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RESEARCH

# Challenges in the treatment of soft-tissue plasmacytoma: a retrospective analysis of 120 patients with extramedullary multiple myeloma

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## Abstract

**Purpose** Despite the development of novel drugs and the widespread use of hematopoietic cell transplantation, the prognosis of patients (pts) with multiple myeloma and extramedullary involvement (soft-tissue plasmacytoma, STP) is rather unfavorable.

**Methods** A retrospective analysis of 120 pts with STP treated between 2007 and 2022 was performed. The effects of demographic and clinical characteristics on treatment response, progression-free survival (PFS), and overall survival (OS) were evaluated.

**Results** The rate of serological response to first-line STP treatment (at least partial remission) was 67%, and the rate of imaging response was 59%. With a median follow-up of 84.2 months, the median PFS was 10.5 months (primary STP: 20.2 months; secondary STP: 5.8 months), and the median OS was 24.5 months (primary STP: 34.5 months; secondary STP: 12.4 months). Based on the multivariate regression analysis, secondary STP ($HR_{PFS}$ 2.75; $HR_{OS}$ 2.63) and organ involvement ($HR_{PFS}$ 1.45; $HR_{OS}$ 1.68) were found to be negative prognostic factors of both PFS and OS. In a prognostic model, pts with at least one of these factors had a significantly worse PFS ($HR_{PFS}$ 3.31) and OS ($HR_{OS}$ 3.45) than those with none risk factor.

**Conclusion** In pts with STP, risk-adapted treatment strategies including immunotherapies and cell therapies are urgently required.

**Keywords** Extramedullary myeloma · Multiple myeloma · Soft-tissue plasmacytoma · Retrospective analysis

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## Introduction

Soft-tissue plasmacytoma (STP) refers to the extramedullary clonal growth of plasmocytes by either direct passage via bone structures into the surrounding space, known as paraskeletal (PS), or hematogenous spread to distant organs, defined as extramedullary disease (EMD). STP has a poorer prognosis than multiple myeloma (MM) without extramedullary spread (Mangiacavalli et al. 2017; Pour et al. 2014; Rosiñol et al. 2021). In addition, EMD has a worse prognosois than PS (Beksac et al. 2020; Mangiacavalli et al. 2017; Pour et al. 2014) due to a more plasmoblastic cell morphology (Weinstock and Ghobrial 2013), higher proliferation index, and more frequent high-risk cytogenetic aberrations (HRCA) (Pour et al. 2014; Usmani et al. 2012; Varettoni et al. 2010, Schinke et al. 2023). The average median overall survival (OS) varies from 7.0 months for EMD to 46.5 months for PS (Beksac et al. 2020; Montefusco et al. 2020; Rasche et al. 2012; Varga et al. 2015).

In addition to local differentiation, MM with soft-tissue involvement can be categorized into primary STP (diagnosed together with MM) and secondary STP (diagnosed in the course of disease progression or relapse). The incidence rate of primary and secondary STP ranges from 5% to > 30% (Rosiñol et al. 2021). Secondary STP has a worse prognosis than primary STP (Mangiacavalli et al. 2017; Short et al. 2011; Varga et al. 2015), with a median OS of 7–38 months (Pour et al. 2014; Rasche et al. 2012) and 28–70 months, respectively (Montefusco et al. 2020; Short et al. 2011). The prognosis of pts with central nervous system (CNS) involvement is unfavorable, with a median survival of < 7 months (Chen et al. 2013; Jurczyszyn et al. 2016).

Access to diagnostic and imaging methods has improved. Further, the use of novel drug classes such as proteasome inhibitors (PI), immunomodulatory drugs (IMiD), and monoclonal antibodies (mAB), which have improved survival probability, has been approved. Hence, the number of pts diagnosed with STP involvement is increasing (Bladé et al. 2015; Jurczyszyn et al. 2016). The site of STP occurrence significantly varies. However, STP are comonly observed in the lymph nodes, skin/soft tissues, liver, kidney, and chest wall/pleura/airways in EMD and in the paravertebral area in PS (Pour et al. 2014; Short et al. 2011; Usmani et al. 2012; Varettoni et al. 2010).

