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Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial

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Running head: CASSIOPEIA Part 2

Trial Registration: NCT02541383

Summary (abstract)

Background CASSIOPEIA Part 1 demonstrated superior depth of response and significantly prolonged progression-free survival (PFS) with daratumumab (DARA), bortezomib, thalidomide, and dexamethasone (D-VTd) vs VTd as induction/consolidation in patients with autologous stem cell transplant (ASCT)-eligible newly diagnosed multiple myeloma (NDMM). In Part 2, we compared DARA maintenance versus observation only (OBS).

Methods CASSIOPEIA (NCT02541383) is a two-part, randomised, open-label phase 3 trial of patients aged 18–65 years with NDMM and Eastern Cooperative Oncology Group performance status 0–2 conducted in 111 European centres. In Part 1, patients were randomised 1:1 to induction/ASCT/ consolidation with D-VTd or VTd. Patients still on study who achieved partial response (PR) or better were randomised 1:1 by an interactive web-response system to DARA 16 mg/kg IV every 8 weeks (reduced frequency compared with standard DARA long-term dosing) or OBS for up to 2 years. Stratification factors were induction treatment and depth of response in Part 1. The Part 2 primary endpoint was PFS from second randomisation. This pre-planned interim analysis of PFS was performed after 281 events and shall be considered the primary analysis of PFS. The interaction between induction/consolidation and maintenance was tested at a two-sided significance level of 0.05 by a stratified Cox regression model that included the interaction term between maintenance treatment and induction/consolidation treatment. The maintenance-specific intent-to-treat population comprised all patients who underwent second randomisation. Safety was analysed in all patients in the DARA group who received at least one dose and all patients randomised to OBS. Long-term follow-up is ongoing.

Findings Between May 30, 2016, and June 18, 2018, 886 patients (458/543 [84.3%] in the D-VTd group and 428/542 [79.0%] in the VTd group) were randomised to DARA (N=442) or OBS (N=444). At a median follow-up of 35.4 (IQR 30.2–39.9) months from second randomisation, median PFS was not reached with DARA vs 46.7 (95% CI 40.0–not evaluable) months with OBS (hazard ratio 0.53, 95% CI 0.42–0.68, $p < 0.0001$). A pre-specified analysis of PFS results showed a significant interaction between maintenance and induction/consolidation therapy ($p < 0.0001$). Grade ≥ 3 adverse events were reported in 122 (27.7%) of 440 patients who received at least 1 dose of DARA and 108 (24.3%) of 444 patients in the OBS group. The most common grade 3/4 adverse events were lymphopenia

(16 [3.6%] of 440 patients in the DARA group vs 8 [1.8%] of 444 patients in the OBS group), hypertension (13 [3.0%] vs 7 [1.6%]), and neutropenia (9 [2.0%] vs 10 [1.6%]). Serious adverse events occurred in 100 (22.7%) and 84 (18.9%) patients in the DARA and OBS groups, respectively; serious adverse events that occurred in more than 1% of patients were pneumonia (11 [2.5%] and 7 [1.6%]) and lung infection (6 [1.4%] and 7 [1.6%]). In the DARA group, two adverse events led to death (septic shock and natural killer-cell lymphoblastic lymphoma); both were related to treatment.

Interpretation DARA maintenance every 8 weeks for 2 years significantly reduced the risk of disease progression or death vs OBS. Longer follow-up and other ongoing studies will shed further light on the optimal DARA-containing post-ASCT maintenance treatment strategy.

Funding Janssen Research & Development, LLC, the Intergroupe Francophone du Myélome, and the Dutch-Belgian Cooperative Trial Group for Hematology Oncology.

Research in context

Evidence before this study No formal literature search was conducted as part of the study-planning process. At the time when the CASSIOPEIA study was designed (2015), no regimens were approved as post–autologous stem-cell transplant (ASCT) maintenance therapy in Europe or the United States, and maintenance therapy was not recommended by the European Society of Medical Oncology clinical practice guidelines. Meta-analyses published in 2012 confirmed the overall and progression-free survival benefits associated with thalidomide, but, long-term maintenance was not recommended due to its significant toxicity. Available evidence in 2015, particularly from the randomised controlled IFM 2005-02, CALGB 100104, and GIMEMA RV-MM-PI-209 trials, showed that lenalidomide maintenance significantly prolonged progression-free survival in patients with newly diagnosed multiple myeloma, but overall survival results were mixed, and rates of second primary malignancies were increased compared with placebo or observation.

Added value of this study To our knowledge, Part 2 of the CASSIOPEIA study is the first randomised controlled trial of daratumumab as maintenance therapy in transplant-eligible patients with newly diagnosed multiple myeloma (NDMM). In this study, daratumumab every 8 weeks (Q8W) significantly prolonged progression-free survival and increased rates of complete response and minimal residual disease negativity compared with observation. Rates of discontinuation due to adverse events were low. The clinical benefit of daratumumab over observation was seen in all pre-specified subgroups except for patients who were treated with daratumumab, bortezomib, thalidomide, and dexamethasone (D-VTd) as induction/consolidation in Part 1 of the study, suggesting that the optimal daratumumab-containing maintenance regimen may vary based on what treatment was used in the frontline setting. Long-term follow-up is ongoing.

Implications of all the available evidence The results of Part 2 of the CASSIOPEIA study add to the body of evidence demonstrating the benefit of maintenance therapy over observation or placebo in patients following ASCT and demonstrate that daratumumab, at a reduced intensity Q8W schedule, can be safely used as maintenance therapy with very low rates of discontinuation due to adverse events. However, the treatment benefit of daratumumab maintenance shows a strong interaction with the prior use of daratumumab in induction/consolidation. A significant PFS benefit could only be demonstrated in daratumumab-naïve patients. This raises questions of the precise strategy for how to

implement daratumumab in the maintenance setting. Updated data from Part 1 support the use of daratumumab as induction/consolidation for patients with transplant-eligible NDMM. Additional studies are ongoing to evaluate daratumumab in combination with other therapies and dosing frequencies as maintenance. Those studies will further inform the potential optimal use of daratumumab in the maintenance setting.

