Sindrome genito urinaria. Terapie ormonali locali e ospemifene. Punto di vista dell'oncologo

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Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

UNIVERSITÀ DEGLI STUDI
DI GENOVA

Disclosure

Relationship	**Company/Organization**
Honorary, consultancy or advisory role (last 2 years)	Roche – Novartis – Pfizer – Takeda – Ipsen – MSD – Agendia– Eisai – Eli Lilly – Seagen– Daiichi Sankyo – Gilead – Exact Sciences – Pierre Fabre – Astrazeneca – GSK

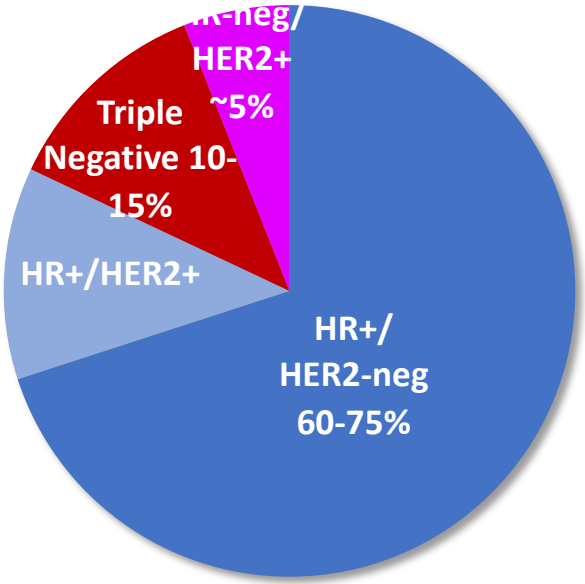
Rango	Maschi			Femmine		
	Età			Età		
	0-49	50-69	70+	0-49	50-69	70+
Totale casi incidenti	100% n=13.297	100% n=80.905	100% n=111.565	100% n=22.430	100% n=64.236	100% n=79.815
1°	Testicolo 12%	Prostata 22%	Prostata 19%	Mammella * 40%	Mammella 35%	Mammella 22%
2°	Cute (melanomi) 9%	Polmone 14%	Polmone 17%	Tiroide 16%	Colon-retto 11%	Colon-retto 16%
3°	Tiroide 8%	Colon-retto 12%	Colon-retto 14%	Cute (melanomi) 7%	Utero corpo 7%	Polmone 7%
4°	LNH 8%	Vescica* 11%	Vescica* 12%	Colon-retto 4%	Polmone 7%	Pancreas 6%
5°	Colon-retto 7%	Vie aerodigestive superiori 5%	Stomaco 5%	Utero cervice 4%	Tiroide 5%	Stomaco 5%

TABELLA 7. Primi cinque tumori in termini di frequenza e proporzione sul totale dei tumori incidenti (esclusi i carcinomi della cute) per sesso e fascia di età. Pool AIRTUM 2010-2015 (i dati presentati non sono frutto di stime ma casi reali forniti dai registri per le annate indicate)

* Comprende sia tumori infiltranti sia non infiltranti.

* Circa 9000 casi pari al 17% di tutti i casi incidenti (53.000)

Epidemiology in a glance



Gong Y et al., Scientific Reports 2017; 7:45411; https://seer.cancer.gov/statfacts/html/breast-subtypes.html; Howlader N et al., JNCI 2014; 106(5):dju055; Breast Cancer NCCN guidelines 2020 vers. 6.2020

American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline

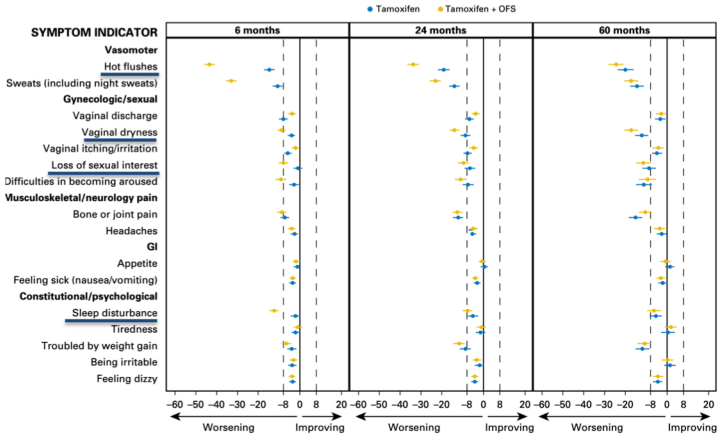
CA CANCER J CLIN 2016;66:43–73

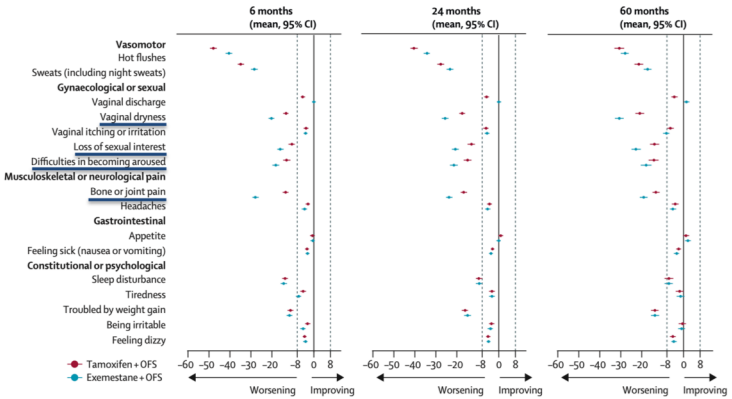
Assessment and management of physical and psychosocial long-term and late effects of breast cancer and treatment

