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# Pleomorphic rhabdomyosarcoma, outcomes of patients with advanced disease treated with systemic agents: Retrospective study from the global pushing ultra-rare sarcomas towards hope (*PUSH*) consortium

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ABSTRACT

*Objectives:* To report the outcomes in adult patients with advanced pleomorphic rhabdomyosarcoma (P-RMS) treated with systemic therapy.

*Methods:* This global, multicenter, retrospective study conducted within the Pushing Ultra-Rare Sarcomas Towards Hope consortium (*PUSH*) included patients > 40 years with histologically confirmed advanced P-RMS, treated with at least one line of systemic therapy between 2013 and 2023. The primary endpoint was progression-free survival from first diagnosis of advanced disease, and from systemic treatment start (PFS-1 and PFS-2). Secondary endpoints included overall response rate (ORR), overall survival from first diagnosis of advanced disease and from treatment start (OS-1 and OS-2), and treatment-specific outcomes.

*Results:* Seventy-seven patients were included from 21 sarcoma reference centers. At a median follow-up of 44 months (IQR: 17.0–74.8), 49 (64%) patients had died and 48 (62%) had progressed. The median OS-1 and PFS-1 were 13.6 (95% confidence interval (CI): 9.4–22.5) and 5.4 (95% CI: 4.2–7.3) months, respectively. Two- and three-year OS-1 were 32.5% and 30.3%.

Anthracycline-based regimens (n = 42) achieved a 50% ORR, with mPFS-2 and mOS-2 of 5.2 and 19.2 months; gemcitabine-based regimens (n = 15) a 42% ORR, with mPFS-2 and mOS-2 of 3.7 and 7.8 months; pazopanib (n = 6) a 33% ORR, with mPFS-2 and mOS-2 of 2.4 and 4.2 months; PD-1 inhibitors (n = 2) induced one response lasting 53 months.

*Conclusions:* This series of advanced P-RMS treated with systemic agents, the largest available to date, showed meaningful activity of anthracycline- and gemcitabine-based regimens, and anecdotal responses to pazopanib and PD-1 inhibitors. Further prospective validation is planned.

## 1. Introduction

Pleomorphic rhabdomyosarcoma (P-RMS) is an ultra-rare sarcoma (incidence ≤1 per 1000,000 per year) that typically arises in the deep soft tissues, most commonly in the lower extremities [1–3]. It primarily affects adults older than 45 years, with the highest incidence occurring in the sixth to seventh decades of life and a male predominance [2]. In recent years, P-RMS has been recognized as a distinct entity, separate from other subtypes of rhabdomyosarcomas (RMS), particularly embryonal and alveolar RMS, which primarily affect pediatric and young adult patients, as well as spindle cell/sclerosing RMS, which may also occur in adults [4,5].

Histologically, P-RMS is a high-grade pleomorphic sarcoma characterized by pleomorphic, spindle, epithelioid and/or round cells and a variable number of cells with brightly eosinophilic cytoplasm displaying skeletal muscle differentiation, as confirmed by expression of desmin and, variably, myogenin or MyoD1. This contrasts with undifferentiated pleomorphic sarcoma, which does not show skeletal muscle differentiation and is currently regarded as a distinct biological and pathological entity according to the WHO classification [2,4,6].

Based on retrospective series, over 70% of patients with P-RMS present with metastatic disease, most often involving the lungs. Median overall survival (m-OS) in cases with advanced disease is about 12–14 months, and 5-year OS ranges between 20% and 40% [7–15]. In localized disease, surgery is the mainstay of treatment, often combined with radiotherapy and/or (neo)adjuvant chemotherapy [8,16].

The evidence supporting the activity of systemic treatment in advanced P-RMS is scarce, and the role of chemotherapy remains uncertain [7–11,13]. To date, no prospective clinical trials have specifically evaluated P-RMS, and available retrospective data are difficult to interpret as P-RMS cases are analyzed together with other RMS subtypes, pooling patients with localised and metastatic disease, and treating them with heterogeneous systemic regimens, ranging from pediatric multi-agent protocols to single-agent anthracyclines. [7–15]. Moreover, most retrospective series lack detailed regimen-specific analyses of response and survival outcomes. However, overall, the data suggest that P-RMS is less chemosensitive than pediatric RMS subtypes [17–20].

Against this background, we conducted a multicenter international retrospective study within the *PUSH (Pushing Ultra-Rare Sarcomas towards Hope)* consortium, involving sarcoma reference centres worldwide. We collected data on adult patients with P-RMS presenting with either localized or advanced disease. Outcomes of patients with localized disease from this series have been reported in a separate manuscript, showing that surgery combined with radiotherapy is the cornerstone of treatment, while the role of (neo)adjuvant chemotherapy remains uncertain, despite some activity [9]. Here, we focus on the advanced disease cohort, reporting the activity of the systemic therapies most commonly used in the sarcoma management.