Introduction

Despite recent treatment advances, virtually all patients with multiple myeloma (MM) eventually relapse, becoming progressively more difficult to treat.¹⁻³ Therefore, there is an urgent need for treatments that can provide deep and durable responses, extending time to disease progression or death without significant negative impact on health-related quality of life.

For transplant-eligible patients with newly diagnosed MM (NDMM), the standard of care includes an induction regimen before an autologous stem-cell transplant (ASCT). Consolidation therapy after ASCT is also often used.^{4,5} Regimens for induction and/or consolidation therapy commonly include a proteasome inhibitor, an immunomodulatory agent, and dexamethasone. Such combinations have shown high rates of deep and sustained responses and progression-free survival (PFS) in randomised trials.^{4,6,7} Based on the results of Part 1 of the CASSIOPEIA study (NCT02541383), daratumumab (DARA) in combination with bortezomib, thalidomide, and dexamethasone (D-VTd) was approved in regions and countries worldwide, including by the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA), as a treatment for transplant-eligible patients with NDMM.^{8,9}

In order to prolong the response to frontline therapy, long-term maintenance treatment may be given.^{4,6,7,10,11} Only lenalidomide is approved by the US FDA and EMA as maintenance therapy in patients with NDMM post ASCT, with approval received in 2017.^{12,13} Lenalidomide maintenance improves PFS and overall survival (OS) but is associated with higher rates of discontinuation due to adverse events (AEs) compared with placebo or observation.¹⁴ There remains an unmet need for alternative well-tolerated maintenance therapies that confer a significant clinical benefit.

Here, we present the results of Part 2 of the CASSIOPEIA study, which compared maintenance with daratumumab monotherapy (DARA) versus observation only (OBS).

Methods

Study design and participants

CASSIOPEIA is a randomised, open-label, active-controlled, parallel group, phase 3 study conducted at 111 European sites (appendix table S1, pp14–15). Study details were described in the primary report.¹⁵

In Part 1, patients aged 18–65 with newly diagnosed, documented multiple myeloma per International Myeloma Working Group (IMWG)¹⁶ diagnostic criteria who were eligible for high-dose therapy and ASCT and had an Eastern Cooperative Oncology Group performance status score of 0–2 were eligible. Patients were excluded from Part 1 if they had prior systemic therapy or ASCT for any plasma cell dyscrasia. Additional exclusion criteria were primary amyloidosis, monoclonal gammopathy of undetermined significance, smouldering multiple myeloma, solitary plasmacytoma, Waldenström’s macroglobulinaemia, grade 2 or higher peripheral neuropathy or grade 2 or higher neuropathic pain (as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4),¹⁷ or prior invasive malignancy (other than multiple myeloma) within 10 years of study start. Required pre-treatment laboratory values included absolute neutrophil count of 1×10^9 per L or more, haemoglobin concentration of 7.5 g/dL or more, platelet count of 70×10^9 per litre or more (if <50% of bone marrow nucleated cells were plasma cells; otherwise, platelet count $>50 \times 10^9$ per L), calculated creatinine clearance of 40 mL/min or more, corrected serum calcium level of 14 mg/dL or less (<3.5 mmol/L), and adequate liver function. Full inclusion/exclusion criteria are included in the appendix (p2). Patients on study post consolidation (day 100 post ASCT) who achieved partial response (PR) or better per IMWG response criteria¹⁸ underwent a second randomisation.

Each study site’s local independent ethics committee or institutional review board approved the study protocol. This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

Randomisation and masking

Patients were randomised 1:1 to D-VTd or VTd in Part 1 of the study and to maintenance therapy with DARA or OBS in Part 2 (appendix figure S1, p5). For both randomisations, the investigator or designated research staff used an interactive web-based system, balanced using permuted blocks of four, to generate treatment assignments. Part 1 stratification factors are shown in the appendix (p2). Part 2 stratification factors were type of induction treatment (D-VTd vs VTd) and depth of response to induction/consolidation therapy (as determined by minimal residual disease [MRD] status and post-consolidation response).

Sponsor personnel or designees involved in the analysis were masked to treatment group assignment until the recommendation by an independent data monitoring committee to consider

the pre-planned interim analysis of PFS in Part 2 as the main analysis. Otherwise, treatment assignments were not masked.

Procedures

In Part 1, patients received four cycles of induction therapy and two cycles of consolidation therapy with either D-VTd or VTd (1 cycle: 28 days). Following second randomisation, we assigned patients to receive either DARA 16 mg/kg intravenously once every 8 weeks (Q8W) or to OBS, limited for a maximum of 2 years. The dosing frequency of Q8W was selected based on the pharmacokinetic and target suppression data available at the time when the CASSIOPEIA trial was designed and initiated. Individual dose reductions of DARA were not permitted. Dose delay was recommended as the primary method for managing treatment-related toxicities. Subsequently, all patients from both groups were followed for disease progression per IMWG criteria¹⁸ (appendix table S2, p16) or death. Pre- and post-infusion medications and reasons for removal from the study are listed in the appendix (p2).

A central laboratory performed disease assessments Q8W after second randomisation. If DARA interference with serum M-protein was suspected, immunofixation reflex assays confirmed CRs. MRD negativity was primarily assessed using NGS assay. MRD was additionally assessed by standardised multiparametric flow cytometry (MFC) based on the recommendations of the EuroFlow Consortium¹⁹ if a sufficient sample was available. Both methods were applied on bone marrow aspirates of patients who achieved VGPR or better in Part 2. The primary count for MRD-negative patients includes those who achieved a response of CR or better before or at the time point of achieving MRD negativity. Additional detail regarding MRD assessment can be found in the appendix (p3). Patients underwent a skeletal survey at screening. During the treatment phase and before disease progression was confirmed, imaging was performed whenever clinically indicated based on symptoms to document response or progression.

