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Collaborators

The following investigators participated in the CASSIOPEIA study:

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Netherlands: A Beeker, Rinske Boersma, G M J Bos, M Brands-Nijenhuis, Annemiek Broijl, C W Choi, J L L M Coenen, Sandra Croockewit, A M De Kreuk, E De Waal, Jolanda Droogendijk, Kon-Siong Jie, M J Kersten, Saskia K Klein, Mark-David Levin, M B L Leys, C M P W Mandigers, M C Minnema, M R Schaafsma, C G Schaar, Claire Siemes, Matthijs Herman Silbermann, H A M Sinnige, S U Soechit, Pieter Sonneveld, W Terpstra, L W Tick, Niels W C J van de Donk, E Van Der Spek, Gerjo Augustien Velders, P A Von Dem Borne, P F Ypma, Sonja Zweegman, O Weerdt, Matthijs Westerman

Supplementary Methods

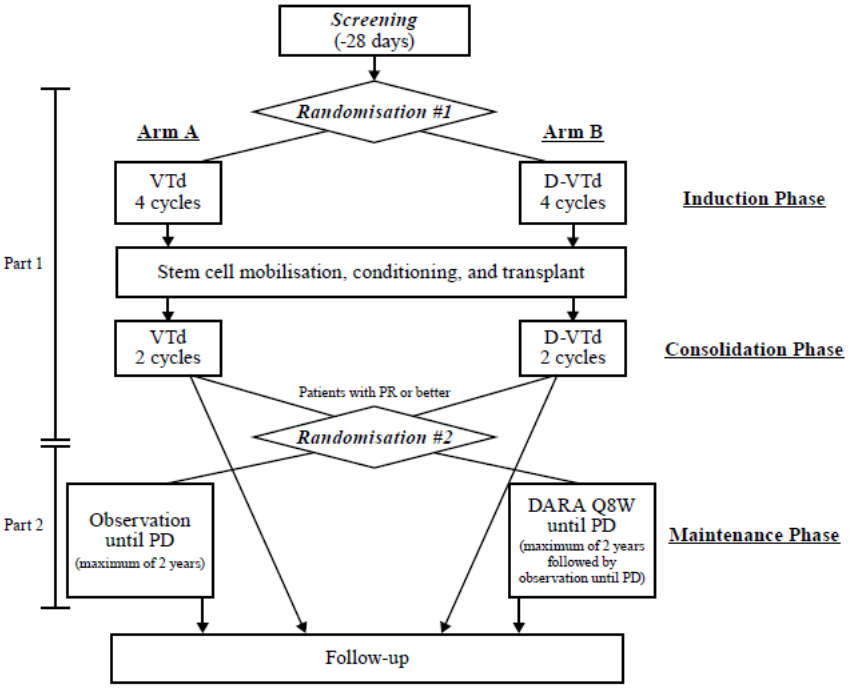
Table S1: **Participating sites, investigators, and number of patients enrolled**

Site Name	Principal Investigator	Patients enrolled (n)
Bordeaux University Hospital Center, Bordeaux, France	Hulin, Cyrille	34
University Hospital Hôtel-Dieu, Nantes, France	Moreau, Philippe	31
Nancy University Hospital, Nancy, France	Feugier, Pierre	30
Dijon University Hospital, Hôpital du Bocage, Dijon, France	Caillot, Denis	29
Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France	Perrot, Aurore	29
Poitiers University Hospital, CHU la Milétrie, Poitiers, France	Leleu, Xavier	26
Institut Paoli Calmettes, Marseille, France	Stoppa, Anne-Marie	25
Saint-Antoine Hospital, Sorbonne University, Paris, France	Mohty, Mohamad	25
Hôpital Claude Huriez, Lille, France	Facon, Thierry	23
Caen University Hospital, Caen, France	Macro, Margaret	21
Hôpital Saint Louis, APHP, Paris, France	Arnulf, Bertrand	21
CHU Henri Mondor, Créteil, France	Belhadj-Merzoug, Karim	20
Lyon University Hospital, Hematology Centre Hospitalier Lyon-Sud, Pierre – Bénite, France	Karlin, Lionel	19
Institut Curie Paris, Paris, France	Kuhnowski, Frederique	16
Tours University Hospital, Hôpital de Bretonneau, Tours, France	Benboubker, Lotfi	16
Centre Hospitalier Annecy Genevois, Pringy, France	Orsini-Piocelle, Frederique	15
University Hospital, Hôpital Hautepierre, Strasbourg, France	Fohrer-Sonntag, Cecile	15
Amiens University Hospital, Amiens, France	Marolleau, Jean-Pierre	14
Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands	Van De Donk, Niels	14
CHU Limoges, Limoges, France	Jaccard, Arnaud	14
Brest University Hospital, Hôpital A Morvan, Brest, France	Eveillard, Jean-Richard	13
Centre Henri Becquerel and Normandie Univ UNIROUEN Rouen France	Lenain, Pascal	13
University Hospital Ghent, Ghent, Belgium	Offner, Fritz	13
University Hospital Jean Minjoz, Besancon, France	Fontan, Jean	13
CHU Montpellier, Montpellier, France	Vincent, Laure	12
Centre Hospitalier Départemental de Vendée, La Roche sur Yon, France	Tiab, Mourad	11
Zuyderland MC, Sittard, Netherlands	Jie, G.K.S.	11
CH de Mulhouse, Hôpital Emile Muller, Mulhouse, France	Eisenmann, Jean-Claude	10
Erasmus MC Cancer Institute, Rotterdam, Netherlands	Sonneveld, Pieter	10
Rennes University Hospital, Hôpital de Pontchaillou, Rennes, France	Escoffre-Barbe, Martine	10
Centre Hospitalier Versailles, Le Chesnay, France	Rigaudeau, Sophie	9
CHU Lille, Lille, France	Bourgeois, Emmanuelle	9
Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium	Meuleman, Nathalie	9
University Teaching Hospital, Nîmes, France	Jourdan, Eric	9
Centre Hospitalier Universitaire de Reims, Reims, France	Kolb, Brigitte	8
La Pitié, Paris, France.	Morel, Veronique	8
Hôpital du Scorff, Lorient, France	Luycx, Odile	8
Polyclinique Bordeaux Nord, Bordeaux, France	Fitoussi, Olivier	8

