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Autologous

A Pilot, Exploratory, Randomized, Phase II Safety Study Evaluating Tumor Cell Mobilization and Apheresis Product Contamination in Patients Treated with Granulocyte Colony-Stimulating Factor Alone or Plus Plerixafor

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A B S T R A C T

Because of the potential risk of tumor cell mobilization with granulocyte colony-stimulating factor (G-CSF), it is crucial to evaluate any potential effect of plerixafor treatment in the presence of G-CSF on multiple myeloma (MM) cell mobilization. This was an open-label, multicenter, randomized, exploratory, safety study (NCT01753453) that investigated the extent of MM cell mobilization after treatment with G-CSF + plerixafor in patients who were deemed poor mobilizers of hematopoietic stem cells. The primary efficacy outcome was the number of MM cells in peripheral blood and apheresis product after G-CSF + plerixafor treatment versus G-CSF alone. Key secondary efficacy outcomes included overall survival and disease status up to 2 years after the first G-CSF dose. Twenty patients were randomized and received at least 1 dose of study treatment. There were no patients with MM cells in peripheral blood up to day 8 G-CSF administration in either treatment group. Up to day 8 no patient in the G-CSF + plerixafor arm and only 1 patient in the G-CSF arm mobilized at least 4.5×10^5 MM cells in the apheresis product. Nine of 10 patients from each treatment arm proceeded to transplantation. MM cells were detected in 5 patients from each treatment arm before and after transplantation. Adverse events observed in the G-CSF + plerixafor arm were consistent with the known safety profile of plerixafor. No MM cells were detected in peripheral blood of either treatment group up to day 8 of mobilization. Only 1 patient in the G-CSF alone group mobilized at least 4.5×10^5 MM tumor cells in apheresis product up to day 8. However, 50% of patients in both treatment arms had detectable amounts of MM cells in their peripheral blood pre- and post-transplantation. There were no new safety concerns with plerixafor.

INTRODUCTION

Autologous transplantation of hematopoietic stem cells (HSCs) is a widely used strategy for hematologic and immunologic recovery after high-dose chemotherapy for hematologic malignancies, such as multiple myeloma (MM), non-Hodgkin lymphoma, Hodgkin disease, and other cancers, including germ cell tumor and neuroblastoma [1]. After chemotherapy induction, regardless of whether or not the chemotherapy has been accompanied by cytokine (usually granulocyte colony stimulating factor [G-CSF]) treatment, or after the patient has received treatment with a cytokine alone (such as G-CSF) without associated chemotherapy, HSCs for transplantation are usually obtained from the peripheral blood.

Plerixafor (Mozobil, Sanofi Genzyme, Oxford, UK) in combination with G-CSF has been approved in the European Union to enhance the mobilization of HSCs to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and MM who are recognized as poor mobilizers of HSCs. Plerixafor is a selective, reversible inhibitor of the CXC4 chemokine receptor (CXCR4) and blocks the binding of its cognate ligand (stromal cell–derived factor 1 [SDF-1], also known as CXCL12) [2]. Disruption of the CXCR4/SDF-1 ligand binding causes the mobilization of $CD34^+$ stem cells from the stromal microenvironment to the peripheral blood but could also potentially cause the mobilization of MM tumor cells [3]. Although CXCR4 is expressed on the surface of many

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tumor cells, it is not always functional; therefore, blocking its function may not result in a measurable mobilization of tumor cells [4].

Concerns have been raised that agents that mobilize cells using the CXCR-4/CXCL12 interaction may theoretically also mobilize tumor cells [5,6]. The likelihood of tumor cell mobilization in peripheral blood and apheresis product at the same time of $CD34^+$ cell mobilization continues to be controversial [7]. One study found that mobilization with G-CSF alone resulted in tumor cell contamination in 25% of patients with MM [8]. However, another study showed significantly fewer tumor cells in apheresis products from patients with MM treated with cyclophosphamide plus G-CSF compared with G-CSF alone [9]. It has been hypothesized that the interruption of the SDF-1/CXCR4 axis using plerixafor could result in the mobilization of tumor cells, particularly leukemia cells from their niche [10,11]. It is believed that targeting the microenvironment could be exploited by sensitizing leukemia cells to chemotherapy [10,12-15]. Indeed, Azab et al. [16] extended this concept by showing that plerixafor disrupted MM cells in the bone marrow and made them more accessible to treatment with bortezomib.