### 1.1. Patients and methods

#### 1.1.1. Patient population

This international, multicentre, retrospective observational study was conducted within the *PUSH* consortium. All consecutive patients aged 40 years or older with histologically confirmed diagnosis of P-RMS, between January 1, 2013, and December 31, 2023 in centres belonging to the *PUSH* consortium were retrospectively identified. Patients with advanced disease (defined as unresectable/-locally advanced or metastatic disease) and treated with at least one line of systemic therapy for the advanced phase of their disease were included in this analysis. The age threshold was set to define an adult population and exclude overlap with paediatric-type RMS with anaplasia.

Systemic treatments were stratified into: anthracycline-based regimens, gemcitabine-based regimens, high-dose ifosfamide monotherapy (HD-IFX), irinotecan-based regimens, pazopanib, or other regimens.

Approval of the retrospective study by the Institutional Review Board of each participating institution was required.

#### 1.1.2. Data collection and study design

Data were extracted from patient files or prospectively maintained institutional clinical databases and entered by each local site investigators in a REDCap-based electronic Case Report Form (eCRF).

A detailed list of inclusion and exclusion criteria can be found in the Study Protocol (Supplementary Method 1).

For all cases, pathologic diagnosis was performed or confirmed by expert sarcoma pathologists at each center, based on predefined criteria aligned with the WHO Classification (5th Edition) [2] and agreed upon by the protocol's pathology steering committee. The key pathological inclusion criteria included: 1) the morphological appearance of a high-grade pleomorphic tumor, characterized by abundant eosinophilic cytoplasm, diffuse expression of desmin, and 2) nuclear expression of rhabdomyoblastic differentiation markers (myogenin and/or MYOD1), typically observed in a minority of neoplastic cells.

Radiological assessment was categorized as response, stable disease and progressive disease based on the local radiologist's judgment, since

standard criteria, like RECIST, cannot be reliably applied retrospectively, and as agreed in a consensus document on how to conduct retrospective studies in ultra-rare sarcomas [21]. Patients were considered evaluable for response if there was radiological measurable disease and imaging was available for review at each participating institution. All participating institutions consistently assessed response through MRI and/or CT scan, as appropriate, repeated every 2–3 months.

In the anthracycline-based regimen group, chemotherapy was administered every 3 weeks, constituting one cycle. In the gemcitabine-based group, gemcitabine was administered as monotherapy on days 1, 8, and 15, of a 28-day cycle, or combined to docetaxel on days 1 and 8, of a 21-day cycle, with each course constituting one cycle. HD-IFX was administered as monotherapy at a dose of 14 g/m$^2$, delivered mostly as a 14-day continuous infusion via an external elastomeric pump, and repeated every 4 weeks (one cycle).

In the irinotecan-based regimen group, chemotherapy was given over five consecutive days every 3 weeks, constituting one cycle.

Pazopanib was administered orally at a starting dose of 400–800 mg per day, continuously (4 weeks of treatment were considered as one cycle).

### *1.1.3. Statistical analysis*

Patients, disease and treatment characteristics were summarized using standard descriptive statistics, overall and separately according to systemic therapy regimen (i.e., anthracycline-, gemcitabine- and irinotecan-based regimens, HD-IFX and pazopanib).

The primary endpoint was progression free survival (PFS). Secondary endpoints were OS and overall response rate (ORR). ORR was calculated as the number of patients with radiological response, divided by the total number of patients evaluable for response.

PFS and OS were estimated with the Kaplan-Meier method and compared with the log-rank test. PFS-1 was defined as the time from first diagnosis of advanced disease (locally advanced or metastatic disease) until first progression or death, whichever occurred first. OS-1 was defined as the time from first diagnosis of advanced disease until death due to any cause, with censored times for patients alive at the date of last known follow-up as from clinical charts. In the treatment-specific analyses, PFS-2 and OS-2 were also estimated, calculated as the time from initiating systemic treatment until first progression or death, whichever occurred first, for PFS-2, or the time until death for OS-2. The association of PFS and OS with potential risk factors was estimated using univariable Cox models.

## 2. Results

In total, 83 patients with advanced P-RMS treated between January 2013 and December 2023 from 21 institutions were retrospectively identified. Of these, 77 patients were eligible for the present analysis, while 6 patients were excluded (3 did not meet the pathological criteria, 3 for other reasons).

