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ORIGINAL ARTICLE

Characteristics, treatment patterns and survival of patients with high-risk early hormone receptor-positive breast cancer in French real-world settings: an exploratory study of the CANTO cohort☆

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Background: Patients with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer (HR+ BC) with unfavorable features have an increased risk of relapse and are currently candidate for additional treatment strategies. We evaluated the real-world clinicopathological characteristics, treatment patterns and survival outcomes of these patients within the CANcer TOxicities study (CANTO, NCT01993498).

Patients and methods: This is a retrospective analysis of the prospective data collected within CANTO between 2012 and 2022. Patients with high-risk HR+ BC were defined either by the identification of at least four positive axillary lymph nodes (LNs) or one to three positive axillary LNs with a tumor size ≥5 cm or histologic grade 3 (cohort 1). The definition 1-3 positive LNs with Ki-67 ≥20% was also considered (cohort 2). The Kaplan—Meier method was used for survival analysis.

Results: Patients with high-risk HR+ BC represented 15.0%-19.6% of HR+ BC (cohort 1 and 2, respectively) in the CANTO cohort. Of the 1266 patients in cohort 1, 617 patients (49.0%) had ≥4 LNs, 327 (26.0%) had tumor ≥5 cm and 727 (57.6%) had grade III tumors. 79.9% had a favorable Charlson comorbidity score and 88.1% stage II/IIIA. Patients with ≥10 LNs accounted for 11.8%. (Neo)adjuvant chemotherapy was administered in 94.2%. Endocrine therapy was prescribed in 97.3%, mostly with aromatase inhibitors and discontinued in 34.3%, mainly for adverse events. Patients enrolled at least 6 years before data extraction had a 5-year invasive disease-free survival and 5-year distant relapse-free survival of 79.9% [95% confidence interval (CI) 77.2% to 82.4%] and 83.5% (95% CI 80.9% to 85.7%), respectively.

Conclusions: This real-world study confirms that patients with HR+ BC and unfavorable clinicopathological features are at risk of relapse early in their adjuvant treatment trajectory, despite (neo)adjuvant chemotherapy. It is imperative to implement innovative treatment approaches for high-risk patients, ideally adding them as early as possible to the adjuvant treatment.

Key words: early breast cancer, high risk, abemaciclib, real-world data, adjuvant CDK4/6 inhibitors

INTRODUCTION

Breast cancer (BC) is the most common malignancy among women with an estimated 2.3 million new cases reported annually and remains among the major causes of cancer-related death with around 0.7 million deaths each year.[1] The hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative BC (HR+ BC) is the most prevalent subtype, accounting for 70% of BC cases.[2] The majority of patients with HR+ BC are diagnosed

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at an early stage, allowing for a curative intent. The standard therapeutic approach starts with surgery, followed by endocrine therapy (ET), and often with radiotherapy and chemotherapy. The Early Breast Cancer Trialists' Collaborative Group has reported a higher risk of any BC-related events in patients with large primary tumor size, high lymph node (LN) involvement, high histologic grade and Ki-67 ≥20%.[3] According to international guidelines, patients with these features might benefit from chemotherapy followed by an extended duration of ET, but ∼20% experience a disease relapse in the first 10 years.[4-10] The monarchE trial has established a new standard of care in patients with HR+ BC at high risk of relapse according to a definition that takes into account the anatomical stage (tumor size and nodal involvement) and biological intricacies reflected in the histologic grade.[11-13] In this trial, the addition of the cyclin-dependent kinase (CDK) 4/6 inhibitor abemaciclib for 2 years to the standard of care reduced the risk of invasive disease-free survival (IDFS) with a 4-year absolute benefit of 6.4% (85.8% versus 79.4%), leading to the approval of abemaciclib by the Food and Drug Administration and European Medicines Agency.[11,13,14] With the same goal, the NATALEE trial has shown that the addition of ribociclib for 3 years to the standard of care improved the 3-year IDFS [hazard ratio 0.75, 95% confidence interval (CI) 0.62-0.91] by 3.0% and 3.2%, respectively, in patients with stage II and stage III disease. However, longer follow-up is needed to better establish the future position of this drug in the treatment landscape of early BC.[15,16]

