Adjuvant chemotherapy and hormonotherapy versus adjuvant hormonotherapy alone for women aged 70 years and older with high-risk breast cancer based on the genomic grade index (ASTER 70s): a randomised phase 3 trial

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Summary

Background For women aged 70 years or older with oestrogen receptor-positive HER2-negative invasive breast cancer, hormonotherapy is a standard adjuvant treatment, while the role of chemotherapy is debated. We aimed to assess the effect of adjuvant chemotherapy on overall survival in these older patients with high-risk tumours according to a prognostic genomic signature.

Methods This phase 3, randomised, superiority study was conducted at 84 clinical sites in France and Belgium in women aged 70 years and older with oestrogen receptor-positive and HER2-negative primary breast cancer or isolated local recurrence before any systemic treatment and after complete surgery. Genomic grade index (GGI) testing was done with a reverse-transcriptase PCR assay of eight genes on paraffin-embedded tumour tissue in a central laboratory. Patients with a GGI high-risk tumour were randomly allocated (1:1) to receive either four cycles of postoperative taxane-based or anthracycline-based chemotherapy given every 3 weeks followed by hormonotherapy (chemotherapy group) or hormonotherapy alone (no chemotherapy group). Randomisation was stratified according to the G8 screening tool score for geriatric frailty, nodal status, and centre. The primary endpoint was overall survival. This study is registered with ClinicalTrials.gov (NCT01564056) and is under active follow-up.

Findings Between April 12, 2012 and April 14, 2016, 1969 patients were screened for GGI, of whom 1089 had a GGI high-risk tumour and were randomly allocated to the chemotherapy group (n=541) or the no chemotherapy group (n=548). Median age was 75·1 years (IQR 72·5 to 78·7) and geriatric frailty (G8 score ≤14) was identified in 437 patients (40%) patients. With a median follow-up time of 7·8 years (95% CI 7·5 to 7·8), overall survival rates were 90·5% (95% CI 87·6 to 92·8) at 4 years and 72·7% (67·8 to 77·0) at 8 years in the chemotherapy group, and 89·3% (86·2 to 91·6) at 4 years and 68·3% (63·3 to 72·7) at 8 years in the no chemotherapy group (stratified log-rank p=0·2100; hazard ratio 0·83 [95% CI 0·63 to 1·11]), yielding statistically non-significant absolute differences in survival probability of 1·3 percentage points (95% CI –2·4 to 5·0) at 4 years and 4·5% (95% CI –2·1 to 11·1) at 8 years. Safety analysis favoured the no chemotherapy group: at least one grade 3 or higher adverse event occurred in 52 (9%) of 548 patients in the no chemotherapy group (including one death not related to treatment), compared with 183 (34%) of 541 patients in the chemotherapy group (including three deaths, of which one was related to treatment).

Interpretation The addition of adjuvant chemotherapy to hormonotherapy conferred no survival benefit in women aged 70 years and above with a GGI high-risk oestrogen receptor-positive HER2-negative breast cancer, and was associated with more adverse events, providing important data on the benefit–risk balance of adding adjuvant chemotherapy to adjuvant hormonotherapy in this older age group.

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Introduction

Cancer incidence increases with age. Currently, patients aged 65 years and older represent approximately 50% while those older than 80 years represent approximately 13% of all cancer incidence, and these rates are projected to reach 60% and 21%, respectively, by the mid-21st

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See **Comment** page 422

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See Online for appendix 1

Research in context

Evidence before this study

Adjuvant chemotherapy has been shown to improve survival in women with early-stage breast cancer. However, less than 5% of the women included in a 2005 meta-analysis of trials comparing chemotherapy with no chemotherapy were 70 years of age or older. Furthermore, older women included in trials are generally selected based on stringent criteria, such as having few comorbidities or no previous primary cancer, making them poorly representative of the general population of older patients with breast cancer. The Société Internationale d'OncoGériatrie (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA) periodically review the literature (PubMed and Embase) on the management of older patients with breast cancer and publish recommendations. In 2012, the two societies concluded that most of the evidence on the benefit of adjuvant chemotherapy concerned patients with oestrogen receptor-negative breast cancer. Genomic signatures might help to refine the assessment of the prognosis of oestrogen receptor-positive tumours and thus identify patients at high risk.

Added value of this study

To our knowledge, ASTER 70s is the first phase 3 superiority trial investigating the benefit of chemotherapy versus no chemotherapy in the adjuvant setting specifically in women aged 70 years or older with oestrogen receptor-positive breast cancer and at high risk according to a genomic signature (the genomic grade index). Using a pragmatic design, we did not identify any statistically significant increase in overall survival when adding four cycles of chemotherapy to hormonotherapy for these patients.

Implications of all the available evidence

The ASTER 70s trial provides important information to improve shared decision making between doctor and patient when discussing adjuvant breast cancer treatment. The results show the ongoing challenge of identifying older patients with oestrogen receptor-positive HER2-negative breast cancer who are suitable candidates for adjuvant chemotherapy in addition to hormonotherapy, consolidating the SIOG and EUSOMA recommendations updated in 2021 on the management of older patients with breast cancer. The results also highlight the risk of extrapolating to this population the results obtained using similar strategies on younger populations, distancing research from defining the right and optimal treatment, which is traditionally still based on achieving its highest intensity, whereas increasing frailty with age calls for frequent de-escalation. Further research is needed into tumour and ageing biomarkers to identify women aged 70 years or older who could benefit from adjuvant chemotherapy. Further, this study demonstrates that pragmatic trials can be conducted to improve the representation of older patients in clinical research, with a view to establishing appropriate guidelines.

century.[1] Breast cancer is the most commonly diagnosed cancer in older women, with a peak incidence near the age of 65 years in many countries.[1] Treating this growing population of older patients is a challenge, as increasing frailty with age is accompanied by greater susceptibility to stressors[2] and higher rates of adverse events, requiring treatments that are tailored to geriatric assessment and often less intensive.[3]

There is little evidence on the benefit of adjuvant chemotherapy in older patients with breast cancer: in the 2005 Early Breast Cancer Trialists' Collaborative Group meta-analysis of trials comparing chemotherapy versus no chemotherapy, less than 5% of the women included were aged 70 years or older.[4] This lack of evidence mainly concerns patients with breast cancer expressing hormone receptors, as those with triple-negative tumours benefit more from adjuvant chemotherapy.[5] Even in the era of genomic signatures used to refine the assessment of the prognosis of oestrogen receptor-positive tumours and decide whether or not to recommend adjuvant chemotherapy, the situation has not improved: in the three 21st century iconic trials, MINDACT,[6] TAILORx,[7] and RxPONDER,[8] the proportions of patients aged 70 years and older randomly allocated to chemotherapy or no chemotherapy were 0·8%, 4·3%, and 11·6% of the total study populations, respectively.