Body image concerns
Lymphedema
Cardiotoxicity
Cognitive impairment

Distress, depression, anxiety
Fatigue
Bone health
Musculoskeletal health
Pain and neuropathy
Infertility
Sexual health
Premature menopause/hot flashes

Endocrine Therapy in Breast Cancer





Side Effect	Prevalence	Associated Risk Factors	Class of ET
Musculoskeletal symptoms	> 50%	Body mass index < 25, previous treatment with taxanes	Tamoxifen and AI (*)
Vasomotor symptoms (hot flashes)	≈ 40%	Weight gain	Tamoxifen and AI (**)
Sexual dysfunction	26%–45%	Anxiety, hot flashes, body image perception	Tamoxifen and AI (**)
Vulvovaginal symptoms (vaginal dryness, dyspareunia)	8%–26%	Age, psychological distress, prior sexual issues	Tamoxifen and AI (**)
Fatigue	30%	Inactivity, psychological distress, pain	Tamoxifen and AI
Insomnia	20%–70%	Hot flashes	Tamoxifen and AI (**)
Weight gain	20%–30%	Premenopausal women, musculoskeletal symptoms	Tamoxifen and AI
Cognitive impairment	35%	Age, chemotherapy	Tamoxifen and AI
Venous thromboembolic events	< 2%	Age > 55, current smoker, family history of coronaropathy, obesity, hypertension, hypercholesterolemia	Tamoxifen (*)
Endometrial cancer	< 1%	Age, treatment duration	Tamoxifen (*)

Ribi K et al, J Clin Oncol 2016;34:1601-10. Bernhard J et al, Lancet Oncol 2015;16:848-58. Vaz-Luis I et al, ASCO Educ Book 2021;41:1-15

Endocrine Therapy in Breast Cancer

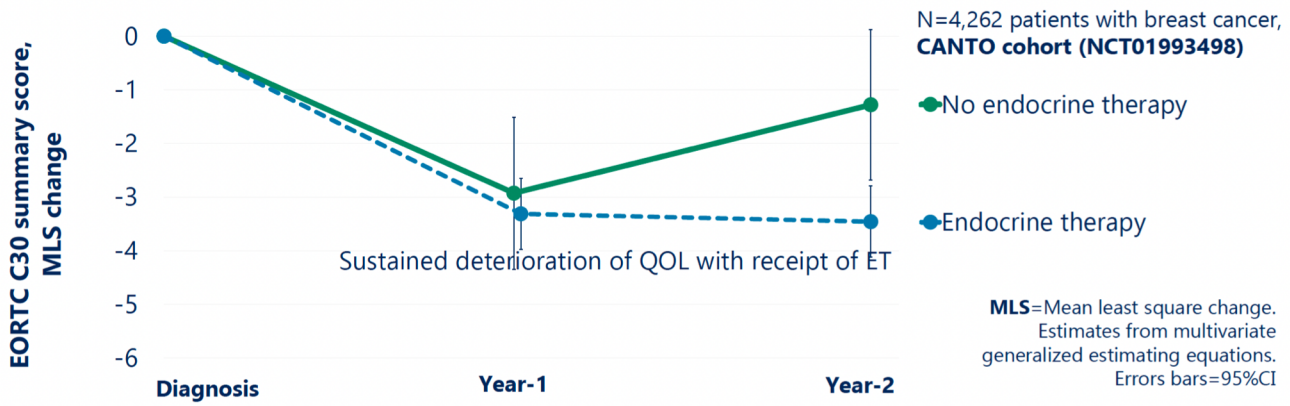
ESMO

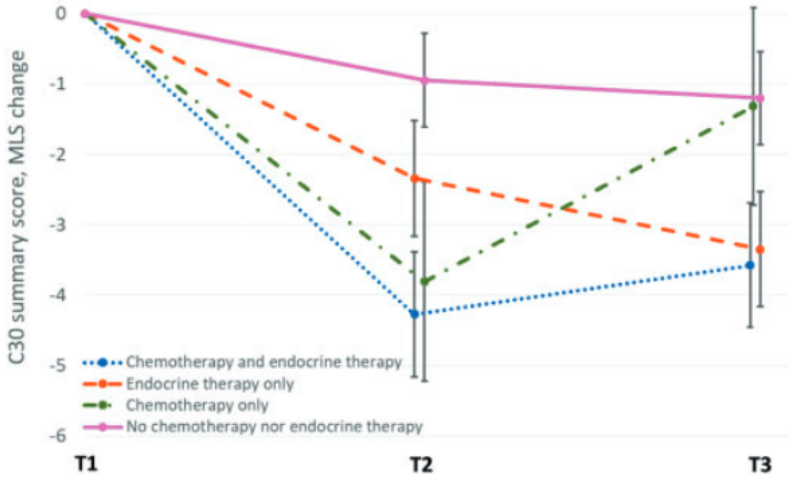
Annals of Oncology 0: 1–12, 2019
doi:10.1093/annonc/mdz298