Randomized controlled trials, such as monarchE and NATALEE, represent the benchmark in evidence-based medicine, offering a rigorous methodology that minimizes biases and confounding variables. However, their stringent eligibility criteria might exclude patients with poorer health performance status and multiple comorbidities, thus limiting the generalizability of the findings to a broader population.[17-22] This limitation can be addressed through the analysis of real-world data (RWD), which provide a promising tool to improve our understanding of clinical and demographic features of patients who could benefit the most from the escalation of adjuvant treatment. In the present study, our aim is to describe clinicopathological characteristics and survival outcomes of patients with HR+ BC at high risk of relapse, using RWD reported in the CANcer TOxicities (CANTO) prospective study.[23]

PATIENTS AND METHODS

Data source

We obtained data from the CANTO study (NCT01993498), a prospective observational study collecting detailed tumor, treatment, toxicities, health-related patient-reported outcomes and biological data relevant to BC since 20 March 2012 (enrolment is still ongoing).[23] CANTO has been enrolling patients ≥18 years of age, with a primary diagnosis of invasive stage cT0-cT3, cN0-3 BC and no previous treatments for BC. Patients were assessed at diagnosis and shortly after primary treatment (i.e. primary surgery, chemotherapy or radiotherapy, whichever came last), at the time of ET prescription, if indicated, and then at years 1, 3 and 5 after the initial post-primary treatment evaluation. Long-term follow-up was collected at years 6, 7, 8 and 10. Data collection at each time point include clinical, treatment (including medication adherence assessed by a trained clinical research nurse), toxicity data, health-related patient-reported outcomes and serum samples.[23]

CANTO is coordinated by UNICANCER, the national cooperative group of French cancer centers. The study was approved by the national regulatory authorities and ethics committee (ID-RCB: 2011-A01095-36, 11-039). All patients enrolled in the study provided written informed consent.[23] This analysis was conducted according to the guidelines of the Declaration of Helsinki, and the reporting followed the ESMO Guidance for Reporting Oncology real-World evidence (GROW).[24]

Patient selection and variable definitions

At the time of the last data extraction (5 September 2022), 11 342 women with newly diagnosed early BC were identified. For the purpose of this study, we included only women with HR+ HER2-negative BC. Cohort 1 included all women diagnosed with non-metastatic HR+ BC at high risk of relapse according to the monarchE trial criteria, defined either (i) by the presence of four or more positive pathological axillary LNs or (ii) one to three positive axillary LNs with a tumor size ≥5 cm or histologic grade 3.[12] We also considered a second cohort (cohort 2) with the definition one to three positive axillary LNs with a Ki-67 index ≥20%. Patients who did not meet the high-risk criteria were classified as 'low/intermediate risk' and were only considered for survival analysis.

Patient, tumor and treatment characteristics were collected from the CANTO dataset. Adherence to ET was defined by medical possession ratio (MPR) ≥80%. MPR was computed by dividing the sum of the days' supply for a given drug in a particular time period by the number of days in the time period.

Statistical analyses

The results of these analyses were reported separately with and without Ki-67 definition. Patient characteristics were described using frequencies and proportion of categorical variables relevant to baseline features and treatment patterns. The Standardized Definitions for Efficacy End Points (STEEP) v2.0 for IDFS and distant relapse-free survival (DRFS) were used to compute survival outcomes.[25] The definition for IDFS included invasive local, regional and distant recurrences; contralateral BC; second non-breast primary cancer; and death from any cause. DRFS is defined as the time from date of inclusion to date of first event of distant recurrence or death (any cause). We computed the 5-year survival outcomes using the Kaplan–Meier method and carried out a secondary analysis using the log-rank test to compare the outcomes of patients with high- and low-/intermediate-risk BC. To ensure adequate

follow-up, the survival analysis only included patients enrolled in the CANTO cohort at least 6 years before data extraction. Patients alive without an event at the last follow-up were censored at last visit available. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc. Cary, NC).