Chemotherapy has side-effects that are typically more serious in older patients,[9] who are also at increased risk of death from competing causes.[3] Seeking to reserve the prescription of adjuvant chemotherapy to patients with a high-risk tumour is relevant in older patients to the same extent as in younger patients, or even more so. Genomic profiling can help to improve this selection among patients with oestrogen receptor-positive tumours. However, more evidence is needed to understand how this profiling can indicate whether or not chemotherapy is necessary for older patients with oestrogen receptor-positive tumours, to provide a benefit similar to that more clearly seen with adjuvant chemotherapy in triple-negative tumours.[5]

The genomic grade index (GGI) prognostic signature, developed by Ipsogen, was initially identified through a microarray analysis of 97 genes related to cell-cycle regulation and proliferation on a frozen tumour sample,[10] showing a strong prognostic discriminating capacity with a good level of evidence, similar to other tools in development at the time.[11] The development of a reliable reverse-transcriptase PCR version of the tool that determines GGI values on a paraffin-embedded tumour tissue[12] enabled a large-scale trial with centralised testing.

We aimed to investigate the effect of adjuvant chemotherapy for oestrogen receptor-positive

HER2-negative breast cancer with a high-risk GGI in women older than 70 years.

Methods

Study design and participants

ASTER 70s was a phase 3, randomised, superiority trial embedded in a large screening programme with a parallel cohort. The trial was conducted at 84 sites (hospitals, university hospitals, clinics, community centres, and private oncology centres) in France and Belgium. Eligible patients were aged 70 years and older and had to have undergone complete surgery for an oestrogen receptor-positive (≥10% by immunohistochemistry) HER2-negative primary breast cancer or isolated local relapse, regardless of any other conventional clinical or pathological criteria such as tumour size, nodal status, or medical history. Patients with contralateral, bilateral, and multifocal tumours were eligible. Neoadjuvant treatment was not permitted. The study allowed the enrolment of patients who had completed treatments for other localised non-breast primary cancers, with no specific time limit. In a pragmatic approach, the two main inclusion criteria were that chemotherapy was considered by the medical team as one of the adjuvant treatments to be discussed and that the patient agreed that the decision on chemotherapy should be guided by GGI (no chemotherapy in the case of GGI low-risk tumours or random allocation to chemotherapy or no chemotherapy in the case of GGI high-risk tumours). The full list of inclusion and exclusion criteria is provided in section 4 of the protocol, (appendix 2 p 23). All patients provided a single written informed consent after surgery for GGI screening and randomisation accordingly, and were registered at the headquarters of Unicancer R&D (Paris, France), the sponsor of the trial. The trial protocol and related documents were approved by regulatory authorities on Jan 2, 2012, by the ethical committee of Ile-de-France VII on Jan 20, 2012. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

This study is registered with ClinicalTrials.gov (NCT01564056) and EudraCT (2011-004744-22), and long-term follow-up is ongoing. The full protocol is provided in appendix 2 (pp 1–96).

Randomisation and masking

Patients with a GGI high-risk profile were randomly assigned in a 1:1 ratio to receive either chemotherapy followed by hormonotherapy (chemotherapy group) or hormonotherapy alone (no chemotherapy group). Randomisation was stratified based on geriatric frailty (screening tool G8 score ≤14 *vs* >14),[13] nodal status (pN+ *vs* pN0), and centre, using the Trans European Network for Clinical Trials Services software.

Procedures

After each patient's surgery, a local pathologist sent one formalin-fixed (10%) paraffin-embedded tumour block to the study pathologist (ML-T, Department of Pathology, Institut Universitaire de Cancérologie de Toulouse-Oncopole, Toulouse, France, and Gustave Roussy, University of Paris Saclay, Villejuif, France), who centrally reviewed standard immunohistochemistry, including oestrogen receptor, progesterone receptor, Ki67, and HER2 status and sent a tumour sample for nucleic acid extraction and GGI assessment by Ipsogen (Marseille, France; appendix 2 pp 50–51). The whole process from the initial shipment by the local pathologist to the reception of the GGI result took less than 3 weeks unless a technical failure necessitated a second sample. Ipsogen provided the results of the GGI with the class assigned, low-risk or high-risk. The high-risk class was given into two subcategories and conditioned eligibility for randomisation. The highest GGI class among all foci assessed for multifocal and bilateral disease was considered for the final group classification.

The chemotherapy regimen consisted of intravenous infusion administered every 3 weeks for four cycles. Each patient's regimen was selected from three options: doxorubicin (60 mg/m²), non-pegylated liposomal doxorubicin (60 mg/m²), or docetaxel (75 mg/m²), each combined with cyclophosphamide (600 mg/m²). Primary prophylaxis against febrile neutropenia using granulocyte colony-stimulating factor was mandatory. Chemotherapy could be given with a 2-week delay and a single 25% dose reduction based on tolerance and physician's decision (permitted once across the four cycles), requiring recovery to grade ≤1 for non-haematological or grade ≤2 for haematological adverse events (based on National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

See Online for appendix 2

The indications for radiotherapy and hormonotherapy followed standard recommendations. Radiotherapy was delivered after chemotherapy and before starting hormonotherapy, allowing a hypofractionated schedule. Hormonotherapy consisted of the administration of either tamoxifen, an aromatase inhibitor, or a sequence of the two, for 5 years, with the possibility of an extension beyond this period depending on the evolution of local guidelines and policy (full details are provided in the protocol; appendix 2 pp 24, 31–32).

No chemotherapy was recommended to patients with a GGI low-risk tumour or those not randomly allocated for any reason (consent withdrawal, technical failure, medical condition, physician's decision, or unknown reasons). Instead, these patients were followed up in a parallel cohort.

In all patients, G8 screening tool score for geriatric frailty[13] and Lee's prognostic index for 4-year mortality in older adults[14] were recorded at baseline, and age-adjusted Charlson comorbidity index[15] was assessed at baseline and yearly for 4 years. Breast cancer surveillance included a clinical visit every 6 months and an annual mammogram for 5 years. Further annual follow-up (vital and disease status) was planned for 10 years after surgery.

Race and ethnicity data were not collected, in accordance with French law.

In randomly allocated patients, G8 score was recorded yearly, while the eight-item scale of instrumental activities of daily living,[16] a Minimal Mental Status Examination,[17] health-related quality-of-life questionnaires by the European Organisation for Research and Treatment of Cancer (EORTC; QLQ-C30[18] and the ELD15 module specific to older patients[19]), and socioeconomic conditions were recorded at baseline, 3 months (matching the end of the chemotherapy period when allocated), and then yearly for 4 years. Chemotherapy acceptability (as used in the previous GERICO 06 trial[20]) was recorded only in the chemotherapy group at 3 months and then yearly for 4 years.