Main patient and treatment characteristics of the 77 eligible patients are reported in Table 1 and Table 2. Ten patients (13%) had locally advanced unresectable disease, while sixty-seven (87%) had metastatic disease. Among those with metastases, 44 (66%) had metachronous and 23 (34%) synchronous metastatic spread. Thirty-seven of 77 patients (28%) had received prior (neo)adjuvant chemotherapy for localized disease. Twenty-four of 77 patients (31%) received one line of systemic therapy, while 24/77 (31%) were treated with multiple lines; 42/77 (54%) received anthracycline-based chemotherapy, 15/77 (19%) gemcitabine-based regimen, 8/77 (10%) pazopanib, and 17/77 (22%) other regimens (including 3 patients treated with HD-IFX and 4 patients treated with irinotecan-based regimens).

Only 2/77 (2%) patients were enrolled in clinical trials during the course of their disease. Molecular screening was performed as part of routine clinical practice and available in 25/77 patients (32%).

At a 44-month median (m)-FU (IQR 17.0–74.8), 48/77 (62%) patients progressed and 49/77 (64%) died. Figure 1 shows Kaplan-Meier curves for PFS-1 and OS-1 for the overall population. Median-PFS-1 of the whole population was 5.4 months (95% CI:4.21–7.27), while m-OS-1 was 13.6 months (95%CI:9.4–22.5). Two- and 3-year OS-1 were 32% and 30%, respectively. Patients who presented with advanced disease at diagnosis had a worse PFS-1 (p = 0.042; Hazard Ratio = HR, metastatic vs. localized disease 1.77, 95%CI:1.03–3–03), in univariate analysis. Older age was associated with worse OS-1 (p = 0.022, HR 1.03, 95% CI:1.01–1.05), in univariate analysis. (Supplementary Table 1).

**Table 1**
Main patient and treatment characteristics.

| | |
|---|---|
| Total number of pts | 77 |
| Age at metastases (years), median (IQR) | 59.0 (50.0–69.0) |
| Male/Female (%) | 50 (65) / 27 (35) |
| **Site** | |
| **Primary site (%)** | |
| *Extremities* | 42 (55) |
| *Chest wall* | 11 (14) |
| *Abdomen/retroperitoneum* | 10 (13) |
| *Other* | 14 (18) |
| **Site of metastases (%)** | |
| *Lung* | 36 (47) |
| *Soft tissues* | 3 (4) |
| *Bone* | 2 (2.7) |
| *Other* | 18 (23) |
| *Multiple sites* | 23 (30) |
| **Treatments of metastatic disease** | |
| **Surgery (%)** | |
| **No** | 55 (73) |
| **Yes** | 21 (27) |
| Primary tumour | 13 (65) |
| Metastatic lesion | 8 (38) |
| *Focal progression* | 6 (75) |
| *Residual disease after response* | 2 (25) |
| *Palliative/symptomatic* | 0 |
| **Missing** | 1 |
| **Radiotherapy (%)** | |
| **No** | 57 (75) |
| **Yes** | 19 (25) |
| Primary tumour | 8 (42) |
| Metastatic lesion | 12 (63) |
| *Focal progression* | 5 (42) |
| *Residual disease after response* | 3 (25) |
| *Palliative/symptomatic* | 4 (33) |
| **Missing** | 1 |
| **Systemic therapies (%)** | 29 (38) |
| **No** | 48 (62) |
| **Yes** | 24 (50) |
| *1 treatment line* | 24 (50) |
| *> 1 treatment lines* | 29 |
| *Missing* | |
| **Anthracycline-based regimens (%)** | 42 (54) |
| *Single agent* | 13 (31) |
| *+ Ifosfamide* | 18 (42) |
| *+ Other agents* | 11 (26) |
| **Gemcitabine-based regimens (%)** | 15 (19) |
| *Single agent* | 4 (27) |
| *+ Docetaxel* | 9 (60) |
| *+ Dacarbazine* | 2 (13) |
| | |
| **Pazopanib (%)** | 8 (10) |
| **Irinotecan-based regimens (%)** | 4 (5) |
| *Single agent* | 2 (50) |
| *+ temozolomide* | 2 (50) |
| **High-dose ifosfamide (%)** | 3 (4) |
| **Other regimens (%)** | 10 (13) |

Legend= IQR: inter-quartile range

### *2.1. Treatment response and outcome by treatment group*

Table 2 presents main details of each systemic treatment regimen.

