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Clinicopathological Features, Treatment Patterns, and Outcomes of High-Risk Early Hormone Receptor–Positive Breast Cancer in a French Real-World Cohort

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ABSTRACT

Patients diagnosed with hormone receptor-positive, HER2-negative breast cancer (HR+ BC) exhibiting poor prognostic factors face a heightened likelihood of disease recurrence and are suitable candidates for escalated therapeutic options. We examined real-world clinicopathological profiles, management strategies, and oncologic outcomes in this population using data from the CANcer TOxicities (CANTO) cohort (NCT01993498).This retrospective review utilized prospectively acquired data from CANTO, spanning 2012 to 2022. High-risk HR+ BC was identified by either ≥4 involved axillary lymph nodes (LNs) or 1–3 involved LNs plus tumor diameter ≥5 cm or grade 3 histology (cohort 1). A separate criterion included 1–3 involved LNs with Ki-67 ≥20% (cohort 2). Survival curves were generated via the Kaplan–Meier approach. Within the CANTO dataset, high-risk HR+ BC cases comprised 15.0%–19.6% of all HR+ BC patients (cohorts 1 and 2, respectively). In cohort 1 (n=1266), 617 individuals (49.0%) showed ≥4 LNs, 327 (26.0%) had tumors ≥5 cm, and 727 (57.6%) displayed grade III histology. A favorable Charlson comorbidity index was observed in 79.9%, with 88.1% presenting stage II/IIIA disease. Involvement of ≥10 LNs occurred in 11.8%. (Neo)adjuvant chemotherapy was given to 94.2% of patients. Endocrine treatment was started in 97.3%, primarily aromatase inhibitors, but stopped in 34.3% due mostly to side effects. For those enrolled ≥6 years before data cutoff, 5-year invasive disease-free survival reached 79.9% [95% confidence interval (CI) 77.2% to 82.4%], while 5-year distant relapse-free survival was 83.5% (95% CI 80.9% to 85.7%). These real-world findings affirm that HR+ BC patients with adverse prognostic indicators continue to experience substantial early recurrence risk during adjuvant therapy, even after (neo)adjuvant chemotherapy. Urgent development and early integration of new treatment modalities into the adjuvant regimen are needed for this high-risk group.

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

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Introduction

Breast cancer (BC) stands as the leading cancer diagnosis in women globally, with roughly 2.3 million incident cases yearly, and ranks high among causes of cancer mortality, responsible for approximately 0.7 million deaths annually [1]. The HR+/HER2-negative subtype dominates, making up 70% of diagnoses [2]. Most HR+ BC patients are identified at localized stages amenable to curative therapy. Typical management involves surgery first, then endocrine therapy (ET), commonly alongside radiation and chemotherapy. Analyses from the Early Breast Cancer Trialists' Collaborative Group highlighted greater rates of breast cancer events among cases with larger tumors, substantial nodal burden, elevated grade, or Ki-67 ≥20% [3]. Guidelines recommend chemotherapy plus prolonged ET for such profiles, yet around 20% still recur within a decade [4-10]. The monarchE study set a novel benchmark for managing high-risk HR+ BC, using criteria blending anatomic extent (tumor dimensions and nodes) with biologic markers like grade [11-13]. Adding the CDK4/6 inhibitor abemaciclib for 2 years to standard care lowered invasive disease-free survival (IDFS) events, providing a 6.4% absolute improvement at 4 years (85.8% vs. 79.4%), resulting in approvals from the Food and Drug Administration and European Medicines

Agency [11, 13, 14]. Similarly, the NATALEE study demonstrated that extending ribociclib for 3 years alongside standard therapy boosted 3-year IDFS [hazard ratio 0.75, 95% CI 0.62-0.91], with absolute gains of 3.0%–3.2% in stage II/III patients, though additional maturation data are required to define its clinical role [15, 16].