Cliniques Universitaires Saint-Luc, Brussels, Belgium	Vekemans, Marie-Christiane	8
University Hospital Leuven, Leuven, Belgium	Delforge, Michel	8
Albert Schweitzer Ziekenhuis, Dordrecht, Netherlands	Levin, M.D.	7
Centre Hospitalier Yves le Foll, Saint-Brieuc, France	Allangba, Olivier	7
CHU de d'Estaing, Clermont-Ferrand, France	Chaleteix, Carine	7
Hôpital Necker-Enfants Malades, Paris, France	Frenzel, Laurent	7
University Hospital, Amiens, France	Vaida, Iona	7
Bretagne Atlantique Hospital, Vannes, France	Godmer, Pascal	6
Centre Hospitalier du Mans, Le Mans, France	Laribi, Kamel	6
Centre Jean Bernard Clinique Victor Hugo, Le Mans, France	Voog, Eric	6
Centre Leon Berard, Lyon, France	Rey, Philippe	6
CH William Morey, Chalon sur Saône, France	Voillat, Laurent	6
CHU Grenoble, Grenoble, France	Mariette, Clara	6
Strasbourg University Hospitals, Strasbourg, France	Maloisel, Frederic	6
Université Catholique de Louvain Mont-Godinne, Yvoir, Belgium	Doyen, Chantal	6
University Medical Center Groningen, Groningen, Netherlands	Choi, C.W.	6
University Medical Center, Utrecht, Netherlands	Minnema, M.C.	6
AZ Sint-Jan Brugge, Brugge, Belgium	Van Droogenbroeck, Jan	5
Centre Hospitalier de la Côte Basque, Bayonne, France	Araujo, Carla	5
Centre Hospitalier de Meaux, Meaux, France	Abarah, Wajed	5
Centre Hospitalier Sud Francilien, Corbeil-Essonnes, France	Joly, Bertrand	5
Centre Hospitalier Universitaire d'Angers, Angers, France	Dib, Mamoun	5
L'Institut de Cancérologie Catherine de Sienne and Hôpital privé du Confluent, Nantes, France	Sadot Lebouvier	5
Northwest Clinics, Alkmaar, Netherlands	Westerman, M.	5
Centre Hospitalier Jolimont-Lobbes, Lobbes, Belgium	Kentos, Alain	4
Centre Hospitalier Universitaire de Liège, Liège, Belgium	De Prijck, Bernard	4
Clinique du Parc, Castelnau-le-Lez, France	Exbrayat, Carole	4
Hôpital de Mercy, Ars-Laquenexy, France	Dorvaux, Veronique	4
Hôpital Henri Duffaut, Avignon, France	Slama, Borhane	4
Hospital Center Du Forez Site De Montbrison, Montbrison, France	Soglu, Gilbert	4
Hospital La Source, Orléans, France	Benbrahim, Omar	4
Meander Medical Centre, Amersfoort, Netherlands	Klein, S.K.	4
St. Antonius Nieuwegein, Nieuwegein, and St. Antonius Utrecht, Utrecht, Netherlands	Weerdt, Okke	4
Ziekenhuis Netwerk Antwerpen Middelheim, Antwerpen, Belgium	Wu, K.L.	4
AZ Turnhout, Turnhout, Belgium	Vrelust, Inge	3
Centre Hospitalier Chambéry, Chambery, France	Hacini, Maya	3
Centre Hospitalier de Cornouaille, Quimper, France	Le Calloch, Ronan	3
CHU de Nice - Hôpital de l'Archet, Nice, France	Richez, Valentine	3
Dunkirk Hospital Center, Dunkerque, France	Pignon, Jean Michel	3
Gelderland Valley Hospital, Ede, Netherlands	Velders, Gerjo Augustien	3
Hôpital Cochin (Hôpitaux Universitaires Paris Centre), Paris, France	Bouscary, Didier	3
Hôpital d'Instruction des Armées de Percy, Clarmart, France	Malfuson, Jean-Valere	3
Hôpital Privé Sévigné, Cesson-Sévigné, France	Bareau, Benoit	3

Hospital Center of Perpignan, Perpignan, France	Sanhes, Laurence	3
Hospital Group Du Havre, Montivilliers, France	Zarnitsky, Charles	3
Leiden Univerity Medical Center, Leiden, Netherlands	Von Dem Borne, P.A.	3
Medisch Centrum Leeuwarden, Leeuwarden, Netherlands	De Waal, Esther	3
Saint-Quentin Hospital Center, Saint Quentin, France	Garidi, Reda	3
Universitair Ziekenhuis Brussel, Brussel, Belgium	Fostier, Karel	3
AMC, Amsterdam, Netherlands	Kersten, M.J.	2
Blois Hospital, Blois, France	El Yamani, Abderrazak	2
Centre Hospitalier Simone Veil, Eaubonne, France	Chaoui, Driss	2
Erasmus University Medical Center, Rotterdam, Netherlands	Siemes, C.	2
Haga Hospital, Den Haag, Netherlands	Ypma, P.F.	2
Hospital Center De Périgueux, Périgueux, France	Rodon, Philippe	2
Maxima Medical Center, Eindhove, Netherlands	Tick, Lidwine Winnifred	2
MST, Enshede, Netherlands	Van Rooijen, Cleo	2
Rijnstate, Arnhem, Netherlands	Van Der Spek, Ellen	2
St. Elisabeth Hospital, Tilburg, Netherlands	Droogendijk, Jolanda	2
Isala Klinieken, Zwolle, Netherlands	Kneppers, Evelien	1
Amphia Hospital Breda, Breda, Netherlands	Boersma, Rinske	1
AZ Delta, Roeselare, Belgium	Deeren, Dries	1
Centre Hospitalier de Bourg-en-Bresse, Bourg-en-Bresse, France	Orfeuvre, Hubert	1
Grand Hôpital de Charleroi- site Notre Dame, Charleroi, Belgium	Mineur, Philippe	1
Hôpital Avicenne, Bobigny, France	Brechignac, Sabine	1
Les Hôpitaux de Chartres - Centre Hospitalier CH, Le Coudray, France	Kone, Moumimi	1
Maasstad Hospital, Rotterdam, Netherlands	Leys, M.B.L.	1
Maastricht University Mecdical School, Maastricht, Netherlands	Bos, Gerard	1
Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands	Terpstra, Wim	1
Radboud University Medical Center, Nijmegen, Netherlands	Croockewit, Sandra	1
Tergooi, Hilversum, Netherlands	Silbermann, Matthijs	1
Reinier de Graaf Gasthuis, Delft, Netherlands	Soechit, S.U.	0
Spaarne Hospital Hoofddorp, Hoofddorp, Netherlands	Beeker, Aart	0

Figure S1: **Trial design**



DARA=daratumumab. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. PD=disease progression. PR=partial response. Q8W=every 8 weeks. VTd=bortezomib, thalidomide, and dexamethasone.

Part 1 stratification factors

For Part 1, stratification factors were:

- Study site affiliation (Intergroupe Francophone du Myélome or the Dutch-Belgian Cooperative Trial Group for Hematology Oncology)
- International Staging System disease stage (I, II, III)
- Presence or absence of del17p or t(4;14) cytogenetic abnormalities

Table S2: **International Myeloma Working Group uniform response criteria[6]**

Response	Definition

sCR	• CR as defined below, plus
	  ○ Normal free light chain ratio, and
	  ○ Absence of clonal plasma cells by immunohistochemistry, immunofluorescence*, or two- to four-colour flow cytometry

CR†	• Negative immunofixation of serum and urine, and • Disappearance of any soft tissue plasmacytomas, and • <5% plasma cells in bone marrow
VGPR‡	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, or • ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
PR	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours • If the serum and urine M-protein are not measurable, a decrease of ≥50% in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable and serum-free light chain assay is also not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% • In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD	• Not meeting criteria for CR, VGPR, PR, or PD

PD	• Increase of 25% from lowest response value in any one of the following
	  ○ Serum M-component (absolute increase must be ≥0·5 g/dL),
	  ○ Urine M-component (absolute increase must be ≥200 mg/24 hours),
	  ○ Only in patients without measurable serum and urine M-protein levels: The difference between involved and uninvolved free light chain levels (absolute increase must be >10 mg/dL)
	  ○ Only in patients without measurable serum and urine M-protein levels and without measurable disease by free light chain levels: Bone marrow plasma cell percentage (absolute percentage must be >10%)
	  ○ Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
	  ○ Development of hypercalcaemia (corrected serum calcium >11·5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

All response categories (sCR, CR, VGPR, PR, and PD) require two consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of ≥1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL. *Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is a kappa/lambda ratio of >4:1 or <1:2. †Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum-free light chain levels: CR in such patients indicates a normal free light chain ratio of 0·26–1·65 in addition to the CR criteria listed above. VGPR in such patients requires a >90% decrease in the difference between involved and uninvolved free light chain levels. ‡Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M-protein and by free light chain levels; "25% increase" refers to M-protein, free light chain, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcaemia, and the "lowest response value" does not need to be a confirmed value. CR=complete response. IMWG=International Myeloma Working Group. PD=disease progression. PR=partial response. sCR=stringent complete response. SD=stable disease. VGPR=very good partial response.

Pre- and post-infusion medications
In Part 2 of CASSIOPEIA, pre-infusion medications were administered to patients who received daratumumab with the intent to prevent or manage infusion reactions. Intravenous or oral paracetamol (650–1000 mg), an antihistamine (H1-receptor agonist, according to institutional standards), and montelukast (10 mg, required on week 1 infusion for patients treated with bortezomib, thalidomide, and dexamethasone in Part 1 and optional before all other daratumumab infusions) were given up to 3 hours prior to daratumumab infusion. On daratumumab infusion days, oral or intravenous dexamethasone was administered as a study treatment 1 hour before the daratumumab infusion at a dose of 40 mg during cycles 1 and 2 and on day 1 of cycles 3 and 4, and at a dose of 20 mg on subsequent dosing days during cycles 3 and 4, and during both consolidation cycles.

