European Journal of Cancer 245 (2026) 116937

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Original research

Chemotherapy type and survival in young *BRCA1/2* carriers with HER2-negative early breast cancer

Rinat Bernstein-Molho [a,1], Tal Sella [b,1], Virginia Delucchi [c], Florence Coussy [d], Hee Jeong Kim [e], Sabine Linn [f], Antonio Di Meglio [g], Katarzyna Pogoda [h], Ava Kwong [i,j,k], Elisa Agostinetto [l], Jyoti Bajpai [m], Yannick Van Herck [n], Alberta Ferrari [o], Judith Balmana [p], Halle C.F. Moore [q], Fedro A. Peccatori [r], Ann H. Partridge [s], Melina Winocur [t], Tiphaine Renaud [u], Christine Rousset-Jablonski [v], Jeong Eon Lee [w], Angela Toss [x,y], Shani Paluch-Shimon [z], Stephanie M. Wong [aa], Alexios Matikas [ab], Cynthia Villarreal-Garza [ac], Claudio Vernieri [ad,ae], Minna Lee [af], Deniz Can Guven [ag], Wanda Cui [ah,ai], Kathryn J. Ruddy [aj], Maria Vittoria Dieci [ak,al], Robert Fruscio [am,an], Laura De Marchis [ao,ap], Zoe Kemp [aq], Pedro A. Meireles [ar], Maria Grazia Razeti [as], Maria Del Pilar Diz [at], Shelley E. Hwang [au], Fabio Puglisi [av,aw], Florian Clatot [ax], Rinat Yerushalmi [ay], Natalia Cichowska-Cwalinska [az], Alessandra Chirco [ba], Carmine De Angelis [bb,bc], Eva Blondeaux [c,*,2], Matteo Lambertini [bd,be,2]

[a] *Susanne Levy Gertner Oncogenetics Unit, The Danek Gertner Institute of Human Genetics, Sheba Medical Center, Tel Hashomer, affiliated to Gray Faculty of Medicine and Health Sciences, Tel Aviv University, Tel Aviv, Israel*
[b] *Institute of Oncology, Sheba Medical Center, Tel Hashomer, Israel*
[c] *AOM - IRCCS Ospedale Policlinico San Martino, U.O. Epidemiologia Clinica - Clinical Trial Unit, Genova, Italy*
[d] *Department of Medical Oncology, Institut Curie - Institut of Women's Cancers, Paris, France*
[e] *Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*
[f] *Departments of Molecular Pathology and Medical Oncology, Netherlands Cancer Institute (NKI), Amsterdam, the Netherlands*
[g] *Cancer Survivorship Team; Université Paris-Saclay, UVSQ, Gustave Roussy, Inserm, CESP, F-94800, Villejuif, France*
[h] *Department of Breast Cancer and Reconstructive Surgery, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[i] *Hong Kong Hereditary and High Risk Breast and Ovarian Cancer Family Registry, Hong Kong, China*
[j] *Cancer Genetics Centre and Breast Surgery Centre, Hong Kong Sanatorium and Hospital, Hong Kong, China*
[k] *Breast Surgery Division, Department of Surgery, Queen Mary and Tung Wah Hospital and and The University of Hong Kong-ShenZhen Hospital, Hong Kong, China*
[l] *Université libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B), Institut Jules Bordet, Service de Oncologie, Rue Meylemeersch 90, 1070 Bruxelles, Belgium*
[m] *Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India*
[n] *Department of Surgical Oncology, University Hospitals Leuven, KU Leuven, Leuven, Belgium*
[o] *Breast Cancer Centre; Hereditary Tumors Surgery Unit, Surgical Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[p] *Hereditary Cancer Genetics Unit, Medical oncology Department, Vall dHebron University Hospital, Vall dHebron Institute of Oncology (VHIO), Barcelona, Spain*
[q] *Department of Medical Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland (OH), USA*
[r] *Gynecologic Oncology Department, European Institute of Oncology IRCCS, Milan, Italy*
[s] *Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA*
[t] *SUMA (Grupo Cooperativo Argentino para el Estudio y la Investigación del Cáncer de Mama), Argentina*
[u] *Cancer Genetics Unit, Bergonie Institute, Bordeaux, France*
[v] *Department of Surgery, Leon Berard Cancer Center, Lyon, France*
[w] *Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea*
[x] *Division of Oncology, Department of Oncology and Haematology, Azienda Ospedaliero- Universitaria di Modena, Modena, Italy*
[y] *Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy*
[z] *Sharett institute of oncology, Hadassah University Hospital & Faculty of Medicine, Hebrew University, Jerusalem, Israel*
[aa] *Stroll Cancer Prevention Centre, Jewish General Hospital, and McGill University Medical School, Montreal, Canada*
[ab] *Department of Oncology/Pathology, Karolinska Institute and Breast Center, Karolinska University Hospital, Stockholm, Sweden*
[ac] *Breast Cancer Center, Hospital Zambrano Hellion - TecSalud, Tecnologico de Monterrey, Monterrey, Mexico*

* Correspondence to: Clinical Trial Unit, U.O. Epidemiologia Clinica, AOM - IRCCS Ospedale Policlinico San Martino, Largo Rosanna Benzi 10, Genova 16132, Italy.
E-mail address: eva.blondeaux@aomliguria.it (E. Blondeaux).

https://doi.org/10.1016/j.ejca.2026.116937
Received 16 April 2026; Received in revised form 14 June 2026; Accepted 6 July 2026
Available online 14 July 2026

[ad] Medical Oncology Department, Breast Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[ae] Oncology and Hematology-Oncology Department, University of Milan, Milan, Italy
[af] Memorial Sloan Kettering Cancer Center MSKCC, New York (NY), USA
[ag] Hacettepe University Cancer Institute, Ankara, Turkey
[ah] Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
[ai] Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Victoria, Australia
[aj] Department of Oncology, Mayo Clinic Comprehensive Cancer Center, Rochester (MN), USA
[ak] Dipartimento di Scienze Chirurgiche, Oncologiche e Gastroenterologiche, Università di Padova, Padova, Italy
[al] Oncologia 2, Istituto Oncologico Veneto IRCCS, via Gattamelata 64, 35128 Padova, Italy
[am] UO Gynecology, Department of Medicine and Surgery, IRCCS San Gerardo dei Tintori, Monza, Italy
[an] Department of Medicine and Surgery, University of Milan Bicocca, Milan, Italy
[ao] Division of Medical Oncology, Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome, Rome, Italy
[ap] Oncological Unit Department of Hematology,Oncology and Pathology, Umberto 1 Policlinico di Roma, Rome, Italy
[aq] Breast Medical Oncology and Cancer Genetics Units, Royal Marsden Hospital, London, United Kingdom
[ar] Medical Oncology Department, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal
[as] Department of Medical Oncology, U.O. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy
[at] Cancer Institute ICESP, Sao Paulo Brazil
[au] Department of Surgery, Duke University, Durham (NC), USA
[av] Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy
[aw] Department of Medicine, University of Udine, Udine, Italy
[ax] Centre Henri Becquerel, Rouen, France
[ay] Davidoff Cancer Center, Rabin Medical Center-Beilinson Hospital, Petah Tikva, Israel, affiliated to Gray Faculty of Medicine and Health Sciences, Tel Aviv University, Tel Aviv, Israel
[az] Department of Oncology and Radiotherapy, Medical University of Gdańsk, and the University Clinical Centre in Gdańsk, Gdańsk, Poland
[ba] SC Oncologia, ASST Papa Giovanni XXIII, Bergamo, Italy
[bb] Clinical and Translational Oncology, Scuola Superiore Meridionale, Naples, Italy
[bc] Istituto Nazionale Tumori Napoli IRCCS "Fondazione Pascale", Naples, Italy
[bd] Department of Internal Medicine and Medical Specialties (DIMI), School of Medicine, University of Genova, Genova, Italy
[be] Academic Medical Oncology Unit, Ente Ospedaliero Ospedali Galliera, Genova, Italy