Safety assessments included AE monitoring, physical examinations, vital sign measurements, ECOG performance status, electrocardiography, and clinical safety laboratory testing. AEs were collected continuously from the time of signed informed consent until 30 days following the last dose (DARA group) or for 2 years after the second randomisation, or upon disease progression, withdrawal of consent, or start of new anticancer therapy (whichever occurred first) (OBS group). An independent data monitoring committee reviewed the safety data.

Outcomes

The primary endpoint of Part 2 was PFS after second randomisation, which was defined as the duration from the date of second randomisation to progressive disease (PD) according to a validated computer algorithm (as described previously²⁰⁻²²) based on the IMWG response criteria.^{18,23}

Major secondary efficacy endpoints in Part 2 were time to progression (TTP) from second randomisation, proportion of patients who achieved complete response (CR) or better per IMWG criteria,¹⁸ proportion of patients who achieved MRD negativity at a threshold of 10^{-5} per next-generation sequencing (NGS), PFS after next line of therapy (PFS2), overall response rate (ORR), and OS from second randomisation.

Other secondary endpoints in Part 2 included rate of improved response during maintenance compared with response status at the end of consolidation (among patients who had not achieved stringent CR as defined by IMWG criteria¹⁸ by second randomisation) and rate of conversion to MRD negativity (proportion of patients who were MRD positive by NGS post consolidation who subsequently achieved de novo MRD-negative status during the maintenance phase).

Secondary endpoints are defined in the appendix (p2–3). Pre-planned subgroups for analysis of PFS were based on sex (male, female), age (<50, 50–60, >60 years), study site (IFM, HOVON), ISS staging (I, II, III), cytogenetics (presence [high risk] or absence [standard risk] of del17p or t[4;14] cytogenetic abnormalities), pre-maintenance baseline renal function, type of MM (immunoglobulin G [IgG], non-IgG), pre-maintenance baseline ECOG performance status (0, ≥1), induction/consolidation treatment (D-VTd, VTd), MRD status (MRD positive, MRD negative), and response (very good partial response [VGPR] or better, PR). Infusion-related reactions (IRRs), second primary malignancies (SPMs), and infections are reported as they were pre-identified in the Statistical Analysis Plan as AEs of clinical interest.

Statistical analysis

The Part 2 hypothesis was that DARA prolongs PFS after ASCT compared with OBS. To achieve 80% power with a significance level of 0.05, 390 PFS events were needed. Assuming a 36-month accrual and 45 months of additional follow-up, approximately 800 patients (400 per arm) were randomised in the second randomisation (DARA vs OBS).

We performed primary and secondary efficacy analyses on the maintenance-specific intent-to-treat population, which comprised all patients included in the second randomisation. The maintenance-specific safety population included all patients randomised to DARA maintenance therapy who received at least one dose of DARA and all patients randomised to OBS. Patients with no post baseline disease assessments on or before subsequent therapies or before death were categorized as “not evaluable.” All protocol deviations of eligibility criteria and those deviations that could impact patient safety or study endpoints were considered major protocol deviations.

We evaluated the proportional hazard assumption for the PFS analysis by a log-log plot. The 2 parallel curves indicated that the proportional hazard assumption held well for PFS. A pre-planned interim analysis of Part 2 assessed efficacy and safety after 281 PFS events (72% of the planned total number of events) with the O’Brien-Fleming efficacy boundary for the primary endpoint (PFS). The efficacy boundary of two-sided $p < 0.0166$ was determined by the pre-specified Lan-DeMet alpha spending function.

We estimated the distribution of PFS from second randomisation per treatment group using the Kaplan-Meier method. The p value from the stratified log-rank test was calculated to compare the two treatment groups. The treatment effect (hazard ratio [HR]) and its two-sided 95% confidence interval (CI) were estimated using a stratified Cox regression model with maintenance treatment as the sole explanatory variable. The stratification factors included type of induction treatment and depth of response. A forest plot was planned for PFS to check the consistency of treatment benefit in a number of pre-specified subgroups.

We conducted a pre-specified interaction test between induction/consolidation and maintenance at a two-sided significance level of 0.05 using a stratified Cox regression model that included the interaction term between maintenance treatment and induction/consolidation treatment. Depth of response was the only stratification factor.

Since the primary endpoint was statistically significant, secondary efficacy endpoints (TTP from second randomisation, overall rate of CR or better, proportion of patients who were MRD negative, and OS from second randomisation) were tested sequentially using a pre-specified hierarchical testing approach. Each endpoint was tested with an overall two-sided alpha of 0.05, except for OS, which had immature data and was expected to be tested at the final analysis. Because of the significant interaction between induction/consolidation and maintenance, we conducted post hoc analyses to compare efficacy endpoints between different treatment policies

of induction/consolidation and maintenance; the results of these exploratory analyses are provided for descriptive purposes only. We performed updated analyses of PFS and OS from Part 1 at the request of the EMA at the time of the regulatory approval of D-VTd in Europe.

We assessed responses and other binary endpoints using the stratified Cochran-Mantel-Haenszel chi-square test (stratified by type of induction treatment and depth of response), and calculated odds ratios (ORs) and two-sided 95% CIs using SAS 9.4. This trial is registered with ClinicalTrials.gov as 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. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 30, 2016, and June 18, 2018, 886 patients who achieved PR or better in Part 1 were randomised to DARA (N=442) or OBS (N=444; figure 1). Of the 886 patients, 764 (86.2%) and 122 (13.8%) came from IFM versus HOVON sites, respectively.

More patients from the D-VTd group (458 of 543, 84.3%) than from the VTd group (428 of 542, 78.9%) underwent second randomisation. A total of 199 patients (18.3% of those randomised in Part 1 [N=1085]) were not randomised to maintenance in Part 2. In both groups, the most common reason for patients not to be randomised to Part 2 was AEs, followed by disease progression during induction/ASCT/consolidation, and response of stable disease or worse post consolidation (appendix table S3, p17). Rates of PD during induction/ASCT/consolidation were similar (22 [4.1%] of 543 patients in the D-VTd group and 23 [4.1%] of 542 patients in the VTd group); more patients in the VTd group than the D-VTd group withdrew consent or decided to discontinue the study (8 [1.5%] of 542 vs 2 [0.4%] of 543 patients) (appendix table S3, p17). Major protocol deviations were reported for 24 (5.4%) of 442 patients in the DARA group and 7 (1.6%) of 444 patients in the OBS group. The majority of these were safety assessment deviations in the DARA group, including but not limited to events concerning DARA infusion volume or speed and safety laboratory assessments (data not shown).