Patients with mild asthma, mild chronic obstructive pulmonary disease, or a higher risk of respiratory complications (eg, patients with a forced expiratory volume in 1 second of <80%) could receive post-infusion medications, including an antihistamine, a short-acting ß2 adrenergic receptor agonist (such as salbutamol), and control medications for lung disease (eg, inhaled corticosteroids ± long-acting ß2 adrenergic receptor agonists for patients with asthma, or long-acting bronchodilators [such as tiotropium or salmeterol] ± inhaled corticosteroids for patients with chronic obstructive pulmonary disease).

Definition of efficacy endpoints
Time to progression from second randomisation was defined as the duration from the date of second randomisation to confirmed PD, according to a validated computer algorithm (described previously[1-3]) based on the IMWG response criteria, [4-5] or death due to PD, whichever occurred first. Deaths due to causes other than PD were censored at the last disease assessment before death.

The rate of overall complete response or better was defined as the proportion of patients in the maintenance-specific intent-to-treat population (mITT) who achieved CR or better from post consolidation onward per a validated computer algorithm (described previously[1-3]) based on the IMWG criteria. [4-5] A CR or better response must be achieved on or prior to the start of subsequent therapies.

Minimal residual disease (MRD) negativity in the maintenance phase was assessed primarily using the next-generation sequencing (NGS) assay at a sensitivity level of 10^{-5} and was additionally assessed by standardised multiparametric flow cytometry based on the recommendations of the Euroflow Consortium.[6] Overall MRD-negativity rate was primarily defined as the proportion of patients who achieved MRD negativity[2] at a threshold of 10^{-5} by NGS from post consolidation onward. MRD negativity also had to be achieved prior to or at the time of initiation of subsequent therapies. For analysis purposes, patients in the mITT population without an MRD assessment were considered to be MRD positive. Only patients who achieved a response of CR or better (per a validated computer algorithm [described previously[1-3]] based on the IMWG criteria[4-5]) before or at the time point of reaching MRD negativity were included in the primary count for MRD negativity.

PFS on next line of therapy from second randomisation (PFS2) was defined as

- The time from second randomisation to second progression or death, whichever came first; the second disease progression was based on investigator judgement
- Any deaths after start of next line of therapy were considered PFS2 events
- Patients who started next line of therapy and were alive and with no disease progression were censored at the last disease assessment
- Patients without any post–second randomisation follow-up were censored at the date of second randomisation
- Otherwise, patients were censored at the minimum of last disease assessment and last date of follow-up

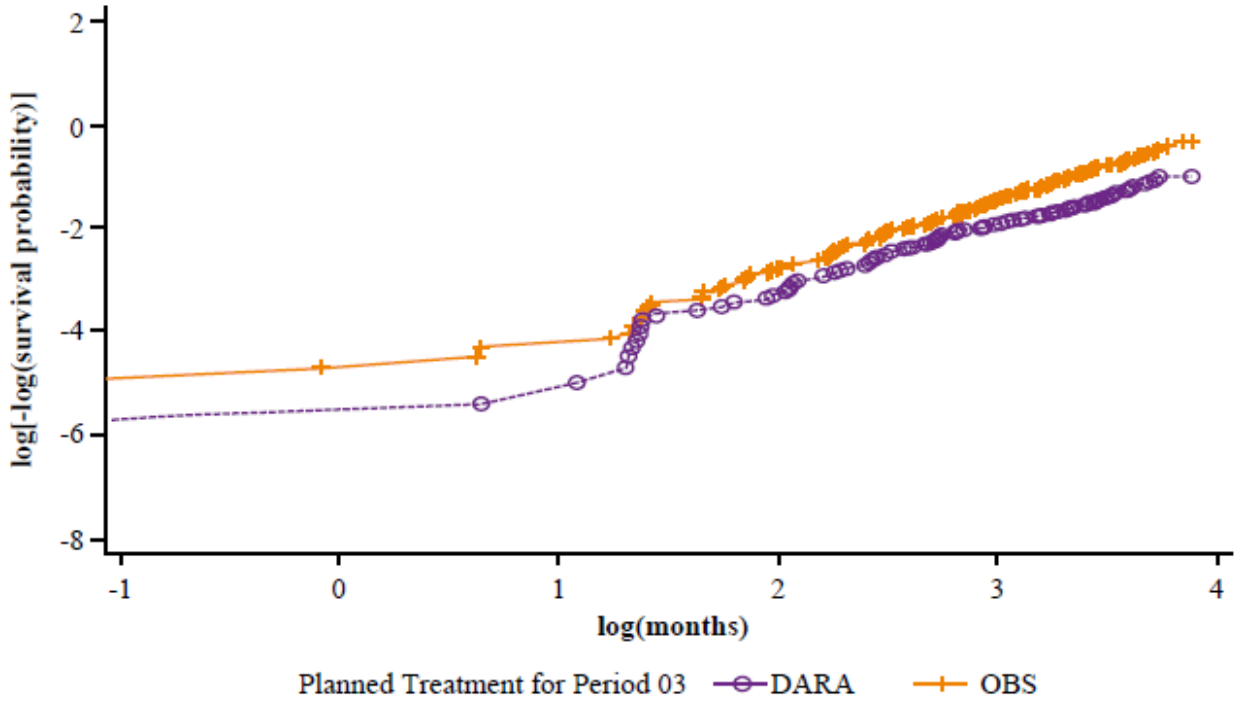
Overall survival from second randomisation was measured from the date of second randomisation to the date of death due to any cause. Patients who were lost to follow-up were censored at the time of loss to follow-up. Patients who were still alive at the clinical cutoff date were censored at the last known alive date, which was determined by the maximum collection/assessment date among the selected data domains within the clinical database.

Rate of improved response during maintenance was defined as the proportion of patients who achieved a better category of response per a validated computer algorithm (described previously[1-3]) based on the IMWG criteria[4-5]

during maintenance compared with the response status at the end of consolidation (up to the second randomisation). Improved response had to be achieved on or prior to the start of subsequent therapies.

The rate of MRD-negativity conversion was defined as the proportion of patients who achieved de novo MRD negativity[7] at a threshold of 10^{-5} by NGS (including achievement of CR or better) during maintenance among those with a post-consolidation response of worse than CR and an MRD-positive measurement at day 100 post ASCT. Patients with missing MRD measurements at day 100 post ASCT were not included.

Figure S2: **Log-log plots used to evaluate the proportional hazards assumption**



Supplementary Results

Table S3: **Summary of reasons for not being re-randomised to maintenance in the intent-to-treat population**

	D-VTd	VTd	Total
Total not re-randomised, n/N (%)	**85/543 (15·7)**	**114/542 (21·0)**	**199/1085 (18·3)**
Reason, n (%)			
Unacceptable/serious adverse event	41 (7·6)	47 (8·7)	88 (8·1)
PD during induction/ASCT/consolidation	22 (4·1)	23 (4·2)	45 (4·1)
Response ≤SD post consolidation	17 (3·1)	26 (4·8)	43 (4·0)
Withdrawal of consent or participant decision	2 (0·4)	8 (1·5)	10 (0·9)
Investigator/sponsor decision	3 (0·6)	6 (1·1)	9 (0·8)
Death during induction/ASCT/consolidation	0	1 (0·2)	1 (0·1)
Other	0	3 (0·6)	3 (0·3)

≤SD=stable disease or worse. ASCT=autologous stem-cell transplant. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. PD=disease progression. VTd=bortezomib, thalidomide, and dexamethasone.

