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

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Summary

Background Bortezomib, thalidomide, and dexamethasone (VTd) plus autologous stem-cell transplantation is standard treatment in Europe for transplant-eligible patients with newly diagnosed multiple myeloma. We evaluated whether the addition of daratumumab to VTd before and after autologous stem-cell transplantation would improve stringent complete response rate in patients with newly diagnosed multiple myeloma.

Methods In this two-part, randomised, open-label, phase 3 CASSIOPEIA trial, we recruited transplant-eligible patients with newly diagnosed multiple myeloma at 111 European sites. Patients were randomly assigned (1:1) to receive four pre-transplant induction and two post-transplant consolidation cycles of VTd alone (VTd group) or in combination with daratumumab (D-VTd group). The primary endpoint of part 1 was stringent complete response assessed 100 days after transplantation. Part 2 (maintenance) is ongoing. The trial is registered with ClinicalTrials.gov, number NCT02541383.

Findings Between Sept 22, 2015, and Aug 1, 2017, 1085 patients were enrolled at 111 European sites and were randomly assigned to the D-VTd group (n=543) or the VTd group (n=542). At day 100 after transplantation, 157 (29%) of 543 patients in the D-VTd group and 110 (20%) of 542 patients in the VTd group in the intention-to-treat population had achieved a stringent complete response (odds ratio 1·60, 95% CI 1·21–2·12, p=0·0010). 211 (39%) patients in the D-VTd group versus 141 (26%) in the VTd group achieved a complete response or better, and 346 (64%) of 543 versus 236 (44%) of 542 achieved minimal residual disease-negativity (10^{-5} sensitivity threshold, assessed by multiparametric flow cytometry; both p<0·0001). Median progression-free survival from first randomisation was not reached in either group (hazard ratio 0·47, 95% CI 0·33–0·67, p<0·0001). 46 deaths on study were observed (14 vs 32, 0·43, 95% CI 0·23–0·80). The most common grade 3 or 4 adverse events were neutropenia (28% vs 15%), lymphopenia (17% vs 10%), and stomatitis (13% vs 16%).

Interpretation D-VTd before and after autologous stem-cell transplantation improved depth of response and progression-free survival with acceptable safety. CASSIOPEIA is the first study showing the clinical benefit of daratumumab plus standard of care in transplant-eligible patients with newly diagnosed multiple myeloma.

Funding The Intergroupe Francophone du Myélome and Dutch-Belgian Cooperative Trial Group for Hematology Oncology.

Introduction

In transplant-eligible patients, induction therapy before autologous stem-cell transplantation and consolidation therapy afterwards is a treatment option for newly diagnosed multiple myeloma.[1,2] Maintenance therapy after transplantation prolongs progression-free survival.[1,3] Improved and sustained responses with consolidation and maintenance therapies have been shown in clinical trials.[4–6] However, few patients are cured, long-term treatment options have undesirable toxicities, and alternative options are needed.

Daratumumab is a human, CD38-targeting, IgG1κ monoclonal antibody with a well characterised mechanism of action.[7] In phase 3 studies, daratumumab added to bortezomib and dexamethasone,[8] lenalidomide and dexamethasone,[9] and bortezomib, melphalan, and prednisone[10] reduced the risk of progression or death by at least 50% and tripled proportions of patients who

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Research in context

Evidence before this study

We searched PubMed for articles published from database inception to March 7, 2019. All fields were searched for "newly diagnosed multiple myeloma" and "monoclonal antibody" and "transplant". Our search identified 41 articles published during this timeframe. Ten were published before the first patient was enrolled in the CASSIOPEIA study in September, 2015, and only one described a clinical trial with a monoclonal antibody. This trial was a phase 2 clinical trial of siltuximab, an interleukin-6 monoclonal antibody, in combination with bortezomib, melphalan, and dexamethasone in transplant-ineligible, newly diagnosed myeloma that failed to show a clinical benefit. Of the 31 articles published after the CASSIOPEIA study was initiated, three were relevant to the search terms. The first was a phase 1 clinical study (n=14) of siltuximab in combination with bortezomib, lenalidomide, and dexamethasone in transplant-ineligible and transplant-eligible, newly diagnosed patients. The second was a phase 3 trial of denosumab versus zoledronic acid for the treatment of bone disease in newly diagnosed multiple myeloma. The third was the ALCYONE phase 3 study of daratumumab in combination with bortezomib, melphalan, and prednisone in transplant-ineligible, newly diagnosed myeloma. Thus, there was an unmet need to evaluate the role of monoclonal antibody-based therapy in patients eligible for autologous stem-cell transplantation.

Added value of this study

Daratumumab had previously shown efficacy in relapsed or refractory multiple myeloma as monotherapy and in combination with standard-of-care regimens. The ALCYONE and MAIA phase 3 clinical studies showed longer progression-free survival with greater incidences of certain toxicities (ie, infections and neutropenia) in patients with newly diagnosed multiple myeloma ineligible for transplant owing to age or comorbidities.

Autologous stem-cell transplantation is the standard of care for eligible patients with newly diagnosed myeloma. The CASSIOPEIA study is the first to show that addition of a monoclonal antibody to an induction and consolidation regimen is effective and well tolerated in transplant-eligible patients. Treatment with daratumumab, bortezomib, thalidomide, and dexamethasone induces significant increases in proportions of patients achieving deep responses, including minimal residual disease negativity, than bortezomib, thalidomide, and dexamethasone alone. The regimen does not affect the ability to perform a stem-cell transplant and enabled a 53% reduction in the risk of progression or death. The effect on overall survival is yet to be determined.

