Daratumumab, Bortezomib, Thalidomide, and Dexamethasone Followed By Daratumumab Maintenance in Transplant-eligible Newly Diagnosed Multiple Myeloma (CASSIOPEIA): >6 Year Update of an Open-label, Randomised, Phase 3 Trial

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ABSTRACT

Background: CASSIOPEIA demonstrated superior depth of response and prolonged progression-free survival with daratumumab/bortezomib/thalidomide/dexamethasone (D-VTd) versus VTd as induction/consolidation in transplant-eligible newly diagnosed myeloma. Daratumumab maintenance significantly improved progression-free survival and increased minimal residual disease (MRD)-negativity rates versus observation. Here, we report long-term study outcomes.

Methods: CASSIOPEIA is a two-part, open-label, phase 3 trial of patients aged 18–65 years with an Eastern Cooperative Oncology Group performance status 0–2 and transplant-eligible newly diagnosed myeloma, conducted in 111 European academic and community-based centres. Patients were randomised (1:1) to pre-transplant induction and post-transplant consolidation with D-VTd or VTd. Patients who completed consolidation and had achieved partial response or better were re-randomised (1:1) to daratumumab maintenance (16 mg/kg intravenously every 8 weeks) or observation for ≤2 years. An interactive web-based system was used for both randomisations to generate treatment assignments, and randomisation was balanced using permuted blocks of four. Stratification factors for the first randomisation (induction/consolidation phase) were site affiliation, International Staging System disease stage, and cytogenetic risk status. Stratification factors for the second randomisation (maintenance phase) were induction treatment and depth of response in the induction/consolidation phase. There was no masking to treatment assignments during the induction/consolidation or maintenance phases, with the exception of sponsor personnel and designees involved in the analysis who 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 for the maintenance phase. The primary endpoint for the induction/consolidation phase was the proportion of patients who achieved a stringent complete response after consolidation; results for this endpoint remain unchanged from those reported previously. The primary endpoint for the maintenance phase was progression-free survival from second randomisation. Efficacy evaluations in the induction/consolidation phase were performed on the intent-to-treat population, and efficacy analyses in the maintenance phase were conducted on the maintenance-specific intent-to-treat population. This analysis represents the final data cutoff at the end of the study. The trial is registered with ClinicalTrials.gov, NCT02541383.

Findings: Between September 22, 2015 and August 1, 2017, 1085 patients were randomised to D-VTd (n=543) or VTd (n=542); between May 30, 2016 and June 18, 2018, 886 were re-randomised to daratumumab maintenance (n=442) or observation (n=444). As of September 1, 2023, median follow-up was 80·1 months (IQR, 75·7–85·6) from first randomisation and 70·6 months (IQR, 66·4–76·1) from second randomisation. Progression-free survival from first randomisation regardless of second randomisation was significantly improved with D-VTd versus VTd (median: 83·7 months [95% CI 70·2–not estimable {NE}] vs 52·8 months [95% CI 47·5–58·7], HR 0·61, 95% CI 0·52–0·72, p<0·0001). Progression-free survival from second randomisation was significantly improved with daratumumab versus observation (median: not reached [95% CI 79·9–NE] vs 45·8 months [95% CI 41·8–49·6], HR 0·49, 95% CI 0·40–0·59, p<0·0001); benefit was observed with D-VTd/daratumumab versus D-VTd/observation (median: not reached [95% CI 74·6–NE] vs 72·1 months [95% CI 52·8–NE], HR 0·76, 95% CI 0·58–1.00, p=0·048) and VTd/daratumumab versus VTd/observation (median: not reached [95% CI

66·9–NE] vs 32·7 months [95% CI 27·2–38·7], HR 0·34; 95% CI 0·26–0·44, p<0·0001). MRD-negativity rates were highest for D-VTd/daratumumab: D-VTd/daratumumab versus D-VTd/observation (10^{-5}: 65·1% vs 58·1%, odds ratio 1·47, 95% CI 0·95–2·26, p=0·080; 10^{-6}: 58·1% vs 48·9%, odds ratio 1·56, 95% CI 1·04–2·34, p=0·031); VTd/daratumumab versus VTd/observation (10^{-5}: 53·5% vs 36·3%, odds ratio 2·33, 95% CI 1·51–3·60, p=0·0001; 10^{-6}: 43·7% vs 26·5%, odds ratio 2·44, 95% CI 1·56–3·81, p<0·0001). Second primary malignancy rates were 11·4% (D-VTd/daratumumab), 6·1% (D-VTd/observation), 12·3% (VTd/daratumumab), and 10·2% (VTd/observation).

Interpretation: D-VTd significantly reduced the risk of progression or death by 39%, with ~2·5 years longer median progression-free survival (~7 vs ~4·5 years) versus VTd. Daratumumab maintenance reduced the risk of progression or death by 51% versus observation. Including daratumumab in both induction/consolidation and maintenance led to the highest MRD-negativity rates, which translated to superior progression-free survival outcomes. Our results support D-VTd induction/consolidation plus daratumumab maintenance as a standard of care for transplant-eligible patients with newly diagnosed multiple myeloma.

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RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed for articles published from database inception to March 5, 2024. No language restrictions were applied. All fields were searched for "newly diagnosed multiple myeloma" and "monoclonal antibody" and "transplant" and "maintenance". Our search identified 49 articles published during this timeframe. Of those, two articles were published before the first patient was enrolled in the CASSIOPEIA study in September 2015, one of which reported the results from a clinical study of a monoclonal antibody. This was a phase 2 randomised study of the IL-6 antibody siltuximab in combination with bortezomib, melphalan, and prednisone (VMP) followed by siltuximab maintenance in transplant-ineligible patients with newly diagnosed multiple myeloma; however, the addition of siltuximab did not improve clinical outcomes versus VMP alone. Of the 47 articles published after the CASSIOPEIA study was initiated, 10 were related to clinical studies of monoclonal antibody-containing induction/consolidation and maintenance therapy in transplant-eligible patients with newly diagnosed multiple myeloma, eight of which reported positive results (seven with daratumumab; one with isatuximab). Two articles reported results from CASSIOPEIA (part 1 and part 2), two articles were related to the phase 2 LYRA study, and one article reported part 1 (induction) results from the phase 3 GMMG-HD7 trial. One article reported the primary results from the phase 3 PERSEUS study and two articles discussed results from the phase 2 GRIFFIN study, both of which provided strong evidence for the addition of daratumumab to bortezomib, lenalidomide, and dexamethasone (VRd) induction/consolidation and to lenalidomide maintenance for transplant-eligible newly diagnosed multiple myeloma. In contrast, two articles

were related to the GMMG-HD6 trial, a phase 3 trial that failed to show clinical benefit with the addition of elotuzumab to VRd induction/consolidation and to lenalidomide maintenance.

Added value of this study

To our knowledge, CASSIOPEIA is the first phase 3 randomised study to show the clinical benefit of adding a monoclonal antibody to an induction/consolidation regimen and the clinical benefit of monoclonal antibody maintenance therapy over observation in transplant-eligible patients with newly diagnosed multiple myeloma. Long-term outcomes from CASSIOPEIA are now available, at a median follow-up of 80·1 months from first randomisation. With this extended follow-up, we now show for the first time that the most pronounced progression-free survival benefit was observed in patients who received daratumumab plus bortezomib, thalidomide, and dexamethasone (D-VTd) induction/consolidation and daratumumab maintenance, and that median overall survival from first randomisation regardless of second randomisation was significantly improved with D-VTd induction/consolidation versus VTd induction/consolidation alone. These results from the CASSIOPEIA study also represent one of the longest durations of follow-up in transplant-eligible patients with newly diagnosed multiple myeloma and provide a comprehensive evaluation of minimal residual disease (MRD), both in terms of length of follow-up and depth of responses. MRD-negativity rates and sustained MRD-negativity rates for ≥12 and ≥24 months at 10^{-5} and 10^{-6} sensitivity were highest for patients who received D-VTd plus daratumumab maintenance therapy.

Implications of all the available evidence

These long-term results from the CASSIOPEIA study demonstrate that the addition of daratumumab to induction/consolidation therapy followed by daratumumab maintenance therapy led to the highest and most durable MRD-negativity rates, which translated to superior progression-free survival outcomes. Taken together, these data suggest that the best treatment outcomes for patients with transplant-eligible newly diagnosed multiple myeloma in the CASSIOPEIA study were seen with D-VTd plus daratumumab maintenance treatment. These findings add to the body of literature (including PERSEUS and GRIFFIN) supporting the use daratumumab-containing quadruplets as induction/consolidation therapy followed by daratumumab-based maintenance therapy for transplant-eligible patients with newly diagnosed multiple myeloma.