ORIGINAL ARTICLE

Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis

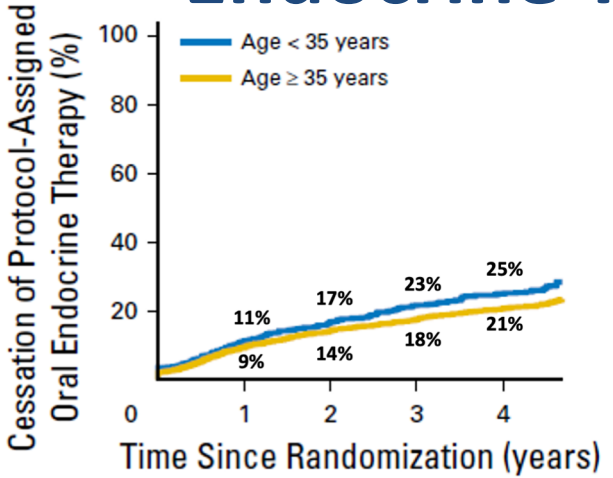
A. R. Ferreira[1,2], A. Di Meglio[1], B. Pistilli[3], A. S. Gbenou[1], M. El-Mouhebb[1], S. Dauchy[4], C. Charles[4], F. Joly[5], S. Everhard[6], M. Lambertini[7,8], C. Coutant[9], P. Cottu[10], F. Lerebours[11], T. Petit[12], F. Dalenc[13], P. Rouanet[14], A. Arnaud[15], A. Martin[6], J. Berille[16], P. A. Ganz[17], A. H. Partridge[18], S. Delaloge[3], S. Michiels[19,20], F. Andre[1,3] & I. Vaz-Luis[1,3]*





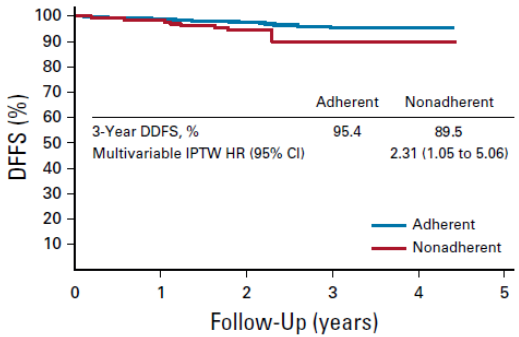
Ferreira AR et al, Ann Oncol 2019;30(11):1784-95

Endocrine Therapy in Breast Cancer



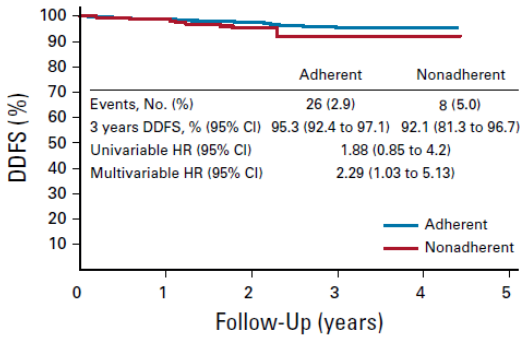
P=0.01

Self-Declaration	Serum Assessment, No. (%) Adherent	Nonadherent	Total
Adherent	928 (93.8)	104 (55.3)	1,032 (87.7)
Nonadherent[a]	61 (6.2)[b]	84 (44.6)	145[c] (12.3)
Total	989 (84.0)	188 (16.0)	1,177



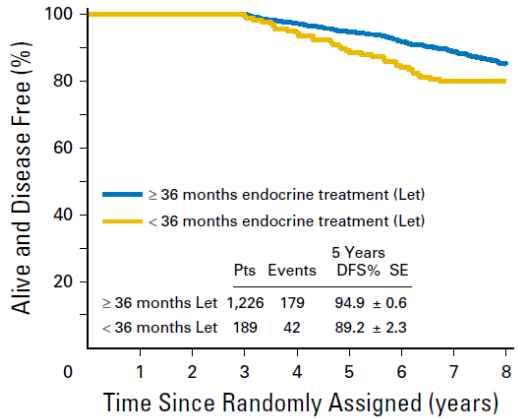
No. at risk:

Adherent	895	873	502	167	36	0
Nonadherent	161	150	84	16	4	0



No. at risk:

