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Treating VVA improves symptom severity and patient-reported outcomes: 6-month PEONY results

Rossella E. Nappi^{a,b} , Maria Cristina Meriggiola^c , Francesca Albani^d, Gloria Bonaccorsi^e , Giovanni Delli Carpini^f , Alessandro Gambera^g , Silvia Marsini^h, Antonio Nicolucciⁱ , Maria Chiara Rossi^j , Valentina Trionfera^h and Paola Villa^j 

^aDepartment of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy; ^bResearch Center for Reproductive Medicine and Gynecological Endocrinology – Menopause Unit, IRCCS S. Matteo Foundation, Pavia, Italy; ^cDivision of Gynecology and Human Reproduction Physiopatology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; ^dGynecological Endocrinology Clinic, Unit of Endocrinology and Metabolic Diseases, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy; ^eMenopause and Osteoporosis Center, University of Ferrara, Ferrara, Italy; ^fGynecologic Section, Department of Odontostomatologic and Specialized Clinical Sciences, Università Politecnica delle Marche, Ancona, Italy; ^gUnit of Gynecological Endocrinology, ASST Spedali Civili/University of Brescia, Brescia, Italy; ^hShionogi S.r.l, Rome, Italy; ⁱCORESEARCH – Center for Outcomes Research and Clinical Epidemiology, Pescara, Italy; ^jUOC Ginecologia Oncologica, Dipartimento di Scienze per la Salute della Donna e del Bambino e di Sanità Pubblica, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

ABSTRACT

Objective: The real-world PatiEnt satisfactiON studY (PEONY) involves postmenopausal women already treated or starting local estrogen therapy (LET) or ospemifene. The aim of the present analysis was to assess treatment satisfaction and persistence, effectiveness and patient-reported outcomes (PROs) in sexual function and quality of life after 6 months of therapy with LET or ospemifene to treat vulvovaginal atrophy (VVA).

Methods: PEONY is an ongoing prospective, observational study conducted in 17 gynecology centers. Participants complete questionnaires at baseline (T0) and after 3 months (T3) and 6 months (T6). The main outcome measures were treatment satisfaction, severity of symptoms, Day-to-Day Impact of Vaginal Aging (DIVA), Female Sexual Function Index (FSFI), Female Sexual Distress Scale – Revised (FSDS-R) and SF-12 Health Survey.

Results: Overall, 385 women were included, of whom 145 started (87.6%) or continued (12.4%) ospemifene and 240 started (66.7%) or continued (33.3%) LET at T0. The likelihood of moderate/severe VVA symptoms decreased by 70–90% and the mean treatment satisfaction score increased overall from 7.3 (95% confidence interval [CI]: 7.0; 7.5) at T3 to 7.7 (95% CI: 7.4; 7.9) at T6 ($p=0.003$). DIVA and FSDS-R scores significantly improved in both groups.

Conclusions: PEONY underlines the importance of proactively treating VVA with LET or ospemifene to alleviate the burden associated with the disease.

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Introduction

Vulvovaginal atrophy (VVA) is a chronic disorder that commonly occurs in postmenopausal women as a consequence of estrogen deficiency and aging [1]. In several surveys and epidemiological studies, the prevalence of VVA generally exceeds 50% and is even higher among patients with a history of breast cancer (BC) [2–6].


VVA starts at menopause (or even before) and unlike other menopausal symptoms is progressive, thus requiring early appropriate interventions to avoid worsening over time [7–9]. Due to the multitude of genital, sexual and urinary symptoms associated with VVA as a result of the anatomical and functional changes of urogenital tissues, in recent years VVA

has been comprised within the umbrella term ‘genitourinary syndrome of menopause (GSM)’ [10,11].

Vaginal dryness along with dyspareunia, burning, itching and dysuria represent the most frequent VVA symptoms; they are recognized to have a relevant impact on the ability to be intimate, to enjoy sexual intercourse and to feel sexual spontaneity [1]. Moreover, VVA symptoms are associated with clinically meaningful decrements in quality of life (QoL) dimensions, comparable to serious conditions such as arthritis, chronic obstructive pulmonary disease, asthma and irritable bowel syndrome [12,13].

Despite its high prevalence and clinical and emotional burden, VVA counseling may be difficult, and therefore the condition may remain undertreated [14]. On one hand,

CONTACT Rossella E. Nappi  r.nappi@smatteo.pv.it  Research Center for Reproductive Medicine and Gynecological Endocrinology – Menopause Unit, IRCCS S. Matteo Foundation, Piazzale Golgi 2, Pavia 27100, Italy

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women feel embarrassed to discuss sexual issues, and on the other healthcare professionals have limited time to face the discussion [1]. Adequate care requires a proactive approach to make a diagnosis based on symptoms and clinical signs, including objective measures obtained through validated tools (e.g. the Vaginal Health Index [VHI]) and questionnaires evaluating general and disease-specific QoL dimensions [15]. When distressing, VVA should be treated also taking into account women's preferences [7–10].

Vaginal moisturizers and lubricants have been indicated by guidelines as the first-line approach to VVA [16]. They may be helpful in improving vaginal dryness-related symptoms but their effects are time limited and do not treat the underlying condition [17]. Vaginal estrogens have been proven to be an effective treatment, but poor compliance (inconvenience, vaginal discharge, difficult application, odor and loss of spontaneity during intercourse) has been shown [1]. Moreover, in patients with BC who significantly report VVA, there are not enough data on the safety of topical estrogens and these treatments should be avoided or prescribed only following a deep discussion on benefits and risks with patients and their oncologists [18]. Other local hormonal therapies with testosterone and dehydroepiandrosterone (DHEA) are available in some countries, but information on long-term safety is lacking [8,9].

Ospemifene currently represents the first non-hormonal and oral option for symptomatic VVA in postmenopausal women and is also indicated in Europe for the increasing number of patients surviving BC, following completion of the oncological treatment, including adjuvant therapy [19]. Unfortunately, few clinical trials have been performed to compare efficacy of different treatments and data are based on indirect comparisons [20]. Finally, vaginal laser and other thermal energies need more evidence regarding their efficacy and (long-term) safety in healthy menopausal women and in BC survivors [21–23].

