Who are the women who enrolled in the POSITIVE trial: A global study to support young hormone receptor positive breast cancer survivors desiring pregnancy

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1. Introduction

Young patients with hormone receptor positive (HR+) breast cancer (BC), receiving modern adjuvant endocrine therapy (ET) have excellent long-term outcomes [1–3]. Fertility and pregnancy are major concerns for young BC survivors, as many have not completed their family planning at diagnosis due to delay in childbearing. Helping Ourselves-Helping Others (HOHO), the Young Women's BC Study based in North America reported 51 % of young patients with BC were concerned about fertility [4]. In 26 % of them, these concerns affected treatment decisions, including ET adherence. The European HOHO cohort, led by the International Breast Cancer Study Group (IBCSG) [5] confirmed these findings: 64 % of participants were concerned about fertility and 15 % did not follow prescribed therapies. Additionally, 54 % of European and 37 % of North American women desired future children before diagnosis but 32 % and 9 %, respectively, were concerned that future pregnancy could increase their recurrence risk.

Despite solid retrospective evidence that pregnancy after BC does not increase the risk of disease recurrence overall and particularly in patients with HR + disease [6], discussing maternity desire after diagnosis is still problematic for both patients and doctors [7]. For women with HR + disease, for whom the prejudice against pregnancy is stronger [7], elucidating safety of pregnancy represents an unmet need. Five–ten years of ET may substantially reduce the chances of a successful conception and interruption of ET to allow pregnancy has never been studied.

In an IBCSG survey of 212 patients aged <37 years with HR + early BC from 5 regions (Europe, US, Canada, Middle East, Asia-Pacific), 37 % were interested in participating in a study of ET interruption to allow pregnancy [8]. Younger patients (<30 years) reported the highest interest (57 %). Pregnancy desire decreased after diagnosis (from 94 % to 75 %), data similarly reported in a web-based US survey [9] and in European patients <35 years [10]. Collectively, these retrospective studies demonstrated interest in and concerns about pregnancy after BC are common, irrespective of age, geographical, social, or cultural differences.

Acknowledging randomisation was impossible in this setting, the POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsIVe breast cancer) trial (IBCG 48–14/Breast International Group (BIG) 8–13/ALLIANCE A221405; NCT02308085) was designed as a single-arm prospective study to assess the risk of BC relapse associated with temporary interruption of ET to attempt conception. We report a comprehensive description of sociodemographic, disease and treatment characteristics, as well as regional variations, of women enrolled in POSITIVE.

2. Materials and methods

POSITIVE planned enrolment of 500 patients ≤42 years with stage I–III, HR + BC, who had received adjuvant ET (SERM alone, GnRH analogue plus SERM or aromatase inhibitor (AI)) for 18–30 months and wished to interrupt therapy to attempt pregnancy. The
study allowed up to 2 years interruption of ET for pregnancy attempt (after a 3-month ET washout period), delivery, and breastfeeding if desired and feasible. This was followed by ET resumption to complete 5–10 years of treatment once pregnancy and breastfeeding were completed or after unsuccessful attempts at conception. Assisted reproductive technology (ART) was allowed and information on its use was collected; additionally, data on pregnancy, offspring outcomes and patterns of breastfeeding were collected.

The primary endpoint of the study was breast cancer-free interval (BCFI), defined as the time from study enrolment to the first invasive BC event (local/regional/distant recurrence or contralateral BC). The statistical design of the POSITIVE study has been reported previously [11], which included 3 interim analyses permitting early trial stopping if the incidence of BC event was higher than anticipated.

Ethical committees of each participating institution and relevant health authorities approved the protocol and all patients provided written informed consent.

### 3. Results

From Dec 2014–Dec 2019, 518 patients enrolled and 517 participated at 116 institutions in 20 countries across 4 continents (Table 1, Fig. 1). Most patients (61.1 %) were from Europe, Spain being the top recruiter (22.5 %), 22.6 % from North America (NA; 75.2 % in the US) and 16.2 % from Asia, including the Pacific Islands and Middle East (73.8 % in Japan and 13.1 % in South Korea).

Patient and disease characteristics in the overall population and by continent are summarized in Table 2. The median age at enrolment was 37 years (range, 27–43 years): 37 years in Europe, 35 years in NA, and 37.5 years in Asia. Proportionally, NA investigators enrolled more patients <35 years (42.7 %) than European (33.2 %) and Asian (26.2 %) colleagues, whereas more patients in the 40–42 age group were enrolled in Asia (32.1 %) compared to Europe (25.6 %) and NA (8.5 %).

