Prognostic and clinical impact of the endocrine resistance/sensitivity classification according to international consensus guidelines for advanced breast cancer: an individual patient-level analysis from the Mammella InterGruppo (MIG) and Gruppo Italiano Mammella (GIM) studies

Matteo Lambertini,[a,b,x,*] Eva Blondeaux,[c,x] Giancarlo Bisagni,[d] Silvia Mura,[e] Sabino De Placido,[f] Michelino De Laurentiis,[g] Alessandra Fabi,[h] Anita Rimanti,[i] Andrea Michelotti,[j] Mauro Mansutti,[k] Antonio Russo,[l] Filippo Montemurro,[m] Antonio Frassoldati,[n] Antonio Durando,[o] Stefania Gori,[p] Anna Turletti,[q] Stefano Tamberi,[r] Ylenia Urracci,[s] Piero Fregatti,[t,u] Maria Grazia Razeti,[a,b] Roberta Caputo,[g] Carmine De Angelis,[f] Valeria Sanna,[e] Elisa Gasparini,[d] Elisa Agostinetto,[v] Evandro de Azambuja,[v] Francesca Poggio,[w] Luca Boni,[c] and Lucia Del Mastro[a,b]

[a]Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genoa, Italy
[b]Department of Medical Oncology, U.O. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[c]Clinical Epidemiology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[d]Department of Oncology and Advanced Technology, Oncology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[e]Department of Medical Oncology, UOC Oncologia Medica, University Hospital of Sassari, Sassari, Italy
[f]Department of Clinical Medicine and Surgery, University of Naples Federico II, Napoli, Italy
[g]Istituto Nazionale per lo Studio e la Cura dei Tumori, Fondazione Pascale IRCCS, Napoli, Italy
[h]Medical Oncology 1, IRCCS Regina Elena National Cancer Institute, Roma, Italy
[i]ASST Mantova, Azienda Ospedaliera Carlo Poma, Mantova, Italy
[j]UO Medical Oncology, S. Chiara Hospital, Pisa, Italy
[k]Academic Hospital Santa Maria della Misericordia, Udine, Italy
[l]Ospedale Giaccone, Palermo, Italy
[m]Multidisciplinary Outpatient Oncology Clinic, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Torino, Italy
[n]Department of Translational Medicine and for Romagna, Clinical Oncology, S. Anna University Hospital, Ferrara, Italy
[o]Breast Unit, Città della Salute e della Scienza, Ospedale S. Anna, Torino, Italy
[p]Medical Oncology, IRCCS Ospedale Sacro Cuore-Don Calabria, Negrar, Verona, Italy
[q]Medical Oncology, Ospedale Martini ASL Città di Torino, Torino, Italy
[r]Oncology Department Area Vasta Romagna, Faenza Hospital, Faenza, Italy
[s]Department of Medical Oncology, Hospital Businco, Cagliari, Italy
[t]Department of Surgery, UOC Clinica di Chirurgia Senologica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[u]Department of Surgical Sciences and Integrated Diagnostic (DISC), School of Medicine, University of Genova, Genoa, Italy
[v]Academic Trials Promoting Team, Institut Jules Bordet, and the Université Libre de Bruxelles (U.L.B.), Brussels, Belgium
[w]Department of Medical Oncology, U.O. Oncologia Medica 2, IRCCS Ospedale Policlinico San Martino, Genova, Italy

Summary

Background **Prior exposure to adjuvant endocrine therapy (ET) and timing to recurrence are crucial factors for first-line treatment choices in patients with hormone receptor-positive/HER2-negative (HR+/HER2–) breast cancer (BC) and in clinical trial eligibility, classifying metastatic HR+/HER2– BC as endocrine sensitive (ES) or primary (1ER)/secondary (2ER) resistant. However, this classification is largely based on expert opinion and no proper evidence exists to date to support its possible prognostic and clinical impact.**

Methods **This analysis included individual patient-level data from 4 adjuvant phase III randomized trials by the Mammella InterGruppo (MIG) and Gruppo Italiano Mammella (GIM) study groups. The impact of endocrine resistance/sensitivity classification on overall survival (mOS, defined as time between date of distant relapse and death) was assessed in both univariate and multivariate Cox proportional hazards models.**

eClinicalMedicine 2023;59: 101931
Published Online 12 May 2023
https://doi.org/10.1016/j.eclinm.2023.101931

*Corresponding author. Medical Oncology Department, U.O.C. Clinica di Oncologia Medica IRCCS Policlinico San Martino Hospital, University of Genova, Largo Rosanna Benzi 10, 16132, Genova, Italy.
E-mail address: matteo.lambertini@unige.it (M. Lambertini).
[x]Matteo Lambertini and Eva Blondeaux contributed equally to this work.

Findings Between November 1992 and July 2012, 9058 patients were randomized in 4 trials, of whom 6612 had HR+/HER2– BC. Median follow-up was 9.1 years (interquartile range [IQR] 5.6–15.0). In the whole cohort, disease-free survival and OS were 90.4% and 96.6% at 5 years, and 79.1% and 89.4% at 10 years, respectively. The estimated hazard of recurrence raised constantly during the first 15 years from diagnosis, being more pronounced during the first 2 years and less pronounced after year 7.

Among the 493 patients with a distant relapse as first disease-free survival event and available date on ET completion, 72 (14.6%), 207 (42.0%) and 214 (43.4%) were classified as having 1ER, 2ER and ES, respectively. Median follow-up from diagnosis of a distant relapse was 3.8 years (IQR 1.6–7.5). Patients with 1ER were significantly more likely to be younger, to have N2/N3 nodal status, grade 3 tumours and to develop visceral metastases. Site of first distant relapse was significantly different between the 3 groups ($p = 0.005$). In patients with 1ER, 2ER and ES breast cancer, median mOS was 27.2, 38.4 and 43.2 months, respectively ($p = 0.03$). As compared to patients with ES disease, a higher risk of death was observed in those with 1 ER (adjusted Hazard Ratio [aHR] 1.54; 95% CI 1.03–2.30) and 2ER (aHR 1.17; 95% CI 0.87–1.56) ($p = 0.11$).

Interpretation This large analysis with long-term follow-up provides evidence on the prognostic and clinical impact of the currently adopted endocrine resistance/sensitivity classification in patients with HR+/HER2– advanced BC. This classification may be considered a valid tool to guide clinical decision-making and to design future ET trials in the metastatic setting.

Funding AIRC.

Keywords: Breast cancer; Endocrine therapy; Endocrine sensitivity; Endocrine resistance; Prognosis

Research in context

Evidence before this study

Patients with hormone receptor-positive/HER2-negative early breast cancer are characterized by distinctive time-dependent and site-specific recurrence patterns. According to international consensus guidelines for advanced disease, prior exposure to and type of adjuvant endocrine therapy as well as the timing of relapse are crucial factors to classify hormone receptor-positive/HER2-negative breast cancer as endocrine sensitive, primary or secondary resistant. Despite its crucial role in first-line treatment choices and trial eligibility, the currently adopted endocrine resistance/sensitivity classification is largely based on expert opinion.

We searched Medline with no language or date restriction on September 1, 2022 by using the search terms "breast cancer", "endocrine therapy", "endocrine resistance" and "endocrine sensitivity". While prior publications have addressed time-dependent and site-specific recurrence patterns in patients with hormone receptor-positive breast cancer with a minority specifically in those with HER2-negative disease, no studies have specifically investigated to date the prognostic and clinical impact of the currently adopted endocrine resistance/sensitivity classification.

