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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Summary

Background CASSIOPEIA part 1 showed superior depth of response and significantly improved progression-free survival with daratumumab, bortezomib, thalidomide, and dexamethasone (D-VTd) versus bortezomib, thalidomide, and dexamethasone (VTd) as induction and consolidation in patients with autologous stem-cell transplant (ASCT)-eligible newly diagnosed multiple myeloma. In part 2, we compared daratumumab maintenance versus observation only.

Methods CASSIOPEIA is a two-part, open-label, randomised, phase 3 trial of patients aged 18–65 years with newly diagnosed multiple myeloma and Eastern Cooperative Oncology Group performance status 0–2, done in 111 European academic and community practice centres. In part 1, patients were randomly assigned (1:1) to induction and consolidation with D-VTd or VTd. Patients still on study who had a partial response or better were randomly assigned (1:1) by an interactive web-response system to daratumumab 16 mg/kg intravenously every 8 weeks (a reduced frequency compared with standard daratumumab long-term dosing) or observation only for up to 2 years. Stratification factors were induction treatment and depth of response in part 1. The part 2 primary endpoint was progression-free survival from second randomisation. This preplanned interim analysis of progression-free survival was done after 281 events and shall be considered the primary analysis of progression-free survival. Sponsor personnel and designees who were involved in the analysis were masked to treatment group until the independent data monitoring committee recommended that the preplanned interim analysis be considered the main analysis of progression-free survival in part 2. Otherwise, treatment assignments were unmasked. The interaction between induction and 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 and consolidation treatment. Efficacy analyses were done in the maintenance-specific intention-to-treat population, which comprised all patients who underwent second randomisation. Safety was analysed in all patients in the daratumumab group who received at least one dose and all patients randomly assigned to observation only. This trial is registered with ClinicalTrials.gov, NCT02541383. Long-term follow-up is ongoing and the trial is closed to new participants.

Findings Between May 30, 2016, and June 18, 2018, 886 patients (458 [84%] of 543 in the D-VTd group and 428 [79%] of 542 in the VTd group) were randomly assigned to daratumumab maintenance (n=442) or observation only (n=444). At a median follow-up of 35·4 months (IQR 30·2–39·9) from second randomisation, median progression-free survival was not reached (95% CI not evaluable [NE]–NE) with daratumumab versus 46·7 months (40·0–NE) with observation only (hazard ratio 0·53, 95% CI 0·42–0·68, p<0·0001). A prespecified analysis of progression-free survival results showed a significant interaction between maintenance and induction and consolidation therapy (p<0·0001). The most common grade 3 or 4 adverse events were lymphopenia (16 [4%] of 440 patients in the daratumumab group *vs* eight [2%] of 444 patients in the observation-only group), hypertension (13 [3%] *vs* seven [2%]), and neutropenia (nine [2%] *vs* ten [2%]). Serious adverse events occurred in 100 (23%) patients in the daratumumab group and 84 (19%) patients in the observation-only group. In the daratumumab group, two adverse events led to death (septic shock and natural killer-cell lymphoblastic lymphoma); both were related to treatment.

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

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Introduction

Despite recent treatment advances, virtually all patients with multiple myeloma 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 substantial negative effects on health-related quality of life.

For patients with newly diagnosed multiple myeloma who are eligible for transplant, 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 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 in randomised trials.[4–7] Based on the results of part 1 of the CASSIOPEIA study, daratumumab in combination with bortezomib, thalidomide, and dexamethasone (D-VTd) was approved in regions and countries worldwide, including by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), as a treatment for patients with newly diagnosed multiple myeloma who are eligible for transplant.[8,9]

To prolong the response to frontline therapy, long-term maintenance treatment might be given.[4–7,10,11] Only lenalidomide is approved by the FDA and EMA as maintenance therapy in patients with newly diagnosed multiple myeloma post ASCT, with approval received in 2017.[12,13] Lenalidomide maintenance improves progression-free survival and overall survival, but is associated with higher rates of discontinuation due to adverse events than placebo or observation.[14] There remains an unmet need

Research in context

Evidence before this study

No formal literature search was done 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 USA, and maintenance therapy was not recommended by the European Society of Medical Oncology clinical practice guidelines. Meta-analyses published in 2012 showed overall survival 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 improved 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. In this study, daratumumab every 8 weeks significantly improved 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 prespecified subgroups except for patients who were treated with daratumumab, bortezomib, thalidomide, and dexamethasone (D-VTd) as induction and consolidation in part 1 of the study, suggesting that the optimal daratumumab-containing maintenance regimen might vary based on what treatment was used in the frontline setting.

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 show that daratumumab, at a reduced intensity schedule (once every 8 weeks), 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 previous use of daratumumab in induction and consolidation. A significant progression-free survival benefit could only be shown in daratumumab-naive patients. This raises questions about the precise strategy for how to implement daratumumab in the maintenance setting. Updated data from part 1 support the use of daratumumab as induction and consolidation for patients with transplant-eligible newly diagnosed multiple myeloma. 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.

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See Online for appendix

for alternative well tolerated maintenance therapies that confer a meaningful clinical benefit. Here, we present the results of part 2 of the CASSIOPEIA study, which compared maintenance with daratumumab monotherapy versus observation only.

Method

Study design and participants

CASSIOPEIA is an open-label, randomised, phase 3 study done at 111 European academic and community-based centres (appendix pp 5–7). Study details have previously been described in the primary report of part 1 of the CASSIOPEIA study.[15]

Briefly, in part 1, patients aged 18–65 years with newly diagnosed, documented multiple myeloma according to the International Myeloma Working Group (IMWG)[16] diagnostic criteria, who were eligible for high-dose therapy and ASCT, and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2 were eligible. Patients were excluded from part 1 if they had previous systemic therapy or ASCT for any plasma cell dyscrasia. Additional exclusion criteria were previous treatment with daratumumab or other anti-CD38 therapies, 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 [NCI-CTCAE], version 4),[17] or previous invasive malignancy (other than multiple myeloma) within 10 years of study start. Required pretreatment 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 L or more (if <50% of bone marrow nucleated cells were plasma cells; otherwise, platelet count $>50\times10^9$ 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. Patients on study post consolidation (day 100 post ASCT) who had a partial response or better according to the IMWG response criteria[18] underwent a second randomisation to daratumumab maintenance or observation only.