**Table 2**
Main systemic treatments details.

| **Anthracycline-based regimens** | |
|---|---|
| **m-FU = 42.8-months (IQR 15.5–89.9)** | |
| Number of cycles, median (IQR) | 4 (2–6) |
| Pts evaluable for response (%) | 38 (90) |
| ORR (%) | 19 (50) |
| Best response | |
| CR/PR | 19 (50) |
| SD | 4 (11) |
| PD | 15 (39) |
| m-PFS, months (95%CI) | 5.2 (4.5–10.7) |
| m-OS, months (95%CI) | 19.1 (11.1–64.1) |
| **Gemcitabine-based regimens** | |
| **m-FU = 18.8-months (IQR 9.8–38.9)** | |
| Number of cycles, median (IQR) | 4 (3–6) |
| Pts evaluable for response (%) | 12 (80) |
| ORR (%) | 5 (42) |
| Best response | |
| CR/PR | 5 (42) |
| SD | 2 (17) |
| PD | 5 (42) |
| m-PFS, months (95%CI) | 3.7 (3.2-NE) |
| m-OS, months (95%CI) | 7.8 (7.4-NE) |
| **Pazopanib** | |
| **m-FU = 47.0-months (IQR 15.6–47)** | |
| Number of cycles, median (range) | 5.5 (1.8–11) |
| Pts evaluable for response (%) | 6 (75) |
| ORR (%) | |
| Best response | |
| CR/PR | 2 (33) |
| SD | 1 (17) |
| PD | 3 (50) |
| m-PFS, months (95%CI) | 2.4 (1.5-NE) |
| m-OS, months (95%CI) | 4.8 (3.2-NE) |
| **Other agents** | |
| *First treatment line* | |
| Pembrolizumab | 1 CR |
| Ifosfamide alone | 1 PD |
| Temozolomide + irinotecan | 1 PD |
| Sunitinib + nivolumab | 1 PD |
| Etposide + Cisplatin + Ifosfamide | 1 PD |
| Trabectedin | 1 PD |
| *Second treatment line* | |
| Carboplatin + Ifosfamide + Etoposide | 1 PR |
| Ifosfamide + etoposide | 2 SD, 1 PD |
| Temozolomide + irinotecan | 1 SD, 1 PD |
| Ifosfamide alone | 2 PD |
| *Third treatment lines* | |
| Vincristine + irinotecan + temozolomide | 1 PD |
| Cyclophosphamide + etoposide + thalidomide + celecoxib | 1 PD |
| *Fourth treatment line* | |
| Topotecan + cyclophosphamide | 1 PD |
| Trabectedin | 1 PD |

Legend= m-FU: median-follow-up; IQR: inter-quartile range; pts: patients; ORR: overall response rate; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; m-PFS: median-progression free survival; m-OS: median-overall survival

o *Anthracycline-based regimens*

Of 42 patients treated with anthracyclines, four (10%) had previously received (neo)-adjuvant anthracycline-based chemotherapy. Anthracyclines were administered as first-line therapy for advanced disease in 34/42 patients (81%), second-line in 6/42 (14%), further-line in 2/42 (4.7%). Treatment was given as a single-agent in 13/42 cases (31%) and as a combination regimen in 29/42 cases (69%), including 18/29 (43%) with anthracyclines plus ifosfamide.

Figure 2 shows Kaplan-Meier curves for PFS-2 and OS-2 with anthracycline-based regimens (all treatment lines). At a 42.8-month m-FU (IQR 15.5–89.9), m-PFS-2 was 5.2 months (95%CI:4.5–10.7) and m-OS-2 was 19.1 months (95%CI:11.1–64.1). One- and 2-year OS were 61% and 38%, respectively. No significant prognostic factors for PFS-2 and OS-2 were identified in univariate analysis (Supplementary Table 2).

Thirty-eight of 42 (90%) patients treated with anthracycline-based regimen were evaluable for response. The ORR was 50% (19/38), with a response rate of 55% (6/11 evaluable patients) for anthracycline as a single-agent and 35% (6/17 evaluable patients) for anthracycline plus ifosfamide.

When modeled as a time-dependent covariate in the Cox analysis for PFS, response with anthracycline-based regimens was not significantly associated with outcome (HR 0.76, 95% CI 0.32–2.29; p = 0.767).

o *Gemcitabine-based regimens*

Gemcitabine was administered as first-line therapy in 2/15 patients (13%), as second-line in 7/15 patients (47%), and as further-line in 6/15 patients (40%). Treatment was given as a single agent in 4/15 cases (27%) and in combination regimens in 11/15 cases (73%) [9/11 (80%) gemcitabine plus docetaxel, 2/11 (20%) gemcitabine plus dacarbazine].

Figure 3 shows Kaplan-Meier curves for PFS-2 and OS-2 with gemcitabine-based regimens (all treatment lines). At an 18.8-month m-FU (IQR 9.8–38.9), m-PFS-2 was 3.7 months (95%CI:3.2-not estimated [NE]) and m-OS-2 was 7.8 months (95%CI:7.4-NE). 1- and 2-year OS were 36% and 27%, respectively. Multi-agent chemotherapy (p = 0.011; HR 0.06, 95%CI: 0.01–0.66) and a higher number of cycles (p = 0.080; HR 0.75, 95%CI: 0.54–1.04) were associated with longer OS-2 in univariate analysis (Supplementary Table 3).