Added value of this study

The present large individual patient-level analysis with long-term follow-up reports prognosis, timing and pattern of recurrence among 6612 patients with hormone receptor-positive/HER2-negative breast cancer enrolled in 4 adjuvant phase III randomized trials conducted by the Mammella InterGruppo (MIG) and Gruppo Italiano Mammella (GIM) study groups.

Overall, patients with hormone receptor-positive/HER2-negative disease experienced a relatively constant raising of the estimated hazard of recurrence during the first 15 years from diagnosis, with bone relapses being the most common site of distant recurrence.

The currently adopted endocrine resistance/sensitivity classification showed prognostic and clinical value. Patients with primary endocrine resistance were relatively younger, had more often node positive disease and grade 3 tumour, and developed more frequently visceral relapses and specifically liver metastases. Moreover, primary endocrine resistance was associated with the worst prognosis.

Implications of all the available evidence

This analysis provides novel information to counsel breast cancer patients with hormone receptor-positive/HER2-negative early breast cancer. Their distinctive time-dependent and site-specific recurrence patterns needs to be considered in the survivorship trajectory of these patients. Considering its prognostic and clinical impact, the currently adopted endocrine resistance/sensitivity classification may be considered a valid tool to guide clinical decision-making and to design future endocrine therapy trials in the metastatic setting.

Introduction

Endocrine therapy is the cornerstone of treatment for patients with hormone receptor-positive breast cancer.[1,2] In the early setting, adjuvant endocrine therapy significantly reduces the risk of relapse and death.[3,4] However, up to 40% of patients will experience loco-regional and/or distant relapses in the first 20 years from diagnosis.[5,6] As compared to other breast cancer subtypes, hormone receptor-positive disease is characterized by a steady risk of recurrence over time as well as a specific pattern of relapse.[7–9]

In patients developing metastatic disease, first-line treatment choices are strongly dependent by prior exposure to and type of adjuvant endocrine therapy as well as by the timing of relapse.[10–12] According to major international guidelines, based on the duration of the relapse-free interval, hormone receptor-positive/HER2-negative breast cancer is classified as endocrine sensitive, primary or secondary resistant.[10–12] Beyond treatment recommendations, this classification strongly impacts also on trial design and eligibility criteria.[13]

Despite its crucial role, the endocrine resistance/sensitivity classification is largely based on expert opinion.[10] No proper evidence exists to date to support the possible prognostic and clinical impact of the timing elapsing between adjuvant endocrine therapy exposure and diagnosis of metastatic disease. A proper understanding of how this interval influences patients' outcomes may contribute to better individualize treatment recommendations and in the design of future trials. To provide evidence on this important issue, we performed the present analysis including patients with hormone receptor-positive/HER2-negative breast cancer enrolled in 4 adjuvant phase III randomized trials conducted by the Mammella InterGruppo (MIG) and Gruppo Italiano Mammella (GIM) study groups.

Methods

Study design and participants

The present analysis included individual patient-level data of patients with hormone receptor-positive/HER2-negative breast cancer enrolled in 4 adjuvant phase III randomized trials conducted by the MIG and GIM study groups (MIG1, GIM2, GIM3, and GIM4).

Details of the included studies were previously reported. Briefly, the MIG1 study was an open-label, multicentre phase III randomized trial comparing standard vs. dose-dense adjuvant anthracycline-based chemotherapy in high-risk breast cancer patients.[14] The GIM2 study was a multicentre, randomized phase III trial with a 2 × 2 factorial design comparing the efficacy and safety of adjuvant anthracycline- and taxane-based chemotherapy with or without the inclusion of fluorouracil administered with a dose-dense schedule or a standard-interval schedule in node-positive breast cancer patients.[15] In both trials, patients with hormone-receptor-positive tumours received adjuvant endocrine therapy following cytotoxic treatment completion.[14,15] The GIM3 study was a multicentre, randomized phase III trial with a 2 × 3 factorial design comparing the three aromatase inhibitors (letrozole vs. anastrozole vs. exemestane) and the upfront vs. switch (after 2 years of tamoxifen) treatment strategy in postmenopausal women with hormone receptor-positive early breast cancer.[16] The GIM4 study was a multicentre, open-label, randomized, phase III trial comparing extended adjuvant endocrine therapy with letrozole for an additional 5 years vs. 2–3 years in postmenopausal breast cancer patients previously exposed to 3-2 years of tamoxifen.[17]

For the purpose of this analysis, the endocrine resistance/sensitivity classification according to international consensus guidelines for advanced breast cancer was used,[10] focusing only on the early setting. Thus, primary endocrine resistance was defined as a relapse while on the first 2 years of adjuvant endocrine therapy, secondary endocrine resistance as a relapse while on adjuvant endocrine therapy but after the first 2 years or a relapse within 12 months of completing adjuvant endocrine therapy, and endocrine sensitivity as a relapse after at least 12 months from adjuvant endocrine therapy completion or a relapse in the context of no prior exposure to adjuvant endocrine therapy.

All the trials were approved by the Independent Review Boards of all participating centers and all included patients provided written informed consent before study entry. The GIM and MIG Steering Committees approved the present analysis before its conduction. Written informed consent was obtained from all patients before study entry.

Outcomes

In the overall cohort of patients with hormone receptor-positive/HER2-negative disease included in the 4 trials, survival outcomes as well as timing and pattern of recurrence over time were assessed.

Then, by including only patients who developed a distant relapse as first recurrence and with known date of adjuvant endocrine therapy completion, a comparison between survival outcomes of the three cohorts of interest (primary endocrine resistant vs. secondary endocrine resistant vs. endocrine sensitive) was performed. Several preplanned subgroup analyses were conducted to compare survival outcomes in the three cohorts according to patients' age at metastatic disease (≤50 years, 51–64 years or ≥65 years), menopausal status at diagnosis (premenopausal or postmenopausal), nodal status (positive [1–3 or ≥4] or negative), tumour size (≤2 cm or >2 cm), estrogen receptor (ER) and progesterone receptor (PgR) status (ER+/PgR+, ER+/PgR– or ER–/PgR+), prior local therapy (breast conserving surgery or mastectomy), histologic type (ductal, lobular or others), baseline body mass index (BMI) (<25, 25–29.9 or ≥30), prior exposure to and

type of chemotherapy (no chemotherapy, anthracycline-only, taxane-based or others), prior exposure to and type of endocrine therapy (no endocrine therapy, aromatase inhibitors, tamoxifen or tamoxifen followed by aromatase inhibitors), type of metastatic presentation (non-visceral or visceral) and metastatic site (brain, liver, lung, bone, or other). For patients who developed distant relapses in more than one site, the site of distant metastasis was defined by prespecified importance in the following order: brain, liver, lung, bone and others.

Statistical analyses

For the entire cohort of patients with hormone receptor-positive/HER2-negative breast cancer, descriptive analyses were used to report baseline clinicopathological characteristics and the pattern of recurrence. According to STEEP criteria version 2.0,[18] disease-free survival (DFS) was computed as the time from early breast cancer diagnosis to the occurrence of one of the following events, whichever occurred first: local recurrence, distant metastasis, contralateral or ipsilateral breast tumour, second primary malignancy, death from any cause. Overall survival (OS) was computed from the date of breast cancer diagnosis to the date of death from any cause. Patients without the event of interest were censored at the last follow up visit. The Kaplan Meier method was used to estimate DFS and OS probabilities. To assess the risk of relapse over time, annual recurrence rate (computed as the percentage of patients experiencing a disease recurrence between X and X+1 years after diagnosis among patients alive and without event X years after diagnosis) and the Epanechnikov Kernel-Smoothed annual hazards of recurrence were calculated.