ARTICLE INFO

Keywords:
BRCA
Early breast cancer
Chemotherapy
Survival outcomes

ABSTRACT

Background: Evidence to guide (neo)adjuvant chemotherapy choices in carriers of germline *BRCA1/BRCA2* pathogenic variants (*BRCA* carriers) with early breast cancer (BC) is limited. We evaluated the association of different chemotherapy regimens with survival outcomes in this population.
Methods: The BRCA BCY Collaboration (NCT03673306) is an international, multicenter, retrospective cohort study of *BRCA* carriers diagnosed with stage I-III BC at age $\leq$ 40 years, between 2000 and 2020. Disease-free survival (DFS) and overall survival (OS) were assessed among patients with HER2-negative disease treated with anthracycline-taxane, anthracycline-no-taxane, or non-anthracycline (neo)adjuvant chemotherapy. The association of platinum use with outcomes was evaluated in triple-negative breast cancer (TNBC).
Results: Among 4200 young *BRCA* carriers from 109 centres who received (neo)adjuvant chemotherapy for HER2-negative BC, 58.7% had TNBC. Median follow-up was 8.1 years (IQR, 4.7–12.6 years). Anthracycline-taxane, anthracycline-no-taxane, and non-anthracycline regimens were used in 74.4%, 19.3%, and 6.3% of patients, respectively. Platinum agents were administered in 19.8% of TNBC cases. After multivariable adjustment, no significant differences in DFS or OS were observed between anthracycline-no-taxane and anthracycline-taxane regimens (DFS adjusted hazard ratio [aHR] 0.88, 95% CI 0.73–1.05; OS aHR 1.20, 95% CI 0.87–1.67) or non-anthracycline regimens (DFS aHR 1.07, 95% CI 0.82–1.38; OS aHR 1.16, 95% CI 0.68–2.0). In TNBC, platinum use was not associated with improved outcomes.
Conclusions: In young *BRCA* carriers with HER2-negative early BC, no statistically significant differences in survival outcomes were detected across different chemotherapy regimens. Our findings may inform future prospective studies evaluating chemotherapy de-escalation strategies in this genetically defined population.

1. Background

Anthracycline/taxane-based polychemotherapy has long been considered the standard of care for high-risk HER2-negative early breast cancer [1]. However, concerns regarding anthracycline-associated toxicity, alongside the emergence of effective alternative cytotoxic agents, have prompted reconsideration of their routine use. A systematic review and meta-analysis of randomized controlled trials evaluating anthracycline omission suggested that, for most patients with HER2-negative early breast cancer (excluding those with higher-risk pN2/3 disease), six cycles of docetaxel/cyclophosphamide were non-inferior to anthracycline/cyclophosphamide-taxane-based chemotherapy in terms of efficacy. Nevertheless, a recent patient-level meta-analysis by the EBCTCG questioned the current trend towards non-anthracycline chemotherapy use by demonstrating a reduction in recurrence rates among patients treated with anthracycline/taxane-based chemotherapy regardless of hormone receptor status, with consistent benefits across all age groups and disease stages [2].

None of the randomized trials comparing various chemotherapy protocols in the EBCTCG meta-analysis [2] specifically evaluated the benefit of these regimens in patients with germline *BRCA1/2* pathogenic/likely pathogenic variants (hereafter referred to as *BRCA* carriers). Emerging evidence shows that germline *BRCA1/2* pathogenic/likely pathogenic variants may influence chemosensitivity patterns across different breast cancer subtypes, with potential implications for treatment optimization. Among patients with hormone receptor-positive breast cancers, *BRCA* carriers represent a minority of the whole population [3], and the potential differential response to chemotherapy in this subgroup has been largely overlooked in clinical trials. However, several recent retrospective analyses suggest increased chemosensitivity

[1] co-first authors
[2] co-last authors

among *BRCA* carriers with hormone receptor-positive disease, as reflected by a larger proportion of patients with higher Oncotype Dx scores [3–5], and higher pathologic complete response (pCR) rates following neoadjuvant chemotherapy. For example, in a cohort from Memorial Sloan Kettering Cancer Center, pCR was achieved in 15.5% of *BRCA* carriers compared with 7.8% of non-carriers ($p < 0.001$) [6]. Similarly, in a cohort from Fondazione Policlinico Universitario Agostino Gemelli IRCCS, the pCR rate was significantly higher in *BRCA* carriers (20.8%) compared with non-carriers (10.9%, $p = 0.044$) [7]. In triple-negative breast cancer (TNBC), although early-phase trials and observational studies showed that the addition of platinum agents to neoadjuvant chemotherapy increases pCR rates [8–12], the addition of carboplatin was not associated with a significantly increased pCR rate specifically among *BRCA* carriers [13]. The unique biology of *BRCA*-associated tumors suggests enhanced susceptibility to DNA-damaging agents due to impaired homologous recombination repair [14,15]; therefore, platinum compounds were expected to exploit this vulnerability by inducing DNA crosslinks that BRCA-impaired cells are unable to effectively repair. For example, in the TBCRC 031 (INFORM) trial, Tung et al. found no significant difference in response rates between single-agent cisplatin and AC in *BRCA* carriers with TNBC [16]. However, the response rate in this trial was numerically lower than that reported by Byrski et al [17], possibly because of the differences in the study populations. On the other hand, in a secondary analysis of the GeparSixto trial, *BRCA* carriers had comparable pCR rates and 3-year survival with and without the addition of platinum to an anthracycline/taxane-based regimen, suggesting that the DNA-damaging effect of carboplatin may be unnecessary in patients with tumors that are already characterized by high sensitivity to anthracycline [18]. Similarly, in a matched cohort substudy from the BrighTNess trial, the use of neoadjuvant carboplatin, with or without veliparib, did not increase the odds of pCR in *BRCA* carriers compared to non-*BRCA* controls [19,20]. Recently presented results of the pooled analysis of the BrighTNess, CALGB 40603, and GeparSixto clinical trials found that the addition of carboplatin significantly improved event-free survival, but not pCR or overall survival (OS) in *BRCA* carriers [21]. These observations raise the question of whether both anthracyclines and platinum agents are necessary to achieve maximal pCR rates in *BRCA* carriers. Despite these mixed data, following the KEYNOTE-522 trial, neoadjuvant regimens combining anthracycline and platinum agents with pembrolizumab are currently favored for stage II-III TNBC, regardless of *BRCA1/2* status [22,23].

Critical questions regarding potential overtreatment of *BRCA* carriers in both the neoadjuvant and adjuvant settings remain unresolved for TNBC and hormone receptor-positive early breast cancer. This analysis evaluated the association of different chemotherapy regimens, in particular the addition of a taxane to anthracycline-based chemotherapy, with the long-term outcomes in young *BRCA* carriers with HER2-negative early breast cancer, as well as the effectiveness of incorporating a platinum agent in patients with TNBC.

