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RAPID COMMUNICATION

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Palbociclib plus endocrine therapy in HER2 negative, hormonal receptor-positive, advanced breast cancer: A real-world experience

Laura Pizzuti[1] | Antonio Giordano[2] | Andrea Michelotti[3] | Marco Mazzotta[4] | Clara Natoli[5] | Teresa Gamucci[6,7] | Claudia De Angelis[3] | Elisabetta Landucci[3] | Lucrezia Diodati[3] | Laura Iezzi[5] | Lucia Mentuccia[6] | Agnese Fabbri[8] | Maddalena Barba[1] | Giuseppe Sanguineti[9] | Paolo Marchetti[4,10] | Silverio Tomao[11] | Luciano Mariani[12] | Ida Paris[13] | Vito Lorusso[14] | Simona Vallarelli[14] | Alessandra Cassano[15] | Francesca Airoldi[15] | Armando Orlandi[15] | Luca Moscetti[16] | Domenico Sergi[1] | Maria Giuseppina Sarobba[17] | Giuseppe Tonini[18] | Daniele Santini[18] | Valentina Sini[19] | Enzo Veltri[20] | Angela Vaccaro[5] | Laura Ferrari[5] | Michele De Tursi[4] | Nicola Tinari[4] | Antonino Grassadonia[4] | Filippo Greco[21] | Andrea Botticelli[2] | Nicla La Verde[22] | Claudio Zamagni[23] | Daniela Rubino[23] | Enrico Cortesi[24] | Valentina Magri[24] | Giulia Pomati[24] | Simone Scagnoli[24] | Elisabetta Capomolla[25] | Ramy Kayal[26] | Angelo Fedele Scinto[27] | Domenico Corsi[27] | Marina Cazzaniga[28] | Lucio Laudadio[29] | Samantha Forciniti[29] | Maria Mancini[29] | Luisa Carbognin[30] | Patrizia Seminara[10] | Sandro Barni[31] | Riccardo Samaritani[32] | Mario Roselli[33] | Ilaria Portarena[33] | Antonio Russo[34] | Corrado Ficorella[35] | Katia Cannita[35] | Silvia Carpano[1] | Mirco Pistelli[36] | Rossana Berardi[36] | Ruggero De Maria[37] | Isabella Sperduti[38] | Gennaro Ciliberto[39] | Patrizia Vici[1]

[1]Division of Medical Oncology 2, IRCCS Regina Elena National Cancer Institute, Rome, Italy

[2]Department of Clinical and Molecular Medicine, "Sapienza" University of Rome, Azienda Ospedaliera Sant'Andrea, Rome, Italy

[3]UO Oncologia Medica I, Ospedale S. Chiara, Dipartimento di Oncologia, Dei Trapianti e Delle Nuove Tecnologie, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

[4]Department of Medical, Oral and Biotechnological Sciences, Centro Scienze Dell'Invecchiamento e Medicina Traslazionale-CeSI-MeT, Chieti, Italy

[5]Medical Oncology Unit, SS Trinità Hospital, Loc. San MarcianoHospital, Sora, Frosinone, Italy

[6]Medical Oncology Unit, SS Trinità Hospital, Sora, Italy

[7]Medical Oncology, Sandro Pertini Hospital, Rome, Italy

[8]Medical Oncology Unit, Belcolle Hospital, Viterbo, Italy

Abbreviations: aBC, advanced breast cancer; AIs, aromatase inhibitors; CB, clinical benefit; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; CR, complete response; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRs, hazard ratios; LHRH, luteinizing hormone-releasing hormone; MBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; N, number; OR, odd ratio; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PgR, progesteron receptor; PI3K, phosphoinositide 3-kinase; PR, partial response; PS, performance status; RCTs, randomized clinical trials; RECIST, response evaluation criteria in solid tumors; SD, stable disease; Tam, tamoxifen.

