



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

Ann H. Partridge^{a,*}, Samuel M. Niman^b, Monica Ruggeri^c, Fedro A. Peccatori^d, Hatem A. Azim Jr.^e, Marco Colleoni^f, Cristina Saura^g, Chikako Shimizu^h, Anna Barbro Sætersdalⁱ, Judith R. Kroep^j, Audrey Mailliez^k, Ellen Warner^l, Virginia F. Borges^m, Frédéric Amant^{n,o}, Andrea Gombos^p, Akemi Kataoka^q, Christine Rousset-Jablonski^r, Simona Borstnar^s, Junko Takei^t, Jeong Eon Lee^u, Janice M. Walshe^v, Manuel Ruíz Borrego^w, Halle CF. Moore^x, Christobel Saunders^y, Fatima Cardoso^z, Snezana Susnjari^{aa}, Vesna Bjelic-Radicic^{ab,ac}, Karen L. Smith^{ad}, Martine Piccart^p, Larissa A. Korde^{ae}, Aron Goldhirsch^{af}, Richard D. Gelber^{ag}, Olivia Pagani^{ah,**}

^a Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA

^b International Breast Cancer Study Group Statistical Center, Department of Data Science, Division of Biostatistics, Dana-Farber Cancer Institute, Boston, MA, USA

^c International Breast Cancer Study Group, Program for Young Patients, Coordinating Center, Effingerstrasse 40, Bern, 3008, Switzerland

^d Fertility and Procreation Unit, Gynecologic Oncology Program, European Institute of Oncology IRCCS, Via Ripamonti 435, Milan, 20141, Italy

^e Breast Cancer Center, Hospital Zambrano Hellion, School of Medicine, Tecnológico de Monterrey, Av. Batallon de San Patricio 112, San Pedro Garza Garcia, 66278, Mexico

^f International Breast Cancer Study Group, Division of Medical Senology, IEO, European Institute of Oncology, IRCCS, Milan, Italy

^g Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Medical Oncology Service, Barcelona, Spain

^h Department of Breast and Medical Oncology, National Center for Global Health and Medicine, Toyama, Shinjuku-ku, Tokyo, 1-21-1, Japan

ⁱ Department of Oncology, Division of Cancer Medicine, Oslo University Hospital, Oslo, Norway

^j Department of Medical Oncology, Leiden University Medical Center, Leiden, the Netherlands

^k Department of Medical Oncology, Centre Oscar Lambret, Lille, France

^l Odette Cancer Center, Sunnybrook Health Sciences Center, Toronto, Canada

^m Division of Medical Oncology, Department of Medicine, University of Colorado Cancer Center, Aurora, CO, USA

ⁿ Department of Oncology, KU Leuven and Leuven Cancer Institute, Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven, Belgium

^o Center for Gynecologic Oncology Amsterdam, Antoni van Leeuwenhoek-Netherlands Cancer Institute, Amsterdam University Medical Center, Amsterdam, the Netherlands

^p Institut Jules Bordet and L'Université Libre de Bruxelles, Brussels, Belgium

^q Breast Oncology Cancer, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

^r Leon Berard Cancer Centre, Centre Léon Bérard, Department of Surgery, Lyon, France

^s Division of Medical Oncology, Institute of Oncology, Ljubljana, Slovenia

^t St Luke's International Hospital, Breast Center, Tokyo, Japan

^u Breast Division, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Department of Clinical Research and Evaluation, SAHST, Sungkyunkwan University, Seoul, South Korea

^v Cancer Trials Ireland and Medical Oncology Department, St. Vincent's University Hospital and Tallaght University Hospital, Dublin, Ireland

^w Hospital Virgen del Rocío Sevilla, GEICAM Spanish Breast Cancer Group, Sevilla, Spain

^x Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA

^y Division of Surgery, Faculty of Health and Medical Sciences, University of Western Australia, Crawley, WA, Australia

[☆] **Previously presented:** 2020 San Antonio Breast Cancer Symposium (Virtual).

* Corresponding author. Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA, 02215, USA.

** Corresponding author. Riviera-Chablais Hospital, Route du Vieuz Sequoia 20, 1847 Rennaz, Switzerland.

E-mail addresses: ann_partridge@dfci.harvard.edu (A.H. Partridge), sniman@jimmy.harvard.edu (S.M. Niman), monica.ruggeri@ibscg.org (M. Ruggeri), fedro.peccatori@ieo.it (F.A. Peccatori), hatem.azim@gmail.com (H.A. Azim), marco.colleoni@ieo.it (M. Colleoni), csaura@vhio.net (C. Saura), cshimizu@hosp.ncgm.go.jp (C. Shimizu), ASD@ous-hf.no (A.B. Sætersdal), J.R.Kroep@lumc.nl (J.R. Kroep), a-mailliez@o-lambret.fr (A. Mailliez), ellen.warner@sunnybrook.ca (E. Warner), virginia.borges@cuanschutzedu (V.F. Borges), frederic.amant@uzleuven.be (F. Amant), andrea.gombos@bordet.be (A. Gombos), akemi.kataoka@jfc.or.jp (A. Kataoka), christine.rousset-jablonski@lyon.unicancer.fr (C. Rousset-Jablonski), SBorstnar@onko-i.si (S. Borstnar), takejun@luke.ac.jp (J. Takei), jeongeon.lee@samsung.com (J.E. Lee), Janice.Walshe@svuh.ie (J.M. Walshe), ruizsabater@gmail.com (M.R. Borrego), mooreh1@ccf.org (H.C.F. Moore), christobel.saunders@uwa.edu.au (C. Saunders), fatimacardoso@fundacaochampilimaud.pt (F. Cardoso), suska.sule@gmail.com (S. Susnjari), Vesna.bjelic-radicic@helios-gesundheit.de (V. Bjelic-Radicic), ksmith60@jhmi.edu (K.L. Smith), martine.piccart@bordet.be (M. Piccart), larissa.korde@nih.gov (L.A. Korde), gelber@jimmy.harvard.edu (R.D. Gelber), opagani@bluewin.ch (O. Pagani).