Adherent	896	874	502	166	35	0
Nonadherent	161	151	86	17	5	0



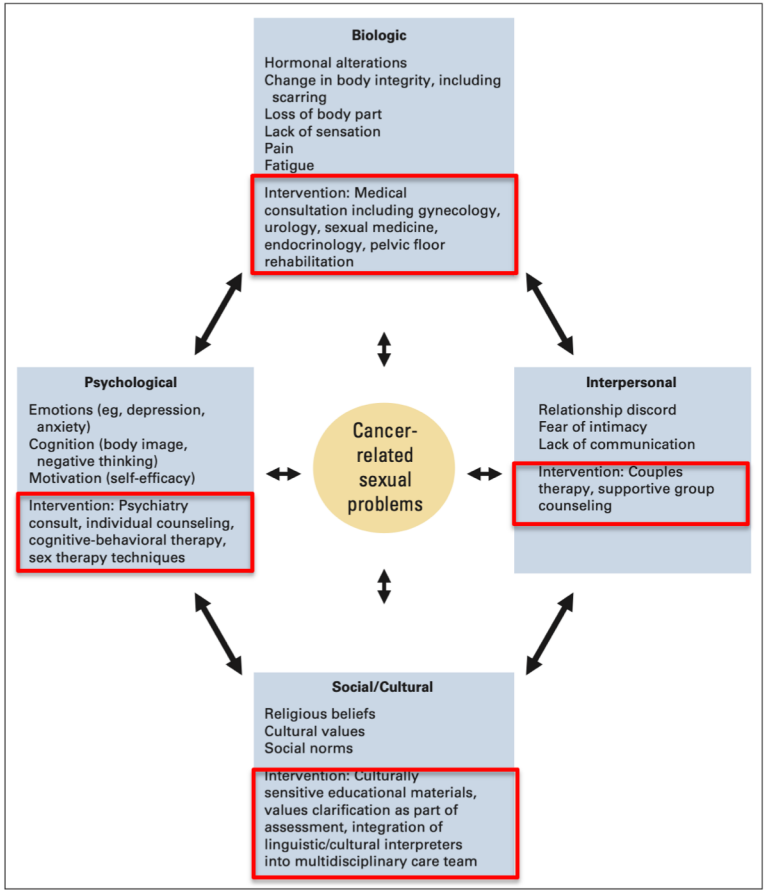
No. at risk

≥ 36 months Let	1,226	1,226	1,226	1,193	1,155	1,097	921	522
< 36 months Let	189	189	189	175	161	150	125	71

Saha P et al, J Clin Oncol 2017;35:3113-22. Pistilli B et al, J Clin Oncol 2020;38(24):2762-72. Chirgwin JH et al, J Clin Oncol 2016;34(21):2452-9

Sexual Dysfunction

- Unlike other side effects, sexual symptoms do not self-resolve
- Untreated sexual dysfunction tends to worsen over time
- Sexual Dysfunction is associated with anxiety, depression and loss of perceived self-efficacy
- **Risk factors for sexual dysfunction:**
  - History of sexual problems
  - Absence of sexual activity
  - Depression/Anxiety
  - Younger age



Brotto LA et al, J Cancer Surviv 2010;4:346-60. Bober S et al, J Clin Oncol 2012;30:3712-9. Leung MW et al, Curr Oncol Rep 2016;18:11

Interventions to Address Sexual Problems in People With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Adaptation of Cancer Care Ontario Guideline

CONDITION: GENITAL SYMPTOMS

Recommendation 6. The Expert Panel believes that for women with symptoms of vaginal and/or vulvar atrophy, such as dryness, *the following stepwise approach should be followed:*

Lubricants for all sexual activity or touch, in addition to vaginal moisturizers to improve vulvovaginal tissue quality, may be tried first. It should be noted that moisturizers may need to be applied at a higher frequency (three to five times per week) in the vagina, at the vaginal opening, and on the external folds of the vulva for symptom relief in female patients with cancer and survivors.[151]

TABLE 1. Sexual Concerns and Interventions Among Women With Cancer

Symptom	Intervention
Vaginal dryness	Vaginal moisturizers Hyaluronic acid–containing moisturizers Vaginal lubricants Local hormone therapy
Pelvic floor dysfunction	Referral to pelvic floor physical therapist Vaginal dilators
Insertional dyspareunia	Topical lidocaine
Sexual response	Assessment of medication lists Psychosocial/psychosexual counseling Sensate focus Mindfulness Exercise Flibanserin* Bremelanotide*
Body image concerns	Psychosocial counseling

*Not evaluated among women with cancer or receiving endocrine therapy.

Interventions to Address Sexual Problems in People With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Adaptation of Cancer Care Ontario Guideline

CONDITION: GENITAL SYMPTOMS

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For those who do not respond or whose symptoms are more severe at presentation, ***low-dose*** vaginal estrogen can be used. For women with hormone-positive breast cancer who are symptomatic and not responding to conservative measures, ***low-dose*** vaginal estrogen can be considered after a ***thorough*** discussion ***of risks and benefits.***

J Clin Oncol 36:492-511. © 2017

Breast Cancer Res Treat (2012) 135:603–609
DOI 10.1007/s10549-012-2198-y

EPIDEMIOLOGY

Local estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case–control study

Isabelle Le Ray · Sophie Dell'Aniello · Franck Bonnetain · Laurent Azoulay · Samy Suissa

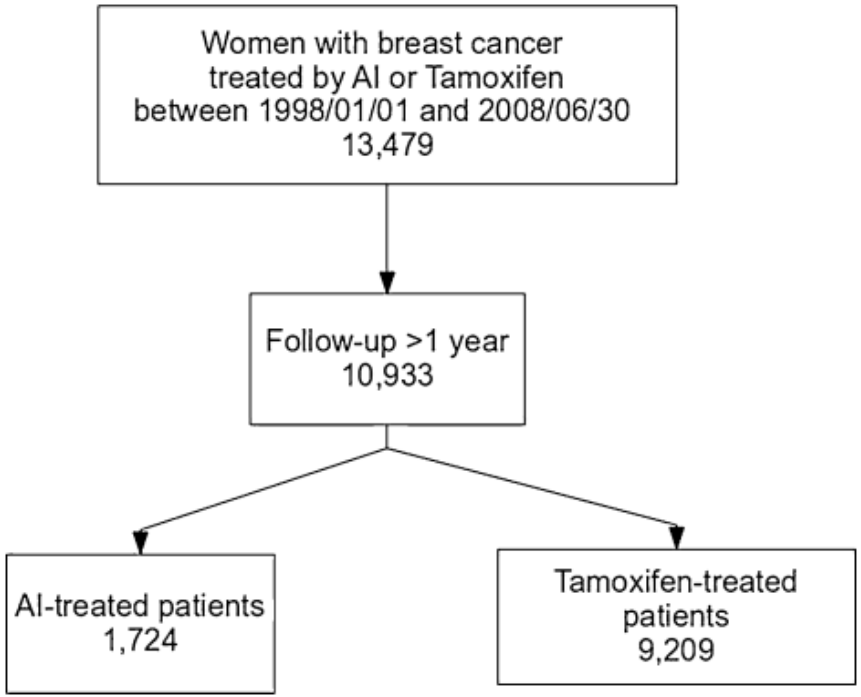


Table 4 Breast cancer recurrence with concurrent use of tamoxifen with local hormonal treatments

