Transfusion Medicine and Hemotherapy

Research Article

Transfus Med Hemother 2023;50:475–490
DOI: 10.1159/000531935

Received: February 21, 2023
Accepted: July 3, 2023
Published online: October 16, 2023

A German-Wide Systematic Study on Mobilization and Collection of Hematopoietic Stem Cells in Poor Mobilizer Patients with Multiple Myeloma prior to Autologous Stem Cell Transplantation

Max Bittrich[a] Katharina Kriegsmann[b, c] Carola Tietze-Stolley[d] Kamran Movassaghi[d] Matthias Grube[e] Vladan Vucinic[f] Daniela Wehler[g] Andreas Burchert[h] Martin Schmidt-Hieber[i] Andreas Rank[j] Heinz A. Dürk[k] Bernd Metzner[l] Christoph Kimmich[l] Marcus Hentrich[m] Christian Kunz[n] Frank Hartmann[o] Cyrus Khandanpour[p, q] Maike de Wit[r] Udo Holtick[s] Michael Kiehl[t] Andrea Stoltefuß[u] Alexander Kiani[v, w] Ralph Naumann[x] Christian W. Scholz[y] Hans-Joachim Tischler[z] Martin Görner[A] Franziska Brand[B] Martin Ehmer[B] Nicolaus Kröger[C]

[a]Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany; [b]Department of Hematology, Oncology and Rheumatology, University Hospital Heidelberg, Heidelberg, Germany; [c]Laborarztpraxis, Laborarztpraxis Rhein-Main MVZ GbR, Limbach Gruppe SE, Frankfurt am Main, Germany; [d]Department of Hematology and Oncology, Stem Cell Facility, University Hospital Charité, Berlin, Germany; [e]Department of Hematology and Internistic Oncology, University Hospital Regensburg, Regensburg, Germany; [f]Klinik und Poliklinik für Hämatologie, Zelltherapie und Hämostaseologie, University Hospital Leipzig, Leipzig, Germany; [g]Klinik und Poliklinik für Innere Medizin III, University Hospital of Mainz, Mainz, Germany; [h]Klinik für Hämatologie, Onkologie und Immunologie, University Hospital of Gießen and Marburg (UKGM), Marburg, Germany; [i]2. Medizinische Klinik für Hämatologie, Onkologie, Pneumologie und Nephrologie, Carl-Thiem Hospital Cottbus gGmbH, Cottbus, Germany; [j]2. Medizinische Klinik – Hämatologie, Internistische Onkologie und Hämostaseologie, University Hospital of Augsburg, Augsburg, Germany; [k]Klinik für Hämatologie und Onkologie, St. Barbara Hospital Hamm-Heessen, Hamm, Germany; [l]Universitätsklinik für Innere Medizin – Onkologie und Hämatologie, University Hospital Klinikum Oldenburg, Oldenburg, Germany; [m]Abteilung für Innere Medizin III – Hämatologie und Onkologie, Rotkreuzklinikum München, Munich, Germany; [n]Innere Medizin I, Westpfalz-Klinikum Kaiserslautern, Kaiserslautern, Germany; [o]Klinik für Onkologie und Hämatologie, Hospital Lippe-Lemgo, Lemgo, Germany; [p]Medizinische Klinik A, University Hospital Münster, Münster, Germany; [q]Klinik für Hämatologie und Onkologie, University Hospital Schleswig-Holstein (Campus Lübeck) and University of Lübeck, Lübeck, Germany; [r]Klinik für Innere Medizin – Hämatologie, Onkologie und Palliativmedizin, Vivantes Hospital Neukölln, Berlin, Germany; [s]Department I of Internal Medicine, Medical Faculty and University Hospital of Cologne, University of Cologne, Cologne, Germany; [t]Medizinische Klinik I, Hospital Frankfurt (Oder), Frankfurt an der Oder, Germany; [u]Klinik für Innere Medizin II, Evangelisches Krankenhaus Hamm, Hamm, Germany; [v]Department of Hematology and Oncology, Klinikum Bayreuth, Bayreuth, Germany; [w]Comprehensive Cancer Center Erlangen-EMN (CCC ER-EMN), Erlangen, Germany; [x]Klinik für Hämatologie, Medizinische Onkologie und Palliativmedizin, St. Marien-Krankenhaus Marien Gesellschaft Siegen gGmbH, Siegen, Germany; [y]Klinik für Innere Medizin – Hämatologie und Onkologie, Vivantes Hospital Am Urban, Berlin, Germany; [z]Universitätsklinik für Hämatologie, Onkologie, Hämostaseologie und Palliativmedizin, Johannes Wesling Hospital Minden, Mühlenkreiskliniken, Minden, Germany; [A]Klinik für Hämatologie, Onkologie, Palliativmedizin und Stammzelltherapie, Hospital Bielefeld-Mitte, Bielefeld, Germany; [B]Sanofi-Aventis Deutschland GmbH, Berlin, Germany; [C]Interdisziplinäre Klinik und Poliklinik für Stammzelltransplantation, University Hospital Hamburg-Eppendorf, Hamburg, Germany

karger@karger.com
www.karger.com/tmh

Correspondence to:
Max Bittrich, bittrich_m@ukw.de

Keywords
Poor mobilizer · Plerixafor · Multiple myeloma · Stem cell collection · Autologous stem cell transplantation

Abstract
Introduction: In patients with a clinical indication for autologous hematopoietic stem cell transplantation (ASCT), sufficient mobilization of $CD34^+$ precursor cells into peripheral blood is essential to ensure adequate hematopoietic stem cell (HSC) collection prior to intensive therapy. However, with standard granulocyte-colony stimulating factor (G-CSF)-based mobilization schemes, an important minority of patients fail to mobilize sufficient (e.g., >10/μL) $CD34^+$ cell counts into the peripheral blood and are considered as poor mobilizers (PM). Because failure to achieve sufficient $CD34^+$ cell mobilization can negatively affect important clinical treatment endpoints, the use of plerixafor (PLX) was approved to increase $CD34^+$ mobilization in PM patients. ***Methods:*** The German non-interventional, multicenter, open-label, prospective OPTIMOB study evaluated HSC mobilization strategies prior to planned ASCT in adult patients with hematologic malignancies (lymphomas or multiple myeloma [MM]) focusing on PM patients. PM patients were defined as follows: (1) never achieving ≥20 $CD34^+$ cells/μL before 1st apheresis, (2) receiving PLX at any timepoint of mobilization, (3) their initially planned stem cell yield had to be reduced, or (4) they had not received apheresis due to low $CD34^+$ count in peripheral blood. ***Results:*** 168 of 475 MM patients (35%) participating in the OPTIMOB study were classified as PM, and 155 of them (92%) received PLX (PM+PLX) during the study. PM patients were 40–78 years old, slightly more often male (n = 97, 58%), mostly newly diagnosed (n = 146, 87%) and received highly individualized previous treatments. Ninety-four of the PMs underwent chemotherapy mobilization (65%), and 51 patients (35%) received steady-state mobilization with G-CSF only during 1st mobilization attempt. 92% of the total PM population (n = 155) underwent apheresis, 78% of them (n = 117) achieved >2.0×10^6 $CD34^+$ cells/kg body weight on the 1st day of apheresis. PM+PLX had a higher median total collection result than those PM patients without PLX support (7.2 vs. 5.7 × 10^6 $CD34^+$ cells/kg body weight). In total, ASCT was performed in 136 PM+PLX (88%) versus 8 PM−PLX patients (62%). ***Conclusion:*** The OPTIMOB study showed that a considerable proportion of adult MM patients in Germany are PMs. Even though most of PMs were supported with PLX in the OPTIMOB study, PM-PLX also successfully mobilized HSCs, allowing ASCT in majority of all PMs. However, further analyses are required for treatment optimization in PMs.

Introduction

In younger patients with newly diagnosed multiple myeloma (MM), high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) represents a standard of care which can lead to an improvement in response rate, the duration of response, and the overall survival [1–5]. Critical for ASCT is the prior collection of a sufficient number of hematopoietic $CD34^+$ progenitor cells (HSCs), allowing rapid recovery of hematopoietic system after myeloablative chemotherapy. Most patients can mobilize at least 2.0×10^6 $CD34^+$ progenitor cells/kg body weight as a minimum requirement for safe ASCT [6]. Some, however, do not achieve this goal, they are so-called "poor mobilizers" (PM). They are characterized by a $CD34^+$ progenitor cell count <20 cells/μL in peripheral blood (PB) on the day of apheresis and/or failure to reach the minimum HSC collection target [6–9]. The European Society for Blood and Marrow Transplantation (EBMT) consensus defined PMs as those who had a $CD34^+$ progenitor cell count <10 cells/μL on day 4 of mobilization or who were not able to obtain half of the number of $CD34^+$ progenitor cells expected for ASCT after one apheresis session [10]. Compared to good mobilizing (GM) patients, PM patients often have longer mobilization phases and need several apheresis procedures and/or a repetition of the entire mobilization process at a later stage. In addition to the risk of interim disease progression due to a delay in the planned high-dose chemotherapy-ASCT, failure of HSC collection may finally result in the cancellation of the planned ASCT [7]. Additionally, mobilization and apheresis are stressful for patients and represent cost-intensive processes.

In the literature, up to 45% of the patients were classified as PM [7, 8, 11–14], forcing the treating physicians to optimize the planning and conduction of mobilization and ASCT in this patient group. The increasing rate of PM patients, especially in those having MM, is associated with the intensified use of induction regimens containing immunomodulatory imide drugs (IMiDs) such as lenalidomide or thalidomide and/or targeted anti-CD38 antibodies [5, 15–20]. Those agents are considered to increase the homing of HSCs in the bone marrow niche and to have a potential direct effect on antigen-carrying progenitor cells, both leading to insufficient HSC mobilization [21–26].