Implications of all the available evidence

With these data, daratumumab-based combinations have now shown significant treatment benefits across the multiple myeloma disease spectrum. Part 2 of the CASSIOPEIA study is ongoing and is evaluating the effect of maintenance treatment with daratumumab monotherapy. In real-world practice, many patients with multiple myeloma might only receive one line of treatment, and regimens that induce deep and durable responses are needed to delay the risk of relapse. Several phase 3 studies, many of which have completed primary analyses but are ongoing for long-term analyses, have shown that daratumumab-based combinations enable such responses over time, including in patients considered high risk. Bortezomib, thalidomide, and dexamethasone is a standard of care in Europe. Daratumumab in combination with bortezomib, lenalidomide, and dexamethasone followed by maintenance is being evaluated in transplant-eligible and transplant-ineligible, newly diagnosed patients. One aim of the ongoing longer-term follow-up of all phase 3 studies is to determine the effect on median overall survival. Encouragingly, the most recent analyses show that median overall survival has not yet been reached in these phase 3 studies with longer follow-up.

were negative for minimal residual disease (sensitivity threshold of 1 tumour cell per 10^5 white cells by next-generation sequencing) in patients with multiple myeloma.[8–12]

Among proteasome inhibitor-based induction and consolidation regimens, bortezomib, thalidomide, and dexamethasone is effective for patients with newly diagnosed multiple myeloma.[1,2,5,6,13–16] We report the primary and final analysis of part 1 of CASSIOPEIA, a randomised, phase 3 trial of this regimen with or without daratumumab as induction and consolidation therapy in newly diagnosed transplant-eligible patients.

Methods

Study design and participants

We did a randomised, open-label, active-controlled, phase 3 trial at 111 European sites consisting of academic and community practice centres. Eligible patients had newly diagnosed, documented multiple myeloma and were eligible for high-dose therapy and autologous stem-cell transplantation. Patients were 18–65 years of age and had an Eastern Cooperative Oncology Group performance status of 0–2, an absolute neutrophil count of 1×10^9 per L or more, a haemoglobin concentration of 7·5 g/dL or more, a platelet count of 70×10^9 per L or more (if <50% of bone marrow nucleated cells were plasma cells, otherwise platelet count $>50 \times 10^9$ per L), a calculated creatinine clearance of 40 mL/min or more, a corrected serum calcium level of 14 mg/dL or less (<3·5 mmol/L), and adequate liver function (appendix p 6). Patients were excluded if they had previous systemic therapy or stem-cell transplantation for any plasma cell dyscrasia or grade 2 or higher peripheral neuropathy or neuropathic pain

(National Cancer Institute Common Terminology Criteria for Adverse Events version 4; complete criteria are in the appendix [p 6]).

All patients provided written informed consent. The trial was done in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The Intergroupe Francophone du Myélome and Dutch-Belgian Cooperative Trial Group for Hematology Oncology sponsored this trial and, with Janssen Research & Development, collaborated in its design. The sponsors compiled and maintained investigator-collected data. All investigators had access to the data and were not restricted by confidentiality agreements. Professional medical writers, funded by Janssen Global Services, LLC, prepared the manuscript. All authors reviewed, revised, and approved the manuscript. The sponsors and authors vouch for data accuracy and completeness and for adherence to the study protocol.

Randomisation and masking

In part 1, patients were randomly assigned (1:1) by use of an interactive web-based system to daratumumab in combination with bortezomib, thalidomide, and dexamethasone (D-VTd) or bortezomib, thalidomide, and dexamethasone (VTd) as induction and consolidation treatments (appendix p 7). Randomisation was balanced by use of permuted blocks (block size 4), and stratification factors included site affiliation (Intergroupe Francophone du Myélome or Dutch-Belgian Cooperative Trial Group for Hematology Oncology), International Staging System disease stage (I, II, or III), and cytogenetic risk status (presence [high risk] or absence [standard risk] of del17p or t[4;14] cytogenetic abnormalities confirmed by centralised analysis during screening). Patients without cytogenetic results were stratified as standard risk and classified as such for consistency with the analyses. There was no masking to treatment assignments.

Procedures

All patients received up to four 28-day, pre-transplant induction cycles and two 28-day, post-transplant consolidation cycles of subcutaneous bortezomib (1·3 mg/m² twice per week in week 1 [days 1 and 4] and week 2 [days 8 and 11] of each cycle), oral thalidomide (100 mg daily in all cycles), and oral or intravenous dexamethasone (40 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 of induction cycles 1 and 2 and days 1 and 2 of induction cycles 3 and 4 and 20 mg on days 8, 9, 15, and 16 of induction cycles 3 and 4 and days 1, 2, 8, 9, 15, and 16 of both consolidation cycles). Daratumumab was administered intravenously at a dose of 16 mg/kg of bodyweight once weekly in induction cycles 1 and 2 and once every 2 weeks during induction cycles 3 and 4 and consolidation. Medications administered before daratumumab infusions are summarised in the appendix (p 4).

After induction cycle 4, patients underwent stem-cell mobilisation with cyclophosphamide (3 g/m² [recommended dose]) and granulocyte colony-stimulating factor, and peripheral blood stem cells were harvested based on response to mobilisation. Plerixafor was permitted according to institutional practice. Patients underwent conditioning with intravenous melphalan 200 mg/m², followed by autologous stem-cell transplantation. Consolidation began after haematopoietic reconstitution but not earlier than 30 days after transplant.

In ongoing part 2, patients achieving a partial response or better at day 100 post-transplant underwent a second randomisation to observation or maintenance therapy with daratumumab (16 mg/kg) every 8 weeks until disease progression or for a maximum of 2 years.

