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Adjuvant endocrine therapy choices in premenopausal patients with hormone receptor-positive early breast cancer: Insights from the prospective GIM23-POSTER study

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ABSTRACT

Background: Most premenopausal patients with early breast cancer (eBC) are diagnosed with hormone receptor-positive disease and therefore candidate for adjuvant endocrine therapy (ET).
Patients and methods: The Gruppo Italiano Mammella (GIM) 23-POSTER (GIM23) is a multicenter, prospective, observational study conducted in 26 Italian institutions, aiming to evaluate ET choices for premenopausal patients affected by hormone receptor-positive eBC in a real-world setting. Here we report also the results in terms of type of ET prescribed according to the definition of high-risk patients by monarchE and NATALEE trials.
Results: Between October 2019 and June 2022, 600 premenopausal patients were included, with a median age of 46 years. Almost half (271, 45.2 %) of the patients had stage I disease, while 254 (42.3 %) and 60 (10.0 %) patients had stage II and III, respectively. Overall, 149 (25.1 %) patients received tamoxifen alone, 83 (14.0 %) tamoxifen with ovarian function suppression (OFS), while 361 (60.9 %) received aromatase inhibitor (AI) with OFS. Patients treated with AI and OFS had higher number of metastatic axillary nodes, higher grade and more often received chemotherapy (all $p < 0.001$). According to the inclusion criteria of the monarchE and NATALEE trials, 81 patients (15.6 %) were considered high-risk for the monarchE and received AI with OFS in 88.9 % of the cases, while 231 patients (44.4 %) were considered high-risk for the NATALEE trial and received AI with OFS in 74.5 % of cases.

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Conclusions: AI with OFS is the most prescribed adjuvant ET among premenopausal patients, especially in the presence of high-risk features.

1. Background

Between 50 % and 70 % of early breast cancer (eBC) cases in premenopausal women are hormone receptor-positive [1,2] anddjuvant endocrine therapy (ET) represents the cornerstone of the treatments for these patients [3,4]. Risk of breast cancer recurrence varies according to the baseline biological characteristics and the stage of the disease and recurrence rates remain constantly relevant even after the first 5–10 years after diagnosis [5,6]. In premenopausal patients, adjuvant treatment with tamoxifen for 5 years reduced breast cancer recurrences and increased overall survival [7], while in the last years several studies evaluated the benefit of ovarian function suppression (OFS) plus tamoxifen or an aromatase inhibitor (AI) in the adjuvant treatment of hormone receptor-positive breast cancer [8–11]. In the combined analysis of the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) an absolute improvement of 4.6 % in disease-free survival (DFS) and 1.8 % in distant recurrence-free interval (DRFI) was observed for patients that received exemestane in association with OFS as compared to tamoxifen with OFS [11], with greater benefit in patients at higher risk of recurrence, for whom a trend for improved overall survival (OS) was also demonstrated [11]. Current guidelines recommend tamoxifen alone for at least 5 years or OFS in association with tamoxifen or AI for adjuvant ET of premenopausal breast cancer women according to their risk of recurrence [3,4]; however, despite many studies evaluated the benefit of the different strategies of adjuvant ET according to the risk of relapse [7–9,11], to date there are no definitive and shared criteria to guide the choice among adjuvant ET.

Further escalation strategies of adjuvant therapy in combination with ET in patients at higher risk of recurrence have been presented recently [12–14], with both monarchE and NATALEE studies demonstrating a significant benefit in terms of invasive disease-free survival (iDFS) with the addition of a CDK4/6i to adjuvant ET [14,15]. However, in a real world-setting, few data are available to date on the characteristics of premenopausal patients at high-risk of relapse according to the criteria for enrolment in the two trials [16].

The Gruppo Italiano Mammella (GIM) 23 - POSTER (GIM23) study is a prospective, multicenter, observational study that aimed to assess the choices of adjuvant ET in premenopausal patients with hormone receptor-positive eBC. The present analysis was conducted to analyze the baseline patient and tumor characteristics according to the prescribed adjuvant ET and to evaluate the proportion of patients potentially candidated to receive CDK4/6i in combination with adjuvant ET according to the monarchE and NATALEE trials.

2. Methods

2.1. Study design and participants

The GIM23 study is an ongoing, multicenter, prospective, observational study carried out in 26 Italian institutions affiliated with the GIM group aiming to assess in a real-world setting the choice of adjuvant ET in premenopausal patients with hormone receptor-positive eBC.

Eligible patients were premenopausal women with ≥18 years of age affected by hormone receptor-positive eBC candidates to start adjuvant ET. Patients may have received chemotherapy in the neoadjuvant and/or adjuvant setting but must not have received previous adjuvant ET.

Patients could receive one of the following adjuvant endocrine treatments: tamoxifen alone, tamoxifen plus OFS or AI plus OFS. Choice of the type of ET was made by each investigator according to current guidelines [3,4]. These treatments could also be combined with any target therapy that are currently available in clinical practice (i.e., abemaciclib or olaparib). The study was approved by the Ethic Committees of all participating centers and all patients provided written informed consent before study entry.