	Cases ($n = 811$)	Controls ($n = 7950$)	Crude RR (95 % CI)	Adjusted RR (95 % CI)[a]
Tamoxifen only, *n* (%)	790 (97.4)	7,688 (96.7)	1.00	1.00 (Reference)
Concurrent use of tamoxifen with LHT, *n* (%)	19 (2.3)	240 (3.0)	0.78	0.83 (0.51–1.34)
Use of hormonal treatment after end of tamoxifen use	2 (0.2)	22 (0.3)	0.90	0.95 (0.22–4.14)

LHT local hormonal treatment, *RR* risk ratio

[a] Adjusted for obesity (BMI $\geq$30), smoking, excessive alcohol use, history of oophorectomy, previous use of hormone replacement therapy, anti-depressants (other than CYP2D6 substrates), anti-diabetic agents, NSAIDS (other than CYP2D6 substrates), benzodiazepines, antipsychotic drugs (other than CYP2D6 substrates), CYP2D6 inhibitors and statins

CONDITION: GENITAL SYMPTOMS

Recommendation 6. The Expert Panel believes that for women with symptoms of vaginal and/or vulvar atrophy, such as dryness, *the following stepwise approach should be followed:*

Lubricants for all sexual activity or touch, in addition to vaginal moisturizers to improve vulvovaginal tissue quality, may be tried first. It should be noted that moisturizers may need to be applied at a higher frequency (three to five times per week) in the vagina, at the vaginal opening, and on the external folds of the vulva for symptom relief in female patients with cancer and survivors.[151]

For those who do not respond or whose symptoms are more severe at presentation, ***low-dose*** vaginal estrogen can be used. For women with hormone-positive breast cancer who are symptomatic and not responding to conservative measures, ***low-dose*** vaginal estrogen can be considered after a ***thorough*** discussion ***of risks and benefits.***

Lidocaine can also be offered for persistent introital pain and dyspareunia.[152]

For women with current or a history of breast cancer who are on aromatase inhibitors and have not responded to previous treatment, clinicians may offer vaginal dehydroepiandosterone.[20-23]

JAMA Oncology | Original Investigation

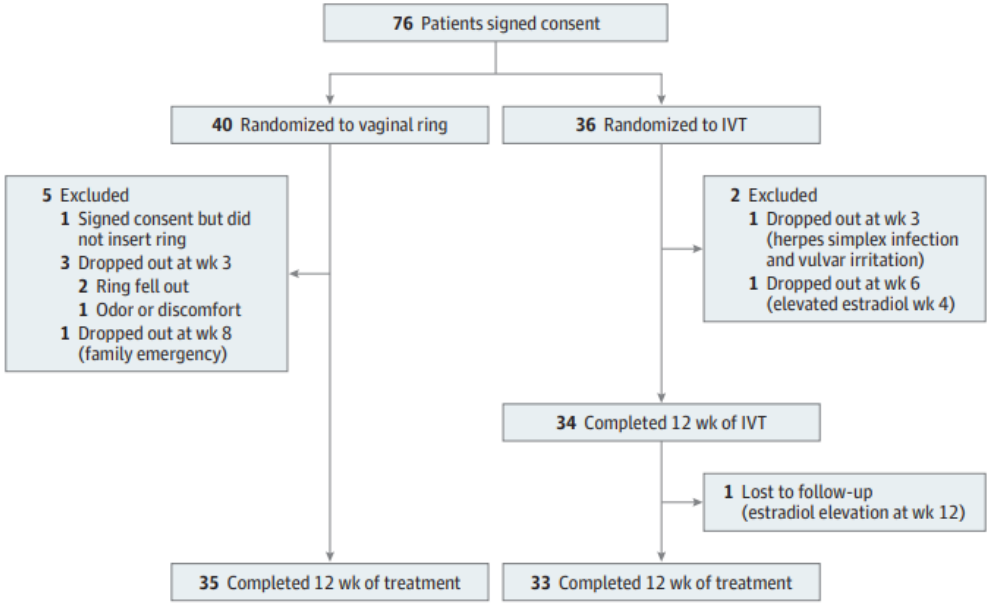
Vaginal Testosterone Cream vs Estradiol Vaginal Ring for Vaginal Dryness or Decreased Libido in Women Receiving Aromatase Inhibitors for Early-Stage Breast Cancer

A Randomized Clinical Trial

Michelle E. Melisko, MD; Mindy E. Goldman, MD; Jimmy Hwang, PhD; Amy De Luca, BA; Sally Fang, BA;

OBJECTIVE To evaluate safety of intravaginal testosterone cream (IVT) or an estradiol-releasing vaginal ring (7.5 µg/d) in patients with early-stage breast cancer (BC) receiving an AI. Intervention was considered unsafe if more than 25% of patients had persistent elevation in estradiol (E_2), defined as E_2 greater than 10 pg/mL (to convert to pmol/L, multiply by 3.671) and at least 10 pg/mL above baseline after treatment initiation on 2 consecutive tests at least 2 weeks apart.