Given these premises, the PatiEnt satisfactiON study (PEONY) is an ongoing multicenter, longitudinal, real-world study involving women already treated with or initiating local estrogen therapy (LET) or ospemifene, which was designed to provide a comprehensive picture of postmenopausal women with moderate to severe VVA in Italy. These two treatments were selected because they were the most common hormonal choices with Level A evidence [16] available in Italy at the time the study was designed. Moreover, we took into account an expert Italian opinion [1] indicating the importance of individualizing treatment according to preference and level of satisfaction reported by postmenopausal women. Baseline data [24], collected during a routine visit, confirmed that VVA was associated with severe symptoms and negative impact on well-being, especially in women with BC. Almost half (44%) of the PEONY study sample had never been treated for VVA, while lubricants had been prescribed to 12.6% of women, moisturizers to 14.1%, vaginal laser to 7.2% and radiofrequency to 1.8%. At study entry, VVA therapies were proactively prescribed or reviewed taking into consideration patients' characteristics and preferences. Our analysis showed that the use of LET increased from 25.0% to 61.1%, while the use of ospemifene increased from 7.6% to

38.9%. Patients treated with the two options systematically differed, in terms of symptom severity, prevalence of BC and QoL [24].

The primary aim of the present analysis of the PEONY data was to assess treatment satisfaction after 6 months of therapy with LET or ospemifene. Secondary aims were impact on symptom severity, treatment persistence and patient-reported outcomes (PROs) in sexuality and QoL.

Methods

The PEONY is a longitudinal, prospective, observational study conducted in 17 gynecology centers throughout Italy.

Data were collected at baseline (T0), after 3 months (T3) and after 6 months (T6). An additional follow-up visit at 12 months (T12) was planned.

The inclusion criteria were: age ≥ 18 years; postmenopausal state; moderate to severe VVA based on clinical judgment; and already treated or initiating LET or ospemifene at study entry, irrespective of other concomitant treatments for VVA (moisturizers, lubricants, laser and radiofrequency).

The exclusion criteria were: ongoing hormone replacement therapy, administered orally or transdermally.

The primary endpoint was a treatment satisfaction score after 6 months from study entry overall and by treatment class (ospemifene or LET). Secondary endpoints were: treatment satisfaction score after 3 months; treatment discontinuation rate of oral and local therapy and reasons for discontinuation after 3 and 6 months; and effectiveness and impact on QoL scores after 3 and 6 months.

Baseline characteristics included: age; type of menopause; history of BC; symptoms, severity and duration of VVA; body mass index (BMI); and history of abortion/childbirths, hysterectomy, prolapse/urinary incontinence, relevant comorbidities, current chronic therapies and prescribed treatment for VVA.

The VHI was used to evaluate vaginal elasticity, secretions, pH, the presence of petechiae on the epithelial mucosa and hydration [25–27]. The VHI score can vary between 5 and 25, with a cut-off < 15 representing an index of atrophic vagina. The Vulvar Health Index (VuHI) was used to evaluate the vulva status, including vulvar inflammation, musculature contraction, pain at speculum insertion and epithelial integrity [25–27]. The score can vary from 0 to 24, with a cut-off > 8 representing an index of atrophic vulva.

Participating women were administered self-reported questionnaires at T0, T3 and T6. The patient questionnaire contained information about socio-demographic characteristics, lifestyle, satisfaction with VVA treatment and persistence with therapy or reasons for discontinuation.

Satisfaction with current VVA treatment was assessed through a numeric rating scale ranging from 0 (very low) to 10 (very high).

The physical and psychological impact of VVA was assessed using the following questionnaires:

- Symptoms of VVA were assessed using the specific section of the European Vulvovaginal Epidemiological

Survey (EVES) [27]. Women were asked to score their symptoms of VVA, based on a list of 19 potentially VVA-related complaints on a 4-point severity scale (absent, mild, moderate or severe). Vaginal symptoms included vaginal dryness (internal), pain during intercourse (internal), pain during intercourse at penetration, bleeding during intercourse, bleeding during sexual contact, burning or irritation (internal), itching (internal) and vaginal discharge. Vulvar symptoms include vaginal dryness (external), burning or irritation (external), itching (external) and pain during exercise. Urinary symptoms include urinary incontinence, urinary urgency, urinary frequency, urinary difficulties, recurrent urinary tract infections (RUIs) and post-coital cystitis. In addition, a single question investigated the presence and severity of abdominal pain.

- The Day-to-Day Impact of Vaginal Aging (DIVA) questionnaire is a structured, validated, self-administered instrument assessing the multidimensional impact of vaginal symptoms on functioning and well-being [28]. The DIVA instrument consists of four multi-item domain scales addressing major dimensions of functioning and well-being affected by postmenopausal vaginal symptoms: activities of daily living (five items); emotional well-being (four items); self-concept and body image (five items); and sexual functioning (nine items for a long version appropriate for sexually active women, and five items for a shorter version appropriate for women without a recent history of sexual activity). The questionnaire addresses symptom impact in the 4 weeks prior to survey self-administration. Each scale is designed to be scored from 0 to 4, with higher scores indicating greater impact of symptoms on the relevant domain.
- The Female Sexual Distress Scale – Revised (FSDS-R) is a self-administered questionnaire consisting of 13 items that relate to different aspects of sexual distress. Every item requires an answer that is rated as 0–4 (never = 0, rarely = 1, occasionally = 2, frequently = 3, always = 4). The total score, ranging from 0 to 52, provides a measure of sexual distress, in which the higher the score, the higher the level of sexual distress. The FSDS-R is identical to the FSDS except for the addition of one question that asks women to rate their level of distress related to low sexual desire [29].
- The Female Sexual Function Index (FSFI) is a 19-item self-reported measure of female sexual function over the past 4 weeks [30]. The instrument provides scores on six domains of sexual function as well as a total score. The domains include: desire (two items), arousal (four items), lubrication (four items), orgasm (three items), satisfaction (three items) and pain (three items). The full-scale score ranges from 2.0 to 36.0, where a higher score is associated with lower severity of sexual dysfunction.
- The SF-12 Health Survey is a 12-item questionnaire used to assess generic health outcomes from the patient's perspective [31]. The SF-12 consists of a

subset of 12 items from the SF-36 Health Survey. A Physical Component Summary Score (PCS) and a Mental Component Summary Score (MCS) can be calculated. The PCS and MCS are standardized so that in the normal population a value of 50 with a standard deviation of 10 is expected. SF-12 summary measures are scored so that a higher score indicates a better health state.

All information was collected on electronic case report forms and data were anonymous.

The study protocol was approved by local ethics committees and all patients signed the informed consent. All procedures were conducted in compliance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

Statistical analysis

The study has purely descriptive purposes. As such, no formal sample size estimation was performed, and all consecutive eligible women seen in participating centers during 12 months were enrolled, irrespective of the ongoing treatment for VVA.

