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Systemic treatment in advanced phyllodes tumor of the breast: a multi-institutional European retrospective case-series analyses

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Abstract

Background We aimed at investigating outcome of systemic treatments in advanced breast PT.

Methods All cases of advanced breast PT treated with systemic treatments from 1999 to 2019, in one of the referral sarcoma centers involved in the study, were retrospectively reviewed.

Results 56 female patients were identified. Median age was 52 (range of 25–76) years. Patients received a median number of 2 systemic treatments (range of 1–4). Best responses according to RECIST were 1 (3.7%) CR, 11 (40.7%) PR, 6 (22.2%) SD, 9 (33.3%) PD with anthracyclines plus ifosfamide (AI); 2 (16.7%) PR, 4 (33.3%) SD, 6 (50.0%) PD with anthracycline alone; 3 (18.8%) PR, 4 (25.0%) SD, 9 (56.3%) PD with high-dose ifosfamide given as a continuous infusion (HD-IFX); 3 (20.0%) SD, 12 (80.0%) PD with a gemcitabine-based regimen (with 2 patients not evaluable); 1 (8.3%) PR, 2 (16.7%) SD, 9 (75.0%) PD with trabectedin (with 1 patient not evaluable); 1 (16.7%) PR, 1 (16.7%) SD, 4 (66.7%) PD with tyrosine-kinase inhibitors (TKI). The median PFS were 5.7 (IQR 2.5–9.1) months with AI; 3.2 (IQR 2.2–5.0) months with anthracycline alone; 3.4 (IQR 1.4–6.7) months with HD-IFX; 2.1 (IQR 1.4–5.2) months with gemcitabine-based chemotherapy; 1.8 (IQR 0.7–6.6) months with trabectedin; 3.4 (IQR 3.1–3.8) months with TKI. With a median follow-up of 35.3 (IQR 17.6–66.9) months, OS from the start of first-line systemic treatment was 15.2 (IQR 7.6–39.6) months.

Conclusion In this series of advanced PT (to our knowledge, the largest reported so far), AI was associated with a high rate of responses, however, with a median PFS of 5.7 months. Other systemic treatments were poorly active.

Keywords Breast tumor · Phyllodes · Sarcoma · Chemotherapy · Advanced setting

Abbreviations

PT	Breast phyllodes tumor
HD-IFX	High-dose ifosfamide
TKI	Tyrosine-kinase inhibitors
CTCAE	Cancer Institute Common Toxicity Criteria
RECIST	Response Evaluation Criteria in Solid Tumors
ORR	Overall response rate
PFS	Progression-free survival
OS	Overall survival
AI	Anthracycline plus ifosfamide
CR	Complete response
PR	Partial response

SD	Stable disease
PD	Progressive disease

Background

Accounting for less than 1% of all breast neoplasms, phyllodes tumors of the breast are a rare group of biphasic fibroepithelial neoplasms with a double-layered epithelial component surrounded by a hypercellular stromal/mesenchymal component. According to WHO, they are classified into benign, borderline, or malignant on the basis of a combination of several pathological features, including the degree of stromal hyper-cellularity, mitosis, cytological atypia, stromal overgrowth, and nature of tumor borders/margins. Most phyllodes tumors are benign, while malignant lesions account for 10–20% of all cases [1].

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Overall, phyllodes tumors have a low risk of developing metastases (about 2%), reaching 20–25% if they are malignant [2–4]. The management of metastatic disease is poorly studied and it is generally based on the use of soft tissue sarcoma systemic treatments. However, given the rarity of this disease and its low metastatic potential, available data on systemic treatments are limited and our knowledge is based on small case reports or individual case reports [5–8].

The aim of this international, collaborative study, including several referral sarcoma centers in Europe, was to report on activity and efficacy of systemic treatments in adult patients with advanced PT.

Materials and methods

All patients with locally advanced/metastatic PT of breast treated with systemic treatment, over the period from 1999 to 2019, in one of the centers involved in the study, were included in this analysis. Patients treated within the context of the Italian Rare Cancer Network were also considered. Patients treated in adjuvant/neoadjuvant setting were excluded.

Data were extracted from clinical databases. The following data were collected: date of birth, gender, date of diagnosis, treatments received for local disease, treatments received for advanced disease, survival. For each systemic treatment received for advanced disease date of start, toxicity related to treatment, radiological response, and time to progression were reported. Details on pathological characteristics of tumor at diagnosis were also recorded.

