

Clinical Characteristics, Management Strategies, and Survival of High-Risk Early Hormone Receptor-Positive Breast Cancer in Routine French Practice: Insights from the CANTO Cohort☆

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Abstract

Patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer who present with high-risk clinicopathological features face a heightened likelihood of disease recurrence and may benefit from treatment intensification. Using data from the CANcer TOxicities (CANTO; NCT01993498) cohort, we examined real-world patient characteristics, therapeutic approaches, and survival outcomes in this population. Using data prospectively gathered in the CANTO study between 2012 and 2022, we conducted a retrospective evaluation of patients with high-risk hormone receptor-positive breast cancer. High-risk disease was defined by either extensive nodal involvement (≥ 4 positive axillary lymph nodes) or limited nodal involvement (1–3 positive axillary lymph nodes) accompanied by unfavorable tumor features, including a tumor diameter of at least 5 cm or histologic grade 3 (cohort 1). A second high-risk classification was also explored, comprising patients with 1–3 positive axillary lymph nodes and elevated proliferative activity, defined by a Ki-67 index of 20% or higher (cohort 2). Time-to-event outcomes were estimated using Kaplan–Meier survival analyses.

Within the CANTO population, patients classified as having high-risk hormone receptor-positive breast cancer accounted for 15.0% and 19.6% of all HR+ cases according to cohorts 1 and 2, respectively. Among the 1,266 individuals included in cohort 1, nearly half (49.0%) presented with involvement of four or more axillary lymph nodes, while 26.0% had primary tumors measuring at least 5 cm and 57.6% were diagnosed with histologic grade III disease. Most patients exhibited a low comorbidity burden, with 79.9% having a favorable Charlson comorbidity index, and 88.1% were diagnosed at stage II or IIIA. Extensive nodal disease (≥ 10 positive lymph nodes) was observed in 11.8% of cases. Systemic treatment was widely used, with 94.2% of patients receiving (neo)adjuvant chemotherapy. Endocrine therapy was initiated in 97.3% of patients, predominantly aromatase inhibitors; however, treatment was prematurely discontinued in 34.3% of cases, most often due to treatment-related toxicity. Among patients with a minimum follow-up of six years, the estimated 5-year invasive disease-free survival was 79.9% (95% confidence interval [CI], 77.2%–82.4%), and the 5-year distant relapse-free survival reached 83.5% (95% CI, 80.9%–85.7%). This real-world analysis demonstrates that individuals with hormone receptor-positive breast cancer and adverse clinicopathological characteristics experience a substantial risk of early recurrence, even when treated with standard (neo)adjuvant chemotherapy. These findings highlight the urgent need for novel therapeutic strategies for patients at high risk, with particular emphasis on their early integration into the adjuvant treatment setting.

Keywords: High-risk early breast cancer, Adjuvant CDK4/6 inhibitors, Abemaciclib, Real-world data

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Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in women, with roughly 2.3 million new cases each year, and remains a leading cause of cancer-related death, causing around 0.7 million fatalities annually [1]. The most prevalent subtype is hormone receptor-

positive, human epidermal growth factor receptor 2–negative (HR+ HER2–) BC, which accounts for approximately 70% of all cases [2]. Most patients are identified at an early stage, when treatments aim for cure. Standard therapy typically involves surgery followed by endocrine therapy (ET), often in combination with radiotherapy and chemotherapy.

Patients with high-risk features—such as large tumor size, extensive lymph node (LN) involvement, high histologic grade, or Ki-67 $\geq 20\%$ —have an increased likelihood of recurrence, according to data from the Early Breast Cancer Trialists' Collaborative Group [3]. International guidelines recommend that these patients receive adjuvant chemotherapy followed by extended ET; nevertheless, nearly 20% still experience relapse within the first ten years after diagnosis [4–10].

The monarchE trial established a new treatment benchmark for HR+ BC patients at high risk of recurrence, using criteria that combine anatomical factors (tumor size and nodal burden) with biological markers such as histologic grade [11–13]. In this study, adding the CDK4/6 inhibitor abemaciclib for two years to standard therapy improved four-year invasive disease-free survival (IDFS) by 6.4% (85.8% versus 79.4%), leading to regulatory approval by the FDA and EMA [11, 13, 14]. Similarly, the NATALEE trial evaluated the addition of ribociclib for three years to standard treatment in stage II–III disease and demonstrated a hazard ratio of 0.75 (95% confidence interval [CI], 0.62–0.91), with absolute improvements in three-year IDFS of 3.0% and 3.2%, although longer follow-up is required to define its long-term role [15, 16].