RESULTS

Among the 11 342 women enrolled in CANTO between 2012 and 2022, 8428 participants (74.3%) had HR+ BC (Figure 1). The first cohort of patients considered at high risk without applying the Ki-67 definition included 1266 participants (15.0% of the HR+/HER2-negative population in the CANTO cohort, representing 11% of the whole CANTO cohort) (Table 1). Median age was 54.3 years in both cohorts; 47.2% of the patients were premenopausal. Six hundred and seventeen patients (49.0%) were considered high risk on the basis of four or more nodes (Table 2). Tumor size ≥5 cm and grade III tumors were reported in 327 (26.0%) and 727 (57.6%) patients, respectively (Table 2). Among the 1122 patients with available Charlson comorbidity index, 897 patients (79.9%) had a score of 0. The proportion of articular, endocrine, cardiovascular and renal comorbidities was, respectively, 51.7%, 32.9%, 32.6% and 9.5% (Table 1). In particular, the most common comorbidity was high blood pressure (24.1%). Other relevant cardiovascular comorbidities were represented by heart rhythm disorder (4.3%). Hypercholesterolemia was the most common endocrine pathology affecting our cohort (13.0%), followed by diabetes (7.4%) and hypothyroidism (7.4%). Articular disorders included mainly osteoarthritis (14.1%) and bone fractures (16.7%). Germline *BRCA1/2* mutations were reported in 11.5%-11.6% of patients with high-risk BC (3.5% and 8.0% for germline *BRCA1* and *BRCA2* mutations, respectively).

Regarding the surgical management of the homolateral axilla, 87.2% of patients had an axillary LN dissection and 38.3% had a sentinel LN biopsy (Table 3). A total of 230 patients (18.2%) had received neoadjuvant chemotherapy, 953 (75.3%) had adjuvant chemotherapy, 9 (0.7%) had both neoadjuvant and adjuvant chemotherapy and 1240 (98.0%) had radiotherapy (Table 3). Aromatase inhibitors were the most prescribed first ET [653 (53.3%) as monotherapy and 34 (2.8%) plus ovarian function suppression], followed by tamoxifen [524 (42.8%) as monotherapy and 13 (1.1%) plus ovarian function suppression]. Three hundred and twenty-seven patients (34.3%) discontinued ET during follow-up, mostly for adverse events (183 patients; 56.0%) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103994). Median duration of first ET was 33.2 months (range 0.3-97.9 months) and 17.1 months (0-66.0 months) for patients included before and after 2016, respectively. Yearly adherence to ET was reported in 95.1% in the first year and 87.1% in the fifth year.

The second cohort of patients, considered at high risk after applying the Ki-67 criteria, included 1650 participants (19.6% of the HR+ BC population in the whole CANTO