Toxicity was recorded using National Cancer Institute Common Toxicity Criteria (CTCAE v5.0) [9]. Since the analysis was focused on activity and efficacy of systemic treatments, only grade 3 or 4 adverse events were sought.

Radiological response was locally assessed according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) [10].

Descriptive statistics and frequency tabulation were used to summarize patient and tumor characteristics. Overall response rate (ORR) was computed as the frequency of patients with complete or partial tumor response among the patients evaluable for response. The corresponding confidence intervals are two-sided 95% exact intervals, calculated by use of the binomial formula.

Progression-free survival (PFS) and overall survival (OS) were estimated with Kaplan–Meier method [11]. For PFS, the event time was computed from the date of treatment start to the date of progression or death or last follow-up. Patients undergoing surgical treatment after systemic treatment were censored at the time of progressive disease after surgical resection or at the last follow-up. For OS, the event time was computed from the date of treatment start to the date of

death due to any cause or last follow-up. Event-free patients were censored at the date of last patient contact. Statistical analyses were carried out with SAS (version 9.4, SAS Institute, Cary, NC, USA) and R software (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria).

Approval by the institutional review board of each institution was obtained. Written informed consent was obtained as required by local regulation.

Results

Fifty-six patients with advanced PT treated with systemic treatments over the study period were identified, 2 (4%) with locally advanced disease and 54 (96%) with metastatic disease at the start of the first systemic treatment. All patients were female. Median age at time of the first systemic treatment was 52 years (interquartile range, IQR 42–57 years). Initial diagnosis was malignant PT in 50 (89.3%) patients and border-line PT in 5 (8.9%) patients (1 missing data). Patients and tumor characteristics are detailed in Table 1.

A median number of systemic treatment lines of 2 was administered. A total number of one, two, three, or more than three lines were administered in 21 (37.5%), 20 (35.7%), 10 (17.9%), and 5 (8.9%) patients, respectively. The most used systemic treatment regimens were as follows: anthracycline plus ifosfamide (27 patients, 48.2%), anthracycline as single agent (12 patients, 21.4%), high-dose ifosfamide given as a continuous infusion for 14 days (16 patients, 28.6%), gemcitabine-based regimens (17 patients, 30.4%), trabectedin (13 patients, 23.2%), and tyrosine-kinase inhibitors (6 patients, 10.7%). The sequence of systemic treatments received by each patient is listed in Table 2. Details on activity, efficacy, and toxicity

Table 1 Patients and tumor characteristics

	Number	%
Number of patients	56	100
Age		
Median, year	52	
IQ range, year	42–57	
Sex		
Female	56	100
Diagnosis		
Malignant PT	50	89.3
Borderline PT	5	8.9
Missing	1	1.8
Extension at systemic treatment start		
Locally advanced	2	3.6
Metastatic	54	96.4

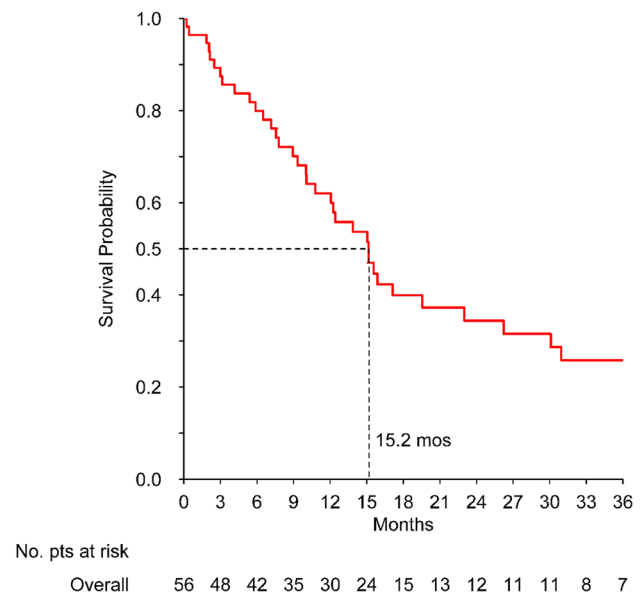
Table 2 Sequences of systemic treatments received by each patient