Overall, 74.9 % of patients had no children at enrolment, and fertility preservation (FP) strategies had been pursued prior to enrolment by 51.5 %. More women in Asia (56.0 %) had used FP, compared to Europe (53.2 %) and NA (43.6 %). Oocyte/embryo freezing was the most-used method in all regions (Table 2). The proportion of women with 1 previous live birth was higher in NA

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### Table 1

| Women Participating | Number | % |
|---------------------|--------|---|
| Total women participating | 517* | 100 |
| Continent | | |
| Europe | | |
| Total | 316 | 61.1 |
| Country/Collaborative Group | | |
| Austria/ABCSG | 7 | 1.4 |
| Belgium/IBCSG | 24 | 4.6 |
| France | 23 | 4.4 |
| Greece/HORG | 2 | 0.4 |
| Ireland/CTI | 13 | 2.5 |
| Italy/IBCSG | 68 | 13.2 |
| Netherlands/BOOG | 23 | 4.4 |
| Norway/NBCG | 25 | 4.8 |
| Portugal/SOLTI | 5 | 1.0 |
| Serbia | 5 | 1.0 |
| Slovenia/IBCSG | 10 | 1.9 |
| Spain/SOLTI/GEICAM | 71 | 13.7 |
| Switzerland/SAKK/IBCSG | 40 | 7.7 |
| North America | 117 | 22.6 |
| Total | 29 | 5.6 |
| Country/Collaborative Group | | |
| USA/Alliance/SWOG/ECOG-ACRIN/NRG | 88 | 17.0 |
| Asia/Pacific/Middle East | 84 | 16.2 |
| Total | | |
| Country/Collaborative Group | | |
| Australia | 8 | 1.5 |
| Israel | 2 | 0.4 |
| Japan/JBCRG | 62 | 12.0 |
| Lebanon/IBCSG | 1 | 0.2 |
| South Korea | 11 | 2.1 |

* A 518th patient was enrolled, but enrolment cancelled immediately due to inadvertent registration.

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Fig. 1. POSITIVE study participation by continent.
### Table 2

Patient and tumor characteristics of POSITIVE participants, overall and according to continent.

