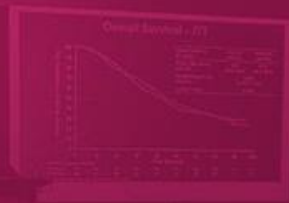


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APOIO



GERENCIAMENTO E PRODUÇÃO



Análise crítica do Especialista: Fertility preservation and assisted reproductive technologies (ART) in breast cancer (BC) patients (pts) interrupting endocrine therapy (ET) to attempt pregnancy

Giuliano Marchetti Bedoschi

Diretor científico da SBRH – biênio 2023-25

Coordenador do comitê de oncofertilidade da SBRH – biênio 2023-25

Doutor em Ciências da Saúde – Faculdade de Medicina de Ribeirão Preto – USP

Ganhador do prêmio CAPES de teses 2019

Research Fellow em Preservação da Fertilidade – New York Medical College

DECLARAÇÃO DE CONFLITO DE INTERESSES

Atualmente não recebo qualquer forma de pagamento ou auxílio financeiro de entidade pública ou privada para pesquisa ou desenvolvimento de métodos diagnósticos e terapêuticos ou ainda, honorários como consultor de indústria farmacêutica.



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Fertility preservation and assisted reproductive technologies in breast cancer patients interrupting adjuvant endocrine therapy to attempt pregnancy

Results from the POSITIVE Trial (IBCSG 48-14 / BIG 8-13 / Alliance A221405)

Hatem A. Azim Jr, MD, PhD

School of Medicine, Monterrey Institute of Technology, MX

On behalf of the POSITIVE Consortium

H. A. Azim Jr , S. M. Niman, A. H. Partridge, I. Demeestere, M. Ruggeri, M. Colleoni, C. Saura, C. Shimizu, A. B. Saetersdal, J. R. Kroep, A. Mailliez, E. Warner, V. F. Borges, F. Amant, A. Gombos, A. Kataoka, C. Rousset-Jablonski, S. Borstnar, J. Takei, J. E. Lee, J. M. Walshe, M. R. Borrego, H. C.F. Moore, C. Saunders, V. Bjelic-Radisic, S. Susnjar, F. Cardoso, N. J. Klar, T. Spanic, K. Ruddy, M. Piccart, L. A. Korde, A. Goldhirsch[†], R. D. Gelber, O. Pagani, F. A. Peccatori