Although the number of STP diagnoses is increasing, the risk factors or prognostic scores of STP have not been fully elucidated. Only a few studies performed multivariate analysis to assess for independent factors (Beksac et al. 2020; Mangiacavalli et al. 2017; Usmani et al. 2012; Varettoni et al. 2010). However, the results of previous studies are inconsistent, and the availability of data from prospective studies on STP is limited. In addition, STP was often poorly or not represented in large randomized myeloma studies (Dimopoulos et al. 2017; Lonial et al. 2015b; Moreau et al. 2016, 2019; Palumbo et al. 2016; San-Miguel et al. 2014; Stewart et al. 2015). In contrast to the encouraging data on bispecific antibodies and chimeric antigen receptor (CAR) T cells in pts with relapsed/refractory MM (Berdeja et al. 2021; Krishnan et al. 2023; Lesokhin et al. 2023; Moreau et al. 2022; Munshi et al. 2021; Schinke et al. 2023), the outcomes of these innovative cellular and immunotherapies in pts with STP have, thus far, been rather disappointing (Table 1).

This retrospective analysis aimed to identify the risk factors of STP outcomes with consideration of the significantly improved treatment options for pts with MM in recent years.

## Materials and methods

### Definitions

The definition and classification of STP was adopted from Rosiñol et al. (2021). Pts with STP were divided into exclusively PS plasmacytoma and pts with hematogenous spread / extramedullary disease (EMD) involving soft-tissues/organs. Pts with both, PS and soft-tissue/organ involvement, or EMD were categorized in pts with "organ involvement". Pts with solitary plasmacytoma were not included in the analysis. Diagnosis of STP at the time of MM diagnosis was classified as primary STP (corresponding to newly diagnosed MM, NDMM), while pts who developed STP during the course of MM disease were categorized as secondary STP (corresponding to relapsed or refractory MM, RRMM).

### Study design and patients

This unicentric, retrospective analysis assessed pts with STP treated at the Department of Internal Medicine III at Klinikum Chemnitz gGmbH. The medical records of the pts were screened. Results showed that 120 pts with primary or secondary STP were treated with systemic therapy between 2000 and 2022 (cut-off: July 31, 2022). The regional ethics committee of the institution (The State Chamber of Physicians of Saxony, EK-BR-118/22 – 1) approved this study.

### Data collection

All data including laboratory and pathological examination results and cytogenetic and imaging findings were collected from the health records of the individual pts. Data on demographic, disease, and treatment characteristics were recorded in a separate database. Missing data were considered to be missing completely at random and were not

**Table 1** Results of STP patients in studies with CAR T therapy **(a)** or bispecific antibodies **(b)**

| | Pts | CR | ORR | DoR | Median PFS | Median OS | Reference |
|---|---|---|---|---|---|---|---|
| **(a) - CAR T therapy** | | | | | | | |
| **Ide-cel** | 50 | 24% | 70% | 9.2 mo | 7.9 mo | n.a. | KarMMa (Munshi et al. 2021; Raje et al. 2020) |
| | 61 | 23% | 56% | n.a. | 7.2 mo | n.a. | KarMMa-3 (Patel et al. 2023; Rodriguet-Otero et al. 2023) |
| | 76 | 43% | 78% | n.a. | < 8.5 mo[3] | n.a. | RWE (Hansen et al. 2023) |
| **Cilta-cel** | 19 | n.a. | 100% | 12.9 mo | 13.8 mo | 2.25 year: 52.1% | CARTITUDE-1 (Lin et al. 2023) |
| | 22 | 55% | 82% | n.a. | 8.9 mo | 14.3 mo | LEGEND-2 (Zhao et al. 2023) |
| **Ide-cel** | 53 | 42% | 78% | n.a. | 6.5 mo | 12.9 mo | RWE (Dima et al. 2023) |
| **Cilta-cel** | 11 | | | | | | |
| **Ide-cel/Cilta-cel/other CAR T cells** | 34 | 53% | 76% | n.a. | 12.4 mo | 24.4 mo | RWE (Pan et al. 2023) |
| **(b) - Bispecific antibodies** | | | | | | | |
| **Teclistamab** | 28 | n.a. | 36% | n.a. | n.a. | n.a. | MajesTEC-1 (Moreau et al. 2022; Miao et al. 2023) |
| | 45 | n.a. | 47% | n.a. | < 5.4 mo[3] | n.a. | RWE (Dima et al. 2024) |
| | 43 | n.a. | 37% | n.a. | 2.1 mo | n.a. | RWE (Riedhammer et al. 2024) |
| **Talquetamab** | 37[1] | n.a. | 43% | 9.3 mo | 3.9 mo | n.a. | MonumenTAL-1 (Krishnan et al. 2023) |
| | 33[2] | n.a. | 48% | n.a. | n.a. | n.a. | MonumenTAL-1 (Krishnan et al. 2023) |
| **Elranatamab** | 39 | 23% | 39% | 15 mo: 78% | 4.1 mo | n.a. | MagnetisMM-3 (Lesokhin et al. 2023; Touzeau et al. 2023) |