The study is registered at ClinicalTrials.gov (Trial Number: NCT05730647).

2.2. Study objectives

The primary objective of the GIM23 study was to assess adjuvant ET choices in premenopausal patients with hormone receptor-positive eBC in a real-world setting.

Secondary objectives included correlation of adjuvant ET choices with both biological characteristics of the disease (i.e., tumor size, lymph node status, tumor grade, Ki67 and HER2-status) and patient characteristics (i.e., age, race, BMI, prior treatment received).

In addition, a descriptive analysis of the proportion of patients who fulfilled the definition of high-risk according to the criteria of the monarchE and NATALEE trials was performed. The characteristics of the patients included in the GIM23 study were evaluated according to clinical high-risk and non-high-risk cohorts of the studies. The criteria for classifying high-risk patients according to the inclusion criteria of the monarchE and NATALEE trials are reported in the Supplementary Methods section.

2.3. Statistical analysis

Continuous variables were summarized using median and interquartile ranges. To test differences between groups, when applicable, Kruskal-Wallis test or Wilcoxon's rank sum test were used. Categorical variables were summarized with absolute frequencies and percentages and comparison was made with Chi-square test. Logistic regression was applied to explore factors associated with adjuvant ET choices. For this purpose, patients receiving OFS in association with Tamoxifen or AI were considered together. Characteristics associated with different choice of ET with a p-value <0.05 at univariate analysis were included in a multivariate model where final variable selection was made using a stepwise approach.

SPSS (version 20.0) and SAS (version 9.4) were used for all statistical analyses. All reported p values were two-tailed and considered statistically significant for a threshold value < 0.05.

3. Results

3.1. Baseline characteristics of the overall population

Between October 2019 and June 2022, 600 patients were enrolled in the GIM23 study. Median age at enrollment was 46 years (IQR 41–49). Baseline demographic and tumors characteristics of the first 600 patients enrolled are shown in Table 1. A total of 271 (45.2 %) patients had stage I, 254 (42.3 %) had stage II and 60 (10.0 %) stage III disease. Most of the patients (407, 67.8 %) had node negative disease. Overall, 67 (11.2 %) patients had HER2-positive disease and 218 (36.3 %) patients received prior chemotherapy.

3.2. Baseline characteristics according to the type of prescribed adjuvant endocrine therapy

Data on adjuvant ET prescribed were available for 593 patients

Table 1
Baseline characteristics of the patients included.

	Overall Population (N = 600)
Age (median, IQR)	46 (41–49)
Race	
White	592 (98.7 %)
Black	5 (0.8 %)
Other	1 (0.2 %)
Unknown	2 (0.3 %)
BMI	
<18.5	24 (4.0 %)
18,5–24,9	301 (50.2 %)
25 - 29,9	94 (15.7 %)
≥30	36 (6.0 %)
Unknown	145 (24.1 %)
Stage at diagnosis	
I	271 (45.2 %)
II	254 (42.3 %)
III	60 (10.0 %)
Unknown	15 (2.5 %)
Tumor size	
T1	279 (46.5 %)
T2	221 (36.8 %)
T3	79 (13.2 %)
Unknown	21 (3.5 %)
Lymph node involvement	
N0	407 (67.8 %)
N1	154 (25.7 %)
N2	25 (4.2 %)
N3	9 (1.5 %)
Unknown	5 (0.8 %)
Tumor grade	
G1	117 (19.5 %)
G2	324 (54.0 %)
G3	138 (23.0 %)
Unknown	21 (3.5 %)
Ki67 status	
<20 %	297 (49.5 %)
≥20 %	282 (47.0 %)
Unknown	21 (3.5 %)
HER2 status	
Negative	520 (86.7 %)
Positive	67 (11.2 %)
Unknown	13 (2.2 %)
Prior chemotherapy	
No	376 (62.7 %)
Yes	218 (36.3 %)
Unknown	6 (1.0 %)
Prior chemotherapy purpose	
Neoadjuvant	61 (28.0 %)
Adjuvant	125 (57.3 %)
Neoadjuvant + adjuvant	30 (13.9 %)
Unknown	2 (0.3 %)
pCR[a]	
Yes	33 (36.3 %)
No	48 (52.7 %)
Unknown	10 (11.0 %)

Abbreviations: IQR, inter-quartile range; BMI, body mass index; pCR, pathological complete response.

[a] Percentages are evaluated on the total of the patients which received neoadjuvant chemotherapy, including patients with HER2-positive disease.

(Supplementary Fig. 1); among them, 149 (25.1 %) patients received adjuvant tamoxifen alone, 83 (14.0 %) patients tamoxifen in combination with OFS, and 361 (60.9 %) the combination of AI with OFS (Fig. 1). Baseline characteristics according to the type of prescribed ET are reported in Table 2.

Among those patients that received tamoxifen alone, a higher frequency of patients had stage I disease (102, 68.5 %) while only a small proportion of those with stage II and III received tamoxifen alone and often received AI + OFS ($p < 0.001$) (Fig. 2A). In the tamoxifen alone group, almost all patients had node negative disease (92.6 %), while the percentage of patients with positive lymph nodes increased in the tamoxifen + OFS (22.9 %) and in the AI + OFS groups (44.1 %) ($p < 0.001$) (Table 2 and Fig. 2B).