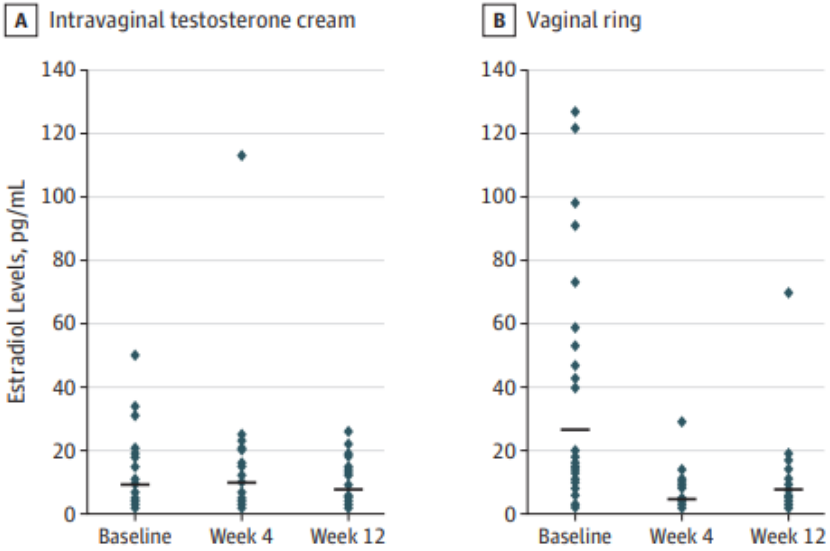
Figure 1. CONSORT Flow Diagram for Patients Treated With an Estradiol-Releasing Vaginal Ring[a] and IVT



IVT indicates intravaginal testosterone cream.

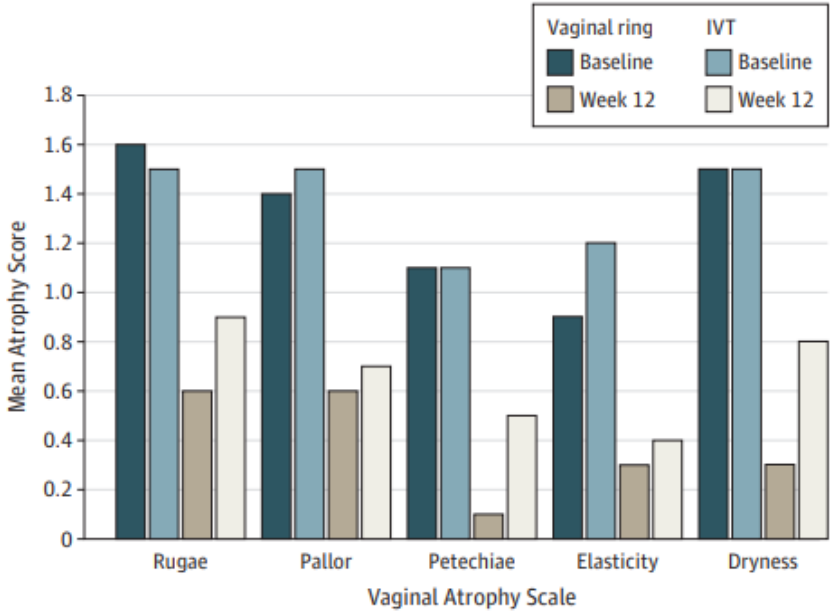
[a] 7.5 µg/d (Estring 2 mg; Pfizer).

Figure 2. Estradiol Levels for Patients Who Completed 12 Weeks of Treatment



Overall, 34 patients completed treatment with intravaginal testosterone cream; 35 patients completed treatment with an estradiol-releasing vaginal ring (7.5 µg/d [Estring 2 mg; Pfizer]).

Figure 3. Vaginal Atrophy Score Changes From Baseline to Week 12



Overall, 34 patients completed treatment with intravaginal testosterone cream; 35 patients completed treatment with an estradiol-releasing vaginal ring (7.5 µg/d [Estring 2 mg; Pfizer]). IVT indicates intravaginal testosterone cream.

CONCLUSIONS AND RELEVANCE In PM women with early-stage BC receiving AIs, treatment with a vaginal ring or IVT over 12 weeks met the primary safety end point. Baseline elevation in E_2 was common and complicates this assessment. Vaginal atrophy, sexual interest, and sexual dysfunction were improved. Further study is required to understand E_2 variability in this setting.

Sexual Dysfunction

- ***Pharmacological strategies:***

Treatment for VVA	Specific Therapy/Use
Vaginal Estrogen	Local (not systemic) therapy Tablet/ring/cream
Vaginal DHEA	Intravaginal ovules (prasterone)
Lidocaine	For insertional pain. Topical application to vestiblule (4% aqueous lidocaine) before sexual activity
Off-label vaginal testosterone	Controversial
Off-label fractional CO_2 laser	No evidence-base for use

Treatment for Low Desire	Mechanism of Action
Flibanserin (daily use at bedtime)	5-HT1A serotonin receptor agonist and 5-HT2A receptor antagonist
Bremalanotide (on-demand use)	Melanocortin 1 & 4 receptor agonist

Franzoi MA et al, Lancet Oncol 2021;22(7):e303-13

Interventions to Address Sexual Problems in People With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Adaptation of Cancer Care Ontario Guideline

Clinicians may offer flibanserin to premenopausal women who are experiencing hypoactive sexual desire disorder. [14,15]
CCO Qualifying Statement. It is the opinion of the Expert Panel that any kind of regular stimulation (including masturbation) would likely be of benefit for improving sexual response, regardless of the stimulation used.