| Overall | Continent | Europe | North America | Asia/Pacific/Middle East |
|---------|-----------|--------|---------------|--------------------------|
|         | N        | %     | N            | %            | N            | %            | N            | %            |
| Total women participating | 517 | 100 | 316 | 100 | 117 | 100 | 84 | 100 |
| Age at enrolment | | | | | | | | |
| <35 | 177 | 34.2 | 105 | 33.2 | 50 | 42.7 | 22 | 26.2 |
| 35-39 | 222 | 42.9 | 130 | 41.1 | 57 | 48.7 | 35 | 41.7 |
| 40-42 | 118 | 22.8 | 81 | 25.6 | 10 | 8.5 | 27 | 32.1 |
| Body mass index (BMI) at enrolment (kg/m²) | | | | | | | | |
| <25 | 372 | 72.0 | 232 | 73.4 | 70 | 59.8 | 70 | 83.3 |
| 25-30 | 90 | 17.4 | 52 | 16.5 | 30 | 25.6 | 8 | 9.5 |
| ≥30 | 49 | 9.5 | 28 | 8.9 | 15 | 12.8 | 6 | 7.1 |
| Unknown | 6 | 1.2 | 4 | 1.3 | 2 | 1.7 | 0 | 0 |
| BRCA testing | | | | | | | | |
| Not tested | 236 | 45.6 | 145 | 45.9 | 26 | 22.2 | 65 | 77.4 |
| Tested | 279 | 54.0 | 171 | 54.1 | 90 | 76.9 | 18 | 21.4 |
| Negative | 226 | 43.7 | 141 | 44.6 | 71 | 60.7 | 14 | 16.7 |
| Positive | 38 | 7.4 | 21 | 6.6 | 15 | 12.8 | 2 | 2.4 |
| BRCA1 Positive | 18 | 3.5 | 10 | 3.2 | 7 | 6.0 | 1 | 1.2 |
| BRCA2 Positive | 20 | 3.9 | 11 | 3.5 | 8 | 6.8 | 1 | 1.2 |
| Results not available | 15 | 2.9 | 9 | 2.8 | 4 | 3.4 | 2 | 2.4 |
| Unknown | 2 | 0.4 | 0 | 0 | 1 | 0.9 | 1 | 1.2 |
| Prior live births | | | | | | | | |
| 0 | 387 | 74.9 | 237 | 75.0 | 82 | 70.1 | 68 | 81.0 |
| 1 | 107 | 20.7 | 67 | 21.2 | 27 | 23.1 | 13 | 15.5 |
| 2 | 20 | 3.9 | 11 | 3.5 | 7 | 6.0 | 2 | 2.4 |
| 3 | 2 | 0.4 | 1 | 0.3 | 0 | 0 | 1 | 1.2 |
| Unknown | 1 | 0.2 | 0 | 0 | 1 | 0.9 | 0 | 0 |
| Fertility preservation after diagnosis and prior to any therapy | | | | | | | | |
| Yes | 266 | 51.5 | 168 | 53.2 | 51 | 43.6 | 47 | 56.0 |
| No | 250 | 48.4 | 148 | 46.8 | 65 | 55.6 | 37 | 44.0 |
| Unknown | 1 | 0.2 | 0 | 0 | 1 | 0.9 | 0 | 0 |
| Fertility preservation by oocyte/embryo freezing (ovarian stimulation with gonadotropins ± letrozole or tamoxifen) | | | | | | | | |
| Yes | 183 | 35.4 | 103 | 32.6 | 40 | 34.2 | 40 | 47.6 |
| No | 333 | 64.4 | 213 | 67.4 | 76 | 65.0 | 44 | 52.4 |
| Unknown | 1 | 0.2 | 0 | 0 | 1 | 0.9 | 0 | 0 |
| Fertility preservation by use of GnRH analogue during chemotherapy | | | | | | | | |
| Yes | 77 | 14.9 | 56 | 17.7 | 13 | 11.1 | 8 | 9.5 |
| No | 439 | 84.9 | 260 | 82.3 | 103 | 88.0 | 76 | 90.5 |
| Unknown | 1 | 0.2 | 0 | 0 | 1 | 0.9 | 0 | 0 |
| Fertility preservation by ovarian tissue harvest | | | | | | | | |
| Yes | 30 | 5.8 | 25 | 7.9 | 4 | 3.4 | 1 | 1.2 |
| No | 486 | 94.0 | 291 | 92.1 | 112 | 95.7 | 83 | 98.8 |
| Unknown | 1 | 0.2 | 0 | 0 | 1 | 0.9 | 0 | 0 |
| TNM stage | | | | | | | | |
| I | 242 | 46.8 | 147 | 46.5 | 52 | 44.4 | 43 | 51.2 |
| II | 240 | 46.4 | 147 | 46.5 | 57 | 48.7 | 36 | 42.9 |
| III | 31 | 6.0 | 19 | 6.0 | 7 | 6.0 | 5 | 6.0 |
| Unknown | 4 | 0.8 | 3 | 0.9 | 1 | 0.9 | 0 | 0 |
| No. positive lymph nodes | | | | | | | | |
| pN0 | 341 | 66.0 | 211 | 66.8 | 66 | 56.4 | 64 | 76.2 |
| pN1-3 | 152 | 29.4 | 88 | 27.8 | 48 | 41.0 | 16 | 19.0 |
| pN4-9 | 23 | 4.4 | 17 | 5.4 | 2 | 1.7 | 4 | 4.8 |
| Unknown | 1 | 0.2 | 0 | 0 | 1 | 0.9 | 0 | 0 |
| Histologic grade | | | | | | | | |
| 1 | 89 | 17.2 | 45 | 14.2 | 20 | 17.1 | 24 | 28.6 |
| 2 | 251 | 48.5 | 157 | 49.7 | 50 | 42.7 | 44 | 52.4 |
| 3 | 172 | 33.3 | 112 | 35.4 | 44 | 37.6 | 16 | 19.0 |
| Unknown | 5 | 1.0 | 2 | 0.6 | 3 | 2.6 | 0 | 0 |
| HER2 status | | | | | | | | |
| Negative | 381 | 73.7 | 226 | 71.5 | 84 | 71.8 | 71 | 84.5 |
| Positive | 134 | 25.9 | 89 | 28.2 | 32 | 27.4 | 13 | 15.5 |
| Unknown | 2 | 0.4 | 1 | 0.3 | 1 | 0.9 | 0 | 0 |

*One patient was 42 when she was informed about the study but had turned 43 by the time she was registered.*
(23.1 %) and Europe (21.2 %) and lowest in Asia (15.5 %). Overall, 17.4 % of the patients were overweight (BSA 25–29) and 9.5 % obese (≥30). Overweight/obese patients accounted for 25.6 %/12.8 % of the NA population, 16.5 %/8.9 % of the European, 9.5 %/7.1 % of the Asian populations. Fifty-four percent of patients had undergone BRCA mutation testing (54.1 % in Europe, 76.9 % in NA, 21.4 % in Asia). Overall, 13.6 % of women tested were reported as positive for BRCA1/2 germline mutation(s) (12.3 %, 16.7 %, 11.1 %, respectively) (data not shown).

At diagnosis, most patients had stage I (46.8 %) or II (46.4 %) disease. Two-thirds of patients were node-negative (66 %) and 29.4 % had 1-3 positive nodes. Nearly half of patients (48.5 %) had grade 1 disease and to 35.5 % of those with grade 3 tumours, histologic grade: tamoxifen alone was given to 59.6 % of women with grade 1 disease and to 35.5 % of those with grade 3 tumours, whereas 29.4 % had 1-3 positive nodes. The proportion of women with HER2 tumours was lower in Asian than in NA and European patients: 19.2 %, respectively. ET escalation paralleled disease burden: ET prior to enrolment was 23.4 months (range 17.9–35). This was similar in all continents. Most patients with HER2+ tumours (97.0 %) received HER2-targeted therapy.