Within the group of patients experiencing a distant event as first recurrence and with known date of adjuvant endocrine therapy completion, clinico-pathological characteristics, pattern of relapse and clinical outcomes were compared between the primary endocrine resistant, secondary endocrine resistant and endocrine sensitive cohorts. For the purpose of this analysis, OS was defined as the time between the date of distant relapse and death from any cause (mOS). Categorical variables were summarised with proportions and differences tested using chi-square test; continuous variables were reported using medians and inter-quartile ranges and differences tested using Wilcoxon rank-sum test or Kruskal–Wallis tests. Before applying non-parametric methods, distributional assumptions were assessed using the Kolmogorov–Smirnov test. Survival probabilities for mOS according to the endocrine resistance/sensitivity definition were estimated using the Kaplan Meier method and the log-rank test was used for comparison. A log-rank trend test was used to assess whether survival increases across the three cohorts. Pairwise comparison of the endocrine resistance/sensitivity classification was made using Scheffé's multiple-comparison adjustment. The impact of the endocrine resistance/sensitivity definition on mOS was assessed in both univariate and multivariate Cox proportional hazards models. The endocrine resistance/sensitivity classification was used in different Cox models as both a continuous variable (for the trend test) and as categorical variable. The proportional hazards assumption was checked assessing the Schoenfeld plot. In the multivariate model, adjustment was made for known or potential prognostic factors in metastatic breast cancer associated with mOS at a conservative 20% level in univariate analysis. Explored potential prognostic factors were age at metastasis, type of administered adjuvant endocrine treatment, visceral involvement and year of metastatic diagnosis. To account for the potential different treatments available in the metastatic setting, the cutoff date of 31st December 2002 (i.e., when aromatase inhibitors became available in Italy for treatment of metastatic breast cancer) was used to categorize year of metastatic diagnosis. Univariate and multivariate analyses were conducted after single imputation of missing values on covariates with missing values in less than 15% of the patients (i.e., nodal status, menopausal status, BMI, type of locoregional treatment, histological subtype, tumour size, grading, hormone receptor status, type of chemotherapy, site of metastatic presentation). No covariates with missing values in more than 15% were present. Single imputation was performed assuming monotone missing patterns and using the logistic regression method. A sensitivity analysis was performed on complete case analysis. An exploratory analysis was conducted among patients that relapsed after receiving extended endocrine treatment (defined as duration of endocrine treatment more than 65 months). To account for clustering, all analyses were stratified by trial.

Statistical analyses were performed using SAS software v. 9.4. Statistical analyses were two-sided; p values of ≤ 0.05 were considered statistically significant. The trials were registered with ClinicalTrials.gov, NCT00433420 (GIM2), NCT00541086 (GIM3), NCT01064635 (GIM4).

Role of the funding source

This analysis was supported by the Italian Association for Cancer Research ("Associazione Italiana per la Ricerca sul Cancro", AIRC; MFAG 2020 ID 24698). The funder of the study had no role in study design, data collection, analysis, interpretation, or writing of the report, and they had no access to the data.

ML, EB, LB and LDM had full access to the data and had final responsibility for the decision to submit for publication.

Results

Between November 1992 and July 2012, 9058 patients were randomized in the 4 included trials, of whom 6612 had hormone receptor-positive/HER2-negative breast

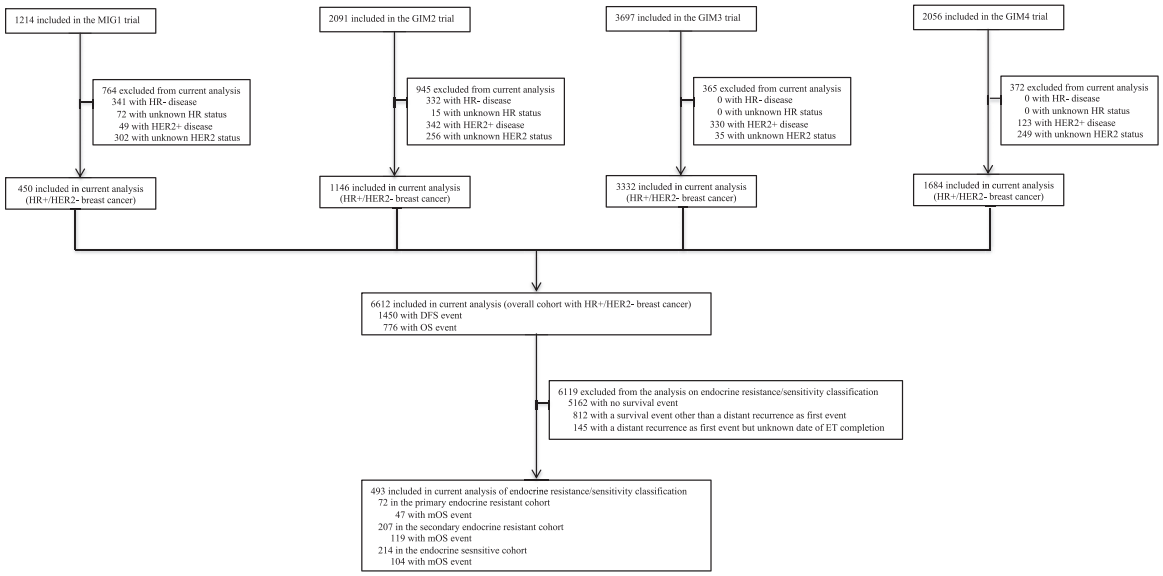

***Fig. 1:* Trial profile**. HR, hormone receptor; HR–, hormone receptor-negative; HR+, hormone receptor-positive; HER2+, HER2-positive; HER2–, HER2-negative; ET, endocrine therapy; DFS, disease-free survival; OS, overall survival computed from the date of breast cancer diagnosis to the date of death from any cause; mOS, OS computed from the date of distant relapse to the date of death from any cause.

cancer and were included in the present analysis (Fig. 1). Median age of the patients was 60 years (Appendix pp2–3). A total of 3677 (55.6%) patients received chemotherapy, of whom 1968 (53.5%) underwent an anthracycline- and taxane-based regimen. The majority of patients (6468, 97.8%) received adjuvant endocrine therapy; among them, 895 (13.8%), 1919 (29.7%) and 3654 (56.5%) received tamoxifen, aromatase inhibitors or tamoxifen followed by an aromatase inhibitor, respectively (Appendix pp2–3).

In the whole cohort, median follow-up from breast cancer diagnosis was 9.1 years (IQR 5.6–15.0) (Appendix pp4). A total of 1450 DFS and 776 OS events were reported. In terms of type of first DFS event, 638 (9.7%) patients developed a distant recurrence (Appendix pp5). Among patients with a first distant relapse, bone (38.9%) was the most common metastatic site (Appendix pp6). DFS and OS estimates were 90.4% (89.6–91.1) and 96.6% (96.1–97.0) at 5 years, 79.1% (77.9-80.3) and 89.4% (88.5-90.3) at 10 years, respectively (Appendix pp12). The annual recurrence rate was relatively constant at 3% over time (Fig. 2A). The estimated hazard of recurrence for DFS raised constantly during the first 15 years from diagnosis, with a slope of