Twelve of 15 (80%) patients treated with gemcitabine-based regimens were evaluable for response. The ORR was 42% (5/12), with one response among 3 evaluable patients treated with gemcitabine as a single-agent, three responses in the group treated with gemcitabine plus docetaxel and one response among two patients treated with gemcitabine plus dacarbazine.

When modeled as a time-dependent covariate in the Cox analysis for PFS, response to gemcitabine-based chemotherapy was not significantly associated with outcome (95%CI: 0.15–3.17; p = 0.642).

o *Pazopanib*

Pazopanib was administered as first- or second-line in 4/8 patients (50%), and as a later-line in 4/8 patients (50%).

At a 47-month m-FU (IQR 15.6–47), m-PFS-2 was 2.4 months (95%CI:1.5-NE) and m-OS-2 was 4.8 months (95%CI:3.2-NE). Six of eight (75%) patients treated with pazopanib were evaluable for response. The ORR was 33% (2/6).

o *Other regimens*

Table 2 summarizes other systemic agents used in the treatment of the disease.

Three patients received HD-IFX, with no responses.

Four patients received irinotecan-based regimens, either as monotherapy or combined with temozolomide, with no responses.

With second-line etoposide–ifosfamide 2 of 4 patients achieved stable disease lasting 6 months.

A prolonged response lasting more than five years was observed in one patient who received first-line pembrolizumab, out of two treated with PD-1 inhibitors.

## 3. Discussion

This retrospective study, conducted within the *PUSH* consortium, reports outcomes from a cohort of 77 patients aged > 40 years with advanced P-RMS collected across 21 institutions worldwide, representing the largest series to date providing detailed data on systemic treatment outcomes in this patient population. Given the extreme rarity of P-RMS, assembling such a cohort was feasible only through coordinated collaboration among sarcoma reference centers, as fostered by the *PUSH* initiative. To ensure data quality and minimize the risk of

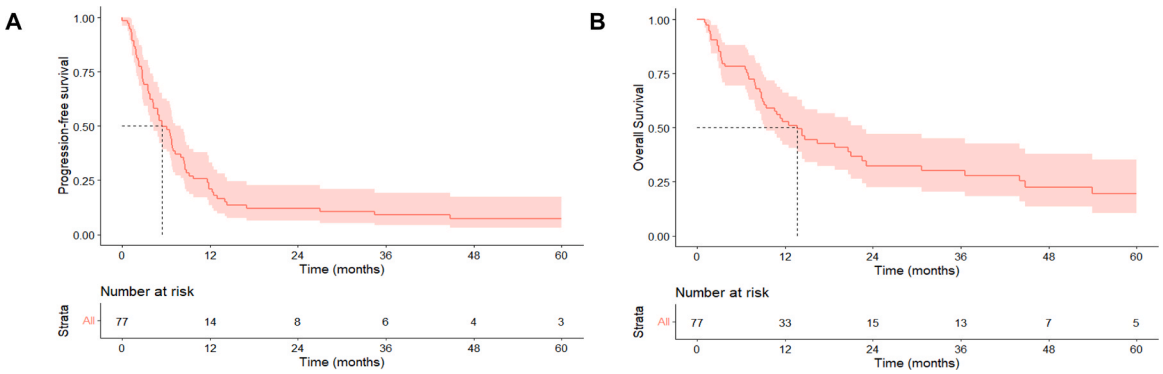


**Fig. 1.** Kaplan-Meier curves for PFS-1 (A) and OS-1 (B) for the overall population (N = 77).

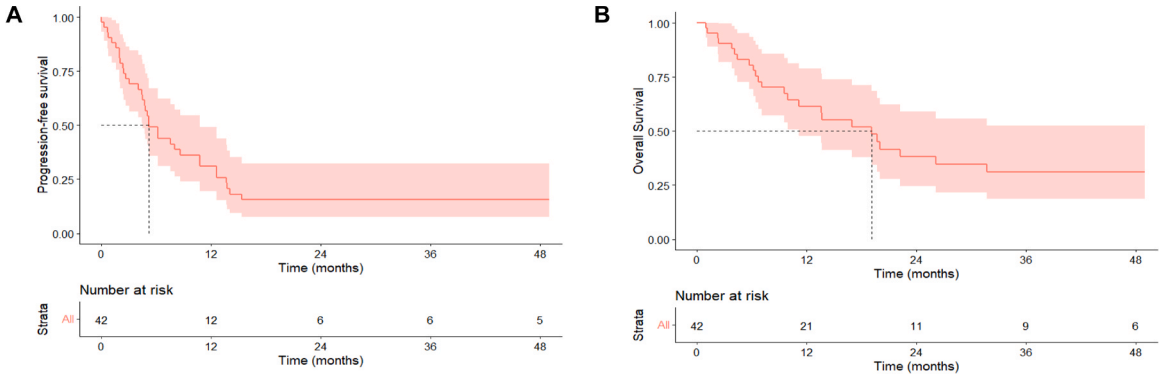


**Fig. 2.** Kaplan-Meier curves for PFS-2 (A) and OS-2 (B) with anthracycline-based regimens (all treatment lines). (N = 42).