<https://doi.org/10.1016/j.breast.2021.07.021>

0960-9776/© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

^z Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal^{aa} Department of Medical Oncology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia^{ab} Breast Unit, Helios University Hospital Wuppertal, University Witten/Herdecke, Wuppertal, Germany^{ac} Medical University Graz, Department Gynaecology, Graz, Austria^{ad} Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA^{ae} Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD, USA^{af} International Breast Cancer Study Group, IEO European Institute of Oncology, IRCCS, Milan, Italy^{ag} International Breast Cancer Study Group Statistical Center, Department of Data Science, Division of Biostatistics, Dana-Farber Cancer Institute, Frontier Science and Technology Research Foundation, Harvard TH Chan School of Public Health and Harvard Medical School, Boston, MA, USA^{ah} Interdisciplinary Cancer Service Hospital Riviera-Chablais Rennaz, Geneva University Hospitals, Lugano University, Swiss Group for Clinical Cancer Research (SAKK), Vaud, Switzerland

ARTICLE INFO

Article history:

Received 1 June 2021

Received in revised form

22 July 2021

Accepted 30 July 2021

Available online 3 August 2021

Keywords:

Breast cancer

Young women

Premenopausal women

Pregnancy desire

Endocrine therapy

Treatment interruption

ABSTRACT

Background: Premenopausal women with early hormone-receptor positive (HR+) breast cancer receive 5–10 years of adjuvant endocrine therapy (ET) during which pregnancy is contraindicated and fertility may wane. The POSITIVE study investigates the impact of temporary ET interruption to allow pregnancy. **Methods:** POSITIVE enrolled women with stage I–III HR + early breast cancer, ≤42 years, who had received 18–30 months of adjuvant ET and wished to interrupt ET for pregnancy. Treatment interruption for up to 2 years was permitted to allow pregnancy, delivery and breastfeeding, followed by ET resumption to complete the planned duration.

Findings: From 12/2014 to 12/2019, 518 women were enrolled at 116 institutions/20 countries/4 continents. At enrolment, the median age was 37 years and 74.9 % were nulliparous. Fertility preservation was used by 51.5 % of women. 93.2 % of patients had stage I/II disease, 66.0 % were node-negative, 54.7 % had breast conserving surgery, 61.9 % had received neo/adjuvant chemotherapy. Tamoxifen alone was the most prescribed ET (41.8 %), followed by tamoxifen + ovarian function suppression (OFS) (35.4 %). A greater proportion of North American women were <35 years at enrolment (42.7 %), had mastectomy (59.0 %) and received tamoxifen alone (59.8 %). More Asian women were nulliparous (81.0 %), had node-negative disease (76.2%) and received tamoxifen + OFS (56.0 %). More European women had received chemotherapy (69.3 %).

Interpretation: The characteristics of participants in the POSITIVE study provide insights to which patients and doctors considered it acceptable to interrupt ET to pursue pregnancy. Similarities and variations from a regional, sociodemographic, disease and treatment standpoint suggest specific sociocultural attitudes across the world.

© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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 (IBCSG 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

Table 1
 POSITIVE study participation by continent and country.

		Women Participating	
		Number	%
Total women participating		517 ^a	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	Total	117	22.6
	Country/Collaborative Group		
	Canada/CCTG	29	5.6
	USA/Alliance/SWOG/	88	17.0
	ECOG-ACRIN/NRG		
Asia/Pacific/Middle East	Total	84	16.2
	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 A 518th patient was enrolled, but enrolment cancelled immediately due to inadvertent registration.

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

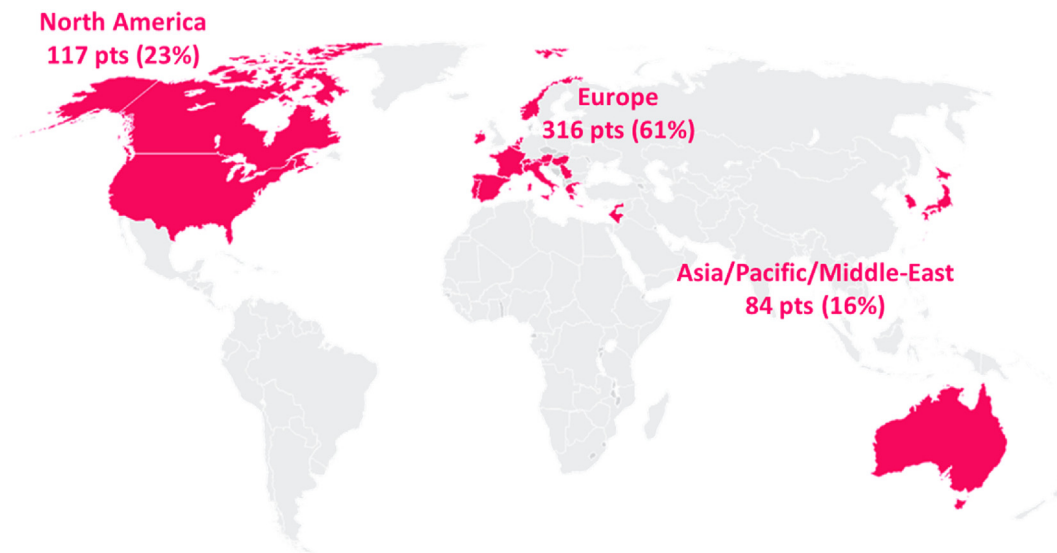


Fig. 1. POSITIVE study participation by continent.

Table 2
Patient and tumor characteristics of POSITIVE participants, overall and according to continent.

	Overall		Continent					
	N	%	Europe		North America		Asia/Pacific/Middle East	
			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/m ²)								
<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
pN+ 1-3	152	29.4	88	27.8	48	41.0	16	19.0
pN+ 4-9	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.

Table 3
Prior treatment of POSITIVE participants, overall and by continent.

	Overall		Continent					
	N	%	Europe		North America		Asia/Pacific/Middle East	
			N	%	N	%	N	%
Total women participating	517	100	316	100	117	100	84	100
Most extensive primary surgery								
Breast conserving surgery	283	54.7	189	59.8	47	40.2	47	56.0
Mastectomy	233	45.1	127	40.2	69	59.0	37	44.0
Unknown	1	0.2	0	0	1	0.9	0	0
Prior (neo)adjuvant chemotherapy								
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								
SERM only	216	41.8	116	36.7	70	59.8	30	35.7
SERM + OFS	183	35.4	127	40.2	9	7.7	47	56.0
AI + OFS	82	15.9	54	17.1	23	19.7	5	6.0
Other ^a	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		17.9–33.1		18.0–31.3	

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

^a 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.