Demographics and disease characteristics after second randomisation were well balanced (table 1). Rates of pre-maintenance CR or better and MRD negativity and CR or better are

shown in appendix table S4, (p18). During Part 2, 100 (26.6%) of 440 patients in the DARA group and 128 (28.8%) of 444 patients in the OBS group discontinued, most often due to disease progression (figure 1).

All 442 (100%) patients in the DARA group received at least 1 administration of DARA and 441 (99.3%) of 444 patients in the OBS group completed at least 1 OBS visit. The median number of DARA administrations received during the maintenance phase was 14.0 (IQR 13.5–14.0). The median duration on study from second randomisation was 24 months (IQR 23.7–24.2) for DARA and 24 months (IQR 22.1–24.9) for OBS.

After a median follow-up of 35.4 months (IQR: 30.2–39.9) from second randomisation, median PFS was not reached with DARA versus 46.7 months (95% CI 40.0–not evaluable [NE]) with OBS (HR 0.53, 95% CI 0.42–0.68, $p < 0.0001$; figure 2). There were 108 PFS events in the DARA group vs 173 events in the OBS group. The PFS benefit of DARA vs OBS was observed in all pre-specified subgroups, except for the subgroup who received D-VTd induction/consolidation treatment (figure 3). DARA reduced the risk of disease progression or death in patients with high-risk cytogenetics (HR 0.43, 95% CI 0.25–0.73) and in patients with standard cytogenetic risk (HR 0.62, 95% CI 0.48–0.82).

Rates of CR or better, improved response, MRD negativity (assessed by NGS at 10^{-5}) and CR or better, and conversion to MRD negativity were higher in the DARA group than in the OBS group (CR or better: 322 [72.9%] of 442 vs 270 [60.8%] of 444, OR 2.17, 95% CI 1.54–3.07, $p < 0.0001$; improved response: 188 [61.8%] vs 153 [47.2%], OR 1.95, 95% CI 1.40–2.72, nominal $p < 0.0001$; MRD negativity and CR or better: 259 [58.6%] vs 209 [47.1%], OR 1.80, 95% CI 1.33–2.43, $p = 0.00010$; MRD conversion: 128 [43.5%] vs 91 [29.8%], OR 1.84, 95% CI 1.31–2.58, nominal $p = 0.00040$; appendix figure S2, p6–7). MRD negativity and CR or better was also assessed at a threshold of 10^{-6} using NGS and 10^{-5} using MFC (appendix table S5, p19). ORR was similar in both groups (440 [99.5%] of 442 patients in the DARA group and 441 [99.3%] of 444 patients in the OBS group (appendix table S6, p21).

Median TTP was not reached in the DARA group vs 46.7 months (95% CI 40.0–NE) in the OBS group (HR 0.49, 95% CI 0.38–0.62, $p < 0.0001$). Overall, 209 (23.6%) of 886 patients received one or more subsequent anti-myeloma treatments (79 [17.9%] of 442 patients in the DARA group and 130 [29.3%] of 444 patients in the OBS group).

PFS2 was immature but numerically favoured DARA (HR 0.62, 95% CI 0.40–0.96). Additional information regarding PFS2 and subsequent anti-myeloma treatments is shown in the appendix (p4). Median OS was not reached in either group. A total of 29 and 27 deaths occurred in the DARA and OBS groups, respectively (appendix table S7, p22). The most common cause of death was progressive disease (13 [44.8%] in the DARA group and 22 [81.5%] in the OBS group). All other causes occurred in only 1 patient each (appendix table S76, p22). Long-term follow-up is ongoing.

Demographics and disease characteristics by induction/consolidation regimen are included in appendix table S8 (p22).

A pre-specified analysis for interaction of PFS results showed significant interaction between maintenance and induction/consolidation therapy ($p < 0.0001$).

A median PFS of 33.6 months (95% CI 27.2–37.4) was reached in the VTd/OBS group. Median PFS was not reached in the D-VTd/DARA, D-VTd/OBS or VTd/DARA groups. A strong and substantial PFS benefit was observed in the VTd/DARA group compared with the VTd/OBS group (HR 0.32, 95% CI 0.23–0.46, nominal $p < 0.0001$). PFS was not significantly different for D-VTd/DARA vs D-VTd/OBS (HR 1.02, 95% CI 0.71–1.47, nominal $p = 0.91$; appendix figure S3, p8). The number of PFS events was similar in the D-VTd/DARA and D-VTd/OBS groups (59 vs 56) and lower with VTd/DARA compared with VTd/OBS (49 vs 117).

Among patients who received VTd as induction/consolidation, rates of CR or better, improved response, MRD negativity and CR or better, and conversion to MRD negativity were higher in the DARA group than in the OBS group (CR or better: 147 [69.0%] of 213 vs 106 [49.3%] of 215, OR 3.14, 95% CI 1.93–5.10, nominal $p < 0.0001$; improved response: 104 [65.4%] of 213 vs 57 [35.2%] of 215, OR 3.77, 95% CI 2.32–6.13, nominal $p < 0.0001$; MRD negativity and CR or better: 112 (52.6%) of 213 vs 77 (35.8%) of 215, OR 2.26, 95% CI 1.47–3.48, nominal $p = 0.00020$; MRD conversion: 69 (42.9%) of 161 vs 31 (19.4%) of 160, OR 3.12, 95% CI 1.89–5.15, nominal $p < 0.0001$; appendix figure S4, p9–10). ORR was similar in the DARA (212 [99.5%] of 213 patients) and OBS groups (212 [98.6%] of 215 patients) (appendix table S6, p21).