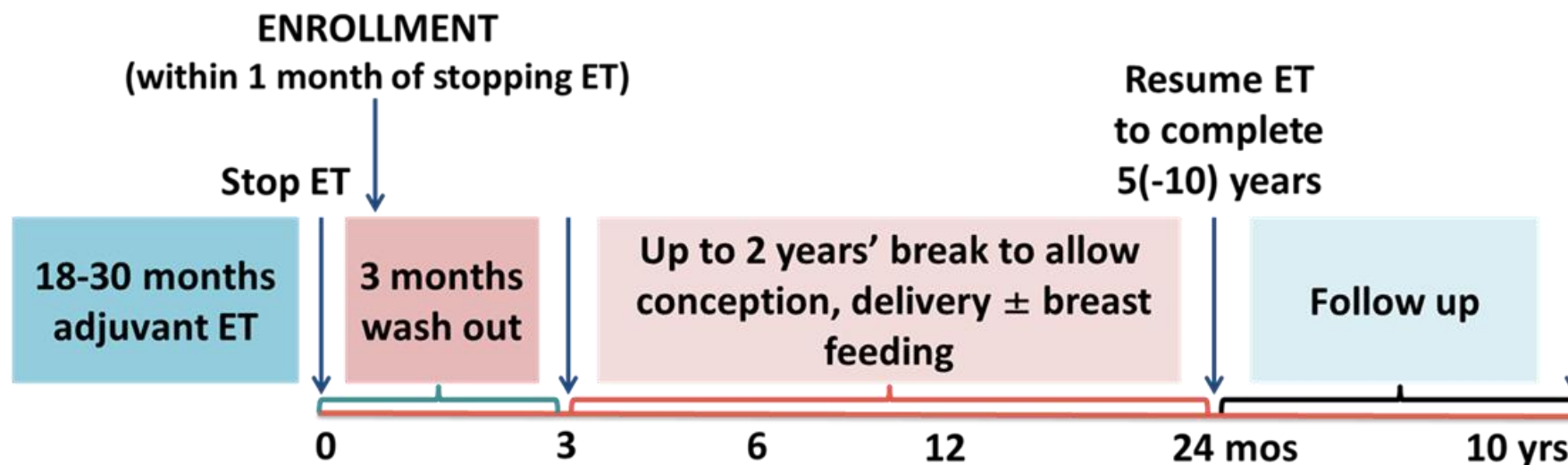
Background

- Pregnancy after breast cancer (BC) does not worsen disease outcomes, regardless of hormone receptor (HR) status ^{1, 2}
- The primary results of the POSITIVE trial showed that temporary interruption of endocrine therapy (ET) to attempt pregnancy does not impact disease outcomes, at a median follow-up (FU) of 41 months ³
- Adjuvant therapy often affects measures of ovarian function including menses, and may compromise chances of future fertility ⁴
- Uncertainty exists regarding the efficacy and safety of ovarian stimulation for fertility preservation and use of assisted reproductive technologies (ART) in women with early HR+ BC desiring future pregnancy

1. Azim HA Jr et al. J Clin Oncol 2013, 2. Lambertini M et al. J Clin Oncol 2021, 3. Partridge A et al. N Engl J Med 2023, 4. Oktay K et al. Fertil Steril 2022

POSITIVE trial design

- Prospective, international, multicenter, investigator-initiated, single-arm trial





Key eligibility criteria

- Premenopausal women stage I-III HR+ BC
- Wishing to become pregnant
- Age ≤ 42 years at study entry
- At least 18 months and no more than 30 months of prior adjuvant ET
- No clinical evidence of recurrence

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516 pacientes seguidas por 3.4 anos:

Recorrência de **8.9% (44 eventos)** vs. 9.2% (coorte externa)



Endpoints

- **Primary**

- **Breast cancer-free interval (BCFI)** = time from enrollment (after 18-30 months of ET) to the first ipsilateral / locoregional / contralateral invasive disease or distant recurrence

- **Secondary**

- Pregnancy outcomes
- Offspring outcomes
- Breastfeeding
- **Menstruation recovery**
- **Use of assisted reproductive technology (ART)**
- Adherence to endocrine treatment
- Distant recurrence-free interval (DRFI) = time from enrollment to the first BC distant recurrence

Trial procedures

- At enrollment, all patients were asked to complete a menstrual diary for 2 years
- Information on use of fertility preservation **at diagnosis, prior to enrollment** was collected:
 - Ovarian stimulation for oocyte/embryo cryopreservation
 - GnRHa use during chemotherapy
 - Ovarian tissue cryopreservation
- Use of any ART modality **on study** was allowed (per physician/patient discretion) including:
 - Transfer of cryopreserved embryo
 - Ovarian stimulation for IVF
 - Intrauterine insemination
 - Clomiphene use
 - Embryo/egg donation

GnRHa: gonadotropin releasing hormone analogues, ART: assisted reproductive technologies, IVF: in-vitro fertilisation