2. Methods

The BRCA BCY Collaboration (NCT03673306) is an international, multicenter, retrospective cohort study of *BRCA* carriers diagnosed with breast cancer at ≤ 40 years, between January 2000 and December 2020 [24]. For this analysis, we included patients with stage I-III HER2-negative breast cancer treated with (neo)adjuvant chemotherapy. Patients were excluded if they had de novo metastatic breast cancer, HER2-positive disease, unknown HER2 status or hormone receptor status, unknown type of chemotherapy, or if they had not received (neo) adjuvant chemotherapy. Additionally, patients with unknown uptake of risk-reducing mastectomy (RRM) and/or risk-reducing salpingo-oophorectomy (RRSO) were excluded because of the potential impact of these procedures on clinical outcomes [25].

The primary objective was to evaluate the association between chemotherapy type and survival outcomes in young *BRCA* carriers with HER2-negative stage I-III breast cancer. Three mutually exclusive (neo) adjuvant chemotherapy categories were defined: anthracycline/taxane-based (regimens containing both anthracycline and taxane); anthracycline-no-taxane (anthracycline-containing regimens without taxanes); other non-anthracycline-based regimens (regimens not containing any anthracycline, irrespective of taxane administration). The effectiveness of using a platinum agent (Yes *vs* No) on survival outcomes in TNBC was also evaluated. Detailed chemotherapy regimens and scheduling data (dose-dense vs standard-interval) were not available across participating centers. Disease-free survival (DFS) and OS were the primary endpoints, with time-to-event endpoints defined according to STEEP criteria (version 2) [26].

Clinicopathologic features and survival outcomes were compared by chemotherapy regimens (anthracycline/taxane-based *vs* anthracycline-no-taxane *vs* non-anthracycline-based regimens) and, among patients with TNBC, by platinum use (Yes *vs* No).

Descriptive statistics were used to summarize continuous and categorical variables. Continuous variables were reported as median and interquartile range (IQR), and categorical variables as frequencies and percentages. The number of DFS events per 100 person-years was calculated according to the type of chemotherapy. Associations between comparison groups and clinicopathologic features were analyzed using the chi-square test or Kruskal-Wallis/Wilcoxon rank-sum test, for categorical or continuous variables, as appropriate.

Median follow-up from breast cancer diagnosis in the entire cohort and by treatment groups was estimated using the reverse Kaplan-Meier method. Unadjusted and adjusted Cox models were used to assess associations between treatment groups and survival outcomes. Models included stratification for variables with known prognostic implications that were unbalanced between groups (i.e., country, year of breast cancer diagnosis, tumor size, nodal status, type of breast cancer surgery, setting of systemic therapy, and radiotherapy use), and the uptake of risk-reducing surgeries (RRM and RRSO) as time-dependent covariates. To account for potential immortal time bias related to post-diagnosis genetic testing, two sensitivity analyses were performed: first, adjusted survival models were restricted to patients who underwent genetic testing before or within 6 months of breast cancer diagnosis, and second, adjusted survival models with left truncation at the time of *BRCA* testing were carried out [27]. Survival curves were plotted using the Kaplan–Meier method.

Subgroup analyses were performed by gene (*BRCA1* vs. *BRCA2*), hormone receptor status, and nodal status. To avoid the exclusion of cases with missing data, single imputation using logistic regression under the assumption of a monotone missingness pattern was performed on the covariates included in the survival models.

All statistical analyses were 2-sided, with $p < .05$ considered statistically significant. No adjustment was made for multiple comparisons. Analyses were performed using SAS version 9.4 (SAS Institute Inc).

The Institut Jules Bordet (Brussels, Belgium) functioned as both the coordinating centre and the central ethics committee. Ethical approval was obtained from the relevant local, regional, or national institutional review boards of participating centres whenever required by local regulations.

3. Results

Of 5660 patients from 109 centers worldwide, this analysis included 4200 young *BRCA* carriers who received (neo)adjuvant chemotherapy for HER2-negative breast cancer (Fig. 1); 2467 (58.7%) patients had TNBC, 2864 (68.2%) were *BRCA1* carriers, and 2036 (48.5%) had node-positive disease (Table 1). The median age at breast cancer diagnosis was 35 years (IQR 31–37). Anthracycline/taxane-based, anthracycline-no-taxane, and non-anthracycline regimens were used in 3126 (74.4%), 809 (19.3%), and 265 (6.3%) patients, respectively. Platinum agents were used in 488 (19.8%) patients with TNBC, of whom 82.6% received them with anthracycline/taxane-based, 8.0% with anthracycline-no-

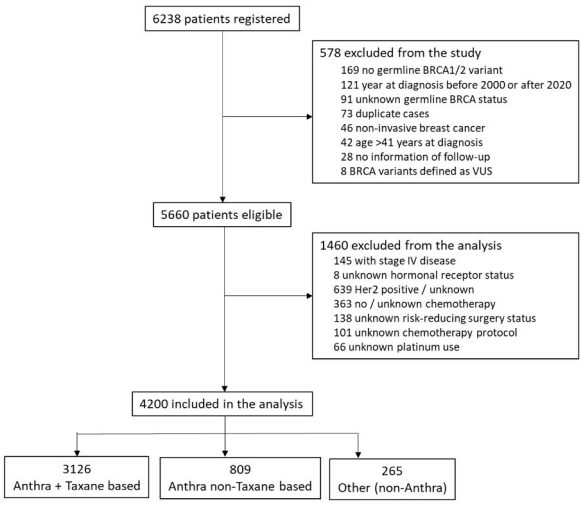

Fig. 1. STROBE diagram.

taxane, and 9.4% with non-anthracycline regimens.

Chemotherapy regimens were associated with geographic region, year of diagnosis, disease stage, type of primary breast surgery, treatment setting (adjuvant vs neoadjuvant), and radiotherapy use, but not with patient age, the specific *BRCA* gene, or hormone receptor status (Table 1). Use of anthracycline/taxane-based regimens increased from 32% in 2000–2004 to 89% in 2017–2020, whereas anthracycline-no-taxane regimens declined from 58% to 5.4% over the same period. Patients receiving anthracycline/taxane combinations had higher-stage disease, larger tumors (T3/4: 16.8% vs 7.7% with anthracycline-no-taxane) and greater nodal involvement (N+: 55.4% vs 27.9%). In contrast, anthracycline-no-taxane and non-anthracycline regimens were more often used in patients with smaller or node-negative tumors (N0: 70.0% with anthracycline-no-taxane; 67.9% with non-anthracycline). Treatment setting was also strongly associated with regimen choice: anthracycline/taxane-based regimens predominated in the neoadjuvant setting (52.3%), whereas anthracycline-no-taxane and non-anthracycline regimens were more commonly administered in the adjuvant setting (77.5% and 73.6%, respectively). Radiotherapy and the type of breast surgery showed similar patterns of variation, while age, *BRCA* gene (*BRCA1* vs *BRCA2*), and hormone receptor status were not associated with the selection of the specific chemotherapy regimen. Among patients with TNBC, platinum was used in 19.8% of cases overall, but was more frequently incorporated into non-anthracycline (33.6%) than anthracycline/taxane-based (21.8%) or anthracycline-no-taxane regimens (8.1%).