Treatment strategies varied by patient and disease characteristics (Table 4a,b). Patients tested for BRCA mutations more frequently underwent mastectomy irrespective of test results, the proportion of mastectomies being higher in BRCA-negative patients (45.1 %) than in untested women (38.1 %). Among BRCA positive patients, the vast majority (78.9 %) opted for mastectomy. ET prescription varied by age: tamoxifen alone was prescribed to 41.8 % of patients (33.9 % of women 45–51 years, 43.7 % of those 35–39 years, 50.0 % of women 40–42 years), tamoxifen + OFS to 17.9 % of women 40–42 years, and 17.1 % of women 45–51 years, respectively. ET prescription also varied by histologic grade: tamoxifen alone was given to 59.6 % of women with grade 1 disease and to 35.5 % of those with grade 3 tumours, tamoxifen + OFS to 29.2 % and 37.8 % and Al + OFS to 9.0 % and 19.2 %, respectively. ET escalation paralleled disease burden: tamoxifen alone was given to 26.1 % of women with pN2 disease, OFS (plus tamoxifen or Al) in 73.9 % of cases. OFS was also given more frequently to women who had received chemotherapy compared to those that did not (56 % vs 42.9 %) and to those who had HER2+ compared with HER-2 negative disease (58.2 % vs 49.1 %). Chemotherapy prescription varied by age and disease characteristics (Table 4c). Chemotherapy use decreased with increasing patient age (74.0 % of women <35 years versus 53.4 % of the older age group). Chemotherapy use increased as expected with

### Table 3

Prior treatment of POSITIVE participants, overall and by continent.

| Overall | Continent | Europe | North America | Asia/Pacific/Middle East |
|---------|-----------|--------|---------------|--------------------------|
| N %     | N %       | N %    | N %           | N %                      |
| Breast conserving surgery | 517 100 | 316 100 | 117 100 | 84 100 |
| Mastectomy | 283 54.7 | 189 59.8 | 47 40.2 | 47 56.0 |
| Unknown | 233 45.1 | 127 40.2 | 69 59.0 | 37 44.0 |
| Prior (neo)adjuvant chemotherapy | 1 0.2 | 0 0 | 1 0.9 | 0 0 |
| Yes | 320 61.9 | 219 69.3 | 66 56.4 | 35 41.7 |
| Anthracycline alone | 32 6.2 | 26 8.2 | 4 3.4 | 2 2.4 |
| Anthracycline + Other | 1 0.2 | 0 0 | 0 0 | 1 1.2 |
| Taxane alone | 58 11.2 | 32 10.1 | 21 17.9 | 5 6.0 |
| Taxane + Other | 2 0.4 | 0 0 | 2 1.7 | 0 0 |
| Anthracycline + Taxane | 203 39.3 | 157 49.7 | 20 17.1 | 26 31.0 |
| Other | 24 4.6 | 4 1.3 | 19 16.2 | 1 1.2 |
| No chemo | 196 37.9 | 97 30.7 | 50 42.7 | 49 58.3 |
| Unknown | 1 0.2 | 0 0 | 1 0.9 | 0 0 |
| ET prior to enrolment | 216 41.8 | 116 36.7 | 70 59.8 | 30 35.7 |
| SERM only | 183 35.4 | 127 40.2 | 9 7.7 | 47 56.0 |
| SERM + OFS | 82 15.9 | 54 17.1 | 23 19.7 | 5 6.0 |
| Al + OFS | 36 7.0 | 19 6.0 | 15 12.8 | 2 2.4 |
| Months of ET prior to enrolment | Median 23.4 | 23.3 | 22.3 | 23.6 |
| Range 17.9–35.0 | 17.9–35.0 | 17.9–35.0 | 17.9–35.0 | 18.0–31.3 |

Abbreviations: ET = endocrine therapy; SERM = selective estrogen receptor modulator; OFS = ovarian function suppression; Al = aromatase inhibitor.

* Other ET prior to enrolment includes: 33 reported SERM, AI and OFS had been taken (switching strategy); 1 reported SERM and AI (but not OFS); 1 reported OFS only; 1 is unknown.
4. Discussion

In the POSITIVE study, 517 women with HR + early BC, interested in interrupting ET to attempt pregnancy, agreed to participate across 4 continents. While the study aims to answer the crucial question of whether temporary ET interruption for pregnancy adversely impacts BC relapse, it will provide a unique dataset detailing a diverse group of women from different ethnic and socio-cultural backgrounds, key information on pregnancy and offspring outcomes, patterns of use of ART and breastfeeding, and ET resumption after the break. Considerable information will be obtained for women of Asian origin (Japanese and South Korean), who represent 14.1 % of the entire population. Unfortunately, African American (1.4 %) and Middle Eastern women (0.6 %) were underrepresented, preventing any relevant observation in these ethnicities [12]. Intriguing variations across continents emerged, although generalizability is hindered by small numbers, the specificity of the patient population, and the trend of patient accrual (starting in Europe, followed by NA, and Asia).