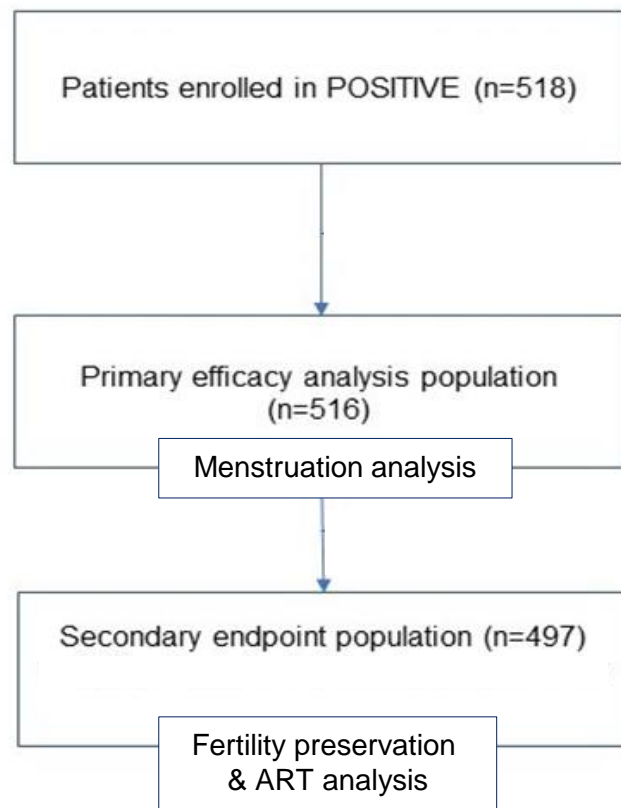
Statistical considerations

In this analysis, at 41 months median follow-up from enrollment, we evaluated:

- **Time to menstruation recovery:** Cumulative incidence* in the presence of competing risks** at **6 & 12-months** according to prior use of chemotherapy \pm GnRHa
- **Time to 1st pregnancy:** Cumulative incidence* in the presence of competing risks*** at **1 and 2 years**
- **Factors associated with time to pregnancy:** Fine & Gray competing risks regression adjusted for use of chemo \pm GnRHa, age, prior ET, prior birth, and menstrual status at enrollment
- **Association of ART use and achieving pregnancy:** Logistic regression adjusted for age, and use of chemo \pm GnRHa
- **Association of ovarian stimulation for embryo/oocyte cryopreservation at diagnosis on breast cancer free interval (BCFI)****:** Cumulative incidence (1 – Kaplan-Meier) of BCFI events estimated at **3-years**
- **Association of ovarian stimulation for IVF after enrollment on BCFI:** Cumulative incidence (1 – Kaplan-Meier) curves in a 24-month landmark analysis by ART use after enrollment

*using 1 – event-type specific survival function, **resumption of ET, pregnancy, cancer event, ***resumption of ET, cancer event, no longer trying, death, ****BCFI: Time from enrollment until the first BC event (invasive local, regional, or distant recurrence or contralateral disease)