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[9]Department of Radiation Oncology, IRCCS Regina Elena National Cancer Institute, Rome, Italy
[10]Department of Clinical and Molecular Medicine, A Oncology Division, "Sapienza" University of Rome, Rome, Italy
[11]Department of Clinical and Molecular Medicine, A Oncology Division, La "Sapienza" University of Rome, Rome, Italy
[12]HPV Unit, Department of Gynaecologic Oncology, IRCCS Regina Elena National Cancer Institute, Rome, Italy
[13]Gynecology Oncology Unit, Catholic University of the Sacred Heart, Rome, Italy
[14]Division of Medical Oncology, IRCCS, Giovanni Paolo II Hospital, Bari, Italy
[15]Department of Medical Oncology, Catholic University of Sacred Heart, Rome, Italy
[16]Division of Medical Oncology, Department of Oncology and Hematology, University Hospital of Modena, Modena, Italy
[17]Division of Medical Oncology, Ospedale San Francesco, Nuoro, Italy
[18]Department of Oncology, University Campus Biomedico of Rome, Rome, Italy
[19]Oncology Unit, ASL Roma 1, Santo Spirito Hospital, Rome, Italy
[20]Division of Medical Oncology, Ospedale S. Maria Goretti, Latina, Italy
[21]ASST Fatebenefratelli Sacco PO Fatebenefratelli, Department of Oncology, Milan, Italy
[22]Department of Oncology, ASST Fatebenefratelli Sacco PO Fatebenefratelli, Milan, Italy
[23]SSD Oncologia Medica "Addarii", S. Orsola-Malpighi Hospital, Bologna, Italy
[24]Medical Oncology, Policlinico Umberto I, Sapienza, University of Rome, Rome, Italy
[25]Medical Oncology, Ospedale "Parodi-Delfino", Colleferro, Italy
[26]Department of Radiology, IRCCS Regina Elena National Cancer Institute, Rome, Italy
[27]Medical Oncology Unit, Ospedale San Pietro Fatebenefratelli, Rome, Italy
[28]Oncology Unit, ASST Monza, Monza, Italy
[29]Medical Oncology, Ospedale F. Renzetti, Lanciano, Italy
[30]Department of Pathology, Surgery and Oncology, "Mater Salutis" Hospital, ULSS21, Verona, Italy
[31]Department of Oncology, Oncology Unit, ASST Bergamo Ovest, Treviglio, Italy
[32]Medical Oncology Unit, "Regina Margherita" Hospital, Rome, Italy
[33]Medical Oncology Unit, Department of Systems Medicine, Tor Vergata Clinical Center University Hospital, Tor Vergata University Hospital, Rome, Italy
[34]Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy
[35]Medical Oncology Department, S. Salvatore Hospital, University of L'Aquila, L'Aquila, Italy
[36]Azienda Ospedaliero Universitaria Ospedali Riuniti Clinica di Oncologia, Università Politecnica delle Marche, Ancona, Italy
[37]Institute of General Pathology, Catholic University of the Sacred Heart, Rome, Italy
[38]Bio-statistics Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy
[39]Scientific Direction, IRCCS Regina Elena National Cancer Institute, Rome, Italy

Correspondence
Isabella Sperduti, Biostatistics Unit, IRCCS Regina Elena National Cancer Institute, Via Elio Chianesi, 53-00144 Rome, Italy.
Email: isabella.sperduti@ifo.gov.it
Maddalena Barba, Division of Medical Oncology 2, IRCCS Regina Elena National Cancer Institute, Via Elio Chianesi, 53-00144 Rome, Italy.
Email: maddalena.barba@gmail.com

Abstract

Data from 423 human epidermal growth factor receptor 2-negative (HER2−), hormone receptor-positive (HR+) advanced breast cancer (aBC) patients treated with palbociclib and endocrine therapy (ET) were provided by 35 Italian cancer centers and analyzed for treatment outcomes. Overall, 158 patients were treated in first line and 265 in second/later lines. We observed 19 complete responses and 112 partial responses. The overall response rate (ORR) was 31% (95% confidence interval [CI], 26.6–35.4) and clinical benefit was 52.7% (95% CI, 48–57.5). ORR was negatively affected by prior exposure to everolimus/exemestane ($p = 0.002$) and favorably influenced by early line-treatment ($p < 0.0001$). At 6 months, median progression-free survival was 12 months (95% CI, 8–16) and median overall survival was 24 months (95% CI, 17–30). More favorable outcomes were associated with palbociclib in early lines, no visceral metastases and no prior everolimus/exemestane. The main toxicity reported was neutropenia. Our results provide further support to the use of palbociclib with ET in HER2−, HR+ aBC. Differences in outcomes across patients subsets remain largely unexplained.

KEYWORDS
advanced breast cancer, hormonal therapy, endocrine resistance, palbociclib, real-world setting

1 | INTRODUCTION

Approximately two-third of breast cancer patients are diagnosed with hormone receptor-positive (HR+) tumors. In advanced disease, endocrine therapy (ET) showed efficacy in more than a half of the patients. Unfortunately, both de novo and acquired resistance usually occur, making it particularly relevant research fostering, innovative treatments (Matutino, Joy, Brezden-Masley, Chia, & Verma, 2018). Key components of cell cycle have been long investigated in breast and other cancer in the attempt to broaden our knowledge of the underlying biological mechanisms and orient research on therapeutic targets (Giordano et al., 1991, 1989; Roy, Sil, & Chakraborty, 2018; Zhao et al., 2018).

Novel therapeutic strategies include the combination with agents targeting growth factors and angiogenesis and, more recently, specific targets such as the mammalian target of rapamycin (mTOR) pathway, phosphoinositide 3-kinase (PI3K), or cyclin-dependent kinase 4/6 (CDK4/6; D'Souza, Spicer, & Lu, 2018).

Results from Phase 3 randomized trials have provided consistent support to the addition of CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) to an aromatase inhibitor in the first-line setting for most patients with human epidermal growth factor receptor 2 negative (HER2−), HR+, advanced breast cancer (aBC) with substantial improvement in progression-free survival (PFS) and overall response rate (ORR) and manageable toxicity (Finn et al., 2016; Goetz et al., 2017; Hortobagyi et al., 2016). Recently, the combination of ribociclib and the selective estrogen receptor (ER) downregulator fulvestrant has shown high efficacy when used as first-line treatment (Slamon et al., 2018).