	Number	%
A	4	7.1
A + HDIFX	2	3.6
A + G	1	1.8
A + O	3	5.4
AI	10	17.9
AI + HDIFX	3	5.4
AI + HDIFX + G	1	1.8
AI + HDIFX + G + TKI	1	1.8
AI + HDIFX + TKI	2	3.6
AI + HDIFX + TKI + G	1	1.8
AI + G	1	1.8
AI + G + HDIFX	1	1.8
AI + G + HDIFX + A	1	1.8
AI + G + O + T	1	1.8
AI + TKI	1	1.8
AI + O	2	3.6
AI + O + G + O	1	1.8
AI + T + TKI	1	1.8
HDIFX + A	1	1.8
HDIFX + G	1	1.8
G	1	1.8
G + HDIFX	1	1.8
G + T	1	1.8
G + T + HDIFX	1	1.8
G + T + TKI	1	1.8
O	4	7.1
O + TKI + G	1	1.8
O + TKI + O	1	1.8
O + O	1	1.8
O + TKI	1	1.8
O + TKI + O	1	1.8
T	2	3.6
T + G	1	1.8
Overall	56	100

AI anthracycline plus ifosfamide, A anthracycline as single agent, HDIFX high-dose ifosfamide, G gemcitabine-based regimen, T trabectedin, TKI tyrosine-kinase inhibitors, O other treatments

of each of these systemic treatments are described hereafter. After systemic treatment, seventeen patients (30.4%) received also surgery for metastatic disease.

The median OS from the start of the first systemic treatment was 15.2 months (IQR 7.6–39.6 months). At the time of the analyses, with a median follow-up of 35.3 months (IQR 17.6–66.9 months) from the start of the first systemic treatment, 38 patients had died. 18 patients were alive: 12 with disease and 6 with no evidence of disease, after one line of systemic treatment and a subsequent surgery. Figure 1 shows the OS curve of all patients included in the analyses.

Entire series (56 unique patients): Overall Survival, global**Fig. 1** OS curve of the entire population in the study

Anthracycline plus ifosfamide

Twenty-seven patients received anthracycline plus ifosfamide (AI), all as first-line systemic treatment. Epirubicin plus ifosfamide was used in 19 (70.4%) patients, doxorubicin plus ifosfamide in 7 (25.9%) patients, and liposomal doxorubicin plus ifosfamide in 1 (3.7%) patient. Out of 19 patients evaluable for toxicity, grade 3–4 toxicity events were observed in 14 (73.7%) patients. Grade 3–4 toxicities events included anemia, neutropenia, thrombocytopenia, febrile neutropenia, and mucositis.

All 27 patients were evaluable for response. Best response according to RECIST was complete response (CR) in 1 (3.7%) patient, partial response (PR) in 11 (40.7%) patients, stable disease (SD) in 6 (22.2%) patients, and progressive disease (PD) in 9 (33.3%) patients. The ORR was 44.4% (95% CI 25.5–64.7%).

The median PFS was 5.7 months (IQR 2.5–9.1 months). Among the 18 patients who obtained CR, PR, or SD, 7 (38.9%) patients and 5 patients (27.8%) were free from progression after 9 months and one year, respectively, from the start of AI. Figure 2a shows the PFS curve of patients who received AI.

Anthracycline as single agent

Twelve patients received anthracycline as single agent: as first-line systemic treatment in 10 (83.3%) cases, as second-line in 1 (8.3%) case, and as further-line in 1 (8.3%) additional case. Doxorubicin was used in 11 (91.7%) patients and