Approved mobilization strategies are treatments with granulocyte-colony stimulating factor (G-CSF) with or without chemotherapy prior to apheresis [8, 27]. Plerixafor (PLX) is also frequently used to prevent mobilization failure and to improve collection outcome. Pivotal trials of PLX use in adult patients have shown that PLX plus G-CSF is superior to G-CSF alone in MM patients regarding mobilization of HSCs into the PB, increasing

the number of collected $CD34^+$ progenitor cells, and reduction of the number of necessary apheresis procedures [28]. Those results were confirmed by retrospective studies indicating that a prophylactic use of PLX (vs. without PLX) reduced the number of apheresis procedures and simultaneously increased the success rate in PM patients [29, 30].

The guideline on autologous stem cell mobilization from the German working group for HSC transplantation and cellular therapies e.V., lists PMs and PM mobilization strategies, such as the required $CD34^+$ progenitor cell count in PB for the use of PLX [31]. However, clinical approaches and the use of PLX are not consistent in German clinical practice. Reduction of the (optimal) $CD34^+$ collection target of $>5.0 \times 10^6$ $CD34^+$ progenitor cells/kg body weight to the necessary minimum of $>2.0 \times 10^6$ $CD34^+$ progenitor cells/kg body weight is often done to reduce both, the treatment burden in affected patients and treatment costs. However, reduction of the HSC collection target to the minimum, limits the possibilities of implementing several transplantations and the option of administering a high HSC dose in MM. As a result, this may delay the hematopoietic recovery [32] leading to an increased risk of infections and, consequently, negatively impacting treatment outcome and prognosis. Until now, consistent information concerning the distribution and type of mobilization treatment of adult, transplant-eligible patients with MM or lymphoma classified as PM is rare. Therefore, the OPTIMOB study was initiated to systematically assess the current approach of HSC mobilization, apheresis, and ASCT focusing on the appropriate choice of therapy in PM patients. In this manuscript, results from the MM cohort are presented.

Materials and Methods

Study Design and Study Population

The prospective, multicenter, open-label, non-interventional OPTIMOB study evaluated HSC mobilization procedures and collection parameters of adult patients suffering from MM or lymphoma who were eligible for ASCT in routine clinical practice in Germany. The aim of the study was to analyze the mobilization and HSC collection strategies focusing on PMs. The OPTIMOB study was conducted at 28 sites, mainly departments of hematology and medical oncology (89%, $n = 25$). Adult patients with MM or lymphoma confirmed by World Health Organization criteria eligible for autologous stem cell mobilization and transplantation who gave their informed consent were documented in the OPTIMOB study. Patients who had another disease for which ASCT is indicated, who were no longer candidates for ASCT according to medical recommendations/internal clinic standards at the time of the $CD34^+$ progenitor cell count in the PB on the day before apheresis, and/or had other hematological or solid tumors were not eligible for study participation. The median duration of the observational period was 6 months (range: 1 day to 29 months) with large variations between patients due to highly individualized treatments.

Study Objectives

The primary objective of the study was a successful mobilization in PM patients as measured by the number of HSCs collected on day 1 of apheresis ($>2.0 \times 10^6$ $CD34^+$ progenitor cells/kg body weight). Secondary objectives included the evaluation of mobilization efficacy defined as increase of $CD34^+$ progenitor cell count between the day before and the first day of apheresis, the rates of poor mobilizing patients in German clinical practice, of those patients reaching a total collection result of $>2.0 \times 10^6$ $CD34^+$ progenitor cells/kg body, of patients achieving their individual pre-specified target $CD34^+$ progenitor cell yield, the engraftment data, and the rate of patients with mobilization failure defined as nonperformance or discontinuation of apheresis.

Data Collection

Data collection took place between July 2018 and November 2021 and started for all patients with the assessment of baseline data before the first mobilization. Individual mobilization status (PM or GM) was determined after HSC mobilization. In light of the multiple interpretations of "PM" patients, our study chose to formulate an all-embracing definition of PM patients. PM patients were those, (1) who never achieved ≥20 $CD34^+$ progenitor cells/μL before first apheresis, (2) who received PLX at any timepoint during the observational period, (3) for whom the initially planned $CD34^+$ progenitor cell yield was reduced due to failed mobilization or HSC collection, and (4) who had not received apheresis due to low $CD34^+$ progenitor cell count. We entrusted the physicians at our participating sites with the responsibility to identify the most fitting category. Nevertheless, it is essential to highlight that patients might resonate with more than one predefined category in the course of the disease (from GM to PM). Reasons for this were no achievement of the initially requested number of $CD34^+$ progenitor cells during apheresis or necessity of PLX administration during remobilization due to a poor outcome of the 1st mobilization attempt performed without PLX support. PM patients were evaluated in detail and stratified into two groups (PM patients with PLX support and PM patients without PLX support). In contrast to PM patients, for GM patients, limited data were recorded at the time of the initial observation, identification of the mobilization status, as well as after stem cell collection (shown in Fig. 1).

Statistical Analysis

Due to the non-interventional character of the observational study, all analyses in this study were explorative. Statistical analyses were performed using SAS version 9.4. Categorical variables are presented as n and %. Quantitative variables are shown as median with range. All enrolled patients who gave their informed consent and were eligible to participate in the study were included in the intention-to-treat set (ITT set). The modified ITT set (mITT set) comprised all patients of the ITT set for whom the number of collected stem cells on day 1 of apheresis was available. Demographic data, medical history, disease characteristics, and previous treatments were summarized descriptively. The primary and the secondary endpoint variables were calculated with summary statistics. The primary objective was calculated for PM patients of the mITT set; for secondary objectives, the ITT set was used. Recovery of the hematopoietic system was evaluated by the number of days until the absolute neutrophil count was $>0.5 \times 10^9$/L and platelet counts were $>50 \times 10^9$/L after ASCT. A grading of adverse events (AEs) and serious AEs was not documented in the study.

Ethical Statement

This study was conducted in compliance with Local Ethics Committees (EC), informed consent regulations, and local regulatory requirements. The observational plan, informed consent

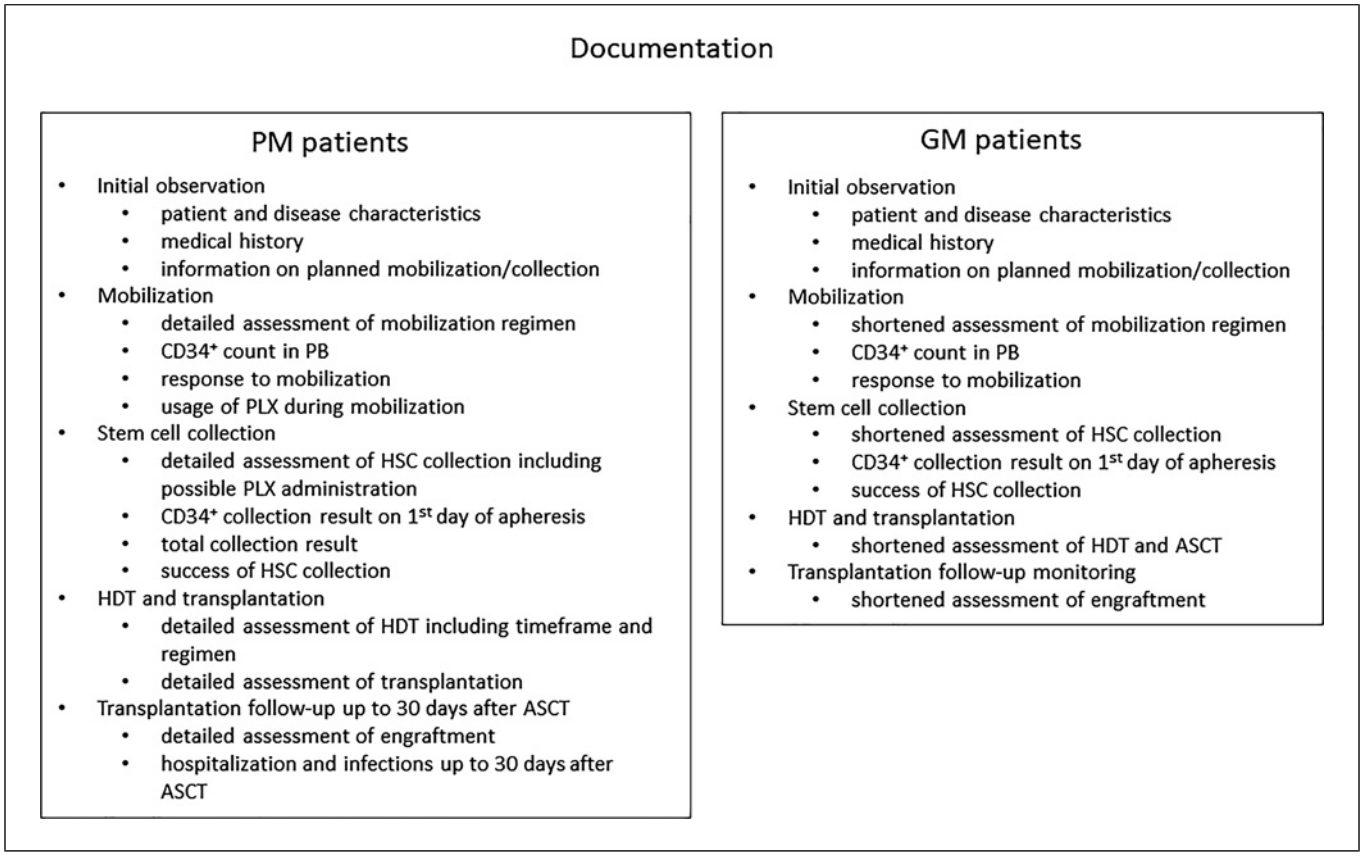


Fig. 1. Data collection stratified by mobilization status. ASCT, autologous stem cell transplantation; GM, good mobilizer; HDT, high-dose chemotherapy; HSC, hematopoietic stem cells; PB, peripheral blood; PM, poor mobilizer; PLX, plerixafor.

documents, and any other appropriate study-related documents were approved by the Ethikkommission der Ärztekammer Hamburg, Hamburg, Germany, as the responsible Central Ethics Committee, and by all other Ethics Committees of state chambers of the participating physicians. All patients gave their written informed consent before documentation started.