All patients consented to biological sampling, including freezing a tumour sample whenever possible and, if randomised, to blood and serum collection at baseline, 3 months, 1 year, and 4 years. Together with the tumour blocks used for GGI determination, these samples were stored at the Unicancer biorepository resource centre in Lyon for future translational research.

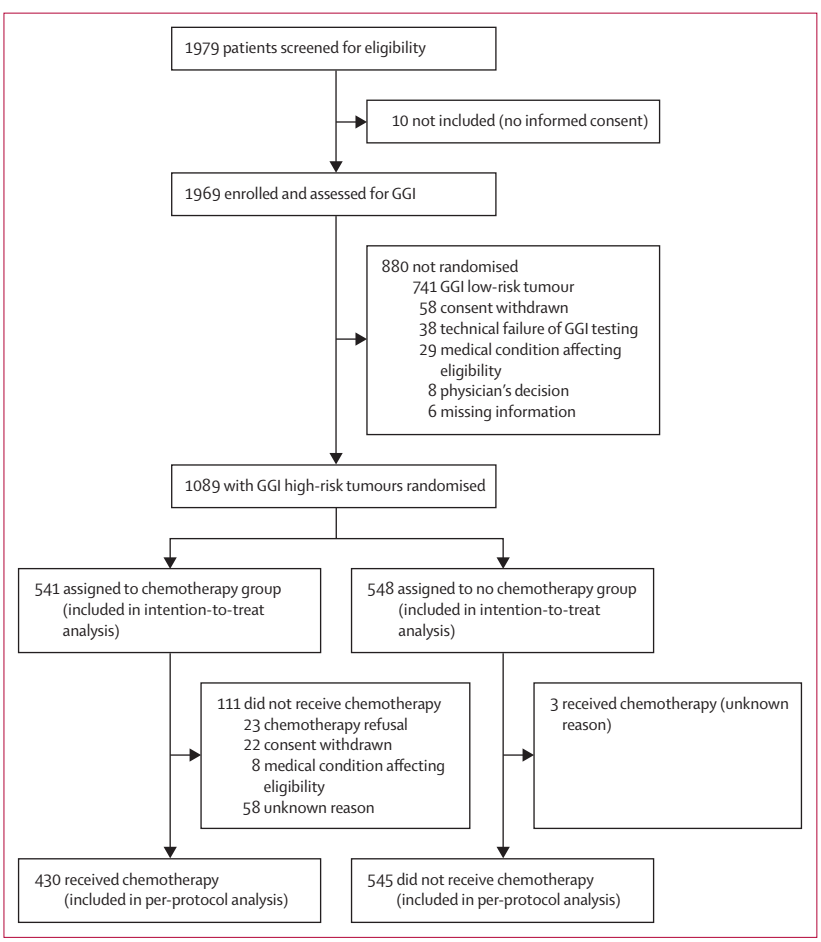

Figure 1: **Trial profile**
GGI=genomic grade index.

Outcomes

The primary endpoint was overall survival, defined as the time from the date of randomisation to death from any cause. Living patients were censored at the last follow-up date.

The main secondary endpoints included invasive disease-free survival (defined as time from randomisation to invasive breast cancer relapse [including contralateral tumour], any second invasive cancer [breast or other], or death from any cause) and breast cancer-specific survival (defined as time from randomisation to death due to breast cancer) based on the Definition for the Assessment of Time-to-Event Endpoints in Cancer Trials consensus.[21] Secondary safety endpoints were based on NCI-CTCAE v4.0 definitions. The full list of secondary endpoints can be found in section 6.2 of the protocol (appendix 2 pp 33–36). A thorough analysis of quality of life using EORTC QLQ-C30 and ELD15 questionnaires, as well as analyses of the acceptability of chemotherapy and cost-effectiveness, will be reported later.

Statistical analysis

4-year overall survival was hypothesised to be 87·5% with chemotherapy, based on the projection of early results observed in a population of older patients with oestrogen receptor-positive tumours treated with intravenous adjuvant chemotherapy in the CALGB 49907 trial.[22] In the absence of specific solid data in the literature on adjuvant treatment without chemotherapy after the age of 70 years, we used the projected 4-year overall survival observed in patients who received oral chemotherapy in the same trial (80·0%) as an indirect reference for our null hypothesis (no chemotherapy group).[22] To test the primary outcome, the study was designed with a two-sided type I error of α=0·05, 80% power, and a planned interim analysis at 50% of the fraction information (86 death events) to test early efficacy or futility with the α expenditure function and O'Brien–Fleming limits. Assuming a hazard ratio (HR) of 0·61 under the alternative hypothesis in the chemotherapy group with an exponential distribution for overall survival curves, 4 years as an accrual duration, and minimal trial participation time per patient, we initially determined that 680 patients would need to be randomly allocated for 129 deaths to be observed.

Following the recommendations of the first independent data monitoring committee meeting, which reported a 15% dropout rate and 20% of patients in the chemotherapy group not receiving chemotherapy, the planned sample size and power were increased to 1080 and 90%, respectively, requiring 171 overall survival events. With an expected rate of 54% GGI high-risk cases, 2000 patients eventually needed to be screened. The primary analysis for the main objective was planned under the intention-to-treat principle with a log-rank test stratified by the randomisation stratification factors.

Patient characteristics were described according to treatment, with median and IQR reported for continuous variables and frequency and percentage for categorical variables. Survival times were estimated using the Kaplan–Meier method. Forest plots and a Cox proportional-hazards model interaction term p value were used to explore the differential effects of treatment groups in prespecified subgroups according to stratification factors, age (≤75 years *vs* >75 years), Lee score (<6 *vs* 6–9 *vs* >9), and GGI high-risk subcategory. The proportionality assumption in Cox regression models was tested using Schoenfeld residuals. Median follow-up was estimated using the reverse Kaplan–Meier method. Sensitivity analyses of the primary endpoint and secondary efficacy endpoints were first done using the restricted mean survival time method to compensate for the lack of power of the log-rank test in the case of non-proportional risks, and then on the per-protocol population (defined as patients who started the treatment they were allocated to). In a complementary approach, a Fine and Gray model was used to address the effects of competing events on invasive disease-free survival and breast cancer-specific survival.

Longitudinal analysis of EORTC QLQ-C30 questionnaires was conducted using time-until-definitive deterioration and a mixed model for repeated measures approaches.

All analyses were done with SAS (version 9.3) and R (version 4.1). A p value of 5% was considered statistically significant for the primary analysis of the primary endpoint. All other p values were provided for exploratory purposes. The statistical analysis plan is provided in appendix 3 (pp 1–16).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 12, 2012 and April 14, 2016, 1979 women aged 70 years and older were screened for eligibility. Among them, 1969 signed informed consent for participation and underwent GGI assessment. Testing was successful in 1901 patients, including 1160 (61%) with a GGI high-risk tumour (observed threshold –0·277 or higher), split in two subcategories: GGI –0·277 to 0·278 (411 [35%] patients) and GGI greater than 0·278 (749 [65%] patients). 1089 women with a high-risk GGI score were randomly allocated to the chemotherapy group (n=541) or no chemotherapy group (n=548). Of the 880 patients who were not randomly allocated, 741 (84%) had a low-risk GGI score, GGI testing failed in 38 (4%), 58 (7%) withdrew consent, and trial participation was halted in 43 (5%) for other reasons (figure 1).