Among patients with TNBC, platinum use was uncommon in earlier years, administered to fewer than 10% of patients diagnosed before 2012, and increased over time, rising to 26% in 2013–2016 and reaching 39.7% in 2017–2020. Patients receiving platinum presented with larger tumors (T3/4: 21.9% vs 13.5%) and more advanced nodal disease (N2/3: 14.3% vs 8.9%), more often received neoadjuvant therapy (78.3% vs 41.3%), and were more likely to undergo mastectomy (76.0% vs 51.5%) (Table 2).

The median follow-up was 8.1 years (IQR, 4.7–12.6 years). In the primary analysis, no significant differences in DFS were observed between anthracycline/taxane-based and anthracycline-no-taxane regimens (adjusted hazard ratio [aHR] 0.88, 95% CI 0.73–1.05) or between non-anthracycline and anthracycline-no-taxane regimens (aHR 1.07, 95% CI 0.82–1.38), Fig. 2A, Table 3. Number and type of DFS events per 100 person-years are presented in Table S1. Similarly, no differences in OS were observed between anthracycline/taxane-based and anthracycline-no-taxane regimens (aHR 1.20, 95% CI 0.87–1.67) or between non-anthracycline and anthracycline-no-taxane regimens (aHR 1.16, 95% CI 0.68–2.10) (Fig. 2B, Table 4).

When restricting to patients who underwent *BRCA1/2* testing within 6 months of breast cancer diagnosis, the aHR was 0.86 (95% CI 0.57–1.28) for DFS and was 0.77 (95% CI 0.38–1.55) for OS when comparing anthracycline/taxane-based with anthracycline-no-taxane regimens. For non-anthracycline vs anthracycline-no-taxane regimens, the aHR for DFS was 1.65 (95% CI 0.96–2.85) and for OS was 0.97 (95% CI 0.35–2.68), Tables 3, 4. To further account for delayed entry, Cox models with left truncation at the time of *BRCA* testing were run, showing similar direction of effect despite shift in the point estimate (Tables 3, 4). Subgroup analyses showed no statistically significant interaction between treatment effect and the predefined subgroups, including specific gene, hormone receptor status, and nodal status (all p for interaction > 0.05). Among patients with hormone receptor-positive breast cancer, non-anthracycline regimens were associated with worse OS when compared to anthracycline-no-taxane chemotherapy (aHR 2.37, 95% CI 1.08–5.21; Tables S2, S3). In patients with N2/3 disease, the difference between non-anthracycline and anthracycline-no-taxane regimens was numerically large but accompanied by wide confidence intervals: aHR 3.41 (95% CI 1.47–7.94) for DFS, aHR 2.82 (95% CI 0.86–9.26) for OS (Tables S2, S3). Non-anthracycline regimens, compared with anthracycline-no-taxane regimens, were associated with inferior OS in *BRCA2* carriers (aHR 2.99, 95% CI 1.13–7.91), but not in *BRCA1* carriers (aHR 0.82, 95% CI 0.44–1.56), Tables S2, S3.

Among patients with TNBC, the use of platinum was not associated with significant differences in DFS (aHR 0.89, 95% CI 0.67–1.19) or OS (aHR 0.78, 95% CI 0.48–1.28) (Fig. 3). Number and type of DFS events per 100 person-years in TNBC patients according to platinum use are presented in Table S4. Results of sensitivity analyses were consistent with the results of the primary analyses (Tables S5, S6). Similarly, subgroup analyses revealed no statistically significant interaction between treatment effect and predefined subgroups, including *BRCA* gene (*BRCA1* vs *BRCA2*) or nodal status (Tables S7, S8).

4. Discussion

Although (neo)adjuvant anthracycline/taxane-based chemotherapy regimens are a well-established standard for high-risk HER2-negative early breast cancer, their incremental benefit in young germline *BRCA1/2* carriers remains uncertain. In this context, our international, multicenter, retrospective cohort study enrolling more than 4000 young *BRCA* carriers treated over 20 years, provides the most extensive real-world assessment to date of (neo)adjuvant chemotherapy strategies in this population.

Results of our study provide several clinically relevant observations. First, we did not observe statistically significant differences in DFS or OS across chemotherapy regimens, including when comparing anthracycline-based regimens with and without a taxane, an association that has not been specifically examined in randomized trials limited to *BRCA* carriers. However, these results should not be interpreted as evidence of equivalence or as support for de-escalation. Second, among *BRCA* carriers with TNBC, the use of platinum derivatives was not associated with statistically significant differences in adjusted analyses. These data should be interpreted cautiously because they do not directly address platinum's role in contemporary multimodality regimens incorporating immunotherapy, while KEYNOTE−522 enrolled unselected stage II/III TNBC patients rather than *BRCA* carriers specifically [23]. Given the retrospective design and relatively limited platinum exposure during the study period (19.8%, increasing from <10% pre−2012 to 39.7% 2017–2020), these findings should be regarded as hypothesis-generating. Prior studies evaluating tumor sensitivity to chemotherapy among *BRCA* carriers have yielded heterogeneous results, were largely limited to neoadjuvant endpoints such as pCR [13, 16–19], and rarely reported survival outcomes specifically in *BRCA* carriers. In this large real-world study, we focused on long-term survival outcomes and found no statistically significant evidence that taxanes or platinum derivatives improved survival when combined with

Table 1
Baseline characteristics – Overall cohort.