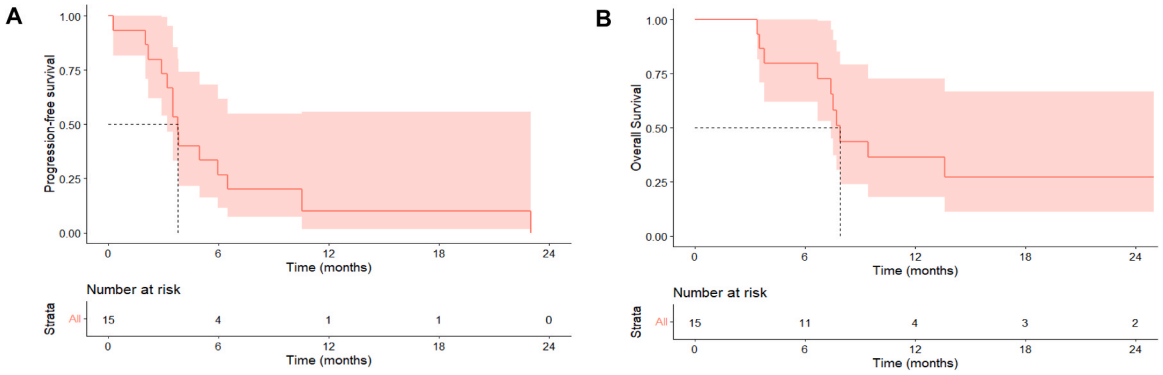


**Fig. 3.** Kaplan-Meier curves for PFS-2 (A) and OS-2 (B) with gemcitabine-based regimens (all treatment lines). (N = 15).

misclassification with other RMS subtypes, only cases reviewed by expert pathologists and confirmed by predefined pathologic inclusion criteria were included, with an age threshold of > 40 years applied, as recommended by the study steering committee pathologists, to reduce potential overlap and the associated risk of misdiagnosis with pediatric-type RMS with anaplasia.

Our study provides novel insights into the management of advanced P-RMS.

Although OS was poor (m-OS 13.6 months), consistent with available literature [7–15], 30% of patients were alive at 3 years from diagnosis of advanced disease, suggesting that a subset of P-RMS patients may achieve durable disease control even in this setting. Outcomes remain markedly inferior to those reported in patients with pediatric-type RMS treated with multi-agent chemotherapy [17–20]. Moreover, when compared with other pleomorphic soft tissue sarcomas (STS), particularly undifferentiated pleomorphic sarcoma (UPS), P-RMS appears to be associated with a poorer prognosis. In fact, in large retrospective UPS series, mOS in advanced disease generally ranges from 15 to 25 months, with 5-year OS rates of approximately 20–30% [2,22–25]. By contrast, advanced P-RMS is consistently associated with a mOS of < 14 months.

Currently available systemic therapies for STS showed a higher ORR in P-RMS than previously reported. In our cohort, 19 of 38 patients (50%) treated with anthracycline-based chemotherapy achieved an objective response. Although this response rate remains lower than the ~80% ORR typically reported in pediatric-type RMS [17–20], it compares favorably with historical data in P-RMS and exceeds the ~30% ORR generally reported in STS [8,10,11,26]. However, with all the limits of a retrospective analysis, this apparent activity did not translate into durable clinical benefit, as median PFS was only 5.4 months, and anthracycline use was not significantly associated with improved survival. In the retrospective series by Noujaim including 14 patients with advanced P-RMS, conventional multi-agent regimens chemotherapy

typically employed in pediatric RMS yielded only one response, with m-PFS and m-OS of 2.3 and 7 months; however, interpretation is limited by the small sample size and heterogeneity in treatment approaches [8].

Interestingly, data from patients with localized P-RMS collected within the *PUSH* retrospective observational study, as reported earlier, found that anthracycline-based regimens administered in neoadjuvant setting had comparable activity, with an ORR of 50% [9]. Collectively, these findings support the use of anthracycline-based chemotherapy in the disease, both in fit patients with advanced disease and in localized disease with cytoreductive intent, particularly to enable subsequent surgical interventions. To enhance available evidence, a prospective observational study on P-RMS is currently being initiated within the framework of the *PUSH* initiative.