Because of the potential risk of tumor cell mobilization with G-CSF, it is crucial to evaluate any potential effect of plerixafor treatment in the presence or absence of G-CSF on MM tumor cell mobilization. This European Medicines Agency postapproval safety study investigated whether G-CSF + plerixafor treatment compared with G-CSF alone, when used for the mobilization of HSCs in patients with MM, also affected the mobilization of tumor cells.

METHODS

Study Design

This was an open-label, multicenter, randomized, exploratory, safety study (ClinicalTrials.gov Identifier NCT01753453) that investigated the extent of MM tumor cell mobilization after treatment with G-CSF alone or + plerixafor in patients who were deemed poor mobilizers of HSCs. The study design is shown in Figure 1.

Eligibility included patients aged $\geq$ 18 years with a diagnosis of MM in partial or complete response who were to receive autologous HSC transplantation and were considered potentially poor mobilizers of HSCs. A potentially poor mobilizer was defined as a person who before study entry in the judgment of the investigator may not mobilize HSCs successfully for reasons such as prior lenalidomide use. Exclusion criteria included patients without Eastern Cooperative Oncology Group performance status of 0 to 1, a history of acute or chronic leukemia, prior allogeneic or autologous transplantation, less than 3 to 6 weeks since last anticancer treatment, bone marrow involvement of >10% plasma cells before first G-CSF, treatment with G-CSF or other cytokines within 14 days before first dose of G-CSF for mobilization, and previous plerixafor treatment (see Supplementary Methodology for other exclusions).

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. For all sites, approval of the protocol was obtained from the governmental authorities and Institutional Review Board(s).

Randomization

Each patient was assigned an identification number at screening and randomized into the study on day 4 after receiving 4 doses of G-CSF if they had reached a minimum of $\geq$10 $CD34^+$ stem cells/μL of peripheral blood required for apheresis. If the target number of HSCs required for randomization was not collected, the patient was discontinued from the study. Discontinued patients were replaced until patients in each arm had undergone at least 1 apheresis. Eligible patients were randomized 1:1 to receive either nonpegylated G-CSF + plerixafor or nonpegylated G-CSF alone. Doses were administered according to the current label .24 mg/kg of plerixafor. Patients were allocated to treatment according to a computer-generated randomization performed by Interactive Voice/Web Response System.

Primary Endpoint Analysis

The primary efficacy endpoint of the study was to evaluate the MM tumor cells in peripheral blood and in the apheresis product after G-CSF + plerixafor treatment (compared with G-CSF alone) using the flow cytometry technology. A 6-color flow cytometry assay was used to assess the presence of different phenotypes of cells in peripheral blood and apheresis product (see Supplementary Methodology for details). The presence of MM tumor cells in peripheral blood was analyzed by flow cytometry analysis at scheduled time points on days 1 to 3, day 4 (before randomization), and days 5 to 8. Samples were also collected for blood analysis pretransplantation, 100 days post-transplantation $\pm$ 14 days, and 6 months after the first dose of G-CSF $\pm$ 14 days (see Supplementary Methodology for details of mobilization assessments). The proportion of patients who mobilized at least 4.5×10^5 MM tumor cells/kg body weight as measured in each apheresis product were summarized by study arm. A cell threshold was applied: 4.5×10^5 MM tumor cells/kg body weight. This was an agreed value in Europe to provide enough infused cells to restart the tumor growth when apheresing the $CD34^+$ cells [3,10]. The percentage of patients for tumor cell mobilizations into peripheral blood was summarized by study arm as MM tumor cell/$CD34^+$ cell count.