Descriptive data were summarized as the mean and standard deviation or proportion. Characteristics of the study population were assessed overall and by treatment group (ospemifene or LET) and compared using the Mann–Whitney *U*-test in the case of continuous variables and the chi-square test for categorical variables.

For treatment satisfaction, changes from T3 to T6 were assessed, since many patients were not treated before study entry with either ospemifene or LET. For all other questionnaires, changes in scores from T0 to T6 were assessed using mixed models for repeated measurements. Results are expressed as the estimated mean or estimated mean difference from baseline with their 95% confidence interval (CI). A paired *t*-test derived from linear mixed models for repeated measurements was applied for within-group comparisons.

As categorical secondary outcomes, the proportions of patients with FSDS-R score ≥ 11 , FSFI score ≤ 26 and moderate or severe VVA symptoms at each visit were evaluated using mixed-effects models. The results are expressed as the probability (which is equivalent to the prevalence) and odds ratio (OR) with relative 95% CI.

Since women treated with ospemifene and those treated with LET systematically differed for many of the characteristics investigated, between-group comparisons were not performed. $p < 0.05$ was considered statistically significant.

Results

Between September 2021 and December 2022, 414 postmenopausal patients with VVA were enrolled, of whom 385 were included in the study; 25 patients were excluded since at study entry neither ospemifene nor LET was prescribed. Four additional patients were excluded as the baseline questionnaire was not available. Among eligible patients, 145

(37.7%) were treated with ospemifene, of whom 87.6% started and 12.4% continued ospemifene at study entry. The remaining 240 women (62.3%) either started (66.7%) or continued (33.3%) LET at study entry. LET included estradiol tablets, estriol vaginal gel, capsules or creams, and promestriene vaginal capsules or creams. Intravaginal prasterone capsules were also included in the LET group because this molecule displays local estrogenic activity.

Overall, 81.4% of women in the ospemifene group and 84.6% of those in the LET group completed the 6-month follow-up (Supplementary Figure 1).

Baseline characteristics overall and by VVA treatment are presented in Table 1. The data show that, compared to women in the LET group, women treated with ospemifene more often had a past history of BC (44.1% vs. 6.7%; $p < 0.0001$), younger age at menopause (48.3 ± 5.0 years vs. 49.9 ± 4.2 years, $p = 0.002$) and a lower rate of physiological menopause (61.6% vs. 86.8%; $p < 0.0001$). Women treated with ospemifene were also more likely to present urinary incontinence (29.3% vs. 19.5%; $p = 0.03$), more frequently treated with drugs for osteoporosis (17.9% vs. 9.6%; $p = 0.02$) and less likely to be treated with antihypertensive drugs (12.4% vs. 22.9%; $p = 0.01$). At enrollment, women in the ospemifene group were more likely than those in the LET group to present severe VVA (40.4% vs. 19.3%; $p = 0.0001$); a VHI score < 15 was reported in 89.4% of women in the ospemifene group and 76.4% of those in the LET group ($p = 0.002$), and a VuHI score > 8 was reported in 85.7% of women in the ospemifene group and 62.9% of those in the LET group ($p < 0.0001$).

Among patients with 6-month follow-up data available, 81.9% of women treated with ospemifene and 85.2% of those treated with LET were still on treatment. The main reasons for discontinuation were need for treatment intensification (6.7%) in the ospemifene group and discomfort in daily life (5.4%) in the LET group (Supplementary Table 1).

Results relative to the primary endpoint are shown in Figure 1. Overall, the mean treatment satisfaction score increased from 7.3 (95% CI: 7.0; 7.5) at T3 to 7.7 (95% CI: 7.4; 7.9) at T6 ($p = 0.003$). In the ospemifene group, the score improved from 7.0 (95% CI: 6.6; 7.4) at T3 to 7.9 (95% CI: 7.4; 8.4) at T6 ($p = 0.0003$), while in the LET group a non-statistically significant improvement from 7.4 (95% CI: 7.1; 7.6) to 7.6 (95% CI: 7.2; 7.9) ($p = 0.25$) was documented.

The main results relative to longitudinal analyses are presented in Tables 2 and 3 (complete results are reported in Supplementary Tables 2 and 3). The prevalence of women with moderate/severe VVA symptoms decreased in both groups for dryness, pain during sexual intercourse, genital discomfort during physical activity, bleeding, burning or irritation and itching (Table 2 and Supplementary Table 2). The likelihood of moderate/severe levels of these symptoms decreased at follow-up by 70–90% in both groups, as indicated by ORs ranging from 0.1 to 0.3.

Regarding urinary problems, the proportion of women with moderate/severe urinary incontinence significantly decreased in the LET group, moderate/severe urinary urgency and RUIs decreased in the ospemifene group and cystitis decreased in both groups. In particular, the likelihood of RUIs

and cystitis associated with sexual intercourse decreased by 70% overall, by 80% in the ospemifene group and by 50–60% in the LET group.

All of the scores relative to the DIVA questionnaire significantly improved after 6 months in both treatment groups (Table 3 and Supplementary Table 3). Of note, average scores of the four DIVA domains were higher in the ospemifene group at T0, indicating a greater baseline impact of VVA symptoms in daily life of women receiving the oral treatment.

Sexual distress, as assessed by the FSDS-R score, significantly improved in both treatment groups, with an average reduction of 6.6 (95% CI: -8.7 ; -4.5) in the ospemifene group and 4.8 (95% CI: -6.4 ; -3.2) in the LET group (Table 3 and Supplementary Table 3). In the ospemifene group, the prevalence of sexual distress (FSDS-R ≥ 11) decreased from 80.7% (95% CI: 73.4; 86.3) to 76.3% (95% CI: 68.1; 83.0); this translated into a 20% lower likelihood of having sexual distress at T6 versus T0, although statistical significance was not reached (OR = 0.8; 95% CI: 0.5; 1.2) (Supplementary Table 4). In the LET group, the prevalence of sexual distress decreased from 67.9% (95% CI: 61.7; 73.5) to 58.1% (95% CI: 51.4; 64.6; $p = 0.22$); this translated into a 30% lower likelihood of having sexual distress at T6 versus T0 (OR = 0.7; 95% CI: 0.5–0.9; $p = 0.002$) (Supplementary Table 4).

As for sexual functioning as assessed with the FSFI, the total score did not significantly improve in both groups. However, the domain relative to pain significantly improved in both groups, while lubrication only improved in the ospemifene group. Desire and satisfaction worsened in both groups (Table 3 and Supplementary Table 3).

As for general QoL as assessed by SF-12, physical functioning (PCS) significantly improved in the ospemifene group only, whereas mental functioning (MCS) significantly improved in both groups (Table 3 and Supplementary Table 3).