(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 2 tumours, 33.3 % had grade 3 disease, 88.2 % had invasive ductal invasive histology, and 73.7 % had HER2-negative disease. Stage distribution was different across continents. Asian patients more frequently had stage I, grade 1 and node-negative disease (51.2 %, 28.6 % and 76.2%, respectively) compared to European (46.5 %, 14.2 % and 66.8 %) and NA (44.4 %, 17.1 % and 56.4 %) women. Among Asian women, only 19.0 % had 1-3 positive nodes and 19.0 % grade 3 tumours; the proportions were 27.8 % and 35.4 % in Europe, 41.0 % and 37.6 % in NA, respectively. The proportion of women with HER2+ tumours was lower in Asian than in NA and European women (15.5 %/27.4 %/28.2 %, respectively).

Treatments received prior to enrolment are summarized in Table 3. Breast conserving surgery (BCS) had been performed in 54.7 % of patients, mastectomy in 45.1 % of women, and 61.9 % of women had received chemotherapy. Treatment variations emerged across continents. Mastectomy was more frequent in NA (59.0 % of patients) than in Asia (44.0 %) and Europe (40.2 %). Chemotherapy was more frequently administered in Europe (69.3 %) than in NA (56.4 %) and Asia (41.7 %). ET prior to enrolment varied substantially across continents. Amongst NA patients, 59.8 % took tamoxifen alone, ovarian function suppression (OFS) was added to tamoxifen

in another 7.7 % of participants, and 19.7 % received AI + OFS. In Asia, most patients had received tamoxifen + OFS (56.0 %), followed by tamoxifen alone (35.7 %), only a minority receiving AIs + OFS (6.0 %). In Europe, tamoxifen + OFS was the most frequently administered ET (40.2 % of the participants), followed by tamoxifen alone (36.7 %) and AIs + OFS (17.1 %). The median duration of 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 <35 years, 43.7 % of those 35–39 years and 50.0 % of women 40–42 years), tamoxifen + OFS to 35.4 % (from 41.2 % to 31.1 % and 34.7 %), AIs + OFS to 15.9 % of women (from 15.3 % to 18.5 % and 11.9 %). 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 AIs + 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 AIs) 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 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	%
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

increasing tumour grade (30.3 % of grade 1 disease versus 88.4 % of grade 3 disease) and disease stage (53.7 % of pN0 versus 95.7 % of patients with pN2 disease). Tamoxifen alone was prescribed to 43.0 % of low-weight women, and 34.7 % of obese women, and OFS was added to 51.1 % and 44.9 % of them, respectively (Table 4b).

ET selection changed amongst enrolled women from the first half of the accrual period (up until June 30, 2017) to the second half in all regions (Table 5). Prescription of tamoxifen alone remained stable whereas the combination of AI + OFS doubled at the expense of tamoxifen + OFS. In Europe, tamoxifen + OFS use decreased by 12.8 % and AI + OFS increased by 10 %. In NA, tamoxifen + OFS use declined by 8.7 %, paralleled by a 11.8 % increase in AI + OFS. In Asia, tamoxifen use dropped by 12.4 %, prescription of AI + OFS increased by 7.0 %, with no patient receiving this combination in the first accrual period, and tamoxifen + OFS increased by 2.5 %.

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

	Overall N	Prior Endocrine Therapy							
		SERM only		SERM + OFS		AI + OFS		Other*	
		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	136	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
pN+ 1-3	152	56	36.8	44	28.9	35	23.0	17	11.2
pN+ 4-9	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 N	Prior (Neo)adjuvant Chemotherapy					
		Yes		No		Unknown	
		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
pN+ 1-3	152	115	75.7	37	24.3	0	0
pN+ 4-9	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

Table 5
Adjuvant therapies prior to enrolment, according to period of enrolment^a and continent. Note percentages sum across the rows, within type of therapy.

Continent	Accrual	Overall N	Prior Endocrine Therapy								Prior (Neo)adjuvant Chemotherapy					
			SERM only		SERM + OFS		AI + OFS		Other ^b		Yes		No		Unknown	
			N	%	N	%	N	%	N	%	N	%	N	%	N	%
Europe	Total	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
North America	2nd half	218	83	38.1	79	36.2	44	20.2	12	5.5	158	72.5	60	27.5	0	0
	Total	117	70	59.8	9	7.7	23	19.7	15	12.8	66	56.4	50	42.7	1	0.9
	Period															
Asia/Pacific/Middle East	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
	Total	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.

^a 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.

^b 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.

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 + OFS in Europe and NA and of tamoxifen alone in Asia. The consensus guidelines published in 2019 by the Asian Breast Cancer Cooperative Group (ABCCG) [34] could not have significantly impacted treatment choices for the POSITIVE population because 18–30 months of prior ET was required for POSITIVE eligibility. Additionally, the observed changes over time reflect the selected population and attitudes of countries and/or institutions that joined the trial later during the recruitment period.

The descriptive findings of the baseline characteristics of women enrolled in the POSITIVE study are limited by the lack of a control group of women who are not interested in becoming

pregnant. Further, at this time, we are unable to report on certain characteristics (e.g., data on menses recovery, patients' concerns and decisional conflict) and outcomes given the study is still ongoing or they are part of the Psycho-oncological Companion Study, whose data will be available in the future.

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.