Outcomes

Efficacy analyses, including the proportion of patients with negative status for minimal residual disease, were done on the intention-to-treat population, which included all patients who underwent the first randomisation. The primary endpoint was the proportion of patients who achieved a stringent complete response after consolidation, systematically assessed at 100 days after autologous stem-cell transplantation (or immediately after consolidation if >100 days) in accordance with International Myeloma Working Group criteria[17] (appendix p 10). Key secondary efficacy endpoints included the proportion of patients who were minimal residual disease-negative after consolidation, the proportion of patients who achieved a complete response or better after consolidation, and progression-free survival and overall survival from first randomisation. Other endpoints included the proportion of patients who achieved a stringent complete response after induction, very good partial response or better, and overall response as defined in the appendix (p 5).

A central laboratory performed disease assessments on day 1 of each cycle in cycles 1–6, day 28 of cycle 4, and day 100 after autologous stem-cell transplantation. If daratumumab interference with serum M-protein was suspected, immunofixation reflex assays confirmed complete responses.[18] Minimal residual disease was primarily evaluated by EuroFlow-based multiparametric flow cytometry[19] and additionally with next-generation sequencing[20] of bone marrow aspirates (appendix p 6). Safety assessments, including adverse event monitoring, physical examinations, electrocardiography, clinical safety laboratory testing, and vital sign measurements, were done in the safety population of patients who underwent the first randomisation and received at least one dose of trial treatment. An independent data monitoring committee reviewed the safety data.

Statistical analysis

On the basis of the assumption that 75% of patients in part 1 would be eligible to be randomly assigned for part 2

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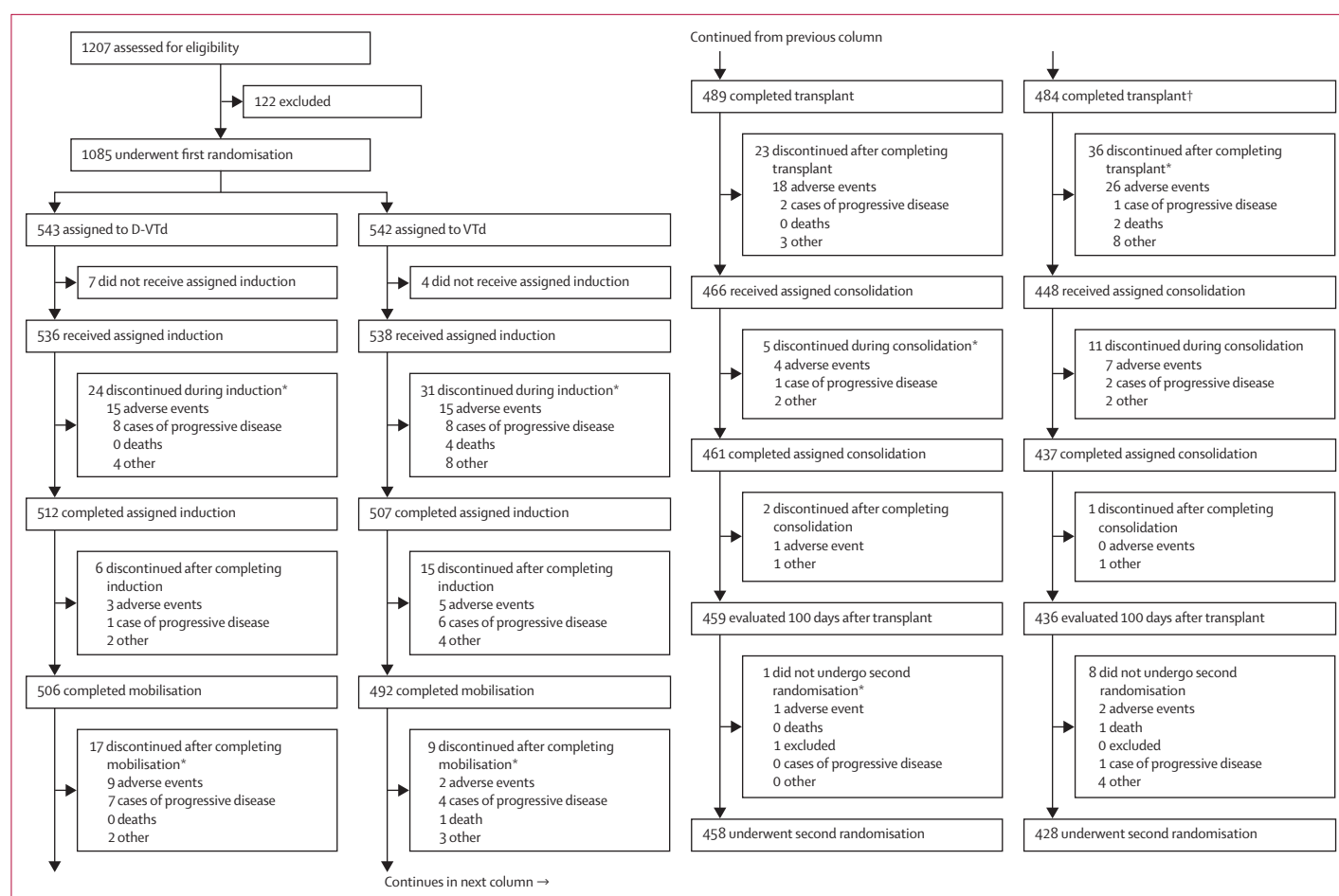
See Online for appendix

Figure 1: Study profile
Other includes patient withdrawal, investigator decision, and other. D-VTd=daratumumab plus bortezomib, thalidomide, and dexamethasone. VTd=bortezomib, thalidomide, and dexamethasone.
*Reasons for discontinuation are not mutually exclusive. †One patient had successful CD34+ stem cell collection without any previous mobilisation treatment.