Each study site's local independent ethics committee or institutional review board approved the study protocol. This study was done 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 randomly assigned (1:1) to D-VTd or bortezomib, thalidomide, and dexamethasone (VTd) in part 1 of the study and to maintenance therapy with daratumumab or observation only in part 2 (appendix p 8). 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 (p 9). Part 2 stratification factors were type of induction treatment (D-VTd *vs* VTd) and depth of response to induction and consolidation therapy (as determined by minimal residual disease [MRD] status and post-consolidation response). Sponsor personnel and designees involved in the analysis were masked to treatment group assignment until the recommendation by an independent data monitoring committee to consider the preplanned interim analysis of progression-free survival 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 randomisation to part 2, we assigned patients to receive either 16 mg/kg of daratumumab intravenously once every 8 weeks or to observation only, up to a maximum of 2 years. The dosing frequency of once every 8 weeks was selected on the basis of the pharmacokinetic and target suppression data available at the time when the CASSIOPEIA trial was designed and initiated. Individual dose reductions of daratumumab were not permitted. Dose delay was recommended as the primary method for managing treatment-related toxicities. Subsequent to completing daratumumab maintenance or observation, all patients from both groups were followed up for disease progression per IMWG criteria[18] (appendix p 10) or death. Preinfusion and postinfusion medications are listed in the appendix (p 11). Patients could be removed from the study for the following reasons: lost to follow-up, withdrawal of consent for study participation, death, termination of the study by the sponsor, or screening failure.

A central laboratory did the disease assessments once every 8 weeks after the second randomisation. If daratumumab interference with serum M-protein was suspected, immunofixation reflex assays confirmed complete responses. Minimal residual disease negativity was primarily assessed using next-generation sequencing assay at a sensitivity level of 10^{-5}. Minimal residual disease was additionally assessed by standardised multiparametric flow cytometry on the basis of the recommendations of the EuroFlow Consortium[19] if a sufficient sample was available. Both methods were applied on bone marrow aspirates of patients who had a very good partial response or better in part 2. The primary count for patients who were minimal residual disease-negative included those with a complete response or better before or at the same time as their negative minimal residual disease assessment. Additional details regarding minimal residual disease assessment are in the appendix (pp 11–12). Patients underwent a skeletal

survey (x-ray or local standard of care imaging [eg, low-dose CT]) at screening. During the treatment phase, and before disease progression was confirmed, imaging was done whenever clinically indicated based on symptoms to document response or progression using the same imaging modality as during the screening phase.

Safety assessments included adverse event monitoring, physical examinations, vital sign measurements, ECOG performance status, electrocardiography, and clinical safety laboratory testing. Adverse events, assessed according to the NCI-CTCAE version 4, were collected continuously from the time of signed informed consent until 30 days following the last dose (daratumumab 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; observation-only group). An independent data monitoring committee reviewed the safety data.

Outcomes

The primary endpoint of part 2 was progression-free survival after second randomisation, which was defined as the duration from the date of second randomisation to progressive disease, according to a validated computer algorithm (as described previously[20–22]), based on the IMWG response criteria,[18,23] or death, whichever occurred first.

Major secondary efficacy endpoints in part 2 were time to progression from second randomisation, proportion of patients who had complete response or better per IMWG criteria,[18] proportion of patients who had minimal residual disease negativity at a threshold of 10^{-5} per next-generation sequencing, progression-free survival after next line of therapy, overall response rate, and overall survival from second randomisation. Secondary efficacy endpoints are defined in the appendix (pp 11–12). Preplanned sensitivity analyses evaluated the proportion of patients with minimal residual disease negativity at a threshold of 10^{-6} by next-generation sequencing and at at a threshold of 10^{-5} by multiparametric flow cytometry.

Other secondary endpoints in part 2 were rate of improved response during maintenance compared with response status at the end of consolidation (in patients who had not had stringent complete responses as defined by IMWG criteria[18] by second randomisation) and rate of conversion to minimal residual disease negativity (proportion of patients who were minimal residual disease-positive by next-generation sequencing post consolidation who subsequently had de novo minimal residual disease-negative status during the maintenance phase), and safety.

Statistical analysis

The hypothesis of part 2 of the study was that daratumumab maintenance improves progression-free survival after ASCT compared with observation only. To achieve 80% power with a significance level of 0·05, 390 progression-free events were needed. Assuming a 36-month accrual and 45 months of additional follow-up, approximately 800 patients (400 per group) were randomly assigned in the second randomisation (daratumumab *vs* observation only).

We did the 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 randomly assigned to daratumumab maintenance therapy who received at least one dose of daratumumab and all patients randomly assigned to observation only. Patients with no post baseline disease assessments on or before subsequent therapies or before death were categorised as not evaluable. All protocol deviations of eligibility criteria and those deviations that could affect patient safety or study endpoints were considered major protocol deviations.

We evaluated the proportional hazard assumption for the progression-free survival analysis by a log-log plot. The two parallel curves indicated that the proportional hazard assumption held well for progression-free survival (appendix p 13). This preplanned analysis of part 2 assessed efficacy and safety after 281 progression-free survival events (72% of the 390 planned total number of events) with the O'Brien-Fleming efficacy boundary for the primary endpoint (progression-free survival). The efficacy boundary of two-sided $p<0·0166$ was determined by the prespecified Lan-DeMet α spending function.

We estimated the distribution of progression-free survival 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% 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 progression-free survival to check the consistency of treatment benefit in a number of prespecified subgroups. Preplanned subgroups for analysis of progression-free survival were based on sex (male or female), age (<50, 50–60, or >60 years), study site (Intergroupe Francophone du Myélome [IFM] or Dutch-Belgian Cooperative Trial Group for Hematology Oncology [HOVON]), ISS staging (I, II, or III), cytogenetics (presence [high risk] or absence [standard risk] of 17p deletion [del17p] or t[4;14] cytogenetic abnormalities), premaintenance baseline renal function (creatinine clearance >90 mL/min *vs* ≤90 mL/min), type of multiple myeloma (immunoglobulin G [IgG] or non-IgG), premaintenance baseline ECOG performance status (0 or ≥1), induction and consolidation treatment (D-VTd or VTd), minimal residual disease status (positive or negative), and response (very good partial response or better or partial response). Data on