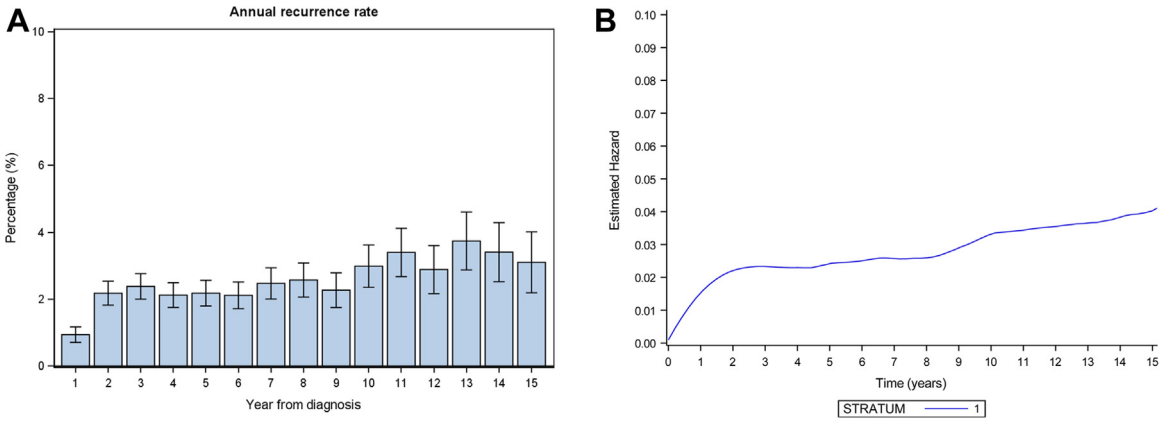

***Fig. 2:* Time-course changes of annual recurrence rates among patients with hormone receptor-positive/HER2-negative early breast cancer (A). Epanechnikov Kernel-Smoothed annual hazards of recurrence for disease-free survival among patients with hormone receptor-positive/HER2-negative early breast cancer (B)**.

the curve more pronounced during the first 2 years from diagnosis and less pronounced after year 7 (Fig. 2B). While the estimate hazard of recurrence for distant DFS was slightly lower compared to the DFS estimate, the time variation was similar (Appendix p14).

Out of 638 patients with distant recurrence as first DFS event, 145 were excluded due to missing information on the date of endocrine treatment completion. Clinicopathological characteristics of excluded and included patients are reported in the Appendix (pp7–8). Median mOS (computed from the date of distant relapse to death) was 3.9 years (IQR 1.7–8.4) for the 145 excluded patients and 3.2 years (IQR 1.5–6.0) for the 493 included patients (stratified log-rank p = 0.07).

Among the 493 patients with a distant relapse as first DFS event and available data on adjuvant endocrine therapy completion, 72 (14.6%), 207 (42.0%) and 214 (43.4%) were classified in the primary endocrine resistant, secondary endocrine resistant and endocrine sensitive cohorts, respectively (Fig. 1). The distribution of adjuvant endocrine therapy duration before relapse in the three cohorts is reported in the Appendix p15. As compared to patients in the secondary endocrine resistant and endocrine sensitive cohorts, those in the primary endocrine resistant cohort were significantly more likely to be relatively younger (median age at metastatic diagnosis 61 vs. 62 vs. 65 years, p = 0.008), to have N2/N3 nodal status (59.7% vs. 42.0% vs. 39.3%, p = 0.042), grade 3 tumour (55.6% vs. 35.3% vs. 33.6%, p = 0.011), higher BMI (median BMI 27.8 vs. 26.6 vs. 25.7, p = 0.006), and to receive prior anthracycline- and taxane-based (neo) adjuvant chemotherapy (62.5% vs. 50.7% vs. 43.0%, p = 0.002; Table 1). Type and site of first distant relapse was significantly different between the 3 groups: a higher incidence of visceral relapse and specifically liver metastases were described in the primary endocrine resistant cohort and of non-visceral relapse and specifically bone metastases in the endocrine sensitive cohort (p = 0.005) (Table 1). Clinicopathological characteristics of patients experiencing a distant DFS event as first recurrence according to trial are presented in the Appendix (pp9–10).

Median follow-up from the occurrence of distant relapse was 3.8 years (IQR 1.6–7.5) (Appendix pp4). In patients within the primary endocrine resistant, secondary endocrine resistant and endocrine sensitive cohorts, median mOS was 27.2 (IQR 14.9–50.1), 38.4 (IQR 16.3–66.9) and 43.2 (IQR 20.4–81.8) months, respectively (stratified log rank p = 0.03) (Fig. 3). Results from the log-rank trend test demonstrated a statistically significant trend (stratified log-rank p_{trend} = 0.006). Results of the pairwise comparison indicated a statistically significant survival difference for the comparison of primary endocrine resistant vs. endocrine sensitive (log-rank adjusted p = 0.05), while no difference was observed in the other two comparisons (primary endocrine resistant vs. secondary endocrine resistant adjusted log-rank p = 0.79; secondary endocrine resistant vs. endocrine sensitive adjusted log-rank p = 0.49). The Cox model confirmed a linear trend for the increase in survival across the three groups. In univariate analyses, as compared to patients in the endocrine sensitive cohort, a significantly higher risk of death was observed in those in the primary endocrine resistant (HR 1.64; 95% CI 1.11–2.44) and secondary endocrine resistant (HR 1.24; 95% CI 0.93–1.66) cohorts (p = 0.05). In the multivariate model, the impact of the endocrine resistance/sensitivity classification was slightly reduced (adjusted HR 1.54; 95% CI 1.03–2.30 for primary endocrine resistant and adjusted HR 1.17; 95% CI 0.87–1.56 for secondary endocrine resistant as compared to the endocrine sensitive cohort, p = 0.11) (Appendix pp 11).

Subgroup analyses of mOS are reported in Table 2. The prognostic impact of the endocrine resistance/sensitivity classification was consistently observed in all the analysed subgroups.

In the sensitivity analysis including only complete cases (n = 373), similar results were observed: adjusted HR 1.48; 95% CI 0.94–2.35 for primary endocrine resistant and adjusted HR 1.19; 95% CI 0.86–1.65 for secondary endocrine resistant as compared to the endocrine sensitive cohort (p = 0.24).

Among the 207 and 214 patients classified as secondary endocrine resistant and endocrine sensitive respectively, 17 (8.2%) and 35 (16.4%) were treated with extended adjuvant endocrine therapy. No statistically significant difference in mOS was observed among patients that received standard or extended endocrine therapy duration (Appendix pp 12).

Discussion

This large individual patient-level analysis with long-term follow-up reports prognosis, timing and pattern of recurrence among 6612 patients with hormone receptor-positive/HER2-negative disease included in 4 adjuvant phase III randomized trials. Overall, patients with hormone receptor-positive/HER2-negative disease were characterized by a relatively constant raising in the risk of recurrence over time, being more pronounced in the first 2 years and less pronounced after year 7, with a tendency for higher likelihood of non-visceral and specifically bone relapses. The currently adopted endocrine resistance/sensitivity classification according to international consensus guidelines for advanced breast cancer showed to have prognostic and clinical impact. Patients with primary endocrine resistance tended to be relatively younger, to have more often node positive disease and grade 3 tumour, and to develop more frequently visceral relapses and specifically liver metastases. Primary endocrine resistance was associated with the worst survival outcomes irrespective of patient, tumour, treatment characteristics or type of metastatic