[1]patients and results of 0.8 mg/kg/Q2W dose cohort; [2]patients and results of 0.4 mg/kg/QW dose cohort; [3]survival of all patients including STP as independent prognostic factor in multivariate analysis. CR: Complete remission, DoR: Duration of Response, n.a.: not available, ORR: Overall response rate; OS: Overall survival, PFS: Progression-free survival, RWE: Real-world evidence

adjusted for analysis. Pts who were lost to follow-up were censored at the last point of visit or at the end of the study period. The minimum follow-up time was 3 months.

## Outcome measurements

Pts with MM/STP according to the International Myeloma Working Group (IMWG) criteria (International Myeloma Working Group 2003; Rajkumar et al. 2014) were included in this study, and the outcome based on the medical records was analyzed. Revised international staging system (R-ISS) were calculated based on laboratory results according to Palumbo et al. (2015). The primary endpoints were progression-free survival (PFS) and OS. PFS was defined as the time from STP diagnosis until disease progression, relapse, or death from any cause. OS was defined as the period between STP diagnosis and death from any cause. The assessment of overall response rate (ORR) was based on the IMWG criteria (Durie et al. 2006; Kumar et al. 2016). The reported response was assessed as the best response achieved after first-line STP treatment.

## Statistical analysis

The Kaplan–Meier method was used to determine the median OS and PFS. The inverse Kaplan–Meier method was used to determine the follow-up time. Survival curves were compared using the two-sided log-rank test. An alpha value of 0.05 was considered statistically significant. Univariate and multivariate Cox proportional hazards analysis of the selected prognostic indicators were performed. The indicators were as follows: Sex (male vs. female), age (< 65 years vs. ≥65 years), STP type (primary vs. secondary), STP location (PS vs. organ involvement), non-paraverebral PS (no vs. yes), CNS involvement (no vs. yes), HRCA (no vs. yes), LDH (normal vs. elevated), Beta-2-Microglobulin (≤ 5.5 mg/L vs. >5.5 mg/L), serum albumin (≥ 3.5 g/dL vs. <3.5 g/dL), R-ISS stage (R-ISS I + II vs. R-ISS III), single HRCA [t(4;14), t(14;16), del17p13, dupl1q21, tripl1q21, ampl1q21; no vs. yes], HRCA high-risk (no vs. yes), MM light chains (kappa vs. lambda), year of MM diagnosis (2000–2013 vs. 2014–2022), prior autologeous hematopoietic cell transplantation (AHCT, no vs. yes), first-line STP treatment with HCT (no vs. yes), and first-line therapy withPI + IMiD (no vs. yes), STP first-line therapy with PI + IMID and/or CD38-mab (no vs. yes). The multivariate Cox proportional hazards model was established using a selection approach based on the univariate analysis with a p-value of < 0.1 as entry criterion (complete model) for selected variables considering multicollinearity and overfitting due to the limited number of pts in the study population. Moreover, a stepwise reduction approach was applied with a p-value of > 0.1 as removal criterion (reduced model). Data analysis and visualization were performed with SPSS® (version 27, IBM Inc.) and GraphPad Prism (version 6.07).