As previous experience with study treatments could have influenced patient perception, relevant outcomes were also assessed in the subgroup of women naïve to both treatments (127 women starting ospemifene and 160 women starting LET at study entry). The results (reported in Supplementary Table 5) show significant improvements in both groups, with changes very similar to those documented in the overall population.

Discussion

The PEONY shows a high level of satisfaction for VVA treatments, either ospemifene or LET, with an increase at 6 months as compared to 3 months. Around 8 out of 10 women were still on treatment after 6 months with both treatment approaches indicating a high level of adherence to both therapies. In addition, VVA treatments were associated with a marked reduction in the proportion of women with moderate/severe VVA symptoms.

Although women from the ospemifene group differed from those treated with LET in terms of higher VVA severity and comorbidities such as history of BC and urinary incontinence at baseline, they showed a significant improvement with treatment.

Table 1. Baseline patient characteristics overall and by subgroup.

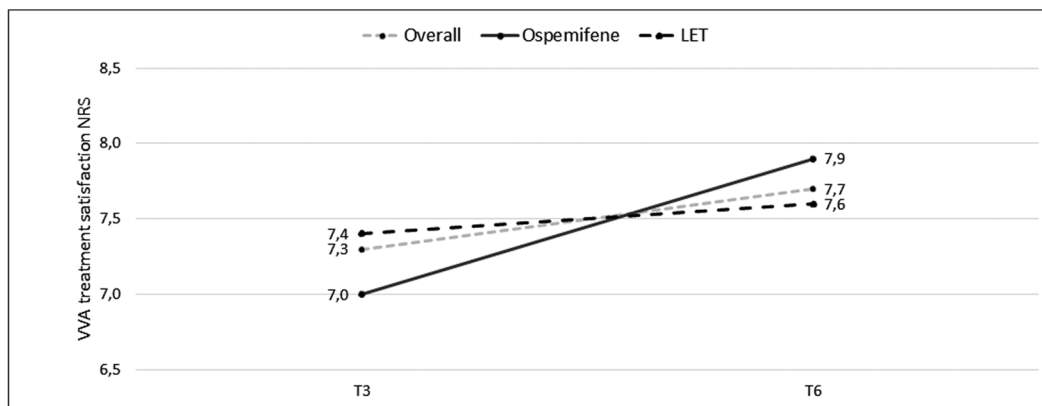
Characteristic	Overall	Ospemifene	LET	p-Value
<i>N</i>	385	145	240	
Socio-demographic				
Age (years)	57.6±6.4	57.0±6.8	57.9±6.2	0.23
Nationality (%)				
Italian	98.6	99.3	98.2	0.42
Other	1.4	0.7	1.8	
Education (%)				
<High school	19.9	17.6	21.4	0.39
≥High school	80.1	82.4	78.6	
Marital status (%)				
Married	76.2	77.7	75.3	0.64
Single	8.9	7.7	9.6	
Widow	1.4	2.3	0.9	
Relation	13.5	12.3	14.2	
Employment (%)				
Employed	62.0	63.6	61.0	0.89
Unemployed/housewife	20.5	19.4	21.1	
Retired	17.6	17.1	17.9	
Clinical				
Age at menopause (years)	49.3±4.6	48.3±5.0	49.9±4.2	0.002
Menopause type (%)				
Physiological	77.3	61.6	86.8	<0.0001
Surgical	10.1	13.0	8.4	
Treatment-related	12.6	25.4	4.8	
BMI (kg/m ²)	23.3±3.6	23.3±3.5	23.3±3.6	0.89
At least one abortion (%)	26.6	22.6	29.1	0.18
Delivery type (%)				
None	24.2	25.5	23.3	0.63
Spontaneous	51.7	53.1	50.8	0.67
Cesarean	35.8	33.8	37.1	0.51
History of breast cancer (%)	20.8	44.1	6.7	<0.0001
Comorbidities (%)				
Hysterectomy	7.7	5.7	8.8	0.27
Prolapse	5.5	5.7	5.3	0.87
Urinary incontinence	23.2	29.3	19.5	0.03
Other chronic diseases	81.8			
Chronic therapies (%)				
None	35.6	32.4	37.5	0.31
Urinary urgency treatment	0.3	0.0	0.4	0.44
Antihypertensive drugs	19.0	12.4	22.9	0.01
Lipid-lowering drugs	11.9	15.2	10.0	0.13
Glucose-lowering drugs	3.9	4.8	3.3	0.46
Osteoporosis treatment	12.7	17.9	9.6	0.02
Other	33.8	37.2	31.7	0.26
Lifestyle				
Smoke (%)				
No	73.9	74.1	73.8	0.24
Ex	16.6	19.3	14.9	
Yes	9.6	6.7	11.3	
If yes, number of cigarettes/day	9.1±5.2	8.1±4.8	9.5±5.4	0.50
Alcohol (%)				
No	60.7	57.3	62.8	0.38
Sometimes	33.5	35.1	32.6	
Regularly	5.7	7.6	4.6	
Coffee (%)				
No	21.1	19.5	22.0	0.85
≤3 cups a day	63.8	65.4	62.8	
>3 cups a day	15.2	15.0	15.2	
Physical exercise (%)				
No	37.2	35.6	38.2	0.52
1–2 times a week	43.2	41.7	44.1	
≥3 times a week	19.6	22.7	17.7	
VVA characteristics				
VVA duration (months)	2.1±8.1	3.3±11.5	1.4±4.8	0.3
Severity degree at enrollment by physician judgment (%)				
Mild	9.2	5.7	11.5	0.0001
Moderate	63.3	53.9	69.2	
Severe	27.5	40.4	19.3	
VHI				
Score	12.3±2.7	11.7±2.4	12.6±2.8	0.002
VHI < 15	81.4	89.4	76.4	0.002
VuHI				
Score	11.3±4.6	12.8±4.4	10.3±4.4	<0.0001
VuHI > 8	71.5	85.7	62.9	<0.0001

(Continued)

Table 1. Continued.

Characteristic	Overall	Ospemifene	LET	p-Value
Treatment (%)				
Naïve	43.6	37.9	47.1	0.08
Already treated with any VVA treatment	56.4	62.1	52.9	
Concomitant treatments at T0 (%)				
Lubricants	3.2	3.4	2.9	0.77
Hydrating	2.6	2.1	2.9	0.61
Laser	1.3	2.1	0.8	0.30
Radiofrequency	0.3	0.0	0.4	0.44

Data presented as mean and standard deviation or frequency and proportion. *p*-values derived from unpaired *t*-test or the Mann–Whitney *U*-test in the case of continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Statistically significant *p*-values ($p < 0.05$) are in bold. BMI, body mass index; LET, local estrogen therapy; VHI, Vaginal Health Index; VuHI, Vulvar Health Index; VVA, vulvovaginal atrophy.