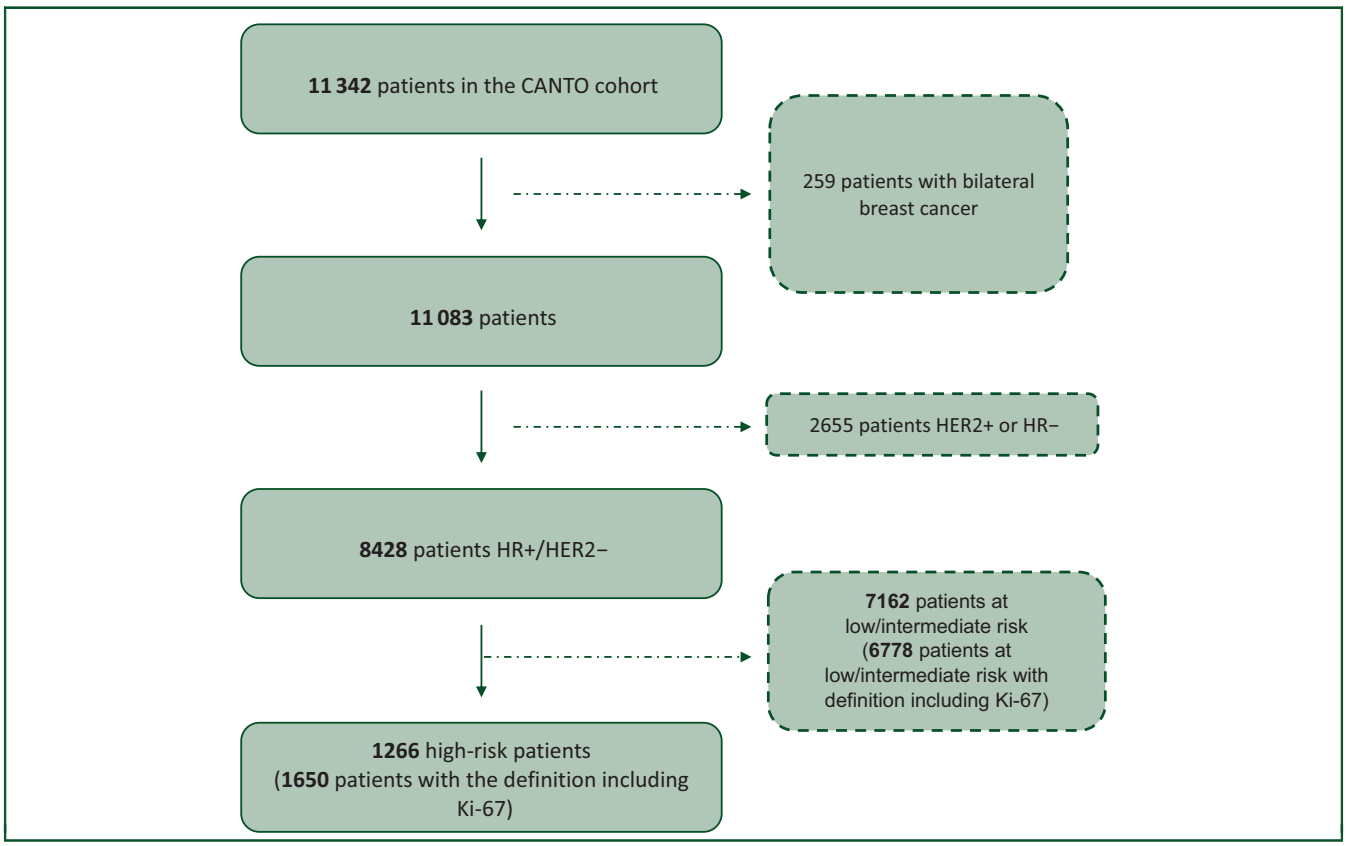

Figure 1. CONSORT diagram.
CONSORT, Consolidated Standards of Reporting Trials; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

Table 1. Clinical characteristics and tumor characteristics of patients with high-risk hormone receptor-positive breast cancer in the whole CANTO cohort

Patient characteristics		CANTO High risk w/o Ki-67 (total = 1266), *n* (%)	CANTO High risk w/ Ki67 (total = 1650), *n* (%)
Age	Median, range	54.3 (22.2-87.5)	54.3 (22.2-87.5)
	<65 years	1019 (80.6)	1330 (80.7)
	≥65 years	245 (19.4)	318 (19.3)
	Missing	2	2
Gender	Female	1266 (100)	1650 (100)
	Male	0	0
Menopausal status	Premenopausal	589 (47.2)	760 (46.9)
	Postmenopausal	659 (52.8)	861 (53.1)
	Missing	18	29
Germline *BRCA* mutations	*BRCA1*	12 (3.5)	14 (3.3)
	BRCA2	27 (8.0)	35 (8.3)
	Missing	927	1228
Charlson comorbidity index	0	897 (79.9)	1171 (79.6)
	1-2	196 (17.5)	260 (17.7)
	≥3	29 (2.6)	40 (2.7)
	Missing	144	179
ECOG performance status	0	1085 (94.8)	1416 (95.1)
	1	54 (4.7)	66 (4.4)
	2	6 (0.5)	7 (0.5)
	Missing	121	161
Comorbidities	Cardiovascular	413 (32.6)	545 (33.0)
	Renal	120 (9.5)	159 (9.6)
	Endocrine	417 (32.9)	561 (34.0)
	Osteoarticular	654 (51.7)	851 (51.6)

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

cohort, representing 14.9% of the whole CANTO cohort). Overall, the patients had similar clinicopathological characteristics and treatment patterns of the first cohort (Tables 1-3).