Phase III trials like monarchE and NATALEE provide gold-standard evidence through controlled designs that limit bias. However, narrow enrollment rules often bar patients with reduced functional status or comorbidities, restricting broader applicability [17-22]. Real-world evidence helps overcome this by illuminating patient traits and outcomes in routine practice. Here, we report clinicopathological details and survival metrics for high-risk HR+ BC cases drawn from the prospective CANTO cohort [23].

Materials and Methods

Data source

Data were derived from the CANTO cohort (NCT01993498), an ongoing prospective observational investigation that has been gathering comprehensive information on tumors, treatments, adverse effects, patient-reported health outcomes, and biological specimens related to breast cancer since 20 March 2012 (recruitment continues) [23]. CANTO recruits individuals aged ≥18 years with newly diagnosed invasive stage cT0-cT3, cN0-3 breast cancer who have received no prior breast cancer therapy. Assessments occur at baseline, soon after completion of primary therapy (surgery, chemotherapy, or radiotherapy—whichever is latest), at the start of endocrine therapy when prescribed, and subsequently at years 1, 3, and 5 following the initial post-primary treatment visit. Extended follow-up data are obtained at years 6, 7, 8, and 10. Each assessment captures clinical details, treatment information (including adherence to medications evaluated by a dedicated clinical research nurse), toxicity profiles, patient-reported outcomes related to health, and blood samples [23].

The CANTO study is managed by UNICANCER, the French national network of cancer centers. It received approval from relevant national authorities and ethics committees (ID-RCB: 2011-A01095-36, 11-039). Every participant provided written informed consent [23]. This analysis adhered to the principles of the Declaration of Helsinki, and reporting complied with the ESMO Guidance for Reporting Oncology real-World evidence (GROW) [24].

Patient selection and variable definitions

As of the final data extraction on 5 September 2022, 11 342 women with newly diagnosed early-stage breast cancer were recorded. For this investigation, only those with hormone receptor-positive, HER2-negative disease were selected. Cohort 1 comprised women with non-metastatic HR+ breast cancer meeting high-risk criteria from the monarchE trial, specifically either (i) ≥4 pathologically involved axillary lymph nodes or (ii) 1–3 involved axillary nodes combined with tumor diameter ≥5 cm or grade 3 histology [12]. A separate cohort (cohort 2) was defined using the criterion of 1–3 involved axillary nodes plus Ki-67 index ≥20%. Individuals not fulfilling high-risk definitions were categorized as ‘low/intermediate risk’ and included solely in survival comparisons.

Details on patient demographics, tumor features, and treatments were extracted from the CANTO database. Adherence to endocrine therapy was classified as a medical possession ratio (MPR) ≥80%, calculated by dividing the total days’ supply of the medication within a defined period by the length of that period.

Statistical analyses

Findings were presented separately for analyses incorporating or excluding the Ki-67 criterion. Baseline characteristics and treatment details were summarized using counts and percentages for categorical variables. Survival endpoints followed the Standardized Definitions for Efficacy End Points (STEEP) v2.0 criteria for invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) [25]. IDFS encompassed invasive locoregional or distant recurrence, contralateral breast cancer, secondary non-breast malignancy, or death from any cause. DRFS was measured from enrollment to the first distant recurrence or death (regardless of cause). Five-year survival estimates were generated with the Kaplan–Meier method, and a supplementary log-rank test compared outcomes between high-risk and low-/intermediate-risk groups. To guarantee sufficient follow-up duration, survival analyses were restricted to patients enrolled at least 6 years prior to data extraction. Those without events at last contact were censored at their most recent visit. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results and Discussion