	Primary endocrine resistant cohort (n = 72)	Secondary endocrine resistant cohort (n = 207)	Endocrine sensitive cohort (n = 214)	p
Median age at metastasis, years (range)	61 (33–81)	62 (39–87)	65 (34–89)	0.008
Age				0.053
≤50	8 (11.1%)	25 (12.1%)	22 (10.3%)	
51–64	35 (48.6%)	95 (45.9%)	74 (34.6%)	
≥65	29 (40.3%)	87 (42.0%)	118 (55.1%)	
Menopausal status				0.106
Premenopausal	6 (8.3%)	31 (15.0%)	40 (18.7%)	
Postmenopausal	66 (91.7%)	176 (85.0%)	174 (81.3%)	
Type of surgery				0.087
Breast conserving surgery	35 (48.6%)	128 (61.8%)	115 (53.7%)	
Mastectomy	37 (51.4%)	79 (38.2%)	99 (46.3%)	
Histologic type				0.790
Ductal	50 (69.4%)	158 (76.3%)	162 (75.7%)	
Lobular	18 (25.0%)	38 (18.4%)	40 (18.7%)	
Other	4 (5.6%)	11 (5.3%)	12 (5.6%)	
Tumor size (T)				0.361
pT1	26 (36.1%)	93 (44.9%)	97 (45.3%)	
pT2/3/4	46 (63.9%)	114 (55.1%)	117 (54.7%)	
Nodal status (N)				0.042
N0	11 (15.3%)	37 (17.9%)	43 (20.1%)	
N1	18 (25.0%)	83 (40.1%)	87 (40.7%)	
N2/3	43 (59.7%)	87 (42.0%)	84 (39.3%)	
Tumor grading (G)				0.011
G1	4 (5.6%)	8 (3.9%)	11 (5.1%)	
G2	28 (38.9%)	126 (60.9%)	131 (61.2%)	
G3	40 (55.6%)	73 (35.3%)	72 (33.6%)	
Hormone receptor status				0.146
ER+/PgR+	67 (93.1%)	193 (93.2%)	197 (92.1%)	
ER+/PgR−	5 (6.9%)	14 (6.8%)	12 (5.6%)	
ER−/PgR+	0 (0.0%)	0 (0.0%)	5 (2.3%)	
Treatment received				0.149
Standard	46 (63.9%)	105 (50.7%)	113 (52.8%)	
Experimental	26 (36.1%)	102 (49.3%)	101 (47.2%)	
Average BMI (range)	27.8 (19.5–48.5)	26.6 (16.9–45.3)	25.7 (14.8–41.5)	0.006
BMI				0.055
<25	23 (31.9%)	74 (35.8%)	93 (43.5%)	
25–29.9	21 (29.2%)	78 (37.7%)	73 (34.1%)	
≥30	28 (38.9%)	55 (26.6%)	48 (22.4%)	
Previous (neo) adjuvant chemotherapy and type				0.002
No chemotherapy	15 (20.8%)	34 (16.4%)	28 (13.1%)	
Anthracycline-based	10 (13.9%)	58 (28.0%)	87 (40.7%)	
Anthracycline- and taxane-based	45 (62.5%)	105 (50.7%)	92 (43.0%)	
Taxane-based	2 (2.8%)	8 (3.9%)	3 (1.4%)	
Other	0 (0.0%)	2 (1.0%)	4 (1.9%)	
Adjuvant endocrine therapy				NA
None	0 (0.0%)	0 (0.0%)	27 (12.6%)	
Tamoxifen only	14 (19.4%)	41 (19.8%)	37 (17.3%)	
Aromatase inhibitors	25 (34.7%)	57 (27.5%)	18 (8.4%)	
Tamoxifen → aromatase inhibitors	33 (45.8%)	109 (52.6%)	132 (61.7%)	
Duration of endocrine therapy (months, range)	15.1 (0.1–24.0)	42.9 (2.0–97.6)	60.4 (0.0–100.5)	NA
Type of metastatic presentation				0.005
Non visceral	26 (36.1%)	99 (47.8%)	123 (57.5%)	
Visceral	46 (63.9%)	108 (52.2%)	91 (42.5%)	

(Table 1 continues on next page)

	Primary endocrine resistant cohort (n = 72)	Secondary endocrine resistant cohort (n = 207)	Endocrine sensitive cohort (n = 214)	p
(Continued from previous page)				
Metastatic site				0.003
Brain	6 (8.3%)	14 (6.8%)	8 (3.7%)	
Liver	33 (45.8%)	65 (31.4%)	47 (22.0%)	
Lung	7 (9.7%)	29 (14.0%)	36 (16.8%)	
Bone	25 (34.7%)	81 (39.1%)	100 (46.7%)	
Other	1 (1.4%)	18 (8.7%)	23 (10.8%)	
Study				NA
MIG1	6 (8.3)	17 (8.2)	45 (21.0)	
GIM2	18 (25.0)	51 (24.6)	54 (25.2)	
GIM3	47 (65.3)	99 (47.8)	32 (15.0)	
GIM4	1 (1.4)[a]	40 (19.3)	83 (38.8)	
Year of diagnosis of metastatic disease[b]				0.281
<2003	6 (8.3)	17 (8.2)	27 (12.6)	
≥2003	66 (91.7)	190 (91.8)	187 (87.4)	

Data are n (%). ER, estrogen receptor; PgR, progesterone receptor; BMI, body mass index; NA, not applicable. [a]This patient was not eligible to the trial and she did not receive study treatment. [b]Based on the availability of aromatase inhibitors in Italy.

Table 1: **Clinicopathological characteristics of patients experiencing a distant disease-free survival event as first recurrence and with available data on adjuvant endocrine therapy completion.**

presentation. Differences became smaller between the secondary endocrine resistant and endocrine sensitive cohorts. Therefore, this classification may be considered a valid tool to guide clinical decision-making and to design future endocrine therapy trials in the metastatic setting.

Hormone receptor expression is considered a positive prognostic factor in breast cancer and a predictive marker of response to endocrine therapy.[1,2] In interpreting the survival outcomes observed in the present analysis, it should be considered that most of the included trials were restricted to patients with high-risk features (31.9%, 49.8% and 23.2% of patients had ≥ T2 size, node-positive status and grade 3 tumour, respectively). Moreover, not all the administered treatments in these trials correspond to current practice. Among patients receiving chemotherapy, 19.9% underwent anthracycline only-based regimens. A total of 33.6% of

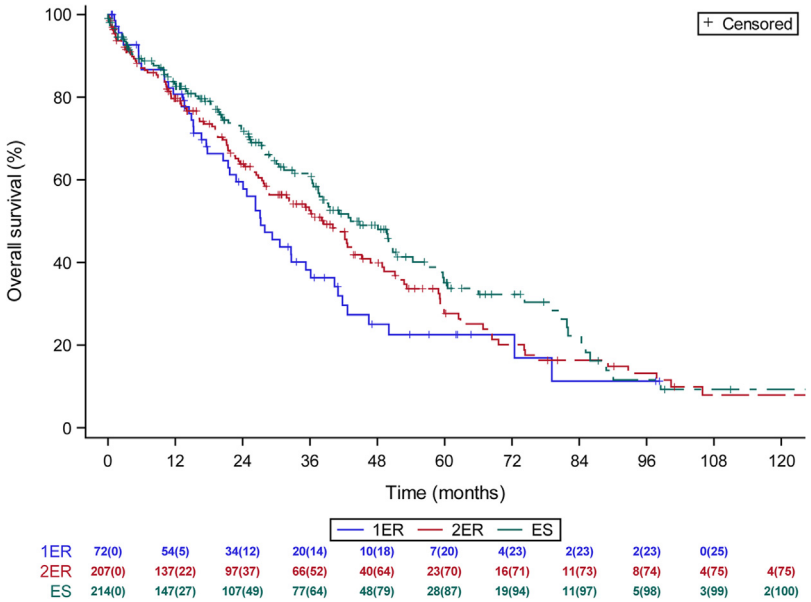

Fig. 3: **Overall survival computed from the date of distant relapse and death from any cause between endocrine sensitive, primary or secondary endocrine resistant cohorts.** 1ER, primary endocrine resistant; 2ER, secondary endocrine resistant; ES, endocrine sensitive.