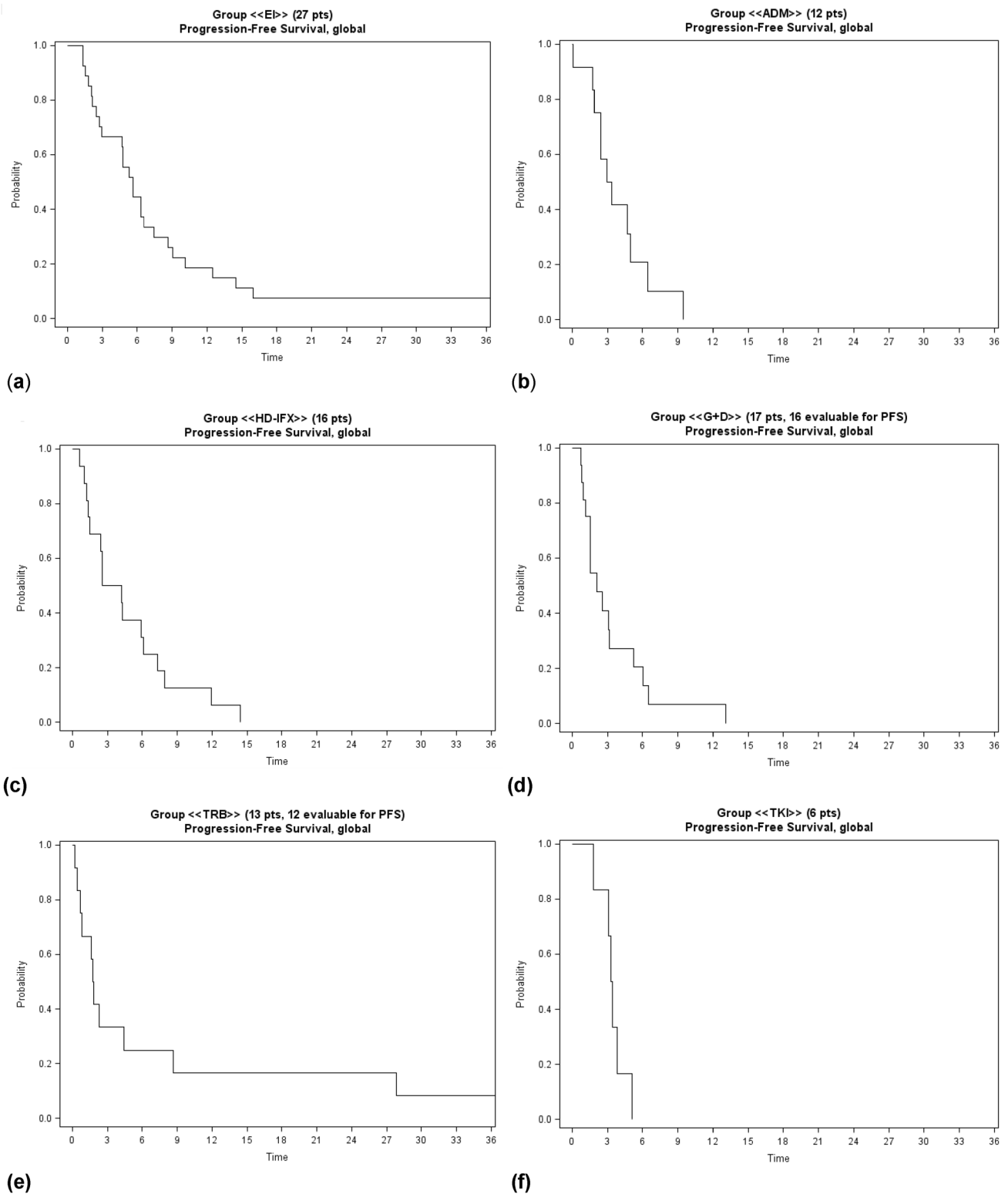


Fig. 2. **a** PFS curve of pts treated with AI; **b** PFS curve of patients treated with anthracycline; **c** PFS curve of pts treated with HD-IFX; **d** PFS curve of pts treated with gemcitabine-based regimen; **e** PFS curve of pts treated with trabectedin; **f** PFS curve of pts treated with TKI

epirubicin in 1 (8.3%) patient. Out of 10 patients evaluable for toxicity, grade 3–4 toxicity events were observed in 4 (40%) patients. Grade 3–4 toxicities events included anemia, neutropenia, febrile neutropenia, and thrombosis.

All 12 patients were evaluable for response. Best response according to RECIST was PR in 2 (16.7%) patients, SD in 4 (33.3%) patients, and PD in 6 (50.0%) patients. The ORR was 16.7% (95% CI 2.1–48.4%).

The median PFS was 3.2 months (IQR 2.2–5.0 months). Among the 6 patients who obtained PR or SD, 2 (33.3%) patients were free from progression after 6 months from the start of anthracycline monotherapy. Figure 2b shows the PFS curve of patients who received anthracycline as single agent.