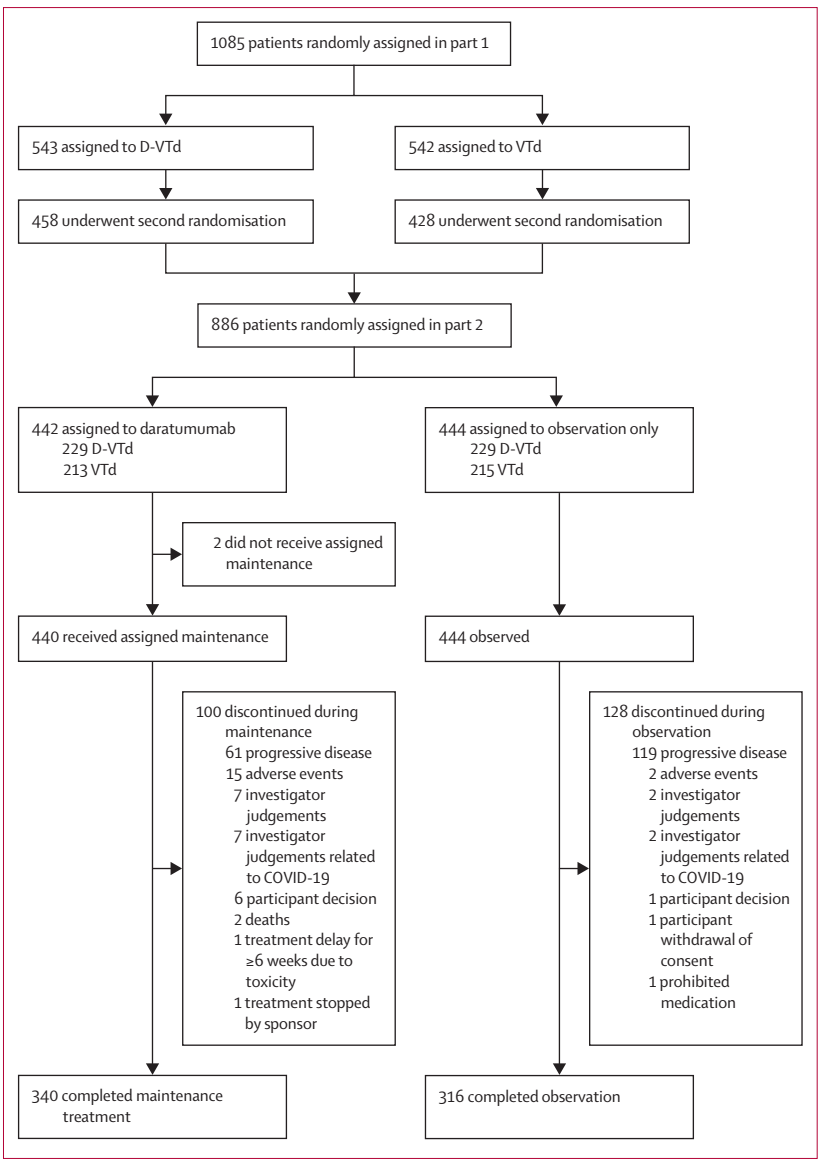

Figure 1: **Study profile**
D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. VTd=bortezomib, thalidomide, and dexamethasone.

infusion-related reactions, second primary malignancies, and infections were reported descriptively as they were preidentified in the statistical analysis plan as adverse events of clinical interest.

We did a prespecified interaction test between induction and 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 and consolidation treatment. Depth of response was the only stratification factor.

Since the primary endpoint was significant, the key secondary endpoints of time to progression from second randomisation, overall rate of complete response or better, proportion of patients who were minimal residual disease negative, and overall survival from second randomisation were tested sequentially for daratumumab versus observation only using a prespecified hierarchical testing approach. Each endpoint was tested with an overall two-sided alpha of 0·05, except for overall survival, which had immature data and was expected to be tested at the final analysis. The p values for the primary endpoint and key secondary endpoints included in the statistical testing hierarchy carry formal statistical inference and can be used to make a claim of statistical significance. All other p values are nominal. Because of the significant interaction between induction and consolidation and maintenance, we did prespecified analyses to compare progression-free survival, time to progression, and overall survival, and post-hoc analyses to compare depth of response, improved response, minimal residual disease negativity, and conversion to minimal residual disease negativity, between subgroups of patients based on the different combinations of induction and consolidation and maintenance regimens; the results of these exploratory analyses are provided for descriptive purposes only. Other post-hoc comparisons between subgroups based on induction and consolidation and maintenance therapies were minimal residual disease assessment at a threshold of 10^{-6} by next-generation sequencing and at 10^{-5} by multiparametric flow cytometry, time to improved response, time to conversion to minimal residual disease negativity, and loss of minimal residual disease negativity. We did updated analyses of progression-free survival and overall survival from part 1 at the request of the EMA at the time of the regulatory approval of D-VTd in Europe. The updated analysis of progression-free survival used the inverse probability weighting method, consistent with what was done in part 1.[15]

We assessed responses and other binary endpoints using the stratified Cochran-Mantel-Haenszel χ^2 test (stratified by type of induction treatment and depth of response), and calculated odds ratios (ORs) and two-sided 95% CIs using SAS (version 9.4). This trial is registered with ClinicalTrials.gov, NCT02541383.

Role of the funding source

The funders designed the trial; collected, analysed, and interpreted the data; and prepared the manuscript in collaboration with the authors.

Results

Between May 30, 2016, and June 18, 2018, 886 patients who had partial response or better in part 1 were randomly assigned to daratumumab (442) or observation only (444; figure 1). 373 (84%) of 442 patients in the daratumumab group and 391 (88%) of 444 patients in the observation-only group were from IFM sites. 69 (16%) of 442 patients in the daratumumab group and 53 (12%) of

444 patients in the observation-only group were from HOVON sites.

458 (84%) of 543 patients in the D-VTd group and 428 (79%) of 542 patients in the VTd group underwent second randomisation. 199 patients (18% of the 1085 randomly assigned in part 1) were not randomly assigned to maintenance in part 2. In both groups, the most common reason for patients not to be randomly assigned to part 2 was adverse events, followed by disease progression during induction, ASCT, or consolidation, and response of stable disease or worse after consolidation (appendix p 14). Rates of progressive disease during induction, ASCT, or consolidation were similar between the groups (23 [4%] of 542 patients in the VTd group and 22 [4%] of 543 patients in the D-VTd group); eight (1%) of 542 patients in the VTd group and two (<1%) of 543 patients in the D-VTd group withdrew consent or decided to discontinue the study (appendix p 14). In part 2, major protocol deviations were reported for 24 (5%) of 442 patients in the daratumumab group and seven (2%) of 444 patients in the observation-only group. Most of these protocol deviations were safety assessment deviations in the daratumumab group, including but not limited to events concerning daratumumab infusion volume or speed and safety laboratory assessments (data not shown).

Demographics and disease characteristics after second randomisation are shown in table 1. Rates of premaintenance complete response or better and minimal residual disease negativity and complete response or better are shown in the appendix (p 15). During part 2, 100 (23%) of 440 patients in the daratumumab group and 128 (29%) of 444 patients in the observation-only group discontinued, most often due to disease progression (figure 1). 440 (>99%) of 442 patients in the daratumumab group received at least one administration of daratumumab and 441 (99%) of 444 patients in the observation-only group completed at least one observation visit. The median number of daratumumab administrations received during the maintenance phase was 14·0 (IQR 13·5–14·0). The median duration of treatment or observation during the maintenance phase was 24·0 months (IQR 23·7–24·2) for daratumumab and 24·2 months (22·1–24·9) for observation only.