Secondary Endpoint Analysis

The yield of $CD34^+$ cells/kg was determined at central laboratories for each day of apheresis according to the following variables: actual and cumulative $CD34^+$ yield in the apheresis product, the proportion of patients reaching the minimal target of $CD34^+$ cell collection (total of 2×10^6 $CD34^+$ cells/kg in the total apheresis product), and the proportion of patients reaching optimal target of $CD34^+$ cell collection (total of 6×10^6 $CD34^+$ cells/kg in the total apheresis product). Survival and disease status were key secondary endpoints and were performed in all patients at 100 days post-transplantation (for randomized patients who received a transplant) and then every 6 months after the first G-CSF dose (for all randomized patients, irrespective of transplant status).

Overall survival was defined as the time interval between the date of randomization and the date of death from any cause. Progression-free survival was defined as the time interval from the date of randomization to the date of progressive disease or death due to any cause, whichever came first. Survival curves were presented in each treatment group using nonparametric Kaplan-Meier estimates [17] as well as survival rate at 6, 12, 18, and 24 months. The median survival was also estimated. The best overall response was the best response for each patient observed from the start of treatment until disease progression or the end of the 2-year follow-up and was summarized for patients with at least 1 available disease status by treatment group.

Exploratory Analysis

Exploratory analysis examined hematopoietic progenitors and MM tumor cells in peripheral blood samples and apheresis samples collected from patients to evaluate CD184 (CXCR4) expression on the relevant cell populations.

Safety

Adverse events (AEs) and treatment-emergent AEs (TEAEs) occurring from the time of informed consent until 30 days after the last dose of study drug or first dose of myeloablative chemotherapy, whichever occurred first, were collected. Medical and surgical history included relevant history other than MM and was coded using the version of Medical Dictionary for Regulatory Activities (MedDRA v19.0, https://www.meddra.org/how-to-use/support-documentation/english).

Statistical Analysis

All primary and secondary endpoint analyses were summarized by treatment group on the intention-to-treat population using descriptive statistics. Continuous data were summarized using the number of available data, mean, standard deviation, median, minimum, and maximum for each treatment group. Categorical and ordinal data were summarized using the number and percentage of patients in each treatment group.

RESULTS

Baseline Characteristics

Of the 28 patients screened, 23 (82.1%) were treated with G-CSF and 5 were screen failures because inclusion criteria were not met. Three patients received G-CSF but were not assigned to a treatment group because of a low $CD34^+$ cell count on day 4 (Figure 1). A total of 20 patients were randomized and received at least 1 dose of study treatment (either G-CSF alone or G-CSF + plerixafor: intention-to-treat and safety populations). Patient demographics are shown in Table 1. The overall mean age was 58.7 $\pm$ 8.69 years with an age range of 42 to 70 years. The mean baseline (last value before randomization) $CD34^+$ cells from peripheral blood were 49.8 $\pm$ 38.7 cells/μL and 26.2 $\pm$ 17.5 cells/μL for the G-CSF alone arm and