ASCO Qualifying Statement. It should be noted that flibanserin has not been evaluated in women with a history of cancer or those on endocrine therapy. In addition, the risk/benefit ratio for this medication is uncertain.

CONDITION: GENITAL SYMPTOMS

Recommendation 6. The Expert Panel believes that for women with symptoms of vaginal and/or vulvar atrophy, such as dryness, *the following stepwise approach should be followed:*

Lubricants for all sexual activity or touch, in addition to vaginal moisturizers to improve vulvovaginal tissue quality, may be tried first. It should be noted that moisturizers may need to be applied at a higher frequency (three to five times per week) in the vagina, at the vaginal opening, and on the external folds of the vulva for symptom relief in female patients with cancer and survivors.[151]

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Lidocaine can also be offered for persistent introital pain and dyspareunia.[152]

For women with current or a history of breast cancer who are on aromatase inhibitors and have not responded to previous treatment, clinicians may offer vaginal dehydroepiandosterone.[20-23]

Finally, clinicians may offer the selective estrogen receptor modulator ospemifene to postmenopausal women without current or a history of breast cancer who are experiencing dyspareunia, vaginal atrophy, or other vaginal pain.[24-26]

Clinicians should offer pain relievers to women on aromatase inhibitors who are experiencing arthralgia that interferes with intimacy.

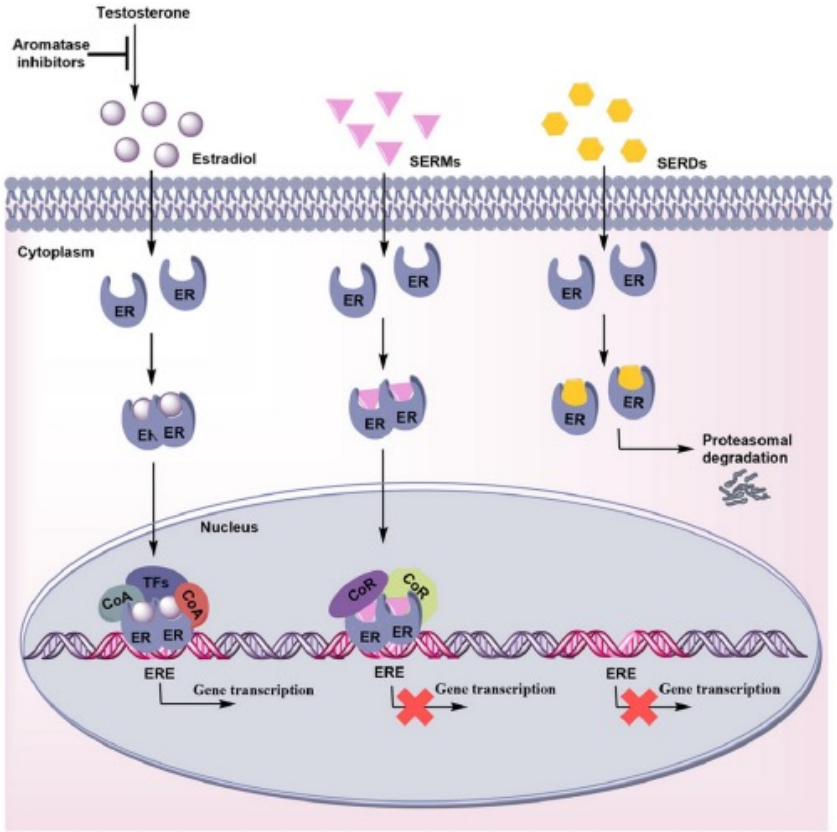


Fig. 1. A) The A–F domains that constitute the estrogen receptor, which include the activation function 1 (AF-1) domain, the DNA binding domain (DBD), the hinge region, and the ligand binding domain (LBD)/activation function 2 (AF-2 domain). B) The effects of endocrine therapies (aromatase inhibitors, SERMs, and SERDs) on the estrogen receptor pathway. Aromatase inhibitors prevent ER signaling by inhibiting synthesis of estradiol, SERMs prevent ER signaling by binding to ER and causing an inactive complex, and SERDs prevent ER signaling by causing degradation of ER.

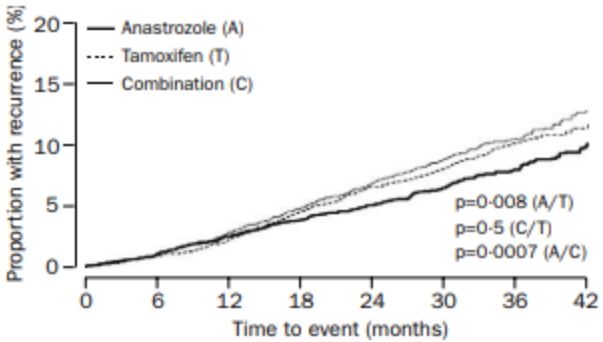


Figure 3: **Probability of recurrence in the intention-to-treat population**

Studio ATAC - Lancet 2002.