The baseline characteristics of randomly allocated patients are presented in table 1. Patients ranged in age from 70·0 years to 92·4 years (median 75·1 years

	Chemotherapy group (n=541)	No chemotherapy group (n=548)
Age, years	75·2 (72·7–79·0)	74·9 (72·4–78·6)
ECOG performance status		
0	340 (63%)	374 (69%)
1	190 (35%)	160 (29%)
2	11 (2%)	11 (2%)
Missing data	0	3
G8 geriatric frailty score*		
>14	318 (59%)	334 (61%)
≤14	223 (41%)	214 (39%)
Lee's prognostic index score†		
<6	108 (20%)	116 (22%)
6–9	371 (69%)	372 (69%)
>9	55 (10%)	50 (9%)
Missing data	7	10
Age-adjusted Charlson comorbidity index		
5	262 (49%)	280 (52%)
6	173 (32%)	166 (31%)
>6	98 (18%)	94 (17%)
Missing data	8	8
Instrumental activities of daily living	8 (8–8)	8 (8–8)
Minimal mental status examination	28 (26–29)	28 (26–30)
History of non-breast cancer	37 (7%)	56 (10%)
Breast cancer local relapse or contralateral tumour	65 (12%)	76 (14%)
pT stage		
1	234 (44%)	238 (44%)
2	270 (50%)	270 (50%)
3	31 (6%)	35 (6%)
4	2 (<1%)	1 (<1%)
Missing data	4	4
pN stage		
0	300 (55%)	300 (55%)
1	179 (33%)	186 (34%)
2	59 (11%)	59 (11%)
pN+ unspecified	3 (1%)	3 (1%)
Histological subtype		
Ductal invasive	389 (72%)	373 (68%)
Lobular invasive	88 (16%)	99 (18%)
Mixed	21 (4%)	25 (5%)
Other	42 (8%)	50 (9%)
Missing data	1	1
Bilateral tumour	23 (4%)	24 (4%)
Multifocal tumour	103 (19%)	106 (19%)
Oestrogen receptor status		
Positive	541 (100%)	547 (100%)
Missing data	0	1
Progesterone receptor status		
Positive	421 (78%)	432 (79%)
Negative	119 (22%)	115 (21%)
Missing data	1	1
Ki67 index, %	20 (15–30)	25 (15–35)

(Table 1 continues on next page)

	Chemotherapy group (n=541)	No chemotherapy group (n=548)
(Continued from previous page)		
HER2 status		
Negative (IHC 0, 1+, or 2+ and FISH–)	534 (>99%)	535 (>99%)
Positive (IHC 3+, or IHC 2+ and FISH+)	1 (<1%)	2 (<1%)
Missing data	6	11
Histological grade		
I	26 (5%)	37 (7%)
II	300 (55%)	302 (56%)
III	215 (40%)	202 (37%)
Missing data	0	7
Genomic grade index		
–0·277 to 0·278	190 (35%)	194 (35%)
>0·278	351 (65%)	354 (65%)
Type of surgery		
Breast-conserving surgery	325 (60%)	335 (61%)
Mastectomy	216 (40%)	211 (39%)
Missing data	0	2

Data are median (IQR) or n (%); percentages are based on non-missing data. ECOG=Eastern Cooperative Oncology Group. FISH=fluorescence in situ hybridisation. IHC=immunohistochemistry. *Screening tool for geriatric frailty; scores ≤14 suggest the presence of frailty and recommend a full geriatric assessment. †Prognostic index for 4-year mortality risk; scores <6 indicate a less than 4% risk, scores of 6–9 indicate a 15% risk, and scores >9 indicate a more than 42% risk.

Table 1: **Baseline and tumour characteristics of randomly allocated patients (n=1089)**

See Online for appendix 3

	Chemotherapy group (n=541)	No chemotherapy group (n=548)
Chemotherapy choice		
Taxane*	281 (52%)	2 (<1%)
Anthracycline†	148 (27%)	1 (<1%)
Other	1 (<1%)	0
None	111 (21%)	545 (99%)
Treatment completion		
Chemotherapy discontinued before cycle 4	44 (8%)	0
Chemotherapy discontinued for toxicity	35 (6%)	0
Hormonotherapy discontinued for toxicity at least once during follow-up	114 (21%)	124 (23%)
Adverse event		
At least one any-grade adverse event	503 (93%)	445 (81%)
At least one grade ≥3 adverse event	183 (34%)	52 (9%)
At least one serious adverse event	88 (16%)	17 (3%)
Death	3 (1%)	1 (<1%)

*Docetaxel plus cyclophosphamide. †Doxorubicin plus cyclophosphamide; or non-pegylated liposomal doxorubicin plus cyclophosphamide.

Table 2: **Treatment and adverse events in randomly allocated patients**

[IQR 72·5–78·7]), 437 (40%) of 1089 had frailty according to G8 (scores ≤14), 105 (10%) of 1072 had a 4-year mortality risk higher than 42% according to Lee's prognostic index (scores >9), and 141 (13%) of 1089 had a locoregional relapse of a previous breast cancer or a contralateral breast tumour. A history of non-breast cancer was reported in 93 (9%) of 1089 patients. Patients who were not randomly allocated had fewer mastectomy procedures, and more often had pT1 tumours with no nodal involvement, of a lobular subtype, and with progesterone expression (appendix 1 p 1).

Among the 541 patients in the chemotherapy group, 281 (52%) received taxane-based regimens, 148 (27%) received anthracycline-based regimens, and 111 (21%) declined chemotherapy altogether (table 2). Those who declined chemotherapy had poorer Eastern Cooperative Oncology Group Performance Status, G8 scores, and Charlson Comorbidity Index scores than those who received chemotherapy as planned (appendix 1 pp 3–5). Similar patient and tumour characteristics were observed irrespective of the type of chemotherapy received (appendix 1 pp 6–7). In the no chemotherapy group, three (1%) patients received chemotherapy for an unknown reason. Chemotherapy was discontinued before cycle 4 in 44 (8%) patients in the chemotherapy group. The median dose intensity of chemotherapy agents in both regimens was above 99% for all drugs (appendix 1 p 8). Hormonotherapy was stopped at least once for toxicity during the follow-up phase of the study in 114 (21%) patients in the chemotherapy group and 124 (23%) in the no chemotherapy group (table 2). Discontinuation of chemotherapy or hormonotherapy was mainly due to adverse events. More details on hormonotherapy compliance in randomly allocated patients is provided in appendix 1 (p 9). Of the 794 patients who were not randomly allocated and for whom information was available, 775 (98%) received no chemotherapy as recommended by the protocol (appendix 1 p 10).