Our series showed that gemcitabine also, either alone or in combination with docetaxel, can be considered a treatment option for P-RMS. Gemcitabine-based regimens showed an ORR of 42% (5/12 evaluable patients). Most patients received gemcitabine beyond the first-line, usually in combination with docetaxel. As gemcitabine was administered as monotherapy in only 3 cases, and responses occurred with both monotherapy and combination, it is not possible to determine whether the combination is superior. To our knowledge, however, this is the first report to demonstrate activity of gemcitabine-based regimens specifically in P-RMS.

The results derived from regimens other than anthracycline- and gemcitabine-based were limited by small patient numbers (i.e., pazopanib, n = 8; irinotecan-based regimens, n = 4; HD-IFX, n = 3; etoposide–ifosfamide n = 4; immune-checkpoint inhibitors, n = 2) that do not allow any conclusions, except that responses to pazopanib (two of 6 evaluable cases) and pembrolizumab (one of 2 patients) were observed. Anedoctal responses to pazopanib in two patients with P-RMS have been previously reported also by Seto et al. [27]. Our observation further support pazopanib potential activity and suggest that it may be considered as a treatment option in later lines in P-RMS population, although prospective validation is lacking. On the other side, the long-lasting response to pembrolizumab, although anecdotal, supports emerging evidence for the potential activity of immune checkpoint inhibitors in P-RMS, particularly in cases characterized by mismatch repair deficiency (dMMR) or PD-L1 positivity. This is illustrated by the series recently published by Poumeaud et al., in which both patients with P-RMS treated with an anti–PD-1 agent achieved prolonged complete responses [28], as well as by a case report by Liu et al., in which a PD-L1-positive patient with pleomorphic RMS achieved a durable partial response to nivolumab after failure of chemotherapy and pazopanib, with relapse-free survival exceeding 45 months, in line with what observed also in our patient who was on pembrolizumab for $>$ 5 years [29].

However, data on dMMR or PD-L1 status were not systematically collected due to the retrospective nature of the study but will be prospectively evaluated within the upcoming *PUSH* observational study.

Molecular screening was performed as part of standard care in only a small subset of patients (32%), using heterogeneous methodologies, including fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS). This variability reflects the long accrual period of the study, during which molecular diagnostic techniques evolved substantially. Consequently, the molecular data were not directly comparable and did not permit a systematic assessment of potentially targetable alterations across the cohort.

Our series represents the largest analysis of patients with advanced P-RMS treated with systemic agents (77 patients versus 16 reported by Bompas et al in the retrospective cohort, and 70 by Deb et al, while the series by Reddy et al was only on patients with localized P-RMS) [13–15]. Our study was intentionally designed to add to available literature by including a highly selected and homogeneous population, applying strict inclusion criteria with respect to pathological definition, age (restricting inclusion to adult patients aged over 40 years) and disease stage, with a specific focus on advanced disease. Larger retrospective series have necessarily adopted broader inclusion criteria, resulting in higher patient numbers but also in more heterogeneous study populations, including both young adult and adult patients, localized and advanced disease, and, in some cases, different histological entities grouped under the definition of P-RMS [13,14,17–20]. For example, earlier studies (e.g., Bompas et al.) included in this definition also spindle cell/sclerosing RMS and RMS not otherwise specified (NOS), which are now recognized as distinct entities according to the latest WHO classification [2]. Moreover, most available studies did not provide detailed analyses of response rates and PFS according to specific systemic treatment regimens. In this context, our work complements the existing literature by focusing exclusively on pathologically well-defined adult P-RMS with advanced disease and by reporting regimen-specific outcome data derived from real-world practice in reference sarcoma centers.

In conclusion, our series support the use of anthracycline- and gemcitabine-based regimens for advanced P-RMS, showing higher activity than previously reported. Pazopanib is an additional option among agents formally approved for treatment of soft tissue sarcomas, while immune-checkpoints inhibitors deserve to be further investigated. The data collected here can be used to inform clinical decision-making and guide the design of future prospective studies with new agents. Also, prospective confirmation of what we observed is desirable and will be pursued within the PROSPER (Prospective and Retrospective Observational Studies Promoting Evidence and Research), an international framework launched by the *PUSH* consortium to conduct observational studies on ultra-rare sarcomas, including P-RMS.