## Results

### Characteristics of the patients

Table 2 presents the demographic and clinical characteristics of 120 pts with STP. The median age of the pts was 68 years, and approximately two-thirds were male. Approximately > 60% of the study population was diagnosed with STP during MM diagnosis. In pts with secondary STP, the median time between MM diagnosis and the first detection of STP was 49.1 (range: 5.1–181.5) months. Approximately two-thirds of the pts had STP with exclusively PS involvement. Meanwhile, 34% of pts were diagnosed with STPinvolving organs (EMD and both PS + EMD). The latter was characterized by the involvement of various organs, including 6 pts with CNS involvement which is associated with a poor survival prognosis (Chen et al. 2013; Jurczyszyn et al. 2016; Rosiñol et al. 2021) and was therefore considered in univariate analysis. More than one third of pts with PS plasmacytoma had exclusively paravertebral involvement, whereas non-paravertebral involvement was characterized by mainly thoracic ($n = 26$) or pelvic ($n = 17$) infiltration. As the retrospective data collection was based on medical records, all pts did not have data on β2-Microglobulin ($n = 62$), R-ISS stage ($n = 63$) and HRCA ($n = 3$), which limited the analysis.

Supplementary Information Table S1 shows the pretreatment of pts with secondary STP. In most cases, pts with STP were diagnosed with MM from 2014 onward ($n = 69$). Meanwhile, in 51 pts, the underlying MM was detected between 2000 and 2013. The group diagnosed with MM from 2014 onward had a significantly lower number of pts with secondary STP ($p = 0.002$) or a more favorable disease status ($p = 0.007$) (Table S2).

### Treatment

More than 90% of pts received at least one of the novel drugs (PI or IMiD or anti-CD38 monoclonal antibodies) as the first-line treatment for STP, regardless of whether they had primary or secondary STP (Table S3). Moreover, approximately one-third of pts who were treated received consolidating autologous HCT (AHCT) as shown in Table 2.

### Outcome

The ORR of the first-line treatment was evaluated according to IMWG criteria as best achieved response after first line STP treatment, as shown in Fig. 1. The serological ORR of the first-line treatment (at least PR) was 67% ($n = 80$), and the imaging ORR was 59% ($n = 71$). Two pts died before the start of STP treatment, and they were classified as events. Figure 1 shows the details.

Figure 2 depicts the PFS and OS of the study population. After a median follow-up of 84.2 months, the median duration of PFS and OS for all 120 STP pts were 10.5 months (95% CI: 8.0–13.0) and 24.5 (95% CI: 18.8–30.2) months, respectively (Fig. 1). The 5- and 7-year PFS and OS rates were 7% and 3% and 21% and 8%, respectively. The study population was stratified by primary STP (in NDMM pts) and secondary STP (in RRMM pts) as well as PS plasmacytoma and STP with organ involvement (Fig. S1). Accordingly, pts with primary STP showed a significantly superior PFS (20.2 months vs. 5.8 months, $p < 0.001$) and OS (34.5 months vs. 12.4 months, $p < 0.001$) compared to pts with STP diagnosis at a later stage of MM. Moreover, pts with exclusively PS had also a significantly improved survival than pts with organ involvement (median PFS: 14.2 vs. 6.4 mo, $p < 0.001$; median OS: 31.3 vs. 17.3 mo, $p < 0.001$). Interestingly, there were no significant differences in terms of outcomes between pts diagnosed with MM up to 2013 and those diagnosed from 2014 onward (Fig. S2).

### Prognostic factors

A univariate Cox proportional hazards analysis was performed based on potential risk factors (detailed results are shown in Table S4). Subsequently, a multivariate Cox proportional hazard regression analysis was conducted (Table S5/complete model). After stepwise reduction, the analysis indicated that secondary STP and organ involvement were remaining prognostic factors of both PFS and OS (Table 3/reduced model). In addition, first-line AHCT improved the PFS, whereas first-line STP that included both PI and IMiD was associated with a better OS. Remaining factors in the reduced model were comparable to the significant variables in the complete model, indicating that the reduced model retained the key predictors for PFS and OS.

A simple numerical prognostic factor was determined based on the two risk factors remaining in the reduced multivariate Cox proportional hazards model for both PFS and OS (secondary STP and organ involvement). Pts with none of these risk factors were stratified and compared with pts with at least one risk factor. As shown in Fig. 3, the PFS (a) and OS (b) differed significantly between these two groups. Pts with at least one risk factors have an approximately threefold increased risk of disease progression and mortality ($HR_{PFS}$: 3.307 [2.209–4.950], $p < 0.001$; $HR_{OS}$: 3.449 [2.213–5.374], $p < 0.001$).