The database was locked on May 30, 2024. With a median follow-up of 7·8 years (95% CI 7·5–7·8) in the intention-to-treat population, there were 279 deaths (135 in the chemotherapy group and 144 in the no chemotherapy group) and 246 relapses or second invasive cancers recorded (109 in the chemotherapy group and 137 in the no chemotherapy group). Overall survival was 90·5% (95% CI 87·6–92·8) at 4 years and 72·7% (67·8–77·0) at 8 years in the chemotherapy group, and was 89·3% (86·2–91·6) at 4 years and 68·3% (63·3–72·7) at 8 years without chemotherapy (HR 0·83 [95% CI 0·63–1·11]; stratified log-rank test p=0·2100; figure 2A). This yielded statistically non-significant absolute differences in overall survival probability of 1·3 percentage points (95% CI –2·4 to 5·0) at 4 years and 4·5 percentage points (–2·1 to 11·1) at 8 years. There was no statistically significant violation of the proportional risk assumption (p=0·059). In a sensitivity analysis, the restricted mean survival time was 8·8 years (95% CI 8·6–9·0) in the chemotherapy group and 8·6 years (8·4–8·9) in the no chemotherapy group.

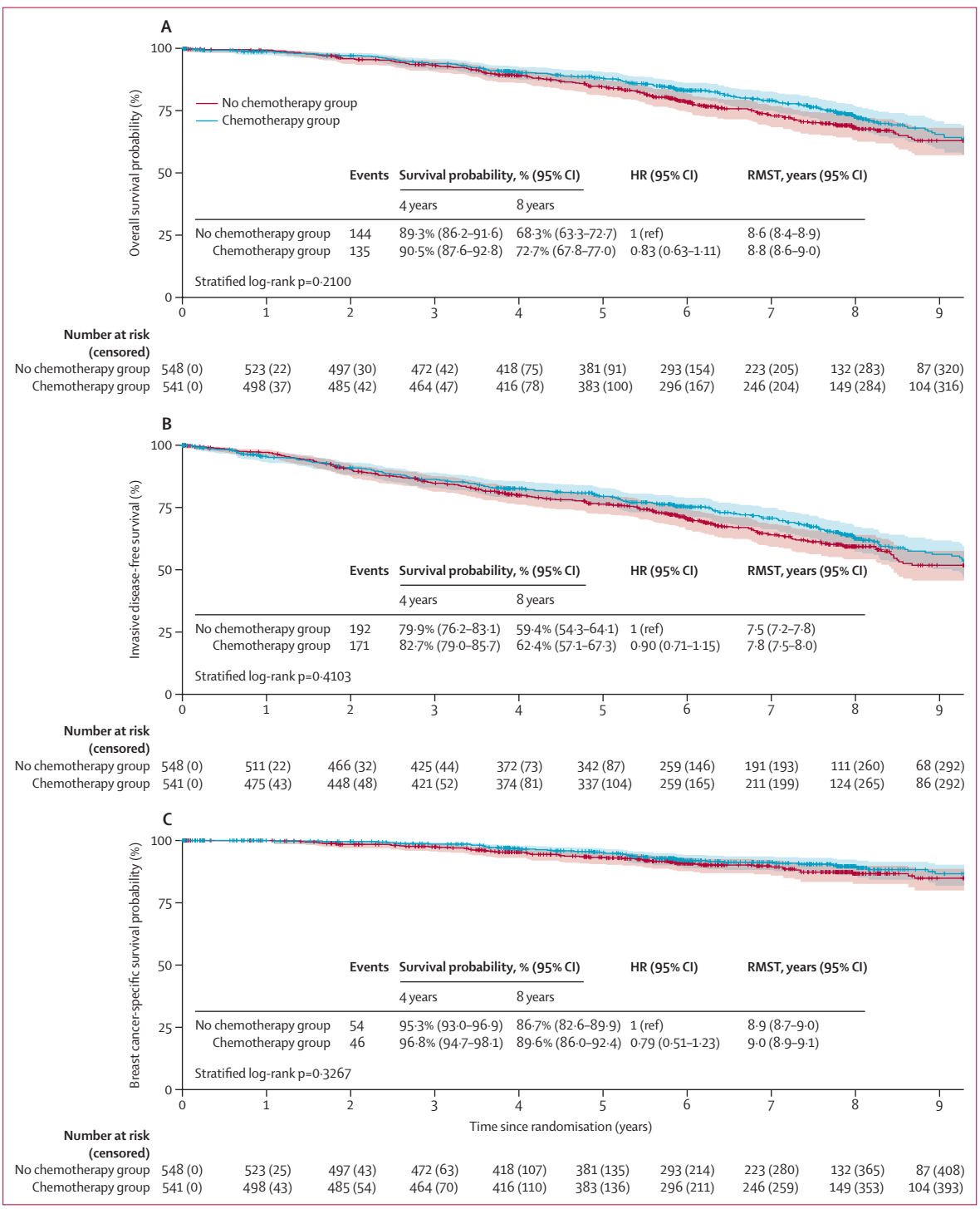

Figure 2: **Kaplan–Meier survival estimates by treatment group in the intention-to-treat population**
(A) Overall survival; events were defined as death due to any cause. (B) Invasive disease-free survival; events were defined as invasive breast cancer relapse (including contralateral tumour), any second invasive cancer (breast or other), or death from any cause. (C) Breast cancer-specific survival; events were defined as death due to breast cancer. Dashed lines indicate 95% CIs. HRs were estimated with Cox regression stratified on pN stage, G8 score, and centre. RMST was estimated until 10 years of follow-up and adjusted for pN stage and G8 score. HR=hazard ratio. RMST=restricted mean survival time.

Additionally, there were no significant differences between groups with regard to invasive disease-free survival (figure 2B) or breast cancer-specific survival (figure 2C).

Of the deaths from known causes that occurred among randomly allocated patients during the follow-up period, 55 (48%) of 114 in the chemotherapy group and 55 (42%) of 132 in the no chemotherapy group were related to comorbidities (table 3). Of the 125 deaths from known causes in patients who were not randomly allocated, comorbidities were responsible for 75 (60%; appendix 1 p 11). Data on the distribution of deaths at 4 years post randomisation and invasive disease-free events are presented in appendix 1 (pp 11–13).

	Chemotherapy group (n=135)	No chemotherapy group (n=144)
Breast cancer	46 (40%)	54 (41%)
Comorbidities	55 (48%)	55 (42%)
Second cancer	12 (11%)	22 (17%)
Toxicity	1 (1%)	1 (1%)
Unknown	21	12

Percentages are based on patients with known causes of death (n=114 in the chemotherapy group and n=132 in the no chemotherapy group).