At the preplanned interim analysis, after a median follow-up of 35·4 months (IQR 30·2–39·9) from second randomisation, median progression-free survival was not reached (95% CI not evaluable [NE]–NE) with daratumumab versus 46·7 months (40·0–NE) with observation only (HR 0·53, 95% CI 0·42–0·68, p<0·0001; figure 2). There were 108 progression-free survival events in the daratumumab group versus 173 events in the observation-only group. Progression-free survival in prespecified subgroups is shown in figure 3.

Rates of complete response or better, improved response, minimal residual disease negativity (assessed by next-generation sequencing at 10^{-5}) and complete response or better, and conversion to minimal residual disease negativity were higher in the daratumumab group than in the observation-only group (complete response or better: 322 [73%] of 442 *vs* 270 [61%] of 444, OR 2·17, 95% CI 1·54–3·07, p<0·0001; improved response: 188 [62%] of 304 *vs* 153 [47%] of 324, OR 1·95, 1·40–2·72, nominal p<0·0001; minimal residual disease negativity and complete response or better: 259 [59%] *vs* 209 [47%], OR 1·80, 1·33–2·43, p=0·0001; conversion to minimal residual disease negativity: 128 [44%] of 294 *vs* 91 [30%] of 305, OR 1·84, 1·31–2·58, nominal p=0·0004; appendix pp 16–17). Minimal residual disease negativity and complete response or better was also assessed at a threshold of 10^{-6} using next-generation sequencing and 10^{-5} using multiparametric flow cytometry (appendix p 18). Overall response rate was similar in both groups (440 [>99%] of 442 patients in the daratumumab group and 441 [99%] of 444 patients in the

	Daratumumab n=442	Observation only n=444
Median age (IQR), years	59 (53–63)	59 (53–63)
Sex		
Male	261 (59%)	254 (57%)
Female	181 (41%)	190 (43%)
Baseline ECOG performance status		
0	252 (57%)	260 (59%)
1	174 (39%)	172 (39%)
≥2	16 (4%)	12 (3%)
ISS staging*		
I	189 (43%)	171 (39%)
II	181 (41%)	214 (48%)
III	72 (16%)	59 (13%)
Cytogenetic profile*		
Standard risk	383/440 (87%)	374/444 (84%)
High risk	57/440 (13%)	70/444 (16%)
Type of induction and consolidation		
D-VTd	229 (52%)	229 (52%)
VTd	213 (48%)	215 (48%)
Stratification factors†		
MRD negative and ≥VGPR	337 (76%)	337 (76%)
MRD positive and ≥VGPR	68 (15%)	69 (16%)
MRD positive and PR‡	37 (8%)	38 (9%)

Data are n (%) unless otherwise stated. Premaintenance baseline is the last non-missing observation on or before the date of second randomisation or week 1 visit, whichever is later. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. ECOG=Eastern Cooperative Oncology Group. ISS=International Staging System. MRD=minimal residual disease. PR=partial response. VGPR=very good partial response. VTd=bortezomib, thalidomide, and dexamethasone. *Preinduction. †As determined by MRD measured by multiparametric flow cytometry at 10^{-4} and post-consolidation response per investigator assessment used for stratification. ‡Six patients (three who received previous D-VTd and three who received previous 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.

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

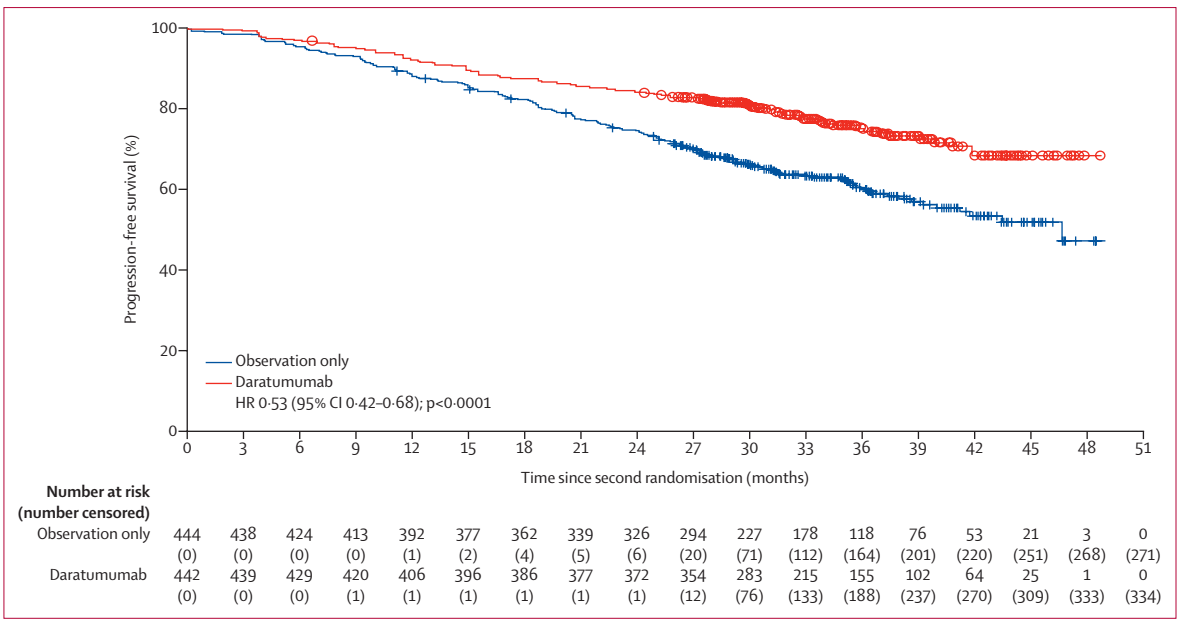

Figure 2: **Kaplan-Meier estimates of progression-free survival in patients in the maintenance-specific intention-to-treat population**
HR=hazard ratio.

observation-only group (appendix p 19). Median time to progression was not reached (95% CI NE–NE) in the daratumumab group versus 46·7 months (40·0–NE) in the observation-only group (HR 0·49, 95% CI 0·38–0·62, p<0·0001); there were 98 events in the daratumumab group and 172 events in the observation-only group. Overall, 209 (24%) of 886 patients received one or more subsequent anti-myeloma treatments (79 [18%] of 442 patients in the daratumumab group and 130 [29%] of 444 patients in the observation-only group; appendix p 20).

Progression-free survival after next line of therapy was immature for both groups (appendix p 21). Median overall survival was not reached in either group (95% CI NE–NE). 29 deaths occurred in the daratumumab group and 27 in the observation-only group (appendix p 22). The most common cause of death was progressive disease (13 [45%] in the daratumumab group and 22 [81%] in the observation-only group). All other causes occurred in only one patient each (appendix p 22). Long-term follow-up is ongoing.