While randomized controlled trials like monarchE and NATALEE provide the highest level of evidence due to their rigorous design and control of bias, their strict inclusion criteria may exclude patients with poorer performance status or significant comorbidities, limiting their applicability to routine clinical practice [17–22]. Real-world data (RWD) analyses help address this gap by offering insights into treatment patterns, patient characteristics, and outcomes outside of clinical trials. The current study uses RWD from the prospective CANcer TOxicities (CANTO) cohort to examine clinicopathologic features and survival outcomes of patients with high-risk HR+ BC [23].

Materials and Methods

Data source

Data for this analysis were derived from the CANTO study (NCT01993498), a prospective observational cohort initiated on March 20, 2012, which continues to enroll patients and collects extensive information on breast cancer (BC) biology, treatments, toxicities, serum samples, and patient-reported outcomes [23]. Eligible participants are adults (≥ 18 years) with a new diagnosis of invasive BC, staged cT0–cT3 and cN0–3, who have not received prior BC therapy.

Participants undergo evaluations at multiple time points: at diagnosis, following completion of primary treatment (surgery, chemotherapy, or radiotherapy, whichever occurred last), at the start of endocrine therapy when indicated, and at years 1, 3, and 5 post-initial post-primary treatment assessment. Extended follow-up assessments are conducted at years 6, 7, 8, and 10. At each visit, detailed information is collected on clinical status, treatment (including adherence monitored by trained research nurses), toxicities, patient-reported outcomes, and biological specimens [23].

The CANTO study is overseen by UNICANCER, the French national network of cancer centers. Regulatory and ethical approvals were obtained (ID-RCB: 2011-A01095-36, 11-039), and all participants provided written informed consent [23]. The present analysis adheres to the Declaration of Helsinki and follows the ESMO Guidance for Reporting Oncology Real-World Evidence (GROW) [24].

Variable definitions and patient selection

At the time of the latest data cut (September 5, 2022), 11,342 women with newly diagnosed early breast cancer were recorded in the CANTO database. For this study, we restricted the analysis to those with hormone receptor–positive, HER2–negative (HR+ HER2–) disease. Patients in cohort 1 were classified as high-risk non-metastatic HR+ BC according to the monarchE trial criteria: either four or more positive axillary lymph nodes, or one to three positive lymph nodes accompanied by a tumor size of ≥ 5 cm or a histologic grade of 3 [12]. A second high-risk group (cohort 2) included patients with one to three positive axillary lymph nodes and a Ki-67 index of $\geq 20\%$. Individuals who did not meet these high-risk definitions were considered low/intermediate risk and were included only in survival analyses.

Demographic, tumor, and treatment data were extracted from the CANTO dataset. Adherence to endocrine therapy (ET) was evaluated using the medical possession ratio (MPR), with patients considered adherent if MPR

was $\geq 80\%$. The MPR was calculated by dividing the total number of days supplied of a given ET medication by the total number of days in the observation period.

Statistical analyses

The findings from these analyses were presented both separately including and excluding the Ki-67 criterion. Baseline characteristics and treatment patterns were summarized using frequencies and proportions for relevant categorical variables. Survival outcomes were calculated according to the Standardized Definitions for Efficacy End Points (STEEP) version 2.0 for invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS)[25]. The IDFS endpoint encompassed invasive ipsilateral, regional, or distant recurrences; contralateral breast cancer; second primary non-breast malignancies; and death from any cause. DRFS was defined as the interval from enrollment to the first distant recurrence or death from any cause. Five-year survival estimates were derived using the Kaplan–Meier method, and a secondary log-rank test was performed to compare outcomes between patients with high-risk and low-/intermediate-risk breast cancer. To guarantee sufficient follow-up duration, the survival analyses were restricted to patients enrolled in the CANTO cohort at least 6 years prior to data extraction. Patients who remained alive and event-free at their last follow-up were censored at the date of that visit. All statistical procedures were performed with SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Results and Discussion

Between 2012 and 2022, 11,342 women were enrolled in the CANTO study, of whom 8,428 (74.3%) had HR+ breast cancer (BC) (Figure 1). Among HR+/HER2-negative patients, 1,266 individuals (15.0%) were classified as high risk without using the Ki-67 criterion, corresponding to 11% of the total CANTO cohort (Table 1). The median age in both cohorts was 54.3 years, and nearly half of the patients (47.2%) were premenopausal.