Score	Visit	Overall			Ospemifene			LET		
		Estimated mean (95%CI)	Estimated mean difference from T3 and 95% CI	<i>p</i> -value*	Estimated mean (95%CI)	Estimated mean difference from T3 and 95% CI	<i>p</i> -value*	Estimated mean (95%CI)	Estimated mean difference from T3 and 95% CI	<i>p</i> -value*
VVA treatment satisfaction NRS	T3*	7.3 (7.0;7.5)	-	-	7.0 (6.6;7.4)	-	-	7.4 (7.1;7.6)	-	-
	T6	7.7 (7.4;7.9)	0.4 (0.1;0.7)	0.003	7.9 (7.4;8.4)	0.9 (0.4;1.3)	0.0003	7.6 (7.2;7.9)	0.2 (-0.1;0.5)	0.25

*Paired *t*-test derived from linear mixed models for repeated measurements. Statistically significant *p*-values ($p < 0.05$) are in bold.

Figure 1. Primary endpoint: VVA treatment satisfaction. CI, confidence interval; LET, local estrogen therapy; NRS, numeric rating scale; VVA, vulvovaginal atrophy.

As regards generic QoL measures, women attending the gynecological clinic for VVA problems had a marked reduction in psychological well-being, while physical well-being showed only a slight reduction compared to the normative values.

After 3 and 6 months of treatment with either ospemifene or LET, a significant improvement in disease-specific and general QoL scores was documented. Larger improvements were obtained in the ospemifene group, despite poorer baseline QoL scores.

Many different cross-sectional surveys and epidemiological studies documented that VVA is a highly prevalent, undertreated condition, associated with a clinical and person-centered burden [1,5,6,12,32].

In comparison with the EVES study, involving 2412 postmenopausal women screened in Italy and Spain [33], women in our study showed poorer scores for all of the dimensions investigated by the DIVA questionnaire, even in comparison with the subgroups of women with severe vaginal, vulvar or urinary symptoms. However, we found a significant reduction in the scores relative to all the domains investigated by the

DIVA questionnaire after 6 months of treatment with either ospemifene or LET, indicating a lower impact of symptoms and ultimately an improvement in QoL.

Baseline data [24] documented, in line with findings deriving from the EVES and REVIVE studies [5,12,26,27], that 9 out of 10 women had FSFI values indicative of sexual dysfunction and three out of four women had FSDS-R values indicative of sexual distress. Longitudinal evaluation shows an improvement in FSDS-R score in both the ospemifene and LET groups. Of note, the reduction in the FSDS-R score was larger in the ospemifene group, despite higher baseline values indicative of a more pronounced sexual distress. As regards the FSFI, no significant changes were documented in the overall score as well as in the components more strictly associated with sexual function (i.e. arousal and orgasm). The only exception was an improvement in lubrication among women treated with ospemifene. It is likely that the FSFI is less capable of discriminating between postmenopausal women with and without sexual dysfunction [34], and in our study sample the time of observation captured only FSFI changes associated with the trophic effects of the given therapy.

Table 2. Changes in the likelihood of moderate/severe VVA symptoms from study entry to 6 months.