Demographics and disease characteristics by induction and consolidation regimen are included in appendix (p 23). A prespecified analysis for interaction of progression-free survival results showed significant interaction between maintenance and induction and consolidation therapy (p<0·0001).

A median progression-free survival of 33·6 months (95% CI 27·2–37·4) was reached in the VTd plus observation-only group. Median progression-free survival was not reached in the D-VTd plus daratumumab (95% CI NE–NE), D-VTd plus observation-only (95% CI NE–NE), or VTd plus daratumumab groups (95% CI NE–NE; appendix p 24). A progression-free survival benefit was observed in the VTd plus daratumumab group compared with the VTd plus observation-only group (HR 0·32 [95% CI 0·23–0·46]; nominal p<0·0001; appendix p 24). Progression-free survival was not significantly different between the D-VTd plus daratumumab group versus the D-VTd plus observation-only group (HR 1·02 [95% CI 0·71–1·47]; nominal p=0.91; appendix p 24). The number of progression-free survival events was similar in the D-VTd plus daratumumab group and D-VTd plus observation-only groups (59 *vs* 56) and lower in the VTd plus daratumumab compared with VTd plus observation-only (49 *vs* 117).

In post-hoc analyses of patients who received VTd as induction and consolidation, rates of complete response or better, improved response, minimal residual disease negativity and complete response or better, and conversion to minimal residual disease negativity were higher in the daratumumab group than in the observation-only group (appendix pp 25–26). Of patients who received VTd induction and consolidation, overall response rate was similar in the daratumumab and observation-only groups (appendix p 27).

In post-hoc analyses of patients who received D-VTd as induction and consolidation, rates of complete response or better, improved response, minimal residual disease negativity and complete response or better, and conversion to minimal residual disease negativity were not statistically different between the daratumumab and observation-only groups (appendix pp 25–26). Overall response rate in patients who received D-VTd as induction and consolidation was similar in the daratumumab and observation-only groups (appendix p 27).

	Observation only (n/N)	Median, months (95% CI)	Daratumumab (n/N)	Median, months (95% CI)	HR (95% CI)
Sex					
Male	107/254	NE (36·4–NE)	73/261	NE (NE–NE)	0·57 (0·42–0·76)
Female	66/190	46·7 (41·2–NE)	35/181	NE (NE–NE)	0·53 (0·35–0·81)
Age					
<50 years	30/68	43·5 (26·7–NE)	13/63	NE (41·9–NE)	0·38 (0·20–0·74)
50–60 years	80/200	NE (37·4–NE)	49/198	NE (NE–NE)	0·56 (0·39–0·79)
>60 years	63/176	46·7 (41·8–NE)	46/181	NE (NE–NE)	0·67 (0·46–0·98)
Site					
IFM	153/391	46·7 (40·0–NE)	91/373	NE (NE–NE)	0·56 (0·43–0·72)
HOVON	20/53	NE (30·0–NE)	17/69	NE (36·1–NE)	0·59 (0·31–1·13)
ISS staging					
I	50/171	NE (43·5–NE)	31/189	NE (NE–NE)	0·50 (0·32–0·78)
II	96/214	41·2 (35·1–NE)	51/181	NE (NE–NE)	0·56 (0·40–0·79)
III	27/59	38·3 (27·7–NE)	26/72	NE (33·0–NE)	0·75 (0·44–1·29)
Cytogenetic risk					
High risk	45/70	27·2 (20·7–33·6)	19/57	NE (34·0–NE)	0·43 (0·25–0·73)
Standard risk	128/374	NE (43·5–NE)	89/383	NE (NE–NE)	0·62 (0·48–0·82)
Premaintenance baseline renal function (CrCl)					
>90 mL/min	126/305	43·5 (38·3–NE)	74/303	NE (NE–NE)	0·51 (0·38–0·68)
≤90 mL/min	47/139	46·7 (38·7–NE)	34/139	NE (NE–NE)	0·72 (0·47–1·12)
Type of multiple myeloma					
IgG	108/270	46·7 (38·3–NE)	72/253	NE (NE–NE)	0·64 (0·48–0·87)
Non-IgG	40/92	40·0 (35·6–NE)	20/93	NE (NE–NE)	0·44 (0·26–0·75)
Premaintenance baseline ECOG performance status					
0	99/260	46·7 (41·8–NE)	59/252	NE (NE–NE)	0·55 (0·40–0·76)
≥1	74/184	41·2 (38·7–NE)	49/190	NE (NE–NE)	0·57 (0·40–0·82)
Induction and consolidation treatment group					
VTd	117/215	33·6 (27·2–37·4)	49/213	NE (NE–NE)	0·34 (0·24–0·47)
D-VTd	56/229	NE (46·7–NE)	59/229	NE (NE–NE)	1·05 (0·73–1·51)
Minimal residual disease					
Minimal residual disease positive	72/107	24·2 (18·8–30·4)	43/105	NE (34·0–NE)	0·46 (0·31–0·67)
Minimal residual disease negative	101/337	NE (46·7–NE)	65/337	NE (NE–NE)	0·61 (0·44–0·83)
Response					
VGPR or better	146/406	NE (43·5–NE)	92/405	NE (NE–NE)	0·58 (0·45–0·75)
PR	27/38	19·5 (15·0–30·7)	16/37	37·6 (28·1–NE)	0·39 (0·21–0·73)

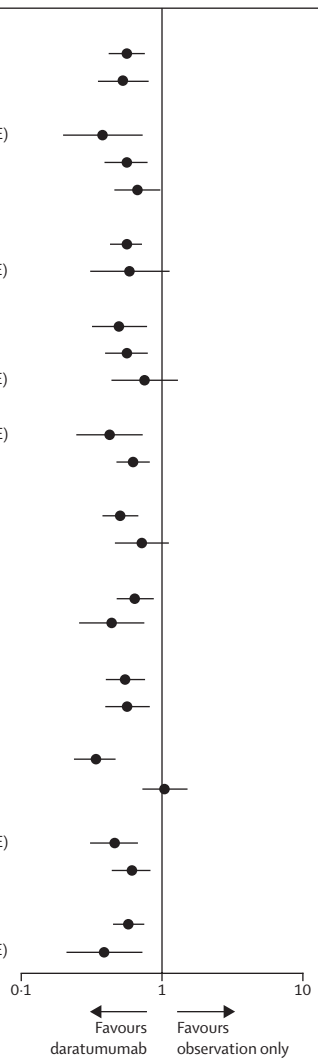

Figure 3: **Progression-free survival in prespecified subgroups of the maintenance-specific intention-to-treat population**
HR (95% CI) based on unstratified Cox regression model. n/N=progression-free survival events over total number of patients in subgroup. ASCT=autologous stem-cell transplant. CrCl=creatinine clearance. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. ECOG=Eastern Cooperative Oncology Group. IFM=Intergroupe Francophone du Myélome. HOVON=Dutch-Belgian Cooperative Trial Group for Hematology Oncology. HR=hazard ratio. IgG=immunoglobulin G. ISS=International Staging System. NE=not estimable. PR=partial response. VGPR=very good partial response. VTd=bortezomib, thalidomide, and dexamethasone.