High-risk status was attributed to 617 patients (49.0%) due to involvement of four or more lymph nodes (Table 2). Tumors measuring ≥ 5 cm were present in 327 patients (26.0%), and 727 patients (57.6%) had grade III tumors (Table 2). Of the 1,122 patients with Charlson comorbidity index data, 897 (79.9%) had a score of 0. The most frequent comorbidities were articular (51.7%), endocrine (32.9%), cardiovascular (32.6%), and renal (9.5%) (Table 1). Hypertension was the leading comorbidity (24.1%), with heart rhythm disorders observed in 4.3% of patients. Among endocrine conditions, hypercholesterolemia was most common (13.0%), followed by diabetes (7.4%) and hypothyroidism (7.4%). Articular issues mainly included osteoarthritis (14.1%) and bone fractures (16.7%). Germline BRCA1/2 mutations were detected in 11.5%–11.6% of high-risk BC patients, specifically 3.5% with BRCA1 and 8.0% with BRCA2 mutations.

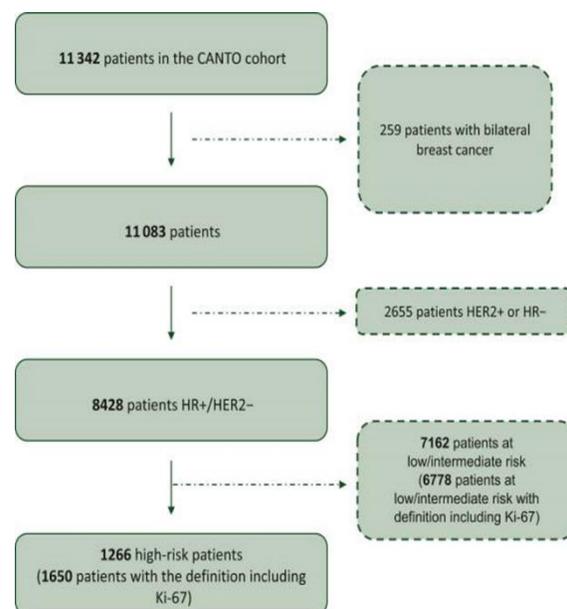


Figure 1. CONSORT diagram.

HR, hormone receptor; HER2, human epidermal growth factor receptor 2; CONSORT, Consolidated Standards of Reporting Trials.

Table 1. Patient and tumor profiles in high-risk HR-positive breast cancer within the CANTO cohort

Characteristic	CANTO High Risk without Ki-67 (N=1266)	CANTO High Risk with Ki-67 (N=1650)
Age - Median (range)	54.3 (22.2-87.5)	54.3 (22.2-87.5)
Age - <65 years	1019 (80.6%)	1330 (80.7%)
Age - ≥ 65 years	245 (19.4%)	318 (19.3%)
Age - Missing	2	2

Gender - Female	1266 (100%)	1650 (100%)
Gender - Male	0 (0%)	0 (0%)
Menopausal status - Premenopausal	589 (47.2%)	760 (46.9%)
Menopausal status - Postmenopausal	659 (52.8%)	861 (53.1%)
Menopausal status - Missing	18	29
Germline BRCA mutations - BRCA1	12 (3.5%)	14 (3.3%)
Germline BRCA mutations - BRCA2	27 (8.0%)	35 (8.3%)
Germline BRCA mutations - Missing	927	1228
Charlson comorbidity index - 0	897 (79.9%)	1171 (79.6%)
Charlson comorbidity index - 1-2	196 (17.5%)	260 (17.7%)
Charlson comorbidity index - ≥ 3	29 (2.6%)	40 (2.7%)
Charlson comorbidity index - Missing	144	179
ECOG performance status - 0	1085 (94.8%)	1416 (95.1%)
ECOG performance status - 1	54 (4.7%)	66 (4.4%)
ECOG performance status - 2	6 (0.5%)	7 (0.5%)
ECOG performance status - Missing	121	161
Comorbidities - Cardiovascular	413 (32.6%)	545 (33.0%)
Comorbidities - Renal	120 (9.5%)	159 (9.6%)
Comorbidities - Endocrine	417 (32.9%)	561 (34.0%)
Comorbidities - Osteoarticular	654 (51.7%)	851 (51.6%)

W/, with; w/o, without; N, number of patients; ECOG, Eastern Cooperative Oncology Group;

Table 2. Characteristics of tumors in patients identified as high-risk with hormone receptor-positive breast cancer within the full CANTO cohort.