High-dose ifosfamide

Sixteen patients received high-dose ifosfamide (HD-IFX) given as a continuous infusion for 14 days, as first-line systemic treatment in 2 (12.5%) cases, as second-line in 11 (68.8%) cases, as third-line in 3 (18.8%) cases. Ten patients had been previously treated with AI. Out of 13 patients evaluable for toxicity, grade 3–4 toxicity events were observed in 3 patients (23.1%). Grade 3–4 toxicities events included anemia, vomiting, and asthenia.

All patients were evaluable for response. Best response according to RECIST was PR in 3 (18.8%) patients, SD in 4 (25.0%) patients, and PD in 9 (56.3%) patients. The ORR was 18.8% (95% CI 4.1–45.7%). Among the 3 patients obtaining PR as best response, 2 patients had already received AI, with PD and PR, respectively.

The median PFS was 3.4 months (IQR 1.4–6.7 months). Among the 7 patients who obtained PR or SD, 2 (28%) patients were free from progression after one year from the start of HD-IFX. Figure 2c shows the PFS curve of patients who received HD-IFX.

Gemcitabine-based regimens

Seventeen patients received a gemcitabine-based regimen, as first-line systemic treatment in 5 (29.4%) cases, as second-line in 7 (41.2%) cases, as third-line in 4 (23.5%) cases, and as further-line in 1 (5.9%) case. Gemcitabine plus docetaxel was used in 8 (47.1%) patients, gemcitabine plus dacarbazine in 2 (11.8%) patients, and gemcitabine as single agent in 7 (41.2%) patients. Out of 14 patients evaluable for toxicity, grade 3–4 toxicity events were observed in 6 patients (42.9%). Grade 3–4 toxicities events included anemia, neutropenia, thrombocytopenia, and asthenia.

Fifteen patients were evaluable for response. Best response according to RECIST was SD in 3 patients (20.0%) and PD in 12 patients (80.0%). No objective responses were observed.

The median PFS was 2.1 months (IQR 1.4–5.2 months). In the group of 3 patients who obtained SD, one (33.3%) patient was free from progression after one year from the start of gemcitabine-based regimen. Figure 2d shows the PFS curve of patients who received a gemcitabine-based regimen.

Trabectedin

Thirteen patients received trabectedin, as first-line systemic treatment in 3 (23.1%) cases, as second-line in 6 (46.2%) cases, as third-line in 3 (23.1%) cases, and as further-line in one (7.7%) patient. Out of 12 patients evaluable for toxicity, grade 3–4 toxicity events were observed in 1 patient (8.3%). Grade 3–4 toxicities events were restricted to liver toxicity.

Twelve patients were evaluable for response. Best response according to RECIST was PR in 1 (8.3%) patient, SD in 2 (16.7%) patients, and PD in 9 patients (75.0%). The ORR was 8.3% (95% CI 0.2–38.5%).

The median PFS was 1.8 months (IQR 0.7–6.6 months). In the group of 3 patients who obtained PR or SD, 2 (66.7%) patients were free of progression after one year from the start of trabectedin. Figure 2e shows the PFS curve of patients who received trabectedin.

Tyrosine-kinase inhibitors

Six patients received tyrosine-kinase inhibitors (TKI), as second-line systemic treatment in 3 (50.0%) cases, as third-line in 2 (33.3%) cases, as further-line in 1 (16.7%) case. Pazopanib was used in 5 (83.3%) patients and regorafenib in 1 (16.7%) patient. All 6 patients were evaluable for toxicity; grade 3–4 toxicity events were observed in 2 (33.3%) patients. Grade 3–4 toxicities events included diarrhea and dental abscess.

Six patients were evaluable for response. Best response according to RECIST was PR in 1 (16.7%) patient (receiving regorafenib), SD in 1 (16.7%) patient, and PD in 4 (66.7%) patients. The ORR was 16.7% (95% CI 0.4–64.1%).

The median PFS was 3.4 months (IQR 3.1–3.8 months). All 2 patients who obtained PR or SD progressed before 6 months from the start of TKI. Figure 2f shows the PFS curve of patients who received TKI.

Discussion

In this international retrospective observational study involving 15 European cancer centers, 56 patients with advanced PT treated with systemic therapy were included. The combination of anthracyclines plus ifosfamide provided a tumor response in almost 45% of patients, with a median PFS of almost 6 months and a few patients being progression-free

at 2–3 years. This is consistent with what is seen with the same regimen in soft tissue sarcomas. A low response rate was seen to other systemic treatments.