Author contribution

Ann H. Partridge, MD, MPH – Conceptualization and study design; Data acquisition; Manuscript writing – original draft; Manuscript review, editing and approval. **Samuel M. Niman, MS** – Manuscript writing – original draft; Statistical analysis; Manuscript review, editing and approval. **Monica Ruggeri** – Conceptualization and study design; Manuscript writing – original draft; Manuscript review, editing and approval. **Fedro A. Peccatori, MD, PhD** – Data acquisition; Manuscript review, editing and approval. **Hatem A Azim Jr, MD, PhD** – Manuscript review, editing and approval. **Marco Colleoni, MD** – Data acquisition; Manuscript review, editing and approval. **Cristina Saura, MD, PhD** – Data acquisition; Manuscript review, editing and approval. **Chikako Shimizu** – Data acquisition; Manuscript review, editing and approval. **Anna Barbro Sætersdal** – Data acquisition; Manuscript review, editing and approval. **Judith R Kroep, MD, PhD** – Data acquisition; Manuscript review, editing and approval. **Audrey Mailliez, MD** – Data acquisition; Manuscript review, editing and approval. **Ellen Warner** – Data acquisition; Manuscript review, editing and approval. **Virginia F. Borges, MD** – Data acquisition; Manuscript review, editing and approval. **Frédéric Amant, MD, PhD** – Data acquisition; Manuscript review, editing and approval. **Andrea Gombos, MD** – Data acquisition; Manuscript review, editing and approval. **Akemi Kataoka** –

Data acquisition; Manuscript review, editing and approval. **Christine Rousset-Jablonski, MD, PhD** - Data acquisition; Manuscript review, editing and approval. **Simona Borstnar, MD, PhD** - Data acquisition; Manuscript review, editing and approval. **Junko Takei** - Data acquisition; Manuscript review, editing and approval. **Jeong Eon Lee, MD, PhD** - Data acquisition; Manuscript review, editing and approval. **Janice M. Walshe, MD** - Data acquisition; Manuscript review, editing and approval. **Manuel Ruíz Borrego, MD** - Data acquisition; Manuscript review, editing and approval. **Halle C.F. Moore, MD** - Manuscript review, editing and approval. **Christobel Saunders, MD** - Data acquisition; Manuscript review, editing and approval. **Fatima Cardoso, MD** - Conceptualization and study design; Data acquisition; Manuscript review, editing and approval. **Snezana Susnjarić, MD, PhD** - Data acquisition; Manuscript review, editing and approval. **Vesna Bjelic-Radisic** - Data acquisition; Manuscript review, editing and approval. **Karen L. Smith** - Data acquisition; Manuscript review, editing and approval. **Martine Piccart, MD, PhD** - Manuscript review, editing and approval. **Larissa A. Korde, MD, MPH** - Conceptualization and study design, Data acquisition; Manuscript review, editing and approval. **Aron Goldhirsch[†], MD** - Conceptualization and study design. **Richard D. Gelber, PhD** - Conceptualization and study design; Statistical analysis; Manuscript writing - original draft; Manuscript review, editing and approval. **Olivia Pagani, MD** - Conceptualization and study design; Data acquisition, Manuscript writing - original draft; Manuscript review, editing and approval.

Funding

The POSITIVE trial and this work are sponsored by the IBCSG in non-North American countries and by the Alliance for Clinical Trials in Oncology in North America, with collaboration of the Breast International Group (BIG) cooperative groups and US National Clinical Trials Network groups.

In Non-North American countries, POSITIVE receives grant support for central and/or local trial conduct from: Frontier Science & Technology Research Foundation, Southern Switzerland (FSE); BIG *against breast cancer* and Baillet Latour Fund, Belgium; Pink Ribbon Switzerland; Swiss Cancer League, Switzerland (KLS-3361-02); San Salvatore Foundation, Switzerland; Rising Tide Foundation for Clinical Research, Switzerland (CCR-15-120); Swiss Cancer Research Group (SAKK), Switzerland and Clinical Cancer Research Foundation of Eastern Switzerland (OSKK); Gateway for Cancer Research, USA (G-15-1900); Breast Cancer Research Foundation (BCRF), USA; Roche Diagnostics International Ltd, Switzerland; Swiss Cancer Foundation, Switzerland; Piajoh Fondazione di Famiglia, Switzerland; Gruppo Giovani Pazienti “Anna dai Capelli Corti”, Switzerland; Baärguf, Switzerland; Schweizer Frauenlauf, Bern, Switzerland; Dutch Cancer Society, Netherlands; Norwegian Breast Cancer Society, Norway; Pink Ribbon, Norway; ELGC K-K., Tokyo, Japan; Pink Ring, Tokyo, Japan; Korea Breast Cancer Foundation, Seoul, South Korea; Mr. Yong Seop Lee, Seoul, South Korea; and other private donors to support the conduct of the POSITIVE study within participating centers worldwide.

In North America, Alliance for Clinical Trials in Oncology receives support from the National Cancer Institute of the National Institutes of Health (NIH) under the Award Number UG1CA189823 (Alliance for Clinical Trials in Oncology NCI Community Oncology Research Program [NCORP] Grant); ECOG-ACRIN receives support under the EA NCORP grant award numbers: UG1CA189828 and UG1CA233196; SWOG Cancer Research Network receives support under the US NIH grant award numbers: UG1CA189974, UG1CA180834, UG1CA180826, UG1CA180828 and UG1CA233320; and NRG Oncology receives support under the US NIH grant award number U10CA180868. Canadian Cancer Trials Group (CCTG)

participation in the POSITIVE trial is supported through its grant from the US National Cancer Institute of the NIH under the award number CA180863. Additional programmatic funding support for the CCTG is provided by the Canadian Cancer Society (#704970) and the Canada Foundation for Innovation. In addition, POSITIVE receives support from RETHINK Breast Cancer, Canada and the Gilson Family Foundation, USA.

Funding sources are not involved in study design; collection, analysis and interpretation of data; writing of the report; nor in the decision to submit the article for publication.