**Table 2** Characteristics and STP first-line treatment including systemic therapy of 120 STP patients

| Characteristic | | *n* | % |
|---|---|---|---|
| Median Age (years, range) | | 68 (37–87) | |
| Age | < 65 years | 45 | 38 |
| | ≥ 65 years | 75 | 62 |
| Sex | Male | 79 | 66 |
| | Female | 41 | 34 |
| MM type | IgG | 73 | 61 |
| | IgA | 22 | 18 |
| | IgD | 2 | 2 |
| | Kappa-LC | 12 | 10 |
| | Lambda-LC | 10 | 8 |
| | Asecretory | 1 | 1 |
| LC involvement[1] | Kappa | 79 | 66 |
| | Lambda | 40 | 34 |
| STP type | Primary | 74 | 62 |
| | Secondary | 46 | 38 |
| STP localization | Paraskeletal | 79 | 66 |
| | Organ involvement | 21 | 18 |
| | Both | 20 | 16 |
| PS involvement[2] | Paravertebral | 37 | 37 |
| | Non-paravertebral | 50 | 51 |
| | both | 12 | 12 |
| Organ involvement[3] | Lymph nodes | 13 | 32 |
| | Lung/Pleura | 9 | 22 |
| | Muscles | 9 | 22 |
| | CNS | 6 | 14 |
| | Gastrointestinal tract | 5 | 12 |
| | ENT (ears, nose, throat) | 5 | 12 |
| | Skin | 4 | 10 |
| | Kidney and adrenal gland | 4 | 10 |
| | Liver | 4 | 10 |
| | Testis | 2 | 5 |
| | Pancreas | 2 | 5 |
| Disease status | Newly diagnosed | 74 | 62 |
| | First relapse | 20 | 17 |
| | Multiple relapse | 16 | 13 |
| | Primary refractory | 3 | 3 |
| | Refractory relapse | 7 | 6 |
| Serum LDH | Normal | 66 | 55 |
| | Elevated | 54 | 45 |
| Serum Albumin | < 3.5 mg/L | 35 | 29 |
| | ≥ 3.5 mg/L | 85 | 71 |
| Serum β2-Microglobulin | < 3.5 mg/L | 21 | 36 |
| | 3.5–5.5 mg/L | 15 | 26 |
| | > 5.5 mg/L | 22 | 38 |
| R-ISS[4] | I | 8 | 14 |
| | II | 36 | 63 |
| | III | 13 | 23 |
| HRCA[5] | t(4;14) | 15 | 13 |
| | t(14;16) | 2 | 2 |
| | t(14;20) | 0 | 0 |
| | del17p13 | 10 | 9 |
| | ampl1q21 | 14 | 12 |
| | Yes[6] | 26 | 22 |
| | No | 91 | 78 |

**Table 2** (continued)

| Characteristic | | *n* | % |
|---|---|---|---|
| STP first-line treatment | PI | 52 | 43 |
| | IMiD | 13 | 11 |
| | anti-CD38-mAB | 1 | 1 |
| | PI + IMiD | 30 | 25 |
| | anti-CD38-mAB + PI | 8 | 7 |
| | anti-CD38-mAB + IMiD | 4 | 3 |
| | anti-CD38-mAB + PI + IMiD | 4 | 3 |
| | Others[7] | 8 | 7 |
| STP first-line treatment - Novel drug classes[8] | 0 | 8 | 7 |
| | 1 | 66 | 55 |
| | 2 | 42 | 35 |
| | 3 | 4 | 3 |
| STP first-line treatment including HCT | Yes | 42 | 34 |
| | 1 autologous | 38 | 90 |
| | ≥ 2 autologous | 3 | 7 |
| | allogeneic | 1 | 3 |

[1]data available for 119 patients (1 asecretory); [2]data of 97 patients with PS plasmacytoma [3]data available for 41 patients, including patients with multiple organ involvement [4]data available for 57 patients; [5]data available for 117 patients; [6]patients with at least 1 HRCA; [7]including classical chemotherapy; [8]PI, IMiD and anti-CD38-mAB. HCT: Hematopoietic cell transplantation; HRCA: High-risk cytogenetic aberrations; IMiD: Immunomodulatory drugs, LC: Light chain; mAB: monoclonal antibody; MM: Multiple myeloma; PI: Proteasome inhibitors; PS: Paraskeletal; STP: Soft-tissue plasmacytoma