	Overall cohort (N = 4200)	Anhtra + Taxane based (N = 3126)	Anthra-no-Taxane (N = 809)	Other (No Anthra) (N = 265)	p-value
Patient characteristics					
Region, No (%)					< 0.001
Center/South America	247 (5.9)	205 (6.6)	23 (2.8)	19 (7.2)	
Australia/Oceania	76 (1.8)	50 (1.6)	19 (2.4)	7 (2.6)	
North Europe	644 (15.3)	466 (14.9)	161 (19.9)	17 (6.4)	
East Europe	275 (6.6)	216 (6.9)	49 (6.1)	10 (3.8)	
North America	466 (11.1)	379 (12.1)	48 (5.9)	39 (14.8)	
South Europe	1602 (38.1)	1243 (39.8)	279 (34.5)	80 (30.2)	
Asia	883 (21.0)	562 (18.0)	229 (28.3)	92 (34.7)	
Africa	7 (0.2)	5 (0.2)	1 (0.1)	1 (0.4)	
Year of diagnosis, No (%)					< 0.001
2000–2004	416 (9.9)	134 (4.3)	243 (30.0)	39 (14.7)	
2005–2008	690 (16.4)	422 (13.5)	229 (28.3)	39 (14.7)	
2009–2012	943 (22.5)	719 (23.0)	163 (20.2)	61 (23.0)	
2013–2016	1046 (24.9)	866 (27.7)	114 (14.1)	66 (24.9)	
2017–2020	1105 (26.3)	985 (31.5)	60 (7.4)	60 (22.6)	
Median age at diagnosis, years (IQR)	35 (31−37)	35 (31−37)	34 (31−37)	35 (32−38)	0.161
Age at diagnosis, years (%)					0.529
≤ 30	902 (21.5)	681 (21.8)	173 (21.4)	48 (18.1)	
31–35	1551 (36.9)	1147 (36.7)	308 (38.1)	96 (36.2)	
36–40	1747 (41.6)	1298 (41.5)	328 (40.5)	121 (45.7)	
Specific BRCA gene, No (%)					0.451
BRCA1	2864 (68.2)	2131 (68.2)	557 (68.9)	176 (66.4)	
BRCA2	1309 (31.2)	977 (31.3)	244 (30.2)	88 (33.2)	
BRCA1 and *BRCA2*	23 (0.6)	14 (0.5)	8 (1.0)	1 (0.4)	
unknown if *BRCA1* or *BRCA2*	4 (0.1)	4 (0.1)	0	0	
Tumor characteristics					
Tumor size at diagnosis, No (%)					< 0.001
T1	1414 (33.7)	949 (30.4)	334 (41.3)	131 (49.4)	
T2	2055 (48.9)	1581 (50.6)	387 (47.8)	87 (32.8)	
T3/4	616 (14.7)	525 (16.8)	62 (7.7)	29 (10.9)	
Unknown	115 (2.7)	71 (2.3)	26 (3.2)	18 (6.8)	
Nodal status at diagnosis, No (%)					< 0.001
N0	2098 (50.0)	1352 (43.3)	566 (70.0)	180 (67.9)	
N1	1491 (35.5)	1261 (40.3)	165 (20.4)	65 (24.5)	
N2/3	545 (13.0)	472 (15.1)	61 (7.5)	12 (4.5)	
Unknown	66 (1.6)	41 (1.3)	17 (2.1)	8 (3.0)	
Hormone receptor status, No (%)					0.055
Negative	2467 (58.7)	1850 (59.2)	480 (59.3)	137 (51.7)	
Positive	1733 (41.3)	1276 (40.8)	329 (40.7)	128 (48.3)	
Primary breast surgery, *No (%)*					< 0.001
None	11 (0.3)	8 (0.3)	2 (0.3)	1 (0.4)	
Conservative	1630 (38.8)	1050 (33.6)	460 (56.9)	120 (45.3)	
Mastectomy	2537 (60.4)	2050 (65.6)	346 (42.8)	141 (53.2)	
Unknown	22 (0.5)	18 (0.6)	1 (0.1)	3 (1.1)	
Setting of treatment, *No (%)*					< 0.001
Neoadjuvant	1887 (44.9)	1636 (52.3)	182 (22.5)	69 (26.0)	
Adjuvant	2309 (55.0)	1487 (47.6)	627 (77.5)	195 (73.6)	
Unknown	4 (0.1)	3 (0.1)	0	1 (0.4)	
Platinum use (in TNBC), *No (%)*					< 0.001
No Platinum	1979 (80.2)	1447 (78.2)	441 (91.9)	91 (66.4)	
Yes Platinum	488 (19.8)	403 (21.8)	39 (8.1)	46 (33.6)	
Endocrine therapy use (in HR positive), *No (%)*					0.707
No	77 (4.4)	53 (4.1)	19 (5.8)	5 (3.9)	
Yes	1648 (95.1)	1217 (95.4)	309 (93.9)	122 (95.3)	
Unknown	8 (0.5)	6 (0.5)	1 (0.3)	1 (0.8)	
Radiotherapy use, *No (%)*					< 0.001
No	1301 (31.0)	945 (30.2)	248 (30.7)	108 (40.7)	
Yes	2863 (68.2)	2152 (68.8)	559 (69.1)	152 (57.4)	
Unknown	36 (0.9)	29 (0.9)	2 (0.2)	5 (1.9)	

Anthra, Anthracyclines; IQR, interquartile range; TNBC, triple-negative breast cancer; HR, hormone receptor.

anthracycline-based chemotherapy. The predominance of non-distant events may partly explain the limited ability to detect differences in OS. The absence of a statistically significant survival benefit may suggest that the incremental value of additional DNA-damaging agents is smaller than often assumed in some BRCA-deficient tumors, suggesting that these findings warrant prospective evaluation in future studies, while not supporting conclusions about treatment de-escalation in these young, genetically defined patients. Results of this study should be interpreted in the context of an evolving therapeutic landscape for early breast cancer, which is characterized by the introduction of several novel systemic agents into routine care, which were rarely used before 2020 in this cohort. This historical cohort largely precedes the routine incorporation of PARP inhibitors and immune checkpoint inhibitors, which are now established components of care for selected *BRCA* carriers. The absence of these agents in our cohort limits direct applicability to current practice, where chemotherapy backbone selection occurs within multimodality regimens. The increasing use of immune checkpoint inhibitors in patients with high-risk *BRCA*-mutated TNBC, and

Table 2
Baseline characteristics – Triple-negative cohort.

	Overall cohort (N = 2467)	No Platinum (N = 1979)	Yes Platinum (N = 488)	p-value
Patient characteristics				
Region, No (%)				< 0.001
Center/South America	156 (6.3)	116 (5.9)	40 (8.2)	
Australia/Oceania	41 (1.7)	39 (2.0)	2 (0.4)	
North Europe	388 (15.7)	276 (14.0)	112 (23.0)	
East Europe	171 (6.9)	122 (6.2)	49 (10.0)	
North America	272 (11.0)	231 (11.7)	41 (8.4)	
South Europe	921 (37.3)	791 (40.0)	130 (26.6)	
Asia	516 (20.9)	404 (20.4)	112 (23.0)	
Africa	2 (0.1)	0	2 (0.4)	
Year of diagnosis, No (%)				< 0.001
2000–2004	250 (10.1)	237 (12.0)	13 (2.7)	
2005–2008	436 (17.7)	412 (20.8)	24 (4.9)	
2009–2012	546 (22.1)	502 (25.4)	44 (9.0)	
2013–2016	610 (24.7)	451 (22.8)	159 (32.6)	
2017–2020	625 (25.3)	377 (19.1)	248 (50.8)	
Median age at diagnosis, years (IQR)	34 (31–37)	34 (31–37)	35 (31–37)	0.061
Age at diagnosis, years (%)				0.210
≤ 30	588 (23.8)	486 (24.6)	102 (20.9)	
31–35	887 (36.0)	709 (35.8)	178 (36.5)	
36–40	992 (40.2)	784 (39.6)	208 (42.6)	
Specific BRCA gene, No (%)				0.844
BRCA1	2229 (90.4)	1791 (90.5)	438 (89.8)	
BRCA2	218 (8.8)	172 (8.7)	46 (9.4)	
BRCA1 and *BRCA2*	18 (0.7)	14 (0.7)	4 (0.8)	
unknown if *BRCA1* or *BRCA2*	2 (0.1)	2 (0.1)	0	
Tumor characteristics				
Tumor size at diagnosis, No (%)				< 0.001
T1	821 (33.3)	714 (36.1)	107 (21.9)	
T2	1271 (51.5)	997 (50.4)	274 (56.2)	
T3/4	375 (15.2)	268 (13.5)	107 (21.9)	
Nodal status at diagnosis, No (%)				< 0.001
N0	1422 (57.6)	1166 (58.9)	256 (52.5)	
N1	798 (32.4)	636 (32.1)	162 (33.2)	
N2/3	247 (10.0)	177 (8.9)	70 (14.3)	
Primary breast surgery, *No (%)*				< 0.001
None	9 (0.4)	7 (0.3)	2 (0.4)	
Conservative	1068 (43.3)	953 (48.2)	115 (23.6)	
Mastectomy	1390 (56.3)	1019 (51.5)	371 (76.0)	
Setting of treatment, *No (%)*				< 0.001
Neoadjuvant	1200 (48.6)	818 (41.3)	382 (78.3)	
Adjuvant	1267 (51.4)	1161 (58.7)	106 (21.7)	
Radiotherapy use, *No (%)*				0.004
No	806 (32.7)	620 (31.3)	186 (38.1)	
Yes	1661 (67.3)	1359 (68.7)	302 (61.9)	

IQR, interquartile range.