INTRODUCTION

Daratumumab is a human IgGκ monoclonal antibody targeting CD38 with direct on-tumor[1-4] and immunomodulatory[5-7] mechanisms of action. Daratumumab is approved as monotherapy and in combination with standard-of-care regimens for patients with relapsed or refractory multiple myeloma and in combination with standard-of-care regimens for transplant-eligible and transplant-ineligible patients with newly diagnosed multiple myeloma.[8,9]

CASSIOPEIA is a two-part, randomised phase 3 trial that evaluated daratumumab in combination with bortezomib, thalidomide, and dexamethasone (D-VTd) as induction therapy before and consolidation therapy after autologous stem-cell transplantation (ASCT), followed by a second randomisation to daratumumab maintenance therapy or observation alone, in transplant-eligible patients with newly diagnosed multiple myeloma.[10,11] In 2015, when the CASSIOPEIA study was designed, there were no regimens approved as maintenance therapy after ASCT in the European Union or the United States, and maintenance therapy was not recommended in the European Society of Medical Oncology clinical practice guidelines.[12] While meta-analyses published in 2012 showed improved progression-free and overall survival with thalidomide maintenance, its long-term use as maintenance therapy was limited by toxicity.[13-15] Results available by 2015 from ongoing trials with lenalidomide maintenance suggested significantly improved progression-free survival compared with placebo or observation,[16-18] but lenalidomide maintenance post transplant was not yet an approved treatment; therefore, an observation control arm represented appropriate standard of care for patients at that time. Additionally, given the deep responses demonstrated by daratumumab in the relapsed/refractory multiple myeloma setting,[19,20] daratumumab was selected as the active comparator to be included in both the

induction/consolidation and maintenance phases of the study, with the aim of inducing and prolonging deep responses to frontline therapy in transplant-eligible patients.

Previously published data from CASSIOPEIA, with a median follow-up of 18·8 months from first randomisation, demonstrated that the addition of daratumumab to bortezomib, thalidomide, and dexamethasone (VTd) induction/consolidation demonstrated superior depth of response, including higher rates of complete response or better and minimal residual disease (MRD) negativity, and significantly prolonged progression-free survival versus VTd induction/consolidation alone (hazard ratio [HR] 0·47, 95% CI 0·33–0·67, p<0·0001), as well as acceptable safety.[10] These results led to the approval of D-VTd as an induction and consolidation treatment in the United States, European Union, and other countries worldwide for transplant-eligible patients with newly diagnosed multiple myeloma.[8,9] After a median follow-up of 35·4 months from second randomisation in CASSIOPEIA, daratumumab maintenance therapy significantly improved progression-free survival (HR 0·53, 95% CI 0·42–0·68, p<0·0001) and achieved higher rates of MRD negativity compared with observation and was well tolerated.[11]

Here, we report the long-term outcomes from CASSIOPEIA after a median follow-up of 80·1 months (nearly 7 years) from first randomisation and 70·6 months (approximately 6 years) from second randomisation.

METHODS

Study design and participants

CASSIOPEIA is a two-part, open-label, randomised, phase 3 study conducted at 111 European academic and community-based research centres (appendix pp 3–6). The study design and complete eligibility criteria have been published previously.[10,11] Briefly, eligible patients were aged 18 to 65 years with newly diagnosed, documented multiple myeloma according to International Myeloma Working Group (IMWG) diagnostic criteria,[21] were candidates for high-dose therapy and ASCT, and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2. Eligible patients also had an 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 $>50 \times 10^9$ 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. Patients were excluded if they had previous systemic therapy or ASCT for any plasma cell dyscrasia, 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 neuropathic pain (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE, version 4]), or previous invasive malignancy (other than multiple myeloma) within 10 years of study start. Patients on study who completed consolidation and had achieved a partial response or better according to the IMWG response criteria[22,23] underwent a second randomisation to daratumumab maintenance or observation only for a maximum duration of 2 years.

All patients provided written, informed consent. The study protocol was approved by a local independent ethics committee or institutional review board at each study site. The 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.

Randomisation and masking

During part 1 of the study (induction/consolidation phase), patients were randomly assigned (1:1) to D-VTd or VTd as induction and consolidation therapy. Patients who completed consolidation and achieved partial response or better were re-randomised (1:1) to daratumumab maintenance or observation only in part 2 (maintenance phase). An interactive web-based system was used for both randomisations to generate treatment assignments, and randomisation was balanced using permuted blocks of four. Stratification factors for the induction/consolidation phase included site affiliation (Intergroupe Francophone du Myélome or Dutch-Belgian Cooperative Trial Group for Hematology Oncology), International Staging System disease stage (I, II, or III), and cytogenetic risk status (presence [high risk] or absence [standard risk] of del[17p] or t[4;14] cytogenetic abnormalities). Stratification factors for the maintenance phase were type of induction treatment (D-VTd vs VTd) and depth of response at the end of consolidation, as determined by MRD status and post-consolidation response. There was no masking to treatment assignments during the induction/consolidation or maintenance phases, with the exception of sponsor personnel and designees involved in the analysis who 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 for the maintenance phase.

Procedures

All patients received up to four cycles of pre-ASCT induction therapy and two cycles of post-ASCT consolidation therapy (1 cycle: 28 days) with bortezomib (1·3 mg/m^2 subcutaneously twice per week in week 1 [days 1 and 4] and week 2 [days 8 and 11] of each cycle), thalidomide (100 mg orally daily), and dexamethasone (40 mg orally or intravenously on days 1, 2, 8, 9, 15, 16, 22, and 23 of induction cycles 1 and 2 and days 1 and 2 of induction cycles 3 and 4; 20 mg on days 8, 9, 15, and 16 of induction cycles 3 and 4 and days 1, 2, 8, 9, 15, and 16 of both consolidation cycles). Patients in the D-VTd group also received daratumumab (16 mg/kg intravenously) once weekly during induction cycles 1 and 2 and once every 2 weeks during induction cycles 3 and 4 and during consolidation. In the maintenance phase, patients were randomly assigned to daratumumab (16 mg/kg intravenously) once every 8 weeks or observation for a maximum of 2 years. If a patient's study treatment was discontinued before the end of the treatment regimen, the patient was not automatically withdrawn from the study. After treatment discontinuation, patients moved into the follow-up phase. Patients were withdrawn from the study for any of the following reasons: lost to follow-up, withdrawal of consent for study participation, death, termination of the study by the sponsor, or screening failure.

Patients who were not eligible for the second randomisation into maintenance either entered the follow-up phase or discontinued the study. Patients who were randomised to maintenance entered the follow-up phase either following treatment discontinuation or disease progression, or after completion of 2 years' fixed duration of daratumumab maintenance therapy/observation. During the follow-up phase, the following data were captured: disease progression, development

of a second primary malignancy, start of subsequent anticancer therapy (including best response and disease progression on subsequent therapy), as well as overall survival. All patients who entered the follow-up phase were followed until death, lost to follow-up, withdrawal of consent, or study end, whichever occurred first.

Tumour response and disease progression were assessed by a validated computer algorithm according to IMWG response criteria.[22,23] Disease evaluations were performed by a central laboratory on day 1 of each cycle in cycles 1 to 6, day 28 of cycle 4, day 100 after ASCT, and once every 8 weeks after second randomisation. For all patients who completed or discontinued study drug without disease progression, disease evaluations continued to be performed every 12 weeks until documented disease progression. MRD was assessed using bone marrow aspirates via multiparametric flow cytometry (induction/consolidation phase) and next generation sequencing (maintenance phase; clonoSEQ assay, version 2·0; Adaptive Biotechnologies). MRD assessments were performed at the end of induction and after consolidation for all patients regardless of response; during maintenance in patients with very good partial response or better at 6, 12, and 24 months of maintenance/observation; and at 1, 2, and 3 years follow-up in patients who were MRD negative at last MRD assessment. For the results presented herein, only patients who achieved a response of complete response or better (per validated computer algorithm based on IMWG criteria[22,23]) before or at the time point of reaching MRD negativity were included in the MRD-negativity analysis.

Aside from second primary malignancies and deaths, no additional safety data were collected during this extended follow-up per the study protocol, as all patients had completed 2 years fixed

duration of maintenance/observation, discontinued study treatment, and completed the 30 days post-treatment window for adverse event reporting at the time of the previous clinical cutoff.[11]

Outcomes

The primary endpoint for the induction/consolidation phase was the proportion of patients who achieved a stringent complete response after consolidation, assessed at 100 days after ASCT; results of the primary endpoint remain unchanged from those reported previously.[10] Major secondary endpoints included the proportion of patients who achieved MRD negativity after consolidation, the proportion of patients who achieved a complete response or better after consolidation, the proportion of patients who achieved a stringent complete response after induction, progression-free survival from first randomisation, time to progression from first randomisation, progression-free survival on next line of therapy from first randomisation, and overall survival from first randomisation. The primary endpoint for the maintenance phase was progression-free survival from second randomisation.[11] Major secondary endpoints included time to progression from second randomisation, the proportion of patients who achieved complete response or better, the proportion of patients who achieved MRD negativity, progression-free survival on next line of therapy from second randomisation, and overall survival from second randomisation. Other secondary endpoints included rate of improved response during maintenance, rate of MRD negative conversion during maintenance, overall response rate, time to subsequent antimyeloma treatment, and safety. For the induction/consolidation phase, updated data on progression-free survival and overall survival from first randomisation are included in the Article. Updated data for the major primary and secondary endpoints for the maintenance

phase are also provided in this article, with the exception of time to progression. Primary and secondary efficacy endpoints are defined in the appendix (pp 7–9).