With all the limitations of a retrospective analysis, this is the largest series on outcome of several systemic treatments in patients with advanced PT. Given the rarity of this disease and the relative low incidence of metastases, available data on systemic treatments in this disease are scarce. Mitus et al. in 2016 described the impact of systemic treatment in 30 metastatic PT patients over a 50-year time interval [6]. Subsequently, Neron et al. published the experience of several French centers within the French Sarcoma Group (FSG-GETO) in the management of metastatic PT patients, including 37 patients treated with systemic treatment over the period 2000–2016 [5]. More recently, Parkers et al. reported the experience of MD Anderson Cancer Center, with 31 metastatic PT patients receiving systemic treatment over the period 1993–2015 [8].

In this series, the combination of anthracycline plus ifosfamide was associated with a response rate (almost 45%) similar to what previously observed by other authors. Neron et al. reported a clinical benefit in 6 out of 13 patients (almost 50%) treated with this combination and Mitus et al. described 1 CR and 2 PR in 3 patients [5, 6]. In the MD Anderson Cancer Center series, anthracycline plus ifosfamide was associated with a response rate of 56% (10 out of 18 patients) [8]. With a response rate in this range, the activity of anthracycline plus ifosfamide in PT looks similar to the activity of this regimen in STS in general [12]. However, the median PFS was 6 months. In the group of patients who had obtained a response or a stabilization with this treatment, almost one third (5 out of 18 pts, 28%) was free from progression after one year from the start of the treatment. On the basis of these results, the use of this combination may be encouraged in advanced PT, especially in symptomatic patients and/or if an integration with surgery is foreseen.

Anthracycline as single agent provided a low response rate (17%) in this series, with a median PFS of 3 months. Previously published papers reported similar results [5, 6]. Neron et al. described a clinical benefit in 1 out of 11 patients treated with doxorubicin alone, while Mitus et al. observed a PR in 4 out of 6 patients treated with doxorubicin alone, but in all the 3 cases survival was shorter than 9 months [5, 6].

The response rate with other chemotherapy regimens included in the current analyses was low, being 19%, 0%, and 8%, with HD-IFX, with gemcitabine-based regimens and with trabectedin, respectively. Of interest, one PR with HD-IFX was seen in a patient who had previously progressed on conventional dose of ifosfamide, given in addition to epirubicin. The median PFS associated to these regimens was low (3.4, 2.1, 1.8 months with HD-IFX, with gemcitabine-based regimens, and with trabectedin, respectively), although

a small number of patients treated with these regimens obtained long-lasting responses/stabilizations. Mitus et al. reported a PR in 1 out of 4 patients treated with ifosfamide alone (25%, 6-month survival) and Neron et al. described a clinical benefit in 3 out of 6 patients (50%) who received an alkylating agent alone. Gemcitabine-based regimens were associated with a response rate of 33% (3 out of 9 patients) in the experience of MD Anderson Cancer Center, but PFS was shorter than 3 months [8]. Trabectedin was not included in previously published studies on PT, aside from one PT patient reported by Grignani et al. who received trabectedin plus olaparib achieving a PR, in the context of a phase I/II study investigating this association in STS [13]. The results of the current analysis showed a poor outcome with HD-IFX, gemcitabine-based regimens and trabectedin in this disease. However, a possible role of HD-IFX and trabectedin, at least in a subset of PT patients, cannot be excluded.

No responses were seen with pazopanib in the current series. Of course, it should be considered that the number of patients included in this group was very limited. One response was seen with regorafenib, even if the duration of disease control was poor. Of interest, Neron et al. reported 1 response with regorafenib, while pazopanib was not reported to be used in the context of the FSG retrospective series [5]. The activity of another TKI, sunitinib, was previously reported by other authors [14]. Further investigations are needed to better understand the role of TKI.

In this series, the median OS from the start of first systemic treatment was 15 months. At a median follow-up of 35 months, 18 patients were alive. Of them, 6 patients were alive with no evidence of disease, after a first-line systemic treatment and a sub-sequence surgery. Of course, this analysis was not aimed to capture the impact of surgery in metastatic PT. However, as in STS in general, surgery may be an option in a selected group of metastatic PT patients [15].

With regard to pathological characteristics at the time of the diagnosis, a diagnosis of borderline PT was made in 5 (8.9%) cases who had a subsequent evidence of metastatic recurrences, suggesting a possible aggressive behavior even in the lack of an up-front diagnosis of malignant PT.