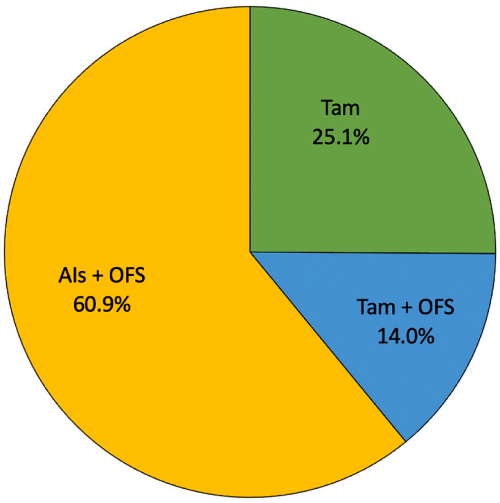

Fig. 1. Adjuvant endocrine therapy prescribed in the overall population.

A total of 45.7 % of patients diagnosed with a grade 1 disease received tamoxifen, while 79.0 % of the patients with grade 3 disease received AI + OFS ($p < 0.001$) (Fig. 2C). Patients with a Ki67 < 20 % received tamoxifen alone in 34.8 % of the cases while patients with Ki67 ≥ 20 % were treated with AI + OFS in 71.8 % of the cases ($p < 0.001$) (Fig. 2D). There were no differences in the proportion of HER2-positive disease among the three groups ($p = 0.3$).

A logistic regression was performed to assess clinical and biological factors related to treatment choices; for this purpose, patients were divided between those treated with OFS, in combination with tamoxifen or AI (N = 444), and those treated with tamoxifen alone (N = 149). At the univariate analysis, an increase in prescription of OFS compared to tamoxifen alone was observed for patients with higher tumor stage, poorly differentiated tumors, high Ki67, and prior chemotherapy (all $p < 0.001$) (Table 3). In the multivariate model higher nodal involvement, higher tumor grade and prior chemotherapy were associated with an increase in the OFS treatment compared to tamoxifen alone (Table 3). Association of BMI in both univariate and multivariate model was driven by patients with unknown BMI. An analysis to assess differences in ET prescribed according with study centers has also been reported in Supplementary Table 1, showing that there is heterogeneity in the prescription pattern of adjuvant ET according to the different centers ($p < 0.001$).

Among the 218 patients who received previous (neo)adjuvant chemotherapy, 81.7 % of patients received AI + OFS, whereas in patients who did not receive chemotherapy, 48.8 % received AI + OFS and 35.2 % of patients received tamoxifen alone ($p < 0.001$) (Supplementary Fig. 2A).

Overall, 91 patients received neoadjuvant chemotherapy and among them, 33 (36.3 %) achieved a pCR, of whom 19 (57.6 %) had an HER2-positive disease. Patients who achieved pCR received AI + OFS in 69.7 % of cases, while 83.3 % of patients received AI + OFS in case of non-pCR (Supplementary Fig. 2B).

Considering patients that received chemotherapy overall, 201/218 (92.2 %) received OFS as part of the adjuvant ET after the end of chemotherapy. It should be highlighted also that 60/218 (27.5 %) of the patients who received (neo)adjuvant chemotherapy received OFS before and during chemotherapy treatment for preservation of ovarian function and of these, 59/60 (98.3 %) of the patients continued OFS as part of adjuvant ET.

Patients received pharmacological OFS in all the cases reported through the administration triptorelin 3.75 mg (monthly) in 202 cases, triptorelin 11.25 mg (3-monthly) in 1 case, leuprorelin 3.75 mg (monthly) in 187 cases, leuprorelin 11.25 mg (3-monthly) in 1 case and

Table 2
Baseline characteristics of the patients according to adjuvant endocrine therapy prescribed.