In patients recurring while on or soon after a previous adjuvant ET or while receiving first-line ET for advanced disease, the use of palbociclib, ribociclib, and abemaciclib, in combination with fulvestrant, is considered the standard of care (Cristofanilli et al., 2016; Slamon et al., 2018; Sledge et al., 2017), showing advantage in PFS and ORR. Subgroup analysis showed benefit with CDK4/6 inhibitors in all the subsets defined upon patient- and tumor-related characteristics (Cristofanilli et al., 2016; Goetz et al., 2017; Hortobagyi et al., 2016; Slamon et al., 2018; Sledge et al., 2017). A clear advantage was seen even in premenopausal/perimenopausal patients with the use of a luteinizing hormone-releasing hormone (LHRH) analogue (Goetz et al., 2017; Tripathy et al., 2018). Overall, quality of life was good (Harbeck et al., 2016) and toxicity manageable with asymptomatic neutropenia being the most common side effect and a very low incidence of febrile neutropenia (Kassem, Shohdy, Lasheen, Abdel-Rahman, & Bachelot, 2018; Verma et al., 2016).

In 2015, the first CDK4/6 inhibitor developed, palbociclib, received accelerated US Food and Drug Administration approval for use in combination with the nonsteroidal competitive aromatase inhibitor letrozole for the treatment of postmenopausal HR+/HER2− aBC as initial, endocrine-based therapy, and subsequently, in combination with fulvestrant in second line, in both premenopausal and postmenopausal patients. Since then, a considerable number of patients have been treated with palbociclib outside of randomized trials. The report from the expanded access of palbociclib/letrozole confirmed the clinical benefit, even in heavily pretreated patients (Brufsky et al., 2018). Moreover, some small reports of palbociclib administered in real-world practice seem to confirm efficacy and toxicity data, although these studies include a quite restricted number of patients (Chiu et al., 2017; Malik et al., 2017). In light of the renowned differences possibly emerging from the comparison between patients enrolled in randomized clinical trials (RCTs) and those from the real-world setting, we herein present additional evidence on the use of palbociclib plus an aromatase inhibitor or fulvestrant in HER2−, HR+, female aBC patients treated at several Italian cancer centers in real-life setting.

2 | PATIENTS AND METHODS

The primary objective of this study was to assess the clinical benefit and tolerability of palbociclib and ET (aromatase inhibitors or fulvestrant) as first or subsequent endocrine lines of therapy in patients with HER2−, HR+ aBC. Secondarily, we aimed to evaluate the efficacy in subgroups defined according to relevant patient- and tumor-related features.

Patients not enrolled in RCTs were retrospectively and sequentially identified and recruited at several Italian cancer centers. Palbociclib, in combination with ET, was given orally at 125 mg/day, in 4-week cycles (3 weeks of treatment followed by 1-week off). Dose reductions/delay/discontinuations of palbociclib due to adverse events were recorded. Treatment was continued until disease progression, unacceptable toxicity, or patient refusal. Treatment efficacy was evaluated by Response Evaluation Criteria In Solid Tumors (version 1.1). Adverse events were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

All the patients signed a written informed consent to treatment and data collection. This study was conducted in accordance with the Declaration of Helsinki. The institutional ethic committees of the coordinating and satellite centers provided their approval to our study conduct.

3 | STATISTICAL METHOD

Descriptive statistics were computed for all the variables of interest. Continuous variables were presented as median and range. Proportions were exemplified by crude numbers and percentages. The Pearson χ^2 test or the Fisher's exact test, when appropriate, were used to estimate the associations between categorical variables.

Survival curves were estimated by the Kaplan–Meier product-limit and the logrank test was used to assess differences between subgroups. Significance was defined at the $p \leq 0.05$ level. The impact of relevant clinical and pathological variables on the ORR and

survival was tested in multivariate logistic models and Cox regressions. Multivariate logistic regression models and multivariate Cox proportional hazard models were developed using stepwise regression (forward selection). Variables testing significant at the univariate analysis were entered into the model, enter limit and remove limit were $p = 0.10$ and 0.15, respectively. The variables considered in univariate analysis included: age, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), stage at first diagnosis, line of treatment, histology, menopausal status, type and number of metastatic sites, treatment free interval, previous treatment with the inhibitor of mTOR everolimus, and fulvestrant pretreatment and dose reduction. The SPSS software (SPSS version 21.0, SPSS Inc., Chicago, IL) was used for all statistical evaluations.

4 | RESULTS

From September 2017 to June 2018, 423 advanced or metastatic HER2−, HR+ breast cancer patients were retrospectively identified and enrolled at 35 Italian cancer centers. Main patient and tumor characteristics are listed in Table 1. Median age was 60 years, with 10.4% of our patients being 75 years and older. The majority of our patients (337, 79.7%) were postmenopausal, whereas 86 (20.3%) were premenopausal, and received a LHRH analogue in combination with ET and palbociclib. Median ECOG PS was 0. Three hundred and one patients had ER-positive tumors, 279 patients had progesteron receptor (PgR)-positive tumors, and 274 patients had tumor expressing both ER and PgR, evaluated in breast tissue samples from primary tumors. In 182 patients, a biopsy of an amenable metastatic lesion was performed to confirm the HER2−/HR+ tumor status. The majority of our patients had visceral metastases (56.7%); bone-exclusive disease was recorded in 18.9% of these patients, and 24.4% had multiple metastatic sites. One hundred and two patients (24.1%) were metastatic at diagnosis.