Characteristic	CANTO High Risk without Ki-67 (N=1266)	CANTO High Risk with Ki-67 (N=1650)
Pathological tumor size (cm) - <2	296 (23.5%)	473 (28.8%)
Pathological tumor size (cm) - 2-5	637 (50.6%)	840 (51.2%)
Pathological tumor size (cm) - ≥ 5	327 (26.0%)	327 (19.9%)
Pathological tumor size - Missing	6	10
Positive axillary lymph nodes - 0	47 (3.7%)	55 (3.4%)
Positive axillary lymph nodes - 1-3	594 (47.2%)	968 (59.0%)
Positive axillary lymph nodes - 4-9	469 (37.3%)	469 (28.6%)
Positive axillary lymph nodes - ≥ 10	148 (11.8%)	148 (9.0%)
Positive axillary lymph nodes - Missing	8	10
Histological grade - Grade 1	53 (4.2%)	83 (5.1%)
Histological grade - Grade 2	482 (38.2%)	833 (50.7%)
Histological grade - Grade 3	727 (57.6%)	727 (44.2%)
Histological grade - Missing	4	7
Ki-67 proliferation index - <20%	316 (33.8%)	316 (23.9%)
Ki-67 proliferation index - $\geq 20\%$	620 (66.2%)	1004 (76.1%)
Ki-67 - Missing	330	330
AJCC prognostic stage - Stage IA	0 (0%)	0 (0%)
AJCC prognostic stage - Stage IIA	217 (17.1%)	432 (26.2%)
AJCC prognostic stage - Stage IIB	304 (24.0%)	471 (28.6%)

AJCC prognostic stage - Stage IIIA	594 (46.9%)	595 (36.1%)
AJCC prognostic stage - Stage IIIB	0 (0%)	0 (0%)
AJCC prognostic stage - Stage IIIC	151 (11.9%)	151 (9.2%)
AJCC prognostic stage - Missing	0	1

W/, with; w/o, without; n, number of patients; AJCC, American Joint Committee on Cancer

For ipsilateral axillary surgery, the majority of patients (87.2%) underwent lymph node dissection, whereas 38.3% had sentinel node biopsy (**Table 3**). Chemotherapy was given in the neoadjuvant setting to 18.2% of patients (n=230), in the adjuvant setting to 75.3% (n=953), and in both settings to 0.7% (n=9); radiotherapy was delivered to 98.0% (n=1240) (**Table 3**). First-line endocrine therapy predominantly involved aromatase inhibitors [monotherapy in 53.3% (n=653) or with ovarian suppression in 2.8% (n=34)], ahead of

tamoxifen [monotherapy in 42.8% (n=524) or with ovarian suppression in 1.1% (n=13)]. Over the course of follow-up, endocrine therapy was stopped by 34.3% of patients (n=327), chiefly because of toxicity (56.0% of discontinuations; n=183). The median time on initial endocrine therapy was 33.2 months overall (range 0.3–97.9) but only 17.1 months (range 0–66.0) for patients enrolled starting in 2016. Reported yearly compliance with endocrine therapy stood at 95.1% during the first year and declined to 87.1% by the fifth year.

Table 3. Treatment patterns among patients with high-risk hormone receptor-positive breast cancer in the whole CANTO cohort

Characteristic	CANTO High Risk without Ki-67 (N=1266)	CANTO High Risk with Ki-67 (N=1650)
Axillary surgery - Sentinel lymph node biopsy (SLNB)	485 (38.3%)	745 (45.2%)
Axillary surgery - Axillary lymph node dissection (ALND)	1104 (87.2%)	1367 (82.8%)
Chemotherapy - None	73 (5.8%)	151 (9.2%)
Chemotherapy - Any	1192 (94.2%)	1498 (90.8%)
Chemotherapy timing - Neoadjuvant	230 (18.2%)	272 (16.5%)
Chemotherapy timing - Adjuvant	962 (76.0%)	1226 (76.3%)
Chemotherapy timing - Missing	1	1
Neoadjuvant chemotherapy regimen - Anthracycline only	4 (1.7%)	5 (1.8%)
Neoadjuvant chemotherapy regimen - Taxane + anthracycline	235 (98.3%)	276 (98.2%)
Neoadjuvant chemotherapy regimen - Taxane only	0 (0%)	0 (0%)
Adjuvant chemotherapy regimen - Taxane only	40 (4.2%)	54 (4.4%)
Adjuvant chemotherapy regimen - Anthracycline only	13 (1.4%)	17 (1.4%)
Adjuvant chemotherapy regimen - Taxane + anthracycline	903 (93.9%)	1149 (93.7%)
Adjuvant chemotherapy regimen - Other	6 (0.6%)	6 (0.5%)
Radiotherapy - Yes	1240 (98.0%)	1613 (97.8%)
Radiotherapy - Missing	1	1
Adjuvant endocrine therapy - Yes	1230 (97.3%)	1611 (97.8%)
Adjuvant endocrine therapy - Missing	2	2
Initial adjuvant endocrine therapy - Aromatase inhibitor	653 (53.3%)	854 (53.3%)
Initial adjuvant endocrine therapy - Aromatase inhibitor + ovarian function suppression (OFS)	34 (2.8%)	41 (2.5%)
Initial adjuvant endocrine therapy - Tamoxifen	524 (42.8%)	694 (43.3%)
Initial adjuvant endocrine therapy - Tamoxifen + OFS	13 (1.1%)	13 (0.8%)