Overall, the relatively high median age at enrolment (37 years) probably reflects patients’ and doctors’ awareness that aging is among the major contributors to infertility after BC treatments [13]. This observation parallels the high proportion of patients (74.9 %) who had no children at enrolment (with an additional 20.7 % of women who had only 1 child before diagnosis) and suggests the study was particularly attractive to women concerned about their ability to conceive after treatment completion. Further, most patients were at relatively low risk of relapse suggesting patients and doctors were more comfortable with ET interruption if the risk of relapse was low.

Regional variations in age and number of prior live births of the enrolled population, specifically the higher participation of older and nulliparous women in Asia, compared to Europe and NA, might reflect the recent steady increase in age at first marriage in East Asia [14] and the consequent late age at first birth, which have become more pronounced than in Western countries. While fertility preservation use overall was similar across continents, adoption of specific fertility preservation strategies varied in the different regions. Oocyte/embryo freezing was more common in Asia, compared to Europe and NA, consistent with recent increased availability and utilization of ART in Asian countries [15–18]. The differences in distribution of disease characteristics across continents, including more lower-risk Asian patients compared to European and NA women, suggest enrolment in a clinical trial might have been considered reasonable in higher-risk patients with a strong maternity desire in some but not all socio-cultural settings. Different cultural and personal values, sociodemographic characteristics, and patient-provider relationships might also have

Table 4a
Primary surgery of POSITIVE participants, according to patient and disease characteristics. Note percentages sum across the rows.

| Overall | Most extensive primary surgery | Breast conserving surgery | Mastectomy | Unknown |
|---------|--------------------------------|---------------------------|------------|---------|
| N | | N | % | N | % | N | % |
| Total women participating | 517 | 283 | 54.7 | 233 | 45.1 | 1 | 0.2 |
| Age at enrolment | | | | | | | |
| <35 | 177 | 82 | 46.3 | 95 | 53.7 | 0 | 0 |
| 35-39 | 222 | 118 | 53.2 | 103 | 46.4 | 1 | 0.5 |
| 40-42 | 118 | 83 | 70.3 | 35 | 29.7 | 0 | 0 |
| No. positive lymph nodes | | | | | | | |
| pN0 | 341 | 209 | 61.3 | 132 | 38.7 | 0 | 0 |
| pN+ 1-3 | 152 | 69 | 45.4 | 83 | 54.6 | 0 | 0 |
| pN+ 4-9 | 23 | 5 | 21.7 | 18 | 78.3 | 0 | 0 |
| Unknown | 1 | 0 | 0 | 0 | 0 | 1 | 100 |
| Histologic grade | | | | | | | |
| 1 | 89 | 61 | 68.5 | 28 | 31.5 | 0 | 0 |
| 2 | 251 | 139 | 55.4 | 112 | 44.6 | 0 | 0 |
| 3 | 172 | 83 | 48.3 | 89 | 51.7 | 0 | 0 |
| Unknown | 5 | 0 | 0 | 4 | 80.0 | 1 | 20.0 |
| BRCA status | | | | | | | |
| Not tested | 236 | 146 | 61.9 | 90 | 38.1 | 0 | 0 |
| Negative | 226 | 124 | 54.9 | 102 | 45.1 | 0 | 0 |
| Positive | 38 | 8 | 21.1 | 30 | 78.9 | 0 | 0 |
| BRCA1 Positive | 18 | 3 | 16.7 | 15 | 83.3 | 0 | 0 |
| BRCA2 Positive | 20 | 5 | 25.0 | 15 | 75.0 | 0 | 0 |
| Results not available | 15 | 4 | 26.7 | 11 | 73.3 | 0 | 0 |
| Unknown | 2 | 1 | 50.0 | 0 | 0 | 1 | 50.0 |
| Prior (neo)adjuvant chemotherapy | | | | | | | |
| Yes | 320 | 168 | 52.5 | 152 | 47.5 | 0 | 0 |
| No | 196 | 115 | 58.7 | 81 | 41.3 | 0 | 0 |
| Unknown | 1 | 0 | 0 | 0 | 0 | 1 | 100 |
fluenced patient-doctor discussion in this challenging scenario. Nonetheless, the desired level of self-involvement in decision-making was relatively independent of cultural and personal values in a recent study conducted in Australia and China [19], suggesting caution against overinterpretation of cultural stereotypes.