4.1 | Treatment received

Among the 423 patients recruited, 158 (37.3%) received palbociclib-based therapy as first-line treatment of advanced disease and 265 (62.7%) as second and later lines (ranging from 1–11), including chemotherapy. Two hundred and seventy-five (65%) patients had received prior adjuvant ET. Among them, 47.3% of patients had been treated with tamoxifen, 39.4% with an aromatase inhibitor, and 11.4% with tamoxifen for 2–3 years followed by an aromatase inhibitor for 2 to 3 years. Six patients had received unspecified adjuvant ET. One hundred and forty-nine patients (35.2%) had recurred while on or within 12 months from the end of adjuvant ET. One hundred and eighty-eight (44.4%) patients had received previous adjuvant chemotherapy followed by ET. Among the 265 patients treated with palbociclib for second and later lines, 224 patients had received at least one previous ET for advanced disease, whereas 41 patients had received only prior chemotherapy for metastatic disease, without ET. The majority of our patients had received an aromatase inhibitor, while 71 (26.8%) patients had received fulvestrant and 84 (31.7%) an everolimus-based treatment before palbociclib.

4.2 | Efficacy

All the patients included in this analysis were evaluable for efficacy (Table 2). We observed 19 (4.5%) complete response (CR) and 112 (26.5%) partial response (PR), for an ORR of 31% (95% confidence interval [CI], 26.6–35.4). Stable disease (SD) was reported in 175 (41.4%) patients. A clinical benefit (CB), that is an objective response or SD lasting for at least 6 months, was observed in 52.7% of the patients (95% CI, 48–57.5). As concerns the line of treatment, when palbociclib-based treatment was administered as first line, we observed an ORR of 50.6% (95% CI, 42.8–58.4), and a CB of 70.2% (95% CI, 63.1–77.4). Among patients treated as first line, those recurred while on or within 12 months from the end of the adjuvant ET had an ORR of 35.9% (95% CI, 24.2–47.7) and a CB of 63% (95% CI, 50.1–75.8). In the 102 patients with metastatic disease at diagnosis, the ORR was 32.4% (95% CI, 23.3–41.4) and the CB was 55.9% (95% CI, 46.2–65.5). In patients treated with palbociclib as second line of treatment, we observed 4 (3.8%) CR and 20 (18.9%) PR, for an ORR of 22.7% (95% CI, 14.7–30.6). When palbociclib-based therapy was given as third or further treatment line, no CR was recorded and 27 (17%) patients reached a PR, for an ORR of 17% (95% CI, 11.1–22.8). Among the 71 patients pretreated with fulvestrant, we observed 5 (7.1%) CR and 16 (22.5%) PR, for an ORR of 29.6% (95% CI, 19–40.2). A CB was reported in 35 (49.3%) patients and progressive disease was observed in 26 (36.6%) patients. Among the 84 patients pretreated with everolimus/exemestane, we reported 1 (1.2%) CR and 13 (15.5%) PR, for an ORR of 16.7% (95% CI, 8.7–24.6). A CB was observed in 35 (41.7%) patients and progressive disease in 40 (47.6%) patients.

In our patient population, a statistically significant difference was observed in terms of ORR in patients pretreated with everolimus/exemestane versus patients who did not receive this latter treatment (16.7% vs. 34.5%, respectively, $p = 0.002$). Conversely, no statistically significant difference in ORR was observed according to previous fulvestrant (31.7% vs. 29.6%, $p = 0.72$). Both the ORR and the CB rate were higher in patients who did not have visceral metastases ($p = 0.0004$ and 0.04, respectively, data available upon request). Treatment efficacy was not influenced by menopausal status, since ORR and CB were similar between premenopausal and postmenopausal patients ($p = 0.10$ and 0.1, respectively).

In multivariate analysis including the overall population (Table 3), the only factor significantly related to ORR benefit was the administration of palbociclib-based treatment as early line-treatment ($p < 0.0001$). In the overall patient population, at a median follow-up of 6 months (95% CI, 2–28), median PFS was 12 months (95% CI, 8–16) and median overall survival (OS) was 24 months (95% CI, 17–30; Figure 1). Preliminary data regarding 1-year PFS and 1-year OS, estimated with Kaplan–Meier analysis, are shown in Table 4. Patients treated with palbociclib in early lines, without visceral

TABLE 1 Main baseline characteristics of the study population ($N = 423$)