Table 3: **Causes of death among randomly allocated patients who died during follow-up**

Regarding adverse events, more adverse events, grade 3 or higher events, and serious adverse events were reported in the chemotherapy group than in the no chemotherapy group (table 2), mostly involving haematological, gastrointestinal, skin, or administration site-related side-effects or infections (appendix 1 p 14), with discontinuation of chemotherapy due to toxicity in 35 patients (7%). In the chemotherapy group, three deaths occurred (one due to peritonitis, one due to a cardiac event, and one due to general deterioration), including one treatment-related death (peritonitis). One death (due to stroke) was reported in the no chemotherapy group.

We did not identify any statistically significant differential treatment effect on overall survival among the subgroups studied (age, G8, Lee score, pN stage, pT stage, and high-risk GGI subcategory; figure 3), nor for invasive disease-free survival and breast cancer-specific survival (appendix 1 pp 15–16). Additionally, sensitivity analyses of overall, breast cancer-specific, and invasive disease-free survival in the per-protocol population showed no significant difference between treatment groups, similar to the intention-to-treat analysis (appendix 1 pp 17–19).

	Deaths/total patients, n/N		8-year overall survival probability, % (95% CI)		HR (95%CI)	$p_{interaction}$
	No chemotherapy group	Chemotherapy group	No chemotherapy group	Chemotherapy group		
Age (years)						0·9223
≤75	65/323	57/294	76·0% (70·0–81·0)	79·5% (73·2–84·4)	0·74 (0·46–1·19)	
>75	79/223	78/247	56·3% (47·7–64·0)	63·9% (55·8–70·9)	0·65 (0·41–1·02)	
G8 frailty score						0·6918
>14	72/334	64/318	74·8% (68·7–79·9)	79·6% (73·7–84·3)	0·88 (0·60–1·30)	
≤14	72/214	71/223	57·2% (48·5–64·9)	62·3% (53·6–69·8)	0·78 (0·52–1·19)	
Lee's prognostic index score						0·7149
<6	20/116	17/108	81·1% (71·8–87·6)	86·1% (76·6–91·9)	0·91 (0·35–2·35)	
6–9	97/372	87/371	68·1% (61·8–73·6)	73·1% (66·9–78·3)	0·72 (0·49–1·05)	
>9	26/50	27/55	35·8% (20·6–51·4)	41·8% (24·9–57·9)	1·54 (0·45–5·24)	
pN stage (0 *vs* +)						0·6425
0	63/300	60/300	74·9% (68·5–80·1)	77·1% (70·4–82·4)	0·90 (0·59–1·37)	
+	81/248	75/241	60·2% (52·3–67·3)	67·7% (60·1–74·2)	0·79 (0·54–1·15)	
pN stage (0 *vs* 1 *vs* 2)						0·6596
0	63/300	60/300	74·9% (68·5–80·1)	77·1% (70·4–82·4)	0·90 (0·59–1·37)	
1	51/186	48/179	65·8% (56·5–73·6)	72·9% (64·2–79·9)	0·81 (0·48–1·36)	
2	30/59	26/59	41·0% (26·0–55·5)	49·5% (33·4–63·7)	0·82 (0·34–2·00)	
pT stage						0·2618
1	45/238	36/234	76·7% (69·4–82·4)	84·5% (77·9–89·3)	0·51 (0·27–0·96)	
2–4	99/306	97/303	61·5% (54·5–67·7)	64·2% (57·1–70·4)	0·83 (0·57–1·21)	
Genomic grade index						0·7941
−0·277 to 0·278	37/194	39/190	77·1% (69·0–83·3)	76·2% (67·7–82·8)	0·86 (0·40–1·87)	
>0·278	107/354	96/351	63·7% (57·3–69·4)	70·9% (64·6–76·2)	0·82 (0·57–1·16)	
Overall	**144/548**	**135/541**	**68·3% (63·3–72·7)**	**72·7% (67·8–77·0)**	**0·83 (0·63–1·11)**	

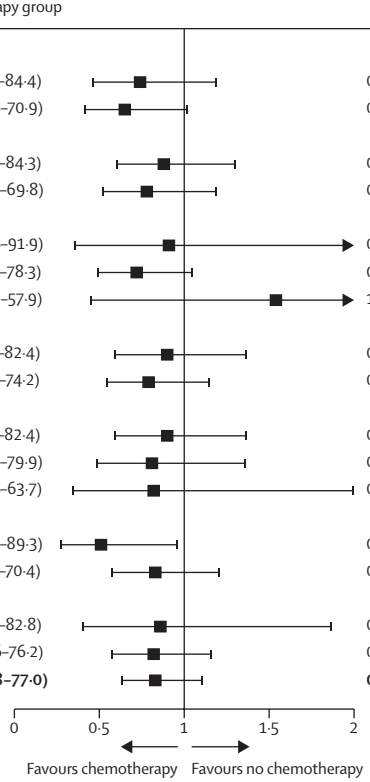

Figure 3: **Forest plot for overall survival among prespecified subgroups in the intention-to-treat population**
HRs were estimated with Cox regression stratified on pN stage, G8 score, and centre. p values are for interaction in the Cox model. HR=hazard ratio.

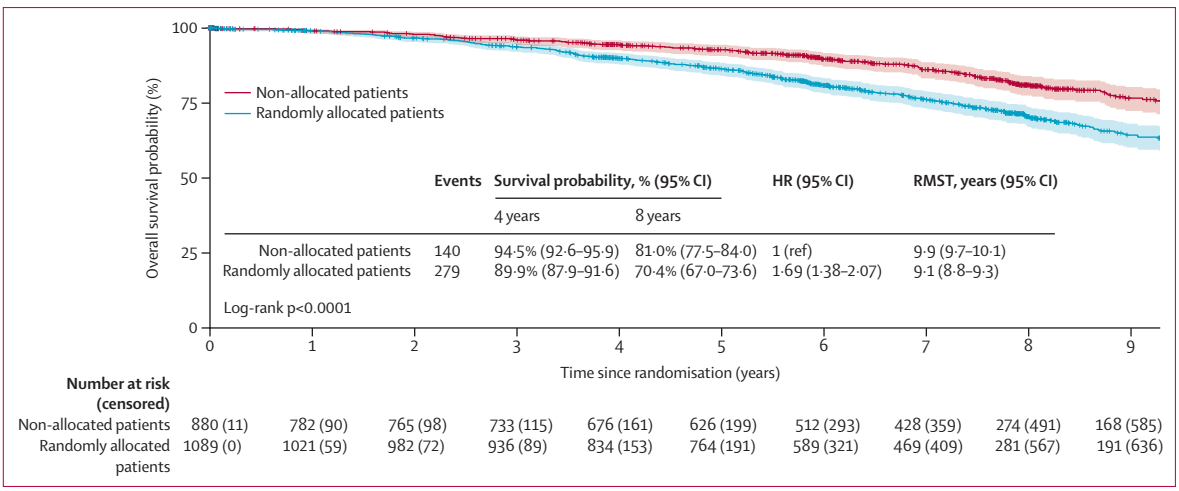

Figure 4: **Kaplan–Meier estimates of overall survival in randomly allocated versus non-allocated patients**
Events were defined as death due to any cause. Dashed lines indicate 95% CIs. RMST was estimated until 10 years of follow-up. HR=hazard ratio. RMST=restricted mean survival time.