Of the 11 342 women recruited into CANTO from 2012 to 2022, 8428 (74.3%) had HR+ breast cancer **(Figure 1).** Cohort 1, defined as high risk without Ki-67 consideration, consisted of 1266 individuals (15.0% of the HR+/HER2-negative subgroup in CANTO, or 11% of the entire cohort) **(Table 1).** Median age was 54.3 years across both cohorts, with 47.2% being premenopausal. High-risk status was attributed to ≥4 nodes in 617 patients (49.0%) **(Table 2).** Tumors ≥5 cm and grade III histology were documented in 327 (26.0%) and 727 (57.6%) cases, respectively **(Table 2).** Among 1122 patients with recorded Charlson comorbidity index, 897 (79.9%) had a score of 0. Rates of articular, endocrine, cardiovascular, and renal comorbidities were 51.7%, 32.9%, 32.6%, and 9.5%, respectively **(Table 1)**. Hypertension was the predominant comorbidity (24.1%). Other notable cardiovascular conditions included arrhythmias (4.3%). Hypercholesterolemia represented the leading endocrine disorder (13.0%), ahead of diabetes (7.4%) and hypothyroidism (7.4%). Articular conditions primarily involved osteoarthritis (14.1%) and prior bone fractures (16.7%). Germline BRCA1/2 pathogenic variants were identified in 11.5%–11.6% of high-risk patients (3.5% for BRCA1 and 8.0% for BRCA2).

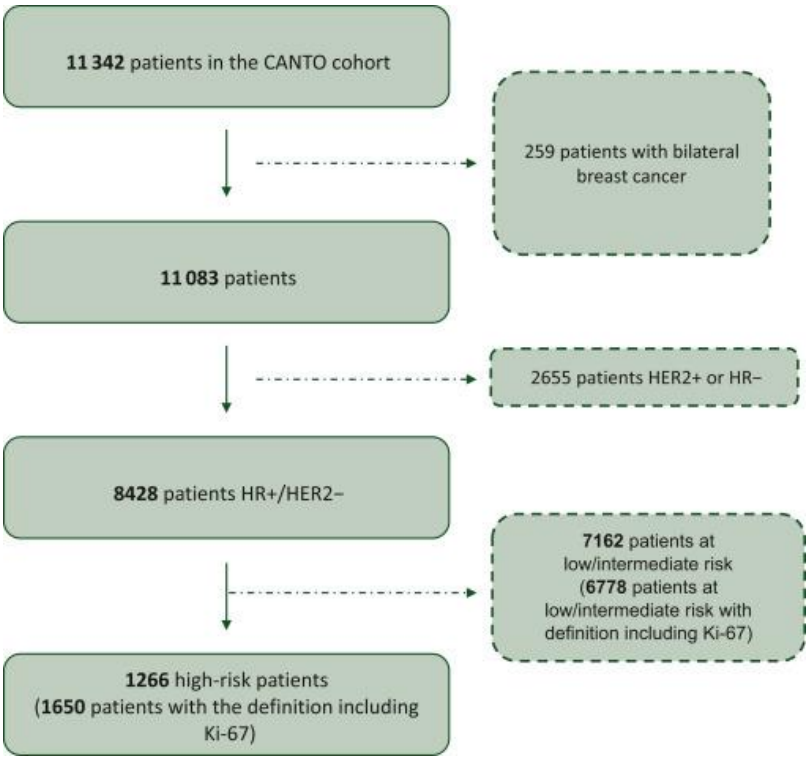

Figure 1. CONSORT diagram.

Table 1. Clinical and tumor features of individuals with high-risk hormone receptor-positive breast cancer across the entire CANTO cohort

Characteristic	CANTO High-Risk with Ki-67 (N = 1650), n (%)	CANTO High-Risk without Ki-67 (N = 1266), n (%)
Age		
Median age (range), years	54.3 (22.2–87.5)	54.3 (22.2–87.5)
Younger than 65 years	1330 (80.7)	1019 (80.6)
65 years or older	318 (19.3)	245 (19.4)
Missing data	2	2
Sex		
Female	1650 (100)	1266 (100)
Male	0	0
Menopausal status		
Premenopausal	760 (46.9)	589 (47.2)
Postmenopausal	861 (53.1)	659 (52.8)