Results

Patient Disposition

A total of 779 patients were screened for eligibility in the OPTIMOB study. Of these, 501 patients had MM and 261 had lymphoma. Seventeen patients were excluded from the study as the underlying disease was missing. Out of 493 MM patients participating in the study, the mobilization status was determined in 475 patients (ITT set, shown in Fig. 2a). In total, 65% of the patients (n = 307) were classified as GM and 35% of the patients (n = 168) as PM (shown in Fig. 2a). Within the PM patient group, 92% of the patients (n = 155) received PLX (PM+PLX) during study participation in contrast to 8% of the patients (n = 13) who did not receive PLX (PM–PLX) (shown in Fig. 2b). The mITT set consists of 151 PM and 304 GM patients (shown in Fig. 2a).

ASCT was conducted in 144 (86%) PM and 294 (95%) GM patients (shown in Fig. 2a). Thirteen GM and four PM patients discontinued the OPTIMOB study prematurely because of death (n = 10) or loss to follow-up (n = 7, shown in Fig. 2a).

Patient demographics and disease-specific data at baseline are provided in Table 1. The study population was aged from 36 to 78 years with a slight male predominance. Patients' activity (Eastern Cooperative Oncology Group [ECOG] performance status/Karnofsky performance status) was not or only marginally limited regardless of their mobilization status. Most of the patients were newly diagnosed (from 69% to 96%) and underwent their first mobilization attempt during the OPTIMOB study (from 85 to 95%).

A combination of bortezomib, cyclophosphamide, and dexamethasone (VCd regimen) was the most common last therapy prior to mobilization in GM patients (43%, n = 132) and in PM patients who received PLX during the study course (28%, n = 43, shown in Table 2). In PM patients without PLX administration, the combination of lenalidomide, bortezomib, and dexamethasone (RVd) was most frequently applied (31%, n = 4), albeit RVd is not approved by the European Medicines Agency (EMA)

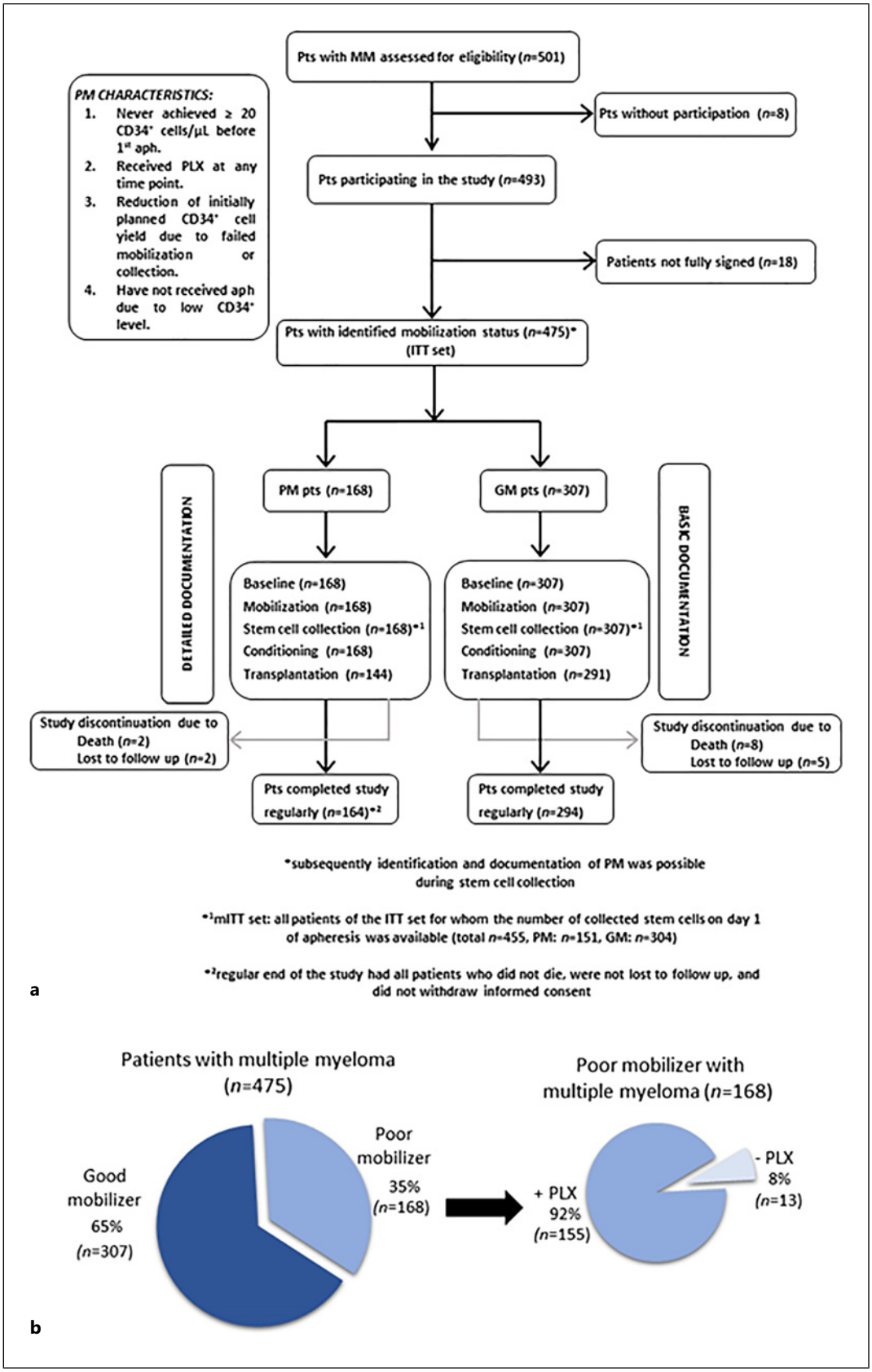


Fig. 2. a Consort flow diagram of the multiple myeloma (MM) patient cohort in the OPTIMOB study. **b** MM patients stratified by mobilization status and PLX administration. Aph, apheresis; GM, good mobilizer; ITT set, intention-to-treat set; mITT set, modified ITT set; MM, multiple myeloma; *n* number of patients; PLX, plerixafor; PM, poor mobilizer; Pts, patients; +PLX, patients with plerixafor administration; –PLX, patients without plerixafor administration.

Table 1. Patient demographics and medical characteristics at baseline

	PM+PLX, *n* (%)	PM–PLX, *n* (%)	GM, *n* (%)
Patients, *n*	155 (100)	13 (100)	307 (100)
Age, median (range), years	61 (40–78)	65 (47–71)	61 (36–76)
Age (categorical) ≥70 years	28 (18)	2 (15)	41 (13)
Weight (range), kg	74.00 (40–125)	77.00 (60–108)	79.00 (47–135)
Sex			
Male	89 (57)	8 (62)	171 (56)
Female	66 (43)	5 (39)	136 (44)
ECOG/Karnofsky scale			
0–1 (= Karnofsky: 70–100%)	104 (67)	7 (54)	211 (69)
2–3 (= Karnofsky: 30–60%)	8 (5)	1 (8)	12 (4)
Missing	43 (28)	5 (38)	84 (27)
Disease status			
Recently diagnosed (no relapse/disease progression)	137 (88)	9 (69)	295 (96)
≥1st relapse	17 (11)	4 (31)	10 (3)
Not evaluated	1 (1)	0 (0)	2 (1)
Mobilization status			
1st mobilization attempt	134 (86)	11 (85)	291 (95)
Remobilization*	6 (4)	0 (0)	3 (1)
2nd mobilization attempt*[1]	13 (8)	2 (15)	5 (2)
Missing/unknown	2 (1)	0 (0)	8 (3)
Subtype MM classification			
MM heavy and light chains	91 (59)	3 (23)	186 (61)
MM light chains	59 (38)	9 (69)	111 (36)
Other*[2]	5 (3)	1 (8)	10 (3)
ISS stadium			
I	45 (29)	3 (23)	115 (37)
II	40 (26)	6 (46)	77 (25)
III	36 (23)	2 (15)	62 (20)
Missing/not evaluated	34 (22)	2 (15)	53 (17)
Thrombocytopenia (yes)	30 (19)	4 (31)	48 (16)*[3]
Leukopenia (yes)	36 (23)	1 (8)	60 (20)*[3]
Relevant comorbidities (yes)*[4]	127 (82)*[3]	13 (100)	232 (76)
Previous or concomitant medication (yes)	139 (90)	12 (92)	193 (63)

+PLX, patients with PLX administration; −PLX, patients without PLX administration; PLX, plerixafor; ECOG, Eastern Cooperative Oncology Score. *Remobilization was defined as mobilization after failed mobilization and/or sampling failure. *[1]Second mobilization attempt was defined as mobilization for 2nd stem cell transplantation. *[2]Including MM not secretory, plasma cell leukemia, solitary plasmacytoma of the bone, primary amyloidosis, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal-protein, skin lesions), other types not further defined. *[3]For 1 patient, data were missing or unknown. *[4]Relevant comorbidities were diabetes type 1 and type 2, cardiovascular diseases, joint disorders (arthritis), hyperlipidemia, arteriosclerosis, infections, coagulation disorders (thrombosis).

for the treatment of newly diagnosed transplant-eligible MM patients (see Table 2). In both the PM+PLX group and the GM group, one quarter (25–27%) of the patients received their last treatment as part of another clinical trial as shown in Table 2 consisting of RVd (+/− other medication, 33%, $n = 40$), KRd (carfilzomib, lenalidomide, dexamethasone, 21%, $n = 26$), or isatuximab in combination with RVd (Isa-RVd, 20%, $n = 24$). Details of the last treatments prior to study inclusion which were part of a clinical trial are provided in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000531935). In general, treatment of MM patients was highly individualized, as more than 15 different treatment regimens were documented for the MM cohort of the OPTIMOB study (shown in online suppl. Table 2). In median, patients in mobilization were in the first line of therapy with a median number of three cycles independent of their mobilization status (shown in online suppl. Table 2).