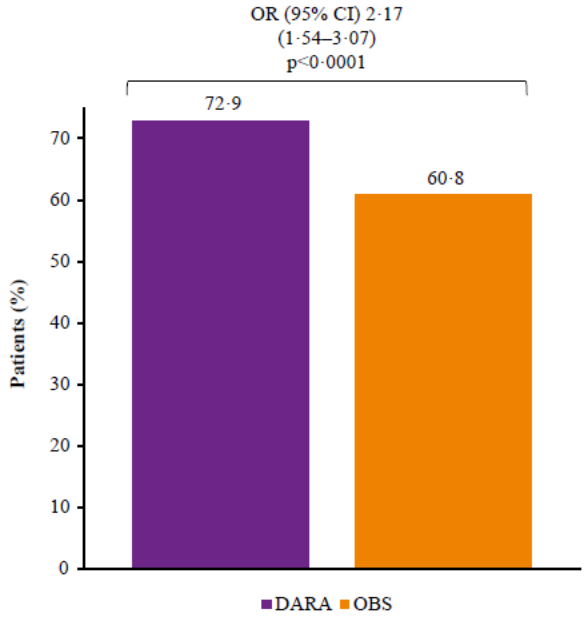
Table S4: **Rates of pre-maintenance response and minimal residual disease negativity for DARA versus OBS in the maintenance-specific intent-to-treat population**

Response, n (%)	**DARA** **n=442**	**OBS** **n=444**	**Total** **N=886**
≥CR	179 (40.5)	154 (34.7)	333 (37.6)
MRD negative and ≥CR	93 (21.0)	92 (20.7)	185 (20.9)

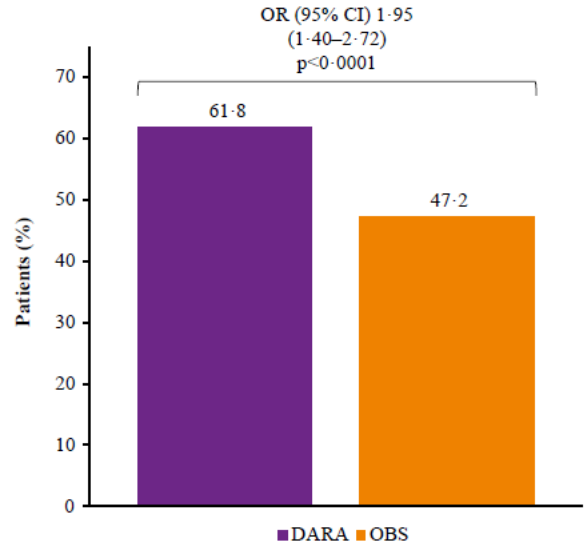
≥CR=complete response or better. DARA=daratumumab. MRD=minimal residual disease. OBS=observation.

Figure S3: **Response and minimal residual disease negativity from second randomisation in the maintenance-specific intent-to-treat population**

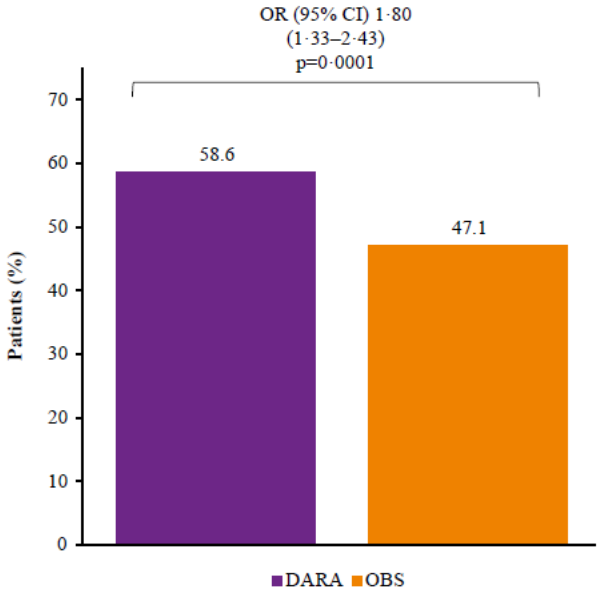
A. Rates of complete response or better



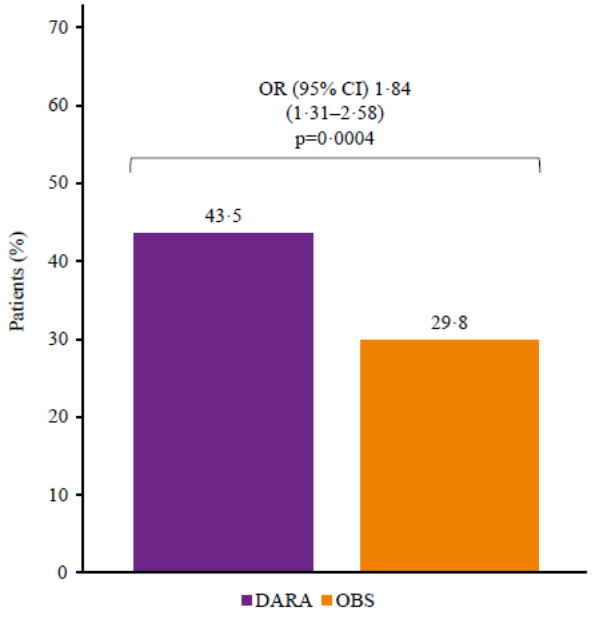
B. Rates of improved response



C. Rates of minimal residual disease negativity by next-generation sequencing at a threshold of 10^{-5} and complete response or better



D. Rates of conversion to minimal residual disease negativity by next-generation sequencing at a threshold of 10^{-5} and complete response or better



CI=confidence interval. DARA=daratumumab. OBS=observation. OR=odds ratio.

Table S5: **Rates of minimal residual disease negativity and complete response or better for DARA versus OBS in the maintenance-specific intent-to-treat population**

	Patients with MRD negativity and ≥CR, n (%)		
Assessment modality and threshold	**DARA N=442**	**OBS N=444**	**Odds ratio (95% CI) p value**
10^{-5} by NGS	259 (58·6)	209 (47·1)	1·80 (1·33–2·43) 0·0001
10^{-6} by NGS	219 (49·5)	163 (36·7)	1·89 (1·40–2·55) <0·0001
10^{-5} by MFC	292 (66·1)	245 (55·2)	1·86 (1·35–2·58) 0·0001

≥CR=complete response or better. CI=confidence interval. DARA=daratumumab. MFC=multiparametric flow cytometry. MRD=minimal residual disease. NGS=next-generation sequencing. OBS=observation.

Table S6: **Overall response rate for DARA versus OBS in the maintenance-specific intent-to-treat population**

Response category, n (%)	**DARA N=442**	**OBS N=444**
≥ PR	440 (99·5)	441 (99·3)
Stable disease	1 (0·2)	2 (0·5)
Progressive disease	1 (0·2)	1 (0·2)

≥PR=partial response or better. DARA=daratumumab. OBS=observation.

Subsequent anti-myeloma treatments
Among patients who received VTd as induction/consolidation, 35 (16·4%) of 213 in the DARA group and 88 (40·9%) of 215 in the OBS group received at least one subsequent anti-myeloma treatment. An anti-CD38 agent was used as subsequent treatment in 8 (22·9%) of 35 patients in the DARA group and 63 (71·6%) of 88 patients in the OBS group and was the first subsequent line of therapy in 1 (12·5%) of 8 patients in the DARA group and 41 (65·1%) of 63 patients in the OBS group.

Among patients who received D-VTd as induction/consolidation, 44 (19·2%) of 229 in the DARA group and 42 (18·3%) of 229 in the OBS group received at least one subsequent anti-myeloma treatment. An anti-CD38 agent was used as subsequent treatment in 5 (11·4%) of 44 patients in the DARA group and 20 (47·6%) of 42 patients in the OBS group and was the first subsequent line of therapy in 5 (100%) of 5 patients in the DARA group and 12 (60·0%) of 20 patients in the OBS group.

PFS2
Median PFS2 was immature but numerically favoured DARA over OBS (HR 0·62, 95% CI, 0·40–0·96).

When patients were analysed by maintenance and induction/consolidation therapies, a higher number of PFS2 events occurred in the D-VTd/OBS group than the D-VTd DARA group, yet without reaching statistical significance (17 *vs* 11, HR 0·66, 95% CI 0·31–1·41), and in the VTd/OBS group than in the VTd/DARA group (31 *vs* 25, HR 0·59, 95% CI, 0·35–1·02).

Among patients who were not randomised to Part 2, PFS2 from first randomisation was immature (appendix p 31).