Among patients who received D-VTd as induction/consolidation, the rates of CR or better, MRD negativity and CR or better, and conversion to MRD negativity were numerically better for DARA vs OBS, although the differences were not statistically significant (CR or better: 175 [76.4%] of

229 vs 164 [71.6%] of 229, OR 1.43, 95% CI 0.87–2.37, nominal $p=0.16$; MRD negativity and CR or better: 147 (64.2%) of 229 vs 132 (57.6%) of 229, OR 1.43, 95% CI 0.93–2.19, nominal $p=0.10$; MRD conversion: 59 (44.4%) of 133 vs 60 (41.4%) of 145, OR 1.13, 95% CI 0.70–1.82, nominal $p=0.62$). The rates of improved response were similar (84 [57.9%] of 229 vs 96 [59.3%] of 229, OR 0.61–1.60, nominal $p=0.95$; appendix figure S4, p9–10) for DARA versus OBS.

Median time to improved response and median time to conversion to MRD negativity were similar irrespective of maintenance and induction/consolidation regimens (~6.0 months for all; data not shown). A total of 342 patients who underwent second randomisation were MRD negative at 10^{-5} by NGS post consolidation. Of these, 25 (7.3%) subsequently lost their MRD negativity during the course of Part 2. In the D-VTd/DARA, D-VTd/OBS, and VTd/DARA groups, ~6% of patients lost MRD negativity, compared with 9 (12.7%) of 71 patients in the VTd/OBS group (data not shown). ORR was similar in the DARA (228 [99.6%] of 229 patients) and OBS groups (229 [100%] of 229 patients) (appendix table S6, p21).

Rate of MRD negativity and CR or better was also assessed at a threshold of 10^{-6} using NGS and 10^{-5} using MFC (appendix table S9, p24).

Updated analyses comparing D-VTd vs VTd with a median of 44.5 months (IQR 38.9–49.1) of follow-up from first randomisation confirmed the findings of the primary analysis of Part 1. D-VTd continued to significantly improve PFS compared with VTd (median PFS not reached vs 51.5 months [95% CI 46.3–NE], HR 0.58, 95% CI 0.47–0.71, $p<0.0001$) after adjustment for the second randomisation using the unbiased inverse probability weighting method (appendix figure S5A, p11). There was a trend toward improved OS, but data remained immature (appendix figure S5B, p12). In the D-VTd and VTd groups, 41 (7.6%) of 543 patients and 73 (13.5%) of 542 patients, respectively, died over the entire course of the study.

Among patients not randomised to Part 2, median PFS was 30.7 months (95% CI 14.3–NE) for those treated with D-VTd ($n=85$) and 25.4 months (95% CI 20.4–33.2) for VTd ($n=114$) induction/consolidation (appendix figure S6A, p13). Among patients not randomised to Part 2, 36 (42.4%) of 85 in the D-VTd group and 57 (50.0%) of 114 in the VTd group had a PFS event.

Treatment-emergent AEs (TEAEs) occurred in 420 (95.5%) of 440 patients in the DARA group and 394 (88.7%) of 444 patients in the OBS group. Serious AEs occurred in 100 (22.7%) of 440 patients in the DARA group and 84 (18.9%) of 444 patients in the OBS group; 32 (32%) of 100 serious AEs in the DARA group were reported to be drug-related. Serious AEs that occurred in

more than 1% of patients in the DARA or OBS groups were pneumonia (11 [2.5%] and 7 [1.6%], respectively) and lung infection (6 [1.4%] and 7 [1.6%], respectively) (appendix table S10, p25). DARA infusions were interrupted in 93 (21.1%) of 440 patients due to AEs and were skipped in ten (2.3%) patients due to AEs; except for one patient, all infusion interruptions were due to IRRs (data not shown). Discontinuation of DARA due to an AE was low (13 [3.0%] of 440 patients in the DARA group; appendix table S10, p25). Two AEs led to death in the DARA group (septic shock and lymphoblastic lymphoma [n=1 each]); there were no AEs that led to death in the OBS group.

The most common AEs during Part 2 are shown in table 2. The most common grade 3-4 AEs were lymphopenia (16 [3.6%] of 440 patients in the DARA group vs 8 [3.6%] of 444 patients in the OBS group), hypertension (13 [3.0%] vs 7 [1.6%]), and neutropenia (9 [2.0%] vs 10 [2.3%]).

IRRs following the first infusion occurred in 115 (54.5%) of 211 patients in the VTd/DARA group (ie, those with no prior DARA exposure) (appendix table S10, p25). The majority of these IRRs (103 [89.6%] of 115) were grade 1 or 2. Two patients, both in the VTd/DARA group, discontinued at the week 1 visit due to an IRR. Of the 229 patients in the D-VTd/DARA group, only five (2.2%) experienced an IRR. One of these occurred at first infusion and four occurred at subsequent infusions. All were grade 1 or 2.

SPMs in Part 2 were observed in 24 (5.5%) of 440 patients in the DARA group and 12 (2.7%) of 444 patients in the OBS group (appendix table S10, p25). Solid-tumour SPMs were more common than haematologic SPMs in the DARA (19 vs 5) and the OBS groups (11 vs 1).

Additional detail regarding number of DARA doses prior to SPM onset, confounding medical history, and pre-existing conditions is shown in appendix table S11 (p26–28). The median time from second randomisation to first onset of SPM was 36.0 months in the DARA group and 44.0 months in the OBS group. SPMs by induction/consolidation and maintenance are shown in appendix table S12 (p29–30).

Infections in Part 2 were reported in 341 (77.5%) of 440 patients in the DARA group and 284 (64.0%) of 444 patients in the OBS group (appendix table S10, p253). The majority (303 of 341 [88.9%] in the DARA group and 254 of 284 [89.4%] in the OBS group) were grade 1 or 2. The incidence of pneumonia and lung infections was low.