Table 2. Most frequently documented last therapies prior to mobilization

	PM+PLX, *n* (%)	PM-PLX, *n* (%)	GM, *n* (%)
Patients, *n*	155 (100)	13 (100)	307 (100)
Dara-Rd (+/− other)	8 (5)	0 (0)	2 (1)
Dara-VTd	3 (2)	0 (0)	7 (2)
Elo-KRd	5 (3)	0 (0)	10 (3)
Isa-RVd	6 (4)	1 (8)	17 (6)
KRd	18 (12)	1 (8)	22 (7)
RVd (+/− other)*	17 (11)	4 (31)	42 (14)
VCd (+/− other)	43 (28)	1 (8)	132 (43)
Share of patients, whose last treatment was part of another clinical trial	41 (26)	4 (31)	77 (25)

Dara-VTd, daratumumab, bortezomib, thalidomide, dexamethasone; Elo, elotuzumab; Isa, isatuximab; Rd, carfilzomib, lenalidomide, dexamethasone; RVd, lenalidomide, bortezomib, dexamethasone; VCd, bortezomib, cyclophosphamide, dexamethasone. *Excluding Isa-RVd.

Treatment Plan

In more than 60% of the patients in both PM patient groups and 76% of the GM patients, mobilization was planned using chemo-mobilization (shown in online suppl. Table 3). In contrast, steady-state mobilization was planned in about 23% of both PM patient groups (PM+PLX: $n = 36$, PM−PLX: $n = 3$) and in 10% of the GM group ($n = 30$, shown in online suppl. Table 3). For all 3 patient, groups a total collection target of median 6.00 × 10^6 $CD34^+$ progenitor cells/kg body weight was aimed (shown in online suppl. Table 3). For the majority of GM (67%, $n = 206$) and PM+PLX patients (65%, $n = 101$), HSC collection was planned to result in two transplantations and one backup (shown in online suppl. Table 3).

Mobilization and Apheresis

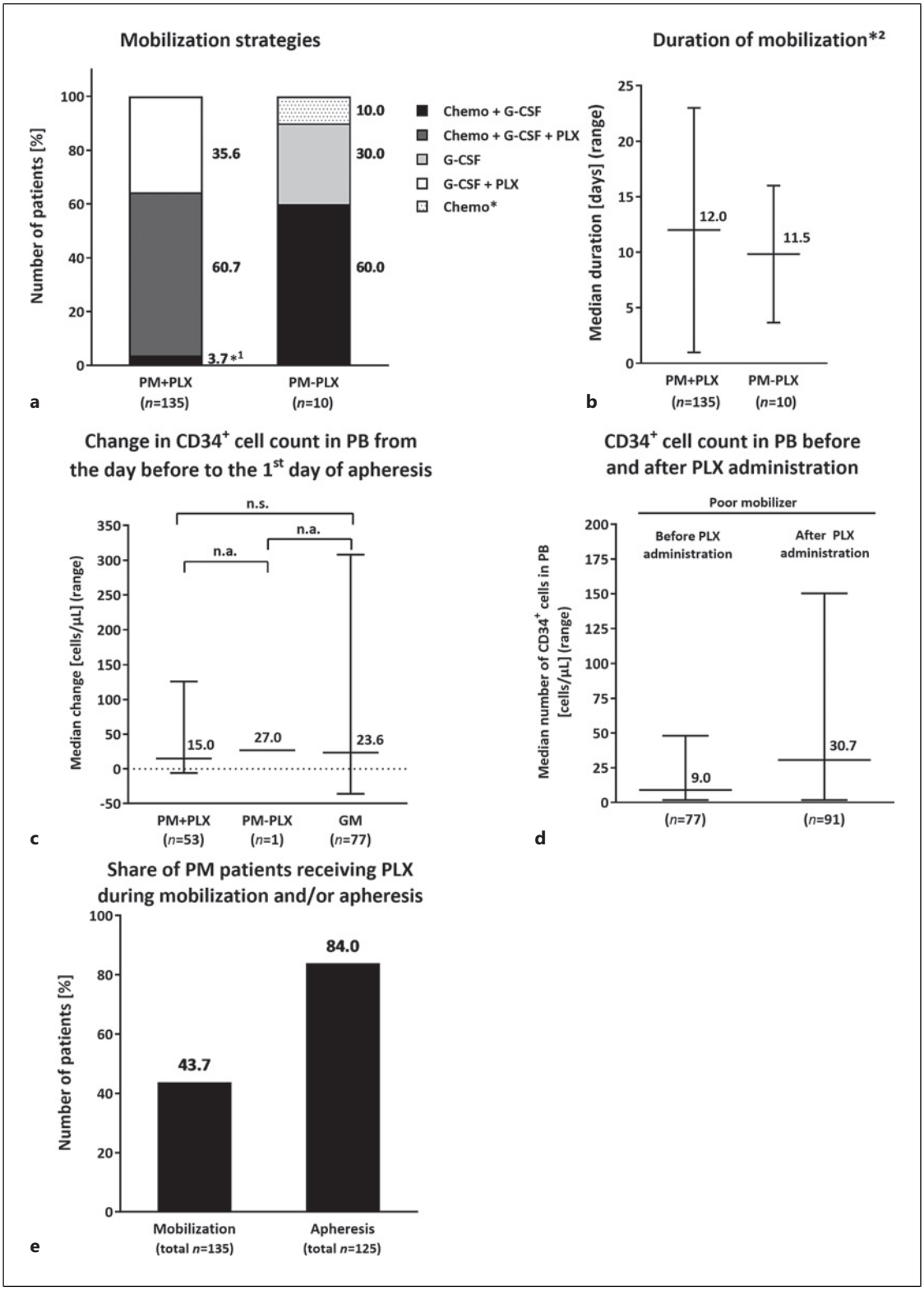
Except for 1 patient from the PM−PLX group, all PM patients received G-CSF during mobilization (shown in Fig. 3a). In the PM+PLX group, most patients underwent chemo-mobilization + G-CSF + PLX (61%, $n = 82$). In 36% of the PM+PLX patients ($n = 48$), mobilization was done with a combination of G-CSF and PLX only. Among PM−PLX patients, most patients received chemo-mobilization combined with G-CSF (60%, $n = 6$, shown in Fig. 3a). One-third (30%, $n = 3$) of the PM−PLX patients underwent "steady state" mobilization with G-CSF only (shown in Fig. 3a). Median duration of mobilization, defined as first day of chemo-mobilization or G-CSF administration until first day of apheresis, was nearly equal to 12 days in PM+PLX and 11.5 days in PM−PLX patients (shown in Fig. 3b). In PM+PLX patients, the median number of $CD34^+$ progenitor cells increased by 15 cells/μL in PB (range: −6 to 126) from the day before to the first day of apheresis (shown in Fig. 3c). In the PM−PLX group, data were only available for 1 patient showing an increase of 27 cells/μL between both days (shown in Fig. 3c). The median number of $CD34^+$ progenitor cells in PB increased markedly after PLX administration as shown in Figure 3d. PLX was given during mobilization and/or apheresis showing a more frequent PLX use during apheresis than during mobilization (84% [$n = 105$] vs. 44% [$n = 59$], shown in Fig. 3e).

As shown in Figure 4a, 94% of the PM patients ($n = 145$) with PLX administration were able to undergo apheresis. In the PM−PLX group, the share of patients was lower (77%, $n = 10$), but for the majority, apheresis was also possible. On day one of apheresis, the median total $CD34^+$ collection result was almost equal in both PM patient groups with 3.5 and 3.2 × 10^6 $CD34^+$ progenitor cells/kg body weight, respectively, but markedly lower than in the GM patient group (shown in Fig. 4b). The median total collection result was higher in the PM+PLX group (7.2 × 10^6 $CD34^+$ progenitor cells/kg body weight) than in the PM−PLX group (5.7 × 10^6 $CD34^+$ progenitor cells/kg body weight, shown in Fig. 4c); however, the range of the values in both groups largely overlap. In the PM+PLX group, more patients reached the requested $CD34^+$ progenitor cell target than in the PM−PLX group (87% [$n = 124$] vs. 56% [$n = 5$], shown in Fig. 4d).

Mobilization Success

Based on the mITT set, more than 75% of the total PM population achieved >2.0 × 10^6 $CD34^+$ progenitor cells/kg body weight on the first day of apheresis with 76% in the PM+PLX ($n = 107$) and 100% in the PM−PLX ($n = 10$) patient group (shown in Table 3). For a total of 66% of the PM patients in the mITT set, the mobilization result was stated as good by the treating physician ($n = 99$, shown in Table 3).

84% of the PM+PLX ($n = 114$) and 90% of the PM−PLX patients ($n = 9$) achieved a total collection result of >2.0 × 10^6 $CD34^+$ progenitor cells/kg body weight and



3

(For legend see next page.)

reached their requested individual optimal cell count, respectively (shown in Table 3). During first mobilization attempt, 8% (n = 11) of the total PM population with MM had a mobilization failure, as shown in Table 3. More than 88% of the PM+PLX patients (n = 136) but only 62% of the PM−PLX patients (n = 8) were able to undergo ASCT (shown in Table 3). Reasons for nonperformance of ASCT in the total PM study population were

progressive disease (n = 1), abortion of unsuccessful mobilization or apheresis (n = 12), other medical reasons (n = 5), patient wish (n = 3), other reasons not further specified (n = 3, shown in online suppl. Table 4).

Engraftment

Successful engraftment was documented by the treating physicians in 85% of the patients with PLX administration (n = 116) who underwent ASCT and in 75% of the patients without PLX support who underwent ASCT (n = 6, presented in Table 4). A minimal difference in the median number of days to achieve the relevant platelet count of $>50 \times 10^9$ cells/L was observed between PM+PLX and GM patients (15 days vs. 14 days, see Fig. 5a). Regarding obtaining absolute neutrophil count $>0.5 \times 10^9$ cells/L, the median number of days to engraftment varied from 11 days in GM and PM+PLX patients to 14 days in PM patients without PLX support (see Fig. 5b). The share of PM patients with infections during engraftment phase was higher in PM patients without PLX support (57% [n = 4] vs. 34% [n = 43]), whereas in the PM+PLX group, a greater share of patients received at least one infusion of thrombocytes (82% [n = 127] vs. 54% [n = 7]), as shown in Table 4.