Recent studies have begun to explore molecular features of malignant PT in little case series. Using next-generation sequencing, mutations in TERT (telomerase reverse transcriptase) promoter and in MED12 (subunit of the multi-protein transcriptional regulator Mediator complex) were frequently found [16–19]. In 8 out of 10 cases, Liu et al. reported genomic aberration in FGFR/EGFR PI-3 kinase and RAS pathways, including activating FGFR1, PIK3CA mutations, inactivating TSC2 mutation, EGFR amplification, and PTEN loss [17]. Additional studies are warranted to improve our knowledge of molecular characterization of PT and possibly lead the development of new therapeutical approaches in this disease.

Conclusion

In conclusion, in this series of advanced breast PT treated with systemic treatments, we observed that systemic treatment as used in other soft tissue sarcomas are associated with a distinct number of responses, which on average have a low duration, and though a few patients being progression-free at 2–3 years.

We think that these data might provide a benchmark for future trials on agents in this disease. Moreover, the present study confirms the value of international, collaborative, retrospective studies among refer all centers to answer relevant clinical questions in very rare neoplasms.

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Author contributions Conceptualization, EP and PGC; methodology, EP, PGC, LM; software, SLV; validation, EP and PGC; formal analysis, SLV, and LM; investigation, all.; resources, all.; data curation, EP, and SLV; writing original draft preparation, EP, and PGC; writing review and editing, all.; visualization, FB, and EP; supervision, PGC All authors have read and agreed to the published version of the manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. EP and SP reports institutional financial interest in Advenchen, Amgen-Dompe, Bayer, Epizyme, Eli Lilly, Daiichi-Sankyo, GlaxoSmithKline, Karyopharm, Novartis, Pfizer, PharmaMar, and SpringWorks Therapeutics. OM reports Advisory Board for Bayer, Blueprint Medicines, MSD, Pfizer, Invited Speaker for BMS, Eli-Lilly, Roche, Servier and Institutional, Financial interest as Local PI for Bayer, Blueprint Medicines, Eli-Lilly, Epizyme. AS reports advisory role for Pharmamar and also travel and congress assistance, research, teaching from Pharmamar, teaching, travel and congress assistance from Lilly, Eisai and travel and congress assistance from Merc, Amgen, Sanofi. CV reports Advisory Board for Bayer, Boehringer Ingelheim, GSK, Lilly, Mundipharma, PharmaMar; Invited Speaker from Roche; Institutional, Financial interest as Local PI from Adaptimmune, Karyopharm, Lilly. GGB reports Honoraria from Eli Lilly, Eisai, PharmaMar and MSD; travel grants from PharmaMar, Pfizer and Eli Lilly; advisory board from Eli Lilly and Glaxo Smith Kline. AB reports Consultancy/Advisory board for Eli Lilly, Eisai, Glaxo Smith Kline; Speakers' fees from PharmaMar; Travel grants from PharmaMar. JMB reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from PharmaMar, Lilly, Bayer, Eisai, Daichii; grants or contracts from Pharmamar, Novartis, Eisai, IMMIX Biopharma; payment for expert testimony from PharmaMar, Lilly, Bayer, Eisai, Daichii; participation on a Data Safety Monitoring Board or Advisory Board for Roche,

Lilly, PharmaMar; Leadership or fiduciary role in board, society, committee or advocacy group for Daiichi Sankyo, Karyopharm, Celgene, Pfizer, BMS, Blueprint, Deciphera, Nektar, Forma, Amgen, Lixte, GEIS, CTOS, ESMO, SELNET. PGC reports honoraria and consultancy or advisory fees from Bayer, Deciphera, Eisai, Eli Lilly, and Pfizer outside the submitted work and institutional financial interest in Advenchen Laboratories, Amgen Dompe, AROG Pharmaceuticals, Bayer, Blueprint Medicines, Daiichi-Sankyo, Deciphera, Eisai, Eli Lilly, Epizyme, GlaxoSmithKline, Karyopharm, Novartis, Pfizer, and Pharma-Mar. Other authors: no competing interests to declare.

Ethical approval The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Fondazione IRCCS Istituto Nazionale Tumori di Milano (protocol code 255/20, date 05/11/2020).

Informed consent Informed consent was obtained from all subjects involved in the study.

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