Characteristics	Patients, N (%)
Age	
Median (range)	60 (31–84)
Menopausal Status	
Post	337 (79.7)
Pre	86 (20.3)
Histology	
Ductal	334 (79.0)
Lobular	68 (16.1)
Other	21 (5.0)
Metastatic at diagnosis	
Yes	102 (24.1)
No	321 (75.9)
Disease-free interval (months)	
0	102 (24.1)
≤12	149 (35.2)
>12	110 (26.0)
Unknown	62 (14.7)
ECOG Performance Status[a]	
0	353 (83.5)
1	53 (12.5)
2	17 (4.0)
Neoadjuvant chemotherapy	
Yes	55 (13.0)
No	368 (87.0)
Adjuvant chemotherapy	
Yes	188 (44.4)
No	235 (55.6)
Adjuvant hormonal therapy	
None (metastatic disease at diagnosis)	102 (24.1)
None (other reasons)	46 (10.9)
Yes	275 (65)
Type of adjuvant hormonal therapy[b]	
Tamoxifen	130 (47.3)
Letrozole	51 (18.5)
Anastrozole	45 (16.4)
Exemestane	12 (4.4)
Tam → AIs	31 (11.3)
Unknown	6 (2.2)
Adjuvant radiotherapy	
Yes	207 (48.9)
No	216 (51.1)
Metastatic sites at palbociclib starting	
Visceral	240 (56.7)
Bone-only	80 (18.9)
Other	103 (24.4)
Number of metastatic sites	
1	150 (35.4)
2	148 (35.0)
≥3	125 (29.6)
Previous treatment of MBC	
Yes	265 (62.6)
No	158 (37.4)
Previous chemotherapy for MBC	
None	258 (61.0)
1 line	80 (18.9)
2 lines	34 (8.0)
≥3 lines	51 (12.1)
Previous hormonal therapy for MBC	
None	197 (46.6)
1 line	131 (31.0)
2 lines	56 (13.2)
>3 lines	39 (9.2)

Note. AIs: aromatase inhibitors; MBC: metastatic breast cancer; Tam: tamoxifen.

[a]Performance status at palbociclib starting.

[b]Only for patients who underwent adjuvant endocrine therapy.

metastases and naïve to everolimus-based treatment seemed to have more favorable long-term outcomes.

In multivariate analysis, PFS was positively affected by lower ECOG PS ($p = 0.001$), no everolimus/exemestane pretreatment ($p = 0.10$), absence of visceral metastases ($p = 0.01$), and early treatment line ($p < 0.0001$), as described in Table 3. In our patient population, palbociclib dose reductions did not influence PFS and OS ($p = 0.49$ and 0.63, respectively).

4.3 | Toxicity

Data on toxicity are reported in Table 5. The main toxicity observed was hematological, with neutropenia of any Grade observed in 314 patients (74.2%), being of Grade 3–4 in 183 patients (43.2%). Neutropenic fever was extremely rare (3.5%). No new safety issues emerged by our analysis. Palbociclib dose reduction was performed in 85 patients (20%). Only one patient discontinued palbociclib treatment due to toxicity (persistent Grade 3–4 neutropenia). Extra-hematological toxicity was manageable with mild nausea and vomiting in 12.8% of these patients and mild to moderate fatigue observed in about half of our patients. No significant differences in toxicity were observed depending on palbociclib treatment line. In addition, no significant differences emerged when comparing toxicities across

TABLE 2 Best responses to palbociclib according to endocrine and/or chemotherapy treatment line ($N = 423$)

	Best response, N (%)			
	Overall	First line	Second line	Third line and beyond
Complete response	19 (4.5)	15 (9.5)	4 (3.8)	0 (0)
Partial response	112 (26.5)	65 (41.1)	20 (18.9)	27 (17.0)
Stable disease	175 (41.4)	51 (32.3)	61 (57.5)	63 (39.6)
Progressive disease	117 (27.6)	27 (17.1)	21 (19.8)	69 (43.4)
Total	423 (100)	158 (100)	106 (100)	159 (100)
Overall response rate	131 (31)	80 (50.6)	24 (22.7)	27 (17.0)
Clinical benefit rate	223 (52.7)	111 (70.2)	48 (45.3)	64 (40.3)

TABLE 3 Multivariate analysis (*N* = 423)

ORR	OR	95% CI	*p*
Treatment line	–	–	<0.0001
1st vs. 2nd	3.50	2.02–6.08	<0.0001
1st vs. >2nd	5.04	2.99–8.42	<0.0001
2nd vs. >2nd	1.43	0.77–2.65	0.25
PFS	HR	95% CI	*p*
ECOG PS			
2 vs. 0–1	2.71	1.47–4.97	0.001
Everolimus pretreatment			
Yes vs. no	1.42	0.94–2.16	0.001
Visceral involvement			
Yes vs. no	1.66	1.13–2.44	0.01
Treatment line	–	–	<0.0001
2nd vs. 1st	1.01	0.59–1.74	0.97
>2nd vs. 1st	2.33	1.43–3.80	0.001
>2nd vs. 2nd	2.31	1.39–3.82	0.001

Note. CI, confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; OR: odd ratio; ORR: overall response rate; PFS: progression-free survival .

categories defined upon age, that is, <75 and ≥75 years (75.7% vs. 68.2%, respectively; $p = 0.28$; data available upon request).