VVA symptom	Visit	Overall			Ospemifene			LET		
		Probability estimates (95% CI)	OR (95% CI)	p-Value ^a	Probability estimates (95% CI)	OR (95% CI)	p-Value ^a	Probability estimates (95% CI)	OR (95% CI)	p-Value ^a
Dryness (inside the vagina)	T0	83.6 (79.5; 87.1)	–	–	90.8 (84.7; 94.6)	–	–	79.2 (73.4; 84)	–	–
	T6	44.8 (39.5; 50.3)	0.2 (0.1; 0.2)	<0.0001	49.3 (40.3; 58.3)	0.1 (0.1; 0.2)	<0.0001	42 (35.4; 48.9)	0.2 (0.1; 0.3)	<0.0001
Dryness (outside/ external genitalia)	T0	83.2 (79.0; 86.6)	–	–	90.1 (83.9; 94.1)	–	–	78.9 (73.1; 83.7)	–	–
	T6	46.3 (40.9; 51.8)	0.2 (0.1; 0.2)	<0.0001	53.2 (44.2; 62.1)	0.1 (0.1; 0.2)	<0.0001	42.3 (35.7; 49.2)	0.2 (0.1; 0.3)	<0.0001
Pain during sexual intercourse (inside the vagina)	T0	79.9 (75.4; 83.6)	–	–	88 (81.5; 92.5)	–	–	74.8 (68.7; 80)	–	–
	T6	35.1 (30.1; 40.6)	0.1 (0.1; 0.2)	<0.0001	45.3 (36.5; 54.5)	0.1 (0.1; 0.2)	<0.0001	29.1 (23.2; 35.7)	0.1 (0.1; 0.2)	<0.0001
Pain during sexual intercourse (on penetration)	T0	80.3 (76; 84.1)	–	–	88.7 (82.3; 93)	–	–	75.2 (69.2; 80.4)	–	–
	T6	42.5 (37.1; 48.0)	0.2 (0.1; 0.2)	<0.0001	51.2 (42.1; 60.2)	0.1 (0.1; 0.2)	<0.0001	37 (30.6; 44)	0.2 (0.1; 0.3)	<0.0001
Genital discomfort during physical activity	T0	22.6 (18.6; 27.2)	–	–	33.2 (25.8; 41.4)	–	–	16.2 (12; 21.6)	–	–
	T6	9.1 (6.4; 12.8)	0.3 (0.2; 0.5)	<0.0001	11.8 (7; 19)	0.3 (0.1; 0.5)	0.0001	7.5 (4.6; 12.1)	0.4 (0.2; 0.8)	0.006
Bleeding during sexual intercourse	T0	19.3 (15.5; 23.6)	–	–	28.9 (22; 37)	–	–	13.2 (9.4; 18.3)	–	–
	T6	4.8 (3.0; 7.7)	0.2 (0.1; 0.4)	<0.0001	9.1 (5.1; 15.8)	0.2 (0.1; 0.5)	<0.0001	2.2 (0.9; 5.4)	0.1 (0.1; 0.4)	0.0002
Bleeding during sexual contact	T0	13.8 (10.6; 17.7)	–	–	18.4 (12.8; 25.7)	–	–	11 (7.6; 15.8)	–	–
	T6	5.2 (3.3; 8.2)	0.3 (0.2; 0.6)	<0.0001	8.2 (4.5; 14.7)	0.4 (0.2; 0.8)	0.01	3.3 (1.6; 6.8)	0.3 (0.1; 0.6)	0.003
Burning or irritation (inside the vagina)	T0	57.5 (52.4; 62.4)	–	–	64.3 (56; 71.8)	–	–	53.3 (46.8; 59.7)	–	–
	T6	19.1 (15.2; 23.7)	0.2 (0.1; 0.2)	<0.0001	23.6 (16.7; 32.1)	0.2 (0.1; 0.3)	<0.0001	16.6 (12.1; 22.3)	0.2 (0.1; 0.3)	<0.0001
Burning or irritation (on the outside/ external genitalia)	T0	55.1 (50.0; 60.1)	–	–	68 (59.8; 75.2)	–	–	47.3 (40.8; 53.8)	–	–
	T6	16.6 (12.9; 21.0)	0.2 (0.1; 0.2)	<0.0001	23.9 (17.1; 32.5)	0.1 (0.1; 0.3)	<0.0001	12.3 (8.5; 17.5)	0.2 (0.1; 0.3)	<0.0001
Itching (inside the vagina)	T0	29.4 (25; 34.3)	–	–	38.9 (31.2; 47.3)	–	–	23.6 (18.5; 29.6)	–	–
	T6	7.9 (5.4; 11.4)	0.2 (0.1; 0.3)	<0.0001	8.7 (4.8; 15.3)	0.1 (0.1; 0.3)	<0.0001	7.5 (4.6; 12)	0.3 (0.1; 0.5)	<0.0001
Itching (on the outside/external genitalia)	T0	31.2 (26.7; 36.1)	–	–	38.2 (30.5; 46.5)	–	–	26.9 (21.6; 33.1)	–	–
	T6	12.0 (8.9; 16.0)	0.3 (0.2; 0.4)	<0.0001	14.4 (9.1; 22)	0.3 (0.1; 0.5)	<0.0001	10.6 (7.1; 15.6)	0.3 (0.2; 0.5)	<0.0001
Vaginal discharge	T0	10.0 (7.3; 13.5)	–	–	9.9 (5.9; 16.1)	–	–	10.1 (6.8; 14.7)	–	–
	T6	6.0 (3.8; 9.2)	0.6 (0.3; 1)	0.06	6.9 (3.5; 13.1)	0.7 (0.3; 1.6)	0.38	5.5 (3; 9.6)	0.5 (0.2; 1.1)	0.08
Urinary incontinence	T0	11.8 (8.8; 15.5)	–	–	14.7 (9.7; 21.6)	–	–	9.9 (6.6; 14.6)	–	–
	T6	6.7 (4.5; 9.8)	0.5 (0.3; 0.8)	0.006	9 (5.1; 15.4)	0.6 (0.3; 1)	0.07	5.2 (2.9; 9.2)	0.5 (0.3; 1)	0.04
Urinary urgency	T0	16.3 (12.8; 20.4)	–	–	21 (15; 28.6)	–	–	13.4 (9.5; 18.5)	–	–
	T6	12.7 (9.5; 16.7)	0.7 (0.5; 1.1)	0.10	13.5 (8.5; 20.7)	0.6 (0.3; 1)	0.045	12.2 (8.4; 17.4)	0.9 (0.6; 1.5)	0.67
Urinary frequency	T0	20.5 (16.7; 24.9)	–	–	23.4 (17.1; 31.2)	–	–	18.7 (14.1; 24.3)	–	–
	T6	14.8 (11.3; 19.0)	0.7 (0.5; 1.0)	0.04	17.1 (11.4; 24.9)	0.7 (0.4; 1.2)	0.16	13.5 (9.5; 18.9)	0.7 (0.4; 1.1)	0.14

(Continued)

Table 2. Continued.

VVA symptom	Visit	Overall			Ospemifene			LET		
		Probability estimates (95% CI)	OR (95% CI)	p-Value ^a	Probability estimates (95% CI)	OR (95% CI)	p-Value ^a	Probability estimates (95% CI)	OR (95% CI)	p-Value ^a
Difficult urination	T0	5.4 (3.5; 8.3)	–	–	3.5 (1.5; 8.3)	–	–	6.6 (4; 10.7)	–	–
	T6	2.5 (1.3; 4.9)	0.5 (0.2; 1.1)	0.06	2.5 (0.8; 7.5)	0.7 (0.2; 3.1)	0.62	2.5 (1.1; 5.9)	0.4 (0.1; 1)	0.06
Recurrent urinary tract infections	T0	13.6 (10.4; 17.5)	–	–	19.8 (14; 27.2)	–	–	9.7 (6.4; 14.3)	–	–
	T6	5.2 (3.3; 8.1)	0.3 (0.2; 0.6)	<0.0001	5.3 (2.5; 10.9)	0.2 (0.1; 0.5)	0.0002	5.1 (2.8; 9)	0.5 (0.2; 1)	0.06
Cystitis associated with sexual intercourse	T0	17.9 (14.3; 22.1)	–	–	27.6 (20.8; 35.6)	–	–	11.9 (8.2; 16.8)	–	–
	T6	5.2 (3.3; 8.3)	0.3 (0.1; 0.4)	<0.0001	6.1 (2.9; 12.2)	0.2 (0.1; 0.4)	<0.0001	4.7 (2.5; 8.6)	0.4 (0.2; 0.8)	0.009
Abdominal pain	T0	8.5 (6.0; 11.8)	–	–	7.0 (3.8; 12.7)	–	–	9.4 (6.3; 14)	–	–
	T6	4.9 (3.0; 7.9)	0.3 (0.1; 0.4)	<0.0001	5.0 (2.3; 10.8)	0.7 (0.3; 1.6)	0.41	4.8 (2.5; 8.8)	0.5 (0.2; 1.1)	0.08

^aResults from mixed-effects models for repeated measurements. Statistically significant *p*-values (*p* < 0.05) are in bold. CI, confidence interval; LET, local estrogen therapy; OR, odds ratio; VVA, vulvovaginal atrophy

LET is the mainstay of treatment for vaginal dryness, dyspareunia and other urogenital symptoms because it may reverse some pathophysiological mechanisms associated with decreasing estrogens and increasing aging [35]. On the other hand, the demand for non-hormonal therapies is increasing due to an increasing number of patients surviving long term after a cancer diagnosis, as well as increased public knowledge of the symptoms of menopause [36].