The survival analysis was restricted to patients enrolled in the CANTO cohort at least 6 years before data extraction to ensure mature follow-up (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.103994). The characteristics and treatment patterns of the patients included in the survival analysis are reported in Supplementary Tables S2-S4, available at https://doi.org/10.1016/j.esmoop.2024.103994. The breakdown of the recurrence events is reported in Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2024.103994. In the first cohort, the median follow-up was 6.4 years (range 0.0-10.4 years), the 5-year IDFS and DRFS were 79.9% (95% CI 77.2% to 82.4%) and 83.5% (95% CI 80.9% to 85.7%), respectively. These rates were shorter than those observed in patients with low/intermediate risk with a 5-year IDFS of 93.7% (95% CI 93.0% to 94.4%) and a 5-year

Table 2. Tumor characteristics of patients with high-risk hormone receptor-positive breast cancer in the whole CANTO cohort

Tumor characteristics		CANTO High risk w/o Ki-67 (total = 1266), *n* (%)	CANTO High risk w/ Ki67 (total = 1650), *n* (%)
Pathological tumor size (cm)	<2	296 (23.5)	473 (28.8)
	2-5	637 (50.6)	840 (51.2)
	≥5	327 (26.0)	327 (19.9)
	Missing	6	10
Positive axillary lymph nodes	0	47 (3.7)	55 (3.4)
	1-3	594 (47.2)	968 (59.0)
	4-9	469 (37.3)	469 (28.6)
	≥10	148 (11.8)	148 (9.0)
	Missing	8	10
Grade	Grade 1	53 (4.2)	83 (5.1)
	Grade 2	482 (38.2)	833 (50.7)
	Grade 3	727 (57.6)	727 (44.2)
	Missing	4	7
Ki-67	<20%	316 (33.8)	316 (23.9)
	≥20%	620 (66.2)	1004 (76.1)
	Missing	330	330
AJCC stage	Stage IA	0	0
	Stage IIA	217 (17.1)	432 (26.2)
	Stage IIB	304 (24.0)	471 (28.6)
	Stage IIIA	594 (46.9)	595 (36.1)
	Stage IIIB	0	0
	Stage IIIC	151 (11.9)	151 (9.2)
	Missing	0	1

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

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

Interventions		CANTO High risk w/o Ki-67 (total = 1266), *n* (%)	CANTO High risk w/ Ki67 (total = 1650), *n* (%)
Axillary surgery (cm)	SLNB	485 (38.3)	745 (45.2)
	ALND	1104 (87.2)	1367 (82.8)
Prior CT	None	73 (5.8)	151 (9.2)
	Any	1192 (94.2)	1498 (90.8)
	Neoadjuvant	230 (18.2)	272 (16.5)
	Adjuvant	962 (76.0)	1226 (76.3)
	Missing	1	1
Type of neoadjuvant CT	Anthracycline only	4 (1.7)	5 (1.8)
	Taxane + anthracycline	235 (98.3)	276 (98.2)
	Taxane only	0	0
Type of adjuvant CT	Taxane only	40 (4.2)	54 (4.4)
	Anthracycline only	13 (1.4)	17 (1.4)
	Taxane + anthracycline	903 (93.9)	1149 (93.7)
	Other	6 (0.6)	6 (0.5)
Radiotherapy	Yes	1240 (98.0)	1613 (97.8)
	Missing	1	1
Adjuvant ET	Yes	1230 (97.3)	1611 (97.8)
	Missing	2	2
First adjuvant ET	Aromatase inhibitor	653 (53.3)	854 (53.3)
	Aromatase inhibitor + OFS	34 (2.8)	41 (2.5)
	Tamoxifen	524 (42.8)	694 (43.3)
	Tamoxifen + OFS	13 (1.1)	13 (0.8)
	Missing	6	9
OFS (any time)	Yes	82 (6.7)	99 (6.2)
	Missing	5	7
Bone-modifying agents (any time)		116 (9.2)	150 (9.1)

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.

DRFS of 96.9% (95% CI 96.3% to 97.3%) ($P < 0.001$, Figure 2). In the second cohort, the 5-year IDFS and DRFS were 82.6% (95% CI 80.3% to 84.6%) and 85.9% (95% CI 83.8% to 87.8%), respectively, shorter than their counterparts who are at low/intermediate risk with a 5-year IDFS and a 5-year DRFS of 93.9% (95% CI 93.2% to 94.5%) and 97.1% (95% CI 95.6% to 96.7%) ($P < 0.001$).