5 | DISCUSSION

Palbociclib is a highly selective inhibitor of CDK4/6, indicated for the treatment of patients with HER2−/HR+, advanced or metastatic breast cancer, in combination with an aromatase inhibitor, as initial ET, and with fulvestrant (plus LHRH analogue in premenopausal women) in patients previously treated with ET. In RCTs, palbociclib in combination with letrozole as first-line treatment in postmenopausal women (Finn et al., 2015, 2016) or in combination with fulvestrant in premenopausal, perimenopausal, or postmenopausal patients with progression after ET (Cristofanilli et al., 2016; Slamon et al., 2018; Sledge et al., 2017), significantly prolonged PFS and improved ORR. The benefit was significant in all prespecified subgroups. Further follow-up is needed to confirm the advantage in OS. Neutropenia was the most commonly reported any Grade and Grade 3 adverse event, with very low incidence of febrile neutropenia (<2%). Hematologic toxicity is usually manageable, through dose delays, transient interruption, or dose reduction. However, these very encouraging data deriving from randomized trials need to be confirmed in real-world setting, in less-selected, and frail or more heavily pretreated patients.

The present retrospective observational study recruited 423 eligible female premenopausal and postmenopausal patients from 35 Italian oncologic centers and, to our knowledge, this is the largest case-series reported in the literature thus far. Overall, our study results are satisfactory, both in terms of efficacy and in terms of tolerability, and seem in line with those of the registrative trials (Cristofanilli et al., 2016; Finn et al., 2015, 2016; Harbeck et al., 2016; Verma et al., 2016) and other retrospective experiences. The results from the expanded access of palbociclib/letrozole in 126 USA patients showed encouraging data, with higher CB in first-line ET (52.9%) than in subsequent lines (30.3%), and a median PFS of 8.6 and 4.4 months in first line and endocrine pretreated patients, respectively. Moreover, the 24-month OS rate was 61.8% in patients with no prior exposure to ET, being 39.8% in endocrine pretreated patients, and 63.1% in chemotherapy naïve, versus 31.8% in chemotherapy pretreated patients. The median OS was 19.8 months in endocrine pretreated patients and 14.9 months in patients having undergone prior chemotherapy. These results highlight the potential benefit of palbociclib-based combinations even in later lines of therapy (Brufsky et al., 2018).

A small trial from a single USA cancer center reports 26.5% of ORR in 22 patients treated with palbociclib and ET, with a median treatment duration of 5 months, an estimated PFS at 18 months of 50%, and G3/4 neutropenia in 45% of the patients, with half of the patients requiring dose reductions (Malik et al., 2017). In a recent

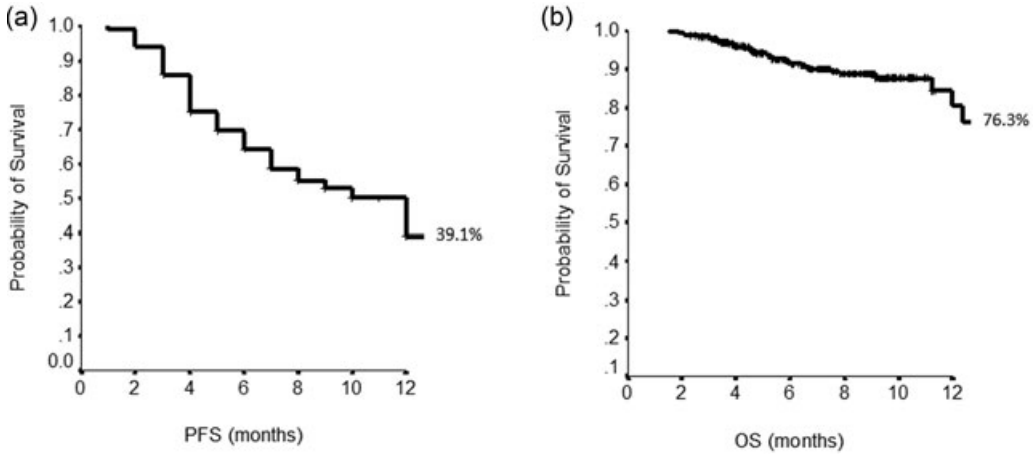

FIGURE 1 PFS (a) and OS (b) in the overall population. OS: overall survival; PFS: progression-free survival

TABLE 4 One-year progression-free survival and 1-year overall survival according to patient characteristics (*N* = 423)

Characteristics	N	1-year PFS	*p*	1-year OS	*p*
Overall	423	39.1	–	76.3	–
Line of treatment					
First line	158	69.9		96.0	
Second line	106	62.5		95.6	
Later lines	159	17.4	<0.0001	62.9	<0.0001
Histology					
Ductal	334	38.2		77.2	
Lobular	68	47.1		81.7	
Other	21	52.8	0.79	84.4	0.45
Stage at first diagnosis					
Early	321	36.1		75.1	
Advanced	102	52.8	0.16	87.8	0.81
Menopausal status					
Yes	337	38.0		77.5	
No	86	57.0	0.72	78.0	0.50
Age					
≥75	44	37.1		78.0	
<75	379	45.2	0.15	83.8	0.05
Visceral involvement					
Yes	240	29.5		69.8	
No	183	59.0	0.001	91.8	0.06
Bone-only metastases					
Yes	80	52.5		90.5	
No	343	35.2	0.35	74.9	0.30
Treatment free interval[a]					
>12 months	33	36.7		83.5	
≤12 months	69	43.3	0.39	85.2	0.95
Everolimus pretreatment					
Yes	84	13.6		64.0	
No	339	51.5	<0.0001	84.8	0.02
Fulvestrant pretreatment					
Yes	71	51.0		73.8	
No	352	42.5	0.44	75.9	0.45