	Primary endocrine resistant vs. endocrine sensitive HR (95% CI)	Secondary endocrine resistant vs. endocrine sensitive HR (95% CI)	p for interaction
Age, years			0.130
≤50	1.77 (0.71–4.47)	1.13 (0.56–2.29)	
51–64	1.93 (1.12–3.31)	0.97 (0.62–1.51)	
≥65	1.29 (0.70–2.37)	1.66 (1.10–2.50)	
Menopausal status			0.865
Premenopausal	2.06 (0.76–5.58)	1.35 (0.74–2.47)	
Postmenopausal	1.55 (1.01–2.36)	1.22 (0.88–1.68)	
Type of surgery			0.851
Breast conserving surgery	1.70 (0.99–2.91)	1.20 (0.82–1.74)	
Mastectomy	1.58 (0.94–2.64)	1.34 (0.88–2.03)	
Histologic type			0.956
Ductal	1.56 (0.98–2.48)	1.23 (0.89–1.70)	
Lobular	1.92 (0.91–4.05)	1.45 (0.74–2.82)	
Other	1.39 (0.32–5.96)	0.80 (0.19–3.40)	
Tumor size (T)			0.692
pT1	1.55 (0.86–2.78)	1.10 (0.71–1.68)	
pT2/3/4	1.75 (1.07–2.84)	1.39 (0.96–2.01)	
Nodal status (N)			0.748
N0	2.61 (1.00–6.81)	1.33 (0.64–2.80)	
N1	1.54 (0.76–3.11)	1.35 (0.89–2.06)	
N2/3	1.39 (0.84–2.30)	1.08 (0.71–1.64)	
Tumor grading (G)			0.444
G1	1.23 (0.24–6.34)	0.63 (0.17–2.28)	
G2	1.20 (0.68–2.13)	1.21 (0.85–1.73)	
G3	2.22 (1.29–3.83)	1.42 (0.88–2.27)	
Hormone receptor status			0.416
ER+/PgR+	1.53 (1.02–2.32)	1.21 (0.89–1.65)	
ER+/PgR−	3.24 (0.96–10.97)	1.13 (0.45–2.87)	
ER−/PgR+	1.53 (1.02–2.32)	1.21 (0.89–1.65)	
Treatment received			0.532
Standard	1.44 (0.89–2.32)	1.28 (0.88–1.87)	
Experimental	2.04 (1.11–3.75)	1.21 (0.80–1.83)	
BMI			0.459
<25	1.50 (0.81–2.78)	1.06 (0.68–1.66)	
25–29.9	2.51 (1.35–4.64)	1.50 (0.94–2.37)	
≥30	1.16 (0.59–2.30)	1.16 (0.66–2.02)	
Previous (neo) adjuvant chemotherapy and type			0.113
No chemotherapy	2.73 (0.97–7.73)	2.29 (0.93–5.61)	
Anthracycline based	3.41 (1.62–7.15)	1.18 (0.72–1.95)	
Anthracycline and taxane based	1.30 (0.79–2.14)	1.11 (0.75–1.64)	
Taxane based	0.13 (0.01–2.90)	0.24 (0.04–1.29)	
Other	2.73 (0.97–7.73)	0.97 (0.16–5.92)	
Adjuvant endocrine therapy			0.776
None	2.15 (1.00–4.62)	1.39 (0.77–2.49)	
Tamoxifen only	2.15 (1.00–4.62)	1.39 (0.77–2.49)	
Aromatase inhibitors	2.32 (0.84–6.42)	1.37 (0.50–3.73)	
Tamoxifen → aromatase inhibitors	1.32 (0.73–2.36)	1.24 (0.84–1.82)	
Type of metastatic presentation			0.209
Non visceral	1.88 (1.05–3.35)	1.50 (0.99–2.27)	
Visceral	1.28 (0.77–2.11)	0.93 (0.64–1.37)	
Metastatic site			0.235
Brain	1.59 (0.46–5.53)	0.93 (0.32–2.68)	
Liver	0.91 (0.49–1.69)	0.71 (0.43–1.16)	

(Table 2 continues on next page)

	Primary endocrine resistant vs. endocrine sensitive HR (95% CI)	Secondary endocrine resistant vs. endocrine sensitive HR (95% CI)	p for interaction
(Continued from previous page)			
Lung	1.41 (0.49–4.08)	0.93 (0.45–1.94)	
Bone	1.87 (1.03–3.40)	1.43 (0.91–2.24)	
Other	–[a]	1.89 (0.69–5.23)	

Data are n (%). ER, estrogen receptor; PgR, progesterone receptor; BMI, body mass index. [a]Not evaluable as only one patient in the primary endocrine resistant group had "other" metastatic site.

Table 2: **Subgroup analysis of overall survival comparing the primary or secondary endocrine resistant cohorts with the endocrine sensitive cohort (ref).**

premenopausal women received ovarian function suppression as part of adjuvant endocrine therapy. Despite the relatively high-risk population, only 16.4% patients received more than 5 years of adjuvant endocrine therapy. Notably, many patients included in the present analysis would be currently eligible to receive adjuvant abemaciclib.[19] Nevertheless, with this caveat in mind, outcomes can be considered relatively favorable.

Among breast cancer subtypes, hormone receptor-positive disease is characterized by a distinctive clinical behavior in terms of time-dependent and site-specific recurrence patterns consisting in a steady risk of recurrence over time that persist at long-term,[20,21] and a tendency for higher likelihood of bone involvement.[7,8] This clinical behavior is confirmed by the current analysis focusing specifically on patients with hormone receptor-positive disease and known HER2-negative status. These findings further highlight the crucial role of long-term follow-up in the (neo)adjuvant trials including patients with hormone receptor-positive/HER2-negative breast cancer, particularly in those investigating endocrine therapy-based treatments. The major drop in survival outcomes observed between year 5 and 10 should be considered in the context of a low percentage of patients receiving extended adjuvant endocrine therapy, a treatment that is currently known to provide benefit in such a relatively high-risk population.[22] Finally, these results may have potential implications in the survivorship trajectory of patients with hormone receptor-positive/HER2-negative breast cancer.[23] While there is no apparent benefit of intensive follow-up strategies particularly in the case of luminal-like disease,[24,25] the present findings should be considered in the design of trials investigating personalized surveillance plans in this specific population.

The time elapsing between adjuvant endocrine therapy completion and relapse is currently considered the key factor for the expert opinion-based endocrine resistance/sensitivity classification currently adopted by international consensus guidelines.[10–12] This concept has been clearly shown in the recent studies investigating endocrine therapy plus CDK4/6 inhibition in which this classification was used as key eligibility criteria and/or stratification factor.[26–28] The present analysis demonstrates that this definition has a clinical and prognostic value. Several biological features have been elucidated over the past years as mechanisms of endocrine therapy resistance.[29] The present analysis shows that also some clinico-pathological features may be associated to endocrine resistance or sensitivity as currently defined. Specifically, relatively younger age, node-positive disease and grade 3 tumour were factors more commonly observed in patients with endocrine resistance disease. Being known prognostic factors in early hormone receptor-positive/HER2-negative breast cancer,[30,31] endocrine resistance according to the current definition could represent also a proxy for higher risk of disease recurrence. The larger number of patients with endocrine resistance disease that received anthracycline- and taxane-based (neo) adjuvant chemotherapy may also be an indirect consequence of their higher risk of recurrence. Interestingly, patients with endocrine resistance disease had also higher BMI with 38.9% of those in the primary endocrine resistance cohort that were obese. These findings are in line with a potential impact of BMI on the efficacy of endocrine therapy.[32]