DISCUSSION

Patients with stage II-III and high proliferative HR+ BC have an increased risk of relapse despite aggressive adjuvant therapies. In the CANTO cohort, these patients account for 15%-20% of the HR+ BC in line with other reported RWD.[26-28] In comparison to the study population enrolled in the pivotal trials, the median age in the CANTO cohort is comparable to monarchE, as well as the menopausal status, whereas expectedly the CANTO cohort had patients with more comorbidities and poorer performance status. While the commonly reported comorbidities rarely constitute a formal contraindication to abemaciclib, they warrant attention to the potential drug—drug interactions. Conversely, cardiac comorbidities can be challenging with ribociclib and sometimes could potentially contraindicate its use in patients with certain arrhythmias.[29] Furthermore, around one-fifth of the patients discontinued ET due to adverse events, raising concerns about introducing an additional drug, such as abemaciclib and ribociclib, without effective targeted interventions to mitigate treatment side-effects.

In this study, the analysis of the high-risk group was conducted both with and without the Ki-67 criterion because the monarchE trial and registration application for abemaciclib in the adjuvant setting considered the use of Ki-67 as a companion diagnostic. It is noteworthy, however, that the drug approvals did not take into consideration this requirement for the corresponding indication.[30-33]

In comparison to monarchE, high-risk patients with HR+ BC in the CANTO cohort had numerically more tumors ≥5 cm (19.9%-26% versus 21.6%-21.7%), grade III (44.2%-57.6% versus 37.7%-38.8%) and Ki-67 ≥20% (66.2%-76.1% versus 43.6%-44.9%) but less N2 and N3 involvement (37.6%-49.0% versus 59.3%-59.8%). The staging thus was more favorable in the CANTO cohort with less patients with stage IIIC (9.2%-11.9% versus 33.8%-34.0%) and more stage IIIA (36.1%-46.9% versus 36.2%-36.6%). The treatment patterns also show noticeable differences in the lower use 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 the CANTO cohort whereas anthracycline use (95.1%-95.3% versus 90.1%-95%) and tamoxifen (43.9%-44.1% versus 30.7%-32.1%) were more common. The time bias can be accounted for these differences given that the study period included patients before the publication of the TEXT and SOFT trials in 2018.[34,35]

Regarding the surgical management of the homolateral axilla, recent guidelines and consensus indicate sentinel LN biopsy as the gold standard approach for locoregional staging when there are no clinical signs of axillary