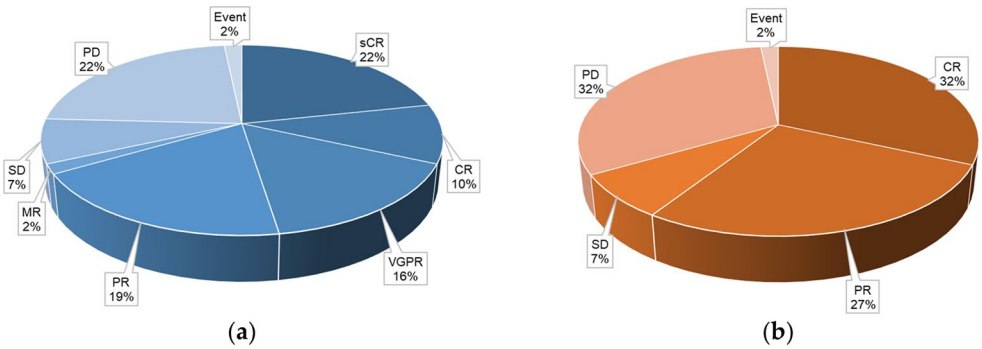


**Fig. 1** Serological (**a**) and imaging (**b**) response of the first-line treatment for 120 patients with STP

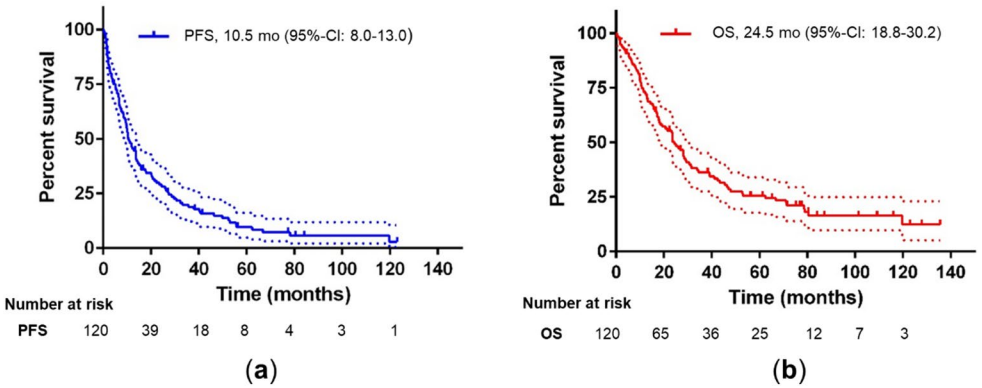


**Fig. 2** Progression-free survival (**a**) and overall survival (**b**) in 120 patients with STP

## Discussion

Pts with STP have a significantly worse prognosis than pts with MM without extramedullary involvement. Therefore, there is a significant need for in-depth studies and comprehensive analyses for this subgroup. In recent years, it has been repeatedly discussed whether PS involvement alone is sufficient for the definition of STP or whether only hematogenously spread diseases should be included in this category. Most studies restrict the definition of STP to cases in which the STP only results from hematogenous dissemination (Rosiñol et al. 2021; Usmani et al. 2012; Weinstock

**Table 3** Hazard ratio (HR, 95%-CI) and p-values of remaining factors of reduced multivariate Cox proportional hazards analysis for progression-free survival (PFS) and overall survival (OS)

| | Factor | Number of Patients | HR (95%-CI) | *p*-value |
|---|---|---|---|---|
| PFS | Secondary STP | 46 | 2.754 (1.728–4.390) | < 0.001 |
| | Organ involvement | 41 | 1.449 (0.954–2.201) | 0.082 |
| | STP first-line treatment with AHCT | 41 | 0.578 (0.365–0.918) | 0.020 |
| OS | Secondary STP | 46 | 2.628 (1.704–4.053) | < 0.001 |
| | Organ involvement | 41 | 1.675 (1.075–2.611) | 0.023 |
| | STP therapy with PI + IMiD | 30 | 0.516 (0.298–0.894) | 0.018 |

AHCT: Autologous hematopoetic cell transplantation; IMiD: Immunomodulatory drugs; PI: Proteasome inhibitors; STP: Soft-tissue plasmacytoma

and Ghobrial 2013). However, pts with PS and EMD have a significantly worse prognosis than those with MM with exclusively myeloid proliferation (Beksac et al. 2020; Mangiacavalli et al. 2017; Montefusco et al. 2020; Pour et al. 2014; Usmani et al. 2012; Varettoni et al. 2010). Since both exclusively PS plasmacytoma and extramedullary organ involvement (with or without PS) have a negative impact on survival (Rosiñol et al. 2021), we included in our study population and considered both as prognostic factor in the univariate and multivariate analysis.