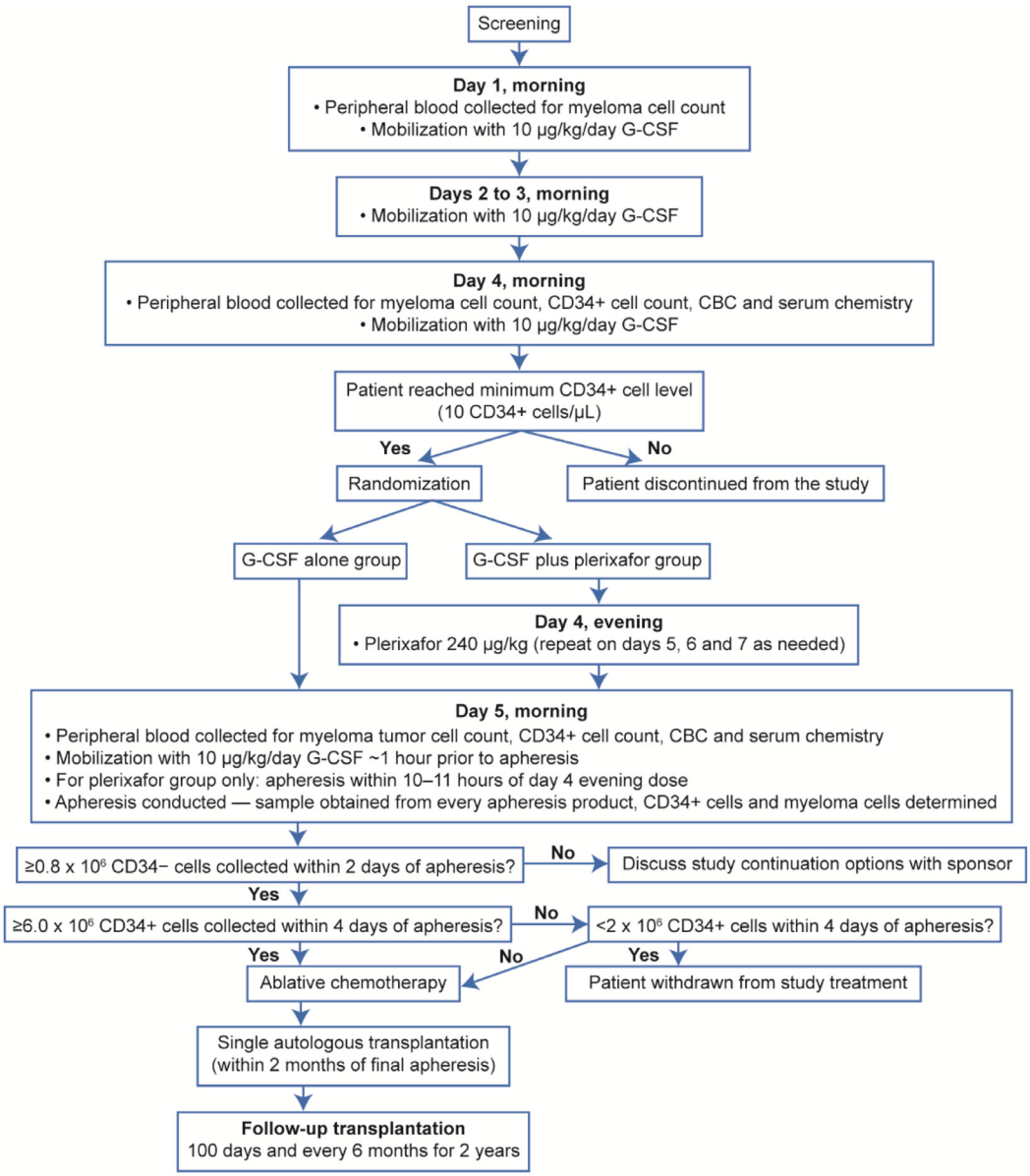

Figure 1. Study design.

G-CSF + plerixafor arm, respectively. MM IgG was reported in 13 patients (65%), MM IgM in 2 patients (1 from each group), light chain MM in 5 patients (2 patients from the G-CSF + plerixafor group and 3 patients from the G-CSF alone group), and 2 patients with IgA MM (1 patient from each group).

Primary Endpoint Analysis

There were no patients with MM tumor cells in peripheral blood at day 5 up to day 8 before G-CSF administration in either treatment group, and no patients in either treatment group with tumor cell mobilization in the peripheral blood from day 4 before G-CSF to day 5 before G-CSF. The number of MM cells in the apheresis product from day 5 to day 8 is shown in Table 2. At day 8 the cumulative mean number of MM cells in the apheresis product in the G-CSF alone and the G-CSF + plerixafor arms was 1.3×10^5 cells/kg and 0.6×10^5 cells/kg, respectively. One patient in the G-CSF alone arm (day 6) mobilized at least 4.5×10^5 MM cells in the cumulative apheresis product and none in the G-CSF + plerixafor arm. The mean percentage of MM tumor cells/CD34$^+$ cells in the apheresis product at day 5 were 2.0% and .7% in patients from the G-CSF alone and the G-CSF + plerixafor arms, respectively (Supplementary Table 1). Overall (days 5 to 8), the mean percentage of MM tumor cells/CD34$^+$ cells was 3.1% and .6% in the G-CSF alone and G-CSF + plerixafor arms, respectively.