	Tamoxifen (N = 149)	Tamoxifen + OFS (N = 83)	Aromatase inhibitors + OFS (N = 361)	p-value
Age (median, IQR)	47 (44–50)	45 (40–49)	45 (40–48)	<0.001
Race				NA
White	148 (99.3 %)	82 (98.8 %)	356 (98.6 %)	
Black	0 (0 %)	1 (1.2 %)	4 (1.1 %)	
Other	0 (0 %)	0 (0 %)	1 (0.3 %)	
Unknown	1 (0.7 %)	0 (0 %)	0 (0 %)	
BMI				0.07
<18.5	8 (5.4 %)	1 (1.2 %)	15 (4.2 %)	
18,5–24,9	71 (47.7 %)	50 (60.2 %)	177 (49.0 %)	
25-29,9	17 (11.4 %)	14 (16.9 %)	63 (17.5 %)	
≥30	6 (4.0 %)	4 (4.8 %)	26 (7.2 %)	
Unknown	47 (31.5 %)	14 (16.9 %)	80 (22.2 %)	
Stage at diagnosis				<0.001
I	102 (68.5 %)	36 (43.4 %)	130 (36.0 %)	
II	41 (27.5 %)	37 (44.6 %)	176 (48.8 %)	
III	1 (0.7 %)	7 (8.4 %)	52 (14.4 %)	
Unknown	5 (3.4 %)	3 (3.6 %)	3 (0.8 %)	
Tumor size				<0.001
T1	94 (63.1 %)	37 (44.6 %)	146 (40.4 %)	
T2	35 (23.5 %)	24 (28.9 %)	161 (44.6 %)	
T3	15 (10.1 %)	19 (22.9 %)	45 (12.5 %)	
Unknown	5 (3.4 %)	3 (3.6 %)	9 (2.5 %)	
Lymph node involvement				<0.001
N0	138 (92.6 %)	64 (77.1 %)	202 (56.0 %)	
N1	9 (6.0 %)	17 (20.5 %)	128 (35.5 %)	
N2	1 (0.7 %)	1 (1.2 %)	23 (6.4 %)	
N3	0 (0 %)	1 (1.2 %)	8 (2.2 %)	
Unknown	1 (0.7 %)	0 (0 %)	0 (0 %)	
Tumor grade				<0.001
G1	53 (35.6 %)	17 (20.5 %)	46 (12.7 %)	
G2	81 (54.4 %)	48 (57.8 %)	193 (53.5 %)	
G3	12 (8.1 %)	17 (20.5 %)	109 (30.2 %)	
Unknown	3 (2.0 %)	1 (1.2 %)	13 (3.6 %)	
Ki67 status				<0.001
<20 %	103 (69.1 %)	43 (51.8 %)	150 (41.6 %)	
≥20 %	41 (27.5 %)	38 (45.8 %)	201 (55.7 %)	
Unknown	5 (3.4 %)	2 (2.4 %)	10 (2.8 %)	
HER2 status				0.3
Negative	136 (91.3 %)	73 (88.0 %)	308 (85.3 %)	
Positive	11 (7.4 %)	10 (12.0 %)	46 (12.7 %)	
Unknown	2 (1.3 %)	0 (0 %)	7 (1.9 %)	
Prior chemotherapy				<0.001
No	132 (88.6 %)	60 (72.3 %)	183 (50.7 %)	
Yes	17 (11.4 %)	23 (27.7 %)	178 (49.3 %)	
Prior chemotherapy purpose				NA
Neoadjuvant	6 (4.0 %)	9 (10.8 %)	46 (12.7 %)	
Adjuvant	8 (5.4 %)	12 (14.5 %)	105 (29.1 %)	
Neoadjuvant + Adjuvant	3 (2.0 %)	2 (2.4 %)	25 (6.9 %)	
Unknown	0 (0 %)	0 (0 %)	2 (1.1 %)	
pCR[a]				NA
Yes	5 (55.5 %)	6 (54.5 %)	22 (36.0 %)	
No	4 (44.5 %)	5 (45.5 %)	39 (64.0 %)	

Abbreviations: OFS, ovarian function suppression; IQR, inter-quartile range; BMI, body mass index; pCR, pathological complete response; NA, not assessed.
[a] Percentages are evaluated on the total of the patients which received neo-adjuvant chemotherapy (N = 91 patients), without Unknown (N = 10 patients).

goserelin 3.6 mg (monthly) in 1 case, while data on the type of pharmacological OFS were not available for 52 patients. Triptorelin was associated with AI in 82.0 % of cases and leuprorelin in 79.0 % of cases.

3.3. Distribution of patients according to clinical high-risk definition for access to CDK4/6-inhibitors in association with adjuvant endocrine therapy

A total of 520 (86.7 %) patients had known HER2-negative disease and were included in this analysis (Supplementary Fig. 1). According to the enrollment criteria of the monarchE and NATALEE trials, 232 (44.6 %) patients resulted at clinical high-risk of recurrence for at least one of the studies, while 288 (55.4 %) resulted non-high-risk of recurrence for both (Fig. 3A and Supplementary Table 2). A total of 81 patients (15.6 %) met the criteria set as high-risk for the monarchE trial, while 231 (44.4 %) patients met the criteria of clinical high-risk for the NATALEE trial. All but 1 (0.2 %) patient considered at high-risk according to monarchE criteria were included in the 231 patients considered at high-risk according to NATALEE criteria (Supplementary Table 2).

Among the high-risk patients by monarchE criteria, 76.5 % received (neo)adjuvant chemotherapy, while in the high-risk group by NATALEE criteria 53.2 % received previous chemotherapy (Supplementary Table 3). Most of the 81 patients at clinical high-risk for monarchE criteria received the combination of AI + OFS (88.9 %) as adjuvant ET, while 7.4 % received tamoxifen + OFS or tamoxifen alone (3.7 %). In high-risk patients by NATALEE criteria, patients who received combination therapy with AI + OFS were 74.5 %, while 15.2 % received tamoxifen + OFS (Supplementary Table 3 and Fig. 3B).