Statistical analysis

The statistical methods for CASSIOPEIA have been published previously.[10,11] The sample size of the study took into consideration the statistical power for the primary comparisons in both phases of the study. For the maintenance phase, 390 progression-free events were needed to achieve 80% power with a significance level of 0·05. Assuming an accrual of 36 months and 45 months of additional follow-up, approximately 800 patients (400 per group) were to be randomly assigned in the second randomisation (daratumumab maintenance versus observation only). Based on the assumption that 75% of patients in the induction/consolidation phase would be eligible for randomisation into the maintenance phase, 1080 patients (540 per group) were to be randomly assigned in the first randomisation (D-VTd versus VTd) to provide at least 85% power to detect an improvement in stringent complete response rate from 25% to 35% at a two-sided alpha of 0.05.

Efficacy evaluations in the induction/consolidation phase were performed on the intent-to-treat population, which included all patients who underwent first randomisation.[10] Efficacy analyses during the maintenance phase were conducted on the maintenance-specific intent-to-treat population, which comprised all patients included in the second randomisation.[11] The proportional hazard assumption for the progression-free survival from second randomisation analysis was evaluated by a log-log plot. The two parallel curves showed that the proportional hazard assumption held well for progression-free survival, as previously reported.[11] This

preplanned analysis represents the final data cutoff at the end of the study, when approximately 350 patients had died or approximately 5 years after the last patient was randomised in the second randomisation (ie, the maintenance phase), whichever came first.

Time-to-event endpoints were compared between treatment groups using a log-rank test (induction/consolidation phase) or stratified log-rank test (maintenance phase). The Kaplan–Meier method was used to estimate distributions; HRs and 95% CIs were estimated using a Cox regression model (induction/consolidation phase) or stratified Cox regression model (maintenance phase), with treatment as the sole explanatory variable. The analysis of progression-free survival and overall survival from first randomisation (for the comparison of D-VTd versus VTd) used the inverse probability weighting method[24] to adjust for the second randomisation. For time-to-event endpoints for the maintenance phase, given that daratumumab and observation were the two randomly assigned (1:1) treatments at second randomisation, these are the comparisons for which HRs, 95% CIs, and p values are provided in further breakdowns of the data by induction/consolidation treatment (D-VTd or VTd). For the primary endpoint of the maintenance phase (progression-free survival from second randomisation), patients were censored at second randomisation if there was no post-second randomisation disease assessment. For withdrawal of consent or loss to follow-up, patients were censored at the last disease assessment prior to withdrawal or loss to follow-up. Informative censoring due to start of subsequent anticancer treatment was done during a sensitivity analysis and the results supported the conclusions of the primary progression-free survival analysis. All other sensitivity analyses for progression-free survival from second randomisation also supported the conclusions of the primary progression-free survival analysis.

MRD-negativity rates were compared between treatment groups using the stratified Cochran–Mantel–Haenszel chi-square test. The Mantel–Haenszel estimate of the common odds ratio for stratified tables was used; the stratification factors were site affiliation, International Staging System disease stage, and cytogenetic risk status for the induction/consolidation phase and depth of response (as assessed by MRD status and post-consolidation response) for the maintenance phase. Sustained MRD-negativity rates were provided as post hoc results. Given that daratumumab and observation were the two randomly assigned (1:1) treatments at second randomisation, these are the comparisons for which odds ratios, 95% CIs, and p values are provided in breakdowns of the data by induction/consolidation treatment (D-VTd or VTd).

Each endpoint was tested with an overall two-sided alpha of 0·05. SAS (version 9·4) was used for all statistical analyses. 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 September 22, 2015 and August 1, 2017, 1085 patients were enrolled; 543 patients were assigned to the D-VTd group and 542 patients were assigned to the VTd group (**Figure 1**).[10] More patients in the D-VTd group than in the VTd group completed consolidation and achieved a partial response or better (458 [84·3%] of 543 patients in the D-VTd group and 428

[79·0%] of 542 patients in the VTd group) and were re-randomised between May 30, 2016 and June 18, 2018 to daratumumab maintenance (n = 442) or observation (n = 444).[11] At the time of clinical cutoff (September 1, 2023), 339 (76·7%) of 442 patients had completed daratumumab maintenance treatment and 317 (71·4%) of 444 patients had completed observation in the maintenance phase. The most common reason for discontinuation during the maintenance phase was disease progression (61 [13·8%] of 442 patients in the daratumumab group and 118 [26·6%] of 444 patients in the observation group). Baseline demographic and clinical characteristics after first randomisation and after second randomisation were well balanced and have been published previously (appendix pp 10–12).[10,11] Data on race/ethnicity were not collected.

At the time of clinical cutoff, median follow-up was 80·1 months (interquartile range [IQR], 75·7–85·6) from first randomisation. Progression-free survival from first randomisation was significantly improved in the D-VTd group versus the VTd group (HR 0·58, 95% CI 0·49–0·68, p<0·0001) after adjustment for the second randomisation using the unbiased inverse probability weighting method. Similar progression-free survival benefit was observed without adjustment for second randomisation; progression-free survival from first randomisation regardless of second randomisation was significantly improved with D-VTd compared to VTd (HR 0·61, 95% CI 0·52–0·72, p<0·0001; **Figure 2A**). Median progression-free survival was 83·7 months (95% CI 70·2–not estimable [NE]) for the D-VTd group versus 52·8 months (95% CI 47·5–58·7) for the VTd group, demonstrating a 30·9-month benefit in median progression-free survival for the D-VTd group. There were 255 progression-free survival events in the D-VTd group versus 335 events in the VTd group. Overall survival from first randomisation was significantly improved with D-VTd compared to VTd after adjustment for the second randomisation using the unbiased

inverse probability weighting method (HR 0·56, 95% CI 0·42–0·73, p<0·0001). Without adjustment for second randomisation, similar overall survival results were obtained (HR 0·55, 95% CI 0·42–0·73, p<0·0001; **Figure 2B**). Median overall survival from first randomisation regardless of second randomisation was not reached in either treatment group; estimated 72-month overall survival rates were 86·7% (95% CI 83·5–89·3) for D-VTd and 77·7% (95% CI 73·9–81·0) for VTd. A total of 83 deaths occurred in the D-VTd group versus 139 deaths in the VTd group.

At a median follow-up of 70·6 months (IQR, 66·4–76·1) from second randomisation, a progression-free survival benefit was seen in the daratumumab group versus the observation group (HR 0·49, 95% CI 0·40–0·59, p<0·0001; **Figure 3A**). Median progression-free survival was not reached (95% CI 79·9–NE) in the daratumumab group versus 45·8 months (95% CI 41·8–49·6) in the observation group; estimated 72-month progression-free survival rates were 57·1% (95% CI 52·1–61·7) and 36·5% (95% CI 31·9–41·2), respectively. There were 186 progression-free survival events in the daratumumab group and 279 events in the observation group. Prespecified subgroup analyses showed consistent progression-free survival benefit in the daratumumab group compared to the observation group (appendix pp 20–21). Progression-free survival benefit was observed in patients who received D-VTd plus daratumumab maintenance versus D-VTd plus observation (HR 0·76, 95% CI 0·58–1·00, p=0·048; **Figure 3B**). Median progression-free survival was not reached (95% CI 74·6–NE) for the D-VTd plus daratumumab group versus 72·1 months (95% CI 52·8–NE) for the D-VTd plus observation group; estimated 72-month progression-free survival rate was 60·3% (95% CI 53·5–66·4) and 50·5% (95% CI 43·8–56·9), respectively. There were 91 progression-free survival events in the D-VTd plus

daratumumab group and 114 events in the D-VTd plus observation group. Progression-free survival benefit was also observed in patients who received VTd plus daratumumab maintenance versus VTd plus observation (HR 0·34, 95% CI 0·26–0·44, p<0·0001; **Figure 3B**). Median progression-free survival was not reached (95% CI 66·9–NE) for the VTd plus daratumumab group versus 32·7 months (95% CI 27·2–38·7) for the VTd plus observation group; estimated 72-month progression-free survival rate was 53·7% (95% CI 46·3–60·6) and 20·8% (95% CI 15·2–27·0), respectively. There were 95 progression-free survival events in the VTd plus daratumumab group and 165 events in the VTd plus observation group.