Secondary Endpoint Analysis

The total yield of CD34$^+$ cells was greater in the G-CSF + plerixafor arm compared with the G-CSF alone arm at each apheresis (Table 3). After the first apheresis patients from the G-CSF alone and G-CSF + plerixafor arms had a mean yield of 4.6×10^6 CD34$^+$ cells/kg and 7.3×10^6 CD34$^+$ cells/kg, respectively. The total mean yield for up to 4 aphereses was 6.8×10^6 CD34$^+$ cells/kg and 8.5×10^6 CD34$^+$ cells/kg for the G-CSF alone and G-CSF + plerixafor groups, respectively. The mean plerixafor treatment exposure was 1.4 days with 7 patients requiring 1 apheresis, 2 patients requiring 2 aphereses, and 1 patient requiring 3 aphereses to reach target cell

Table 1
Patient Demographics at Baseline* (Intention-to-Treat Population)

Parameter	G-CSF Alone(n = 10)	G-CSF + Plerixafor(n = 10)
Age, yr	58.3 ± 9.1	59.1 ± 8.8
Age range, yr	42.0-69.0	43.0-70.0
Age group		
<60 yr	6 (60)	4 (40)
≥60 yr	4 (40)	6 (60)
Sex		
Male	6 (60)	4 (40)
Female	4 (40)	6 (60)
White race	10 (100)	10 (100)
$CD34^+$ cell count, cells/μL	49.8 ± 38.7	26.2 ± 17.5
Range	12.0-112.0	7.0-60.0
Cancer subtype		
MM IgG	6 (60)	7 (70)
MM IgM	0	0
Other	4 (40)	3 (30)
Staging of MM		
I	5 (50)	5 (50)
II	2 (20)	2 (20)
III	3 (30)	2 (20)
Time from initial diagnosis (months)	4.1 ± 1.4	5.5 ± 3.2
Range	2.3-6.4	2.8-12.9
ECOG performance status		
0	7 (70)	3 (30)
1	3 (30)	7 (70)

Values are mean ± SD or n (%), unless otherwise defined. ECOG indicates Eastern Cooperative Oncology Group.
*Baseline value is the last available value before randomization.

Table 2
MM Tumor Cells (10^5 cells/kg) in the Apheresis Product Evaluated from Days 5 to 8 (Intention-to-Treat Population)

Time Point	G-CSF Alone(n = 10)	G-CSF + Plerixafor(n =1 0)
Day 5	(n = 10)	(n = 10)
Mean ± SD	.5 ± 1.1	.5 ± 1.1
Range	.0-3.5	.0-2.8
Day 6	(n = 7)	(n = 3)
Mean ± SD	1.2 ± 2.8	.3 ± .5
Range	.0-7.4	.0-.9
Day 7	(n = 3)	(n = 1)
Mean ± SD	.0 ± .0	.0 (NC)
Range	.0-.0	.0-.0
Day 8	(n = 1)	(n = 0)
Mean ± SD	.0 (NC)	
Range	.0-.0	
Overall	(n = 10)	(n = 10)
Mean ± SD	1.3 ± 3.4	.6 ± 1.3
Range	.0-10.9	.0-3.7

NC indicates not calculated; SD, standard deviation.