Trial enrollment & patient characteristics

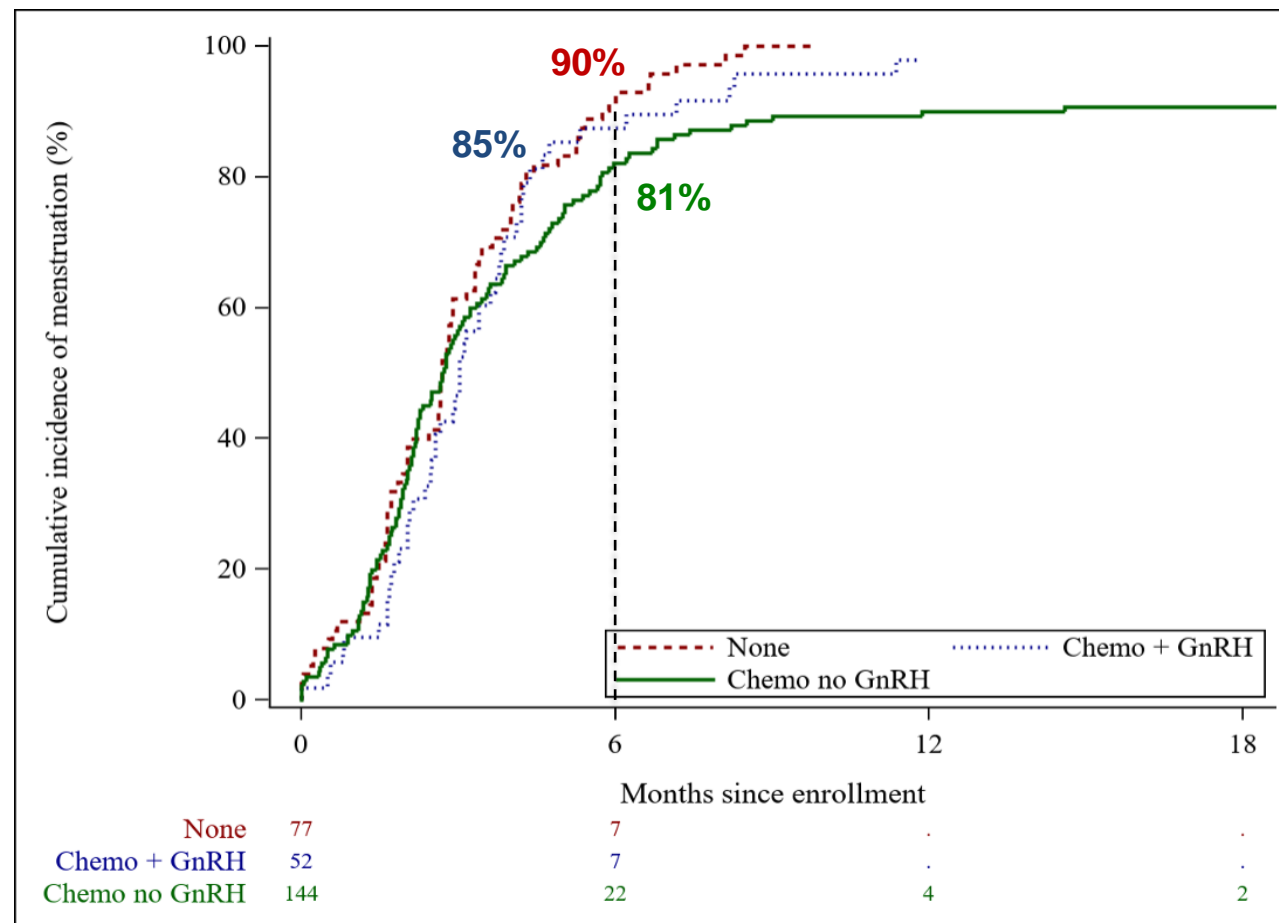


	Menstruation analysis population	FP & ART analysis population
Number	516	497
Age ≥ 35	339 (66%)	329 (66%)
Lymph node positive	174 (34%)	170 (34%)
Prior chemo	320 (62%)	308 (62%)
No prior live birth	387 (75%)	374 (75%)

FP: fertility preservation, ART: assisted reproductive technologies

Menstruation resumption

- All 516 patients included in the 1^{ry} analysis stopped ET within 1 month of study entry
- **273 patients (53%) reported amenorrhea at enrollment**
 - Of whom **255 patients (94%) recovered menses**