Table S7: **All causes of death in CASSIOPEIA Part 2**

	DARA	OBS
Cause of death, n (%)		
Progressive disease	13 (44.8)	22 (81.5)
Acute pancreatitis	0	1 (3.7)
Acute respiratory distress syndrome	1 (3.4)	0
Anaplastic thyroid cancer	1 (3.4)	0
Awaiting death report	1 (3.4)	0
Cardiac and respiratory failure	1 (3.4)	0
Cardiac arrest	1 (3.4)	0
Cardio-respiratory arrest	1 (3.4)	0
Cerebral ischemic accident	1 (3.4)	0
Heart failure	1 (3.4)	0
Left basal pneumonia	0	1 (3.7)
Lung adenocarcinoma	0	1 (3.7)
NK cell lymphoma*	1 (3.4)	0
Peritonitis	0	1 (3.7)
Pneumococcal sepsis	0	1 (3.7)
Pneumonia and pneumosepsis	1 (3.4)	0
Pulmonary carcinoma	1 (3.4)	0
Respiratory distress	1 (3.4)	0
Septic shock*	1 (3.4)	0
Severe sepsis	1 (3.4)	0
Squamous cell carcinoma of the tongue	1 (3.4)	0
Suicide	1 (3.4)	0

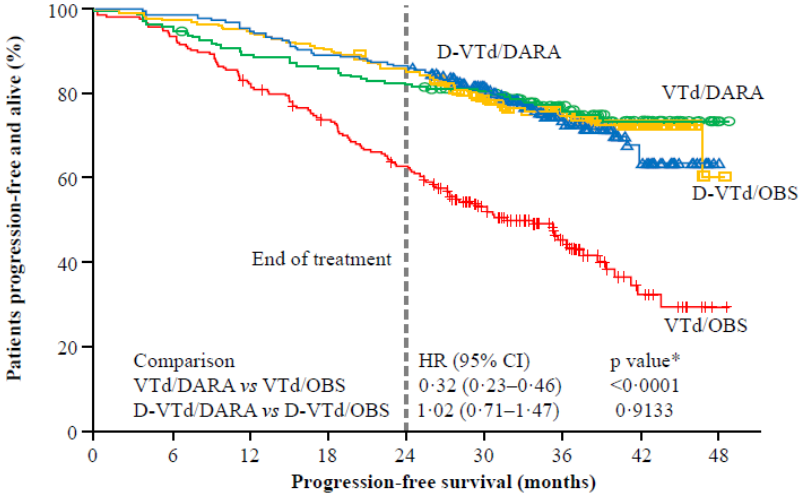
*fatal treatment-emergent adverse event occurring on treatment or within 30 days of last dose
DARA=daratumumab; OBS=observation.

Table S8: **Pre-maintenance baseline* demographics and disease characteristics by prior induction/consolidation therapy in the maintenance-specific intent-to-treat population**

	D-VTd		VTd	
	DARA (N=229)	**OBS (N=229)**	**DARA (N=213)**	**OBS (N=215)**
Median (range) age, years	59 (35–66)	60 (36–66)	59 (27–66)	58 (37–66)
Male sex, n (%)	135 (59·0)	133 (58·1)	126 (59·2)	121 (56·3)
Baseline ECOG performance status, n (%)				
0	136 (59·4)	136 (59·4)	116 (54·5)	124 (57·7)
1	86 (37·6)	90 (39·3)	88 (41·3)	82 (38·1)
≥2	7 (3·1)	3 (1·3)	9 (4·2)	9 (4·2)
ISS staging,† n (%)				
I	96 (41·9)	83 (36·2)	93 (43·7)	88 (40·9)
II	96 (41·9)	118 (51·5)	85 (39·9)	96 (44·7)
III	37 (16·2)	28 (12·2)	35 (16·4)	31 (14·4)
Cytogenetic profile,† n/N (%)				
Standard risk	197/228 (86·4)	196/229 (85·6)	186/212 (87·7)	178/215 (82·8)
High risk	31/228 (13·6)	33/229 (14·4)	26/212 (12·3)	37/215 (17·2)
Stratification factors, n (%)				
MRD negative (10^{-4} by MFC) and ≥VGPR‡	192 (83·8)	192 (83·8)	145 (68·1)	145 (67·4)
MRD positive (10^{-4} by MFC) and ≥VGPR‡	20 (8·7)	20 (8·7)	48 (22·5)	49 (22·8)
MRD positive (10^{-4} by MFC) and PR‡§	17 (7·4)	17 (7·4)	20 (9·4)	21 (9·8)

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

Figure S4: **Progression-free survival from second randomisation by induction/consolidation and maintenance therapies in the maintenance-specific intent-to-treat population**



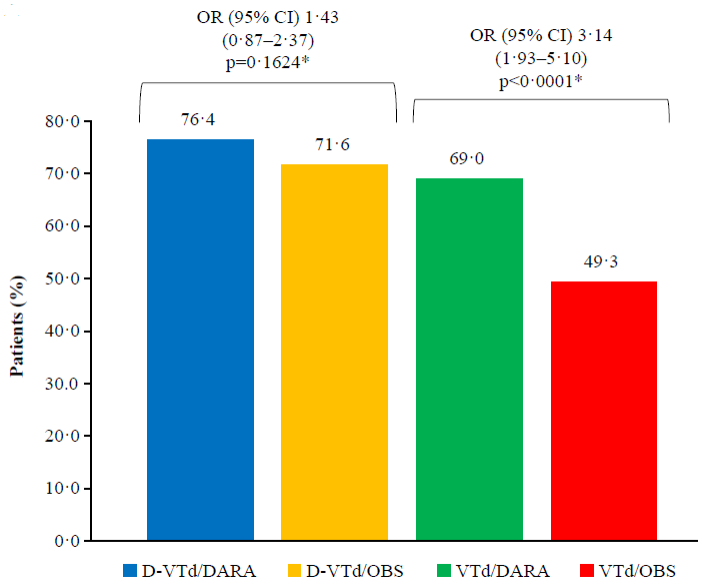
Patients at risk (censored)

VTd/OBS	215 (0)	201 (0)	176 (1)	155 (4)	131 (5)	83 (33)	43 (63)	15 (84)	1 (97)
VTd/DARA	213 (0)	203 (0)	189 (1)	182 (1)	174 (1)	138 (34)	79 (88)	34 (130)	1 163)
D-VTd/OBS	229 (0)	223 (0)	216 (0)	207 (0)	195 (1)	144 (38)	75 (101)	38 (136)	2 (171)
D-VTd/DARA	229 (0)	226 (0)	217 (0)	204 (0)	198 (0)	145 (42)	76 (100)	30 (140)	0 (170)

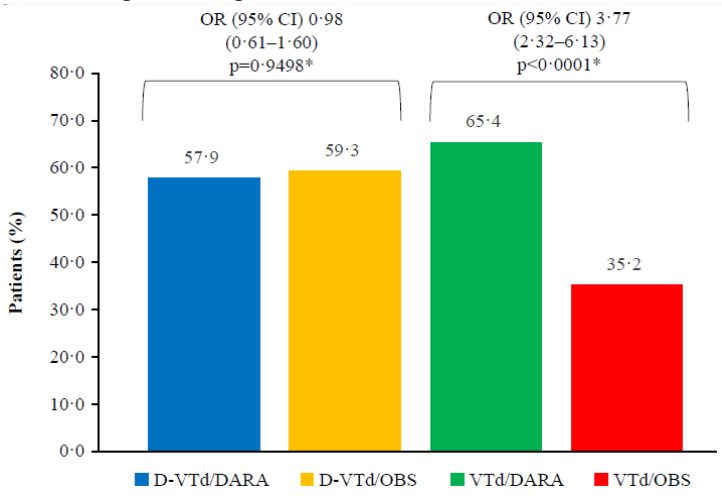
*Nominal p value. CI=confidence interval. DARA=daratumumab. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. HR=hazard ratio. OBS=observation. VTd= bortezomib, thalidomide, and dexamethasone.