Lower proportions of patients assigned to daratumumab maintenance went on to receive subsequent antimyeloma therapy (85 [37·1%] of 229 patients in the D-VTd plus daratumumab group and 75 [35·2%] of 213 patients in the VTd plus daratumumab group) compared with those assigned to observation only (100 [43·7%] of 229 patients in the D-VTd plus observation group and 159 [74·0%] of 215 patients in the VTd plus observation group) (appendix pp 13–14). Time to subsequent antimyeloma therapy from second randomisation was prolonged with D-VTd plus daratumumab versus D-VTd plus observation (HR 0·82, 95% CI 0·61–1·09, p=0·17) and with VTd plus daratumumab versus VTd plus observation (HR 0·31, 95% CI 0.24–0.41, p<0·0001; appendix p 22). Greater proportions of patients who received subsequent therapy received an anti-CD38–based first subsequent therapy in the observation arms (61 [61·0%] of 100 patients in the D-VTd plus observation group and 108 [67·9%] of 159 patients in the VTd plus observation group) compared with the daratumumab arms (32 [37·6%] of 85 patients in the D-VTd plus daratumumab group and 30 [40·0%] of 75 patients in the VTd plus daratumumab group). Of these anti-CD38–based treatments, the most common regimen was daratumumab, lenalidomide,

and dexamethasone (D-Rd) (appendix pp 13–14). Progression-free survival on next line of therapy from second randomisation was significantly improved in the daratumumab maintenance group versus the observation group (HR 0·59, 95% CI 0·45–0·79, p=0·0002; appendix pp 23). There were 40 (17·5%) progression-free survival events on next line of therapy in the D-VTd plus daratumumab group and 37 (16·2%) events in the D-VTd plus observation group; no significant difference was observed in progression-free survival on next line of therapy between the D-VTd plus daratumumab group and the D-VTd plus observation group (HR 1·01, 95% CI 0·64–1·59, p=0·97; appendix pp 24). There were 54 (25·4%) progression-free survival events on next line of therapy in the VTd plus daratumumab group and 78 (36·3%) events in the VTd plus observation group. There was significant improvement in progression-free survival on next line of therapy for VTd plus daratumumab compared to VTd plus observation (HR 0·43, 95% CI 0·30–0·62, p<0·0001; appendix p 24). Overall survival data from second randomisation were immature at the time of clinical cutoff, with only approximately 15% of the maintenance population experiencing an event; deaths had occurred in 25 (10·9%) of 229 patients in the D-VTd plus daratumumab group, 21 (9·2%) of 229 patients in the D-VTd plus observation group, 41 (19·2%) of 213 patients in the VTd plus daratumumab group, and 48 (22·3%) of 215 patients in the VTd plus observation group. The reasons for death are summarized in the appendix (p 15).

Best response rates from second randomisation are summarised in the appendix (p 25). A major secondary objective of the study was overall MRD-negativity rates in the various treatment groups. MRD-negativity rates by multiparametric flow cytometry (10^{-5} sensitivity threshold) were significantly higher in the D-VTd group versus the VTd group both post induction (50 [9·2%] of 543 patients vs 29 [5·4%] of 542 patients, odds ratio 1·79, 95% CI 1·11–2·87,

p=0·015) and post consolidation (183 [33·7%] of 543 patients vs 110 [20·3%] of 542 patients, odds ratio 2·01, 95% CI 1·52–2·66, p<0·0001; appendix p 26). During the maintenance phase of the study, MRD-negativity rates by next generation sequencing were higher with D-VTd plus daratumumab versus D-VTd plus observation at 10^{-5} (149 [65·1%] of 229 patients vs 133 [58·1%] of 229 patients, odds ratio 1·47, 95% CI 0·95–2.26, p=0·080) and 10^{-6} (133 [58·1%] of 229 patients vs 112 [48·9%] of 229 patients, odds ratio 1·56, 95% CI 1·04–2·34, p=0·031; **Figure 4**). MRD-negativity rates were also higher with VTd plus daratumumab versus VTd plus observation at 10^{-5} (114 [53·5%] of 213 patients vs 78 [36·3%] of 215 patients, odds ratio 2·33, 95% CI 1·51–3·60, p=0·0001) and 10^{-6} (93 [43·7%] of 213 patients vs 57 [26·5%] of 215 patients, odds ratio 2·44, 95% CI 1·56–3·81, p<0·0001; **Figure 4**). MRD-negativity rates at both the 10^{-5} and the 10^{-6} sensitivity thresholds were highest for patients who received D-VTd induction/consolidation plus daratumumab maintenance (**Figure 4**).

A post hoc analysis evaluated sustained MRD negativity. Sustained MRD-negativity rates lasting for ≥12 months were significantly higher with D-VTd plus daratumumab versus D-VTd plus observation at 10^{-5} (129 [56·3%] of 229 patients vs 106 [46·3%] of 229 patients, odds ratio 1·61, 95% CI 1·08–2·41, p=0·020) and 10^{-6} (109 [47·6%] of 229 patients vs 83 [36·2%] of 229 patients, odds ratio 1·68, 95% CI 1·13–2·50, p=0·0096), as were sustained MRD-negativity rates lasting for ≥24 months at 10^{-5} (114 [49·8%] of 229 patients vs 84 [36·7%] of 229 patients, odds ratio 1·82, 95% CI 1·23–2·71, p=0·0028) and 10^{-6} (94 [41·0%] of 229 patients vs 64 [27·9%] of 229 patients, odds ratio 1·87, 95% CI 1·25–2·81, p=0·0023; **Figure 5**). Sustained MRD-negativity rates lasting for ≥12 months were also significantly higher with VTd plus daratumumab versus VTd plus observation at 10^{-5} (94 [44·1%] of 213 patients vs 53 [24·7%] of

215 patients, odds ratio 2·71, 95% CI 1·73–4·23, p<0·0001) and 10^{-6} (68 [31·9%] of 213 patients vs 32 [14·9%] of 215 patients, odds ratio 2·92, 95% CI 1·77–4·82, p<0·0001), as were sustained MRD-negativity rates lasting for ≥24 months at 10^{-5} (77 [36·2%] of 213 patients vs 36 [16·7%] of 215 patients, odds ratio 3·15, 95% CI 1·94–5·12, p<0·0001) and 10^{-6} (53 [24·9%] of 213 patients vs 22 [10·2%] of 215 patients, odds ratio 3·11, 95% CI 1·78–5·44, p<0·0001; **Figure 5**). Rates of sustained MRD negativity for ≥12 months and ≥24 months at both 10^{-5} and 10^{-6} were consistently highest for patients who received D-VTd induction/consolidation plus daratumumab maintenance (**Figure 5**).

Adverse events have been reported previously.[10,11] Second primary malignancies observed during the maintenance phase occurred in 26 (11·4%) of 229 patients in the D-VTd plus daratumumab group, 14 (6·1%) of 229 patients in the D-VTd plus observation group, 26 (12·3%) of 211 patients in the VTd plus daratumumab group, and 22 (10·2%) of 215 patients in the VTd plus observation group (appendix pp 16–19).

DISCUSSION

The CASSIOPEIA study represents one of the longest durations of follow-up in transplant-eligible patients with newly diagnosed multiple myeloma.[25-33] At a median follow-up of nearly 7 years from first randomisation, D-VTd induction/consolidation significantly reduced the risk of disease progression or death by 39% compared to VTd induction/consolidation alone, regardless of second randomisation. Median progression-free survival was approximately 2·5 years longer with the addition of daratumumab to VTd (~7 years in the D-VTd group versus ~4·5 years in the VTd group). D-VTd also significantly reduced the risk of death by 45% compared to VTd,

regardless of second randomisation. Although median overall survival was not reached in either group, the overall survival rate at 72 months was higher for D-VTd (86·7%) versus VTd (77·7%). A greater proportion of patients in the D-VTd group than in the VTd group proceeded to second randomisation, further demonstrating the importance of including daratumumab in induction and consolidation. With a median follow-up of approximately 6 years from second randomisation, daratumumab maintenance significantly reduced the risk of disease progression or death by 51%, with a 20% higher 72-month progression-free survival rate compared to observation (57·1% versus 36·5%, respectively). Moreover, a progression-free survival benefit was observed for the first time in patients who received D-VTd plus daratumumab maintenance versus D-VTd plus observation and in patients who received VTd plus daratumumab maintenance versus VTd plus observation. While the addition of daratumumab maintenance therapy to VTd improved progression-free survival versus VTd and observation alone, the longest progression-free survival was observed in patients who received D-VTd plus daratumumab maintenance. Therefore, it can now be concluded that patients treated with D-VTd plus daratumumab maintenance have clinically superior progression-free survival outcomes and that daratumumab maintenance improves progression-free survival, even when taking the impact of induction/consolidation treatment into account. Complete response or better rates remained similar to previously published results, which is expected since all patients had completed active study treatment prior to the earlier clinical cutoff.[11] Patients who received D-VTd plus daratumumab maintenance consistently achieved the highest rates of MRD negativity at both 10^{-5} and 10^{-6} and the highest rates of sustained MRD negativity for ≥12 months and ≥24 months at both 10^{-5} and 10^{-6}. This demonstrates the importance of receiving daratumumab in both induction/consolidation and maintenance to induce the deepest and most durable MRD

responses, which translate to improved progression-free survival outcomes with longer follow-up. These results strengthen the existing evidence[28,29] and further demonstrate the benefit of continuing daratumumab during maintenance in transplant-eligible patients with newly diagnosed multiple myeloma. There were no preplanned statistical analyses comparing the D-VTd plus daratumumab maintenance and VTd plus daratumumab maintenance groups.