The relevance of VVA symptoms, including lower urinary tract symptoms, especially RUIs, has already been documented in a younger clinical population of Italian women with VVA [37]. Indeed, the presence of lower urinary tract symptoms was related to dyspareunia, and distress from lower urinary tract symptoms was inversely related to sexuality [37]. Even in a large study involving more than 18,000 patients, a higher incidence of RUIs was found in women with VVA as compared to women without VVA [38]. Our study shows that treatments for VVA positively impact on these symptoms, thus contributing to the reduction of the overall burden of this condition even in women with urinary impairment [39].

Our study confirms the significant effectiveness of VVA treatments in reducing severity of genitourinary symptoms and some of our findings confirm that such improvement positively influences QoL and sexual function [32]. Interestingly, ospemifene was prescribed in those women reporting poorer QoL indirectly supporting the outcomes of the CRETA (CRoss sectional European sTudy on Adherence) multicenter cross-sectional study in Spain, which has recently shown a better effect of ospemifene on QoL as compared with LET [40].

What the longitudinal design of the PEONY adds to the existing knowledge is the possibility to improve symptoms and burden of VVA by proactively treating the condition both with oral and local validated treatments.

There are no guidelines regarding the optimal duration of therapy, but symptoms commonly reappear when treatment

is discontinued, suggesting that therapy should not be time-limited. Indeed, in their recent update on VVA management, Palacios et al. suggest reviewing women's needs annually to assess efficacy and acceptability of therapy, while updating on any new advice, information or treatment options [8,9]. The PEONY offers a model on how VVA should be assessed and treated in routine care. A further follow-up visit at 12 months is scheduled to assess persistence in therapies and changes in PROs.

This study has strengths and limitations. Among the strengths, to the best of our knowledge, this is one of the largest and most comprehensive real-world studies available on VVA and its treatment, and the first containing a longitudinal evaluation of QoL. This seems highly relevant in light of the recent COMMA (Core Outcomes in Menopause) global initiative for genitourinary symptoms associated with menopause, which includes satisfaction with treatment as a core outcome in order to advance clinical practice in the management of symptomatic women [41]. Other strengths are represented by the multicenter nature of the study and the use of many validated tools to collect data in routine care. Among the limitations, the study may be representative only of the women attending specialized centers and different intravaginal products were considered under the umbrella of LET.

In conclusion, the PEONY documents that proactively treating VVA with LET or ospemifene – that is, those treatment options for which efficacy evidence is available – is associated with 80% persistence after 6 months, a high level of treatment satisfaction and significant improvements in most VVA/GSM symptoms. In addition, the majority of disease-specific and general QoL domains significantly improved. These benefits were particularly relevant in the cohort treated with ospemifene, since women treated with this option represent a more symptomatic VVA phenotype because of more severe symptoms and more frequent presence of BC history.

Table 3. Changes in treatment satisfaction and quality of life scores from study entry to 6 months.

Score	Visit	Overall			Ospemifene			LET		
		Estimated mean levels (95% CI)	Estimated mean difference from T0 (95% CI)	p-Value ^a	Estimated mean levels (95% CI)	Estimated mean difference from T0 (95% CI)	p-Value ^a	Estimated mean levels (95% CI)	Estimated mean difference from T0 (95% CI)	p-Value ^a
DIVA activities of daily living	T0	0.7 (0.7; 0.8)	–	–	0.9 (0.8; 1.1)	–	–	0.6 (0.5; 0.7)	–	–
	T6	0.5 (0.4; 0.6)	–0.2 (–0.3; –0.2)	<0.0001	0.6 (0.5; 0.7)	–0.3 (–0.5; –0.2)	<0.0001	0.4 (0.4; 0.5)	–0.2 (–0.3; –0.1)	0.0001
DIVA emotional well-being	T0	1.5 (1.3; 1.6)	–	–	1.9 (1.7; 2.0)	–	–	1.2 (1.1; 1.3)	–	–
	T6	1.1 (1.0; 1.2)	–0.4 (–0.5; –0.3)	<0.0001	1.4 (1.2; 1.6)	–0.5 (–0.6; –0.3)	<0.0001	0.9 (0.7; 1.0)	–0.3 (–0.5; –0.2)	<0.0001
DIVA sexual functioning	T0	2.1 (2.0; 2.2)	–	–	2.4 (2.2; 2.5)	–	–	1.9 (1.8; 2.1)	–	–
	T6	1.6 (1.5; 1.7)	–0.5 (–0.6; –0.4)	<0.0001	1.8 (1.6; 2.0)	–0.6 (–0.8; –0.4)	<0.0001	1.4 (1.3; 1.6)	–0.5 (–0.6; –0.3)	<0.0001
DIVA self-concept and body image	T0	1.9 (1.8; 2.0)	–	–	2.3 (2.2; 2.5)	–	–	1.7 (1.5; 1.8)	–	–
	T6	1.5 (1.4; 1.6)	–0.4 (–0.5; –0.3)	<0.0001	1.9 (1.7; 2.0)	–0.4 (–0.7; –0.3)	<0.0001	1.3 (1.1; 1.4)	–0.4 (–0.5; –0.2)	<0.0001
FSDS-R	T0	22.2 (20.7; 23.7)	–	–	27.2 (24.8; 29.5)	–	–	19.1 (17.3; 21.0)	–	–
	T6	16.7 (15.3; 18.0)	–5.5 (–6.8; –4.3)	<0.0001	20.6 (18.4; 22.8)	–6.6 (–8.7; –4.5)	<0.0001	14.3 (12.7; 16.0)	–4.8 (–6.4; –3.2)	<0.0001
FSFI total	T0	18.4 (17.7; 19.0)	–	–	18.8 (17.7; 19.9)	–	–	18.1 (17.2; 19.0)	–	–
	T6	19.1 (18.4; 19.8)	0.7 (–0.1; 1.6)	0.08	19.9 (18.8; 21.1)	1.1 (–0.2; 2.5)	0.09	18.6 (17.7; 19.4)	0.5 (–0.5; 1.5)	0.34
FSFI desire	T0	4.7 (4.6; 4.8)	–	–	4.8 (4.6; 5.0)	–	–	4.6 (4.4; 4.7)	–	–
	T6	4.3 (4.2; 4.4)	–0.3 (–0.5; –0.2)	<0.0001	4.4 (4.2; 4.6)	–0.4 (–0.6; –0.2)	0.0004	4.3 (4.1; 4.4)	–0.3 (–0.5; –0.1)	0.0004
FSFI arousal	T0	3.1 (2.8; 3.3)	–	–	3.3 (3.0; 3.6)	–	–	2.9 (2.6; 3.2)	–	–
	T6	3.0 (2.8; 3.2)	–0.1 (–0.3; 0.2)	0.66	3.3 (3.0; 3.7)	0 (–0.4; 0.4)	0.88	2.8 (2.6; 3.1)	–0.1 (–0.4; 0.2)	0.5
FSFI lubrication	T0	2.8 (2.6; 3.0)	–	–	2.8 (2.5; 3.1)	–	–	2.8 (2.6; 3.0)	–	–
	T6	3.1 (2.9; 3.3)	0.3 (0.1; 0.5)	0.01	3.2 (2.9; 3.5)	0.4 (0; 0.8)	0.03	3.0 (2.8; 3.3)	0.2 (–0.1; 0.5)	0.15
FSFI orgasm	T0	2.6 (2.4; 2.8)	–	–	2.7 (2.4; 3)	–	–	2.6 (2.3; 2.8)	–	–
	T6	2.8 (2.6; 3)	0.2 (0; 0.4)	0.09	3 (2.7; 3.3)	0.3 (–0.1; 0.6)	0.14	2.7 (2.5; 3.0)	0.1 (–0.1; 0.4)	0.32
FSFI satisfaction	T0	3.5 (3.4; 3.6)	–	–	3.8 (3.6; 4)	–	–	3.3 (3.2; 3.5)	–	–
	T6	3.1 (3.0; 3.2)	–0.4 (–0.5; –0.2)	<0.0001	3.3 (3.1; 3.5)	–0.5 (–0.8; –0.2)	0.0001	3.0 (2.9; 3.2)	–0.3 (–0.5; –0.1)	0.002
FSFI pain	T0	1.7 (1.6; 1.9)	–	–	1.5 (1.2; 1.8)	–	–	1.9 (1.7; 2.1)	–	–
	T6	2.8 (2.6; 3.0)	1.0 (0.8; 1.3)	<0.0001	2.8 (2.4; 3.1)	1.3 (0.9; 1.7)	<0.0001	2.8 (2.5; 3.1)	0.9 (0.6; 1.2)	<0.0001
SF-12 (PCS)	T0	47.9 (47.1; 48.8)	–	–	47.2 (45.8; 48.6)	–	–	48.4 (47.3; 49.5)	–	–
	T6	48.6 (47.7; 49.5)	0.70 (–0.2; 1.6)	0.13	49.0 (47.5; 50.4)	1.8 (0.3; 3.3)	0.02	48.4 (47.3; 49.5)	0.0 (–1.1; 1.1)	0.96
SF-12 (MCS)	T0	41.9 (40.9; 42.9)	–	–	40.7 (39.0; 42.4)	–	–	42.7 (41.4; 44)	–	–
	T6	44.4 (43.4; 45.4)	2.5 (1.5; 3.5)	<0.0001	43.5 (41.8; 45.2)	2.8 (1.1; 4.5)	0.001	44.9 (43.7; 46.2)	2.3 (1.0; 3.6.0)	0.0006