Median time to improved response and median time to conversion to minimal residual disease negativity were similar irrespective of maintenance and induction and consolidation regimens (post-hoc analyses; data not shown). A total of 342 patients who underwent second randomisation were minimal residual disease negative at 10^{-5} by next-generation sequencing after consolidation. Of these, 25 (7%) subsequently lost their minimal residual disease negativity during part 2. The number of patients who lost minimal residual disease negativity in the D-VTd plus daratumumab group was six (6%) of 108, in the D-VTd plus observation-only group was seven (7%) of 60, in the VTd plus daratumumab group was three (5%) of 60, and in the VTd plus observation-only group was nine (13%) of 71 (post-hoc analyses). Rate of minimal residual disease negativity and complete response or better was also assessed within subgroups based on induction and consolidation and maintenance therapies at a threshold of 10^{-6} using next-generation sequencing and 10^{-5} using multiparametric flow cytometry (appendix p 28; post-hoc analyses).

Updated analyses comparing D-VTd versus 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 progression-free survival compared with

	Daratumumab (n=440)				Observation only (n=444)			
	Grade 1/2	Grade 3	Grade 4	Grade 5	Grade 1/2	Grade 3	Grade 4	Grade 5
Infections and infestations								
Bronchitis	166 (38%)	2 (<1%)	1 (<1%)	0	130 (29%)	4 (1%)	0	0
Nasopharyngitis	76 (17%)	0	0	0	49 (11%)	0	0	0
Upper respiratory tract infection	64 (15%)	0	0	0	35 (8%)	1 (<1%)	0	0
Herpes zoster	30 (7%)	1 (<1%)	0	0	63 (14%)	2 (<1%)	0	0
Pneumonia	18 (4%)	10 (2%)	1 (<1%)	0	13 (3%)	6 (1%)	0	0
Blood and lymphatic system disorders								
Lymphopenia	15 (3%)	14 (3%)	2 (<1%)	0	9 (2%)	3 (1%)	5 (1%)	0
Neutropenia	3 (1%)	9 (2%)	0	0	0	10 (2%)	0	0
Gastrointestinal disorders								
Diarrhoea	56 (13%)	1 (<1%)	0	0	25 (6%)	1 (<1%)	0	0
General disorders and administration site conditions								
Asthenia	60 (14%)	0	0	0	51 (11%)	2 (<1%)	0	0
Influenza-like illness	54 (12%)	0	0	0	49 (11%)	0	0	0
Immune system disorders								
Hypogammaglobulinaemia	53 (12%)	3 (1%)	0	0	13 (3%)	3 (1%)	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	50 (11%)	1 (<1%)	0	0	50 (11%)	2 (<1%)	0	0
Back pain	45 (10%)	2 (<1%)	0	0	59 (13%)	2 (<1%)	0	0
Nervous system disorders								
Peripheral sensory neuropathy	65 (15%)	4 (1%)	0	0	46 (10%)	5 (1%)	0	0
Respiratory, thoracic, and mediastinal disorders								
Cough	78 (18%)	1 (<1%)	0	0	40 (9%)	0	0	0
Vascular disorders								
Hypertension	15 (3%)	13 (3%)	0	0	10 (2%)	7 (2%)	0	0

Data are n (%). Adverse events of grade 1 or 2 that were reported in at least 10% of patients in either treatment group and grade 3–5 adverse events that were reported in at least 2% of patients in either treatment group are listed.

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

VTd (median progression-free survival not reached [95% CI NE–NE] *vs* 51·5 months [46·3–NE], HR 0·58, 95% CI 0·47–0·72, p<0·0001) after adjustment for the second randomisation using the unbiased inverse probability weighting method (appendix p 29). Overall survival was not reached in either group (appendix p 30). 41 (8%) of 543 patients in the D-VTd and 73 (13%) of 542 patients in the VTd groups died over the entire course of the study. Of patients not randomly assigned to part 2, median progression-free survival was 30·7 months (95% CI 14·3–NE) for those treated with D-VTd (n=85) and 25·4 months (20·4–33·2) for those treated with VTd (n=114) induction and consolidation (appendix p 31). Of patients not randomly assigned to part 2, 36 (42%) of 85 in the D-VTd group and 57 (50%) of 114 in the VTd group had a progression-free survival event.

Treatment-emergent adverse events occurred in 420 (95%) of 440 patients in the daratumumab group and 394 (89%) of 444 patients in the observation-only group (appendix p 32). Serious adverse events occurred in 100 (23%) of 440 patients in the daratumumab group and 84 (19%) of 444 patients in the observation-only group; 32 (32%) serious adverse events in the daratumumab group were reported to be drug-related. Serious adverse events that occurred in more than 1% of patients in the daratumumab or observation-only groups were pneumonia (11 [3%] *vs* seven [2%]) and lung infection (six [1%] *vs* seven [2%]). Daratumumab infusions were interrupted in 93 (21%) of 440 patients due to adverse events and were skipped in ten (2%) patients due to adverse events; except for one patient, all infusion interruptions were due to infusion-related reactions. Discontinuation of daratumumab due to an to adverse event occurred in 13 (3%) of 440 patients (appendix p 32). Two adverse events led to death in the daratumumab group (septic shock and lymphoblastic lymphoma [n=1 each]); both were related to treatment. There were no adverse events that led to death in the observation-only group. The most common adverse events during part 2 are shown in table 2. Grade 3 or worse adverse events were reported in 122 (28%) of 440 patients who received at least one dose of daratumumab and 108 (24%) of 444 patients in the observation-only group. The most common grade 3–4 adverse events were lymphopenia (16 [4%] of 440 patients in the daratumumab group *vs* eight [2%] of 444 patients in the observation-only group),

hypertension (13 [3%] *vs* seven [2%]), and neutropenia (nine [2%] *vs* ten [2%]). A table of treatment-emergent adverse events of grade 1 or 2 that were reported in 10% or more patients in either treatment group and all grade 3, 4, and 5 events is in the appendix (pp 33–39).