The response rates are consistent with those in the literature, which shows a lower radiological than serological response (Rosiñol et al. 2006; Zhou et al. 2020). The median PFS and OS in our study (10.5 and 24.5 months) were comparable to those in other studies that considered both PS and EMD and primary and secondary STP. For example, recently, a large cohort of more than 1300 pts has been reported that the median OS rates of pts with PS and those with EMD were 44 and 20 months, respectively (Jiménez-Segura et al. 2022). Mangiacavalli et al. (2017) revealed that the median OS rates of pts with PS and those with EMD were 2.2 and 1.6 years, respectively. This finding is also comparable to our data. The cut-off year 2014 was chosen for stratification because pomalidomide was approved as third-line MM treatment in 2013 and an era of rapid approval of other modern drugs for MM treatment has started. Nevertheless, there was no significant improvement in the median PFS and OS in our study population treated between 2000 and 2013 compared with that treated between 2014 and 2022. Thus, even in the era of novel drug classes for MM, the unfavorable prognosis of STP cannot be overcome, and the treatment results remain below expectations. This is in contrast to the continuous and rapid improvement of treatment outcomes in pts with MM without PS involvement or EMD (Sneyd et al. 2021; Varettoni et al. 2010). The fact that STP is often not considered or analyzed separately in large randomized studies for pts with NDMM (Facon et al. 2021; Gay et al. 2021; Goldschmidt et al. 2022; Moreau et al. 2019) limits the ability to compare NDMM pts with STP versus NDMM pts without STP.

Knowledge about the prognostic factors in pts with STP is limited. This was addressed via a multivariate Cox proportional hazard regression analysis, which showed that secondary STPand organ involvement were independent prognostic factors of PFS and OS. Based on these parameters, a risk score was developed, which indicated that the occurrence of at least one of these factors is associated with a signicantly worse PFS and OS. Several authors have described del17p13 or gain1q21 as strong markers of extramedullary progression (Besse et al. 2016; Billecke et al. 2013; Shin et al. 2015). Nevertheless, the prognostic significance of HRCA in STP remains unclear. In our analysis, del17p13 (included in R-ISS) and ampl1q21 were considered as univariate prognostic factors of PFS and OS, respectively. However, the multivariate model did not confirm this finding. Nevertheless, the proposed prognostic score must be considered preliminary and needs to be validated in independent and larger cohorts.

STP is a prognostically unfavorable aggressive disease (Touzeau and Moreau 2016; Lonial et al. 2015a). Therefore,

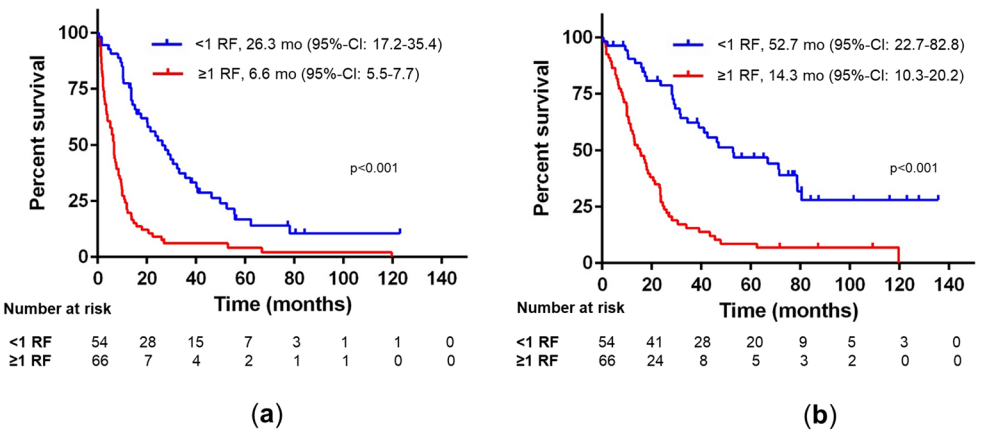


**Fig. 3** Progression-free survival (**a**) and overall survival (**b**) in 120 STP patients with < 1 or ≥ 1 risk factor (RF)