Safety Aspects

Online suppl. Table 5 provides an overview of the safety results of the MM cohort in the OPTIMOB study. The proportion of patients with at least one AE was slightly greater in both PM patient groups (PM+PLX: 63%, n = 98, PM−PLX: 54%, n = 7) than in the GM patient group (42%, n = 129). At least one fatal AE was documented in 4 patients of the MM cohort (PM+PLX: n = 1, PM−PLX: n = 0, GM: n = 3). PLX was well tolerated. Only in 1 patient receiving PLX, an AE was documented with potential causal relationship to PLX (1% of the PM+PLX group, preferred term of the AE: stomatitis, belonging to the system organ class term gastrointestinal diseases, shown in online suppl. Table 5). No new safety issues regarding PLX were identified in the OPTIMOB study.

Discussion

The non-interventional, prospective OPTIMOB study assessed HSC mobilization and collection parameters as well as data regarding ASCT and engraftment of transplant-eligible patients with MM or lymphoma in Germany. In the here presented MM cohort, consisting of 475 evaluable patients, over 35% of the patients were classified as PM, and more than 90% of those were treated with PLX to improve HSC mobilization and collection outcome.

The PM definition used in the OPTIMOB study was much broader as used in the literature by EBMT [10] which may have led to a higher proportion of PM patients in the MM cohort being in the upper range of the data known from the literature [7, 8, 11–14]. However, since the PM criteria in other studies were also broader than postulated in the definition by Mohty et al. [10], more patients were also classified as PMs in these studies.

The primary objective of the study was a collection result of $>2.0 \times 10^6$ CD34$^+$ progenitor cells/kg body weight on day 1 of apheresis, representing a successful HSC mobilization which was reached by 76% of the PM+PLX and by 100% of the PM−PLX patients of the mITT set. In general, mobilization result was stated as good in most of the PM patients (66% of the total PM population). This outcome is supported by the fact, that 86% of all PM patients were able to undergo ASCT. Having a closer look at those PM patients supported by PLX, 65% of them had a good mobilization result assessed by the respective investigator and nearby 88% of them were able to undergo ASCT. Interestingly, in the PM setting without PLX administration, mobilization result was also rather good since all patients of the mITT set achieved $>2.0 \times 10^6$ CD34$^+$ progenitor cells/kg body weight on the first day of apheresis and 90% of the patients had a total collection result of $>2.0 \times 10^6$ CD34$^+$ progenitor cells/kg body weight and reached their individual requested collection target. At first glance, the results seem contradictory since the mobilization of HSCs into the PB is known to be enhanced by PLX administration [28]. Several studies showed that preemptive administration of PLX led to an almost 4-fold increase in CD34$^+$ progenitor cells in PB resulting in mobilization

Fig. 3. Mobilization strategies (**a**), duration of mobilization (defined as 1st day of chemo-mobilization or G-CSF administration until 1st day of apheresis) (**b**), change in CD34$^+$ cell count in PB from the day before to the 1st day of apheresis (**c**), CD34$^+$ cell count in PB before and after PLX administration in PM+PLX patients (**d**), and share of patients who received PLX during mobilization and/or apheresis (**e**) during 1st mobilization attempt. *1 patient from the PM−PLX group received only chemo-mobilization without G-CSF administration. *[1]5 patients were mobilized with chemotherapy plus G-CSF during 1st mobilization attempt but received PLX at remobilization and thus, they were classified as PM+PLX. *[2]Duration of mobilization was defined as beginning with chemo or G-CSF until the first day of apheresis. PB, peripheral blood; PM, poor mobilizer; PLX, plerixafor; +PLX, patients with plerixafor administration; −PLX, patients without plerixafor administration; chemo, chemo-mobilization; G-CSF, granulocyte-colony stimulating factor; n, number of patients; n.s., not significant; n.a., not applicable. **c** p value was calculated using Fisher's Exact test.

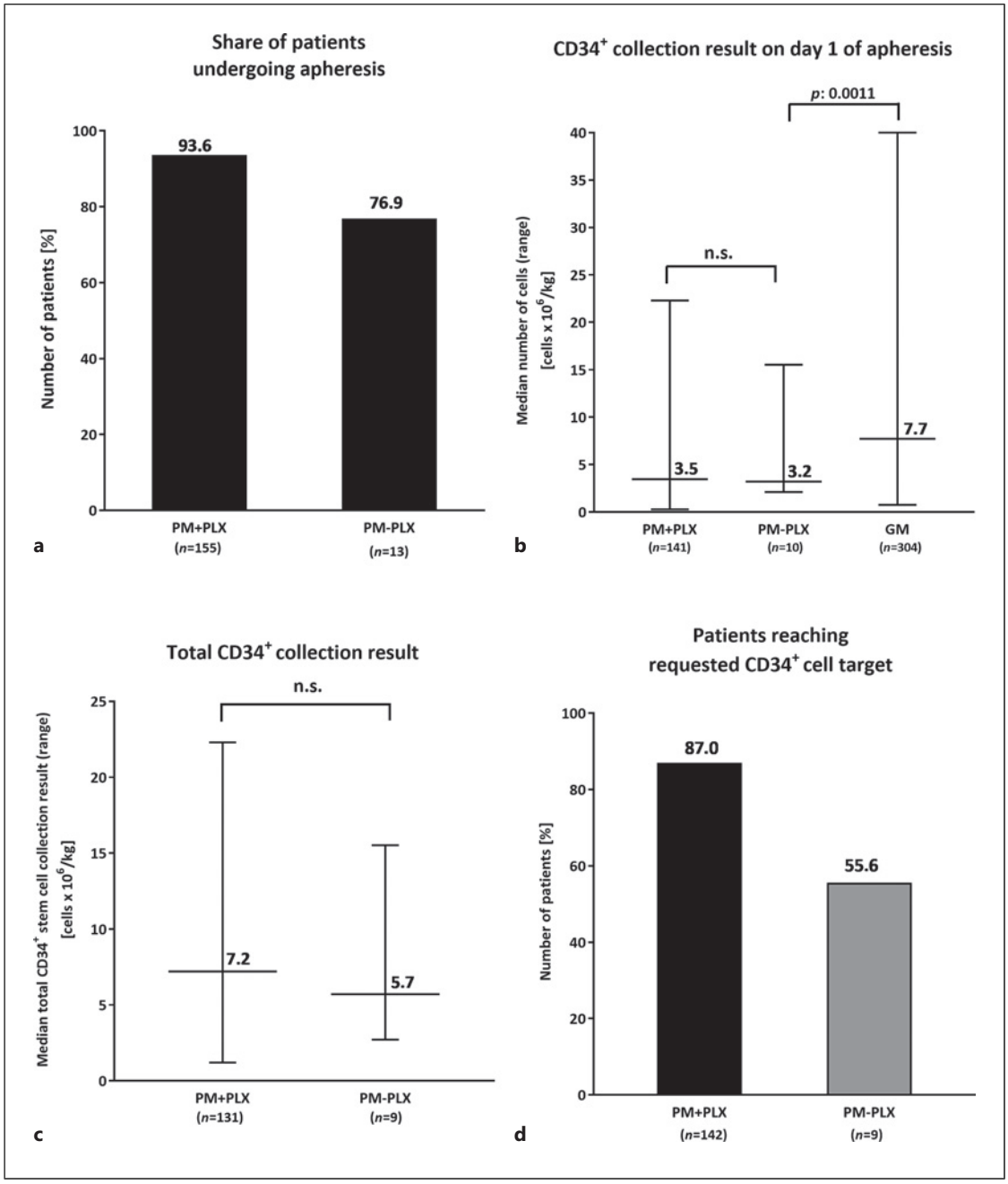


Fig. 4. Share of PM patients undergoing apheresis (**a**) and collection results (**b**–**d**). PLX, plerixafor; +PLX, patients with plerixafor administration; −PLX, patients without plerixafor administration; *n*, number of patients; n.s., not significant. **c** *p* value was calculated using Wilcoxon signed rank test.

rates of >90% [33, 34]. The OPTIMOB study confirmed that the addition of PLX to adult poor mobilizing MM patients resulted in an increase of the median CD34$^+$ cell count in the PB from 9.0 cells/μL to 30.7 cells/μL after PLX administration. Nevertheless, in the OPTIMOB study, even patients without PLX support were able to mobilize enough HSCs. However, as the PM−PLX group was represented by only a small number of patients (n = 13) in the MM cohort of the OPTIMOB study, the validity of this finding may be limited. Moreover, the OPTIMOB study was a non-interventional study without randomization to treatment groups, and the decision not to treat a PM with PLX was based on investigator's and patient's choice. Thus, we cannot exclude, that PM patients with any unknown factors indicating potential mobilization success, were unconsciously selected to the PM−PLX group. Since it was not asked why PLX was omitted in some PM patients, it can only be speculated whether these patients were considered as potential GMs or PMs with a good chance of sufficient mobilization.

Table 3. Efficacy of mobilization, mobilization failure, and share of patients undergoing ASCT in poor mobilizing patients with MM

	PM+PLX, *n* (%)	PM–PLX, *n* (%)	PM total, *n* (%)
Number of patients from the mITT set with available data	141 (100)	10 (100)	151 (100)
Number of patients with a collection result of >2.0 × 10^6 $CD34^+$ cells/kg body weight on day 1 of apheresis	107 (76)	10 (100)	117 (78)
Mobilization result			
Good	92 (65)	7 (70)	99 (66)
Insufficient	48 (34)	3 (30)	51 (34)
Mobilization stopped	1 (1)	–	1 (1)
Number of patients from the ITT set with available data	135 (100)	10 (100)	145 (100)
Number of patients with a total collection result of >2.0 × 10^6 $CD34^+$ cells/kg body weight who reached their requested individual optimal cell count	114 (84)	9 (90)	123 (85)
Patients with mobilization failure during 1st mobilization attempt*	10 (7)	1 (10)	11 (8)
Number of patients from the ITT set with available data	155 (100)	13 (100)	168 (100)
Patients undergoing ASCT	136 (88)	8 (62)	144 (86)

mITT set, modified intention-to-treat set, all patients of the ITT set for whom the number of collected stem cells on day 1 of apheresis was available; ITT set, intention-to-treat set, all enrolled patients who gave their informed consent and participation was possible; ASCT, autologous stem cell transplantation. *Mobilization failure, i.e., collection was not started or apheresis was discontinued.