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 Dhome España SA, Novartis, Pfizer, Philips Healthwork, Pierre Fabre, priME 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. Borges** receives consulting fees from SeaGen. **Frédéric Amant** receives honoraria from AstraZeneca and PharmaMar. **Andrea Gombos** 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 Rousset-Jablonski** receives honoraria or advisory fees from Amgen, AstraZeneca, Eli Lilly, Krka, Merck, Novartis, Pfizer, or Roche; 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 Ruíz Borrego** receives speaker grants 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,

Daiichi-Sankyo, and Sermonix. **Christobel Saunders** receives honoraria from Roche, Pfizer and GenesisCare. **Fatima Cardoso** serves an advisory role for Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, MacroGenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Samsung Bioepis, Seattle Genetics, and Teva; none of these are trial related. **Snezana Susnjar** receives honoraria or advisory fees from Roche, Pfizer, Novartis, AstraZeneca, and Amicus; none of these are trial related. **Vesna Bjelic-Radisic** receives honoraria from Novartis, AstraZeneca, and Roche; receives consulting or advisory fees from Pfizer or Lilly; none of these are trial related conflicts. **Karen L. Smith** reports that her spouse has stock in Abbott Laboratories and Abbvie and that she receives research funding (to her Institution) from Pfizer; one of these are trial-related. **Martine Piccart** receives honoraria from AstraZeneca, Camel-IDS, Debiopharm, Immunomedics, Lilly, Menarini, MSD, Novartis, Odonate, Pfizer, Roche-Genentech, Seattle Genetics, and Immunet; receives research grants (to her Institution) from AstraZeneca, Immunomedics, Lilly, Menarini, MSD, Novartis, Pfizer, Radius, Roche-Genentech, Servier, and Synthon and is a scientific board member for Oncolytics. **Larissa A. Korde** reports no conflicts related to this trial. **Richard D. Gelber** receives research funding (to his Institution) to partially support his salary from Novartis, Pfizer, Merck, Roche, and AstraZeneca. **Olivia Pagani** reports no conflicts related to this trial.

Acknowledgements

We thank the patients who participated in the POSITIVE trial without whom substantial recent progress to improve care for young women with breast cancer would not be possible. We dedicate this paper to the memory of Professor Aron Goldhirsch (1946–2020), medical oncologist and breast cancer specialist, who died on February 26, 2020, and devoted his life to patient care and clinical research. As scientific co-chair of the International Breast Cancer Study Group (IBCSG) and the Breast International Group (BIG), Prof Goldhirsch played a pivotal role to develop and conduct the POSITIVE trial.

APPENDIX. POSITIVE Trial Steering Committee, International Breast Cancer Study Group (IBCSG), International Networks, and Participating Centers/Groups and Principal Investigators

POSITIVE Trial Steering Committee: O. Pagani (International Chair), A.H. Partridge (North American Chair), H.A. Azim Jr (Translational Research Co-Chair), F. Peccatori (Translational Research Co-Chair), K. Ribí (Psycho-oncological Companion Study Chair), C. Abi-Khattar, F. Amant, A. Barbro Sætersdal, V. Bjelic-Radisic, L. Blacher, V. Borges, M.R. Borrego, S. Borstnar, F. Cardoso, M. Colleoni, I. Demeestere, A. Di Leot, J. Eon Lee, T. Ferreira, R. Gelber, K. Gelmon, A. Hiltbrunner, S. El-Abed, M. Ignatiadis, P. Jani, R. Kammler, J.M. Walshe, J. Kroep, S. Loi, A. Mailliez, D. Mavroudis, H. Moore, M. Naughton, S. Niman, S. Paluch-Shimon, M. Rabaglio, M.M. Regan, H. Roschitzki, K. Ruddy, B. Ruepp, M. Ruggeri, C. Saunders, C. Saura, H. Shaw, C. Shimizu, K.L. Smith, T. Spanic, S. Susnjar, F. Symmans, G. Viale.

IBCSG Scientific Committee: M. Colleoni (Chair), S. Loi (Co-Chair).

IBCSG Scientific Executive Committee: M. Colleoni, A. Di Leot, F. Boyle, G. Jerusalem, S. Loi, M.M. Regan, G. Viale.

IBCSG Foundation Council: R. Stahel (President), S. Aebi, F. Boyle, A. Coates, M. Colleoni, A. Di Leot, R. Gelber, A. Goldhirsch, G. Jerusalem, P. Karlsson, I. Kössler, M.M. Regan.

IBCSG Coordinating Center, Bern, Switzerland: A. Hiltbrunner

(Director), G. Achille, S. Adam, I. Campus, A. Carrer-Wagner, D. Celotto, C. Comune, M. Fournarakou, M. Frapolli, A. Gasca, N. Giacomelli, R. Kammler, R. Karagol, L. Keglowich, C. Maddox, M. Mathys, M. Pardo Contreras, M. Nesa, L. Nobs, R. Pfister, M. Rabaglio, H. Roschitzki, B. Ruepp, M. Ruggeri, E. Rugiati, M. Sanchez-Hohl, M. Schneider, J. Schroeder, P. Sicher, S. Troesch, M. Wagner, M. Weber, M. Wenger, F. Wyss, I. Zenklusen.

IBCSG Statistical Center, Division of Biostatistics, Dana-Farber Cancer Institute, Boston, MA, USA: M.M. Regan (Director), C. Bouzan, R. Gelber, S. Gelber, H. Huang, C. Mahoney, S. Niman, L. Northrop, Z. Sun.

IBCSG Data Management Center, Frontier Science & Technology Research Foundation, Amherst, NY, USA:

L. Blacher (Director), P. Jani (Trial Coordinator/Data Manager), S. Fischer (Lead Data Manager), J. Jemison, G. Kassab, L. Mundy, D. Narayanan, V. Palermo, K. Scott, H. Shaw, R. Starkweather, Y. Veira, D. Weinbaum.

IBCSG Quality of Life Office, Bern, Switzerland: J. Bernhard, K. Ribí.

CENTRAL LABORATORIES

IBCSG Central Pathology Office, European Institute of Oncology, Division of Pathology, Milan, Italy: G. Viale (Director), S. Andrighetto, L. Arrigoni, G. Bardeli, E. Benini, O. Biasi, F. Ciocca, P. Dell'Orto, L. Russo.

Research Laboratory on Human reproduction, Université Libre de Bruxelles, Belgium: I. Demeestere (Director), J. Dechene.

Medical Oncology Department & Academic Trials Promoting/Breast Cancer Translational Research Laboratory, Institut Jules Bordet, Université Libre de Bruxelles, Belgium: M. Ignatiadis, F. Rothé, M. Maetens.

NETWORKS

The POSITIVE trial resulted from the collaboration of the Endocrine Working Group of the BIG-NABCG: Co-chairs: A. Goldhirsch (BIG), L. Korde (NABCG).