*Paired t-test derived from linear mixed models for repeated measurements. Statistically significant p-values ($p < 0.05$) are in bold.

DIVA: range 0–4, the higher the scores, the greater impact of vaginal symptoms. FSFI: range 2–36, the higher the score, the less severe sexual dysfunction. FSDS-R: range 0–52, the higher the score, the higher the level of sexual distress; score ≥ 11 discriminates women with sexual distress. SF-12, normalized to 50 ± 10 , the higher the score, the higher the level of mental or physical health. DIVA, Day-to-Day Impact of Vaginal Aging; FSDS-R, Female Sexual Distress Scale – Revised; FSFI, Female Sexual Function Index; LET, local estrogen therapy; MCS, Mental Component Summary Score; PCS, Physical Component Summary Score.

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*PEONY Group

Participating centers: Maria Cristina Meriggiola, Stefania Alvisi and Veronica Amati, Azienda Ospedaliero-Universitaria di Bologna, Bologna; Rossella Nappi, Chiara Cassani, Laura Cucinella and Ellis Martini, Fondazione IRCCS Policlinico 'San Matteo', Pavia; Silvia Maffei, Fondazione CNR-Regione Toscana 'G. Monasterio' per la ricerca clinica e la sanità pubblica, Pisa; Angelamaria Becorpi and Anna Rosa Speciale, Azienda Ospedaliera Universitaria Careggi, Firenze; Paola Villa, Inbal Dona Amar, Elvira Foti and Giovanni Scambia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma; Stefano Salvatore, Arianna Casiraghi, Silvia Messina and Carolina Morgante, IRCCS Ospedale San Raffaele, Milano; Giovanni Delli Carpini and Andrea Ciavattini, Università Politecnica delle Marche, Ancona; Gloria Bonaccorsi and Irene Piccolotti, University of Ferrara, Ferrara; Alessandro Gambera, ASST Spedali Civili, Brescia; Dorella Franchi and Silvia Martella, Istituto Europeo Oncologia, Milano; Francesca Albani, Istituti Scientifici Maugeri, Pavia; Maurizio Guida, Università 'Federico II', Napoli; Valentina Bounous, Azienda Ospedaliera Ordine Mauriziano di Torino, Torino; Massimo Stomati, ASL Brindisi, Ospedale 'Dario Camberlingo', Francavilla Fontana (BR); Tommaso Simoncini, Eleonora Russo, Giulia Misasi, Elena Pisacreta and Marta Caretto, Università di Pisa, Azienda Ospedaliero Universitaria Pisana, Pisa; Angelo Cagnacci, Claudia Massarotti and Giorgia Asinaro, Ospedale San Martino, Genova; Stefano Luisi, Azienda Ospedaliera Universitaria Senese, Siena.

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Disclosure statement

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ORCID

Rossella E. Nappi  <http://orcid.org/0000-0003-1713-6396>
 Maria Cristina Meriggiola  <http://orcid.org/0000-0003-0061-9834>
 Gloria Bonaccorsi  <http://orcid.org/0000-0001-5005-0274>
 Giovanni Delli Carpini  <http://orcid.org/0000-0003-2849-4690>
 Alessandro Gambera  <http://orcid.org/0000-0003-2146-2688>

Antonio Nicolucci  <http://orcid.org/0000-0002-5939-6850>
 Maria Chiara Rossi  <http://orcid.org/0000-0001-8696-4238>
 Paola Villa  <http://orcid.org/0000-0002-4501-3038>

Data availability statement

Data will be made available upon request.

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