The reported geographical variations in treatment strategies may have resulted from a variety of reasons, including the highly-selected patient population participating in the trial, national/institutional guidelines, reimbursement policies, which contribute

### Table 4b
Prior endocrine therapy (ET) of POSITIVE participants, according to patient and disease characteristics. Note percentages sum across the rows.

| Overall | Prior Endocrine Therapy |
|---------|-------------------------|
|         | SERM only | SERM + OFS | AI + OFS | Other* |
| N       | N   | %  | N   | %  | N   | %  | N   | %  |
| Total women participating | 517 | 216 | 41.8 | 183 | 35.4 | 82 | 15.9 | 36 | 7.0 |
| Age at enrolment | | | | | | | | |
| <35 | 177 | 60 | 33.9 | 73 | 41.2 | 27 | 15.3 | 17 | 9.6 |
| 35-39 | 222 | 97 | 43.7 | 69 | 31.1 | 41 | 18.5 | 15 | 6.8 |
| 40-42 | 118 | 59 | 50.0 | 41 | 34.7 | 14 | 11.9 | 4 | 3.4 |
| Body mass index at enrolment | | | | | | | | |
| <25 | 372 | 160 | 43.0 | 126 | 36.6 | 54 | 14.5 | 22 | 5.9 |
| 25-30 | 90 | 36 | 40.0 | 33 | 36.7 | 18 | 20.0 | 3 | 3.3 |
| ≥30 | 49 | 17 | 34.7 | 13 | 26.5 | 9 | 18.4 | 10 | 20.4 |
| Unknown | 6 | 3 | 50.0 | 1 | 16.7 | 1 | 16.7 | 1 | 16.7 |
| Histologic grade | | | | | | | | |
| 1 | 89 | 53 | 59.6 | 26 | 29.2 | 8 | 9.0 | 2 | 2.2 |
| 2 | 251 | 99 | 39.4 | 91 | 36.3 | 41 | 16.3 | 20 | 8.0 |
| 3 | 172 | 61 | 35.5 | 65 | 37.8 | 33 | 19.2 | 13 | 7.6 |
| Unknown | 5 | 3 | 60.0 | 1 | 20.0 | 0 | 0 | 1 | 20.0 |
| No. positive lymph nodes | | | | | | | | |
| pN0 | 341 | 154 | 45.2 | 124 | 36.4 | 45 | 13.2 | 18 | 5.3 |
| pN1-3 | 152 | 56 | 36.8 | 44 | 28.9 | 35 | 23.0 | 17 | 11.2 |
| pN4-9 | 23 | 6 | 26.1 | 15 | 65.2 | 2 | 8.7 | 0 | 0 |
| Unknown | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 100 |
| HER2 status | | | | | | | | |
| Negative | 381 | 171 | 44.9 | 137 | 36.0 | 50 | 13.1 | 23 | 6.0 |
| Positive | 134 | 44 | 32.8 | 46 | 34.3 | 32 | 23.9 | 12 | 9.0 |
| Unknown | 2 | 1 | 50.0 | 0 | 0 | 0 | 0 | 1 | 50.0 |
| Prior (neo)adjuvant chemotherapy | | | | | | | | |
| Yes | 320 | 113 | 35.3 | 117 | 36.6 | 64 | 20.0 | 26 | 8.1 |
| No | 196 | 103 | 52.6 | 66 | 33.7 | 18 | 9.2 | 9 | 4.6 |
| Unknown | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 100 |

Abbreviations: ET = endocrine therapy; SERM = selective estrogen receptor modulator; OFS = ovarian function suppression; AI = aromatase inhibitor.

*Other ET prior to enrolment includes: 33 reported SERM, AI and OFS had been taken (switching strategy); 1 reported SERM and AI (but not OFS); 1 reported OFS only; 1 is unknown.

influenced patient-doctor discussion in this challenging scenario. Nonetheless, the desired level of self-involvement in decision-making was relatively independent of cultural and personal values in a recent study conducted in Australia and China [19], suggesting caution against overinterpretation of cultural stereotypes.