Among the 81 patients with high-risk criteria by monarchE trial, 60.5 % had stage III disease at diagnosis, while among the 231 patients with high-risk according to NATALEE criteria only 22.5 % had stage III disease at diagnosis (Supplementary Table 3). In the group of high-risk patients, 56.8 % and 31.3 % of patients had grade 3 disease according to monarchE and NATALEE study, respectively (Supplementary Table 3).

In Table 4 are reported characteristics of the patients divided according to the high-risk criteria of both studies into three categories: concordant non-high-risk patients (N = 288, 55.4 %), concordant high-risk patients (N = 80, 15.4 %), and patients with discordant high-risk criteria (N = 152, 29.2 %).

Adjuvant ET with AI + OFS was prescribed in 90.0 % of concordant high-risk patients, 65.8 % in discordant high-risk patients and 47.2 % in concordant non-high-risk patients ($p < 0.001$).

4. Discussion

To our knowledge, the GIM23 is the first prospective study aiming to assess which are the adjuvant ET prescribed in premenopausal patients as per current clinical practice. Among 600 patients with a median age of 46 years enrolled between 2019 and 2022 across 26 centers in Italy, the combination of OFS in association with AI was prescribed in 60.9 % of the cases, tamoxifen alone in 25.1 % of the cases and OFS plus tamoxifen in 14.0 % of the cases.

The role of OFS in addition to tamoxifen in premenopausal patients has been demonstrated by the E−3193, INT-0142 trial [17] and the SOFT trial [18,19], where this combination showed a significant improvement in outcomes for women considered at higher risk [17,19], while the joint analysis of the SOFT and TEXT trials demonstrated that the addition of OFS to AI was superior to tamoxifen and OFS (except in patients with HER2-positive disease) [11]. A recent large meta-analysis showed that women assigned to AI + OFS had a lower rate of breast cancer recurrence compared to those treated with tamoxifen + OFS, while no differences were observed in breast cancer mortality [20].

Taking together these results, international guidelines have been progressively updated and at present the indication for the choice of adjuvant ET must be performed on a patient-by-patient basis considering both patient preferences, disease characteristics as well as benefits and side effects of each treatment [3,4,21,22]. The score developed from the SOFT and TEXT data serves as a composite risk assessment tool providing insights into the likelihood of distant recurrence and enhancing the decision-making process for adjuvant ET [23].