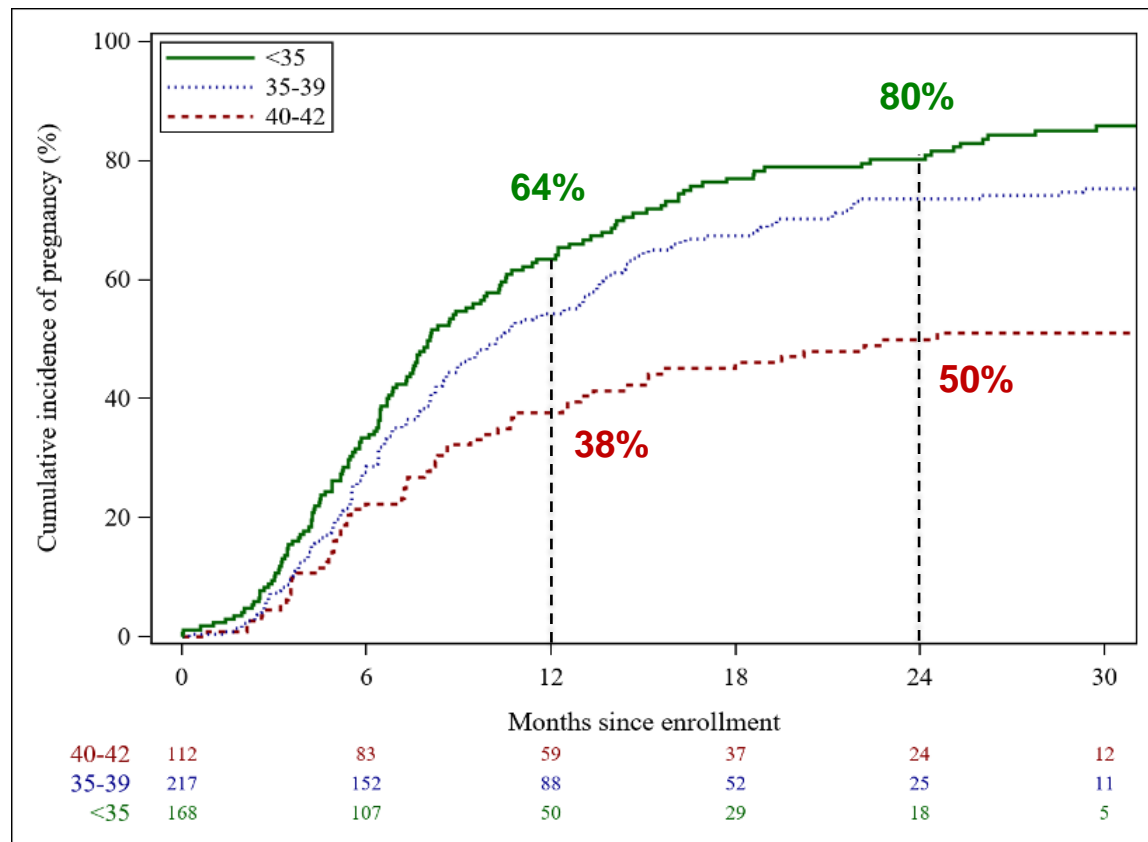






Time to pregnancy

368 patients (74%) reported at least one pregnancy



Multivariable Fine and Gray competing risk model	sHR (95% CI)
Chemo + GnRHa vs Chemo alone	1.29 (0.94 – 1.79)
None vs Chemo alone	1.05 (0.85 – 1.32)
35-39 vs <35	0.74 (0.59 – 0.93)
40-42 vs <35	0.40 (0.29 – 0.56)
SERM+OFS vs SERM only	0.94 (0.71 – 1.24)
AI+OFS vs SERM only	0.94 (0.67 – 1.33)
Prior birth: Yes vs No	0.94 (0.72 – 1.23)
Irregular vs Persistent amenorrhea	1.17 (0.85 – 1.63)
Normal vs Persistent amenorrhea	1.01 (0.78 – 1.32)

sHR: subdistribution hazard ratio, CI: confidence interval, GnRHa: gonotropin releasing hormone analogue, SERM: selective estrogen receptor modulator, OFS: ovarian function suppression, AI: aromatase inhibitor

Fertility preservation and use of ART

- **Fertility preservation at BC diagnosis**

- 252 / 497 (51%) underwent fertility preservation *

- ● **179 (36%) ovarian stimulation for embryo/oocyte cryopreservation**
 - 67 (13%) GnRHa during chemotherapy
 - 30 (6%) ovarian tissue cryopreservation

- **ART use after enrollment**

- 215 / 497 (43%) underwent ART on POSITIVE *

- ● **80 (16%) ovarian stimulation for IVF**
- ● **68 (14%) cryopreserved embryo transfer**
 - 37 (7%) intrauterine insemination
 - 19 (4%) clomiphene

* Some patients underwent more than 1 procedure

ART use and chance of pregnancy

Multivariate logistic regression model	OR (95% CI)
35-39 vs <35	0.50 (0.29 - 0.86)
40-42 vs <35	0.16 (0.08 - 0.29)
Ovarian stimulation for IVF after enrollment vs No ART	0.85 (0.48 - 1.50)
Cryopreserved embryo transfer * vs No ART	2.41 (1.17 - 4.95)
Other ART vs No ART	1.80 (0.92 - 3.57)
Chemotherapy + GnRHa vs Chemotherapy no GnRHa	1.41 (0.70 - 2.82)
None vs Chemotherapy without GnRHa	1.10 (0.70 - 1.75)