Infusion-related reactions following the first infusion occurred in 115 (55%) of 211 patients in the VTd plus daratumumab group (ie, those with no previous daratumumab exposure [either during induction and consolidation or before enrollment in part 1]; appendix p 32). Most of these infusion-related reactions (103 [90%] of 115) were grade 1 or 2. Two patients, both in the VTd plus daratumumab group, discontinued at the week 1 visit due to an infusion-related reaction. Of the 229 patients in the D-VTd plus daratumumab group, five (2%) had an infusion-related reaction. One of these occurred at first infusion and four occurred at subsequent infusions. All were grade 1 or 2.

Secondary primary malignancies in part 2 were observed in 24 (5%) of 440 patients in the daratumumab group and 12 (3%) of 444 patients in the observation-only group (post-hoc; appendix p 32). Solid-tumour secondary primary malignancies were more common than haematological secondary primary malignancies in the daratumumab (19 *vs* five) and the observation-only groups (11 *vs* one). Additional detail regarding number of daratumumab doses before secondary primary malignancy onset, confounding medical history, and pre-existing conditions is shown in the appendix (pp 40–42). The median time from second randomisation to first onset of secondary primary malignancy was 36·0 months in the daratumumab group and 44·0 months in the observation-only group. Secondary primary malignancies by induction and consolidation and maintenance are shown in the appendix (pp 43–44).

Infections in part 2 were reported in 341 (78%) of 440 patients in the daratumumab group and 284 (64%) of 444 patients in the observation-only group (appendix p 32). 303 (89%) of 341 participants in the daratumumab group and 254 (89%) of 284 participants in the observation-only group had grade 1 or 2 infections. The incidence of pneumonia and lung infections was low (appendix p 32).

Discussion

To our knowledge, CASSIOPEIA part 2 is the first study to show the clinical benefit of daratumumab maintenance therapy compared with observation in patients with newly diagnosed multiple myeloma who received ASCT. Treatment with reduced intensity (once every 8 weeks) daratumumab maintenance for a maximum of 2 years resulted in a reduction of risk of disease progression or death compared with observation only. This benefit was observed in nearly all prespecified 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. Daratumumab maintenance therapy significantly improved depth of response compared with observation only, with the highest rates of deep response (ie, minimal residual disease negativity and response of complete response or better) in patients who received D-VTd as induction and consolidation. Daratumumab maintenance therapy was well tolerated, with low rates of discontinuation. Secondary primary malignancies were reported in 24 (5%) of 440 patients in the daratumumab group and 12 (3%) of 444 patients in the observation-only group; however, when those with implausible time to onset (after receiving one or three doses of daratumumab) 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 secondary primary malignancies became more balanced between the two groups.

Of the patients who received VTd as induction and consolidation therapy, daratumumab maintenance substantially improved progression-free survival. Daratumumab maintenance also resulted in significantly deeper responses in these patients, although this was a post-hoc analysis and should be interpreted with caution. A visual inspection of the survival curves (appendix p 24) shows that although patients who received VTd plus daratumumab initially follow a trajectory suggesting poorer outcomes than patients in the D-VTd plus daratumumab and D-VTd plus observation-only groups, there appears to be an inflection point at approximately 30 months from second randomisation, after which the curve becomes more similar to the D-VTd plus daratumumab and D-VTd plus observation-only groups. We hypothesise that this initial downward trajectory might reflect early progression in some patients in this group, possibly due to the suboptimal induction and consolidation regimen of VTd, and the subsequent flattening of the curve illustrates the benefit of daratumumab in those patients who did not progress. Should this be the case, it would be supportive of D-VTd induction and consolidation in order to achieve optimal disease control. Given that no loading (initial weekly dosing) of daratumumab was given in part 2, it is also possible that these visual differences could also be due in part to a slower onset of action related to the dosing frequency of once every 8 weeks, which is less often than standard daratumumab long-term dosing. Of those who received D-VTd as induction and consolidation, progression-free survival was similar in the daratumumab and observation-only groups. Although this finding does not indicate an advantage for daratumumab maintenance following D-VTd induction and consolidation, data maturation is required to assess the effect of daratumumab maintenance on progression-free survival after next line of therapy and overall survival. Updated part 1 results with longer median follow-up showed a significant progression-free survival benefit for D-VTd

versus VTd, further confirming the benefit of adding daratumumab to VTd as induction and consolidation. More patients in the D-VTd group than the VTd group were randomly assigned to part 2. Patients who were not randomly assigned to part 2 (85 in the D-VTd group and 114 in the VTd group) had a far poorer prognosis than those who were randomly assigned 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 and colleagues did 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,[24] CALGB 100104,[25] and GIMEMA RV-MM-PI-209[26]) were analysed. The mean treatment duration was 28 months with lenalidomide versus 22 months within the pooled placebo or observation group. The median progression-free survival for patients who received lenalidomide was twice that of those who received placebo or observation (52·8 [95% CI 45·1–62·6] *vs* 23·5 months [95% CI 21·0–26·2], 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 with placebo or observation. Safety data were available from two of the three trials and showed higher rates of secondary primary malignancies, infections, and treatment-emergent adverse events 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 newly diagnosed multiple myeloma post ASCT.

The phase 3 TOURMALINE-MM3 study compared oral ixazomib maintenance therapy with placebo in 656 patients with newly diagnosed multiple myeloma who had had partial response or better following standard-of-care induction, high-dose melphalan, and ASCT.[27] At a median follow-up of 31 months (IQR 27·3–35·7), median progression-free survival was significantly longer with ixazomib than with placebo (26·5 months [95% CI 23·7–33·8] *vs* 21.3 months [95% CI 18.0–24.7], HR 0·72 [95% CI 0·58–0·89]; p=0·002). The overall survival analysis was inconclusive due to an insufficient number of events. However, rates of adverse events resulting in discontinuation or dose reduction of the study drug were higher with ixazomib than placebo.

In part 2 of CASSIOPEIA, the median progression-free survival observed in the VTd plus observation-only group from start of maintenance was 33·6 months (95% CI 27·2–37·4), which is longer than that of the pooled observation or placebo group of the meta-analysis by McCarthy and colleagues (23·5 months [95% CI 21·0–26·2])[14] as well as that of the placebo group in TOURMALINE-MM3 (21·3 months [95% CI 18·0–24·7]).[27] This difference, as well as the fact that median progression-free survival in the D-VTd plus observation-only group was not reached, reflects the general improvement in the treatment of multiple myeloma and greater clinical benefits of newer induction regimens than earlier therapies. Median progression-free survival was also not reached in either the D-VTd plus daratumumab group or VTd plus daratumumab group, compared with 26·5 months (95% CI 23·7–33·8) in the ixazomib group of TOURMALINE-MM3.[27] With 35·4 months of follow-up, progression-free survival with daratumumab in CASSIOPEIA part 2 appears to be in line with the lenalidomide group of the meta-analysis (median progression-free survival 52·8 months (95% CI [45·1–62·6]) at a median of 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 start of the CASSIOPEIA study (first patient randomly assigned 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 group 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 group of the IFM/DFCI2009 study (NCT01191060), in which patients received lenalidomide maintenance for a fixed duration of 1 year. Given the anticipated long progression-free survival in patients who received ASCT, the 2-year fixed duration maintenance of CASSIOPEIA was considered a reasonable choice.