Initial adjuvant endocrine therapy - Missing	6	9
Ovarian function suppression (at any time) - Yes	82 (6.7%)	99 (6.2%)
Ovarian function suppression - Missing	5	7
Bone-modifying agents (at any time)	116 (9.2%)	150 (9.1%)

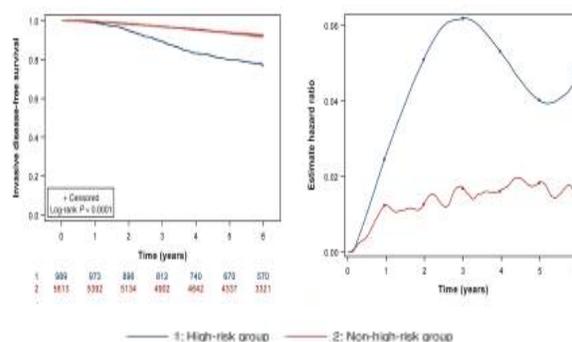
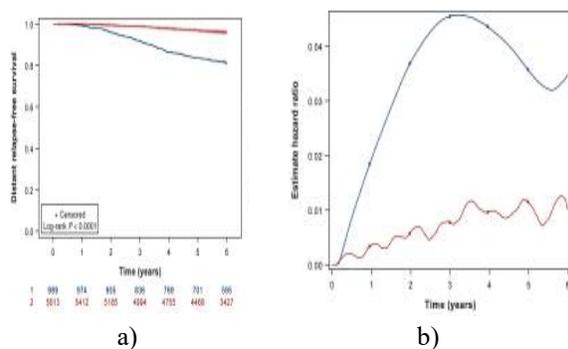
CT, chemotherapy; ALND, axillary lymph node dissection; w/, with; w/o, without; n, number of patients; ET, endocrine therapy; SNLB, sentinel lymph node biopsy; OFS, ovarian function suppression

A second group of patients was classified as high-risk based on Ki-67 levels, comprising 1,650 individuals. This represented 19.6% of the hormone receptor-positive breast cancer population and 14.9% of the overall CANTO cohort. Their clinical and pathological characteristics, as well as treatment approaches, were largely comparable to those seen in the first cohort (Tables 1–3).

For survival assessments, only patients who had been enrolled in the CANTO study for at least six years prior to data extraction were analyzed, ensuring sufficient follow-up.

In the first cohort, the median follow-up duration was 6.4 years (range 0–10.4). Five-year invasive disease-free survival (IDFS) and distant recurrence-free survival (DRFS) were 79.9% (95% CI 77.2–82.4%) and 83.5% (95% CI 80.9–85.7%), respectively, which were notably lower than the rates in patients at low or intermediate risk (5-year IDFS 93.7%, 95% CI 93.0–94.4%; 5-year DRFS 96.9%, 95% CI 96.3–97.3%; $P < 0.001$) (appenure 2).

Within the high-risk Ki-67 cohort, 5-year IDFS and DRFS were slightly higher than in the first cohort at 82.6% (95% CI 80.3–84.6%) and 85.9% (95% CI 83.8–87.8%), but still considerably lower than those for low/intermediate-risk patients, who had 5-year IDFS and DRFS of 93.9% (95% CI 93.2–94.5%) and 97.1% (95% CI 95.6–96.7%), respectively ($P < 0.001$).



c)

d)

Figure 2. Survival outcomes. Kaplan–Meier plots (left) and smoothed hazard ratio curves (right) for distant metastasis-free survival and invasive disease-free survival are shown according to risk groups in the first cohort of hormone receptor-positive breast cancer patients from the CANTO study (risk defined without Ki-67). To guarantee sufficient follow-up, only patients enrolled at least six years prior to data extraction were included in the survival analysis.

Patients with stage II–III, highly proliferative hormone receptor-positive (HR+) breast cancer face a heightened risk of recurrence despite intensive adjuvant treatments. In the CANTO cohort, these high-risk patients represent 15%–20% of the HR+ breast cancer population, consistent with other real-world data (RWD) reports [26–28]. Compared with populations enrolled in pivotal trials, the CANTO cohort shows a similar median age and menopausal status to monarchE participants, although patients in CANTO tended to have more comorbidities and poorer performance status. While most comorbidities do not constitute absolute contraindications for abemaciclib, they require careful attention due to potential drug–drug interactions. Cardiac comorbidities, however, may limit the use of ribociclib, particularly in patients with certain arrhythmias [29]. Notably, approximately one-fifth of patients discontinued endocrine therapy (ET) because of adverse events, raising concerns about adding additional agents, such as

abemaciclib or ribociclib, without effective strategies to mitigate side effects.