Maturitas 142 (2020) 38–44

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

No increase in incidence or risk of recurrence of breast cancer in ospemifene-treated patients with vulvovaginal atrophy (VVA)

Bin Cai[a,*], James Simon[b], Paola Villa[c], Nicoletta Biglia[d], Nicholas Panay[e], Stora Djumaeva[f],

Table 1
Incidence rate of breast cancer per 1000 patients per follow-up year and treatment year.

Crude Analysis	Treated group (N = 1728)	Untreated Group (N = 3456)	Rate Ratio
Assessment per follow-up year			
Total number of patients with breast cancer diagnosis any time on or after treatment index date (%)	9 (0.52)	32 (0.93)	
Total number of treatment years between index date and follow-up end date	4428	9074	
Incidence rate of breast cancer per 1000 patients per follow-up year (95 % CI)	2.03 (1.06 – 3.91)	3.53 (2.49 – 4.99)	0.58 (0.28 – 1.21)
Assessment per treatment year			
Total number of patients with breast cancer diagnosis any time while on treatment (only use first continuous treatment + 90-day gap)	3	–	
Total number of treatment years between treatment start and treatment end	1420	–	
Incidence rate of breast cancer per 1000 patients per treatment year (95 % CI)	2.11 (0.44 – 6.18)		

Table 3
: Recurrence of breast cancer in patients with VVA treated with ospemifene compared to untreated patients.

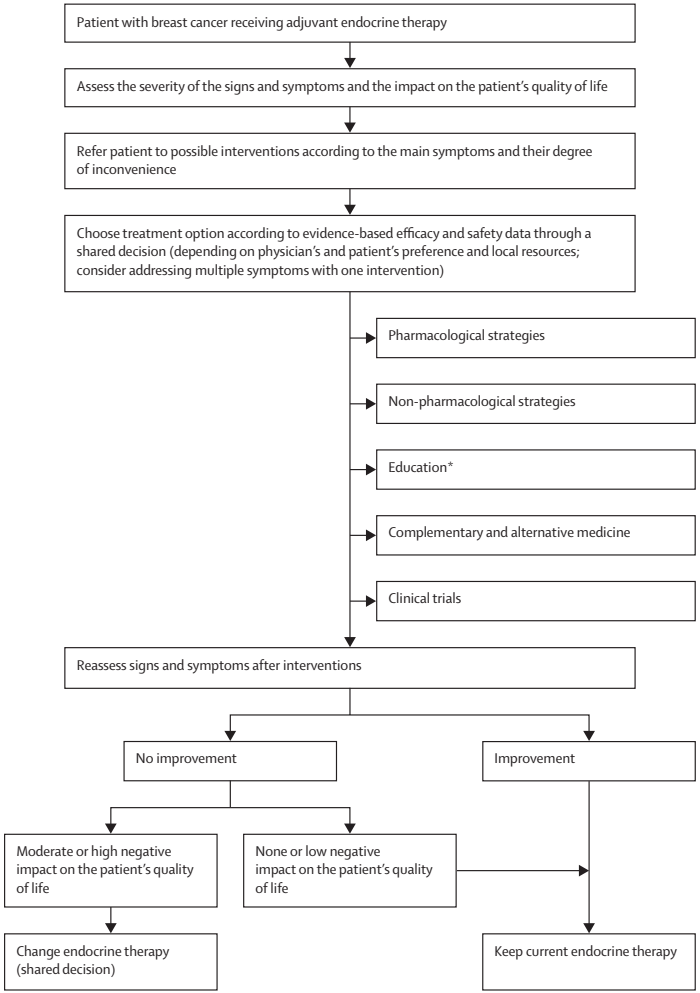
Matching (N cases, N controls)	Patients with Breast Cancer Diagnosis After Treatment Index Date		*p*-value[1]
	Ospemifene-Treated Group (N, %)	Untreated Group (N, %)	
1:1 (46, 46)	14 (30.43 %)	21 (45.65 %)	0.1328
1:2 (31, 62)	10 (32.26 %)	25 (40.32 %)	0.4492
1:3 (20, 60)	7 (35.00 %)	24 (40.00 %)	0.6910

[1] Chi-squared test was used to test for the association between breast cancer occurrence and treatment.

Conclusions

√√√ Probably efficacious (data from RCTs)
√√ Might be efficacious (data from RCTs with smaller samples)
√ Could be effective (single–arm studies)
·· No sufficient data for breast cancer survivors

	Hot flashes	Sexual dysfunction	Weight gain	Musculo-skeletal symptoms	Fatigue
SSRIs and SNRIs	√√√	··	··	√√√	··
Anticonvulsants	√√√	··	··	··	··
Oxybutynin	√√√	··	··	··	··
Aromatase inhibitor switch	··	··	··	√√	··
Vaginal lubricants or moisturisers	··	√√√	··	··	··
Vaginal CO_2 laser	··	√	··	··	··
Stellate ganglion block	√√	··	··	··	··
Cognitive behavioural therapy	√√√	√√√	√√√	√√√	√√√
Physical exercise	··	··	√√√	√√√	√√√
Acupuncture	√√	··	··	√√√	√√
Hypnosis	√√	··	··	··	··
Yoga and mindfulness	√√	··	√	√√	√√



Franzoi MA et al, Lancet Oncol 2021;22(7):e303-13

San Martino Hospital – University of Genoa, Italy
Breast Unit