PARP inhibitors in appropriate settings, underscores the need to re-evaluate chemotherapy backbones in both the neoadjuvant and adjuvant settings, but prospective studies are needed before conclusions about de-escalation can be drawn. For instance, the phase 2 NeoPACT study evaluating a neoadjuvant anthracycline-free regimen of pembrolizumab plus carboplatin and docetaxel, although not limited to *BRCA* carriers, suggested that anthracycline-free chemoimmunotherapy may be feasible in TNBC, and warrants further study in randomized trials [28]. In the phase II NEOTALA trial, which investigated neoadjuvant talazoparib in *BRCA* carriers with TNBC, the observed pCR rate of 46% was encouraging, although cross-trial comparisons with anthracycline- and taxane-based regimens should be interpreted cautiously [29]. Since pCR after neoadjuvant treatments increasingly informs post-neoadjuvant treatment decisions, including eligibility for adjuvant Olaparib [30], our findings highlight the ongoing challenge of balancing short-term response endpoints and long-term outcomes when selecting chemotherapy backbones for *BRCA* carriers. However, because this study did not evaluate toxicity, quality of life, and was not designed to test formal non-inferiority, it cannot be used to conclude that taxane or platinum omission is appropriate. Recent findings by Felsheim et al further underscore the need to distinguish between pathologic response and long-term survival outcomes [21]. In this context, emerging data from the OlympiaN phase II trial further support the exploration of PARP inhibitor–based neoadjuvant strategies. In that study, neoadjuvant olaparib, administered alone or in combination with durvalumab, achieved high pCR rates (68% and 80%, respectively) in patients with early-stage *BRCA*-associated, HER2-negative, estrogen receptor-negative or estrogen receptor-low breast cancer [31]. While these results are preliminary and derived from abstract-level data, they reinforce the hypothesis that biomarker-driven, anthracycline- and taxane-sparing regimens may represent potential neoadjuvant alternatives for selected *BRCA* carriers and merit further validation in randomized trials. In hormone receptor–positive *BRCA* carriers, CDK4/6 inhibitors may now also be incorporated into the management of high-risk disease [32]. A key remaining challenge is determining how to best integrate and sequence available therapies, particularly since, beyond PARP inhibitors, neither pembrolizumab nor CDK4/6 inhibitors have been specifically evaluated in *BRCA* carriers [33]. In this context, the more clinically relevant question in hormone receptor-positive *BRCA* carriers may be whether chemotherapy can be omitted entirely in selected patients, rather than whether one cytotoxic component should be removed from a chemotherapy backbone. Genomic assays such as Oncotype DX, Mammaprint, etc., may help identify such low-risk subsets, while preserving endocrine-based and targeted approaches. However, no large prospective *BRCA*-specific trial has yet formally tested whether the same score cut-offs (e.g., RS ≤ 25) rule out chemotherapy benefit in *BRCA* carriers, so current use in this subpopulation is extrapolated from the general hormone receptor-positive population [34]. We suggest this as another important area for future prospective trials. Importantly, although *BRCA* carriers are often considered a distinct subset of breast cancer patients, they remain a biologically heterogeneous group, as reflected by variability in pCR rates and clinical outcomes across studies. This underscores the need for ongoing molecular and genomic profiling to enable more personalized, risk-adapted treatment strategies.

Despite large sample size and international scope, residual confounding cannot be entirely excluded, and several biases inherent to retrospective data must be acknowledged. The relatively limited use of platinum and anthracycline-no-taxane regimens in earlier years of the study period may have reduced power to detect small but clinically meaningful subgroup differences between anthracycline-based and non-anthracycline regimens. The lack of detailed chemotherapy regimens (especially in the non-anthracycline category) and scheduling information (dose-dense vs standard-interval regimens) represent an additional source of residual heterogeneity that may have contributed to the observed treatment effects. In addition, standard multivariable adjustment cannot fully eliminate confounding by indication, whereby patients with more advanced disease at baseline may be more likely to receive more intensive regimens (higher stage/nodal status in anthracycline/taxane recipients). Furthermore, unmeasured confounders (performance status, comorbidities, physician preference) remain. The mixed neoadjuvant/adjuvant design and 20-year accrual spanning secular improvements (in diagnostic imaging, pathology, surgical techniques, radiotherapy quality, and supportive care) further limit the interpretation. Therefore, residual confounding cannot be excluded despite adjustment for measured covariates. The subgroup analyses

Table 3
Association of chemotherapy type with DFS.

	Unadjusted HR (95%CI)	p-value	Adjusted* HR (95%CI)	p-value	Adjusted* HR (95%CI) pts with *BRCA* test before/at diagnosis	p-value	Adjusted* HR (95%CI) accounting for delayed entry at the time of *BRCA* testing	p-value
Type CT		0.030		0.203		0.033		0.003
Anthra only	Ref.		Ref.		Ref.		Ref.	
Anthra + Taxane	0.90		0.88		0.86		0.92	
	(0.80–1.01)		(0.73–1.05)		(0.57–1.28)		(0.72–1.18)	
Others (No Anthra)	1.11		1.07		1.65		1.61	
	(0.91–1.36)		(0.82–1.38)		(0.96–2.85)		(0.15–2.26)	

Anthra, Anthracyclines; CT, chemotherapy; DFS, disease-free survival; HR, Hazard ratio; Ref, reference protocol.
*Stratified for geographical region, year of diagnosis, tumor size, nodal status, BC surgery, therapy setting, and radiotherapy. Adjusted for RRM and RRSO (time-dependent).

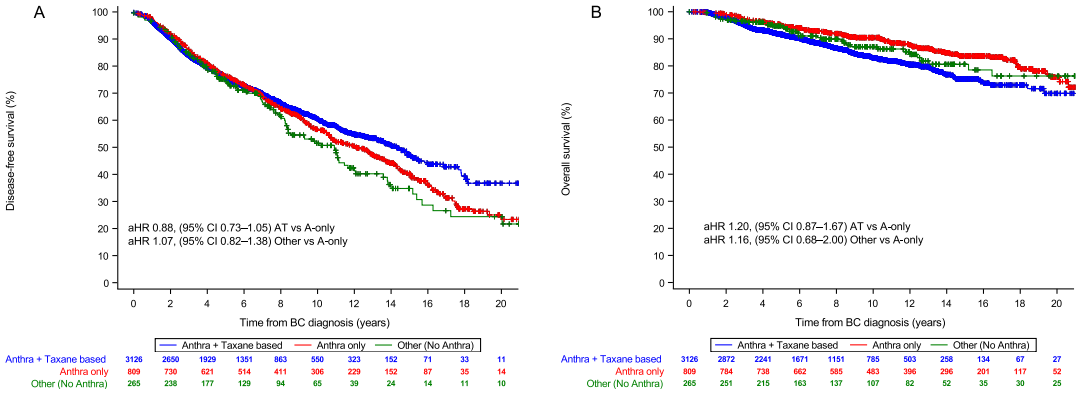

Fig. 2. Survival curves by treatment arms.

Table 4
Association of chemotherapy type with OS.