[a]From adjuvant endocrine treatment. Only for patients who received palbociclib as first line of treatment.

retrospective study, data from a US database of 763 patients treated with palbociclib and ET were analyzed. Six hundred and twelve of them received palbociclib in combination with letrozole. Mean follow-up was 6.4 months, and mean age 64 years. Dose reductions were reported in 20.1% of the patients, and 39.5%, 15.7%, or 13.1% of the patients were treated as first, second, or later lines, respectively. Overall 74.6% of the patients had a neutropenic event, of Grade 3–4 in 47.3% and 8.0% of these patients, respectively. No data on efficacy were reported (Kish et al., 2018). Data from a prospectively implemented database of 54 Chinese patients treated with a palbociclib in combination with aromatase inhibitor or fulvestrant in the real-world setting showed a disease control rate of 70% in 37 evaluable patients, 54% of response in patients with visceral site involvement, and a safety profile not dissimilar from that of the pivotal trials (Chiu et al., 2017). Another retrospective analysis in 24 heavily pretreated patients, treated with palbociclib and an aromatase inhibitor, showed a SD in 58.3% of patients, a median PFS of 4.8 months, and a median OS of 11 months. Treatment was well tolerated (Ban, Miše, Majić, Dražić, & Vrdoljak, 2018). The compassionate use program in Belgium recruited 82 postmenopausal patients who received palbociclib and ET after at least 4 lines of systemic treatment. The median PFS was 3.17 months, with 34 patients not progressing within 6 months, resulting in an overall CB of 41.5%. The safety profile was favorable (Hoste et al., 2018).

Evidence from registrative trials confirms that palbociclib had similar had efficacy in nearly all prespecified subgroups (Finn, Crown, Ettl et al., 2016; Turner et al., 2018). Conversely, in our patient population, both ORR and CB rate were significantly higher in patients without visceral metastases. The results observed in visceral disease seem to translate into significant differences in long-term outcomes, since 1-year PFS is more favorable in patients without visceral involvement compared with patients with metastatic spread to viscera. However, caution is needed when interpreting results from subgroup analyses, given the restricted size and heterogeneity of the subsets compared in terms of disease and patients' characteristics.

As expected, the best outcome, both for 1-year PFS and 1-year OS, was observed when palbociclib was administered as first- and second-line, and no differences were observed according to menopausal status. An intriguing aspect of our study concerns the possibility of evaluating in real-life the efficacy of palbociclib in

TABLE 5 Main toxicities in the study population ($N = 423$)

Toxicity	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Hematologic				
Leukopenia	0.5	0.7	0.7	–
Neutropenia[a]	10.4	20.6	37.1	6.1
Thrombocytopenia	14.7	4.5	2.8	–
Anemia	21.3	5.2	2.4	–
Nonhematologic				
Nausea/vomiting	12.8	1.4	–	–
Mucositis	6.4	0.5	0.2	–
Diarrhea	4.0	0.7	0.2	–
Constipation	3.5	0.2	0.2	–
Abdominal pain	4.5	0.7	–	–
Fatigue	27.2	14.2	2.1	–
Hypertransaminasemia	7.8	1.9	0.2	–
Anorexia	2.4	0.2	–	–
Alopecia	1.4	0.2	–	–
Headache	0.7	–	–	–
Cutaneous toxicity	2.1	0.5	–	–
Arthralgia	0.9	0.5	–	–
QT prolongation	0.5	–	–	–

[a]Febrile neutropenia in 15 patients (3.5%).

patients pretreated with fulvestrant or everolimus. In more detail, pretreatment with everolimus seems to negatively impact the efficacy of palbociclib, in terms of both ORR and long-term outcomes, whereas pretreatment with fulvestrant does not seem to negatively affect the activity of palbociclib-based treatment. Inherent data are scarcely available from randomized control trials in this setting, while some evidence has emerged from studies carried out in the real-world setting. Two hundred and six patients were treated with palbociclib and fulvestrant and/or everolimus in a French compassionate program. Almost a half of them received more than 6 lines, 48% of these patients had previously been treated with fulvestrant and 67.8% with everolimus in combination with ET. The median PFS of patients treated with fulvestrant and palbociclib was 5.46 months, with no significant differences between patients pretreated with fulvestrant or everolimus in univariate analysis (Arnedos et al., 2017). Within a compassionate use program, another single-centre retrospective analysis of 34 heavily pretreated patients showed a disease control rate of 52.9% at Week 12 and 24.4 at Week 24, and a PFS of 3.1 months, with no significant difference between everolimus-pretreated (3.5 months) and everolimus-naïve patients (2.7 months; Maurer et al., 2018). Conversely, another small experience concerning 23 everolimus-pretreated patients showed a median PFS of 2.9 months, without objective responses and a CBR of 17.4%, suggesting limited efficacy of palbociclib after progression with everolimus (Dhakal et al., 2018). This is consistent with our results from the present study. In another study, among 60 everolimus-pretreated patients, with 28 of them having received also fulvestrant and a median of 5 previous line of treatment, the median PFS was 5.8 months, and patients pretreated with fulvestrant had similar PFS, that is 6.4 months (Du Rusquec et al., 2018). Overall, these findings have to be confirmed by prospective, adequately sized clinical trials. Preclinical studies are also needed to specifically address the mechanisms leading to treatment failure in patients treated with ET plus CDK4/6 inhibitors following everolimus treatment. Results from these latter studies will help physicians determine the most appropriate sequence of hormonal therapies at an individual patient level.