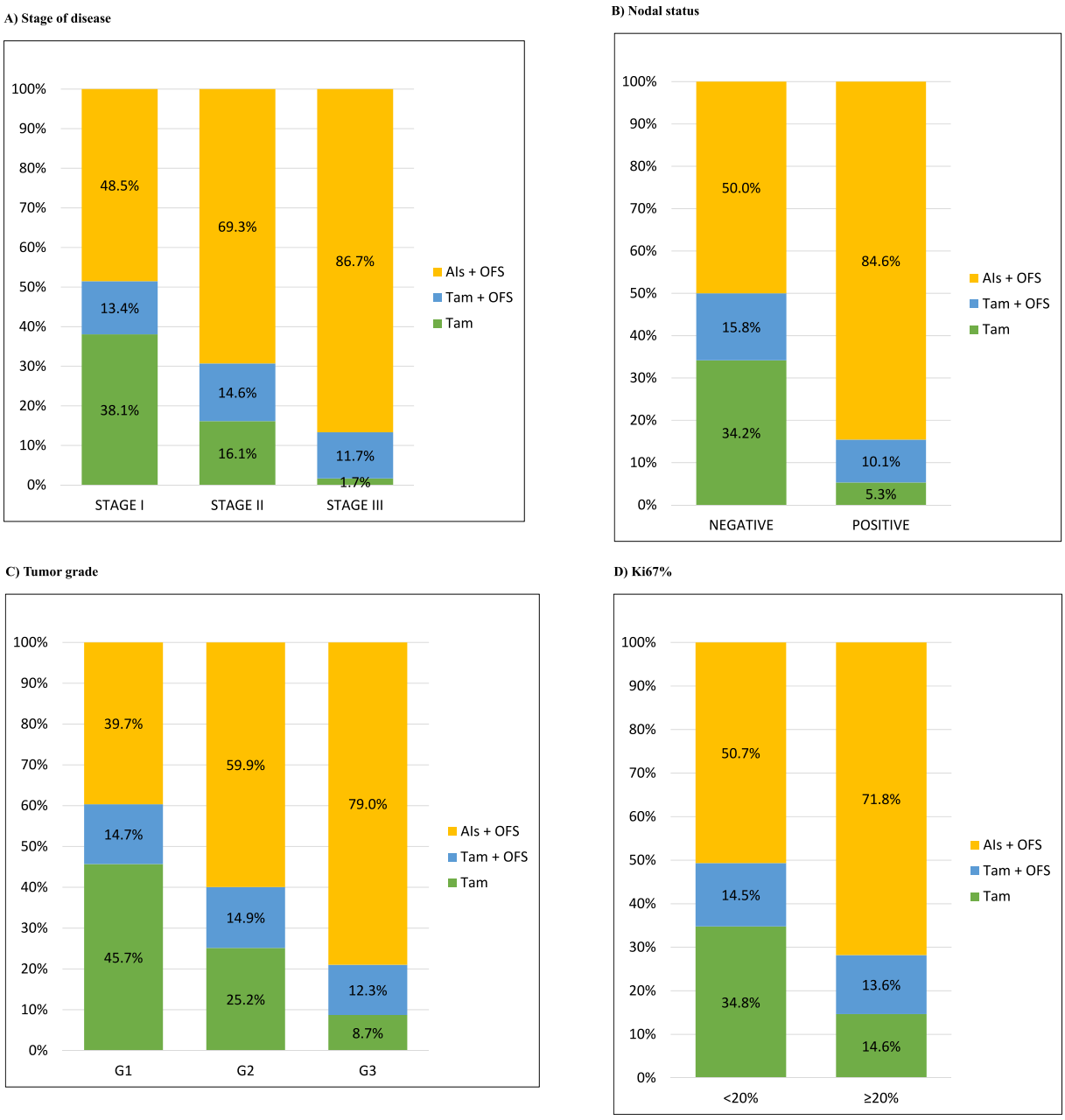

Fig. 2. Adjuvant endocrine therapy prescribed in the overall population according to A) stage of disease B) nodal status C) tumor grade D) Ki67 %.

In the GIM23 study, patients at higher risk of recurrence received OFS plus AI, while tamoxifen alone was prescribed only to patients at lower risk of recurrence, with approximately 70 % of patients in this group having stage I disease, mostly grade 1 and grade 2 disease (90.0 %) and only 11.4 % received prior chemotherapy. On the contrary, patients who received OFS + AI had stage II or III disease in 63.2 % of cases, grade 2 and 3 disease in 83.7 % and almost 50 % had received previous chemotherapy.

These findings are consistent with those from the pooled analysis of the SOFT and TEXT studies, in which patients who benefited the most from OFS plus AI were characterized by young age (<35 years), larger tumor size (>2 cm), nodal involvement (≥4 positive lymph nodes), high grade and high Ki67, and those that received previous chemotherapy.

Among the patients previously treated with chemotherapy in GIM23 study, 81.7 % received OFS plus AI, while only 10.6 % and 7.8 % received tamoxifen plus OFS or tamoxifen alone, respectively. Our data showed however that it is still difficult to determine who are the patients at intermediate risk of recurrence, for whom the choice of therapy could be tamoxifen combined with OFS. In fact, although patients treated with this combination had intermediate risk characteristics (44.6 % stage II, 77.1 % node-negative, 57.8 % G2 disease and 27.7 % received chemotherapy) compared to the other treatment groups, the percentage of patients treated with tamoxifen and OFS combination (only 14.0 % of the patients) is lower than the others strategies [24,25]. Logistic regression confirmed that as the main clinical and biological risk criteria increased, there was an associated increase in the prescription of OFS compared to tamoxifen alone, indicating that all these factors are relevant in the choice of the adjuvant ET.

Concerning the analysis evaluating the patients at high-risk of recurrence according to the monarchE and NATALEE trials, our work also showed that 15.6 % of the patients can be considered at high-risk of recurrence according to enrolment criteria of the monarchE trial, while according to enrolment criteria of the NATALEE trial, 44.4 % would be considered at high-risk of recurrence. Our finding are in line with a

Table 3
Clinical and biologicalcharacteristics associated with the choice of adjuvant endocrine therapy.

	Univariate		Multivariate	
	Tamoxifen vs OFS + Tamoxifen/AIs	p-value	Tamoxifen vs OFS + Tamoxifen/AIs	p-value
BMI		0.01		0.01
<25	REF		REF	
≥25	0.66 (0.39–1.11)		0.72 (0.41–1.27)	
Unknown	1.54 (1.00–2.37)		2.13 (1.29–3.51)	
Stage at diagnosis		<0.001	REMOVED	NA
I	REF			
II	0.31 (0.21–0.48)			
III	0.03 (0.01–0.20)			
Unknown	1.36 (0.40–4.56)			
Tumor size		<0.001	REMOVED	NA
T1	REF			
T2	0.37 (0.24–0.57)			
T3	0.46 (0.25–0.84)			
Unknown	0.81 (0.28–2.37)			
Lymph node involvement		<0.001		<0.001
Node Negative	REF		REF	
Node Positive	0.11 (0.06–0.22)		0.14 (0.07–0.28)	
Unknown	NA		NA	
Tumor grade		<0.001		<0.001
G1	REF		REF	
G2	0.40 (0.26–0.62)		0.45 (0.28–0.73)	
G3	0.12 (0.06–0.23)		0.23 (0.10–0.50)	
Unknown	0.29 (0.08–1.01)		0.29 (0.06–1.46)	
Ki67 status		<0.001	REMOVED	NA
<20 %	REF			
≥20 %	0.32 (0.21–0.48)			
Unknown	0.78 (0.27–2.28)			
HER2 status		0.22	REMOVED	NA
Negative	REF			
Positive	0.55 (0.28–1.08)			
Unknown	0.80 (0.16–3.9)			
Prior chemotherapy		<0.001		<0.001
No	REF		REF	
Yes	0.16 (0.09–0.27)		0.33 (0.18–0.61)	

Abbreviations: AIs, aromatase inhibitors; OFS, ovarian function suppression BMI, body mass index; pCR, pathological complete response; NA, not assessed.

recently published retrospective analysis in which, among 4028 patients in the United States, 557 patients (13.8 % of the total) were identified as high risk according to monarchE criteria [26].