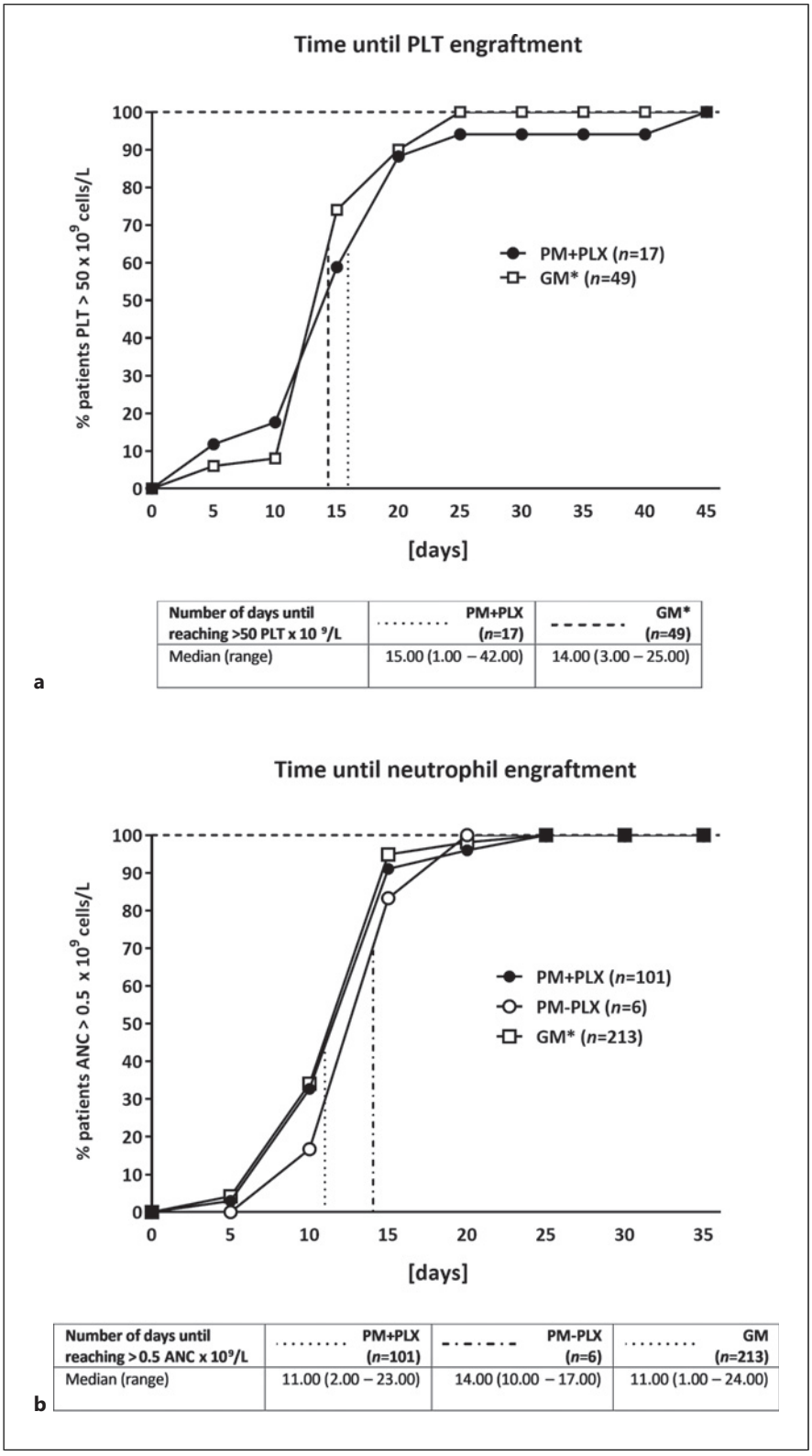
Table 4. Success of engraftment and infections and thrombocyte infusions during regeneration of the hematopoietic system in patients with MM in the OPTIMOB study

Engraftment	PM+PLX, *n* (%)	PM-PLX, *n* (%)	GM, *n* (%)
Number of patients with ASCT	136 (100)	8 (100)	291 (100)
Successful engraftment	116 (85)*	6 (75)*	–*[1]
Number of patients with follow-up	127 (100)	7 (100)	307 (100)
Share of patients with infections (up to 30 days of follow-up after ASCT)	43 (34)	4 (57)	–*[1]
Number of patients with at least one thrombocyte infusion (up to 30 days of follow-up after ASCT)	104 (82)	7 (100)	–*[1]
Median number of thrombocyte infusions (range)	2 (0–12)*[2]	1 (1–5)	–*[1]

ASCT, autologous stem cell transplantation. *Data were missing for 20 PM+PLX and for 2 PM–PLX patients. *[1]For GM patients, no data were collected. *[2]For 23 patients with follow-up, the number of infusion was $n = 0$.

Albeit the OPTIMOB study could not show an obvious difference in the collection result on the first day of apheresis and the total $CD34^+$ collection result between PM patients supported with PLX and those without, the share of patients able to undergo apheresis (94 vs. 77%) and ASCT (88 vs. 62%) were markedly greater in the PM+PLX group of the MM cohort. Additionally, in the PM+PLX setting, 87% of the patients reached the requested $CD34^+$ progenitor cell target, whereas this was the case in only 56.0% of the PM–PLX patients. The majority of PM patients in the MM cohort belonged to the PM+PLX group, thus it can be suggested that our results mainly represent data from those MM patients who received PLX during the observational period. Overall, the OPTIMOB study confirmed the good efficacy of PLX in terms of effectively mobilizing HSCs under routine clinical conditions, even in those with very low $CD34^+$ progenitor cell levels (<5–10 cells/μL) on the day before apheresis and in patients who had reached <20 $CD34^+$ cells/μL with the mobilization [8]. However, patients without PLX administration also achieved good mobilization results, and the reasons for that cannot be determined from our data.

Compared to GM patients, the total collection result was markedly lower in both PM patient groups, albeit PM patients mostly achieved a total collection result of >2 × 10^6 $CD34^+$ progenitor cells/kg body weight. Both PM patient groups in the MM cohort of the OPTIMOB study even reached almost 5 × 10^6 $CD34^+$ progenitor cells/kg body weight usually set as optimal target [5] for successful tandem ASCT. This is in line



a

Number of days until reaching >50 PLT x 10 ^{9}/L	PM+PLX (*n*=17)	GM* (*n*=49)
Median (range)	15.00 (1.00 – 42.00)	14.00 (3.00 – 25.00)

b

Number of days until reaching >0.5 ANC x 10^9/L	PM+PLX (*n*=101)	PM-PLX (*n*=6)	GM (*n*=213)
Median (range)	11.00 (2.00 – 23.00)	14.00 (10.00 – 17.00)	11.00 (1.00 – 24.00)

Fig. 5. Engraftment of platelets (PLT) (**a**)[#] and absolute neutrophils (ANC) (**b**) after ASCT in MM patients stratified by mobilization status. PLT, platelets; ANC, absolute neutrophil count; PM+PLX, poor mobilizer with plerixafor administration; PM–PLX, poor mobilizer without plerixafor administration; GM, good mobilizer; [#]PLT count >50 cells × 10^9/L was not documented for any of the PM–PLX patients in the OPTIMOB study. *1 patient was excluded from the analysis due to invalid data. *n*, number of patients.

with data from the pivotal phase 3 study including MM patients [28], where 76% of the patients receiving PLX were able to achieve ≥6 × 10^6 $CD34^+$ progenitor cells/kg, although collection there was limited to a number ≤4 days, which differs from the OPTIMOB trial where cumulative collection results were not assessed.

The proportion of PM patients with mobilization failure during first mobilization attempt was low with ≤10% in both PM groups. Manifold factors such as

age, gender, the underlying disease including stage and relevant comorbidities, previous treatment (prior myelotoxic chemotherapy, prior use of IMiDs, number of therapy lines), and prior ASCT and/or irradiation may at least contribute mobilization failure [10, 21, 35, 36]. In the present analysis, the maximum age in the two PM patient groups was 78 years and 71 years, respectively, and the proportion of patients aged ≥70 years ranged from 15% in the PM−PLX patient group to 18% in PM+PLX patient group. The high proportion of patients aged ≥70 years was surprisingly high reflecting an aging society with elderly people being fit beyond 70 years. This suggestion is supported by the fact, that ECOG/Karnofsky scale was 0 or 1 in majority of PM patients (66%) at baseline. Furthermore, the proportion of patients with relevant comorbidities was slightly higher in patients without PLX support (100 vs. 82%), but the proportion of patients with mobilization failure was lower. Therefore, advanced age and comorbidities could be ruled out as possible reasons for an increased likelihood in either group to fail mobilization.