Discussion

To our knowledge, CASSIOPEIA Part 2 is the first study to demonstrate the clinical benefit of DARA maintenance therapy compared with observation in patients with NDMM who received ASCT. Treatment with reduced intensity (Q8W) DARA maintenance for a maximum of 2 years resulted in a 47% reduction of risk of disease progression or death compared with OBS. This benefit was observed in nearly all pre-specified subgroups, including patients with high-risk cytogenetics, although only patients with del17p and t(4;14) and not those with other high-risk features such as t(14;16) were included in this subgroup. DARA maintenance therapy significantly improved depth of response compared with OBS, with the highest rates of deep response (ie, MRD negativity and response of CR or better) in patients who received D-VTd as induction/consolidation. DARA maintenance therapy was well tolerated, with low rates of discontinuation. SPMs were reported in 24 (5.5%) of 440 patients in the DARA group and 12 (2.7%) of 444 patients in the OBS group; however, when those with implausible time to onset (after receiving 1 or 3 doses of DARA) or confounding medical history (history of basal cell carcinoma, hepatitis B, hepatitis C, Basedow's [Graves'] disease, oesophageal cancer) or pre-existing conditions (thyroid mass, active smoker) were excluded, the incidence of SPMs became more balanced between the two groups.

Among patients who received VTd as induction/consolidation therapy, DARA maintenance resulted in significantly deeper responses and substantially improved PFS compared with OBS. A visual inspection of the survival curves shows that while patients who received VTd/DARA initially follow a trajectory suggesting poorer outcomes than patients in the D-VTd/DARA and D-VTd/OBS groups, there appears to be an inflection point at ~30 months from second randomisation (appendix figure S3, p8), after which the curve becomes more similar to the D-VTd/DARA and D-VTd/OBS groups. We hypothesize that this initial downward trajectory may reflect early progression in some patients in this group, possibly due to the suboptimal induction/consolidation regimen of VTd, and the subsequent flattening of the curve illustrates the benefit of DARA in those patients who did not progress. Should this be the case, it would be supportive of D-VTd induction/consolidation in order to achieve optimal disease control. Given that no loading (initial weekly dosing) of DARA was given in Part 2, it is also possible that these visual differences may be due in part to a slower onset of action related to the Q8W dosing frequency. Among those who received D-VTd as induction/consolidation, PFS was similar in the DARA and OBS groups. Although this finding does not indicate an advantage for DARA maintenance following D-VTd induction/consolidation, data maturation is required to assess the

effect of DARA maintenance on PFS2 and OS. Updated Part 1 results with longer median follow-up showed a significant PFS benefit for D-VTd vs VTd, further confirming the benefit of adding DARA to VTd as induction/consolidation. A numerically greater proportion of patients in the D-VTd group than the VTd group was able to be randomised to Part 2 (458 of 543 [84.3%] vs 428 of 542 [79.0%]). Patients who were not randomised to Part 2 (85 in the D-VTd group and 114 in the VTd group) had a far poorer prognosis than those who were randomised to Part 2.

Although cross-trial comparisons have inherent limitations due to differences in trial design, patient population, and methodology, it is important to place the results of the current study in the context of previous research. McCarthy et al conducted a meta-analysis of three randomised controlled trials that compared lenalidomide maintenance with placebo or observation after ASCT.¹⁴ A total of 1208 patients in three trials (IFM 2005-02 [NCT00430365]²⁴, CALGB 100104 [NCT00114101]²⁵, and GIMEMA RV-MM-PI-209 [NCT00551928]²⁶) were analysed. The mean treatment duration was 28 months with lenalidomide versus 22 months within the pooled placebo or observation group. The median PFS for patients who received lenalidomide was twice that of those who received placebo or observation (52.8 vs 23.5 months, HR 0.48, 95% CI 0.41–0.55), and there was a significant reduction in the risk of death for patients who received lenalidomide compared to placebo or observation. Safety data were available from two of the three trials and showed higher rates of SPMs, infections, and TEAEs leading to discontinuation with lenalidomide than with placebo or observation. Of note, lenalidomide is the only drug currently approved by the US FDA and EMA as maintenance therapy in patients with NDMM post ASCT.

The phase 3 TOURMALINE-MM3 study (NCT02181413) compared oral ixazomib maintenance therapy vs placebo in 656 patients with NDMM who had achieved PR or better following standard-of-care induction, high-dose melphalan, and ASCT.²⁷ At a median follow-up of 31 months, median PFS was significantly longer with ixazomib than with placebo (PFS HR 0.72, 95% CI 0.58–0.89, $p=0.002$). The OS analysis was inconclusive due to an insufficient number of events. However, rates of AEs resulting in discontinuation or dose reduction of the study drug were higher with ixazomib than placebo.

The median PFS observed in the VTd/OBS group from start of maintenance was 33.6 months (95% CI 27.2–37.4), which is longer than that of the pooled observation/placebo group of the meta-analysis by McCarthy et al (23.5 months)¹⁴ as well as that of the placebo group in TOURMALINE-MM3 (21.3 months).²⁷ This difference, as well as the fact that median PFS in the

D-VTd/OBS group was not reached, reflects the general improvement in the treatment of MM and greater clinical benefits of newer induction regimens. Median PFS was also not reached in either the D-VTd/DARA or VTd/DARA groups,¹⁴ compared with 26.5 months in the ixazomib group of TOURMALINE-MM3.²⁷ With 35.4 months of follow-up, PFS with DARA in CASSIOPEIA Part 2 appears to be in line with the lenalidomide group of the meta-analysis (median PFS 52.8 months at median 79.5 months of follow-up).¹⁴

Several important limitations should be considered when interpreting this study. First, observation rather than lenalidomide was used as the comparator group. Although lenalidomide is currently approved as maintenance therapy in patients who received ASCT, it did not receive approval until 2017.^{12,13} At the time of the start of the CASSIOPEIA study (first patient randomised in September 2015), no maintenance therapy was approved or established as standard of care. This is the reason why observation was chosen as the comparator arm in CASSIOPEIA.

Another potential limitation is the finite duration of the maintenance period. At the time when CASSIOPEIA was designed, the paradigm of treat to progression was not yet widespread. The design of CASSIOPEIA was influenced by the European arm of the IFM/DCF12009 study (NCT01191060), in which patients received lenalidomide maintenance for a fixed duration of 1 year. Given the anticipated long PFS in patients who received ASCT, the 2-year fixed duration maintenance of CASSIOPEIA was considered a reasonable choice.