In this analysis, the high-risk population was evaluated both with and without the Ki-67 criterion, as the monarchE trial and regulatory approval of adjuvant abemaciclib considered Ki-67 as a companion diagnostic. However, drug approvals ultimately did not mandate Ki-67 for this indication [30–33].

Compared with monarchE, high-risk HR+ patients in the CANTO cohort had slightly higher proportions of tumors ≥ 5 cm (19.9%–26% versus 21.6%–21.7%), grade III tumors (44.2%–57.6% versus 37.7%–38.8%), and Ki-67 $\geq 20\%$ (66.2%–76.1% versus 43.6%–44.9%), but lower rates of N2 and N3 nodal involvement (37.6%–49.0% versus 59.3%–59.8%). Consequently, staging appeared more favorable in CANTO, with fewer stage IIIC cases (9.2%–11.9% versus 33.8%–34.0%) and more stage IIIA cases (36.1%–46.9% versus 36.2%–36.6%). Treatment patterns also differed: CANTO patients received less neoadjuvant chemotherapy (16.5%–18.2% versus 36.3%–36.5%), fewer aromatase inhibitors (55.0%–55.3% versus 67.5%–69.1%), less ovarian suppression (6.2%–6.7% versus 21.7%–22.4%), and fewer bone-modifying agents (9.1%–9.2% versus 13.9%–15.8%), while anthracycline use (95.1%–95.3% versus 90.1%–95%) and tamoxifen (43.9%–44.1% versus 30.7%–32.1%) were more frequent. These differences may reflect a time bias, as the study period included patients treated before the publication of the TEXT and SOFT trials in 2018 [34, 35].

Regarding axillary surgery, current guidelines recommend sentinel lymph node biopsy for locoregional staging when no clinical axillary involvement is present at diagnosis or after neoadjuvant therapy [36, 37]. However, whether completion axillary dissection is necessary in patients with positive sentinel nodes to determine eligibility for treatments such as olaparib or abemaciclib remains debated [37, 38]. In the CANTO cohort, axillary dissection was performed in 87.2% of high-risk patients, likely reflecting the enrollment period starting in 2012, prior to the results of axillary de-escalation trials such as ACOSOG Z0011 and AMAROS [39, 40].

Olaparib has also been approved for HR+ patients at high risk of recurrence who carry germline BRCA1/2 mutations [36]. In the absence of direct comparisons between olaparib and abemaciclib, treatment decisions for patients eligible for both rely on approval status, drug availability, long-term efficacy, safety profile, and

patient characteristics and preferences. Within the CANTO cohort, 11.5% of high-risk patients carried germline BRCA mutations (3.5% BRCA1 and 8.0% BRCA2), which exceeds the prevalence observed in unselected HR+ BC patients (1.5%–5.0%) or those selected for high-risk features (2.2%) [28, 41, 42]. Data suggest that overlap of these indications is rare, occurring in approximately 0.9% of patients, with nine individuals presenting both germline BRCA mutations and N2 staging among the 953 patients who did not receive neoadjuvant chemotherapy. The CANTO cohort lacks post-treatment pathological staging, estrogen receptor status, and composite tumor grade (CSP + EG score), limiting precise assessment for neoadjuvant olaparib indications.

Overall, RWD from CANTO indicate suboptimal survival outcomes for high-risk HR+ patients compared with lower-risk individuals, with 5-year IDFS ranging from 79.9% to 82.6% and 5-year DRFS from 82.6% to 85.9%. These outcomes are numerically similar to those achieved with adjuvant abemaciclib in monarchE and superior to the control arm (5-year DRFS 85.6% and 78.5%, respectively) [13]. They also compare favorably with US RWD [28], likely reflecting differences in patient and tumor characteristics, including a lower prevalence of stage IIIC disease in CANTO and an enrichment for tumors with better prognosis and greater sensitivity to endocrine therapy. Notably, the threshold for defining HR positivity in France is $\geq 10\%$, versus 1% in monarchE and US cohorts [28].

This study provides a detailed description of clinicopathological features and survival outcomes for potential candidates for adjuvant abemaciclib in a real-world setting. Limitations include the absence of central Ki-67 assessment and lack of genomic signature data, as most patients were enrolled prior to its routine use in clinical practice. Nevertheless, the CANTO cohort reflects everyday clinical practice and provides valuable insights into high-risk HR+ breast cancer management.