In recent years, the number of new MM therapy regimens has considerably increased resulting in more intensified induction therapies such as quadruple therapies including anti-CD38 antibodies in combination with VTd (bortezomib, thalidomide, dexamethasone) or RVd (lenalidomide, bortezomib, dexamethasone), as used, for example, in the CASSIOPEIA study [15], the GRIFFIN trial [16], and the GMMG-HD7 study [20]. Those studies indicated that quadruple induction regimens improved depth of response [15, 16, 20] and progression-free survival in newly diagnosed MM patients [15, 16]. However, $CD34^+$ progenitor cells are also targets of the anti-CD38 antibodies, which therefore may limit HSC mobilization. The majority of PM patients (87 and 85%) underwent first mobilization attempt, and there was no difference in the number of therapy lines and the number of cycles in the last treatment prior to mobilization between both PM groups. So, the intensity of pretreatment seems to have no obvious effect on the mobilization success. Of note, the extended half-life of anti-CD38 antibodies may also lead to delayed engraftment after ASCT [37]. However, the increased use of PLX is able to attenuate the negative effect of anti-CD38 antibodies on mobilization with ASCT, which is feasible in most patients [15, 16, 20, 38]. For example, in the CASSIOPEIA trial, 22% of the Dara-VTd group received PLX during stem cell mobilization compared to 8% of the VTd group resulting in a sufficient median numbers of $CD34^+$ progenitor cells (6.3×10^6 cells/kg body vs. 8.9×10^6 cells/kg body weight) and a comparable proportion of patients proceeding to ASCT in both treatment groups [15]. In the GMMG-HD7 trial, similar results were observed with more rescue stem cell mobilization in the Isa-RVd arm than in the RVd arm (32 vs. 22%) [20].

In the present study, the share of patients receiving targeted antibodies in combination with IMiDs as last treatment line was ~10% without obvious differences between the GM and the PM patient groups (8–11%). However, in 25% (GM) to 31% (PM−PLX) of the MM cohort, last treatment prior to mobilization was part of a clinical trial. A closer look on the regimens given showed that mostly RVd (± isatuximab) and KRd (± isatuximab or elotuzumab) regimens were used. These regimens belong to the clinical trials GMMG-HD7 (Isa-RVd vs. RVd; NCT03617731) [20], GMMG-CONCEPT (Isa-KRd; NCT03104842) [38], and DSMM XVII (Elo-KRd vs. KRd; NCT03948035) [39] that were conducted in German study sites in parallel to the OPTIMOB study. In the PM+PLX group, 22% received an isatuximab-based and 15% an elotuzumab-based regimen, whereas in the PM−PLX group, only 1 patient was treated with isatuximab (in combination with RVd). In addition, 42% of the GM patients, whose last treatment was part of a clinical trial, also received targeted antibodies. In the OPTIMOB study, it was not assessed whether the type of induction regimens or prior treatment regimens had an impact on the mobilization ability. However, data of the stem cell mobilization in the isatuximab trials (GMMG-CONCEPT and GMMG-HD7) were previously reported showing an increase in rescue stem cell mobilization including use of PLX, but a sufficient stem cell harvest in the majority of patients [20, 38].

PLX is known to positively support the hematopoietic recovery after transplantation in PM patients which is based on a higher collection rate of immature $CD34^+$/CD38 cells and T and NK cells [40, 41]. The lower infection rate of PM+PLX patients (34 vs. 57% in PM−PLX patients) may be due to a faster neutrophil recovery time (11 days vs. 14 days), which is clinically relevant. Infections are an important cause of morbidity and mortality after ASCT, and the risk for infection is elevated during the time period after transplantation due to the reduced number of neutrophils [42]. However, as the number of patients in this analysis was rather low, therefore conclusions must be drawn carefully. Finally, the present data confirm the good safety and tolerability profile of PLX, as already reported in previous studies [28, 43].

Our analysis has some limitations. The absolute number of PM−PLX patients was relatively small in both the MM cohort and the overall cohort, making it difficult to compare the outcomes of PM−PLX patients with those PM patients who received PLX and with GM patients.

Additionally, for some endpoint evaluations, the number of patients was also rather low which might be caused by the observational, non-interventional character of the study without a predefined treatment plan. Due to this, some parameters were not assessed by the participating sites depending on their internal standard procedures. In some cases, such as $CD34^+$ progenitor cell count in the PB, data documentation in the electronic case report form was not mandatory resulting in different patient numbers in the respective evaluation. Further, highly individualized treatment was allowed since the therapeutic approach was in the hands of the treating physicians and not prior specified or harmonized. Therefore, the high proportion of PM patients may represent a bias based on the large number of different therapies, since some are considered to negatively impact mobilization capability. In addition, the definition of PM patients in the OPTIMOB study was broad, which may have artificially increased the number of PM patients.

Conclusion

A considerable proportion of adult MM patients in Germany belong to the PM group. Although high rates of successful stem cell mobilization were achieved in PM patients with and without PLX support, more patients receiving PLX experienced successful engraftment. However, these findings may partly be explained by low patient numbers in the PM–PLX group. However, the OPTIMOB study reflects the clinical routine in German hospitals and provides comprehensive insights in the procedure of HSC mobilization and collection including the use of PLX for PM patients with MM. Nevertheless, further real-world analyses will be still required for treatment optimization in poor mobilizing patients.

Acknowledgments

The investigators thank all patients for participating in the study and all data documentation teams in the respective facilities for the aid in this project. Special thanks go to Anna Gseer, Würzburg, and Emma Pauline Elisabeth Freundt, Heidelberg, for their assistance with data collection.

Statement of Ethics

This study was conducted in compliance with Local Ethics Committees (EC), informed consent regulations, and local regulatory requirements. The observational plan, informed consent documents, and any other appropriate study-related documents were approved by the responsible Central Ethic Committee (Ethikkommission der Ärztekammer Hamburg, Hamburg, Germany, approval number: PV5559, approval date: 22 SEP 2017). All patients gave their written informed consent prior to study inclusion.

Conflict of Interest Statement

M.B. received honoraria for advisory board and consultancy activities from Bristol-Myers Squibb, Sanofi-Aventis Deutschland GmbH, and GlaxoSmithKline GmbH & Co. KG; research funding from Bristol-Myers Squibb (Celgene), Otsuka Pharmaceuticals, Sanofi, Chugai Pharma, AbbVie, AMGEN, and Janssen; and owns shares from AbbVie. K.K. received research funding from Bristol-Myers Squibb and Sanofi-Aventis Deutschland GmbH. C.T.S. received honoraria from Sanofi. M.G. (Matthias Grube) received honoraria from Sanofi, Janssen, and Bayer. V.V. received honoraria from Sanofi, Bristol-Myers Squibb, Novartis, Amgen, and Janssen. D.W. received honoraria for advisory board activities and travel support from Sanofi. A.B. received honoraria from Incyte and AOP Orphan and scientific support from AOP Orphan. M.S.H. received honoraria for consultancy activities from Celgene GmbH, Amgen GmbH, Kite/Pharma Gilead, Sanofi-Aventis Deutschland GmbH, GlaxoSmithKline GmbH & Co. KG, Bristol-Myers Squibb GmbH & Co. KG, Shionogi GmbH, and Stemline Therapeutics (no individual payment) and financial support of educational meetings from Janssen-Cilag GmbH, Takeda Pharma Vertrieb GmbH & Co. KG, Novartis Pharma GmbH, Pfizer Pharma GmbH, Roche Pharma AG, Vifor Pharma Deutschland GmbH, and Celgene GmbH (no individual payment). Additionally, M.S.H. participated in different clinical trials supported by the industry (including the OPTIMOB study). C. K. (Christoph Kimmich) received honoraria from Amgen, Janssen, Kite/Pharma Gilead, Takeda, GlaxoSmithKline GmbH & Co., and Sanofi-Aventis Deutschland GmbH, as well as travel support from Janssen and Kite/Pharma Gilead. M.H. received lecture fees from Amgen, AstraZeneca, Eusa Pharma, Celgene, Janssen, Jazz Pharma, and Takeda, and served on advisory boards of Amgen, Eusa Pharma, Janssen, and Sanofi. C.K. (Christian Kunz) received honoraria for advisory board activities from AbbVie, Sanofi, Bristol-Myers Squibb, and Amgen, as well as financial support for congress participation from AbbVie, Amgen, and Bristol-Meyer Squibb. C.K. (Cyrus Khandanpour) received honoraria and research funding from Sanofi, Bristol-Myers Squibb, AstraZeneca, Novartis, Amgen, and Janssen. M.W. received honoraria for lectures from AstraZeneca, Novartis, Ispen, Roche, Janssen, Sanofi, Medac, Takeda, and Pierre Fabre; travel support from AstraZeneca, AbbVie, and Pfizer; and research funding from AstraZeneca, Bristol-Myers Squibb, Novartis, Pfizer, Roche, Janssen, Takeda, MSD, Boehringer, Pierre Fabre, Amgen, Genzyme, and MorphoSys. U.H. received honoraria from Sanofi and Amgen. R.N. received honoraria for consultancy activities from AvenCell (formerly Cellex Patient Treatment GmbH), Simon Kucher & Partners Strategy & Marketing Consultants GmbH, and Takeda; honoraria for advisory board activities from Sanofi-Aventis Deutschland GmbH, Glaxo Smith Kline GmbH & Co. KG, Oncopeptides, Bristol-Myers Squibb (Celgene), Janssen, Gilead, and Amgen; honoraria for lectures from Forum Medizin Fortbildung (FOMF) and Bildungsinstitut für Gesundheitsberufe Südwestfalen in Siegen (BIGS) GmbH; and honoraria for authorship from Elsevier. C.W.S. received honoraria from Bristol-Myers Squibb, Celgene, Daiichi Sankyo, GILEAD, Hexal, Incyte, Janssen, Lilly, MSD, Merck Serono, Miltenyi Biotec, Novartis, Pfizer, Roche, and Takeda. H.J.T. received honoraria from Sanofi, Bristol-Myers Squibb, and Takeda. F.B. and M.E. are employed by Sanofi-Aventis Deutschland GmbH and may hold stock and/or stock

options in the company. N.K. received honoraria and research funding from Sanofi, Bristol-Myers Squibb, Neovii, Novartis, Amgen, and Riemser. A.K., K.M., A.S., M.G. (Martin Görner), F.H., H.A.D., A.R., B.M., and M.K. have no conflicts of interest to declare.

Funding Sources

The study was funded by Sanofi-Aventis Deutschland GmbH, Berlin, Germany. Medical writing assistance was provided by Katharina Bakhaus, Alcedis GmbH (a HUMA company), Gießen, Germany, and funded by Sanofi-Aventis Deutschland GmbH, Berlin, Germany.