## CRediT authorship contribution statement

**Desar Ingrid DE:** Writing – review & editing, Investigation, Data curation. **Dei Tos Angelo Paolo:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Vladimir Andelkovic:** Writing – review & editing, Investigation, Data curation. **Elena Di Blasi:** Writing – review & editing, Investigation, Data curation. **Fernando Campos:** Writing – review & editing, Investigation, Data curation. **Lazar Alexander J:** Writing – review & editing, Investigation, Data curation. **Roberto Scanferla:** Writing – review & editing, Investigation, Data curation. **Abreu Miguel H:** Writing – review & editing, Investigation, Data curation. **Rosalba Miceli:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Susie Bae:** Writing – review & editing, Investigation, Data curation. **Chen Tom W:** Writing – review & editing, Supervision, Project administration, Investigation, Data curation, Conceptualization. **Sameer Bakhshi:** Writing – review & editing, Investigation, Data curation. **Silvia Stacchiotti:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Data curation, Conceptualization. **Lefler Daniel S:** Writing – review & editing, Investigation, Data curation. **Gloria Marquina:** Writing – review & editing, Investigation, Data curation. **Marta Sbaraglia:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Inga-Marie Schaefer:** Writing – review & editing, Investigation, Data curation. **Silvia Taverna:** Writing – review & editing, Visualization, Project administration. **Koichi Ogura:** Writing – review & editing, Investigation, Data curation. **Alessandro Gronchi:** Writing – review & editing, Investigation, Data curation. **Wong Daniel D:** Writing – review & editing, Investigation, Data curation. **Silva Ljevar:** Writing – review & editing, Formal analysis, Data curation. **Denu Ryan A:** Writing – review & editing, Investigation, Data curation. **Alessandro Mazzocca:** Writing – review & editing, Investigation, Data curation. **Nakazawa Michael S:** Writing – review & editing, Investigation, Data curation. **Khin Thway:** Writing – review & editing. **Baldi Giacomo Giulio:** Writing – original draft, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Han-Soo Kim:** Writing – review & editing, Investigation, Data curation. **Claudia Giani:** Writing – review & editing, Funding acquisition, Data curation. **Cristina Antonescu:** Writing – review & editing, Data curation, Conceptualization. **Ilkyu**

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## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

**All the authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.**

Outside the scope of this work: **Giacomo G Baldi** reports a relationship with PharmaMar SA that includes: consulting or advisory and travel reimbursement. A relationship with Eli Lilly that includes: consulting or advisory and travel reimbursement. A relationship with Glaxo Smith Kline that includes: consulting or advisory. A relationship with Merck Sharp & Dome that includes: consulting or advisory. A relationship with Deciphera that includes: consulting or advisory. A relationship with Istituto Gentili that includes: travel reimbursement.

**Andrea Napolitano:** reports a relationship with Springworks Therapeutics, Deciphera, Glaxo Smith Kline and Pharmamar that includes: consulting or advisory and travel reimbursement. **Daniel S. Lefler:** A relationship with SpringWorks Therapeutics, Aadi Biosciencethat includes: consulting or advisory. **Alessandro Gronchi** reports a relationship with Novartis that includes: consulting or advisory. A relationship with Pfizer that includes: consulting or advisory. A relationship with Bayer that includes: consulting or advisory. A relationship with Eli Lilly that includes: consulting or advisory. A relationship with PharmaMar that includes: consulting or advisory and funding grants. A relationship with Boehringer Ingelheim that includes: consulting or advisory. A relationship with Deciphera that includes: consulting or advisory. A relationship with SpringWorks that includes: consulting or advisory. A relationship with Nanobiotix SA that includes: funding grants. **Stacchiotti Silvia** reports a relationship with Bayer that includes: consulting or advisory and funding grants. A relationship with Boehringer-Ingelheim that includes: consulting or advisory and funding grants. A relationship with Daiichi Sankyo that includes: consulting or advisory and funding grants. A relationship with Deciphera that includes: consulting or advisory and funding grants. A relationship with Istituto Gentili that includes: consulting or advisory. A relationship with Glaxo Smith Kline that includes: consulting or advisory. A relationship with Ikena Oncology Inc that includes: consulting or advisory and funding grants. A relationship with Ipsen that includes: consulting or advisory and funding grants. A relationship with Merk Serono that includes: consulting or advisory. A relationship with NEC Oncoimmunity that includes: consulting or advisory. A relationship with Novartis that includes: consulting or advisory and funding grants. A relationship with Parabilis that includes: consulting or advisory. A relationship with PharmaMar SA that includes: consulting or advisory and funding grants. A relationship with Pharma Essentia that includes: consulting or advisory. A relationship with Servier that includes: consulting or advisory. A relationship with Abbisko that includes: funding grants. A relationship with Advenchen that includes: funding grants. A relationship with Eisai that includes: funding grants. A relationship with Epizyme Inc that includes: funding grants. A relationship with Foghorn Therapeutics that includes: funding grants. A relationship with Hutchinson that includes: funding grants. A relationship with Inhbrix that includes: funding grants. A relationship with Karyopharm Therapeutics Inc that includes: funding grants. A relationship with SpringWorks Therapeutics that includes: funding grants.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116666.

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