Conclusion

This exploratory analysis of the CANTO study, focusing on high-risk HR+ breast cancer patients eligible for adjuvant abemaciclib, demonstrated that the risk of recurrence tends to increase early during adjuvant treatment, even with chemotherapy. These findings highlight the importance of incorporating novel therapies alongside endocrine therapy (ET) as early as possible in

the treatment course. Although most patients have multiple comorbidities, their overall Charlson comorbidity scores are generally favorable; nonetheless, potential drug–drug interactions with newly introduced adjuvant therapies may present challenges in certain cases. Additionally, adherence remains a critical concern, as a substantial proportion of patients already discontinued ET monotherapy due to adverse events, which could significantly influence survival outcomes.

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Ethics Statement: None

References

1. Sung H., Ferlay J., Siegel R.L., et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71:209–249. doi: 10.3322/caac.21660.
2. Howlader N., Altekruse S.F., Li C.I., et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst.* 2014;106 doi: 10.1093/jnci/dju055. dju055-dju055.
3. 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. doi: 10.1056/NEJMoa1701830.
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet.* 2015;386:1341–1352. doi: 10.1016/S0140-6736(15)61074-1.
5. Davies C., Pan H., Godwin J., et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet.* 2013;381:805–816. doi: 10.1016/S0140-6736(12)61963-1.
6. Pistilli B., Lohrisch C., Sheade J., Fleming F.G. Personalizing adjuvant endocrine therapy for early-stage hormone receptor–positive breast cancer. *Am Soc Clin Oncol Educ Book.* 2022;42:60–72. doi: 10.1200/EDBK_350358.
7. Bartlett J.M.S., Sgroi D.C., Treuner K., et al. Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen—To Offer More? (aTTom) trial. *Ann Oncol.* 2019;30:1776–1783. doi: 10.1093/annonc/mdz289.
8. 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. doi: 10.1016/S1470-2045(21)00352-1.
9. Tjan-Heijnen G.C.V., van Hellemond I.E.G., Peer P.G.M., et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. *Lancet Oncol.* 2017;18:1502–1511. doi: 10.1016/S1470-2045(17)30600-9.
 10. Mamounas P.E., Bandos H., Lembersky B.C., et al. Use of letrozole after aromatase inhibitor-based therapy in postmenopausal breast cancer (NRG Oncology/NSABP B-42): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2019;20:88–99. doi: 10.1016/S1470-2045(18)30621-1.
 11. 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. doi: 10.1016/j.annonc.2021.09.015.
 12. Johnston S.R.D., Harbeck N., Hegg R., et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE) *J Clin Oncol.* 2020;38:3987–3998. doi: 10.1200/JCO.20.02514.
 13. Rastogi P., O'Shaughnessy J., Martin M., et al. Adjuvant abemaciclib plus endocrine therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative, high-risk early breast cancer: results from a preplanned monarchE overall survival interim analysis, including 5-year efficacy. *J Clin Oncol.* 2024;42:987–993. doi: 10.1200/JCO.23.01994.
 14. Johnston S.R.D., Toi M., O'Shaughnessy J., et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2023;24:77–90. doi: 10.1016/S1470-2045(22)00694-5.
 15. Hortobagyi G.N., Stroyakovskiy D., Yardley D., et al. San Antonio Breast Cancer Symposium; San Antonio, Texas: 2023. (GS03-03) Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2- early breast cancer: final invasive disease-free survival (iDFS) analysis from the NATALEE trial. Paper presented at the 2023.
 16. Slamon D., Lipatov O., Nowecki Z., et al. Ribociclib plus endocrine therapy in early breast cancer. *N Engl J Med.* 2024;390:1080–1091. doi: 10.1056/NEJMoa2305488.
 17. Townsley C.A., Selby R., Siu L.L. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol.* 2005;23:3112–3124. doi: 10.1200/JCO.2005.00.141.
 18. Van Spall H.G., Toren A., Kiss A., Fowler R.A. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA.* 2007;297:1233–1240. doi: 10.1001/jama.297.11.1233.
 19. Kennedy-Martin T., Curtis S., Faries D., Robinson S., Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials.* 2015;16:495. doi: 10.1186/s13063-015-1023-4.
 20. Buffel Du Vaure C., Dechartres A., Battin C., Ravaud P., Boutron I. Exclusion of patients with concomitant chronic conditions in ongoing randomised controlled trials targeting 10 common chronic conditions and registered at ClinicalTrials.gov: a systematic review of registration details. *BMJ Open.* 2016;6 doi: 10.1136/bmjopen-2016-012265.
 21. Kronish I.M., Fenn K., Cohen L., et al. Extent of exclusions for chronic conditions in breast cancer trials. *JNCI Cancer Spectrum.* 2018;2 doi: 10.1093/jncics/pky059.
 22. He J., Morales D.R., Guthrie B. Exclusion rates in randomized controlled trials of treatments for physical conditions: a systematic review. *Trials.* 2020;21:228. doi: 10.1186/s13063-020-4139-0.
 23. Vaz-Luis I., Cottu P., Mesleard C., et al. UNICANCER: French prospective cohort study of treatment-related chronic toxicity in women with localised breast cancer (CANTO) *ESMO Open.* 2019;4 doi: 10.1136/esmoopen-2019-000562.
 24. Castelo-Branco L., Pellat A., Martins-Branco D., et al. ESMO Guidance for Reporting Oncology real-World evidence (GROW) *Ann Oncol.* 2023;34:1097–1112. doi: 10.1016/j.annonc.2023.10.001.