Figure S5: **Depth of response from second randomisation by induction/consolidation and maintenance therapies in the maintenance-specific intent-to-treat population**

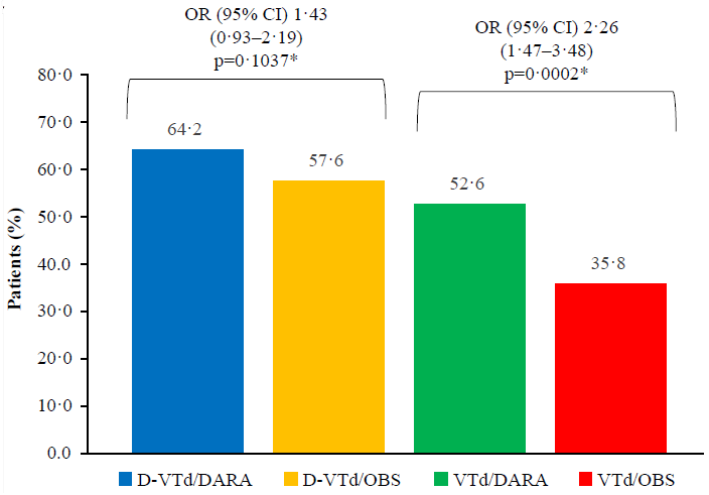
A. Rates of complete response or better



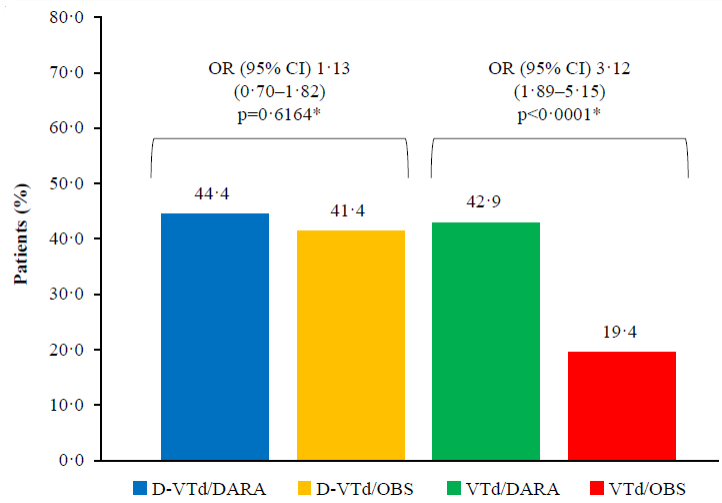
B. Rates of improved response



C. Rates of minimal residual disease negativity by next generation sequencing at a threshold of 10^{-5} and complete response or better



D. Rates of conversion to minimal residual disease negativity by next generation sequencing at a threshold of 10^{-5} and complete response or better



*Nominal p values. CI=confidence interval. DARA=daratumumab. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. OBS=observation. OR=odds ratio. VTd= bortezomib, thalidomide, and dexamethasone.

Table S9: **Overall response rate by induction/consolidation and maintenance treatment in the maintenance-specific safety population**

Response category, n (%)	**D-VTd/DARA n=229**	**D-VTd/OBS n=229**	**VTd/DARA n=213**	**VTd/OBS n=215**
≥ PR	228 (99·6)	229 (100)	212 (99·5)	212 (98·6)
Stable disease	1 (0·4)	0	0	2 (0·9)
Progressive disease	0	0	1 (0·5)	1 (0·5)

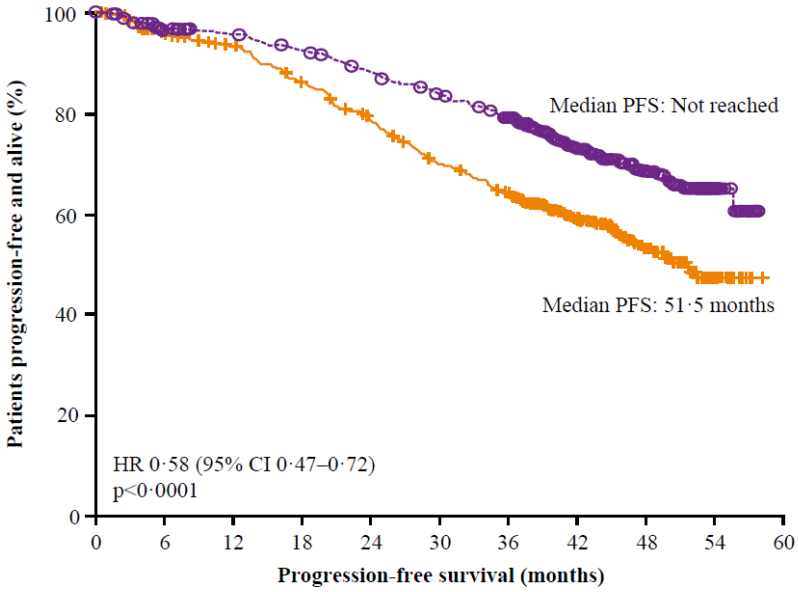
≥PR=partial response or better. DARA=daratumumab. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. OBS=observation. VTd= bortezomib, thalidomide, and dexamethasone.

Table S10: **Rates of minimal residual disease negativity and complete response or better by induction/consolidation and maintenance treatment in the maintenance-specific intent-to-treat population**

	MRD-negative patients (%)			MRD-negative patients (%)		
Assessment modality and threshold	**D-VTd/ DARA**	**D-VTd/ OBS**	**Odds ratio (95% CI) p value[†]**	**VTd/ DARA**	**VTd/ OBS**	**Odds ratio (95% CI) p value[†]**
10^{-5} by NGS	64·2	57·6	1·43 (0·93–2·19) 0·1037	52·6	35·8	2·26 (1·47–3·48) 0·0002
10^{-6} by NGS	56·8	48·5	1·49 (1·0–2·23) 0·0525	41·8	24·2	2·52 (1·61–3·96) <0·0001
10^{-5} by MFC	72·5	65·9	1·55 (0·96–2·49) 0·0723	59·2	43·7	2·18 (1·40–3·39) 0·0004

[*]Nominal p value. CI=confidence interval. DARA=daratumumab. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. MFC=multiparametric flow cytometry. MRD=minimal residual disease. NGS=next-generation sequencing. OBS=observation. VTd=bortezomib, thalidomide, and dexamethasone.

Figure S6: **Updated efficacy outcomes from first randomisation with a median of 44·5 months of follow-up**
A. Results of Kaplan-Meier estimates of progression-free survival

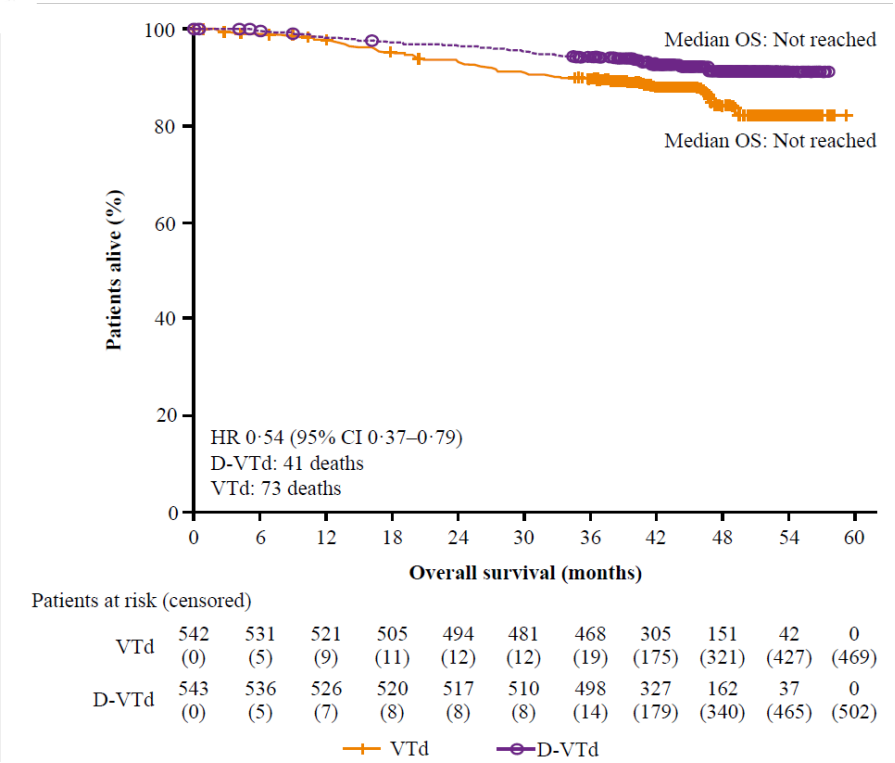


Patients at risk (censored)

VTd	542 (0)	499 (21)	472 (34)	434 (37)	391 (41)	345 (44)	312 (48)	191 (148)	90 (236)	26 (293)	0 (319)
D-VTd	543 (0)	507 (18)	495 (24)	478 (26)	452 (29)	426 (32)	395 (40)	237 (172)	119 (279)	29 (364)	0 (392)

