

### Stem cell yield and transplantation in transplant-eligible newly diagnosed multiple myeloma patients receiving daratumumab plus bortezomib/thalidomide/dexamethasone in the phase III CASSIOPEIA study

High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) is the standard of care for transplant-eligible patients with newly diagnosed multiple myeloma (NDMM).<sup>1,2</sup> An adequate stem cell yield is essential for timely hematopoietic reconstitution after ASCT.<sup>3</sup> Daratumumab is a human immunoglobulin (Ig) G $\kappa$  monoclonal antibody targeting CD38 with a direct on-tumor<sup>4-6</sup> and immunomodulatory mechanism of action.<sup>7-9</sup> Multiple studies have demonstrated the clinical benefits of adding daratumumab to standard-of-care regimens or as monotherapy across lines of therapy in multiple myeloma.<sup>10</sup>

The phase III CASSIOPEIA study investigated daratumumab plus the standard-of-care regimen bortezomib/thalidomide/dexamethasone (D-VTd) versus bortezomib/thalidomide/dexamethasone (VTd) in ASCT-eligible patients with NDMM.<sup>11</sup> In part 1 of the study, patients received induction, ASCT, and consolidation therapy, which was followed by part 2 of the study where patients with a partial response or better after consolidation were re-randomized to receive maintenance therapy

or observation. Here we report stem cell yield/harvest and transplantation results in part 1 of CASSIOPEIA.

The study design and eligibility criteria of CASSIOPEIA have been previously reported (*clinicaltrials.gov. Identifier: NCT02541383*) (Figure 1).<sup>11</sup> Briefly, eligible patients were 18 to 65 years of age, had NDMM, had an Eastern Cooperative Oncology Group performance status of 0 to 2, and were candidates for HDT and ASCT. Major exclusion criteria included the following: hemoglobin concentration <7.5 g/dL; absolute neutrophil count <1.0 $\times$ 10<sup>9</sup>/L; platelet count  $\leq$ 50 $\times$ 10<sup>9</sup>/L (or <70 $\times$ 10<sup>9</sup>/L if <50% of bone marrow nucleated cells were plasma cells); aspartate aminotransferase and alanine aminotransferase levels >2.5 times the upper limit of normal (ULN); total bilirubin level >1.5 times ULN; calculated creatinine clearance <40 mL/min; corrected serum calcium concentration <14 mg/dL (3.5 mmol/L); primary amyloidosis, monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, solitary plasmacytoma, or Waldenström macroglobulinemia; previous systemic therapy or stem cell transplantation for any plasma cell dyscrasia; and grade  $\geq$ 2 peripheral neuropathy or grade  $\geq$ 2 neuropathic pain. All patients provided written informed consent; the trial was approved by Institutional Review Board/ethics committees at each site and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements.