maintenance, 1080 (540 per treatment) were initially randomly assigned to provide at least more than 85% power to detect an improvement in stringent complete response proportions from 25% to 35% at a two-sided α of 0·05. The primary and final analysis of part 1 evaluated efficacy after all patients either completed the day 100 response evaluation or discontinued from study treatment. A validated computer algorithm determined response and disease progression.[8–10] Responses and other binary endpoints were assessed using the stratified Cochran-Mantel-Haenszel chi-square test, and odds ratios (ORs) and two-sided 95% CIs were calculated. If the between-group difference in the primary endpoint was statistically significant, the secondary efficacy endpoints of the proportion for patients who were minimal residual disease-negative and who achieved a complete response or better after consolidation and progression-free survival and overall survival from first randomisation, as ordered here, were to be tested sequentially using a hierarchical testing approach, each with an overall two-sided alpha level of 0·05. Progression-free survival using the inverse

probability weighting method[21] to adjust for the second randomisation was analysed by a sequestered group independent from the study team to preserve the integrity of part 2. This trial is registered with ClinicalTrials.gov, number NCT02541383.

Role of the funding source
The funders in collaboration with the authors designed the trial, collected, analysed, and interpreted the data, and prepared the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Between Sept 22, 2015, and Aug 1, 2017, 1085 patients were enrolled, of which 543 were randomly assigned to the D-VTd group and 542 to the VTd group (figure 1). A total of 1074 patients (536 in the D-VTd group and 538 in the VTd group) received at least one dose of treatment. Demographic and clinical characteristics were well balanced (table 1). The median age was 58·0 years

	D-VTd (n=543)	VTd (n=542)
Age		
Median (range), years	59·0 (22–65)	58·0 (26–65)
Sex		
Male	316 (58·2%)	319 (58·9%)
Female	227 (41·8%)	223 (41·1%)
Eastern Cooperative Oncology Group performance status*		
0	265 (49%)	257 (47%)
1	225 (41%)	230 (42%)
2	53 (10%)	55 (10%)
Type of measurable disease		
IgG	331 (61%)	314 (58%)
IgA	80 (15%)	99 (18%)
Other†	13 (2%)	22 (4%)
Detected in urine only	70 (13%)	67 (12%)
Detected in serum free light chains only	48 (9%)	40 (7%)
Unknown	1 (<1%)*	0
International Staging System disease stage‡		
I	204 (38%)	228 (42%)
II	255 (47%)	233 (43%)
III	84 (15%)	81 (15%)
Cytogenetic profile, n/total (%)§		
Standard risk	460/542 (85%)	454/540 (84%)
High risk¶	82/542 (15%)	86/540 (16%)
Median time since diagnosis of multiple myeloma (range), months	0·92 (0·2–9·4)	0·92 (0·2–22·9)

Data are n (%) unless otherwise stated. D-VTd=daratumumab plus bortezomib, thalidomide, and dexamethasone. VTd=bortezomib, thalidomide, and dexamethasone. *One patient was assessed as light-chain only, despite monoclonal peak in serum and urine. †Includes IgD, IgM, IgE, and biclonal. ‡See appendix p 18 for baseline disease stage based on the revised International Staging System criteria.[22] §Cytogenetic risk was assessed by fluorescence in-situ hybridisation. Patients for whom cytogenetic testing failed were considered standard risk (D-VTd 7·6%; VTd 7·4%). ¶These patients had at least one high-risk abnormality: del17p (≥50% abnormal cells) or t(4;14) (≥30% abnormal cells).

Table 1: Demographic and clinical characteristics in the intention-to-treat population at baseline

	D-VTd (n=543)	VTd (n=542)	p value*
Overall response			
Number with response	503	487	..
Percentage (95% CI)	92·6% (90·1–94·7)	89·9% (87·0–92·3)	0·11
Response			
Stringent complete response	157 (29%)	110 (20%)	0·0010
Complete response or better	211 (39%)	141 (26%)	<0·0001
Complete response	54 (10%)	31 (6%)	..
Very good partial response or better	453 (83%)	423 (78%)	0·024
Very good partial response	242 (45%)	282 (52%)	..
Partial response	50 (9%)	64 (12%)	..
Stable disease	10 (2%)	15 (3%)	..
Progressive disease	20 (4%)	25 (5%)	..
Response could not be evaluated	10 (2%)	15 (3%)	..
MRD-negative status (10⁻⁵)†			
MRD negative regardless of response	346 (64%)	236 (44%)	<0·0001
MRD negative and complete response or better‡	183 (34%)	108 (20%)	<0·0001
MRD negative and very good partial response or better‡	338 (62%)	231 (43%)	<0·0001

Data are n (%) unless otherwise stated. D-VTd=daratumumab plus bortezomib, thalidomide, and dexamethasone. VTd=bortezomib, thalidomide, and dexamethasone. MRD=minimal residual disease. *p values are given only for primary, secondary, and aggregated endpoints. †EuroFlow-based multiparametric flow cytometry.[19] ‡Post-hoc analysis.

Table 2: Summary of responses and minimal residual disease status 100 days after autologous stem-cell transplantation

(range 22–65), median time since diagnosis was 0·9 months (0·2–22·9), and median duration of follow-up was 18·8 months (0·0–32·2).

At the clinical cutoff (June 19, 2018), 461 patients (85%) in the D-VTd group and 437 patients (81%) in the VTd group completed all four induction and both consolidation cycles, and 489 patients (90%) and 484 patients (89%) had undergone autologous stem-cell transplantation (figure 1). A total of 886 patients (82%; 458 patients [84%] in the D-VTd group and 428 patients [79%] in the VTd group) were randomly assigned a second time (figure 1). A total of 24 (4%) patients in the D-VTd group and 31 (6%) patients in the VTd group discontinued treatment during induction, and five (1%) and 11 (2%) patients during consolidation; 23 (4%) and 36 (7%) patients did not continue to consolidation therapy after transplantation (figure 1). The most common reasons for discontinuation

were adverse events, progressive disease, and death (figure 1).