	Unadjusted HR (95%CI)	p-value	Adjusted* HR (95%CI)	p-value	Adjusted* HR (95%CI) pts with *BRCA* test before/at diagnosis	p-value	Adjusted* HR (95%CI) accounting for delayed entry at the time of *BRCA* testing)	p-value
Type CT		< 0.001		0.546		0.717		0.809
Anthra only	Ref.		Ref.		Ref.		Ref.	
Anthra + Taxane	1.58		1.20		0.77		0.99	
	(1.27–1.95)		(0.87–1.67)		(0.38–1.55)		(0.69–1.43)	
Others (No Anthra)	1.15		1.16		0.97		1.19	
	(0.78–1.70)		(0.68–2.00)		(0.35–2.68)		(0.67–2.10)	

Anthra, Anthracyclines; CT, chemotherapy; OS, overall survival; HR, Hazard ratio; Ref, reference protocol.
*Stratified for geographical region, year of diagnosis, tumor size, nodal status, BC surgery, therapy setting, and radiotherapy. Adjusted for RRM and RRSO (time-dependent).

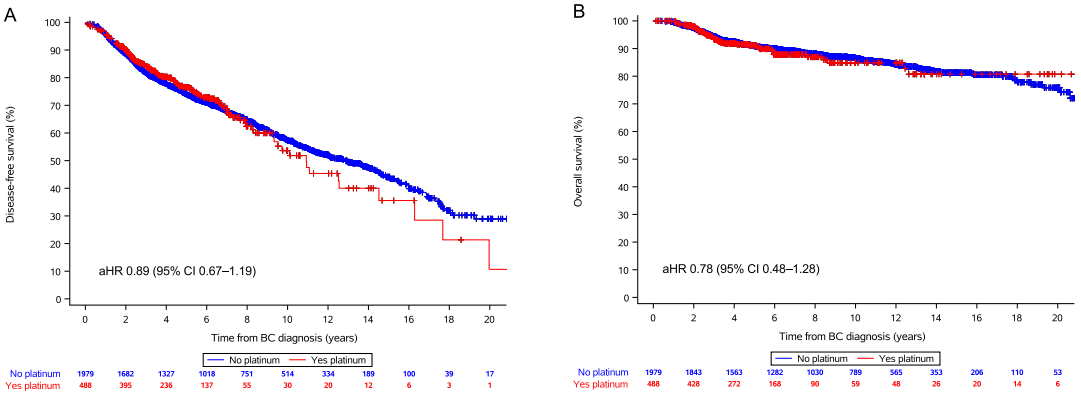

Fig. 3. Survival curves in patients with TNBC by platinum use. aHR,adjusted hazard ratio; A, anthracycline-based regimens; T, taxanes.

were exploratory, limited by multiplicity and wide confidence intervals, and not intended to establish definitive treatment-effect heterogeneity; any observed subgroup signals therefore warrant cautious interpretation and should be confirmed in prospective studies before clinical inference is made. The timing of genetic testing may have introduced lead-time or selection bias, as patients had to survive long enough to undergo testing. However, very early tumor recurrences (within 6 months from diagnosis) are unlikely to have been influenced by chemotherapy type, and this potential bias may have been at least partly similar across treatment groups. Accordingly, the results of the sensitivity analysis restricted to patients tested at or before diagnosis should also be interpreted with appropriate caution.

In summary, no statistically significant differences in survival outcomes were detected across chemotherapy regimens in *BRCA* carriers with early HER2-negative breast cancer. In particular, this retrospective cohort did not show a clear long-term survival advantage from adding taxanes or platinum derivatives to anthracycline-based regimens. These findings should be interpreted as hypothesis-generating and do not support conclusions regarding treatment equivalence or routine de-escalation. Reducing treatment-related toxicity is particularly relevant in *BRCA* carriers, who are often younger at diagnosis and at elevated lifetime risk of second malignancies, infertility, and other therapy-related comorbidities [35]. Future prospective trials should evaluate whether reduced chemotherapy intensity improves toxicity and quality of life while maintaining oncologic outcomes.

CRediT authorship contribution statement

Tal Sella: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation. **Stephanie M. Wong:** Writing – review & editing. **Zoe Kemp:** Writing – review & editing. **Shani Paluch-Shimon:** Writing – review & editing. **Laura De Marchis:** Writing – review & editing. **Florence Coussy:** Writing – review & editing. **Cynthia Villarreal-Garza:** Writing – review & editing. **Maria Grazia Razeti:** Writing – review & editing. **Virginia Delucchi:** Writing – review & editing, Validation, Methodology, Formal analysis, Data curation. **Alexios Matikas:** Writing – review & editing. **Pedro A. Meireles:** Writing – review & editing. **Sabine Linn:** Writing – review & editing. **Minna Lee:** Writing – review & editing. **Shelley E. Hwang:** Writing – review & editing. **Hee Jeong Kim:** Writing – review & editing. **Claudio Vernieri:** Writing – review & editing. **Maria Del Pilar Diz:** Writing – review & editing. **Katarzyna Pogoda:** Writing – review & editing. **Wanda Cui:** Writing – review & editing. **Florian Clatot:** Writing – review & editing. **Antonio Di Meglio:** Writing – review & editing. **Deniz Can Guven:** Writing – review & editing. **Fabio Puglisi:** Writing – review & editing. **Elisa Agostinetto:** Writing – review & editing. **Ava Kwong:** Writing – review & editing. **Kathryn J. Ruddy:** Writing – review & editing. **Jyoti Bajpai:** Writing – review & editing. **Rinat Yerushalmi:** Writing – review & editing. **Alessandra Chirco:** Writing – review & editing. **Natalia Cichowska-Cwalinska:** Writing – review & editing. **Alberta Ferrari:** Writing – review & editing. **Eva Blondeaux:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation. **Yannick Van Herck:** Writing – review & editing. **Carmine De Angelis:** Writing – review & editing. **Halle C.F. Moore:** Writing – review & editing. **Judith Balmana:** Writing – review & editing. **Matteo Lambertini:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation. **Ann H. Partridge:** Writing – review & editing. **Fedro A. Peccatori:** Writing – review & editing. **Tiphaine Renaud:** Writing – review & editing. **Melina Winocur:** Writing – review & editing. **Jeong Eon Lee:** Writing – review & editing. **Christine Rousset-Jablonski:** Writing – review & editing. **Rinat Bernstein-Molho:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Angela Toss:** Writing – review & editing. **Robert Fruscio:** Writing – review & editing. **Maria Vittoria Dieci:** Writing – review & editing.

Funding

The study was partly supported by the Italian Association for Cancer Research (AIRC grant MFAG 2020 ID 24698). M.L. received support from the European Society for Medical Oncology (ESMO) for a translational research fellowship at the Institut Jules Bordet in Brussels, Belgium, at the time this study was initiated. H.J.K. receives support from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant HC20C0135). A.H.P. receives support from the Breast Cancer Research Foundation and Susan G. Komen. Data collection for most Australian participants was through the kConFab Follow-Up Study with support from Cancer Australia and the National Breast Cancer Foundation (PdCCRS 1100868), Cancer Australia (809195), the Australian National Breast Cancer Foundation (IF 17), the Australian National Health and Medical Research Council (454508, 288704, and 145684), the US National Institutes of Health (1RO1CA159868), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania, and South Australia, and the Cancer Foundation of Western Australia. The funders did not play a role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

Rinat Bernstein-Molho – Travel support - Gilead, Pfizer (institutional).