* 82% of patients reported at least 1 pregnancy

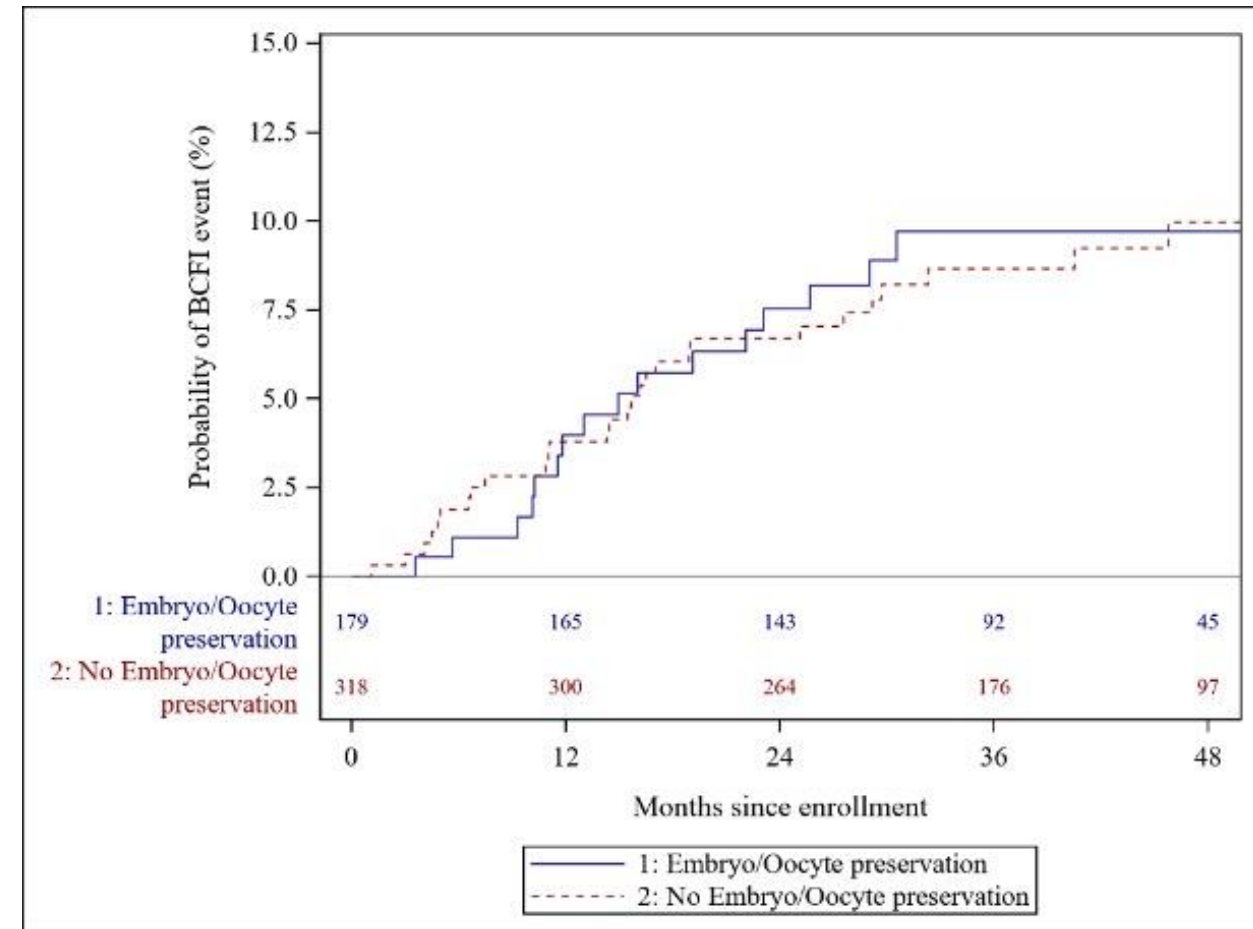
OR: Odds ratio, IVF: in-vitro fertilization, ART: assisted reproductive technology, GnRHa: gonadotropin releasing hormone analogue