Following induction, patients underwent stem cell

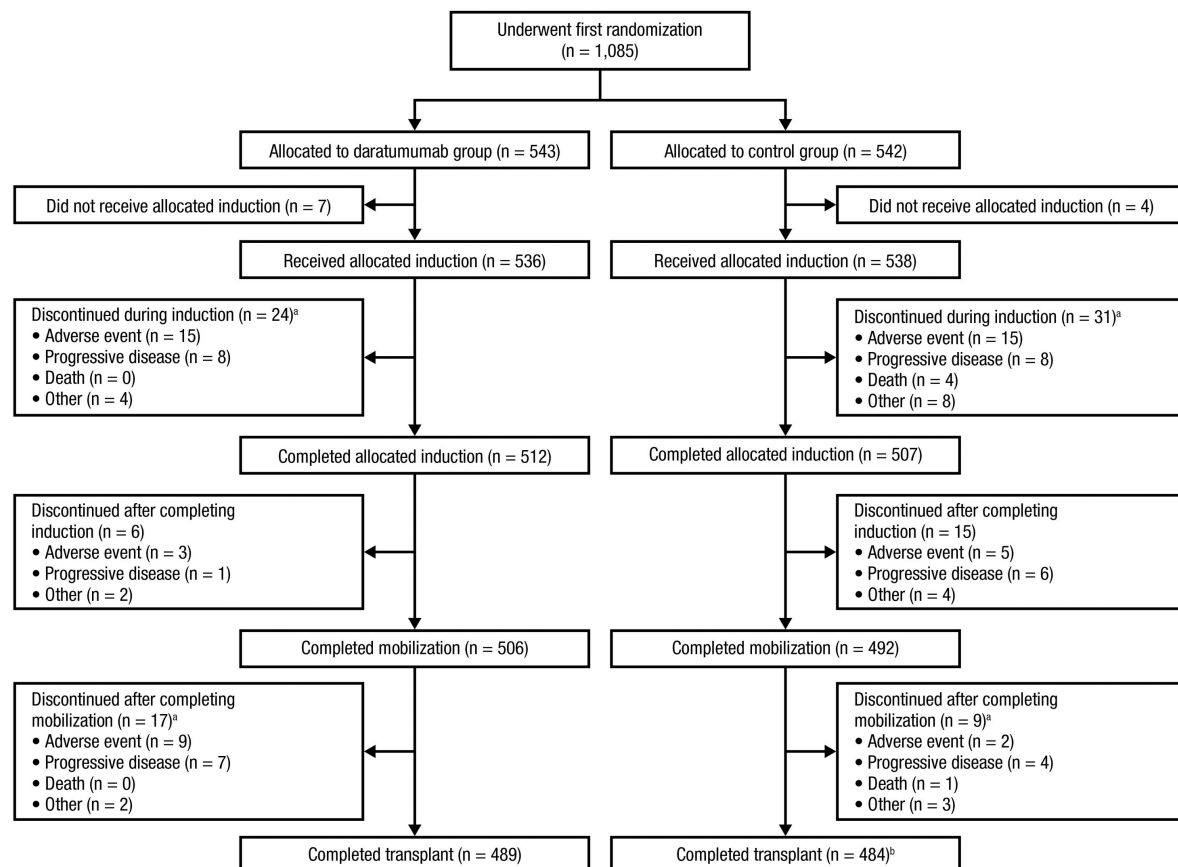


Figure 1. CONSORT diagram for the CASSIOPEIA study. The study flow diagram is shown for the CASSIOPEIA study from first randomization through completion of autologous stem cell transplant. The daratumumab group received daratumumab/bortezomib/thalidomide/dexamethasone; the control group received bortezomib/thalidomide/dexamethasone. Other: includes patient withdrawal, investigator decision, and others. <sup>a</sup>Reasons for discontinuation are not mutually exclusive. <sup>b</sup>One patient had successful CD34<sup>+</sup> stem cell collection without any previous mobilization treatment.

Table 1. Stem cell mobilization, harvesting, and transplantation.

	D-VTd	VTd	P
<b>Patients with stem cell mobilization</b>	<b>N=506</b>	<b>N=492</b>	
PBSC mobilizing agents, n (%) <sup>a</sup>			
Cyclophosphamide/G-CSF	506 (100)	492 (100)	
Plerixafor	110 (21.7)	39 (7.9)	<0.0001 <sup>b</sup>
PBSC apheresis performed, n (%)	504 (99.6) <sup>c</sup>	490 (99.6) <sup>d</sup>	>0.999 <sup>b</sup>
<b>Patients with PBSC apheresis performed</b>	<b>N=504</b>	<b>N=490</b>	
Number of days of apheresis, mean [SD] (range)	1.9 [0.92] (1–6)	1.4 [0.67] (1–4)	<0.0001 <sup>e</sup>
Number of days of apheresis, n (%)			<0.0001 <sup>f</sup>
1	184 (36.5)	327 (66.7)	
2	204 (40.5)	125 (25.5)	
3	91 (18.1)	32 (6.5)	
4	18 (3.6)	6 (1.2)	
5	4 (0.8)	0	
6	3 (0.6)	0	
Total number of CD34 <sup>+</sup> stem cells collected (10 <sup>6</sup> /kg) among patients with PBSC apheresis performed			
Mean [SD] (range)	6.7 [2.63] (0.5–18.7)	10.0 [5.25] (2.2–36.9)	<0.0001 <sup>e</sup>
≥2 × 10 <sup>6</sup> /kg, n (%)	501 (99.4)	490 (100)	0.2494 <sup>b</sup>
≥4 × 10 <sup>6</sup> /kg, n (%)	444 (88.1)	470 (95.9)	<0.0001 <sup>b</sup>
≥5 × 10 <sup>6</sup> /kg, n (%)	380 (75.4)	434 (88.6)	<0.0001 <sup>b</sup>
Patients who underwent transplantation, n (%)	489 (97.0)	484 (98.8)	0.0758 <sup>b</sup>
Number of CD34 <sup>+</sup> stem cells transplanted (10 <sup>6</sup> /kg), Mean [SD] (range)	3.6 [1.59] (0.5–12.6)	5.0 [2.80] (1.2–23.3)	<0.0001 <sup>e</sup>