The reported geographical variations in treatment strategies may have resulted from a variety of reasons, including the highly-selected patient population participating in the trial, national/institutional guidelines, reimbursement policies, which contribute

### Table 4c
Prior chemotherapy receipt of POSITIVE participants, according to patient and disease characteristics. Note percentages sum across the rows.

| Overall | Prior (Neo)adjuvant Chemotherapy |
|---------|--------------------------------|
|         | Yes | No | Unknown |
| N       | N   | %  | N   | %  | N   | %  |
| Total women participating | 517 | 320 | 61.9 | 196 | 37.9 | 1 | 0.2 |
| Age at enrolment | | | | | | |
| <35 | 177 | 131 | 74.0 | 46 | 26.0 | 0 | 0 |
| 35-39 | 222 | 126 | 56.8 | 95 | 42.8 | 1 | 0.5 |
| 40-42 | 118 | 63 | 53.4 | 55 | 46.6 | 0 | 0 |
| Body mass index at enrolment | | | | | | |
| <25 | 372 | 222 | 59.7 | 150 | 40.3 | 0 | 0 |
| 25-30 | 90 | 57 | 63.3 | 33 | 36.7 | 0 | 0 |
| ≥30 | 49 | 38 | 77.6 | 11 | 22.4 | 0 | 0 |
| Unknown | 6 | 3 | 50.0 | 2 | 33.3 | 1 | 16.7 |
| Histologic grade | | | | | | |
| 1 | 89 | 27 | 30.3 | 62 | 69.7 | 0 | 0 |
| 2 | 251 | 139 | 55.4 | 112 | 44.6 | 0 | 0 |
| 3 | 172 | 152 | 88.4 | 20 | 11.6 | 0 | 0 |
| Unknown | 5 | 2 | 40.0 | 2 | 40.0 | 1 | 20.0 |
| No. positive lymph nodes | | | | | | |
| pN0 | 341 | 183 | 53.7 | 158 | 46.3 | 0 | 0 |
| pN1-3 | 152 | 115 | 75.7 | 37 | 24.3 | 0 | 0 |
| pN4-9 | 23 | 22 | 95.7 | 1 | 4.3 | 0 | 0 |
| Unknown | 1 | 0 | 0 | 0 | 0 | 1 | 100 |
| HER2 status | | | | | | |
| Negative | 381 | 197 | 51.7 | 184 | 48.3 | 0 | 0 |
| Positive | 134 | 123 | 91.8 | 11 | 8.2 | 0 | 0 |
| Unknown | 2 | 0 | 0 | 1 | 50.0 | 1 | 50.0 |
to the variability of BC management in different countries, not always following international evidence-based recommendations [20]. Considering most patients had low-stage disease, breast-conserving surgery was more common than mastectomy in the overall population, apart from in NA, possibly confirming different socio-cultural information and decision-making processes [21,22].

The observation of prior chemotherapy being more frequent in Europe than in NA and Asian participants contrasts with previous data in premenopausal women with HR+ early disease [23]. Discussions at the time of BC diagnosis regarding pregnancy desire may have influenced chemotherapy decision-making. The shift in chemotherapy indications might also arise from the increasing utilization of gene signatures such as Mammaprint or Oncotype DX in HR+ patients, supported by some guidelines [24–27], which have reduced chemotherapy prescription [28–32]. The validity of these tests in premenopausal women is controversial as current ET applications do not correspond to those in the trials using gene signatures [33]. As POSITIVE does not collect data on gene signature utilization, we cannot support or refute this trend in this population.

Overall, tamoxifen alone was the most prescribed ET followed by tamoxifen + OFS. AI + OFS was received by only 15.9% of participating women, suggesting most clinicians who chose OFS preferred the combination with tamoxifen instead of AIs in this selected population. The ET prescription changed in the second half of the recruitment period (after July 2017) in all continents, likely due to results of the SOFT/TEXT trials [2,3] demonstrating absolute improvements in all disease outcomes, including overall survival, by escalating ET, most clinically-meaningful in patients with higher-risk disease. Overall, OFS administration was stable over time in the enrolled population in all regions but its use with AIs doubled at the expense of tamoxifen [33]. As POSITIVE does not collect data on gene signature [33].

### 5. Conclusions

The POSITIVE study enrolled a diverse group of young survivors receiving adjuvant ET for early HR+ BC united by their desire for pregnancy. The similarities and differences of these women from a sociodemographic, disease and treatment standpoint as well as regional specificities may allow improved understanding of the needs of this unique patient population and provide insights into different sociocultural attitudes of patients and investigators. These findings may inform not only future research in this area, but clinical practice and national policies to improve the care of these patients.

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**Table 5**

Adjuvant therapies prior to enrolment, according to period of enrolment and continent. Note percentages sum across the rows, within type of therapy.