Finally, the use of Q8W dosing is another potential limitation. At the time of study design, pharmacokinetic data supported this treatment schedule. Subsequently, data from the phase 2 CENTAURUS study (NCT02316106) suggested that Q8W dosing could be insufficient to maintain target suppression,²⁸ and as a result, Q4W dosing has become the preferred DARA regimen in ongoing maintenance studies. It is unknown how patients in CASSIOPEIA Part 2 could have benefitted from more frequent dosing during the maintenance phase. The Q4W dosing frequency of DARA is currently being investigated in the phase 2 GRIFFIN study (NCT02874742) and the phase 3 PERSEUS (NCT03710603), AURIGA (NCT03901963), and DRAMMATIC (NCT04071457) studies, although other differences in maintenance regimens will preclude formal statistical comparisons with CASSIOPEIA.

These limitations preclude a paradigm shift for maintenance therapy in the treatment of multiple myeloma based on these study data. Nevertheless, our findings provide valuable information for

clinicians, particularly until results from other, more recent randomised studies of post-ASCT maintenance become available.

In summary, the results of CASSIOPEIA Part 2 show that DARA maintenance significantly improved outcomes compared with observation and was well tolerated in patients with NDMM who received VTd as induction/consolidation therapy and ASCT. Longer follow-up is required to assess potential benefit in terms of PFS2 and OS in patients who received induction/consolidation with D-VTd. The updated results of Part 1 with longer follow-up show a sustained PFS benefit in the D-VTd group compared with the VTd group and support the early use of DARA in transplant-eligible patients with NDMM. These results are further supported by the numerically higher rates of dropout among patients in the VTd group compared with the D-VTd group. Ongoing studies including GRIFFIN, PERSEUS, and AURIGA will provide valuable data to determine optimal treatment strategies using DARA plus lenalidomide as maintenance therapy in patients with NDMM.

Contributors

All authors in their role as either Intergroupe Francophone du Myélome, Dutch-Belgian Cooperative Trial Group for Hematology Oncology, or Janssen Research and Development investigators participated in the conception and design of the work being described in the publication, acquisition or collection of data, and analysis or interpretation of data. All authors participated in drafting and revising the manuscript and approved the final version before submission. PM and KZ have accessed and verified the data.

Declaration of interests

PM reports personal fees from Celgene, Amgen, Takeda, Janssen, and AbbVie, outside the submitted work. CH reports personal fees from Janssen, AbbVie, Amgen, and Celgene, outside the submitted work. AP reports personal fees from Celgene, Amgen, Janssen, Sanofi, and Takeda, outside the submitted work. BA reports grants from Amgen, Celgene, Sanofi, and Janssen, during the conduct of the study; personal fees from Amgen, Celgene/Bristol Myers Squibb, Sanofi, GlaxoSmithKline, Takeda, and Janssen, outside the submitted work; and advisory board participation from Amgen, Celgene/Bristol Myers Squibb, Sanofi, GlaxoSmithKline, and Janssen, outside the submitted work. KB reports grants from Celgene outside the submitted work; personal fees from Celgene, Janssen, Takeda, and Amgen, outside the submitted work; and non-financial support from Celgene, AbbVie, and Takeda, outside the submitted work. SZ reports grants from Celgene, Janssen, and Takeda, during the conduct of the study. MD reports grants from Celgene and Janssen during the conduct of the study; participation on an advisory board for Celgene, Takeda, Janssen, Sanofi, and Oncopeptides, outside the submitted work. TD reports grants from Celgene and Janssen, during the conduct of the study; and personal fees and advisory board participation from Celgene, Takeda, Janssen, and Amgen, outside of the submitted work. CD reports personal fees from Janssen, outside the submitted work. TF reports personal fees from Janssen, Bristol Myers Squibb, Takeda, Amgen, Roche, Karyopharm, Sanofi, and Oncopeptides, outside the submitted work. CS reports personal fees from Celgene, outside the submitted work. MM grants from Stemline, BMS, Amgen, Jazz Pharmaceuticals, Novartis, Takeda, Janssen, GSK, Sanofi, and Celgene; non-financial support from Stemline, BMS, Amgen, Jazz Pharmaceuticals, Novartis, Takeda, Janssen, GSK, Sanofi, and Celgene; and personal fees from Stemline, BMS, Amgen, Jazz Pharmaceuticals, Novartis, Takeda, Janssen, GSK, Sanofi, and Celgene, outside the submitted work. LK reports personal fees from Amgen, Janssen, Celgene, Takeda, and AbbVie, outside

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Data sharing

The Intergroupe Francophone du Myélome and the Dutch-Belgian Cooperative Trial Group for Hematology Oncology, in partnership with Janssen, will make the data available according to the data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson, available at <https://www.janssen.com/clinical-trials/transparency>. As noted on that site, requests for access to the study data can be submitted through Yale Open Data Access Project site at <http://yoda.yale.edu>.

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Figure Legends

Figure 1: CONSORT flow diagram

DARA=daratumumab. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. OBS=observation. VTd=bortezomib, thalidomide, and dexamethasone.

Figure 2: Results of Kaplan-Meier estimates of progression-free survival among patients in the maintenance-specific intent-to-treat population

CI=confidence interval. DARA=daratumumab. HR=hazard ratio. OBS=observation. PFS=progression-free survival.

Figure 3: Results of an analysis of progression-free survival in pre-specified subgroups of the maintenance-specific intent-to-treat population

*Result is from the unstratified Cox regression model. ASCT=autologous stem-cell transplant. CI=confidence interval. CrCl=creatinine clearance. DARA=daratumumab. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. ECOG=Eastern Cooperative Oncology Group. EVT=event. IFM=Intergroupe Francophone du Myélome. HOVON= Dutch-Belgian Cooperative Trial Group for Hematology Oncology. HR=hazard ratio. IgG=immunoglobulin G. ISS=International Staging System. MM=multiple myeloma. MRD=minimal residual disease. NE=not estimable. OBS=observation. PR=partial response. VGPR=very good partial response. VTd=bortezomib, thalidomide, and dexamethasone.