Median durations of treatments and median relative dose intensities of treatments are in the appendix (pp 12, 13).

With regard to the primary endpoint, 157 (29%) of 543 patients in the D-VTd group and 110 (20%) of 542 patients in the VTd group achieved a stringent complete response after consolidation (odds ratio 1·60, 95% CI 1·21–2·12, p=0·0010; table 2). At the same assessment, the proportion of patients who achieved a complete response or better was significantly higher in the D-VTd group versus the VTd group (211 [39%] vs 141 [26%], p<0·0001), as was the proportion of patients who achieved a very good partial response or better (453 [83%] vs 423 [78%], p=0·024). Responses improved over time (figure 2A). Prespecified subgroup analyses of the primary endpoint showed that the greater numbers of patients achieving a stringent complete response in the D-VTd group compared with the VTd group were consistent across all subgroups, with the exception of patients with a high-risk cytogenetic profile or International Staging System disease stage III (figure 2B).

The proportion of patients with negative status for minimal residual disease (at a threshold of 1 tumour cell per 10⁵ white cells) following consolidation was larger in the D-VTd group than in the VTd group (346 [64%] of 543 vs 236 [44%] of 542, p<0·0001 when assessed by multiparametric flow cytometry; table 2;
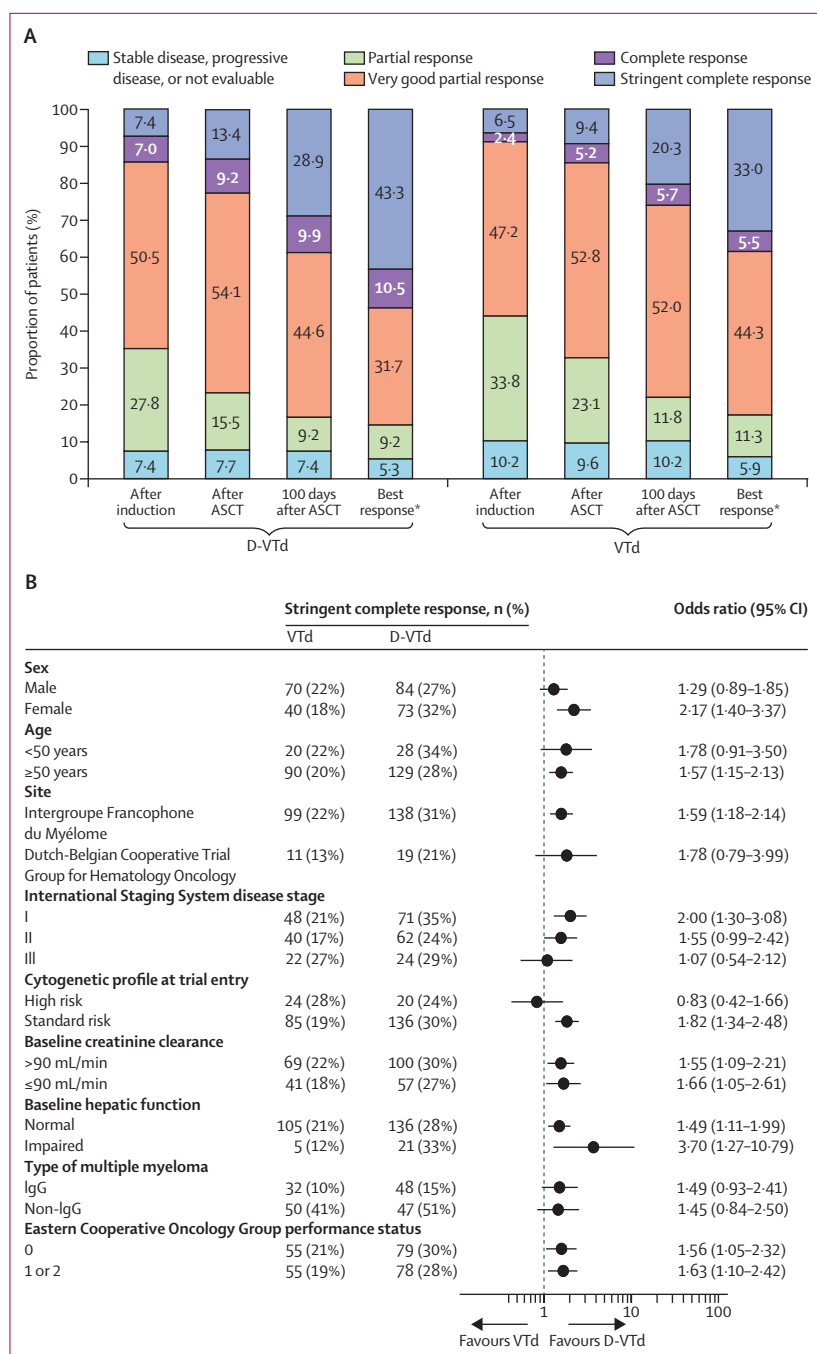
Figure 2: Summary of responses and subgroup analysis of stringent complete response after consolidation
(A) Responses over the course of the study. (B) Results of an analysis of stringent complete response in prespecified subgroups of the intention-to-treat population that were defined according to baseline characteristics. ASCT=autologous stem-cell transplantation. D-VTd=daratumumab plus bortezomib, thalidomide, and dexamethasone. VTd=bortezomib, thalidomide, and dexamethasone. *At clinical cutoff (June 19, 2018) for the primary analysis of part 1 and regardless of second randomisation (post-hoc analysis).

disease and complete response or better was larger in the D-VTd group versus the VTd group (183 [34%] vs 108 [20%], p<0·0001), as well as the proportion of patients with negative status for minimal residual disease and very good partial response or better (338 [62%] vs 231 [43%], p<0·0001; table 2). Prespecified subgroup analyses of minimal residual disease negativity favoured the D-VTd group across all subgroups (appendix p 8).