VTd D-VTd

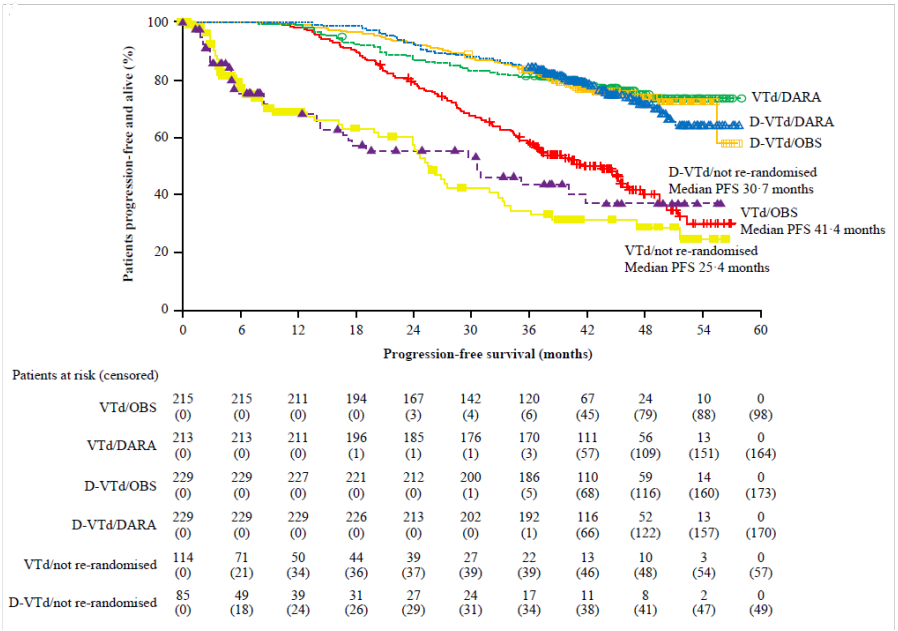
B. Results of Kaplan-Meier estimates of overall survival



CI=confidence interval. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. HR=hazard ratio. NR=not reached. OS=overall survival. PFS=progression-free survival. VTd=bortezomib, thalidomide, and dexamethasone.

Figure S7: **Progression-free survival from first randomisation by induction/consolidation and maintenance therapies among patients in the intent-to-treat population**

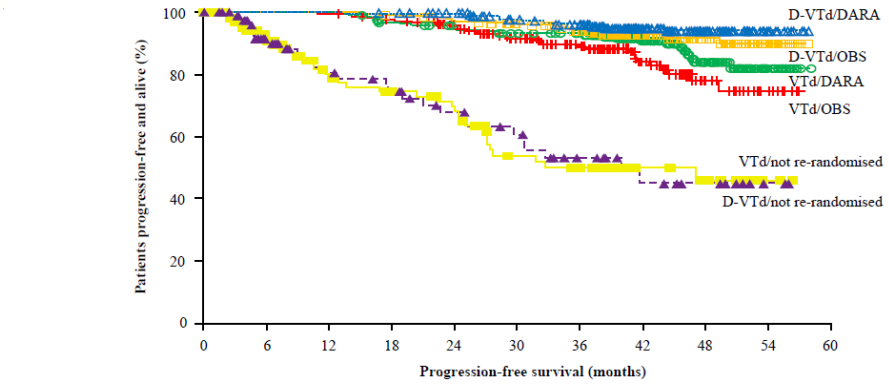
A. Results of Kaplan-Meier estimates of progression-free survival from first randomisation with patients who were not re-randomised analysed separately



Patients at risk (censored)

VTd/OBS	215 (0)	215 (0)	211 (0)	194 (0)	167 (3)	142 (4)	120 (6)	67 (45)	24 (79)	10 (88)	0 (98)
VTd/DARA	213 (0)	213 (0)	211 (0)	196 (1)	185 (1)	176 (1)	170 (3)	111 (57)	56 (109)	13 (151)	0 (164)
D-VTd/OBS	229 (0)	229 (0)	227 (0)	221 (0)	212 (0)	200 (1)	186 (5)	110 (68)	59 (116)	14 (160)	0 (173)
D-VTd/DARA	229 (0)	229 (0)	229 (0)	226 (0)	213 (0)	202 (0)	192 (1)	116 (66)	52 (122)	13 (157)	0 (170)
VTd/not re-randomised	114 (0)	71 (21)	50 (34)	44 (36)	39 (37)	27 (39)	22 (39)	13 (46)	10 (48)	3 (54)	0 (57)
D-VTd/not re-randomised	85 (0)	49 (18)	39 (24)	31 (26)	27 (29)	24 (31)	17 (34)	11 (38)	8 (41)	2 (47)	0 (49)

B. Results of Kaplan-Meier estimates of progression-free survival from next line of therapy after first randomisation with patients who were not re-randomised analysed separately



Patients at risk (censored)

VTd/OBS	215 (0)	215 (0)	214 (0)	207 (3)	187 (19)	160 (38)	134 (60)	73 (116)	26 (159)	10 (174)	0 (184)
VTd/DARA	213 (0)	213 (0)	213 (0)	202 (4)	192 (10)	186 (13)	179 (20)	118 (77)	57 (132)	13 (175)	0 (188)
D-VTd/OBS	229 (0)	229 (0)	229 (0)	226 (1)	220 (3)	208 (13)	192 (24)	114 (100)	61 (152)	14 (198)	0 (212)
D-VTd/DARA	229 (0)	229 (0)	229 (0)	227 (1)	221 (7)	206 (18)	195 (26)	118 (101)	54 (164)	13 (205)	0 (218)
VTd/not re-randomised	114 (0)	81 (24)	56 (41)	49 (44)	44 (46)	27 (54)	22 (57)	13 (66)	10 (68)	3 (75)	0 (78)
D-VTd/not re-randomised	85 (0)	56 (23)	42 (31)	37 (33)	30 (37)	25 (39)	17 (44)	11 (48)	8 (51)	2 (57)	0 (59)

DARA=daratumumab. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. OBS=observation. PFS=progression-free survival. VTd=bortezomib, thalidomide, and dexamethasone.

Table S11: **Safety overview from the maintenance phase* in the maintenance-specific safety population**

Patients, n (%)	**DARA N=440**	**OBS N=444**
Any TEAE	420 (95·5)	394 (88·7)
Any serious TEAE	100 (22·7)	84 (18·9)
Grade ≥3 TEAEs	122 (30·0)	108 (24·3)
Discontinuation of DARA due to TEAE	13 (3·0)	n/a
Fatal AEs	2 (0·5)	0
Neutropenia		
Grade 3	9 (2·0)	10 (2·3)
Grade 4	0	0
Second primary malignancy†	24 (5·5)	12 (2·7)
Haematologic	5 (1·1)	1 (0·2)
Solid tumour	19 (4·3)	11 (2·5)
Infusion-related reactions	115 (54·5)‡	n/a
Infections§	341 (77·5)	284 (64·0)
Pneumonia	29 (6·6)	19 (4·3)
Lung infection	21 (4·8)	15 (3·4)

*During treatment until 30 days of last DARA dose/OBS visit or initiation of subsequent line of therapy, whichever was earlier. †Haematologic second primary malignancies were DARA: T-cell lymphoma (2), blastic plasmacytoid dendritic cell neoplasia (1), myelodysplastic syndrome (1), natural killer-cell lymphoblastic lymphoma (1) and OBS: Acute myeloid leukaemia (1). ‡Among patients (n=211) who received VTd as induction therapy (ie, no prior DARA exposure). Most (103 of 115 [89·6%]) were grade 1 or 2. §The majority of infections (303 of 331 [88·9%] in the DARA group and 254 of 284 [89·4%] in the OBS group) were grade 1 or 2. AE=adverse event. DARA=daratumumab. n/a=not applicable. OBS=observation. TEAE=treatment-emergent AE. VTd=bortezomib, thalidomide, and dexamethasone.