Breast International Group (BIG): M. Piccart, S. Hultsch, S. Schmitz, S. El-Abed, H. De Swert, M. Jooris, J. Leemans, G. Questiaux, C. Straehle.

North American Breast Cancer Group (NABCG): L. Korde, M. Mooney.

Participating Centers/Groups and Principal Investigators: International Breast Cancer Study Group (IBCSG; Accrual 141). Italy (Accrual 66).

Istituto Europeo di Oncologia, Milano; M. Colleoni. U·O Medicina Oncologica Ospedale di Carpi; F. Artigli. Ospedale di Bolzano; E Cretella.

Ospedale Multimedica, Castellanza; E Gallerani.

Ospedale di Prato, Azienda USL Toscana Centro, Prato; G. Sanna.

Ospedale di Circolo, Varese; C. Chini.

Ospedale di Trento, Trentino; A. Ferro.

IRCCS Centro di Riferimento Oncologico (CRO), Aviano; S. Spazzapan.

Ospedale Degli Infermi, Ponderano; E Seles.

Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, FC; U. De Giorgi.

Switzerland, Swiss Group for Clinical Cancer Research (SAKK; Accrual 40).

Brust-Zentrum AG Zurich; C. Tausch.

Oncology Institute of Southern Switzerland (IOSI), Bellinzona; L. Rossi.

Inselspital Bern; M. Rabaglio.

CHUV Lausanne; K. Zaman.

- Universit tsspital Basel; M. Vetter.
 University Hospital Zurich; K. Dedes.
 University Hospital Geneva; A. Bodmer.
 Kantonsspital Baden AG; C. Leo.
 Kantonsspital St. Gallen; S. Riniker.
 Oncocare Bern; M. Borner.
 Hospital de Sion; V. Membrez.
Belgium (Accrual 24).
 UZ Leuven, Leuven; F. Amant.
 Institut Jules Bordet, Bruxelles; A. Gombos.
 CHU Sart-Tilman, Li ge; G. Jerusalem.
 Clinique St. Elisabeth, Namur; C. Quaghebeur.
 Slovenia (Accrual 10).
 Institute of Oncology, Ljubljana; S. Borstnar.
Lebanon (Accrual 1).
 American University of Beirut Medical Center; N.S. El Saghir.
SOLTI Group (Accrual 63), Spain, Portugal.
 Hospital Vall D'Hebron, Barcelona; C Saura.
 Hospital General de Valencia; V. Iranzo.
 Hospital Son Espases, Palma; A. Perell .
 Centro Integral Oncologico Clara Campal, Madrid; A.M. Luna Barrera.
 Hospital General de Catalunya, Barcelona; X. Gonz lez.
 Champalimaud Clinical Center, Lisbon; F. Cordosa.
 Hospital Universitario de Fuenlabrada, Madrid; J. Guerra.
 Hospital Universitario Virgen de la Arrixaca, Murcia; P. Sanchez Henarejos.
 Hospital Quiron Sagrado Corazon, Sevilla; J.A. Virizuela.
 Complejo Hospitalario Universitario de Santiago, A Coru na; R. L pez.
 Hospital Clinico Universitario Lozano Blesa, Zaragoza; R. Andr s.
Japan Breast Cancer Research Group (JBCRG; Accrual 62).
 The Cancer Institute Hospital of JFCR, Tokyo; A. Kataoka.
 St. Luke's International Hospital, Tokyo; J. Takei.
 Showa University Hospital, Tokyo; S. Nakamura.
 Okayama University Hospital; T. Shien.
 St. Marianna University School of Medicine Hospital, Kawasaki;
 K. Tugawa.
 University of Tsukuba; H. Bando.
 Kyoto University Hospital; M. Kawashima.
 NHO Kyushu Cancer Center, Fukuoka; E. Tokunaga.
 Tohoku University Hospital, Sendai; H. Tada.
 Social Medical Corporation Hakuaiikai Sagara Hospital, Kagoshima; J. Kawano.
 NHO Osaka National Hospital; N. Masuda.
 Seirei Hamamatsu General Hospital; M. Yoshida.
 NHO Shikoku Cancer Center, Matsuyama; M. Takahashi.
 National Cancer Center Hospital, Tokyo; K. Tamura.
 Kansai Rosai Hospital, Amagasaki; C. Egawa.
 National Center for Global Medicine, Tokyo; C. Shimuzu.
Alliance for Clinical Trials in Oncology (Accrual 60).
 Dana-Farber Cancer Institute, Boston, MA; A.H. Partridge.
 Georgetown University Hospital, Washington, D.C.; A. A. Dilawari.
 Northwestern University, Evanston, IL; E. Flaum.
 Cedars Sinai Medical Center, Los Angeles, CA; P.F. McAndrew.
 Sharp Memorial Hospital, San Diego, CA; C.M. Casteel.
 Johns Hopkins University, Baltimore, MD; K.L. Smith.
 IHA Hematology Oncology Consultants-Ann Arbor, MI; T. Al Baghdadi.
 Weill Cornell Medical University, New York, NY; T. Cigler.
 Montefiore Medical Center-Einstein Campus, The Bronx, NY; J.A. Sparano.
 Rocky Mountain Cancer Center, Aurora, CO; N. DiBella.
 Regional Hematology Oncology Practice Associates, Newark, DE;
 G.A. Masters.
 Fairview Southdale Hospital, Edina, MN; D.M. Anderson.
 UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC;
 K.E. Reeder-Hayes.
 Duke University Medical Center, Durham, NC; J. Crawford.
 Margaret R Pardee Memorial Hospital, Hendersonville, NC; J.E. Radford.
 Dartmouth Hitchcock Medical Center, Lebanon, NH; G.N. Schwartz.
 University of New Mexico, Albuquerque, NM; Z. Ruiz Dayao.
 Lehigh Valley Hospital - Muhlenberg, Bethlehem, PA; T. Al Baghdadi.
 Huntsman Cancer Institute, Salt Lake City, UT; A.C. Beck.
 Bon Secours Saint Francis Medical Center, Midlothian, VA; I.J. William.
Canadian Cancer Trial Group (CCTG; Accrual 29).
 Odette Cancer Center Sunnybrook Health Sciences Center, Toronto, ON; E. Warner.
 Vancouver Cancer Center, Vancouver, BC; K.A. Gelmon.
 Tom Baker Cancer Center, Calgary, AB; M. Webster.
 St. Michael's Hospital, Toronto, ON; R. Haq.
 Mount Sinai Hospital, Toronto, ON; C. Elser.
 Center Hospitalier Universitaire de Sherbrooke, QC; M. Pavic.
 CHA-Hospital Du St-Sacrement, Quebec, QC; C. Desbiens.
Norwegian Breast Cancer Group (NBCG; Accrual 25).
 Norwegian Radium Hospital, Oslo University; A. Barbro S tersdal.
Dutch Breast Cancer Research Group (BOOG; Accrual 23).
 Leiden University Medical Center; J.R. Kroep.
France (Accrual 23).
 Center Oscar Lambret, Lille; A. Mailliez.
 French Lyon Cancer Center; C. Rousset-Jablonski.
 Institut Bergonie, Bordeaux; M. Debled.
SWOG Cancer Research Network (Accrual 20).
 Anschutz Cancer Pavilion, Aurora, CO; V. F. Borges.
 Yale University-Yale Cancer Center, New Haven, CT; T.B. Sanft.
 Seattle Cancer Care Alliance, Seattle, WA; R.L. Yung.
 Northwestern University, Evanston, IL; E. Flaum.
 Smilow Cancer Hospital Care Center at Saint Francis, North Haven, CT; T.B. Sanft.
 Smilow Cancer Hospital Care Center-Trumbull, CT; T.B. Sanft.
Spanish Breast Cancer Group (GEICAM; Accrual 14).
 Hospital Clinico Universitario San Carlos, Madrid; J.  ngel Garc a-S enz.
 Universitario Virgen del Roc o, Sevilla; M. Ruiz-Borrego.
 Hospital Virgen del la Victoria, Malaga; M. Jos  Bermejo P rez.
 Complejo Hospitalario de Navarra, Pamplona; J. J. Illarramendi.
 Instituto Catalan de Oncologia, Barcelona; S. Del Barco.
Cancer Trials Ireland (CTI; Accrual 13).
 St. Vincents University Hospital, Dublin; J.M. Walshe.
 University Hospital Limerick; G. Korpanty.
 Galway University Hospital; M. Keane.
 St James's Hospital, Dublin; J. Kennedy.
South Korea (Accrual 11).
 Samsung Medical Center, Seoul; J.E. Lee.
 Asan Medical Center, Seoul; H. Jeong Kim.
Australia (Accrual 8).
 St. John of God Hospital, Subiaco; C. Saunders.
Austrian Breast & Colorectal Cancer Study Group (ABCSCG; Accrual 7).
 Univ. Klinik f. Frauenheilkunde u. Geburtshilfe, Graz; V. Bjelic-Radic.
 LKH Salzburg; R. Greil.
 Univ. Klinik f. Frauenheilkunde Innsbruck; T. Czech.
Serbia (Accrual 5).