In sensitivity analyses in the intention-to-treat population considering death due to causes other than breast cancer as a competing risk, subdistribution HRs (sHRs) similar to those in the main analyses were observed for breast cancer-specific survival (sHR 0·85 [95% CI 0·57–1·26]) and for invasive disease-free survival (0·80 [0·62–1·03]; appendix 1 pp 20–21). In the competing risks analysis of breast cancer-specific survival, the cumulative incidence estimates for deaths due to causes other than breast cancer were similar between groups (0·97 [0·73–1·30]; appendix 1 p 20).

Randomly allocated patients had significantly worse overall survival than patients who were not allocated (figure 4). In Kaplan–Meier analyses of overall, invasive disease-free, and breast cancer-specific survival by GGI category (including GGI low-risk patients), patients in the highest GGI category (>0·278) had the highest risk of survival events of interest (appendix 1 pp 22–24).

In patients receiving chemotherapy, overall survival did not differ whether taxanes or anthracyclines were used (log-rank p=0·6952; appendix 1 p 25). The time until the definitive deterioration of quality of life was shorter for patients in the chemotherapy group than for those in the no chemotherapy group, in several dimensions (role and social functioning, nausea and vomiting, pain, dyspnoea, appetite loss, constipation, and diarrhoea). Furthermore, the mixed model for repeated measures yielded similar results (appendix 1 p 26). Results from other questionnaires will be described later in a dedicated paper.

Discussion

In this superiority trial, adjuvant chemotherapy did not provide any statistically significant benefit in terms of overall survival compared with hormonotherapy alone in women aged 70 years or older with GGI high-risk oestrogen receptor-positive HER2-negative breast cancer, whether the analysis was done by intention-to-treat or per-protocol, and regardless of the statistical method used. Similar results were observed for invasive disease-free survival and breast cancer-specific survival. We also did not identify any statistically significant differential effect of the addition of chemotherapy in the subgroups studied according to age, G8 frailty score, Lee's score, GGI high-risk subcategory, tumour size, or nodal status. However, safety and longitudinal analyses of health-related quality of life favoured the no chemotherapy group. The excellent prognosis of patients who were not randomly allocated in this study (of whom 741 [84%] had a GGI low-risk tumour and most of whom were not treated with chemotherapy, as recommended in the protocol) supports the high-risk profile selected for randomisation and suggests that adjuvant chemotherapy would not have provided a clinically substantial benefit regardless of GGI. The large size of the trial limited random error and imprecision of estimates. Overall survival as the primary endpoint was robust, reproducible, and patient-centred. In the absence of a blinded procedure, the main intention-to-treat analysis of overall survival, randomisation, and similar conclusions from the per-protocol analysis in two comparable groups limited the potential effect of systemic errors on the main conclusion. Moreover, the consistency of the conclusions of the sensitivity analyses—using restricted mean survival time and considering competing risks—reinforces the robustness of the main result. Collectively, these results allow a message of caution regarding the use of adjuvant chemotherapy in this population.

The selection of chemotherapy regimens was an important consideration in the trial. Only adjuvant regimens of less than 3 months were allowed, based on the best available evidence in the literature for the use of

adjuvant chemotherapy in the older adult population, who are persistently under-represented, representing at best 10% of cases, with a low cutoff of 65 years in a 2023 meta-analysis on the benefits of anthracycline-based and taxane-based regimens.[23] The choice of four cycles of either taxanes or anthracyclines avoided the longer duration of sequential or concomitant schedules (18–24 weeks) that carry an increased risk of serious adverse events.[3,24] Such a short duration of chemotherapy was feasible with excellent dose intensity, as shown by our group in similar setting,[20] allowing for an unbiased analysis of the treatment effect. Although treatment regimens combining anthracyclines and taxanes might have offered greater benefit in some patients, such regimens double the risk of having a poor mean relative dose intensity rate (less than 85%) in older patients compared with regimens given in less than 12 weeks (risk 27% *vs* 14%, respectively; p<0·004), compromising the intended benefit,[25] thereby raising questions about their feasibility and their qualification as standard treatment in this population.[26]

The choice of overall survival to assess the benefit of adjuvant chemotherapy was also an important decision. Although not exclusive to advanced age, a primary endpoint in older patients should ideally include health-related quality of life and survival.[27] When designing the study, we considered that this objective could be better achieved with a global measure such as overall survival encompassing competing risks for disease outcome, rather than with evaluation criteria related solely to the tumour, and supplemented by health-related quality of life as secondary endpoint. It is important to note that the studies setting a threshold of a 3–5% absolute survival benefit to justify the use of adjuvant chemotherapy date back to the early 2000s and involved a very small number of patients older than 65 years,[28] an age-based discrimination that has hardly changed since.[29] In these studies, inter-individual variability was large, with an absolute benefit greater than 10% deemed insufficient to justify chemotherapy in 15–20% of patients.[28] Given the decline in health-related quality of life, the lower tolerance observed under chemotherapy, and the decrease in life expectancy observed with increasing age, the time until definitive deterioration in quality of life could be a more relevant evaluation criterion in older adult patients, combined with systematic analysis of competing risks due to the large number of events not directly related to the cancer under study. In line with our ambitious statistical hypothesis on overall survival (HR 0·61), these observations highlight the hazard of extrapolating the usual threshold of 3–5% absolute improvement in survival to a population of older adults who, although selected for their high risk of tumour recurrence, are more prone to side-effects due to the increasing frailty associated with age, and who have not been properly studied. In the future, this threshold should be reviewed according to age, actively seeking patient participation and agreement on trial design to limit gaps between what researchers and patients deem to be relevant.[30,31]

Unexpectedly, the distribution of causes of death observed in patients who were randomly allocated and the analysis of competing risks did not suggest accelerated ageing under chemotherapy, as others have noted.[32] Despite the presence of frailty in nearly 40% of patients and the collection of specific age-related data, we were unable to find a subgroup of patients for whom chemotherapy could be beneficial. This finding somewhat goes against the widespread idea that biological age, as approximated by geriatric assessment, should always take precedence over chronological age in order to adapt treatment to the considerable heterogeneity of ageing. This finding also serves as a reminder of the importance of not completely ignoring chronological age when assessing these older subjects, as emphasised by its inclusion in the G8 frailty screening tool[13] and the greater homogeneity of life expectancy at an advanced age.[33]