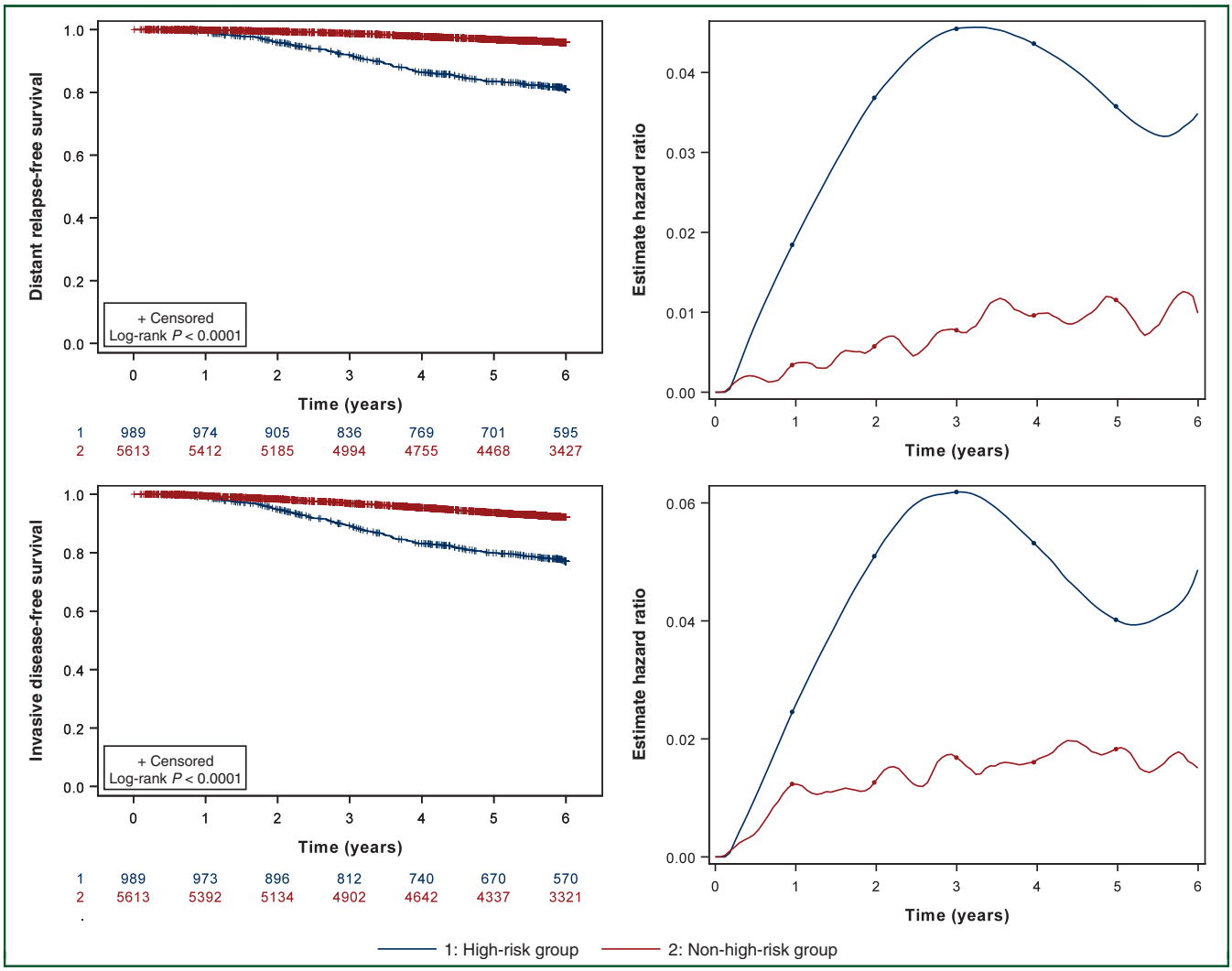

Figure 2. Survival outcomes. Kaplan—Meier curves (left) and smooth hazard ratios (right) of invasive disease-free survival and distant metastasis-free survival by risk group within the CANTO cohort of patients with hormone receptor-positive breast cancers in the first cohort (definition without Ki-67).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

involvement at diagnosis or after neoadjuvant chemotherapy.[36,37] However, the appropriateness of completing the axillary dissection in patients with positive sentinel LN biopsy in order to determine eligibility for treatments, such as olaparib and abemaciclib, is a matter of current debate.[37,38] This analysis shows that axillary LN dissection is commonly carried out (87.2%) in high-risk patients but this proportion could be affected by the timeframe of enrolment that started in 2012, given that axillary de-escalation surgical trials such as ACOSOC Z0011 and AMAROS followed thereafter.[39,40]

Olaparib was also approved in HR+ BC patients at high risk of relapse harboring germline *BRCA1/2* mutations.[36] In the absence of a head-to-head comparison between olaparib and abemaciclib, the choice of adjuvant therapy in patients eligible for both drugs relies on approval, drug access, long-term efficacy, safety profile and patients' characteristics and preference. In the CANTO cohort, patients with germline *BRCA1/2* mutations accounted for 11.5% of high-risk patients (3.5% and 8.0% for germline *BRCA1* and *BRCA2* mutations, respectively) which exceeds the prevalence of germline *BRCA* mutations in HR+ BC patients not selected for high risk of relapse (between 1.5% and 5.0%) or selected for it (2.2%).[28,41,42] The CANTO data showed that the overlap of the two indications may occur in around 0.9% in the adjuvant setting with 9 patients presenting germline *BRCA* mutations and N2 staging among the 953 patients who did not receive neoadjuvant chemotherapy. Unfortunately, the CANTO cohort does not report the post-treatment pathological stage, estrogen receptor status and tumor grade score (CSP + EG score) to have a more accurate estimate covering the neoadjuvant indications of olaparib. Compared with patients without high-risk features, these RWD show that the survival outcomes of patients with high-risk HR+ BC are suboptimal, with a 5-year IDFS at 79.9%-82.6%, and a 5-year DRFS at 82.6%-85.9%. Numerically, these findings are similar to those reported with the use of abemaciclib in monarchE and are thereby superior to the control arm (5-year DRFS 85.6% and 78.5%, respectively).[13] They are also better than the