Percentages were calculated with N in each group as the denominator. <sup>a</sup>Several PBSC mobilizing agents were possible. <sup>b</sup>P-value calculated from Fisher's exact test. <sup>c</sup>Bone marrow harvest was performed for one patient in the D-VTd arm and no patients in the VTd arm. No patients had only bone marrow collection. The D-VTd patient received a stem cell collection from bone marrow in addition to apheresis from peripheral blood. Here both numbers are summed as a total of CD34<sup>+</sup> stem cells collected from this patient. <sup>d</sup>Based on available information from the investigator, one patient in the VTd arm had successful CD34<sup>+</sup> stem cell collection without a record of mobilization treatment. However, unrecorded mobilization likely occurred, although details are undocumented. <sup>e</sup>P-value calculated from two-sample *t*-test. <sup>f</sup>P-value calculated from Cochran-Armitage trend test. D-Vtd: daratumumab/bortezomib/thalidomide/dexamethasone; VTd: bortezomib/thalidomide/dexamethasone; PBSC: peripheral blood stem cell; G-CSF: granulocyte colony-stimulating factor; SD: standard deviation.

mobilization with cyclophosphamide (recommended dose, 3 g/m<sup>2</sup>) and granulocyte colony-stimulating factor (G-CSF) (recommended dose, 10 µg/kg/day until the last day of the collection for a maximum of 10 days) after cycle 4. The recommended cyclophosphamide dose (3 g/m<sup>2</sup>) was not mandatory and varied by region (e.g., more patients received 2 g/m<sup>2</sup> in the Netherlands and Belgium, while more received 3 g/m<sup>2</sup> in France). Plerixafor use was permitted per institutional practice in case of failure. Peripheral blood stem cells were harvested based on response to mobilization. Patients underwent conditioning with intravenous melphalan 200 mg/m<sup>2</sup> prior to ASCT. Per protocol, sufficient stem cells should be harvested to enable multiple transplants, in accordance with institutional standards. Cell counting after harvesting was conducted locally, per institutional practice. Consolidation therapy was initiated after hematopoietic reconstitution, but not earlier than 30 days after transplantation. Intergroupe Francophone du Myélome and Janssen statisticians were involved in all stages of the study and data analysis.

A total of 1,085 patients were randomized to D-VTd (n=543) or VTd (n=542) (Figure 1). Results for stem cell mobilization, harvesting, and transplantation are presented in Table 1. At the clinical cutoff of June 19, 2018, among those undergoing induction (D-VTd, n=536; VTd, n=538), 506 (94.4%) patients in the D-VTd group and 492 (91.4%) patients in the VTd group received

cyclophosphamide/G-CSF; 504 (94.0%) and 490 (91.1%) patients, respectively, underwent stem cell harvesting. Plerixafor was administered in the course of stem cell mobilization to 110 patients (21.7% of the 506 patients who underwent mobilization) in the D-VTd group *versus* 39 patients (7.9% of the 492 patients who underwent mobilization) in the VTd group (*P*<0.0001). One patient who received VTd had no record of mobilization treatment but had successful collection of CD34<sup>+</sup> cells from peripheral blood in 2 consecutive days of apheresis; this patient received HDT with stem cell transplant with engraftment. One patient in the D-VTd group had stem cells collected from bone marrow in addition to apheresis from peripheral blood. Five patients (D-VTd, n=2; VTd, n=3) who received mobilizing agents did not undergo stem cell harvesting; of these, mobilization failure was noted in three patients (D-VTd, n=2; VTd, n=1). The two patients in the D-VTd group who failed mobilization underwent two mobilization procedures and failed both. The single patient in the VTd group who failed mobilization did not have a second procedure. The remaining two patients in the VTd group who received mobilizing agents did not undergo stem cell harvest and discontinued treatment due to death (n=1; serious adverse event of large intestine perforation with a history of sigmoid diverticulosis) or disease progression (n=1).

The mean number of days of apheresis were 1.9 for D-VTd *versus* 1.4 for VTd (*P*<0.0001; Table 1). Apheresis

Table 2. Stem cell transplantation outcomes.