In another retrospective work on a population of 1738 patients treated in two large German university cancer centers, 43 % of the patients met the NATALEE inclusion criteria, in line with our result of 44 % [27]; however, it should be noted that these analyses did not only include premenopausal patients, therefore these results should be cautiously compared to the results of the GIM23.

Overall, the clinical and biological characteristics of the patients considered at high-risk according to monarchE criteria in the GIM23 study were rather similar to those of the patients enrolled in the monarchE trial (32.6 % patients with stage II and 73.8 % stage III disease, tumor grade 3 in 38.2 % and high Ki67 in 44.2 %), while those at high-risk according to the monarchE trial in GIM23 study had 38.3 % stage II and 60.5 % stage III disease, tumor grade 3 in 56.8 % and high Ki67 in 72.8 % of the cases. It should be noted that 76.5 % of the patients who resulted as potential candidates for abemaciclib in GIM23 had received previous chemotherapy, whereas in the monarchE trial almost all patients (95.6 %) received prior chemotherapy. Patients enrolled in the NATALEE trial had stage II in 40 % and stage III in 60 % of the cases, whereas among GIM23 population eligible for ribociclib, 77.5 % of the patients had stage II of disease and stage III in 22.5 % of the patients, while more similar characteristics were observed regarding tumor

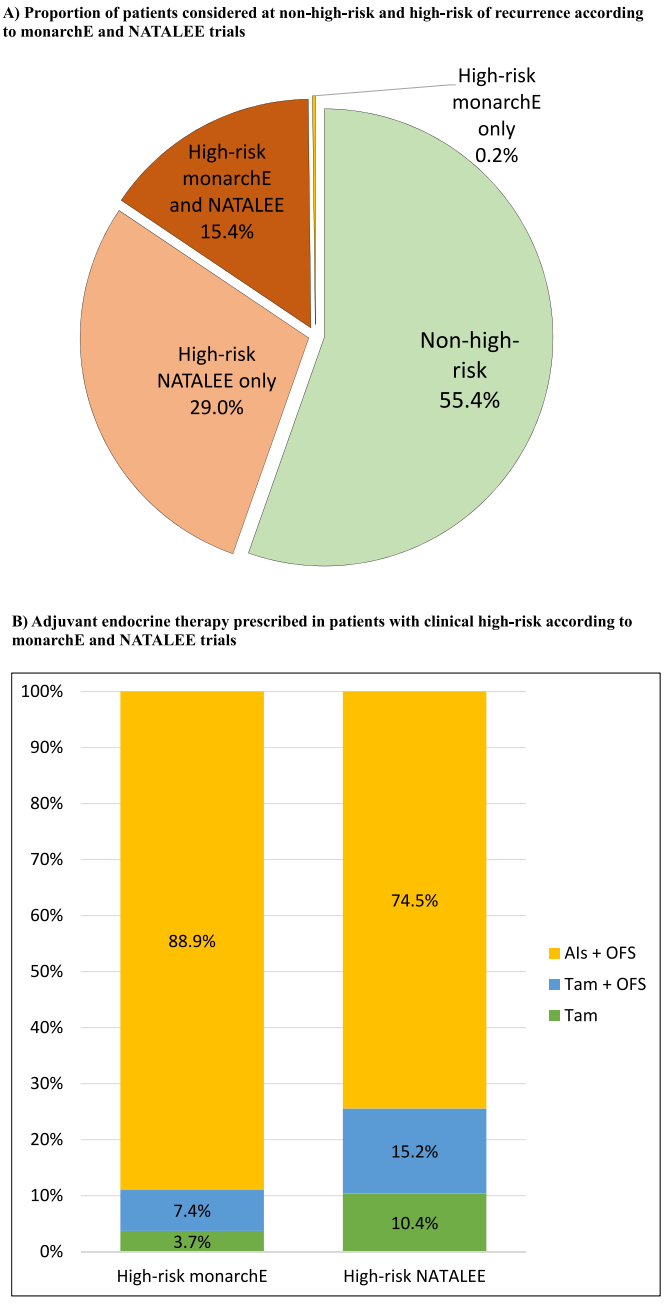

Fig. 3. Analysis according to A) Proportion of patients considered at non-high-risk and high-risk of recurrence according to monarchE and NATALEE trials and B) Adjuvant endocrine therapy prescribed according with risk categories of monarchE and NATALEE trials.

grading (grade 3 in 29.0 % of the population in NATALEE vs. 31.2 % in GIM23) and high Ki67 (36.3 % in NATALEE and 55.8 % in GIM23). Patients enrolled in NATALEE trial had received chemotherapy in 88.0 % of cases, whereas chemotherapy was administered to almost half of the patients (53.2 %) in GIM23 study according to NATALEE criteria.