| Continent         | Accrual | Overall | Prior Endocrine Therapy | Prior (Neo)adjuvant Chemotherapy |
|-------------------|---------|---------|-------------------------|---------------------------------|
|                   | N       | %      | N %                     | N %                             |
|                   | SERM only | SERM + OFS | AI + OFS | Other | Yes | No | Unknown |
| Europe            | 316     | 116     | 36.7                   | 127    | 40.2 | 54 | 17.1 | 19 | 6.0 | 219 | 69.3 | 97 | 30.7 | 0 | 0 |
| Period            |         |         |                       |                                 |                                 |     |      |    |     |     |       |   |      |   |     |     |       |   |     |   |   |
| 1st half          | 98      | 33      | 33.7                   | 48     | 49.0 | 10 | 10.2 | 7 | 7.1 | 61 | 62.2 | 37 | 37.8 | 0 | 0 |
| 2nd half          | 218     | 83      | 38.1                   | 79     | 36.2 | 44 | 20.2 | 12 | 5.5 | 158 | 72.5 | 60 | 27.5 | 0 | 0 |
| North America     | 117     | 70      | 59.8                   | 9      | 7.7  | 23 | 19.7 | 15 | 1.2 | 66 | 56.4 | 50 | 42.7 | 1 | 0.9 |
| Period            |         |         |                       |                                 |                                 |     |      |    |     |     |       |   |      |   |   |
| 1st half          | 28      | 16      | 57.1                   | 4      | 14.3 | 3  | 10.7 | 5 | 17.9 | 13 | 46.4 | 15 | 53.6 | 0 | 0 |
| 2nd half          | 89      | 54      | 60.7                   | 5      | 5.6  | 20 | 22.5 | 10 | 11.2 | 53 | 59.6 | 35 | 39.3 | 1 | 1.1 |
| Asia/Pacific/Middle East | 84 | 30 | 35.7 | 47 | 56.0 | 5 | 6.0 | 2 | 2.4 | 35 | 41.7 | 49 | 58.3 | 0 | 0 |
| Period            |         |         |                       |                                 |                                 |     |      |    |     |     |       |   |      |   |   |
| 1st half          | 13      | 6       | 46.2                   | 7      | 53.8 | 0  | 0    | 0 | 0   | 7  | 53.8 | 6  | 46.2 | 0 | 0 |
| 2nd half          | 71      | 24      | 33.8                   | 40     | 56.3 | 5  | 7.0  | 2 | 2.8 | 28 | 39.4 | 43 | 60.6 | 0 | 0 |

Abbreviations: SERM = selective estrogen receptor modulator; OFS = ovarian function suppression; AI = aromatase inhibitor.

* The 1st half includes patients enrolled from December 4, 2014 to June 30, 2017; the 2nd half includes patients enrolled from July 1, 2017 to December 31, 2019.

† Other endocrine therapy prior to enrolment included: 33 reported SERM, AI and OFS had been taken (switching strategy); 1 reported SERM and AI (but not OFS); 1 reported OFS only; 1 is unknown.
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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

Ann H. Partridge reports no conflicts related to this trial. Samuel M. Niman reports no conflicts related to this trial. Monica Ruggeri reports no conflicts related to this trial. Fedro A. Peccatori receives honoraria from Roche Diagnostic and Ipsen. Hatem A Azim Jr receives honoraria from Novartis, serves on the Roche Advisory Board and is employed with Innate Pharma. Marco Colleoni reports no conflicts related to this trial. Cristina Saura receives consulting or advisory fees from AstraZeneca, Celgene, Daiichi Sankyo, Eisai, F. Hoffmann-La Roche Ltd, Genomic Health, Merck, Sharp and Dohme España SA, Novartis, Pfizer, Philips Healthwork, Pierre Fabre, prfME Oncology, Puma biotechnology, Synthon, Seattle Genetics, and Sanoﬁ Aventis. Chikako Shimizu receives honoraria from Pfizer, Chugai, and Novartis and has a research grant from Eli-Lilly; none of these are trial related. Anna Barbro Sætersdal reports no conflicts related to this trial. Judith R Kroep reports no trial related conflicts. Audrey Mailliez reports no trial related conflicts. Ellen Warner reports no conflicts related to this trial. Virginia F. Borjes receives consulting fees from SeaGen. Frédéric Amant receives honoraria from AstraZeneca and PharmaMar. Andrea Combos is on the advisory boards of Lilly and Daiichi Sankyo, receives a travel grant from Pfizer; none of these are related to this trial. Akemi Kataoka reports no conflicts related to this trial. Christine Roussset-Jablonski receives honoraria or advisory fees from AstraZeneca and Pfizer. Jessica Liu, received honoraria from AstraZeneca and Pfizer, serves on the advisory boards for Mylan Medical, Roche, and BMS; none of these are trial related. Simona Borstnar serves on the advisory boards for Mylan Medical, Roche, and BMS; none of these are trial related. Junko Takei reports no conflicts related to this trial. Jeong Eon Lee reports no conflicts related to this trial. Janice M. Walshe receives honoraria from Novartis, consulting or advisory fees from Pierre Fabre, Pfizer, or Roche. Manuel Ruiz Borrego receives speaker fees from Pfizer, Novartis, Puma, AstraZeneca, and Roche; and receives advisory honoraria from Pfizer, Novartis, and Puma. Halle C.F. Moore receives research funding (to her institution) from AstraZeneca, Roche/Genentech,
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