Institute of Oncology & Radiology of Serbia, Belgrade; S. Susnjari.
ECOG-ACRIN Cancer Research Group (Accrual 4).

Sibley Memorial Hospital, Washington, D.C.; K.L. Smith.
 Indiana University Medical Center, Indianapolis, IN; T.J.
 Ballinger.

NRG Oncology (Accrual 4).

Stanford Cancer Center, Palo Alto, CA; I.L. Wapnir.
 Poudre Valley Hospital, Fort Collins, CO; V.F. Borges.

Emory University, Atlanta, GA; J.L. Meisel.

Sanford Roger Maris Cancer Center, Fargo, ND; P.D. Steen.

Hellenic Oncology Research Group (HORG; Accrual 2).

University General Hospital of Heraklion, Irakleio; D. Mavroudis.

Israel (Accrual 2).

Chaim Sheba Medical Center, Ramat Gan; B. Kaufman.

Italy (Accrual 2).

Regina Elena National Cancer Institute, Rome; P. Vici.

References

- [1] Partridge AH, Hughes ME, Warner ET, Ottesen RA, Wong YN, Edge SB, et al. Subtype-dependent relationship between young age at diagnosis and breast cancer survival. *J Clin Oncol* 2016;34(27):3308–14.
- [2] Pagani O, Regan MM, Walley BA, Fleming GF, Colleoni M, Lang I, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014;371(2):107–18.
- [3] Francis PA, Pagani O, Fleming GF, Walley BA, Colleoni M, Lang I, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med* 2018;379(2):122–37.
- [4] Ruddy KJ, Gelber SI, Tamimi RM, Ginsburg ES, Schapira L, Come SE, et al. Prospective study of fertility concerns and preservation strategies in young women with breast cancer. *J Clin Oncol* 2014;32(11):1151–6.
- [5] Ruggeri M, Pagan E, Bagnardi V, Bianco N, Gallerani E, Buser K, et al. Fertility concerns, preservation strategies and quality of life in young women with breast cancer: baseline results from an ongoing prospective cohort study in selected European Centers. *Breast* 2019;47:85–92.
- [6] Lambertini M, Kroman N, Ameye L, Cordoba O, Pinto A, Benedetti G, et al. Long-term safety of pregnancy following breast cancer according to estrogen receptor status. *J Natl Cancer Inst* 2018;110(4):426–9.
- [7] Lambertini M, Di Maio M, Pagani O, Curigliano G, Poggio F, Del Mastro L, et al. The BCY3/BCC 2017 survey on physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in young breast cancer patients. *Breast* 2018;42:41–9.
- [8] Pagani O, Ruggeri M, Manunta S, Saunders C, Peccatori F, Cardoso F, et al. Pregnancy after breast cancer: are young patients willing to participate in clinical studies? *Breast* 2015;24(3):201–7.
- [9] Partridge AH, Gelber S, Peppercorn J, Sampson E, Knudsen K, Laufer M, et al. Web-based survey of fertility issues in young women with breast cancer. *J Clin Oncol* 2004;22(20):4174–83.
- [10] Senkus E, Gomez H, Dirix L, Jerusalem G, Murray E, Van Tienhoven G, et al. Attitudes of young patients with breast cancer toward fertility loss related to adjuvant systemic therapies. EORTC study 10002 BIG 3-98. *Psycho Oncol* 2014;23(2):173–82.
- [11] Sun Z, Niman SM, Pagani O, Partridge AH, Azim Jr HA, Peccatori FA, et al. Estimation of historical control rate for a single arm de-escalation study - application to the POSITIVE trial. *Breast* 2020;53:1–7.
- [12] Niranjani SJ, Martin MY, Fouad MN, Vickers SM, Wenzel JA, Cook ED, et al. Bias and stereotyping among research and clinical professionals: perspectives on minority recruitment for oncology clinical trials. *Cancer* 2020;126(9):1958–68.
- [13] Lambertini M, Goldrat O, Clatot F, Demeestere I, Awada A. Controversies about fertility and pregnancy issues in young breast cancer patients: current state of the art. *Curr Opin Oncol* 2017;29(4):243–52.
- [14] Raymo JM, Park H, Xie Y, Yeung WJ. Marriage and family in East Asia: continuity and change. *Annu Rev Sociol* 2015;41:471–92.
- [15] Fang YY, Wu QJ, Zhang TN, Wang TR, Shen ZQ, Jiao J, et al. Assessment of the development of assisted reproductive technology in Liaoning province of China, from 2012 to 2016. *BMC Health Serv Res* 2018;18(1):873.
- [16] Committee for assisted reproductive technology S, Korean society for assisted R, lee GH, song HJ, choi YM, han HD. The status of assisted reproductive technology in Korea in 2012. *Clin Exp Reprod Med* 2017;44(1):47–51.