Overall survival data from second randomisation are still immature, with only approximately 15% of the maintenance population experiencing an event; however, daratumumab maintenance therapy significantly reduced the risk of disease progression or death on the next line of therapy versus observation alone. Progression-free survival event rates on next line of therapy were low in patients who received D-VTd in the induction/consolidation phase; therefore, there was no significant difference observed between the D-VTd plus daratumumab group and the D-VTd plus observation group for progression-free survival on next line of therapy. In contrast, higher progression-free survival event rates on next line of therapy were observed in patients who received VTd in the induction/consolidation phase, and there was significant improvement in progression-free survival on next line of therapy with VTd plus daratumumab versus VTd plus observation. In addition, daratumumab maintenance increased time to the start of subsequent antimyeloma treatment in the D-VTd plus daratumumab arm versus the D-VTd plus observation arm and in the VTd plus daratumumab arm versus the VTd plus observation arm. It is important to consider the subsequent antimyeloma therapy data when looking at overall survival and progression-free survival on next line of therapy outcomes, as many of the patients who did not receive daratumumab maintenance received a daratumumab-based treatment as first subsequent therapy. This is likely to influence the overall survival and progression-free survival on next line

of therapy results, especially as many of the patients in the observation groups went on to receive second-line D-Rd, which may be a more effective maintenance regimen compared with daratumumab maintenance alone. With longer follow-up and more mature overall survival data, it may be possible to explore the impact of the greater use of daratumumab-based treatments, including D-Rd, as first subsequent therapy in the observation groups versus the daratumumab maintenance groups on overall survival. Taken together, these data suggest that the best treatment outcomes for patients with transplant-eligible newly diagnosed multiple myeloma in the CASSIOPEIA study were observed with D-VTd plus daratumumab maintenance treatment, but longer-term additional survival follow-up is needed. Patients still in follow-up at the closure of CASSIOPEIA will be followed in a Registry study in order to further evaluate the impact of daratumumab maintenance on overall survival.

The occurrence of second primary malignancies has remained low and relatively consistent with approximately 6 years of follow-up. As expected, with longer follow-up, the number of patients with a second primary malignancy increased in all four treatment arms.[11]

The clinical benefits observed with D-VTd induction/consolidation followed by daratumumab maintenance therapy in this longer-term follow-up of CASSIOPEIA complement those observed in the phase 3 PERSEUS study and the phase 2 GRIFFIN study. In the primary analysis of the phase 3 PERSEUS study, with a median follow-up of almost 4 years, the addition of daratumumab to bortezomib, lenalidomide, and dexamethasone (D-VRd) induction/consolidation and the addition of daratumumab to lenalidomide maintenance therapy significantly improved progression-free survival among transplant-eligible patients with newly diagnosed multiple

myeloma.[28] D-VRd induction/consolidation and daratumumab-lenalidomide maintenance also increased rates of deep and durable responses, including MRD negativity (10^{-5} and 10^{-6}) and sustained MRD negativity for ≥12 months (10^{-5}) versus VRd induction/consolidation and lenalidomide maintenance alone. Likewise, in the final analysis of GRIFFIN, at a median follow-up of approximately 4 years, the addition of daratumumab to VRd induction/consolidation and the addition of daratumumab to lenalidomide maintenance improved progression-free survival compared to VRd induction/consolidation and lenalidomide maintenance alone in transplant-eligible patients with newly diagnosed multiple myeloma.[29] MRD-negativity rates were more than doubled in the D-VRd group versus the VRd group at both 10^{-5} and 10^{-6}, and rates of sustained MRD negativity for ≥12 months were also higher in the D-VRd group. The data reported herein for CASSIOPEIA, combined with the results from the PERSEUS and GRIFFIN studies, provide strong rationale for the use of a daratumumab-containing quadruplet regimen as induction/consolidation therapy followed by daratumumab-based maintenance as a standard of care for transplant-eligible patients with newly diagnosed multiple myeloma. While the results from PERSEUS support the use of daratumumab-lenalidomide maintenance (rather than daratumumab monotherapy maintenance), the CASSIOPEIA study demonstrated significant clinical benefit with daratumumab maintenance therapy compared to observation and that the greatest benefit was observed in patients who received daratumumab during both the induction/consolidation and maintenance phases. Results from ongoing and future phase 3 randomised trials are awaited to further clarify and define the optimal role of CD38 antibodies in induction/consolidation and maintenance therapy for the treatment of patients with newly diagnosed multiple myeloma.

Potential limitations of this study were that the study was exclusively conducted in European countries, and data on race and ethnicity were not captured. Another potential limitation of the study was the every-8-week dosing schedule for daratumumab maintenance. This dosing schedule was supported by pharmacokinetic data available at the time the CASSIOPEIA study was designed, but, based on subsequent results from the phase 2 CENTAURUS study,[34] an every-4-week dosing schedule has become the preferred schedule in ongoing studies that include daratumumab maintenance. The extent to which patients in CASSIOPEIA may have benefitted from every-4-week daratumumab dosing during the maintenance phase remains unknown. However, every-4-week daratumumab dosing maintenance has or is currently being investigated in the phase 2 GRIFFIN study[29] and phase 3 PERSEUS,[28] AURIGA (NCT03901963), and DRAMMATIC (NCT04071457) studies.

In summary, the results of this long-term follow-up of CASSIOPEA demonstrate that D-VTd induction/consolidation therapy followed by daratumumab maintenance therapy led to the highest and most durable rates of MRD negativity, which translated to superior progression-free survival outcomes. These results support D-VTd induction/consolidation plus daratumumab maintenance as a standard of care for transplant-eligible 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, LLC 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 JW 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 served on advisory boards for and received honoraria from Janssen, Bristol Myers Squibb, Amgen, Takeda, AbbVie, Sanofi, and Pfizer. CH received honoraria from Janssen, Bristol Myers Squibb, Amgen, AbbVie, and Pfizer. AP served in a consulting or advisory role for Bristol Myers Squibb, Janssen, and Pfizer; and received research funding from Bristol Myers Squibb, Sanofi, and Takeda. BA received research funding (to his institution) from Bristol Myers Squibb; received honoraria from Janssen, Bristol Myers Squibb, Sanofi, and GlaxoSmithKline; received travel funding from Janssen, Bristol Myers Squibb, and Sanofi; and served on an advisory board for Janssen, Bristol Myers Squibb, and Takeda. KB has a direct financial relationship with Janssen, Bristol Myers Squibb, Amgen, Sanofi, and Pfizer. LB has nothing to disclose. SZ has received research support from Janssen and Takeda; and served on advisory boards (no personal fees) for Janssen, Bristol Myers Squibb, Sanofi, Oncopeptides, Amgen, and Takeda. HC has nothing to disclose. DC has nothing to disclose. HA-L has nothing to disclose. MD received honoraria from and served in a consulting or advisory role for Amgen, Bristol Myers Squibb, Janssen, Sanofi, and Stemline; and received research funding from Janssen. TD has nothing to disclose. TF has nothing to disclose. CS has received consulting fees or honoraria from Takeda, Bristol Myers Squibb, Janssen, Amgen, Sanofi, and Pfizer. JF has nothing to disclose. MMohty received honoraria from Adaptive Biotechnologies, Amgen, Bristol Myers Squibb, Celgene,

Janssen, Takeda, Novartis, and Sanofi; and received research funding from Celgene, Janssen, and Sanofi. K-SJ has nothing to disclose. LK received honoraria from, served on advisory boards for, or received travel funding from AbbVie, Amgen, Janssen, Celgene/Bristol Myers Squibb, Pfizer, Sanofi, and Takeda. FK has nothing to disclose. JL has nothing to disclose. XL has nothing to disclose. MMacro has received honoraria from and served in a consulting or advisory role for Janssen, Bristol Myers Squibb/Celgene, Sanofi, and Takeda; received research funding from Janssen and Takeda; and received travel, accommodations, or expenses from Janssen and Sanofi. FO-P has served on boards for Janssen, Sanofi, and Pfizer. MR has served on an advisory board for Janssen and Pfizer; received research funding from Bristol Myers Squibb, Janssen, and Sanofi; gave lectures for Amgen, Bristol Myers Squibb, Janssen, and Takeda; and had travel, accommodations, or other expenses paid or reimbursed by Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Pfizer, Sanofi, and Takeda. JMSdC served on an advisory board and received honoraria from Janssen, Sanofi, GlaxoSmithKline, and AbbVie; and received accommodations from Pfizer and Amgen. NWCJvdD has received research support from Janssen, Amgen, Celgene, Novartis, Cellectis, and Bristol Myers Squibb; and serves on advisory boards for Janssen, Amgen, Celgene, Bristol Myers Squibb, Sanofi, Takeda, Roche, Novartis, Bayer, Adaptive, Merck, Pfizer, AbbVie, and Servier (all paid to institution). SW has nothing to disclose. AB served on advisory boards for Janssen, Sanofi, Amgen, and Bristol Myers Squibb. CT served on an advisory board for and received honoraria from Janssen. MT has nothing to disclose. J-PM has nothing to disclose. NM served on an advisory board for Janssen. M-CV received travel support from Janssen and Sanofi. MW has nothing to disclose. SKK has nothing to disclose. M-DL received travel expenses from Janssen. FO has nothing to disclose. ME-B has nothing to disclose. J-RE has nothing to disclose. RG has nothing to disclose. WH is an

employee of Cytel Inc. and is a contractor for Johnson & Johnson. JW, CdB, MR, VV, RC, and JV are employees of Janssen and hold stock in Johnson & Johnson. AT is an employee of Janssen. JC served on advisory boards for Sanofi and Bristol Myers Squibb; served as a consultant for Janssen, Sanofi, Bristol Myers Squibb, Pfizer, and Adaptive; received research support from Sanofi and Bristol Myers Squibb; and received travel support from Janssen, Sanofi, Bristol Myers Squibb, and Pfizer. PS has served on an advisory board for Amgen, Bristol Myers Squibb, Celgene, Janssen, Karyopharm, and Pfizer; and received research funding from Amgen, Bristol Myers Squibb, Celgene, Janssen, and Karyopharm.