Tal Sella – Honoraria as a speaker: Stemline, Roche, Lilly, Novartis, AstraZeneca, MSD, Pfizer, Gilead; Advisory board: Roche, Novartis, Pfizer; Travel support: Roche, Gilead, Pfizer, AstraZeneca, Oncotest.

Katarzyna Pogoda - honoraria for consultations, lectures, training activities, participation in clinical trials, and payment of conference fees from AstraZeneca, Gilead, Roche, Novartis, Eli Lilly, Pfizer, MSD, Sandoz, Bayer, Swixx, and Exact Sciences. All disclosed relationships are outside the scope of the submitted work.

Elisa Agostinetto – Advisory role and/or honoraria from Eli Lilly, AstraZeneca, Bayer, Abscint, Gilead, Novartis; research grant to her institution from Gilead BeLux; meeting/travel grants from Novartis, Roche, Eli Lilly, Daiichi Sankyo, AstraZeneca, Abscint, Menarini, Gilead (all outside the submitted work).

Halle C.F. Moore – research funding (institutional): AstraZeneca, Daiichi-Sankyo, Seromix, SeaGen, Pfizer.

Shani Paluch-Shimon - Role in advisory boards/consultancy (to institution): Eli Lilly, Pfizer, Novartis, Roche, Eli Lily, Gilead, Stemline, Astra Zeneca; Honoraria as a speaker (to institution): Eli Lilly, Pfizer, Novartis, Roche, Gilead, Stemline, Astra Zeneca, MSD; Grants (to the Institution): Pfizer; Travel (to the Institution): Roche.

Stephanie M. Wong – Advisory board: AstraZeneca; Honoraria for educational lectures: Merck, AstraZeneca, Novartis.

Alexios Matikas - Speaker (no personal payment): Seagen, Roche, AstraZeneca; Expert testimony (no financial or non-financial compensation): Veracyte, Roche, AstraZeneca; Research funding (paid to institution): MSD, Novartis, Veracyte, AstraZeneca; Advisory Board (no financial or non-financial compensation): Nordic Pharma.

Claudio Vernieri – Role in advisory boards/consultancy: Eli Lilly, Pfizer, Novartis, Roche, Gilead, Menarini Stemline, Astra Zeneca, Daaichi Sankyo; Honoraria as a speaker: Eli Lilly, Pfizer, Novartis, Roche, Gilead, Menarini Stemline, Astra Zeneca, Daaichi Sankyo, MSD, Istituto Gentili, Accademia Nazionale di Medicina; Grants (to the Institution): Roche, Giuliani Foundation, AIRC, AIRC 5x1000, ERC, Astra Zeneca/Daiichi Sankyo.

Maria Vittoria Dieci – Invited Speaker, Personal: AstraZeneca, Daiichi Sankyo, Eli Lilly, Exact Sciences, Menarini-Stemline, Novartis, Roche; Advisory Board, Personal: AstraZeneca, Daiichi Sankyo, Eli lilly, Exact Sciences, Gilead, MSD, Novartis,Seagen; Travel/accommodation: Eli Lilly, Gilead, Roche; Consultancy, Personal: AstraZeneca, Pfizer, Roche; Research grant (institutional): Roche, AstraZeneca.

Maria Grazia Razeti – personal fees from Daiichi-Sankyo, Istituto Gentili; non-financial support from Sophos Biotech.

Natalia Cichowska-Cwalinska – honoraria for lectures/ training/ clinical trials and payment of conference fees from Novartis, AstraZeneca, Gilead, Roche, Syneos Health, all outside the submitted work.

Alessandra Chirco – Honoraria as a speaker: Novartis, AstraZeneca; Travel support: Sophos and Genetics.

Carmine De Angelis - advisory role for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Gilead, Daiichi Sankyo, Menarini, Exact Sciences, and GSK; speaker honoraria from Roche, Lilly, Novartis, AstraZeneca, Pfizer, Gilead, Daiichi Sankyo, Menarini, Exact Sciences, and GSK; Travel Grants from Gilead, Pfizer, Roche; research support (to the Institution) from Novartis, GILEAD and Daiichi Sankyo outside the submitted work.

Eva Blondeaux - Speaker fee from Eli Lilly and Astrazeneca; funding (to the institution) from Gilead Science.

Matteo Lambertini - advisory role for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD, Pierre Fabre, Menarini, Exact Sciences, Nordic Pharma, Bayer; receiving speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Takeda, Ipsen, Menarini, AstraZeneca; receiving travel grants from Gilead, Roche, and Daiichi Sankyo; receiving research funding (to his institution) from Gilead, all outside the submitted work.

Ava Kwong - Financial Interests - AstraZeneca Global, Invited Speaker, Personal, Invited speaker; AstraZeneca Hong Kong Ltd, Invited Speaker, Personal, Invited speaker for a OlympiA LaunchingSymposium; AstraZeneca Hong Kong Ltd, Other, Institutional, Sponsor doctor to attend oversea conference; AstraZeneca Hong Kong Ltd, Invited Speaker, Personal, Invited speaker of the BRCA in Hong Kong Dinner Symposium; Chongqing Haifu Medical Technology Co., Ltd, Invited Speaker, Personal, Invited Speaker; Merck Sharp & Dohme (Asia) Limited, Invited Speaker, Personal, Invited speaker; Merck Sharp & Dohme (Asia) Limited, Invited Speaker, Institutional, Invited speaker; Merck Sharp & Dohme (Asia) Ltd., Other, Personal, Lead a study supported by MSD and act as consultant. Roche Hong Kong, Other, Institutional, Sponsor doctor to attend oversea conference; AstraZeneca, Local PI, Institutional, , Support genetic testing for research; Gilead Sciences Inc., Local PI, Institutional, , Clinical Trials; Merck Sharp & Dohme (Asia) Limited, Local PI, Institutional, , Clinical Trials; Olema Pharmaceuticals Inc, Local PI, Institutional, , Clinical Trials; Roche Hong Kong Limited, Local PI, Institutional, , Clinical TrialsNon-Financial Interests - Hong Kong Hereditary Breast Cancer Family Registry (Charity), Member of Board of Directors, Chairman ofcharitable organization; The Hong Kong Society of Breast Surgeons Limited, Other, Council Member; IceCure Medical Ltd, Other, donation of Probes and IceCure Machine to the instiution.

Fabio Puglisi - Honoraria for advisory boards, activities as a speaker, travel grants, research grants - Astrazeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, Italfarmaco, Menarini, MSD, Novartis, Pierre Fabre, Pfizer, Roche. All disclosed relationships are outside the submitted work.

Research funding - Astrazeneca, Eisai, Roche (institutional).

Angela Toss - Advisory role and/or honoraria from Eli Lilly, AstraZeneca, Gilead, Novartis, Menarini Stemline, Daiichi Sankyo; research grant to her institution from Gilead; meeting/travel grants from Novartis, Daiichi Sankyo, Gilead, Menarini Stemline, AstraZeneca (all outside the submitted work).

Laura De Marchis - Honoraria as speaker: Astra Zeneca , MSD

All other authors have declared no conflicts of interest.

Acknowledgment

The study was presents at the poster session at the ESMO Congress 2025 (Berlin, Germany) on October 20, 2025.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116937.

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