Table 3
$CD34^+$ (10^6 cell/kg) Yield in the Apheresis Product (Intention-to-Treat Population)

Apheresis Number	G-CSF Alone(n = 10)	G-CSF + Plerixafor(n = 10)
1	(n = 10)	(n = 10)
Mean ± SD	4.6 ± 3.2	7.3 ± 4.5
Range	1.4-9.9	.5-15.1
2	(n = 7)	(n = 3)
Mean ± SD	2.6 ± 1.1	3.6 ± 2.4
Range	1.6-4.6	1.5-6.2
3	(n = 3)	(n = 1)
Mean ± SD	1.3 ± .3	1.7 ± (NC)
Range	1.0-1.5	1.7-1.7
4	(n = 1)	(n = 0)
Mean ± SD	.1 ± (NC)	
Range	.1-.1	
Overall (apheresis 1-4)	(n = 10)	(n = 10)
Mean ± SD	6.8 ± 2.9	8.5 ± 3.3
Range	2.1-11.2	5.3-15.1

NC, not calculated; SD, standard deviation.

Table 4
Best Overall Response to Treatment (Intention-to-Treat Population)*

Response, n (%)	G-CSF Alone (n = 10)†	G-CSF + Plerixafor (n = 10)
Stringent complete response	0	1 (10%)
Complete response	0	2 (20%)
Very good partial response	6 (60%)	4 (40%)
Partial response	2 (20%)	2 (20%)
Stable disease	0	0
Progressive disease	1 (10%)	1 (10%)

*Best overall response observed from randomization until disease progression or the end of the 2 years follow-up.
†One patient randomized but did not receive study treatment.

numbers. All patients in both treatment arms reached the minimum target of $\geq 2 \times 10^6$ $CD34^+$ cells/kg and 4 of 10 in the G-CSF alone and 7 of 10 patients in the G-CSF + plerixafor arms reached the optimal target of $\geq 6 \times 10^6$ $CD34^+$ cells/kg. Analyses on peripheral blood and apheresis product showed that 2 of 10 patients (20%) and 7 of 10 patients (70%) in the G-CSF alone and G-CSF + plerixafor arms, respectively, required only 1 apheresis procedure to reach $\geq 6 \times 10^6$ $CD34^+$ cells/kg (exceeding the target value for engraftment of $\geq 2 \times 10^6$ cells).

Nine of 10 patients from each treatment arm proceeded to transplantation. The mean time to transplantation was 15.1 days and 11.0 days for the G-CSF and G-CSF + plerixafor arms, respectively. The best overall response to treatment from randomization until disease progression or the end of the 2-year follow-up period is shown in Table 4. Two patients from the G-CSF + plerixafor arm experienced complete response to treatment compared with no patients in the G-CSF arm alone. Six patients from the G-CSF alone arm had a very good partial response compared with 4 patients from the G-CSF + plerixafor arm. Two patients from the G-CSF alone arm and 3 patients from the G-CSF + plerixafor arm died before the end of the 2-year follow-up period. Disease progression was reported in 2 patients from each arm of the study.

Exploratory Analysis

Cell subtype analyses were performed on peripheral blood and apheresis samples that had mobilized MM tumor cells, either $CD38^{++}/CD138^+/CD19^-/CD56^+$ cells (reported as MM1 cells) and $CD38^{++}/CD138^+/CD19^-/CD56^-$ cells (reported as MM2 cells). MM1 and/or MM2 cells were detected at different time points in 10 of 18 transplanted patients in both treatment arms before and after autologous transplantation (5 patients in the G-CSF alone arm and 5 patients in the G-CSF + plerixafor arm) (Figure 2). Among these 10 patients MM cells were detected after transplantation in 4 patients (1 in G-CSF and 3 in G-CSF + plerixafor arms, respectively). However, at the last follow-up visit MM cells were not detectable in 7 of 10 transplant patients (4/5 patients in G-CSF alone and 3/5 patients in G-CSF + plerixafor groups).