Author Contributions

All authors were involved in collection, analysis, and interpretation of the data. Nicolaus Kröger, Max Bittrich, Katharina Kriegsmann, and Franziska Brand were involved in drafting of the manuscript and revising it critically for intellectual content. All authors approved the final version of this manuscript and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data supporting the findings of this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

References

1 Carreras E, Dufour C, Mohty M, Kröger N. The EBMT handbook: hematopoietic stem cell transplantation and cellular therapies. 7th ed. Cham: Springer; 2019.
2 Moreau P, Attal M, Facon T. Frontline therapy of multiple myeloma. Blood. 2015 May;125(20):3076–84.
3 Rajkumar SV, Kumar S. Multiple myeloma current treatment algorithms. Blood Cancer J. 2020 Sep;10(9):94.
4 Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, et al. Diagnosis and management of multiple myeloma: a review. JAMA. 2022 Feb;327(5):464–77.
5 Al Hamed R, Bazarbachi AH, Malard F, Harousseau JL, Mohty M. Current status of autologous stem cell transplantation for multiple myeloma. Blood Cancer J. 2019 Apr;9(4):44.
6 Duong HK, Savani BN, Copelan E, Devine S, Costa LJ, Wingard JR, et al. Peripheral blood progenitor cell mobilization for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2014 Sep;20(9):1262–73.
7 Wuchter P, Ran D, Bruckner T, Schmitt T, Witzens-Harig M, Neben K, et al. Poor mobilization of hematopoietic stem cells-definitions, incidence, risk factors, and impact on outcome of autologous transplantation. Biol Blood Marrow Transplant. 2010 Apr;16(4):490–9.
8 Nademanee AP, DiPersio JF, Maziarz RT, Stadtmauer EA, Micallef IN, Stiff PJ, et al. Plerixafor plus granulocyte colony- stimulating factor versus placebo plus granulocyte colony-stimulating factor for mobilization of CD34(+) hematopoietic stem cells in patients with multiple myeloma and low peripheral blood CD34(+) cell count: results of a subset analysis of a randomized trial. Biol Blood Marrow Transplant. 2012 Oct;18(10):1564–72.
9 Ataca Atilla P, Bakanay Ozturk SM, Demirer T. How to manage poor mobilizers for high dose chemotherapy and autologous stem cell transplantation? Transfus Apher Sci. 2017 Apr;56(2):190–8.
10 Mohty M, Hübel K, Kröger N, Aljurf M, Apperley J, Basak GW, et al. Autologous haematopoietic stem cell mobilisation in multiple myeloma and lymphoma patients: a position statement from the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 2014 Jul;49(7):865–72.
11 Giralt S, Costa L, Schriber J, Dipersio J, Maziarz R, McCarty J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. Biol Blood Marrow Transplant. 2014 Mar;20(3):295–308.
12 Pusic I, Jiang SY, Landua S, Uy GL, Rettig MP, Cashen AF, et al. Impact of mobilization and remobilization strategies on achieving sufficient stem cell yields for autologous transplantation. Biol Blood Marrow Transplant. 2008 Sep;14(9):1045–56.
13 Gertz MA. Current status of stem cell mobilization. Br J Haematol. 2010 Sep;150(6):647–62.
14 Olivieri J, Attolico I, Nuccorini R, Pascale SP, Chiarucci M, Poiani M, et al. Predicting failure of hematopoietic stem cell mobilization before it starts: the predicted poor mobilizer (pPM) score. Bone Marrow Transplant. 2018 Apr;53(4):461–73.
15 Moreau P, Attal M, Hulin C, Arnulf B, Belhadj K, Benboubker L, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019 Jul;394(10192):29–38.
16 Voorhees PM, Kaufman JL, Laubach J, Sborov DW, Reeves B, Rodriguez C, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020 Aug;136(8):936–45.
17 Chari A, Usmani SZ, Krishnan A, et al. Daratumumab (DARA) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in patients with newly diagnosed multiple myeloma (MMY1001): updated results from an open-label, phase 1b study [abstract]. Blood. 2017;130:3110.
18 Jadoon Y, Siddiqui MA. Immunotherapy in multiple myeloma. Cancer Treat Res Commun. 2021;29:100468.
19 Kocoglu MH, Badros AZ. Newly diagnosed multiple myeloma: current treatment strategies, emerging therapeutic approaches and beyond. Expert Rev Hematol. 2020 Jun;13(6):669–86.
20 Goldschmidt H, Mai EK, Bertsch U, Fenk R, Nievergall E, Tichy D, et al. Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. Lancet Haematol. 2022 Nov;9(11):e810–21.
21 Keklik Karadağ F, Akad Soyer N, Pashayev T, Sevgili B, Sahin F, Töbü M, et al. Predictive factors of poor mobilization in multiple myeloma patients. Poster presented at the 48th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT); 2022.
22 Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Gastineau DA, et al. Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. Leukemia. 2007 Sep;21(9):2035–42.
23 Mazumder A, Kaufman J, Niesvizky R, Lonial S, Vesole D, Jagannath S. Effect of lenalidomide therapy on mobilization of peripheral blood stem cells in previously untreated multiple myeloma patients. Leukemia. 2008 Jun;22(6):1280–1; author reply 1281-2.
24 Paripati H, Stewart AK, Cabou S, Dueck A, Zepeda VJ, Pirooz N, et al. Compromised stem cell mobilization following induction therapy with lenalidomide in myeloma. Leukemia. 2008 Jun;22(6):1282–4.
25 Popat U, Saliba R, Thandi R, Hosing C, Qazilbash M, Anderlini P, et al. Impairment of filgrastim-induced stem cell mobilization after prior lenalidomide in patients with multiple myeloma. Biol Blood Marrow Transplant. 2009 jun;15(6):718–23.

26 Li S, Fu J, Ma H, Mapara MY, Lentzsch S. Lenalidomide-induced upregulation of CXCR4 in CD34+ hematopoietic cells, a potential mechanism of decreased hematopoietic progenitor mobilization. Leukemia. 2013 Jun;27(6):1407–11.
27 Wallis WD, Qazilbash MH. Peripheral blood stem cell mobilization in multiple myeloma: growth factors or chemotherapy? World J Transplant. 2017 Oct;7(5):250–9.
28 DiPersio JF, Stadtmauer EA, Nademanee A, Micallef IN, Stiff PJ, Kaufman JL, et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. Blood. 2009 Jun;113(23):5720–6.
29 Hundemer M, Engelhardt M, Bruckner T, Kraeker S, Schmitt A, Sauer S, et al. Rescue stem cell mobilization with plerixafor economizes leukapheresis in patients with multiple myeloma. J Clin Apher. 2014 Dec;29(6):299–304.
30 Hübel K, Fresen MM, Salwender H, Basara N, Beier R, Theurich S, et al. Plerixafor with and without chemotherapy in poor mobilizers: results from the German compassionate use program. Bone Marrow Transplant. 2011 Aug;46(8):1045–52.
31 German working group for hematopoietic stem cell transplantation and cellular therapies e.V. [Internet]. Hamburg: Guideline on autologous stem cell transplantation from the German working group for hämatopoietic stem cell transplantation and cellular therapies e.V. 2018 [cited 2022 July 21]. Available from: https://dag-hszt.de/Leitlinien_zur_autologen_SCT.html.
32 Jillella AP, Ustun C. What is the optimum number of CD34+ peripheral blood stem cells for an autologous transplant? Stem Cells Dev. 2004 Dec;13(6):598–606.
33 Bilgin YM, de Greef GE. Plerixafor for stem cell mobilization: the current status. Curr Opin Hematol. 2016 Jan;23(1):67–71.
34 Worel N, Fritsch G, Agis H, Böhm A, Engelich G, Leitner GC, et al. Plerixafor as preemptive strategy results in high success rates in autologous stem cell mobilization failure. J Clin Apher. 2017 Aug;32(4):224–34.
35 Boccadoro M, Palumbo A, Bringhen S, Merletti F, Ciccone G, Richiardi L, et al. Oral melphalan at diagnosis hampers adequate collection of peripheral blood progenitor cells in multiple myeloma. Haematologica. 2002 Aug;87(8):846–50.
36 Morris CL, Siegel E, Barlogie B, Cottler-Fox M, Lin P, Fassas A, et al. Mobilization of $CD34^+$ cells in elderly patients (>/=70 years) with multiple myeloma: influence of age, prior therapy, platelet count and mobilization regimen. Br J Haematol. 2003 Feb;120(3):413–23.
37 Al Saleh AS, Sidiqi MH, Gertz MA, Muchtar E, Lacy MQ, Warsame RM, et al. Delayed neutrophil engraftment in patients receiving Daratumumab as part of their first induction regimen for multiple myeloma. Am J Hematol. 2020 Jan;95(1):E8–10.
38 Leypoldt LB, Besemer B, Asemissen AM, Hänel M, Blau IW, Görner M, et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in front-line treatment of high-risk multiple myeloma: interim analysis of the GMMG-CONCEPT trial. Leukemia. 2022 Mar;36(3):885–8.
39 ClinicalTrialsgov [Internet]. Elotuzumab in combination with carfilzomib, lenalidomide and dexamethasone (E-KRd) versus KRd. in multiple myeloma (NCT03948035) [cited 2023 January 10]. Available from: https://clinicaltrials.gov/ct2/show/NCT03948035.
40 Saraceni F, Shem-Tov N, Olivieri A, Nagler A. Mobilized peripheral blood grafts include more than hematopoietic stem cells: the immunological perspective. Bone Marrow Transplant. 2015 Jul;50(7):886–91.
41 Porrata LF. Autograft immune effector cells and survival in autologous peripheral blood hematopoietic stem cell transplantation. J Clin Apher. 2018 Jun;33(3):324–30.
42 Hatzimichael E, Tuthill M. Hematopoietic stem cell transplantation. Stem Cells Cloning. 2010 Aug;3:105–17.
43 Yang X, Wan M, Yu F, Wang Z. Efficacy and safety of plerixafor for hematopoietic stem cell mobilization for autologous transplantation in patients with non-Hodgkin lymphoma and multiple myeloma: a systematic review and meta-analysis. Exp Ther Med. 2019 Aug;18(2):1141–8.