Progression-free survival from first randomisation, based on inverse probability weighting, was significantly improved in the D-VTd group compared with the VTd group (hazard ratio [HR] 0·47, 95% CI 0·33–0·67, p<0·0001) and was consistent when analysed without adjustment for the second randomisation (figure 3A; appendix p 14). A total of 45 events of disease progression or death occurred in the D-VTd group versus 91 events in the VTd group. Median progression-free survival was not reached in the D-VTd group or in the VTd group (figure 3A). The probability of progression-free survival at 18 months was 93% (95% CI 90–95) in the D-VTd group and 85% (95% CI 81–88) in the VTd group. In the time-to-event analysis of disease progression, a total of 118 events (in 42 [8%] of 543 patients in the D-VTd group vs 76 [14%] of 542 patients in the VTd group) were observed (HR 0·52, 95% CI 0·36–0·76, p=0·0006). Subgroup analysis based on response showed that achievement of stringent complete response was associated with prolonged progression-free survival (figure 3B). Prespecified subgroup analyses of progression-free survival showed that improvements were consistent across baseline characteristics (figure 3C).

14 deaths on study occurred in the D-VTd group and 32 in the VTd group (appendix p 15). Median overall survival from first randomisation regardless of second randomisation was not reached in either treatment group (HR 0·43, 95% CI 0·23–0·80; appendix p 9). These data are immature with longer-term follow-up ongoing.

The most common adverse events of any grade (occurring in ≥20% of patients in either group) were peripheral sensory neuropathy, constipation, asthenia, peripheral oedema, nausea, neutropenia, pyrexia, paraesthesia, and thrombocytopenia (table 3). The most common grade 3 or 4 adverse events (in ≥10% of patients in either group) were neutropenia, lymphopenia, stomatitis, and thrombocytopenia (table 3).

Serious adverse events occurred in 251 patients (47%) in the D-VTd group and 255 patients (47%) in the VTd group. The most common serious adverse events (occurring in ≥3% of patients in either group) were neutropenia (21 patients [4%] in the D-VTd group and eight patients [1%] in the VTd group), pneumonia (19 [4%] and nine [2%]), pyrexia (15 [3%] and 23 [4%]), and pulmonary embolism (eight [1%] and 20 [4%]).

40 (7%) patients in the D-VTd group and 45 (8%) in the VTd group discontinued treatment owing to treatment-emergent adverse events. Treatment-emergent adverse events leading to death were observed in one patient in
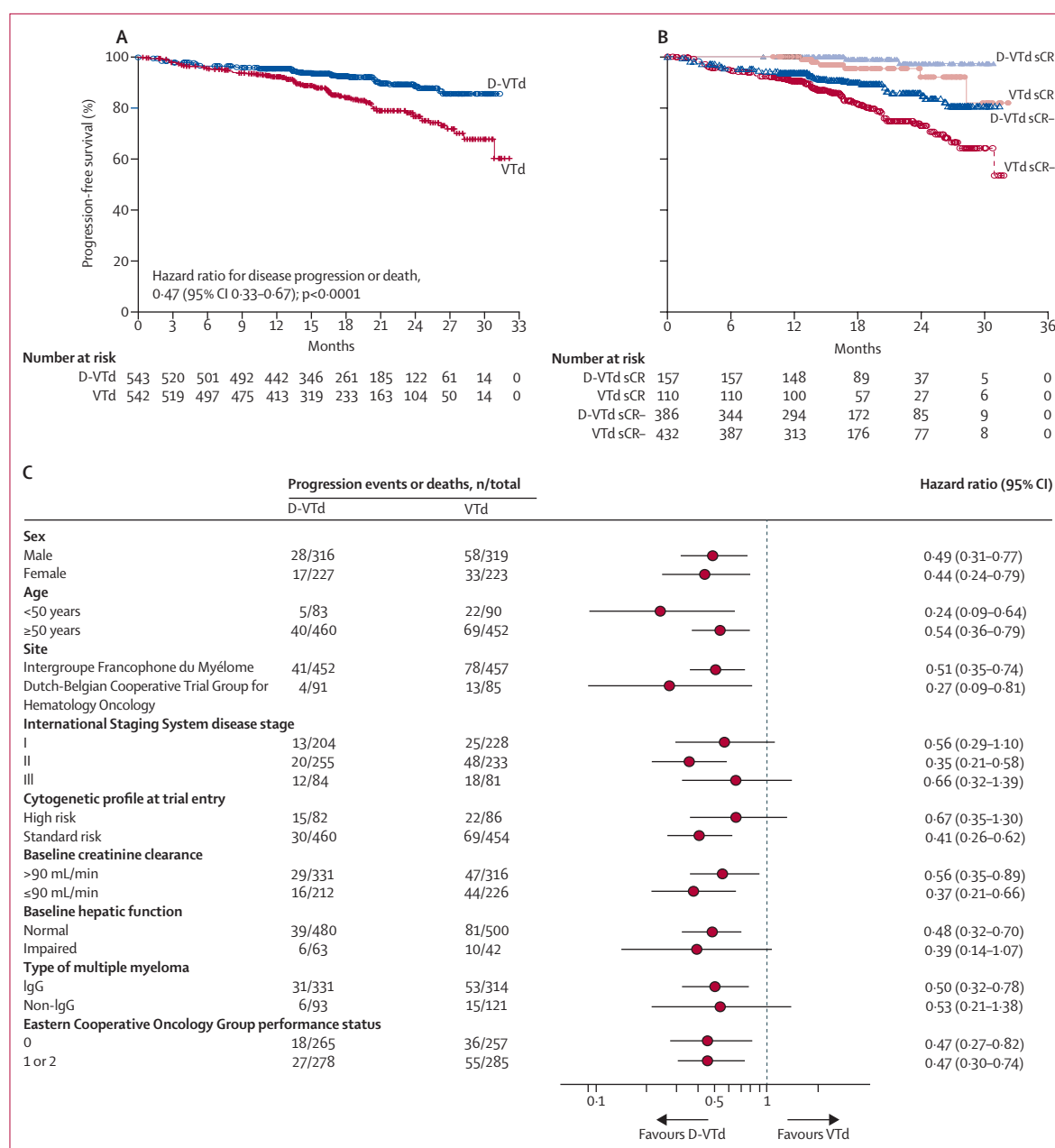
210 [57%] of 371 vs 134 [37%] of 364, p<0·0001 when assessed by next-generation sequencing). Based on flow cytometry, post-hoc analyses showed that the proportion of patients with negative status for minimal residual