Missing data	29	18
Germline BRCA mutation status		
BRCA1 mutation	14 (3.3)	12 (3.5)
BRCA2 mutation	35 (8.3)	27 (8.0)
Missing data	1228	927
Charlson comorbidity index		
Score = 0	1171 (79.6)	897 (79.9)
Score 1–2	260 (17.7)	196 (17.5)
Score ≥3	40 (2.7)	29 (2.6)
Missing data	179	144
ECOG performance status		
ECOG 0	1416 (95.1)	1085 (94.8)
ECOG 1	66 (4.4)	54 (4.7)
ECOG 2	7 (0.5)	6 (0.5)
Missing data	161	121
Reported comorbid conditions		
Cardiovascular disorders	545 (33.0)	413 (32.6)
Renal disease	159 (9.6)	120 (9.5)
Endocrine disorders	561 (34.0)	417 (32.9)
Osteoarticular conditions	851 (51.6)	654 (51.7)

ECOG, Eastern Cooperative Oncology Group; n, number of patients; w/, with; w/o, without.

Table 2. Tumor features of individuals with high-risk hormone receptor-positive breast cancer across the entire CANTO cohort

Characteristic	CANTO High-Risk with Ki-67 (N = 1650), n (%)	CANTO High-Risk without Ki-67 (N = 1266), n (%)
Pathological tumor size (cm)		
Less than 2 cm	473 (28.8)	296 (23.5)
2–5 cm	840 (51.2)	637 (50.6)
5 cm or larger	327 (19.9)	327 (26.0)
Missing data	10	6
Number of involved axillary lymph nodes		
0 positive nodes	55 (3.4)	47 (3.7)
1–3 positive nodes	968 (59.0)	594 (47.2)
4–9 positive nodes	469 (28.6)	469 (37.3)
10 or more positive nodes	148 (9.0)	148 (11.8)
Missing data	10	8
Histological grade		
Grade 1	83 (5.1)	53 (4.2)
Grade 2	833 (50.7)	482 (38.2)
Grade 3	727 (44.2)	727 (57.6)
Missing data	7	4
Ki-67 proliferation index		
<20%	316 (23.9)	316 (33.8)
≥20%	1004 (76.1)	620 (66.2)
Missing data	330	330
AJCC stage		
Stage IA	0	0
Stage IIA	432 (26.2)	217 (17.1)
Stage IIB	471 (28.6)	304 (24.0)
Stage IIIA	595 (36.1)	594 (46.9)
Stage IIIB	0	0
Stage IIIC	151 (9.2)	151 (11.9)
Missing data	1	0

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

In terms of ipsilateral axillary surgery, 87.2% underwent full axillary lymph node dissection, and 38.3% underwent sentinel lymph node biopsy **(Table 3).** Neoadjuvant chemotherapy was delivered to 230 patients (18.2%), adjuvant chemotherapy to 953 (75.3%), perioperative (both neoadjuvant and adjuvant) chemotherapy to 9 (0.7%), and radiotherapy to 1240 (98.0%) **(Table 3).** First-line endocrine therapy consisted predominantly of aromatase inhibitors [653 (53.3%) as single agent and 34 (2.8%) with ovarian function suppression], followed by tamoxifen [524 (42.8%) as single agent and 13 (1.1%) with ovarian function suppression]. During the observation period, 327 patients (34.3%) ceased endocrine therapy, mainly due to side effects (183 patients; 56.0%). The median length of initial endocrine therapy was 33.2 months (range 0.3-97.9 months) in the overall group and 17.1 months (0-66.0 months) among those enrolled after 2016. Yearly compliance with endocrine therapy stood at 95.1% during the first year and 87.1% during the fifth year.