Patients with endocrine resistant or endocrine sensitive disease are also characterized by different site-specific recurrence patterns with visceral relapses and specifically liver metastases more commonly observed in patients within the primary endocrine resistance cohort. Organ-specific signatures of relapse in breast cancer have been previously identified[33–36]; however, the mechanisms behind site specificity in patients with hormone receptor-positive/HER2-negative disease and at what extent they are influenced by the timing to relapse need to be further investigated. Based on the present findings, primary endocrine resistance may be considered a marker of increased risk of recurrence and not per se of lack of sensitivity to endocrine therapy; hence, as suggested by guidelines also taking into account the current effective targeted therapies available in patients with luminal-like advanced breast cancer, chemotherapy is not the preferred first-line choice in this setting unless in the situation of visceral crisis.[10–12]

Importantly, the currently adopted endocrine resistance/sensitivity classification has prognostic value with median mOS ranging from 27.2 months to 43.2 months between the primary endocrine resistant and endocrine sensitive cohorts. Our analysis for trend showing that mOS appears to improve with an increase in the time elapsing between adjuvant endocrine therapy

completion and relapse may support the expert opinion-based hypothesis that endocrine resistance is a continuum.[10] The prognostic impact of such classification was consistently observed in the multivariable analysis and irrespective of patient, tumour, adjuvant treatment characteristics or type of metastatic presentation. Hence, besides clinical differences at the time of relapse between the three cohorts, endocrine resistance (both primary and, at a lower extent, also secondary) remains an independent poor prognostic factor. Considering the different prognosis and the known risk of attrition bias in the advanced setting,[37,38] particular attention should be paid to patients with endocrine resistant disease in the choice of the optimal first-line treatment and in the proper sequencing of subsequent lines.

Among study limitations, it should be acknowledged that this analysis was not preplanned in the protocols of the original trials and the power of the performed statistical analyses was not prespecified. Out of 6612 patients randomized in the four included trials, for the present analysis testing the value of the prognostic and clinical impact of the endocrine resistance/sensitivity classification, only 493 were eligible of whom 72 in the primary endocrine resistant cohort. Moreover, some adjuvant treatments that were administered do not fully represent the standard clinical practice. Particularly, despite the high-risk population, the unavailability of adjuvant abemaciclib, the low percentage of patients receiving extended adjuvant endocrine therapy and the low uptake of ovarian function suppression among premenopausal women might impact the results. In addition, the heterogeneity between trial population might have affected the timing of the distant relapse and thus the probability of being classified as having primary endocrine resistant, secondary endocrine resistant or endocrine sensitive disease. Hormone receptor and HER2 status were assessed by local laboratories; genomic tests were not available. Finally, no information on the treatments administered in the advanced setting was collected in the trials.

Nevertheless, major strengths of this analysis are that the included population derives from 4 large phase III adjuvant studies and that patients were followed over a long period of time according to trial criteria.

In conclusion, the present large analysis of 4 adjuvant phase III randomized trials with long-term follow-up showed that patients with hormone receptor-positive/HER2-negative disease are characterized by a distinctive clinical behavior in terms of time-dependent and site-specific recurrence patterns. Moreover, this analysis provides evidence that the currently adopted endocrine resistance/sensitivity classification according to international consensus guidelines for advanced breast cancer has prognostic and clinical impact supporting its use in guiding clinical decision-making and in the design of future endocrine therapy trials in the metastatic setting.

Contributors

ML, EB, LB and LDM designed the study and analysed, interpreted and collected the data; ML and EB wrote and approved the final report; ML, EB, LB, EdA and LDM contributed to data analysis and interpretation; ML and EB contributed to writing the manuscript; ML and LDM obtained funding and supervised the study; all the authors contributed to data collection, critical revision of the manuscript and material support.

Data sharing statement

All of the individual participant data collected during the study, after de-identification, are already shared with Early Breast Cancer Trialists' Cooperative Group.

Individual participant data that underlies the results reported in this article, after de-identification (text, tables, figures and appendix) will be available for further sharing. Data will be available beginning 9 months and ending 5 years following article publication. Data will be shared with researchers who provide a methodologically sound proposal. The types of analyses allowed will be those able to achieve aims in the approved proposal. Proposal should be directed to matteo.lambertini@unige.it.

Declaration of interests

ML reports advisory role for Roche, Lilly, Novartis, Astrazeneca, Pfizer, Seagen, Gilead, MSD and Exact Sciences; speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, and Takeda; travel Grants from Gilead outside the submitted work. EB reports research grant (to the Institution) from Gilead Science. SDP reports honoraria from Roche, Novartis, Pfizer, Celgene, Eli Lilly, AstraZeneca, Clovis, Seagen, Daichii Sankyo, and MSD outside the submitted work. MDL reports personal fees from Pfizer, Novartis, Roche, AstraZeneca, Eli Lilly, MSD, Daiichi-Sankyo, GSK, Sanofi, Celtrion, Organon and Seagen, outside the submitted work. MM reports consulting fees/honoraria and participation on Advisory Board from Roche, Novartis, Lilly, Pfizer, MSD, Gilead, Seagen, Astra Zeneca, Gentili outside the submitted work. FM reports consultancy fees from Roche, Astra Zeneca, Daiichi Sankyo, SeaGen, MSD, Eli Lilly, Pierre Fabre, Novartis; travel Grants from Roche outside the submitted work. AFr reports advisory role for Roche, Astrazeneca, Lilly, Novartis, Seagen, Daiichi Sankyo, Gilead outside the submitted work. AT reports honoraria from Novartis, Pfizer, Lilly, Roche; travel/accommodation expenses from Roche, AstraZeneca, Gentili, Pfizer outside the submitted work. ST reports consultant fee for Incyte MSD, Roche, Merck, AStrazeneca outside the submitted work. RC reports consultant fees for Novartis, Lilly, Roche, MSD, Gilead, Daiichi Sankyo, AstraZeneca outside the submitted work. CDA reports consulting/advisory role for Roche, AstraZeneca, Lilly, GSK, Novartis, Pfizer, Seagen; speaker honoraria from Novartis, Pfizer, Lilly; research funding to the Institution: Novartis, Daiichi Sankyo; travel/accommodation expenses from Roche, AstraZeneca, Lilly, GSK, Novartis, Celgene, Pfizer outside the submitted work. EA reports consultancy fees/honoraria from Eli Lilly, Sandoz; travel grants from Novartis, Roche, Eli Lilly, Genetic, Istituto Gentili outside the submitted work. EdA reports honoraria and/or advisory board from Roche/GNE, Novartis, Seattle Genetics, Zodiac, Libbs and Pierre Fabre; Travel grants from Roche/GNE and GSK/Novartis; research grant to his institution from Roche/GNE, Astra-Zeneca, GSK/Novartis and Servier. FP reports participation on Advisory Board from AstraZeneca; consultancy fees/honoraria from Eli Lilly, and Novartis; travel grants from Daichii Sankyo, and Gilead outside the submitted work. LDM reports grants or contracts from Eli Lilly, Novartis, Roche, Daiichi Sankyo, and Seagan; fees/honoraria from Roche, Novartis, Pfizer, Eli Lilly, AstraZeneca, MSD, Seagen, Gilead, Pierre Fabre, Eisai, Exact Sciences, and Ipsen; support for attending meetings or travel from Roche, Pfizer, and Eisai; participation on a Data Safety Monitoring Board or Advisory Board from Novartis, Roche, Eli Lilly, Pfizer, Daiichi Sankyo, Exact Sciences, Gilead, Pierre Fabre, Eisai, and AstraZeneca outside the submitted work.