there is a need for risk-adapted treatment concepts. However, the role of consolidating autologous tandem HCT (Gagelmann et al. 2018) or allogeneic HCT (Rasche et al. 2016; Yin et al. 2018) remains unclear. The use of classical chemotherapy (without novel drugs) is probably limited to relapsed STP and should be followed by HCT to achieve long-term survival (Rasche et al. 2014).

In our study population, the combination of PI and IMiD as the first-line treatment was a superior univariate factor (PFS and OS) and remained a signficant factor after stepwise reduction in the multivariate analysis of OS. Consistently, for several years, PI (Rosiñol et al. 2006; Zhou et al. 2020) and IMiD (Besse et al. 2016; Calvo-Villas et al. 2011; Short et al. 2011) in pts with STP are known to have a high efficacy. The efficacy of additional anti-CD38-mAb treatment remains unclear due to its infrequent administration as first-line treatment in our study cohort. Previous studies investigated the efficacy of anti-CD38-mAb daratumumab or isatuximab (Dimopoulos et al. 2021; Jullien et al. 2019; Pick et al. 2018). The rate of response to daratumumab treatment as monotherapy in pts with STP in those studies was < 25%.

The poor outcome in this retrospective analysis confirmed the urgent need for the development of novel treatment options for pts with STP. The approval of advanced therapy medicinal products such as CAR T cells and bispecific antibodies has significantly improved the treatment of pts with relapsed/refractory MM. However, its long-term benefit in STP should still be evaluated. In large pivotal trials on CAR T cell therapies for MM, STP accounted for approximately 20–40% of all cases. This subgroup showed a consistent PFS benefit compared with standard therapy in both approved CAR T products ide-cel and cilta-cel (Lin et al. 2023; Munshi et al. 2021). Moreover, the ORR of pts with and without STP are comparable. However, the PFS of this subgroup is still poor (< 8.5 months), which emphasizes the need for novel treatment strategies. In pivotal studies on the bispecific antibodies teclistamab (Miao et al. 2023), talquetamab (Krishnan et al. 2023), and elranatamab (Touzeau et al. 2023), pts with extramedullary manifestations, which are negative prognostic factors, had reduced ORR or poor PFS.

In conclusion, although a retrospective analysis has various limitations, our study showed that the prognosis of pts with STP remains poor. Secondary STP and organ involvement were found to be relevant independent risk factors. Neither intensive chemotherapy with autologous and/or allogeneic HCT nor the novel cell-/immunotherapies (CAR T cells, bispecific antibodies) have, thus far, improved the treatment outcomes of pts with STP similar to that of pts with RRMM. Therefore, the establishment of risk-adapted standardized guidelines and treatments remains an important challenge in the future. In addition to the development of novel (targeted) drugs, databases (multicenter registry studies, establishment of STP biobanks) is required in order to improve pts outcomes and apply the novel treatment algorithms in clinical practice.

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**Author contributions** DZ was responsible for data collection, research implementation, and data analysis. He was responsible for writing the first draft including literature review. SK supported the data collection and analysis and the review of the manuscript. PW supported the statistical analysis, data visualization, and manuscript preparation. JZ and MP assisted with data collection and evaluation and the preparation of the first draft of the manuscript. RH, AH, and AM provided feedback on the study design and the first draft of the manuscript. SI was the statistician responsible for the preliminary data evaluation and the statistical models. SF was involved in the interpretation of the results and the review of the manuscript. MH supervised the work, provided feedback and was responsible for the initial data collection and project administration.

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**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Ethical approval** The study was approved by the regional ethics committee of the institution (The State Chamber of Physicians of Saxony, EK-BR-118/22 – 1).

**Patient consent** Patient consent was waived in accordance with the ethical approval due to retrospective design of the analysis and anonymization.

**Competing interests** The authors declare no competing interests.

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