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.

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FIGURE LEGENDS

Figure 1: Study profile

Note: "Pre–progressive disease follow-up" includes any patient who was in follow-up without progressive disease by computerised algorithm. "Post–progressive disease follow-up" includes patients who were in follow-up and had progressive disease by computerised algorithm.

*Patients may have multiple reasons for treatment discontinuation due to multiple treatments taken within each induction arm.

D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. VTd=bortezomib, thalidomide, and dexamethasone.

Figure 2: Progression-free survival and overall survival from first randomisation regardless of second randomisation

(A) The results of the Kaplan–Meier estimates of progression-free survival among patients in the intention-to-treat population. (B) The results of the Kaplan–Meier estimates of overall survival among patients in the intention-to-treat population.

D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. HR=hazard ratio. VTd=bortezomib, thalidomide, and dexamethasone.

Figure 3: Progression-free survival from second randomisation

(A) The results of the Kaplan–Meier estimates of progression-free survival from second randomisation among patients in the maintenance-specific intention-to-treat population. (B) The results of the Kaplan–Meier estimates of progression-free survival from second randomisation by induction/consolidation and maintenance therapies in the maintenance-specific intention-to-treat

population. Daratumumab and observation were the two randomly assigned (1:1) treatments at second randomisation; therefore, these are the comparisons with HRs, 95% CIs, and p values provided in the further breakdown of the data by induction/consolidation treatment (D-VTd or VTd).

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

Figure 4: MRD-negativity rates at any time during maintenance and follow-up*

The proportion of patients who achieved complete response or better and MRD negativity in the maintenance-specific intention-to-treat population. MRD was assessed using bone marrow aspirates via next generation sequencing. Daratumumab and observation were the two randomly assigned (1:1) treatments at second randomisation; therefore, these are the comparisons with p values provided in the breakdown of the data by induction/consolidation treatment (D-VTd or VTd).

DARA=daratumumab. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. MRD=minimal residual disease. OBS=observation. VTd=bortezomib, thalidomide, and dexamethasone.

*Post-consolidation after the second randomisation.

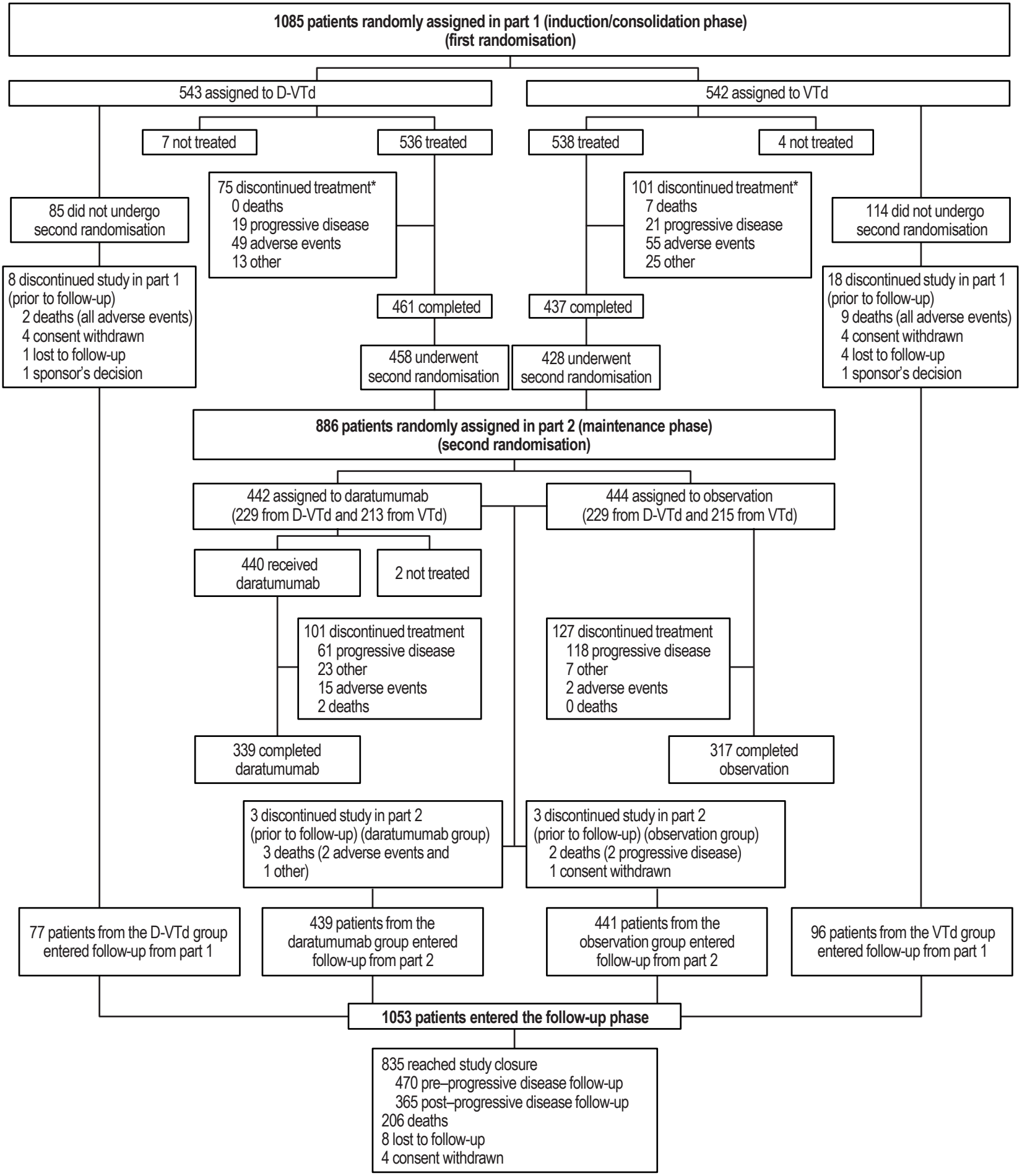
Figure 5: Sustained MRD-negativity rates at any time during maintenance and follow-up*

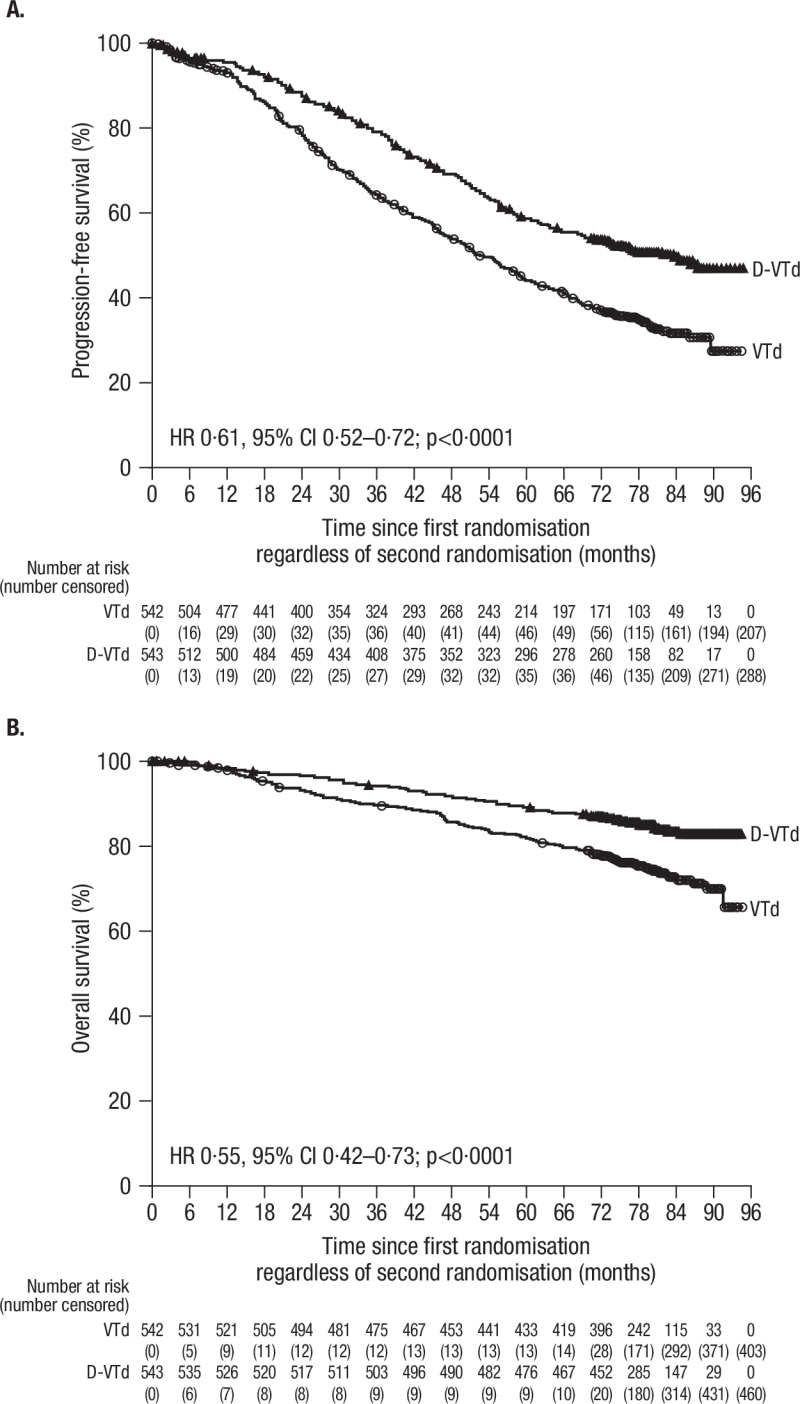
Post hoc analysis of the proportion of patients who achieved complete response or better and sustained MRD negativity for ≥12 months and ≥24 months in the maintenance-specific intention-to-treat population. MRD was assessed using bone marrow aspirates via next generation