All other authors declare no competing interests.

Acknowledgements

The authors thank patients, physicians, nurses, and trial coordinators who participated in the trials. We acknowledge Giovanni Cucchiara and

Carlo Panzano of Clinical Research Technology, Salerno, Italy, for clinical record online management.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101931.

References

1 Harbeck N, Gnant M. Breast cancer. *Lancet*. 2017;389:1134–1150.
2 Waks AG, Winer EP. Breast cancer treatment: a Review. *JAMA*. 2019;321:288–300.
3 Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;378:771–784.
4 Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Dowsett M, Forbes JF, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386:1341–1352.
5 Pan H, Gray R, Braybrooke J, et al. 20-Year risks of breast-cancer recurrence after stopping endocrine therapy at 5 Years. *N Engl J Med*. 2017;377:1836–1846.
6 Pedersen RN, Esen BÖ, Mellemkjær L, et al. The incidence of breast cancer recurrence 10-32 Years after primary diagnosis. *J Natl Cancer Inst*. 2022;114:391–399.
7 Kimura M, Yanagita Y, Fujisawa T, Koida T. Study of time-course changes in annual recurrence rates for breast cancer: data analysis of 2,209 patients for 10 years post-surgery. *Breast Cancer Res Treat*. 2007;106:407–411.
8 Metzger-Filho O, Sun Z, Viale G, et al. Patterns of Recurrence and outcome according to breast cancer subtypes in lymph node-negative disease: results from international breast cancer study group trials VIII and IX. *J Clin Oncol*. 2013;31:3083–3090.
9 Lambertini M, Campbell C, Gelber RD, et al. Dissecting the effect of hormone receptor status in patients with HER2-positive early breast cancer: exploratory analysis from the ALTTO (BIG 2-06) randomized clinical trial. *Breast Cancer Res Treat*. 2019;177:103–114.
10 Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. 2020;31:1623–1649.
11 Burstein HJ, Somerfield MR, Barton DL, et al. Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO guideline update. *J Clin Oncol*. 2021;39:3959–3977.
12 Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol*. 2021;32:1475–1495.
13 Seidman AD, Bordeleau L, Fehrenbacher L, et al. National cancer institute breast cancer steering committee working group report on meaningful and appropriate end points for clinical trials in metastatic breast cancer. *J Clin Oncol*. 2018;36:3259–3268.
14 Blondeaux E, Lambertini M, Michelotti A, et al. Dose-dense adjuvant chemotherapy in early breast cancer patients: 15-year results of the Phase 3 Mammella InterGruppo (MIG)-1 study. *Br J Cancer*. 2020;122:1611–1617.
15 Del Mastro L, Poggio F, Blondeaux E, et al. Fluorouracil and dose-dense adjuvant chemotherapy in patients with early-stage breast cancer (GIM2): end-of-study results from a randomised, phase 3 trial. *Lancet Oncol*. 2022;23:1571–1582.
16 De Placido S, Gallo C, De Laurentiis M, et al. Adjuvant anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, in endocrine-sensitive breast cancer (FATA-GIM3): a randomised, phase 3 trial. *Lancet Oncol*. 2018;19:474–485.
17 Del Mastro L, Mansutti M, Bisagni G, et al. Extended therapy with letrozole as adjuvant treatment of postmenopausal patients with early-stage breast cancer: a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22:1458–1467.
18 Tolaney SM, Garrett-Mayer E, White J, et al. Updated standardized definitions for efficacy end points (STEEP) in adjuvant breast cancer clinical trials: STEEP version 2.0. *J Clin Oncol*. 2021;39:2720–2731.
19 Harbeck N, Rastogi P, Martin M, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. *Ann Oncol*. 2021;32:1571–1581.
20 Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. *J Clin Oncol*. 1996;14:2738–2746.
21 Cossetti RJD, Tyldesley SK, Speers CH, Zheng Y, Gelmon KA. Comparison of breast cancer recurrence and outcome patterns between patients treated from 1986 to 1992 and from 2004 to 2008. *J Clin Oncol*. 2015;33:65–73.
22 Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol*. 2019;37:423–438.
23 Vaz-Luis I, Masiero M, Cavaletti G, et al. ESMO expert consensus statements on cancer survivorship: promoting high-quality survivorship care and research in Europe. *Ann Oncol*. 2022;33:1119–1133.
24 Moschetti I, Cinquini M, Lambertini M, Levaggi A, Liberati A. Follow-up strategies for women treated for early breast cancer. *Cochrane Database Syst Rev*. 2016;2016(5):CD001768.
25 Schumacher JR, Neuman HB, Yu M, et al. Surveillance imaging vs symptomatic recurrence detection and survival in stage II-III breast cancer (AFT-01). *J Natl Cancer Inst*. 2022;114(10):djac131.
26 Gao JJ, Cheng J, Bloomquist E, et al. CDK4/6 inhibitor treatment for patients with hormone receptor-positive, HER2-negative, advanced or metastatic breast cancer: a US Food and Drug Administration pooled analysis. *Lancet Oncol*. 2020;21:250–260.
27 Schettini F, Giudici F, Giuliano M, et al. Overall survival of CDK4/6-inhibitor-based treatments in clinically relevant subgroups of metastatic breast cancer: systematic Review and meta-analysis. *J Natl Cancer Inst*. 2020;112:1089–1097.
28 Gao JJ, Cheng J, Prowell TM, et al. Overall survival in patients with hormone receptor-positive, HER2-negative, advanced or metastatic breast cancer treated with a cyclin-dependent kinase 4/6 inhibitor plus fulvestrant: a US Food and Drug Administration pooled analysis. *Lancet Oncol*. 2021;22:1573–1581.
29 Hanker AB, Sudhan DR, Arteaga CL. Overcoming endocrine resistance in breast cancer. *Cancer Cell*. 2020;37:496–513.
30 Partridge AH, Hughes ME, Warner ET, et al. Subtype-dependent relationship between Young age at diagnosis and breast cancer survival. *J Clin Oncol*. 2016;34:3308–3314.
31 Nguyen D, Yu J, Reinhold WC, Yang SX. Association of independent prognostic factors and treatment modality with survival and recurrence outcomes in breast cancer. *JAMA Netw Open*. 2020;3:e207213.
32 Jiralerspong S, Goodwin PJ. Obesity and breast cancer prognosis: evidence, challenges, and opportunities. *J Clin Oncol*. 2016;34:4203–4216.
33 Kang Y, Siegel PM, Shu W, et al. A multigenic program mediating breast cancer metastasis to bone. *Cancer Cell*. 2003;3:537–549.
34 Minn AJ, Gupta GP, Siegel PM, et al. Genes that mediate breast cancer metastasis to lung. *Nature*. 2005;436:518–524.
35 Bos PD, Zhang XH-F, Nadal C, et al. Genes that mediate breast cancer metastasis to the brain. *Nature*. 2009;459:1005–1009.
36 Klein A, Olendrowitz C, Schmutzler R, et al. Identification of brain- and bone-specific breast cancer metastasis genes. *Cancer Lett*. 2009;276:212–220.
37 Seah DSE, Luis IV, Macrae E, et al. Use and duration of chemotherapy in patients with metastatic breast cancer according to tumor subtype and line of therapy. *J Natl Compr Cancer Netw*. 2014;12:71–80.
38 Nuzzolese I, Montemurro F. Attrition in metastatic breast cancer: a metric to be reported in randomised clinical trials? *Lancet Oncol*. 2020;21:21–24.