Figure 3: Progression-free survival from first randomisation regardless of the second randomisation
(A) The results of the Kaplan-Meier estimates of progression-free survival among patients in the intention-to-treat population. (B) The results of the Kaplan-Meier estimates of progression-free survival among patients who did and did not achieve sCR (post-hoc analysis). (C) The results of an analysis of progression-free survival in prespecified subgroups of the intention-to-treat population that were defined according to baseline characteristics. Median progression-free survival was not reached in all subgroups in either treatment group, except for International Staging System disease stage III (VTd 30·9 months). D-VTd=daratumumab plus bortezomib, thalidomide, and dexamethasone. VTd=bortezomib, thalidomide, and dexamethasone. sCR=stringent complete response.

the D-VTd group and nine patients in the VTd group (appendix p 17).

As an adverse event of interest, infections (any grade) were more common in the D-VTd group (351 [65%] of 536) versus the VTd group (306 [57%] of 538), but the numbers of grade 3 or 4 infections were similar (118 [22%] *vs* 105 [20%]). Treatment-emergent adverse

events of infections led to discontinuation of daratumumab in six patients [1%].

Daratumumab-related infusion reactions occurred in 190 (35%) of 536 patients. These occurred mainly during the first infusion (144 [27%]), with ten (2%) occurring during the second infusion and 62 (12%) during subsequent infusions (of which 50 [11% of 466 patients]

	D-VTd (n=536)		VTd (n=538)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Haematological adverse events				
Neutropenia	157 (29%)	148 (28%)	89 (17%)	79 (15%)
Thrombocytopenia	109 (20%)	59 (11%)	73 (14%)	40 (7%)
Lymphopenia	99 (18%)	91 (17%)	67 (12%)	52 (10%)
Non-haematological adverse events				
Peripheral sensory neuropathy	314 (59%)	47 (9%)	340 (63%)	46 (9%)
Constipation	272 (51%)	7 (1%)	262 (49%)	7 (1%)
Asthenia	171 (32%)	7 (1%)	155 (29%)	6 (1%)
Peripheral oedema	162 (30%)	3 (<1%)	148 (28%)	7 (1%)
Nausea	162 (30%)	21 (4%)	130 (24%)	12 (2%)
Pyrexia	140 (26%)	14 (3%)	114 (21%)	12 (2%)
Paraesthesia	118 (22%)	4 (<1%)	108 (20%)	6 (1%)
Stomatitis	86 (16%)	68 (13%)	104 (19%)	88 (16%)
Second primary malignancy	10 (2%)	NA	12 (2%)	NA
Any infusion-related reaction	190 (35%)	19 (4%)	NA	NA

Data are n (%). D-VTd=daratumumab plus bortezomib, thalidomide, and dexamethasone. VTd=bortezomib, thalidomide, and dexamethasone. NA=not applicable. *Adverse events of any grade that were reported in at least 20% of patients in either treatment group and grade 3 or 4 adverse events that were reported in at least 10% of patients in either treatment group are listed.

Table 3: Most common adverse events during treatment in the safety population*

occurred at the first infusion after transplant). Infusion reactions associated with D-VTd treatment were mainly mild, with grade 3 reactions occurring in 17 (3%) patients and grade 4 reactions occurring in 2 (<1%) patients. Second primary malignancies occurred in 10 patients (2%) in the D-VTd group and 12 patients (2%) in the VTd group (table 3).

Median numbers of CD34+ cells collected were $6 \cdot 3 \times 10^6$ per kg (IQR $5 \cdot 0 \times 10^6$ to $8 \cdot 0 \times 10^6$) in the D-VTd group and $8 \cdot 9 \times 10^6$ per kg ($6 \cdot 6 \times 10^6$ to $12 \cdot 1 \times 10^6$) in the VTd group. Median numbers of cells transplanted were $3 \cdot 3 \times 10^6$ per kg (IQR $2 \cdot 6 \times 10^6$ to $4 \cdot 2 \times 10^6$) in the D-VTd group and $4 \cdot 3 \times 10^6$ per kg ($3 \cdot 2 \times 10^6$ to $5 \cdot 9 \times 10^6$) in the VTd group. 110 (22%) of 506 patients who completed mobilisation in the D-VTd group and 39 (8%) of 492 in the VTd group received plerixafor during stem-cell mobilisation. The proportion of patients proceeding to autologous stem-cell transplantation did not differ between groups nor did the proportion of patients achieving haemopoietic reconstitution (figure 1).

Discussion

This was the first phase 3 trial of daratumumab in patients with transplant-eligible, newly diagnosed multiple myeloma and met its primary endpoint. A significantly larger proportion of patients who achieved a stringent complete response was observed in the D-VTd group than the VTd group. The CASSIOPEIA study is the largest to use the current global standard of the 10^{-5} sensitivity threshold. Significant improvements in the secondary endpoint of minimal residual disease negativity after consolidation were observed in the D-VTd group.