Ovarian stimulation & breast cancer outcome

1) As part of embryo/oocyte cryopreservation
- at breast cancer diagnosis

At 3-years, BCFI-events cumulative incidence

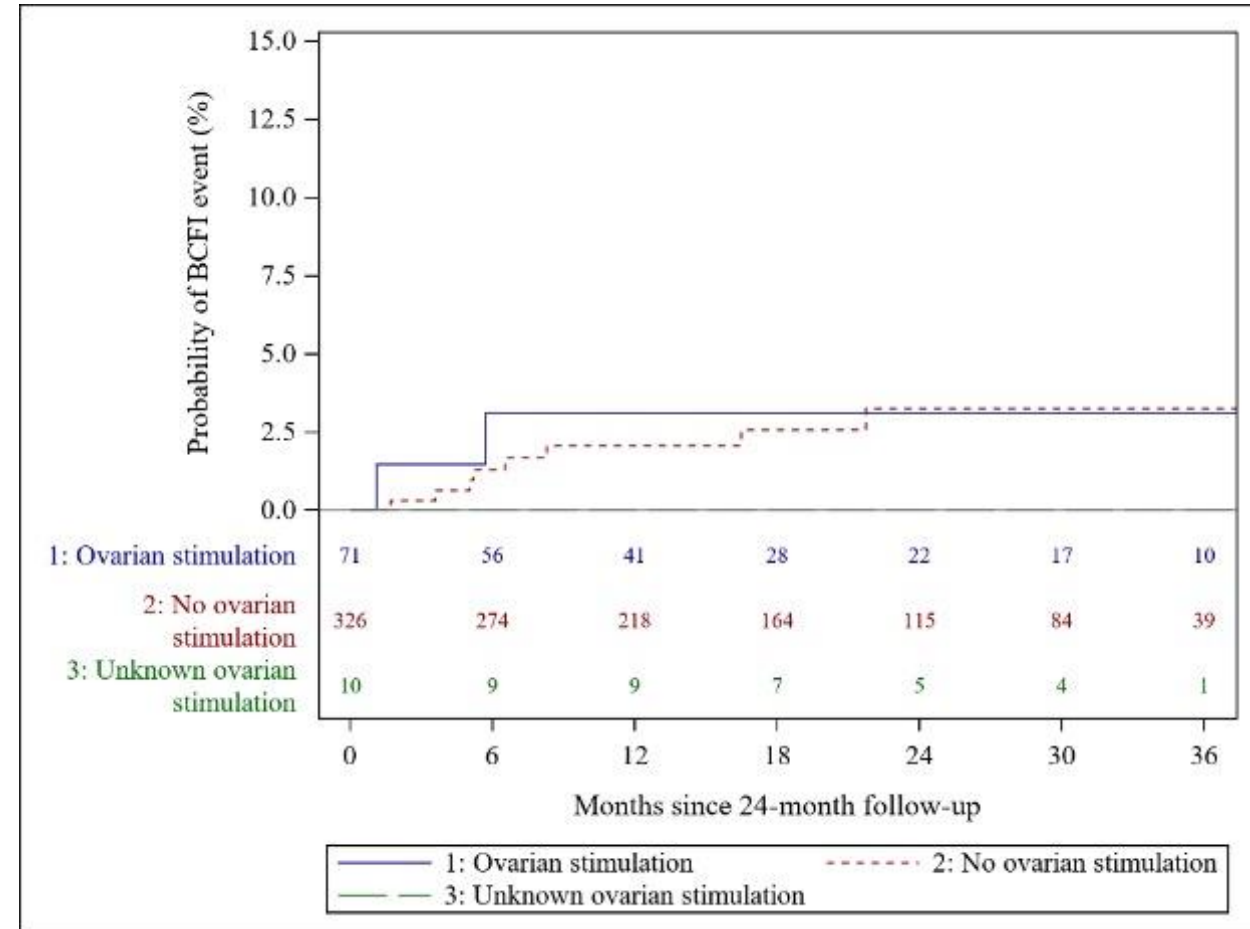
- **9.7%** (95% CI: 6.0% to 15.4%) for the 179 patients who underwent ovarian stimulation
- **8.7%** (95% CI: 6.0% to 12.5%) for the 318 patients who did not



Ovarian stimulation & breast cancer outcome

2) As part of ART - after enrollment

- **397 patients alive and BC free at 24-months (landmark analysis)**
 - 2 BC events amongst 71 patients in the ovarian stimulation group
 - 8 BC events amongst 326 patients in the non-ovarian stimulation group



Conclusions

- This is the largest prospective study to investigate fertility preservation and ART in patients with early HR+ BC who desired pregnancy
- More than 90% of women presenting with amenorrhea resumed menses, most during the first 6 months
- Young age was the main factor associated with shorter time to pregnancy
- Embryo/oocyte cryopreservation at BC diagnosis followed by embryo transfer after endocrine therapy interruption had higher pregnancy rates and was not associated with worse prognosis
- No increase in breast cancer events was observed in patients undergoing IVF on study albeit few events – longer follow-up is needed
- These data are of paramount importance for oncofertility counselling of young BC patients

Obrigado!