Table 3. Treatment approaches for individuals with high-risk hormone receptor-positive breast cancer across the entire CANTO cohort

Intervention	CANTO High-Risk with Ki-67 (N = 1650), n (%)	CANTO High-Risk without Ki-67 (N = 1266), n (%)
Axillary surgical procedure		
Sentinel lymph node biopsy (SLNB)	745 (45.2)	485 (38.3)
Axillary lymph node dissection (ALND)	1367 (82.8)	1104 (87.2)
Previous chemotherapy exposure		
None	151 (9.2)	73 (5.8)
Any chemotherapy	1498 (90.8)	1192 (94.2)
Neoadjuvant	272 (16.5)	230 (18.2)
Adjuvant	1226 (76.3)	962 (76.0)
Missing data	1	1
Type of neoadjuvant chemotherapy		
Anthracycline-based only	5 (1.8)	4 (1.7)
Combined taxane and anthracycline	276 (98.2)	235 (98.3)
Taxane-only regimen	0	0
Type of adjuvant chemotherapy		
Taxane-only regimen	54 (4.4)	40 (4.2)
Anthracycline-based only	17 (1.4)	13 (1.4)
Combined taxane and anthracycline	1149 (93.7)	903 (93.9)
Other regimens	6 (0.5)	6 (0.6)
Radiotherapy		
Received	1613 (97.8)	1240 (98.0)
Missing data	1	1
Adjuvant endocrine therapy		
Received	1611 (97.8)	1230 (97.3)
Missing data	2	2
Initial adjuvant endocrine regimen		
Aromatase inhibitor	854 (53.3)	653 (53.3)
Aromatase inhibitor + ovarian function suppression (OFS)	41 (2.5)	34 (2.8)
Tamoxifen	694 (43.3)	524 (42.8)
Tamoxifen + OFS	13 (0.8)	13 (1.1)
Missing data	9	6
Ovarian function suppression (any time)		
Yes	99 (6.2)	82 (6.7)
Missing data	7	5
Use of bone-modifying agents (any time)	150 (9.1)	116 (9.2)

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

The alternative high-risk group (cohort 2), which incorporated the Ki-67 threshold, encompassed 1650 individuals (19.6% of all HR+ breast cancer cases in CANTO, equivalent to 14.9% of the total cohort). Broadly, clinicopathological profiles and therapeutic strategies in this group mirrored those of cohort 1 **(Tables 1-3).**

To achieve reliable maturity of data, survival evaluations were confined to participants who entered the CANTO study at least 6 years before the data cutoff. For cohort 1, median follow-up duration was 6.4 years (range 0.0-10.4 years); 5-year invasive disease-free survival (IDFS) was 79.9% (95% CI 77.2% to 82.4%), and 5-year distant relapse-free survival (DRFS) was 83.5% (95% CI 80.9% to 85.7%). Both outcomes were notably inferior compared with low/intermediate-risk cases, whose 5-year IDFS reached 93.7% (95% CI 93.0% to 94.4%) and 5-year DRFS reached 96.9% (95% CI 96.3% to 97.3%) (P < 0.001), **(Figure 2).** In cohort 2, corresponding 5-year rates were 82.6% for IDFS (95% CI 80.3% to 84.6%) and 85.9% for DRFS (95% CI 83.8% to 87.8%), again substantially lower than in low/intermediate-risk patients, with 5-year IDFS of 93.9% (95% CI 93.2% to 94.5%) and 5-year DRFS of 97.1% (95% CI 95.6% to 96.7%) (P < 0.001).