These responses translated into a 53% reduction in the risk of progression or death for the D-VTd group versus the VTd group. As observed in other phase 3 studies of daratumumab-based regimens, proportions of patients achieving deep responses increased over time compared with the VTd group.[11,12]

Newer therapies allow most patients with newly diagnosed multiple myeloma to achieve complete or very good partial responses when combined with autologous stem-cell transplantation. Deep responses, including stringent complete responses, translate into improved overall survival in patients undergoing early autologous stem-cell transplantation, supporting its predictive value as a surrogate endpoint.[23–26] However, as treatment progresses, approaches to detect minimal residual disease-negativity are being optimised, because improved outcomes are consistently observed when patients achieve minimal residual disease-negative status.[24–26] We anticipated this progression by including a prospective comprehensive analysis of minimal residual disease. The assessment of minimal residual disease in all patients provides an opportunity to further understand the kinetics of bone marrow clearance of malignant cells in relation to and regardless of obtaining conventional deep responses according to International Myeloma Working Group criteria.[17]

The proportions of patients who were minimal residual disease-negative were larger than of those who achieved a complete response or better. Complete response confirmation includes the elimination of detectable M-protein, whereas minimal residual disease assessment measured a different parameter of bone marrow tumour cell eradication. Of note, accounting for minimal residual disease-negativity only in patients who achieved complete response or better also showed a significant benefit of adding daratumumab to VTd. Ongoing analyses will explore the relationship between minimal residual disease and the kinetics of M-protein clearance.[27]

A potential limitation of the analysis is that the second randomisation for maintenance might have influenced interpretation of progression-free survival in part 1. The per-protocol statistical analysis by inverse probability weighting method[21] was implemented to mitigate any potential effects of second randomisation on the progression-free survival outcomes of part 1. However, the effect of the second randomisation was minimal at the time of this evaluation because a similar and high percentage of patients in both groups (84% in the D-VTd group and 79% in the VTd group) were randomly assigned to part 2, and with the follow-up time for this analysis the duration of maintenance was short.

The benefit of D-VTd relative to VTd was consistent across prespecified subgroups in analyses of stringent complete response, with the exception of patients with poor prognosis (ie, high-risk cytogenetic profile and International Staging System disease stage III), and CIs for these subgroups were wide. However, benefit was

observed in terms of progression-free survival and proportions of patients who were minimal residual disease-negative. These observations show that benefit from daratumumab is not limited to those who achieve stringent complete response.

Cross-trial comparisons are confounded by differences in trial design, methodology, and inclusion criteria and should be interpreted with caution. Our study strictly implemented response criteria using a computerised algorithm. However, on the basis of very good partial response or better, responses were comparable to similar front-line myeloma trials.[6,28] 18-month progression-free survival further confirms the comparability of outcomes.

Adding daratumumab to bortezomib, thalidomide, and dexamethasone did not increase overall toxicity. The dosing schedule used is typical of real-world practice, and adverse events were clinically manageable and consistent with the known toxicities of bortezomib, thalidomide, and dexamethasone[5,6,14–16] as well as daratumumab.[29] Except for haematological events, no clinically meaningful differences in adverse events were observed between treatment groups. The incidence of infusion-related reaction was consistent with other daratumumab studies.[8,9,29] Although the median stem-cell yield was smaller and more patients received plerixafor in the D-VTd group, successful transplantation was not affected.

In summary, in patients with newly diagnosed multiple myeloma eligible for autologous stem-cell transplantation, daratumumab plus bortezomib, thalidomide, and dexamethasone resulted in significant and clinically meaningful benefit compared with bortezomib, thalidomide, and dexamethasone. The study continues in part 2, and assessment of the effect of randomly assigning patients with a partial response or better from both groups to daratumumab or observation is underway.

Contributors
All authors in their role as either Intergroupe Francophone du Myélome, Dutch-Belgian Cooperative Trial Group for Hematology Oncology, or Janssen Research & Development investigators contributed to study design, study conduct, and data analysis and interpretation. All authors participated in drafting and revising the manuscript and approved the final version before submission.

Declaration of interests
PM receives honoraria from AbbVie, Amgen, Celgene, Janssen, and Takeda, is a member of AbbVie's, Amgen's, Celgene's, Janssen Pharmaceuticals', and Takeda's Board of Directors or advisory committees, and is a member of AbbVie's, Amgen's, Celgene's, and Janssen Pharmaceuticals' Speakers Bureau. CH receives honoraria from Amgen, Celgene, Janssen Pharmaceuticals, and Takeda and receives research funding from Celgene and Janssen Pharmaceuticals. BA receives honoraria from Amgen, Celgene, and Janssen Pharmaceuticals. KB is a consultant for and receives honoraria from Amgen, Celgene, Janssen Pharmaceuticals, and Takeda. AB receives honoraria from Amgen, Bristol-Myers Squibb, Celgene, and Janssen Pharmaceuticals. CD is a consultant for and is a member of Janssen Pharmaceuticals' Board of Directors or advisory committees. TF is a member of Amgen's, Celgene's, Janssen Pharmaceuticals', Karyopharm's, Oncopeptides', Sanofi's, and Takeda's Board of Directors or advisory committees and is a member of Celgene's, Janssen Pharmaceuticals', and Takeda's Speakers Bureau. CS is a consultant for and receives honoraria from Celgene. LK receives honoraria from and is a member of the Board of Directors or advisory

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For **Janssen Clinical Trial Data Transparency** see https://www.janssen.com/clinical-trials/transparency

For **Yale Open Data Access** see http://yoda.yale.edu

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