Patients with transplantation	D-VTd N=489	VTd N=484	P
Patients with hematopoietic reconstitution, n (%)	488 (99.8)	482 (99.6)	0.6227 <sup>a</sup>
Platelet recovery (achieving sustained platelets >20,000 cells/mm <sup>3</sup> without transfusion), n (%)	413 (84.5)	361 (74.6)	0.0001 <sup>a</sup>
Number of days to achieve sustained platelets >20,000 cells/mm <sup>3</sup> without transfusion, mean [SD] (range)	14.9 [5.38] (2–56)	13.6 [4.64] (1–47)	0.0004 <sup>b</sup>
Neutrophil recovery (achieving sustained absolute neutrophil counts >500 cells/mm <sup>3</sup> ), n (%)	475 (97.1)	474 (97.9)	0.5363 <sup>a</sup>
Number of days to achieve sustained absolute neutrophil counts >500 cells/mm <sup>3</sup> , mean [SD] (range)	14.4 [4.07] (6–54)	13.7 [4.20] (4–43)	0.0155 <sup>b</sup>

D-VTd: daratumumab/bortezomib/thalidomide/dexamethasone; VTd: bortezomib/thalidomide/dexamethasone; SD: standard deviation. <sup>a</sup>P-value calculated from Fisher's exact test. <sup>b</sup>P-value calculated from two-sample t-test.

lasting 4–6 days occurred in 5.0% (25 of 504) and 1.2% (six of 490) of patients in the D-VTd and VTd groups who received apheresis. The mean number of CD34<sup>+</sup> stem cells collected was lower for patients receiving D-VTd versus VTd ( $6.7 \times 10^6/\text{kg}$  vs.  $10.0 \times 10^6/\text{kg}$ , respectively;  $P < 0.0001$ ; Table 1). Nevertheless, among those who received apheresis, a similar percentage of D-VTd-treated patients and VTd-treated patients underwent ASCT (97.0% vs. 98.8%, respectively;  $P = 0.0758$ ; Table 1). Of the patients who completed mobilization without receiving transplant, the most common reasons for discontinuation were adverse events in the D-VTd group (D-VTd, n=8; VTd, n=2) and disease progression in the VTd group (D-VTd, n=7; VTd, n=4).

ASCT was undergone by 489 patients in the D-VTd group and 484 patients in the VTd group. The mean number of CD34<sup>+</sup> stem cells transplanted was  $3.6 \times 10^6/\text{kg}$  in the D-VTd group compared with  $5.0 \times 10^6/\text{kg}$  in the VTd group ( $P < 0.0001$ ; Table 1). Hematopoietic reconstitution rates were high and similar in transplanted patients receiving D-VTd and VTd (99.8% vs. 99.6%, respectively;  $P = 0.6227$ ; Table 2). The mean (standard deviation) time to achieve sustained platelet counts >20,000 cells/mm<sup>3</sup> without transfusion was 14.9 days for D-VTd versus 13.6 days for VTd ( $P = 0.0004$ ), and the mean time to achieve sustained absolute neutrophil counts >500 cells/mm<sup>3</sup> was 14.4 days for D-VTd versus 13.7 days for VTd ( $P = 0.0155$ ; Table 2). Despite the greater mean number of days needed to achieve sustained platelet counts >20,000 cells/mm<sup>3</sup> without transfusion and absolute neutrophil counts >500 cells/mm<sup>3</sup> with D-VTd versus VTd, the percentage of patients who achieved platelet recovery was higher with D-VTd (84.5% vs. 74.6%;  $P = 0.0001$ ) and the percentages of patients who achieved neutrophil recovery were similar between the two treatment groups (97.1% vs. 97.9%;  $P = 0.5363$ ; Table 2).

Although there was lower stem cell yield and higher plerixafor use in the D-VTd group, the addition of daratumumab to VTd did not impair the feasibility and safety of performing transplant or the success of engraftment post transplant. Potential reasons why daratumumab results in lower stem cell yield in this study are unknown; however, daratumumab may possibly cause some degree of interference through an unknown mechanism, as CD34<sup>+</sup> committed stem cells express a low level of CD38.<sup>12</sup> Factors that have previously been demonstrated to impact yield, such as age, sex and weight, are not specifically associated with daratumumab or daratumumab-treated patients.<sup>13,14</sup> Close monitoring and early implementation of plerixafor could be considered for patients with risk factors for lower yield.<sup>15</sup>

Differences between treatment arms reached statistical significance for several parameters of stem cell mobilization, harvesting, and transplant. However, these differences were ultimately not clinically relevant, as post-transplant hematopoietic reconstitution was nearly identical (99.8% vs. 99.6%) in both treatment arms. Transplantation should be managed on an individual basis and with clinical judgment considering the overall situation of the patient.

In conclusion, the addition of daratumumab to VTd during induction therapy did not impair the feasibility and safety of transplantation with successful engraftment, even though stem cell yield was lower with D-VTd. Combined with the primary efficacy and safety data reported previously, D-VTd is considered a valid treatment option for patients with NDMM who are transplant-eligible.

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