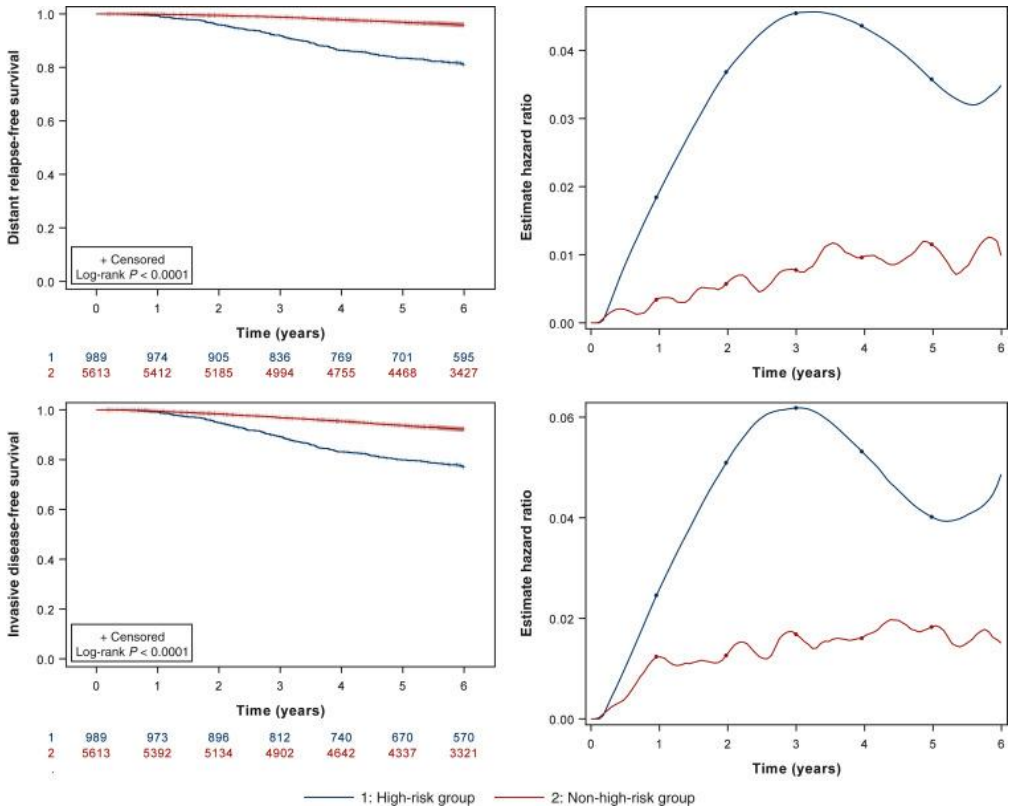

Figure 2. Survival outcomes. Kaplan–Meier curves (left) and smooth hazard ratios (right) of invasive disease-free survival and distant metastasis-free survival by risk group within the CANTO cohort of patients with hormone receptor-positive breast cancers in the first cohort (definition without Ki-67). To ensure adequate follow-up, the survival analysis only included patients enrolled in the CANTO cohort at least 6 years before data extraction.

Individuals with stage II-III hormone receptor-positive (HR+) breast cancer exhibiting high proliferation face a greater likelihood of recurrence even after intensive adjuvant treatments. Within the CANTO cohort, such cases represent 15%-20% of all HR+ breast cancer patients, consistent with other real-world datasets [26-28]. Relative to participants in key registration trials, the median age in CANTO aligns closely with that in monarchE, as does menopausal distribution; however, as anticipated, CANTO includes more individuals with comorbidities and reduced performance status. Although frequent comorbidities seldom represent absolute contraindications to abemaciclib, they necessitate vigilance regarding possible drug–drug interactions. In contrast, cardiac conditions may complicate ribociclib administration and occasionally preclude its use in those with specific arrhythmias [29]. Additionally, approximately one-fifth of patients stopped endocrine therapy owing to toxicity, highlighting potential difficulties in adding agents like abemaciclib or ribociclib without robust strategies to manage side effects.

The present analysis evaluated the high-risk population both including and excluding the Ki-67 threshold, since the monarchE trial and initial regulatory submission for adjuvant abemaciclib incorporated Ki-67 as a companion diagnostic. Notably, final approvals for this indication did not mandate this requirement [30-33].

Compared with monarchE, high-risk HR+ breast cancer cases in CANTO displayed numerically higher rates of tumors ≥5 cm (19.9%-26% versus 21.6%-21.7%), grade III disease (44.2%-57.6% versus 37.7%-38.8%), and Ki-67 ≥20% (66.2%-76.1% versus 43.6%-44.9%), but lower N2/N3 nodal involvement (37.6%-49.0% versus 59.3%-59.8%). Overall staging was thus more favorable in CANTO, with fewer stage IIIC cases (9.2%-11.9% versus 33.8%-34.0%) and more stage IIIA (36.1%-46.9% versus 36.2%-36.6%). Treatment differences were evident, including reduced utilization of neoadjuvant chemotherapy (16.5%-18.2% versus 36.3%-36.5%), aromatase inhibitors (55.0%-55.3% versus 67.5%-69.1%), ovarian suppression (6.2%-6.7% versus 21.7%-22.4%), and bone-modifying agents (9.1%-9.2% versus 13.9%-15.8%) in CANTO, while anthracyclines (95.1%-95.3% versus 90.1%-95%) and tamoxifen (43.9%-44.1% versus 30.7%-32.1%) were employed more frequently. These variations likely reflect temporal biases, as the enrollment period encompassed patients treated prior to the 2018 publication of the TEXT and SOFT trials [34, 35].