Table 1: Pre-maintenance baseline* demographics and disease characteristics in the maintenance-specific intent-to-treat population

	DARA n=442	OBS n=444	Total N=886
Median (range) age, years	59.0 (27–66)	59.0 (36–66)	59.0 (27–66)
Male sex, n (%)	261 (59.0)	254 (57.2)	515 (58.1)
Baseline ECOG performance status, n (%)			
0	252 (57.0)	260 (58.6)	512 (57.8)
1	174 (39.4)	172 (38.7)	346 (39.1)
≥2	16 (3.6)	12 (2.7)	28 (3.1)
ISS staging, [†] n (%)			
I	189 (42.8)	171 (38.5)	360 (40.6)
II	181 (41.0)	214 (48.2)	395 (44.6)
III	72 (16.3)	59 (13.3)	131 (14.8)
Cytogenetic profile, [†] n/N (%)			
Standard risk	383/440 (87.0)	374/444 (84.2)	757/884 (85.6)
High risk	57/440 (13.0)	70/444 (15.8)	127/884 (14.4)
Type of induction/consolidation, n (%)			
D-VTd	229 (51.8)	229 (51.6)	458 (51.7)
VTd	213 (48.2)	215 (48.4)	428 (48.3)

Stratification factors, † n (%)			
MRD negative and ≥VGPR	337 (76.2)	337 (75.9)	674 (76.1)
MRD positive and ≥VGPR	68 (15.4)	69 (15.5)	137 (15.5)
MRD positive and PR [§]	37 (8.4)	38 (8.6)	75 (8.5)

*pre-maintenance baseline is the last non-missing observation on or before the date of second randomisation or Week 1 visit, whichever is later, †pre-induction, ‡as determined by MRD measured by multiparametric flow cytometry at 10^{-4} and post-consolidation response per investigator assessment used for stratification. [§]Six patients (3 who received prior D-VTd and 3 who received prior VTd) were MRD negative with a response of PR at post consolidation and were categorised as MRD positive and PR due to the lack of specific stratum defined in the protocol for such patients. DARA=daratumumab. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. ECOG=Eastern Cooperative Oncology Group. ISS=International Staging System. MRD=minimal residual disease. OBS=observation. PR=partial response. VGPR=very good partial response. VTd=bortezomib, thalidomide, and dexamethasone.

Table 2: Most common adverse events during treatment or observation in the maintenance-specific safety population

Adverse event ≥10% in either group, n (%)	DARA (N=444)				OBS (N=440)			
	Grade 1/2	Grade 3	Grade 4	Grade 5	Grade 1/2	Grade 3	Grade 4	Grade 5
Infections and infestations	303 (68.9)	33 (7.5)	4 (0.9)	1 (0.2)	254 (57.2)	26 (5.9)	4 (0.9)	0 (0)
Bronchitis	166 (37.7)	2 (0.5)	1 (0.2)	0 (0)	130 (29.3)	4 (0.9)	0 (0)	0 (0)
Nasopharyngitis	76 (17.3)	0 (0)	0 (0)	0 (0)	49 (11.0)	0 (0)	0 (0)	0 (0)
Upper respiratory tract infection	64 (14.5)	0 (0)	0 (0)	0 (0)	35 (7.9)	1 (0.2)	0 (0)	0 (0)
Herpes zoster	30 (6.8)	1 (0.2)	0 (0)	0 (0)	63 (14.2)	2 (0.5)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	199 (45.2)	9 (2.0)	0 (0)	0 (0)	191 (43.0)	13 (2.9)	0 (0)	0 (0)
Arthralgia	50 (11.4)	1 (0.2)	0 (0)	0 (0)	50 (11.3)	2 (0.5)	0 (0)	0 (0)
Back pain	45 (10.2)	2 (0.5)	0 (0)	0 (0)	59 (13.3)	2 (0.5)	0 (0)	0 (0)
General disorders and administration site conditions	189 (43.0)	0 (0)	0 (0)	0 (0)	156 (35.1)	9 (2.0)	0 (0)	0 (0)
Asthenia	60 (13.6)	0 (0)	0 (0)	0 (0)	51 (11.5)	2 (0.5)	0 (0)	0 (0)

Influenza-like illness	54 (12.3)	0 (0)	0 (0)	0 (0)	49 (11.0)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	167 (38.0)	8 (1.8)	1 (0.2)	0 (0)	84 (18.9)	7 (1.6)	1 (0.2)	0 (0)
Cough	78 (17.7)	1 (0.2)	0 (0)	0 (0)	40 (9.0)	0 (0)	0 (0)	0 (0)
Nervous system disorders	153 (34.8)	12 (2.7)	0 (0)	0 (0)	117 (26.4)	9 (2.0)	1 (0.2)	0 (0)
Peripheral sensory neuropathy	65 (14.8)	4 (0.9)	0 (0)	0 (0)	46 (10.4)	5 (1.1)	0 (0)	0 (0)
Gastrointestinal disorders	152 (34.5)	11 (2.5)	0 (0)	0 (0)	80 (18.0)	4 (0.9)	1 (0.2)	0 (0)
Diarrhoea	56 (12.7)	1 (0.2)	0 (0)	0 (0)	25 (5.6)	1 (0.2)	0 (0)	0 (0)
Nausea	42 (9.5)	2 (0.5)	0 (0)	0 (0)	6 (1.4)	0 (0)	0 (0)	0 (0)
Immune system disorders	57 (13.0)	3 (0.7)	1 (0.2)	0 (0)	21 (4.7)	4 (0.9)	0 (0)	0 (0)
Hypogammaglobulinaemia	53 (12.0)	3 (0.7)	0 (0)	0 (0)	13 (2.9)	3 (0.7)	0 (0)	0 (0)

DARA=daratumumab. OBS=observation.