This study has limitations. In the absence of clear age-specific data in the literature, we used the oral chemotherapy group of the CALGB 49907 trial as an indirect reference for our null hypothesis, given the significant and strong interaction between treatment and hormone receptor status from the first follow-up at less than 3 years,[22] with a persistent effect of standard intravenous chemotherapy only in older patients with oestrogen receptor-negative tumours after 10 years of follow-up.[34] Nevertheless, this approach is supported a posteriori by the recently published results of the ICE trial, which show no difference in disease outcomes between use of adjuvant ibandronate with capecitabine or ibandronate alone in patients aged 65 years and older.[35] In fact, the chemotherapy-free reference group in ASTER 70s fared much better than anticipated in our hypothesis (4-year overall survival of nearly 90·0% *vs* the expected 80·0%). However, this discrepancy is a common observation in many trials and is linked to a change in the natural history of breast cancer induced by a general positive effect of disease management over time.[36]

The finding that 111 (21%) of the 541 patients allocated to receive chemotherapy did not start treatment is not far from the rates of non-adherence with chemotherapy observed in MINDACT (128 [17%] of 749),[6] TAILORx (608 [18%] of 3449),[7] or RxPONDER (462 [18%] of all 2547 patients, and 326 [20%] of 1658 menopausal patients),[8] which largely excluded older patients, accentuating the debate on the validity of their conclusions in all age groups. This non-adherence rate calls into question whether the use of two separate consents for screening and randomisation would have resulted in better adherence, albeit with a possible bias in the selection of the population, and without evidence that this strategy contributed to significantly higher compliance in the comparable trials mentioned above conducted in the standard adult population. However, the non-adherence rate did not influence the conclusion of ASTER 70s, as

shown by the per-protocol analysis, in which the patients in the two randomised groups had similar initial characteristics. Notably, self-reported discontinuation of hormonotherapy in both groups of the ASTER 70s study was close to the non-adherence rate for chemotherapy, suggesting that patient preference between a short intense treatment and a prolonged treatment could be an important research question, similar to the question of preference for local radiotherapy versus hormonotherapy after breast-conserving surgery for small tumours with good prognosis in the ongoing EUROPA trial.[37]

Finally, among patients successfully screened for GGI, 61% had a high-risk profile, a proportion three times that found in TAILORx and RxPONDER trials based on recurrence score, a 21-gene breast-cancer assay ranging from 0 to 100, with higher scores (≥26 and 11–25 *vs* ≤10) indicating a worse prognosis and potential benefit from chemotherapy.[7,8] We recognise that the marketing of GGI has been discontinued and that there is no comparison of its discriminatory ability with the most commonly used tests today. Consequently, a collaborative effort is under way to reanalyse the entire series of tumours collected in ASTER 70s trial with the recurrence score. This will make it possible to test retrospectively whether or not the proportions and characteristics of the risk categories overlap between the tests, and whether such an alternative signature would produce different conclusions in the ASTER 70s population. However, comparisons have already been published showing the similarity of prognostic information generated by several genomic signatures despite differences in risk categorisation and subtypes,[38] which suggests that the general message on adjuvant chemotherapy provided by ASTER 70s is valid.

Together with other recent landmark initiatives (NCT04134598[37] and EORTC1745/NCT04134598), ASTER 70s shows the feasibility of large, randomised, distributive, and inclusive research incorporating geriatric and health-related quality-of-life assessments, challenging popular beliefs and misconceptions that cancer clinical trials are difficult to conduct in older populations. The success of the ASTER 70s programme relied on its pragmatic design, covering any practice condition in a strong territorial network of oncologists and geriatricians, developed over 20 years of French initiatives (cancer plans, research calls, curricula, and units of coordination in geriatric oncology).[39] Despite the length of the study, interest in the role of adjuvant chemotherapy in older patients has not waned. The absence of a statistically significant benefit of adjuvant chemotherapy in the ASTER 70s trial underlines the persistent challenge of identifying older patients who would benefit from such a strategy and the risk of extrapolating the results obtained in younger cohorts to this population. Although the statistically negative results of the ASTER 70s superiority trial do not exclude the possibility that a smaller beneficial effect of chemotherapy might exist and that a subgroup of patients in this selected high-risk older population might benefit from the addition of chemotherapy to hormonotherapy, this trial provides important data to inform the shared decision making between doctor and patient when discussing adjuvant treatment in this age group. Future research directions include combining the best information obtained from tumour biology and from patients for risk selection, as shown in tools such as the PORTRET algorithm[40] and the Age Gap Decision Tool,[30] which outperfom PREDICT,[41] and replacing chemotherapy with wider use of better-tolerated adjuvant bisphosphonates[42] or optimised hormonotherapy combined with CDK4/6 inhibitors (EORTC1745/NCT04134598).

Contributors

Conception or design of the work: EB and DV. Data collection: all authors. Data analysis and interpretation: EB, DV, JH, TR, and JL. Drafting the article: EB, DV, JH, TR, and JL. Critical revision of the article: all authors. EB, JH, DV, TR, and JL accessed and verified the data underlying the study. All authors had access to the study data and had final responsibility for the decision to submit for publication.

Declaration of interests

EB reports consulting fees from Exact Sciences, Menarini, Pfizer, Sandoz; payment or honoraria for lectures and presentations from AstraZeneca, Daiichi, Eli Lilly, Exact Sciences, Incyte, Novartis, Pfizer, and Takeda; support for attending meetings and/or travel from AstraZeneca, Daiichi, Exact Sciences, Gilead, Novartis, and Pfizer; and participation on a data safety monitoring board or advisory board from Daiichi. OM reports stock or stock options and other financial or non-financial interests from Amgen. FPD reports grants or contracts from Fondation Belge Contre le Cancer; consulting fees from Roche, Pfizer, AstraZeneca, Eli Lilly, Novartis, Amgen, Daiichi, Pierre Fabre, Gilead, Seagen, MSD, Menarini, Mundi Pharma, and Teva; and support for attending meetings and/or travel from Amgen, Roche, Teva, Daiichi, AstraZeneca, Pfizer, Gilead, Menarini, and MSD. ML-T reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Myriad genetics. DV reports consulting fees from Gercor, Cure51, CellProtera SAS, Apmonia Therapeutics, Incyte, Veracyte, Lysarc, Invectys, Novartis, and Netris Pharma. All other authors declare no competing interests.

Data sharing

The data collected and analysed for the present manuscript are not immediately available due to ethical and legal restrictions. However, Unicancer will grant access to all de-identified individual data underlying the published results upon written and detailed request originating from all personnel involved in cancer research, sent to gerico11@unicancer.fr

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