Safety

The mean number of days of treatment with G-CSF was 6.0 days and 5.4 days for the G-CSF alone and the G-CSF + plerixafor groups, respectively. The mean G-CSF total dose was similar between treatment groups (59.5 ± 13.1 μg/kg G-CSF alone and 53.8 ± 7.7 μg/kg G-CSF + plerixafor). The average dose of plerixafor per body weight was .24 μg/kg/day. Ten patients (50%) experienced TEAEs (3 G-CSF alone and 7 G-CSF + plerixafor), of which 9 TEAEs were regarded as related

		Detection before transplantation: AP &/or PB		Detection after transplantation: PB		Status
		MM1	MM2	MM1	MM2	
G-CSF 5 patients	1	0.01% pre-transplant in **AP**	No detection	No detection	No detection	**FUP5** No detection
	2	0.01% pre-transplant in **AP**	0.01% day 5 **AP** 0.01% day 6 **AP**	No detection	No detection	**FUP5** No detection
	3	No detection	0.01% day 1 **AP**	No detection	No detection	**FUP5** No detection
	4	No detection	No detection	No detection	0.01% **FUP 6** months	**FUP5** No detection
	5	0.09% day 6 **AP** & pre-transplant	No detection	0.31% **FUP1** 0.27% **FUP2** 0.13% **FUP3**	0.06% **FUP1** 0.19% **FUP2** 0.19% **FUP3**	Deceased
G-CSF+plerixafor 5 patients	6	No detection	No detection	No detection	0.04% **FUP2**	**FUP5** No detection
	7	No detection	No detection	0.03% **FUP3**	0.01% **FUP3**	No tumor cells FUP4 Deceased
	8	No detection	No detection	0.03% **FUP1**	0.02% **FUP1**	**FUP5** No detection
	9	0.01% day 1 **PB** & pre-transplant	0.01% day 6 **AP**	1.48% **FUP1**	0.04% **FUP1**	No tumor cells **FUP2** Deceased
	10	No detection	0.02% day 5 **AP**	No detection	No detection	**FUP5** No detection

Figure 2. Patients with MM cells detected in either apheresis product and/or peripheral blood.
AP indicates apheresis product; FUP, follow-up of patients after transplantation; PB, peripheral blood. FUP 1 = 100 days; FUP 2 = 6 months; FUP 3 = 12 months; FUP 4 = 18 months; FUP 5 = 24 months post-transplantation. % of MM cells are expressed among WBCs.

to study treatment (3 G-CSF and 6 G-CSF + plerixafor). One patient from the G-CSF + plerixafor arm experienced a grade 3 TEAE (pleural effusion), which was also reported as a serious TEAE. There were no AEs leading to the permanent discontinuation of treatment or death in either treatment group. Overall, 7 patients (2 patients receiving G-CSF, 5 patients receiving G-CSF + plerixafor) reported 12 post-treatment serious AEs (11 disease progression, 1 multiple-organ dysfunction syndrome). Five patients died due to disease progression during the post-treatment follow-up period. The most frequently reported TEAEs were associated with the system organ class of musculoskeletal and connective tissue disorders (3 patients receiving G-CSF and 6 patients receiving G-CSF + plerixafor).

DISCUSSION

The primary endpoint of this study was to evaluate the presence of MM tumor cells in peripheral blood and in the apheresis product after G-CSF + plerixafor treatment. The study showed no evidence that administration of G-CSF + plerixafor had an effect on the number of MM cells mobilized compared with G-CSF administration alone. There were no patients with MM tumor cells in peripheral blood evaluated at day 4 before G-CSF administration up to day 8 before G-CSF administration in either treatment group. At day 5 no patients in either treatment arm had mobilized $\geq 4.5 \times 10^5$ MM tumor cells/kg in the apheresis product (although a single patient in the G-CSF alone group exceeded this threshold number of MM tumor cells on day 6), which others have shown is a sufficient number of cells for tumor cell proliferation and poor clinical outcome [3,10]. The mean cumulative number of MM tumor cells from days 5 to 8 also remained below the threshold of $\geq 4.5 \times 10^5$ MM tumor cells/kg in the apheresis product. The overall (days 5 to 8) percentage of MM tumor cells/$CD34^+$ cells in the apheresis product was also low at .03% and .01% for the G-CSF alone and G-CSF + plerixafor groups, respectively.