Current guidelines and expert consensus recommend sentinel lymph node biopsy as the preferred method for axillary staging in the absence of clinical nodal involvement at diagnosis or post-neoadjuvant chemotherapy [36, 37]. Nevertheless, the need for completion axillary dissection following positive sentinel biopsy—to establish eligibility for therapies such as olaparib or abemaciclib—remains controversial [37, 38]. This study reveals that axillary lymph node dissection was performed in 87.2% of high-risk cases, though this rate may be influenced by the cohort's recruitment beginning in 2012, before widespread adoption of de-escalation approaches from trials like ACOSOG Z0011 and AMAROS [39, 40].

Olaparib has also gained approval for high-risk HR+ breast cancer patients with germline BRCA1/2 mutations [36]. Without direct comparative data versus abemaciclib, selection between these agents in dual-eligible patients depends on regulatory status, availability, long-term efficacy, tolerability, and individual patient factors and preferences. In CANTO, germline BRCA1/2 mutations were present in 11.5% of high-risk individuals (3.5% BRCA1 and 8.0% BRCA2), exceeding rates reported in unselected HR+ breast cancer (1.5%-5.0%) or high-risk subsets (2.2%) [28, 41, 42]. Overlap between olaparib and abemaciclib eligibility was estimated at approximately 0.9% in the adjuvant context, with 9 patients showing germline BRCA mutations and N2 disease among 953 without neoadjuvant therapy. Regrettably, CANTO lacks post-treatment pathologic stage, estrogen receptor expression details, and combined clinical/pathologic plus grade (CSP + EG) scoring needed for precise neoadjuvant olaparib eligibility assessment. Relative to lower-risk counterparts, these real-world data demonstrate inferior survival for high-risk HR+ cases, with 5-year invasive disease-free survival (IDFS) of 79.9%-82.6% and 5-year distant relapse-free survival (DRFS) of 82.6%-85.9%. These rates align numerically with abemaciclib-treated patients in monarchE and surpass the trial's control arm (5-year DRFS 85.6% versus 78.5%, respectively) [13]. Outcomes also appear superior to U.S. real-world reports [28]. Disparities likely stem from differences in patient and tumor profiles, particularly lower stage IIIC and N2/N3 prevalence in CANTO. Furthermore, potential enrichment with endocrine-sensitive tumors—due to France's higher HR-positivity threshold (≥10% versus 1% in monarchE and the U.S.)—may contribute [28].

This investigation details clinicopathological features and survival among a substantial real-world group potentially suitable for adjuvant abemaciclib. Limitations include absence of centralized Ki-67 review; however, as a practice-reflecting cohort, this mirrors routine care. Additionally, genomic risk signatures were unavailable for most patients, as they were enrolled before routine clinical adoption of these assays.

Conclusion

This exploratory evaluation from the CANTO cohort, focusing on HR+ breast cancer patients at elevated recurrence risk and eligible for abemaciclib, indicates that relapse hazard escalates early during adjuvant therapy despite chemotherapy, underscoring the urgency of integrating innovative agents with endocrine therapy from the outset. Although most patients exhibit multiple comorbidities despite favorable Charlson scores, drug–drug interactions with new adjuvant options could complicate management in select cases. Finally, adherence challenges may intensify with these additions, considering the substantial proportion already discontinuing endocrine monotherapy due to toxicity and the established link between compliance and survival.

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Ethics Statement: None

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