reported outcomes of RWD in the US population.[28] These differences can primarily be attributed to the patients' and tumor characteristics, notably the lower prevalence of stage IIIC in the CANTO cohort, specifically patients with N2 and N3 involvement. Moreover, the enrichment of the CANTO cohort with tumors exhibiting better prognosis and higher sensitivity to ET may also contribute to the difference in outcomes given that the threshold used in France to define HR positivity is set at $\geq$10% in contrast to 1% in monarchE and the United States.[28]

This work reports on a large cohort of patients in which clinicopathological characteristics and survival of potential candidates for adjuvant abemaciclib in a real-world setting are described. It is limited by the lack of a central assessment for Ki-67. However, given that the CANTO study is a real-world cohort, it mirrors the daily clinical practice. Secondly, this study lacked genomic signature data, a potential criterion to define patients with high genomic risk, because the large majority of the patients considered for this analysis were enrolled before the introduction of this tool in clinical practice.

Conclusions

This exploratory analysis of the CANTO study, portraying patients with HR+ BC at increased risk of relapse eligible for abemaciclib, showed that the risk of recurrence tend to raise early in the adjuvant treatment journey, despite the use of chemotherapy, thus underlying the necessity for introducing novel therapies alongside adjuvant ET as early as possible in the treatment plan. While the majority of these patients present numerous comorbidities albeit a favorable Charlson comorbidity score, potential drug—drug interactions both with novel therapies added in the adjuvant setting may pose challenges in certain patients. Lastly, the issue of adherence may come to the forefront again with these therapies given the rate of patients already discontinuing ET monotherapy due to adverse events and the impact of adherence on survival outcomes.

DISCLOSURE

ER: travel, accommodations, expenses: Pfizer, Roche, Mundipharma, Eli Lilly, Novartis; grants: Gilead (institutional); honoraria: Eli Lilly, Seagen, Novartis. BP: consulting/advisor: Puma Biotechnology, Novartis, Myriad Genetics, Pierre Fabre; personal fees: Novartis, AstraZeneca, MSD Oncology, Pfizer; research funding: Daiichi-Sankyo, Puma Biotechnology, Novartis, Merus, Pfizer, AstraZeneca. GC: receipt of grants/research supports: Merck; receipt of honoraria or consultation fees: Merck, Lilly, Pfizer, Daichii Sankyo, Seagen, Novartis, Roche, Astra Zeneca, Ellipsis; participation in a sponsored speakers' bureau: Seagen, Novartis, Lilly, Pfizer, Daichii Sankyo. FA: consulting or advisory role: Guardant Health (Inst), AstraZeneca (Inst), Lilly, Daiichi Sankyo (Inst), Roche (Inst), Lilly (Inst), Pfizer (Inst), Owkin (Inst), Novartis (Inst), N-Power Medicine (Inst), Servier (Inst), Gilead Sciences (Inst), Boston Pharmaceuticals (Inst); research funding: AstraZeneca (Inst), Novartis (Inst), Pfizer (Inst), Lilly (Inst), Roche (Inst), Daiichi (Inst), Owkin (Inst), Guardant Health (Inst); travel, accommodations, expenses: Novartis, Roche, GlaxoSmithKline, AstraZeneca. MC: advisory board: Astra Zeneca, Novartis, Abbvie, Sanofi, Lilly, Pfizer, Sandoz, ACCORD, G1 Therapeutic, Seagen, Gilead, Daiichi-Sankyo; consultant: Pierre Fabre Oncology, Sanofi, Novartis, Servier, Daiichi-Sankyo, PET-Therapy; speaker bureau: Novartis, Lilly; travel: Pfizer, Novartis, Roche, Astra Zeneca. All other authors have declared no conflicts of interest.

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