In our study, the efficacy of palbociclib treatment was not affected by dose reductions, most frequently due to neutropenia. Our results are fully consistent with those from a retrospective report from the MD Anderson Cancer Center, which investigated the impact of dose delays and reductions on PFS in 334 patients receiving palbociclib in real-life setting (Clifton et al., 2017). In terms of safety, no new issues emerged in our patient population and no cumulative toxicity was reported. In addition, notwithstanding the quite restricted number of patients aged at least 75 years ($N = 44$), the present study supports the use of palbociclib in elderly patients, with no significant increase in toxicity observed by increasing age (75.7% vs. 68.2%, respectively; $p = 0.28$; data available upon request).

Our study has some limitations. Although our results are consistent with those from the registrative trials and prior studies carried out in the real word setting, our follow-up is still particularly short and further data evaluation is needed following longer observation. The observational retrospective design deserves to be mentioned in light of the tendency towards confounding and biases which characterizes this type of studies and which invites caution in results' interpretation. In addition, as previously mentioned, data have come from 35 Italian cancer centers. The participation of such a remarkable number of cancer centers has provided our study with its greatest strength, that is, a sample size of 423 patients. At the same time, the lack of standardized operative procedures (SOPs) shared by each of the participating institutions diminishes somewhat our confidence in the chance of completely excluding heterogeneity in the biological and clinical assessment. However, at the single-centre level, SOPs are in place and quality controls are regularly performed relatively to the diagnostic workout. In addition, patients' therapeutic management and follow-up is in key with the good clinical practice.

The strength of the present analysis is that it represents, to our knowledge, the largest cohort of palbociclib-based treatment in real-life setting, providing a considerable amount of data in support of the efficacy and tolerability of an innovative treatment in aBC outside of clinical trials. In these respects, the topic we addressed is of actual interest to a clinical research agenda. Our data also provide evidence concerning prior treatment with fulvestrant and/or everolimus, confirming no detrimental effect of fulvestrant pretreatment on palbociclib-based treatment outcome, whereas our results seem to suggest a less favorable outcome in everolimus-pretreated patients.

In conclusions, the development of CDK4/6 inhibitors and the introduction of palbociclib, the first agent of this class, into clinical practice certainly represent an important addition to the therapeutic armamentarium in HER2−, HR+ metastatic breast cancer. However, several open questions remain concerning the role of CDK4/6 inhibitors in daily practice, such as the increased costs, the optimal place and sequence, the treatment beyond progression, and the identification of predictive markers. Data from the real word setting may have a confirmative role concerning the evidence on the efficacy of the treatment of interest in unselected patients' populations. At the same time, such data, notwithstanding the previously discussed limitations, may help reveal still unexplored traits of specific patients' subsets, for example, patients previously exposed to everolimus-based treatment, whose characteristics may have not clearly emerged from prior RCTs and whose needs may remain unmet unless studies like ours take an appropriate place in the available literature.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

P. V., A. G., C. N., and T. G.: study conception and critical revision of the manuscript for important contents. T. G., L. P., M. M., M. B., I. S., and P. V.: manuscript drafting, study conduct, and data collection and analysis planning; A. M., M. M. S., G. S., P. M., S. T., R. D. M., and G. C. critically revised the manuscript for important intellectual content; I.S.: statistical analysis; C. D. A., E. L., L. D., L. I., L. M., A. F., I. P., V. L., S. V., A. C., F. A., A. O., L. M., D. S., G. S., G. T., D. S., V. S., E. V., A. V., L. F., M. D. T., N. T., A. G., F. G., A. B., N. L. V., C. Z., D. R., E. C., V. M., G. P., S. S., E. C., R. K., A. F. S., D. C., M. E. C., L. L., S. F., M. M., L. C., P. S., S. B., R. S., M. R., I. P., A. R., C. F., K. C., S. C., M. P., and R. B. data collection, database set up and implementation, and contribution to data analysis. All authors read and approved the final version of this manuscript and are responsible for all the aspects of the work.

ORCID

Antonio Russo http://orcid.org/0000-0002-4370-2008
Patrizia Vici http://orcid.org/0000-0001-7528-9783

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