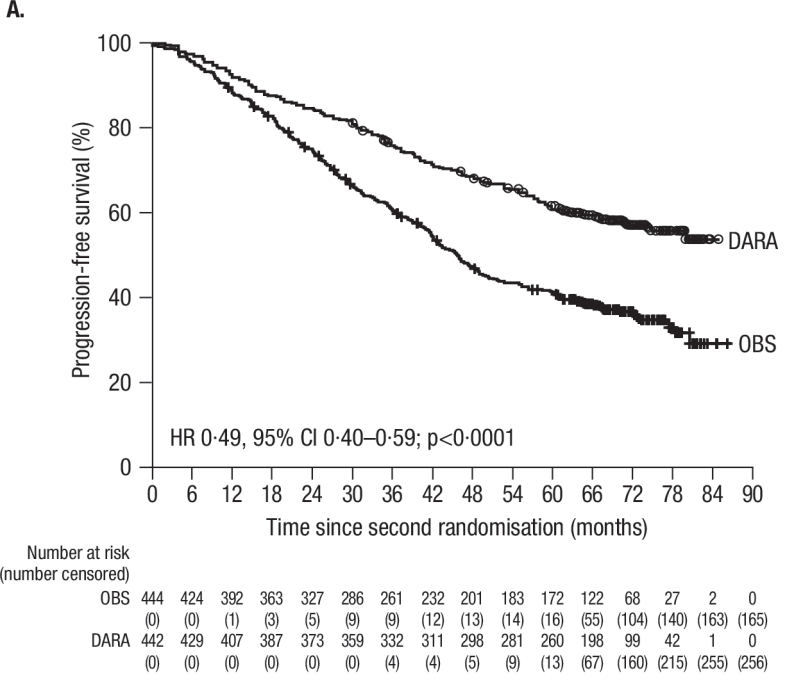
sequencing. Daratumumab and observation were the two randomly assigned (1:1) treatments at second randomisation; therefore, these are the comparisons with p values provided in the breakdown of the data by induction/consolidation treatment (D-VTd or VTd).

DARA=daratumumab. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. MRD=minimal residual disease. OBS=observation. VTd=bortezomib, thalidomide, and dexamethasone.

*Post-induction after the second randomisation.

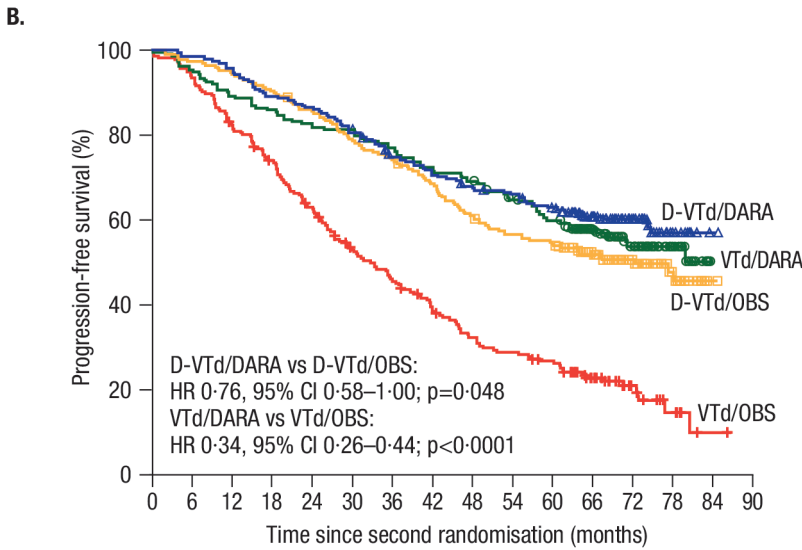

1085 patients randomly assigned in part 1 (induction/consolidation phase) (first randomisation)
543 assigned to D-VTd
542 assigned to VTd
7 not treated
536 treated
538 treated
4 not treated
75 discontinued treatment*
0 deaths
19 progressive disease
49 adverse events
13 other
101 discontinued treatment*
7 deaths
21 progressive disease
55 adverse events
25 other
85 did not undergo second randomisation
114 did not undergo second randomisation
8 discontinued study in part 1 (prior to follow-up)
2 deaths (all adverse events)
4 consent withdrawn
1 lost to follow-up
1 sponsor's decision
18 discontinued study in part 1 (prior to follow-up)
9 deaths (all adverse events)
4 consent withdrawn
4 lost to follow-up
1 sponsor's decision
461 completed
437 completed
458 underwent second randomisation
428 underwent second randomisation
886 patients randomly assigned in part 2 (maintenance phase) (second randomisation)
442 assigned to daratumumab (229 from D-VTd and 213 from VTd)
444 assigned to observation (229 from D-VTd and 215 from VTd)
440 received daratumumab
2 not treated
101 discontinued treatment
61 progressive disease
23 other
15 adverse events
2 deaths
127 discontinued treatment
118 progressive disease
7 other
2 adverse events
0 deaths
339 completed daratumumab
317 completed observation
3 discontinued study in part 2 (prior to follow-up) (daratumumab group)
3 deaths (2 adverse events and 1 other)
3 discontinued study in part 2 (prior to follow-up) (observation group)
2 deaths (2 progressive disease)
1 consent withdrawn
77 patients from the D-VTd group entered follow-up from part 1
439 patients from the daratumumab group entered follow-up from part 2
441 patients from the observation group entered follow-up from part 2
96 patients from the VTd group entered follow-up from part 1
1053 patients entered the follow-up phase
835 reached study closure
470 pre–progressive disease follow-up
365 post–progressive disease follow-up
206 deaths
8 lost to follow-up
4 consent withdrawn


A.
Progression-free survival (%)
100
80
60
40
20
0
D-VTd
VTd
HR 0·61, 95% CI 0·52–0·72; p<0·0001
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96
Time since first randomisation
regardless of second randomisation (months)
Number at risk
(number censored)
VTd 542 504 477 441 400 354 324 293 268 243 214 197 171 103 49 13 0
(0) (16) (29) (30) (32) (35) (36) (40) (41) (44) (46) (49) (56) (115) (161) (194) (207)
D-VTd 543 512 500 484 459 434 408 375 352 323 296 278 260 158 82 17 0
(0) (13) (19) (20) (22) (25) (27) (29) (32) (32) (35) (36) (46) (135) (209) (271) (288)
B.
Overall survival (%)
100
80
60
40
20
0
D-VTd
VTd
HR 0·55, 95% CI 0·42–0·73; p<0·0001
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96
Time since first randomisation
regardless of second randomisation (months)
Number at risk
(number censored)
VTd 542 531 521 505 494 481 475 467 453 441 433 419 396 242 115 33 0
(0) (5) (9) (11) (12) (12) (12) (13) (13) (13) (13) (14) (28) (171) (292) (371) (403)
D-VTd 543 535 526 520 517 511 503 496 490 482 476 467 452 285 147 29 0
(0) (6) (7) (8) (8) (8) (9) (9) (9) (9) (9) (10) (20) (180) (314) (431) (460)