The secondary endpoint of the study included the $CD34^+$ stem cell yield in the apheresis product, and in line with previous studies the G-CSF + plerixafor arm yielded a larger total yield of $CD34^+$ stem cells despite the lower baseline peripheral blood $CD34^+$ cell count in the plerixafor group compared with G-CSF treatment alone [18-23]. All patients in both treatment groups reached the minimum target of $\geq 2 \times 10^6$ $CD34^+$ cells/kg, but more patients in the G-CSF + plerixafor (70%) group reached the optimal number of $CD34^+$ cells/kg ($\geq 6 \times 10^6$ $CD34^+$ cells/kg) compared with G-CSF (40%) treatment alone. Furthermore, our study confirms the findings from previous studies that plerixafor added to G-CSF improves the yield of $CD34^+$ stem cells in apheresis product compared with G-CSF alone in patients who are considered to be poor mobilizers of $CD34^+$ cells based on preapheresis peripheral blood $CD34^+$ cell counts [7,24-26].

The effect of G-CSF plus plerixafor on tumor cell contamination of peripheral blood and apheresis product has been investigated in several studies [6,7,27,28]. One study of 12 patients (10 patients with lymphoma and 2 patients with myeloma) treated with plerixafor + G-CSF for stem cell mobilization showed no detectable tumor cells were present in the peripheral blood or apheresis product [6]. This finding was supported by the findings from another study that showed the absence of tumor cell mobilization after treatment with G-CSF and plerixafor in myeloma patients known to be poor mobilizers [7].

Our findings support the results of these previous studies showing that tumor cells are not enhanced in the peripheral blood or apheresis products of patients with MM treated with G-CSF + plerixafor compared with G-CSF alone [6,7].

In our study 18 patients (9 patients from each arm) proceeded to transplantation, and 2 patients in the G-CSF + plerixafor arm achieved a complete response to treatment. The number of patients proceeding to transplantation from both treatment arms is in line with findings from larger randomized studies [29]. The mean time of transplantation from the last apheresis was 15.1 days for the G-CSF alone group and 11.0 days for the G-CSF + plerixafor group. MM (MM1 and MM2) tumor cells were detected in both treatment arms before and after autologous transplantation (5 patients from each arm). Among these 10 patients MM cells were detected in 4 patients (1 from the G-CSF alone arm and 3 from G-CSF + plerixafor arm) after transplantation and in patients during follow-up (Figure 2). This may be due to the low number of MM tumor cells detected in the apheresis product per $CD34^+$ cells (a mean of 3.1% MM tumor cells in the G-CSF alone arm and .6% MM cells in the G-CSF + plerixafor arm). However, at the last follow-up visit MM cells were no longer detectable in 7 of 10 patients (4 patients from the G-CSF alone and 3 patients from the G-CSF + plerixafor arm). AEs observed in the G-CSF + plerixafor arm of the study were consistent with the known safety profile of plerixafor, with no new safety concerns detected [7,18,19,21-23,25,29-31].

In conclusion, the primary endpoint of the study was to evaluate the presence of MM tumor cells in peripheral blood and in the apheresis product after plerixafor treatment. This study showed no evidence that the administration of plerixafor in addition to G-CSF had an effect on the number of MM cells mobilized compared with G-CSF administration alone. There were no patients with MM tumor cells/$CD34^+$ cell count in peripheral blood evaluated at day 5 up to day 8 before G-CSF administration in either treatment group. Nine of 10 patients (90%) from each treatment arm proceeded to transplantation, but MM tumor cells were detected in either the apheresis product and/or in the peripheral blood post-transplantation in 50% of patients in each treatment arm. The G-CSF + plerixafor arm yielded a larger total yield of $CD34^+$ cells than the G-CSF alone arm at each apheresis. The safety profile of plerixafor observed in this study is consistent with that already documented for this drug, with no new safety concerns detected.

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Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.08.020.

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