It seems therefore that in general both the monarchE and NATALEE trials enrolled a slightly higher-risk population when compared to the characteristics of the patients considered at high-risk of recurrence according to the monarchE and NATALEE trials included in the GIM23 study; however, it must be considered that both trials randomized not only premenopausal patients, and characteristics according to menopausal status are not reported so far.

Concerning the adjuvant ET prescribed in high-risk patients, those with concordant high-risk of recurrence in the GIM23 study received

Table 4
Characteristics of patients grouped according to concordance between non-high-risk and high-risk populations across monarchE and NATALEE trials.

	Concordant non-high-risk populations (N = 288)	Discordant high-risk populations (N = 152)	Concordant high-risk populations (N = 80)	p-value
Age				0.01
≤35	10 (3.5 %)	16 (10.5 %)	6 (7.5 %)	
36-40	31 (10.8 %)	31 (20.4 %)	14 (17.5 %)	
41-45	69 (24.0 %)	38 (25.0 %)	21 (26.2 %)	
46-50	136 (47.2 %)	49 (32.2 %)	28 (35.0 %)	
51-56	42 (14.6 %)	18 (11.8 %)	11 (13.8 %)	
Unknown	0 (0 %)	0 (0 %)	0	
BMI				0.10
<18.5	9 (3.1 %)	3 (2.0 %)	5 (6.3 %)	
18,5–24,9	152 (52.7 %)	78 (51.3 %)	36 (45.0 %)	
25-29,9	37 (12.8 %)	27 (17.8 %)	15 (18.8 %)	
≥30	18 (6.3 %)	5 (3.3 %)	6 (7.5 %)	
Unknown	72 (25.0 %)	39 (25.7 %)	18(22.5 %)	
Stage at diagnosis				NA
I	241 (83.7 %)	1 (0.7 %)	0 (0 %)	
II	39 (13.5 %)	148 (97.4 %)	31 (38.8 %)	
III	0 (0 %)	3 (2.0 %)	49 (61.3 %)	
Unknown	8 (2.8 %)	0 (0 %)	0 (0 %)	
Histologic subtype				0.492
Ductal	223 (77.4 %)	121 (79.6 %)	65 (81.2 %)	
Other	62 (21.5 %)	31 (20.4 %)	15 (18.8 %)	
Unknown	3 (1.0 %)	0 (0 %)	0 (0 %)	
Prior chemotherapy				<0.001
No	253 (87.8 %)	91 (59.9 %)	18 (22.5 %)	
Yes	33 (11.5 %)	61 (40.1 %)	62 (77.5 %)	
Unknown	2 (0.7 %)	0 (0 %)	0 (0 %)	
Endocrine therapy prescribed				<0.001
Tamoxifen	111 (38.5 %)	23 (15.1 %)	2 (2.5 %)	
Tamoxifen + OFS	38 (13.2 %)	29 (19.1 %)	6 (7.5 %)	
Aromatase inhibitors + OFS	136 (47.2 %)	100 (65.8 %)	72 (90.0 %)	
Unknown	3 (1.0 %)	0 (0 %)	0 (0 %)	

Abbreviations: IQR, inter-quartile range; OFS, ovarian function suppression; BMI, body mass index; NA, not assessed.
*Percentages are evaluated on the total of the patients with hormone receptor-positive, HER2-negative disease (n = 520 patients).

OFS + AI in 90 % of cases, while patients in the monarchE trial received OFS (at any time) in only 22.1 % of cases, with 31.4 % of patients receiving tamoxifen alone and tamoxifen plus OFS in 7.6 % of cases. Interestingly, of the 231 patients considered high-risk according to NATALEE criteria, 25.6 % received tamoxifen alone or in association with OFS; considering that tamoxifen should not be administered concurrently with ribociclib, this proportion of patients, if candidates for ribociclib, needs to modify the choice of adjuvant ET.

Some limitations of this observational study should be reported, like the lack of data on treatment discontinuation or drug non-adherence and side effects, useful to evaluate the quality of life of patients, and social or pharmaco-economic aspects, but these information are being collected and will be analysed in future publications.

5. Conclusions

In conclusion, our results demonstrate that the most frequently prescribed adjuvant ET in a population of premenopausal patients is the combination of OFS and AI. This regimen is administered as the first choice particularly in a population with clinical and biological characteristics of higher risk of recurrence. According to monarchE and NATALEE criteria, less than one sixth of the included patients are candidates for adjuvant abemaciclib, while almost half of the premenopausal patients could potentially be eligible for treatment with ribociclib. The study is ongoing, and we are prospectively collecting both adherence to treatment and any rate of discontinuation, interruption, and the associated reasons, including tolerance to treatments. These data will be reported later, when the target number of patients in the study will be reached and the follow-up of the study will be adequate.

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Declaration of competing interest

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

Eva Blondeaux: speaker fee from Eli Lilly and research support from Gilead Science (to the institution).

Valentina Guarneri: personal fees from EliLilly, Exact Sciences, Novartis, Pfizer, Gilead, MSD, Amgen, Sanofi, Merck Serono, and Eisai outside the submitted work.

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All the other authors declare no conflict of interest.

Appendix A. Supplementary data

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