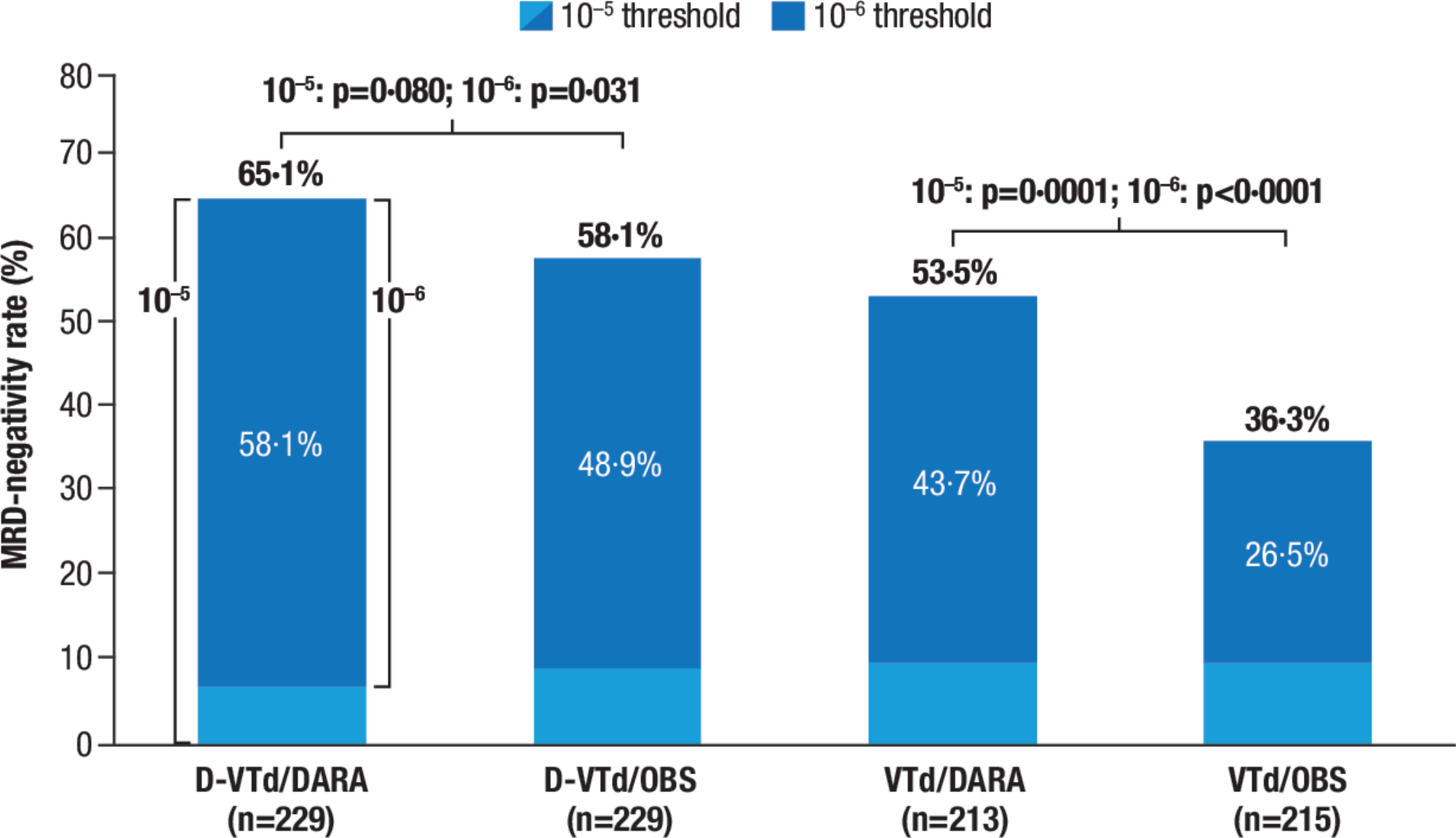
Number at risk (number censored)

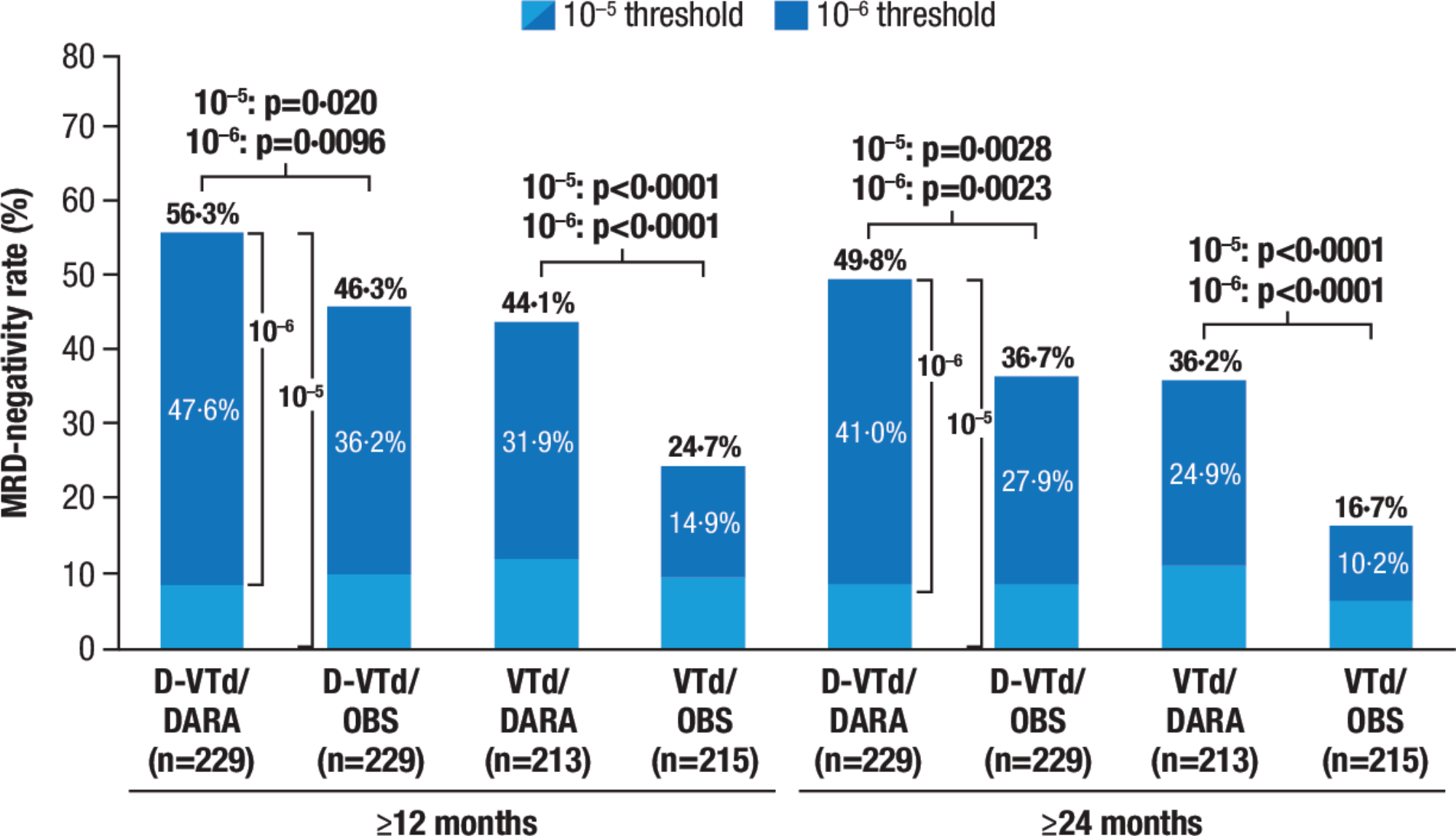
OBS	444	424	392	363	327	286	261	232	201	183	172	122	68	27	2	0
	(0)	(0)	(1)	(3)	(5)	(9)	(9)	(12)	(13)	(14)	(16)	(55)	(104)	(140)	(163)	(165)
DARA	442	429	407	387	373	359	332	311	298	281	260	198	99	42	1	0
	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(4)	(5)	(9)	(13)	(67)	(160)	(215)	(255)	(256)



Number at risk (number censored)

VTd/OBS	215	201	176	156	132	107	92	77	63	56	50	32	13	5	1	0
	(0)	(0)	(1)	(3)	(4)	(8)	(8)	(10)	(11)	(11)	(13)	(24)	(41)	(46)	(49)	(50)
VTd/DARA	213	203	190	183	175	172	164	153	147	135	123	92	48	23	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(5)	(32)	(71)	(96)	(118)	(118)
D-VTd/OBS	229	223	216	207	195	179	169	155	138	127	122	90	55	22	1	0
	(0)	(0)	(0)	(0)	(1)	(1)	(1)	(2)	(2)	(3)	(3)	(31)	(63)	(94)	(114)	(115)
D-VTd/DARA	229	226	217	204	198	187	168	158	151	146	137	106	51	19	1	0
	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(4)	(5)	(6)	(8)	(35)	(89)	(119)	(137)	(138)


10⁻⁵ threshold
10⁻⁶ threshold
MRD-negativity rate (%)
80
70
60
50
40
30
20
10
0
10⁻⁵: p=0·080; 10⁻⁶: p=0·031
65·1%
10⁻⁵
10⁻⁶
58·1%
48·9%
58·1%
10⁻⁵: p=0·0001; 10⁻⁶: p<0·0001
53·5%
43·7%
36·3%
26·5%
D-VTd/DARA (n=229)
D-VTd/OBS (n=229)
VTd/DARA (n=213)
VTd/OBS (n=215)


10⁻⁵ threshold
10⁻⁶ threshold
MRD-negativity rate (%)
80
70
60
50
40
30
20
10
0
10⁻⁵: p=0·020
10⁻⁶: p=0·0096
56·3%
47·6%
46·3%
36·2%
10⁻⁶
10⁻⁵
10⁻⁵: p<0·0001
10⁻⁶: p<0·0001
44·1%
31·9%
24·7%
14·9%
10⁻⁵: p=0·0028
10⁻⁶: p=0·0023
49·8%
41·0%
36·7%
27·9%
10⁻⁵: p<0·0001
10⁻⁶: p<0·0001
36·2%
24·9%
16·7%
10·2%
D-VTd/ DARA (n=229)
D-VTd/ OBS (n=229)
VTd/ DARA (n=213)
VTd/ OBS (n=215)
D-VTd/ DARA (n=229)
D-VTd/ OBS (n=229)
VTd/ DARA (n=213)
VTd/ OBS (n=215)
≥12 months
≥24 months