25. Tolaney S.M., 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. doi: 10.1200/JCO.20.03613.
26. Tarantino P., Jin Q., Mittendorf E.A., King T.A., Curigliano G., Tolaney S.M. Clinical and pathological features of breast cancer patients eligible for adjuvant abemaciclib. *Ann Oncol.* 2022;33:845–847. doi: 10.1016/j.annonc.2022.04.069.
27. Dannehl D., Volmer L.L., Weiss M., et al. Feasibility of adjuvant treatment with abemaciclib—real-world data from a large German Breast Center. *J Personal Med.* 2022;12:382. doi: 10.3390/jpm12030382.
28. Sheffield K.M., Peachey J.R., Method M., et al. A real-world US study of recurrence risks using combined clinicopathological features in HR-positive, HER2-negative early breast cancer. *Future Oncol.* 2022;18:2667–2682. doi: 10.2217/fon-2022-0310.
29. Fogli S., Del Re M., Curigliano G., et al. Drug-drug interactions in breast cancer patients treated with CDK4/6 inhibitors. *Cancer Treat Rev.* 2019;74:21–28. doi: 10.1016/j.ctrv.2019.01.006.
30. Antonarelli G., Valenza C., Mayer E.L., Loibl S., Curigliano G. Cyclin dependent kinase 4/6 inhibitors in early breast cancer: what is the role of Ki-67? *Lancet Oncol.* 2022;23:325–328. doi: 10.1016/S1470-2045(21)00756-7.
31. Dowsett M., Nielsen T.O., Rimm D.L., Hayes D.F. Ki67 as a companion diagnostic: good or bad news? *J Clin Oncol.* 2022;40:3796–3799. doi: 10.1200/JCO.22.00581.
32. FDA expands early breast cancer indication for abemaciclib with endocrine therapy. 2023. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-early-breast-cancer-indication-abemaciclib-endocrine-therapy> Available at.
33. EMA Committee for Medicinal Products for Human Use (CHMP) February 2022 EC decision April 2022. https://www.ema.europa.eu/en/documents/minutes/minutes-chmp-meeting-09-12-october-2023_en.pdf Available at.
34. Francis P.A., Pagani O., Fleming G.F., et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med.* 2018;379:122–137. doi: 10.1056/NEJMoa1803164.
35. Pagani O., Walley B.A., Fleming G.F., et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer: long-term follow-up of the combined TEXT and SOFT trials. *J Clin Oncol.* 2023;41:1376–1382. doi: 10.1200/JCO.22.01064.
36. Loibl S., André F., Bachelot T., et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2024;35:159–182. doi: 10.1016/j.annonc.2023.11.016.
37. Curigliano G., Burstein H.J., Gnant M., et al. Understanding breast cancer complexity to improve patient outcomes: The St Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023. *Ann Oncol.* 2023;34:970–986. doi: 10.1016/j.annonc.2023.08.017.
38. Mittendorf E.A., King T.A., Tolaney S.M. Impact of RxPONDER and monarchE on the surgical management of the axilla in patients with breast cancer. *J Clin Oncol.* 2022;40:3361–3364. doi: 10.1200/JCO.22.00173.
39. Giuliano A.E., Ballman K.V., McCall L., et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA.* 2017;318:918–926. doi: 10.1001/jama.2017.11470.
40. Donker M., van Tienhoven G., Straver M.E., et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol.* 2014;15:1303–1310. doi: 10.1016/S1470-2045(14)70460-7.
41. Hu C., Hart S.N., Gnanaolivu R., et al. A population-based study of genes previously implicated in breast cancer. *N Engl J Med.* 2021;384:440–451. doi: 10.1056/NEJMoa2005936.
42. Tung N., Lin N.U., Kidd J., et al. Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of patients with breast cancer. *J Clin Oncol.* 2016;34:1460–1468. doi: 10.1200/JCO.2015.65.0747.