Finally, the use of dosing once every 8 weeks is another potential limitation. At the time of study design, pharmacokinetic data supported this treatment schedule. Subsequently, data from the phase 2 CENTAURUS study suggested that dosing once every 8 weeks could be insufficient to maintain target suppression,[28] and as a result, dosing every 4 weeks has become the preferred daratumumab 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 frequency of daratumumab dosing every 4 weeks of 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 daratumumab maintenance significantly improved outcomes compared with observation and was well tolerated in patients with newly diagnosed multiple myeloma who received VTd as induction and consolidation therapy and ASCT. Longer follow-up is required to assess potential benefit in terms of progression-free survival after next line of therapy and overall survival in patients who received induction and consolidation with D-VTd. The updated results of part 1 with longer follow-up show a sustained progression-free survival benefit in the D-VTd group compared with the VTd group and support the early use of daratumumab in transplant-eligible patients with newly diagnosed multiple myeloma. These results are further supported by the higher rates of dropout of patients in the VTd group than the D-VTd group. Ongoing studies including GRIFFIN, PERSEUS, and AURIGA will provide valuable data to determine optimal treatment strategies using daratumumab plus lenalidomide as maintenance therapy in patients with newly diagnosed multiple myeloma.

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. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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. MMo reports 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 the submitted work. XL reports personal fees from Janssen, outside the submitted work. MMa reports personal fees from and advisory board participation for Amgen, Celgene, Janssen, and Takeda, outside the submitted work. A-MS reports personal fees from Celgene outside the submitted work. NWCJvdD reports grants from Amgen, Bristol Myers Squibb, Celgene, Janssen, and Novartis, during the conduct of the study; and personal fees from Amgen, Bristol Myers Squibb, Celgene, Janssen, Novartis, Bayer, Roche, Servier, and Takeda, outside the submitted work. AB reports personal fees from Amgen, Celgene, Janssen, and Bristol Myers Squibb, outside the submitted work. CT reports personal fees from Janssen, outside the submitter work. MR reports grants from Janssen, during the conduct of the study; personal fees and travel support from Celgene, Amgen, Sanofi, Takeda, and Janssen, outside the submitted work. M-DL reports grants from AbbVie, Amgen, Janssen, Roche, and Takeda, during the conduct of the study; and personal fees and advisory board participation from AbbVie, Janssen, Roche, and Takeda, outside the submitted work. TA reports employment and equity ownership from Genmab. MK reports employment with Janssen. KZ reports employment with Janssen. CdB reports employment and equity ownership from Janssen. SV reports employment with Janssen. TK reports employment with Janssen. VV reports employment with Janssen. JV reports employment with Janssen. HA-L reports grants from Celgene and Janssen, during the conduct of the study; and personal fees from Celgene, Amgen, Bristol-Myers Squibb, Sanofi, and Janssen, outside the submitted work. PS reports personal fees from Celgene and Janssen, outside the submitted work. All other authors declare no competing interests.

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. As noted on that site, requests for access to the study data can be submitted through the Yale Open Data Access Project site.

For **Janssen Pharmaceutical Companies of Johnson & Johnson** see https://www.janssen.com/clinical-trials/transparency

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

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References

1 Dimopoulos MA, San-Miguel JF, Anderson KC. Emerging therapies for the treatment of relapsed or refractory multiple myeloma. *Eur J Haematol* 2011; **86:** 1–15.

2 Kumar SK, Therneau TM, Gertz MA, et al. Clinical course of patients with relapsed multiple myeloma. *Mayo Clin Proc* 2004; **79:** 867–74.

3 Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. *Br J Haematol* 2016; **175:** 252–64.

4 Engelhardt M, Terpos E, Kleber M, et al. European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. *Haematologica* 2014; **99:** 232–42.

5 Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2021; **32:** 309–22.

6 Cavo M, Rajkumar SV, Palumbo A, et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. *Blood* 2011; **117:** 6063–73.

7 Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; **28** (suppl 4)**:** iv52–61.

8 Janssen. DARZALEX (daratumumab) injection, for intravenous use. 2020. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX-pi.pdf (accessed Sept 15, 2020).

9 EMA. Darzalex (daratumumab) summary of product characteristics. 2020. https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf (accessed Sept 15, 2020).

10 Ludwig H, Durie BG, McCarthy P, et al. IMWG consensus on maintenance therapy in multiple myeloma. *Blood* 2012; **119:** 3003–15.

11 Sengsayadeth S, Malard F, Savani BN, Garderet L, Mohty M. Posttransplant maintenance therapy in multiple myeloma: the changing landscape. *Blood Cancer J* 2017; **7:** e545.

12 Bristol Myers Squibb. REVLIMID (lenalidomide) capsules, for oral use. 2019. https://packageinserts.bms.com/pi/pi_revlimid.pdf (accessed Sept 17, 2020).

13 EMA. Revlimid (lenalidomide) summary of product characteristics. 2020. https://www.ema.europa.eu/en/documents/product-information/revlimid-epar-product-information_en.pdf (accessed Sept 17, 2020).

14 McCarthy PL, Holstein SA, Petrucci MT, et al. lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. *J Clin Oncol* 2017; **35:** 3279–89.

15 Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. *Lancet* 2019; **394:** 29–38.

16 Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014; **15:** e538–48.

17 US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf (accessed Sept 15, 2020).

18 Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia* 2006; **20:** 1467–73.

19 Flores-Montero J, Sanoja-Flores L, Paiva B, et al. Next Generation Flow for highly sensitive and standardized detection of minimal residual disease in multiple myeloma. *Leukemia* 2017; **31:** 2094–103.

20 Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; **375:** 754–66.

21 Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; **375:** 1319–31.

22 Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *N Engl J Med* 2018; **378:** 518–28.

23 Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood* 2011; **117:** 4691–95.

24 Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 2006; **108:** 3289–94.

25 McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012; **366:** 1770–81.

26 Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med* 2014; **371:** 895–905.

27 Dimopoulos MA, Gay F, Schjesvold F, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet* 2019; **393:** 253–64.

28 Landgren CO, Chari A, Cohen YC, et al. Daratumumab monotherapy for patients with intermediate-risk or high-risk smoldering multiple myeloma: a randomized, open-label, multicenter, phase 2 study (CENTAURUS). *Leukemia* 2020; **34:** 1840–52.