- [17] Kushnir VA, Barad DH, Albertini DF, Darmon SK, Gleicher N. Systematic review of worldwide trends in assisted reproductive technology 2004–2013. *Reprod Biol Endocrinol* 2017;15(1):6.
- [18] Suzuki N. Clinical practice guidelines for fertility preservation in pediatric, adolescent, and young adults with cancer. *Int J Clin Oncol* 2019;24(1):20–7.
- [19] Dolan H, Alden DL, Friend JM, Lee PY, Lee YK, Ng CJ, et al. Culture, self, and medical decision making in Australia and China: a structural model analysis. *MDM Policy Pract* 2019;4(2). 2381468319871018.
- [20] Cowppli-Bony A, Tretarre B, Marrer E, Defossez G, Daubisse-Marliac L, Coureau G, et al. Compliance with clinical guidelines for breast cancer management: a population-based study of quality-of-care indicators in France. *PloS One* 2019;14(10):e0224275.
- [21] Tan MP, Silva E. Addressing the paradox of increasing mastectomy rates in an era of de-escalation of therapy: communication strategies. *Breast* 2018;38:136–43.
- [22] Chhaba N, Tin Tin S, Zhao J, Abrahami S, Elwood JM. Geographic variations in surgical treatment for breast cancer: a systematic review. *Annals of Cancer Epidemiology* 2020;4.
- [23] Regan MM, Pagani O, Walley B, Torrissi R, Perez EA, Francis P, et al. Premenopausal endocrine-responsive early breast cancer: who receives chemotherapy? *Ann Oncol* 2008;19(7):1231–41.
- [24] Krop I, Ismaila N, Andre F, Bast RC, Barlow W, Collyar DE, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American society of clinical oncology clinical practice guideline focused update. *J Clin Oncol* 2017;35(24):2838–47.
- [25] Henry NL, Somerfield MR, Abramson VG, Ismaila N, Allison KH, Anders CK, et al. Role of patient and disease factors in adjuvant systemic therapy decision making for early-stage, operable breast cancer: update of the ASCO endorsement of the cancer care ontario guideline. *J Clin Oncol* 2019;37(22):1965–77.
- [26] Burstein HJ, Curigliano G, Loibl S, Dubsy P, Gnant M, Poortmans P, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. *Ann Oncol* 2019;30(10):1541–57.
- [27] Paluch-Shimon S, Cardoso F, Partridge AH, Abulkhair O, Azim Jr HA, Bianchi-Micheli G, et al. ESO-ESMO 4th international consensus guidelines for breast cancer in young women (BCY4). *Ann Oncol* 2020.
- [28] Thibodeau S, Voutsadakis IA. The Oncotype dx assay in ER-positive, HER2-negative breast cancer patients: a real life experience from a single cancer center. *Eur J Breast Health* 2019;15(3):163–70.
- [29] Levine MN, Julian JA, Bedard PL, Eisen A, Trudeau ME, Higgins B, et al. Prospective evaluation of the 21-gene recurrence score assay for breast cancer decision-making in ontario. *J Clin Oncol* 2016;34(10):1065–71.
- [30] McVeigh TP, Kerin MJ. Clinical use of the Oncotype DX genomic test to guide treatment decisions for patients with invasive breast cancer. *Breast cancer*, vol. 9. Dove Med Press; 2017. p. 393–400.
- [31] Pestalozzi BC, Tausch C, Dedes KJ, Rochlitz C, Zimmermann S, von Moos R, et al. Adjuvant treatment recommendations for patients with ER-positive/HER2-negative early breast cancer by Swiss tumor boards using the 21-gene recurrence score (SAKK 26/10). *BMC Canc* 2017;17(1):265.
- [32] Leung RC, Yau TC, Chan MC, Chan SW, Chan TW, Tsang YY, et al. The impact of the Oncotype DX breast cancer assay on treatment decisions for women with estrogen receptor-positive, node-negative breast carcinoma in Hong Kong. *Clin Breast Canc* 2016;16(5):372–8.
- [33] Regan MM, Fleming GF, Walley B, Francis PA, Pagani O. Adjuvant systemic treatment of premenopausal women with hormone receptor-positive early breast cancer: lights and shadows. *J Clin Oncol* 2019;JCO1802433.
- [34] Yeo W, Ueno T, Lin CH, Liu Q, Lee KH, Leung R, et al. Treating HR+/HER2-breast cancer in premenopausal asian women: asian breast cancer cooperative group 2019 consensus and position on ovarian suppression. *Breast Canc Res Treat* 2019;177(3):549–59.