.0 (9.0)	8.0 (1.3)	0.0 (0.0)	0.0 (0.0)	39.0 (6.2)	5.0 (0.8)	0.0 (0.0)
Infection	127.0 (20.0)	37.0 (5.8)	2.0 (0.3)	0.0 (0.0)	122.0 (19.4)	33.0 (5.3)	0.0 (0.0)	0.0 (0.0)
Alopecia	390.0 (61.4)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	354.0 (56.4)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Mucositis/stomatitis	291.0 (45.8)	12.0 (1.9)	0.0 (0.0)	0.0 (0.0)	300.0 (47.8)	20.0 (3.2)	0.0 (0.0)	0.0 (0.0)
Cough	62.0 (9.8)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	39.0 (6.2)	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)
Nail toxicity	66.0 (10.4)	2.0 (0.3)	0.0 (0.0)	0.0 (0.0)	238.0 (37.9)	60.0 (9.6)	0.0 (0.0)	0.0 (0.0)
Headache	101.0 (15.9)	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)	44.0 (7)	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)
Dry eye	107.0 (16.9)	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)	148.0 (23.5)	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)
Dry mouth	46.0 (7.2)	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)	23.0 (3.7)	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)
Dysgueusia	95.0 (15)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	179.0 (28.5)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
SGPT increased	219.0 (34.5)	4.0 (0.6)	0.0 (0.0)	0.0 (0.0)	240.0 (38.2)	10.0 (1.6)	1.0 (0.2)	0.0 (0.0)
SGOT increased	164.0 (25.8)	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)	201.0 (32.0)	4.0 (0.6)	1.0 (0.2)	0.0 (0.0)
Drug-related edema	34.0 (5.3)	2.0 (0.3)	0.0 (0.0)	0.0 (0.0)	112.0 (17.8)	2.0 (0.3)	0.0 (0.0)	0.0 (0.0)
Cardiac toxicity								0.0 (0.0)
Ischemia/infarction	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)	1.0 (0.2)	3.0 (0.5)	2.0 (0.3)	0.0 (0.0)	0.0 (0.0)
Hypertension	11.0 (1.7)	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)	16.0 (2.5)	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)
Hypotension	19.0 (3.0)	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)	19.0 (3.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Left ventricular systolic dysfunction	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Other	41.0 (6.4)	1.0 (0.2)	0.0 (0.0)	0.0 (0.0)	24.0 (3.9)	1.0 (0.2)	1.0 (0.2)	0.0 (0.0)
Toxic death				2.0 (0.3)				3.0 (0.5)

NOTE. Data are given as No. (%) unless otherwise noted.
Abbreviation: DC, docetaxel-capecitabine.
[a]Grade 2 only.

TABLE A3. Alopecia by Treatment Arm (exploratory)

	During Treatment		During Follow-Up	
Grade	**Control Arm (n = 635)**	**DC Arm (n = 628)**	**Control Arm (n = 635)**	**DC Arm (n = 628)**
0	245.0 (38.6)	274.0 (43.6)	596.0 (93.9)	572.0 (91.1)
1	49.0 (7.7)	87.0 (13.9)	24.0 (3.8)	29.0 (4.6)
2	341.0 (53.7)	267.0 (42.5)	15.0 (2.4)	27.0 (4.3)

NOTE. During follow-up means that this event has been described at any time during the long-term follow-up period. Of note, no dates or relations are available. It cannot be assessed with any certainty how long alopecia has really lasted, whether the observed residual alopecia is really long term, and whether it is related to chemotherapy or endocrine therapy, for instance. Median follow-up of the whole trial population is 5.0 years.

Abbreviation: DC, docetaxel-capecitabine.