Table S12: **Treatment-emergent adverse events* during Part 2 by system organ class, preferred term, and maximum toxicity grade in the maintenance-specific safety population**

	DARA N=440				OBS N=444			
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Infections and infestations								
Septic shock	0	0	0	1 (0·2)	0	0	0	0
Appendicitis	0	1 (0·2)	0	0	0	0	0	0
Arthritis, bacterial	0	0	0	0	0	1 (0·2)	0	0
Bacterial pyelonephritis	0	1 (0·2)	0	0	0	0	0	0
Bronchitis	166 (37·7)	2 (0·5)	1 (0·2)	0	130 (29·3)	4 (0·9)	0	0
Chronic sinusitis	2 (0·5)	0	0	0	0	1 (0·2)	0	0
Epstein-Barr virus infection	0	0	1 (0·2)	0	0	0	0	0
Gastroenteritis salmonella	0	0	1 (0·2)	0	0	0	0	0
Haemophilus infection	0	0	0	0	0	1 (0·2)	0	0
Herpes zoster	2 (0·5)	0	1 (0·2)	0	0	1 (0·2)	0	0
Influenza	30 (6·8)	1 (0·2)	0	0	63 (14·2)	2 (0·5)	0	0
Localised infection	17 (3·9)	1 (0·2)	0	0	10 (2·3)	1 (0·2)	0	0
Lung infection	1 (0·2)	1 (0·2)	0	0	0	0	0	0
Metapneumovirus infection	15 (3·4)	6 (1·4)	0	0	9 (2·0)	5 (1·1)	1 (0·2)	0
Nasopharyngitis	0	0	0	0	0	1 (0·2)	0	0
Penumocystis jirovecii pneumonia	76 (17·3)	0	0	0	49 (11·0)	0	0	0
Pneumonia	0	2 (0·5)	0	0	0	0	1 (0·2)	0
Pneumonia, bacterial	18 (4·1)	10 (2·3)	1 (0·2)	0	13 (2·9)	6 (1·4)	0	0
Pneumonia, influenzal	0	2 (0·5)	0	0	1 (0·2)	0	0	0
Pneumonia, legionella	0	1 (0·2)	0	0	0	0	0	0
Pneumonia, pnemococcal	0	1 (0·2)	0	0	0	0	0	0
Pneumonia, respiratory syncytial virus	0	1 (0·2)	0	0	0	1 (0·2)	0	0
Pneumonia, serratia	2 (0·5)	0	0	0	0	1 (0·2)	0	0
Pneumonia, viral	0	0	0	0	0	1 (0·2)	0	0
Respiratory syncytial virus infection	2 (0·5)	1 (0·2)	0	0	0	0	0	0

Respiratory tract infection	0	0	0	0	0	0	1 (0·2)	0
Sepsis	10 (2·3)	1 (0·2)	0	0	5 (1·1)	0	0	0
Sinusitis	1 (0·2)	0	0	0	0	0	1 (0·2)	0
Spinal cord infection	29 (6·6)	1 (0·2)	0	0	24 (5·4)	1 (0·2)	0	0
Streptococcal endocarditis	0	0	0	0	0	1 (0·2)	0	0
Tooth infection	0	0	0	0	0	0	1 (0·2)	0
Upper respiratory infection	2 (0·5)	1 (0·2)	0	0	5 (1·1)	0	0	0
Varicella	64 (14·5)	0	0	0	35 (7·9)	1 (0·2)	0	0
Varicella zoster virus infection	2 (0·5)	1 (0·2)	0	0	3 (0·7)	1 (0·2)	0	0
Viral diarrhoea	2 (0·5)	0	0	0	0	1 (0·2)	0	0
Vulvovaginal candidiasis	0	0	0	0	0	1 (0·2)	0	0
Neoplasms, benign, malignant, and unspecified								
Natural killer-cell lymphoblastic lymphoma	0	0	0	1 (0·2)	0	0	0	0
Anaplastic thyroid cancer	0	0	1 (0·2)	0	0	0	0	0
Basal cell carcinoma	3 (0·7)	0	0	0	1 (0·2)	1 (0·2)	0	0
Bladder cancer	0	1 (0·2)	0	0	0	0	0	0
Bladder cancer, recurrent	0	1 (0·2)	0	0	0	0	0	0
Blastic plasmacytoid dendritic cell neoplasia	0	0	1 (0·2)	0	0	0	0	0
Gastrointestinal tract adenoma	0	0	0	0	0	1 (0·2)	0	0
Intraductal proliferative breast lesion	0	1 (0·2)	0	0	0	0	0	0
Lung adenocarcinoma	0	0	0	0	0	1 (0·2)	0	0
Myelodysplastic syndrome	0	0	1 (0·2)	0	0	0	0	0
Pituitary tumour, benign	0	0	0	0	0	1 (0·2)	0	0
Prostate cancer	0	2 (0·5)	1 (0·2)	0	0	1 (0·2)	0	0
Squamous cell carcinoma of skin	0	2 (0·5)	0	0	1 (0·2)	0	0	0
T-cell lymphoma	0	1 (0·2)	0	0	0	0	0	0
Blood and lymphatic system disorders								
Anaemia	9 (2·0)	1 (0·2)	0	0	8 (1·8)	2 (0·5)	0	0
Febrile neutropenia	1 (0·2)	1 (0·2)	0	0	1 (0·2)	0	0	0

Histiocytosis, hematophagic	0	1 (0·2)	1 (0·2)	0	0	0	0	0
Immune thrombocytopenic purpura	0	0	0	0	0	0	1 (0·2)	0
Lymphopenia	15 (3·4)	14 (3·2)	2 (0·5)	0	9 (2·0)	3 (0·7)	5 (1·1)	0
Neutropenia	3 (0·7)	9 (2·0)	0	0	0	10 (2·3)	0	0
Thrombocytopenia	12 (2·7)	3 (0·7)	2 (0·5)	0	5 (1·1)	2 (0·5)	1 (0·2)	0
Cardiac disorders								
Acute coronary syndrome	0	1 (0·2)	0	0	0	0	0	0
Cardiac amyloidosis	1 (0·2)	3 (0·7)	0	0	4 (0·9)	0	0	0
Cardiac failure, congestive	0	1 (0·2)	0	0	0	0	0	0
Myocardial infarction	0	0	0	0	0	0	1 (0·2)	0
Myocardia ischemia	0	0	0	0	0	1 (0·2)	0	0
Pericarditis	0	0	0	0	1 (0·2)	1 (0·2)	0	0
Ventricular fibrillation	1 (0·2)	0	0	0	0	1 (0·2)	0	0
Eye disorders								
Cataract	4 (0·9)	2 (0·5)	0	0	1 (0·2)	4 (0·9)	0	0
Chalazion	0	0	0	0	0	1 (0·2)	0	0
Eyelid function disorder	0	0	0	0	0	1 (0·2)	0	0
Maculopathy	0	1 (0·2)	0	0	0	0	0	0
Retinal detachment	1 (0·2)	1 (0·2)	0	0	0	1 (0·2)	0	0
Retinal vein occlusion	0	1 (0·2)	0	0	0	0	0	0
Gastrointestinal disorders								
Abdominal pain	11 (2·5)	3 (0·7)	0	0	8 (1·8)	1 (0·2)	0	0
Chronic gastritis	1 (0·2)	0	0	0	1 (0·2)	1 (0·2)	0	0
Diarrhoea	56 (12·7)	1 (0·2)	0	0	25 (5·6)	1 (0·2)	0	0
Inflammatory bowel disease	0	0	0	0	0	1 (0·2)	0	0
Inguinal hernia	3 (0·7)	1 (0·2)	0	0	1 (0·2)	2 (0·5)	0	0
Nausea	42 (9·5)	2 (0·5)	0	0	6 (1·4)	0	0	0
Oesophagitis	1 (0·2)	0	0	0	1 (0·2)	1 (0·2)	0	0
Pancreatitis	0	0	0	0	1 (0·2)	0	1 (0·2)	0

Pancreatitis, acute	0	1 (0·2)	0	0	0	0	0	0
Umbilical hernia	2 (0·5)	1 (0·2)	0	0	0	0	0	0
Vomiting	37 (8·4)	3 (0·7)	0	0	5 (1·1)	0	0	0
General disorders and administration site conditions								
Asthenia	60 (13·6)	0	0	0	51 (11·5)	2 (0·5)	0	0
Fatigue	30 (6·8)	0	0	0	24 (5·4)	1 (0·2)	0	0
General physical health deterioration	0	0	0	0	3 (0·7)	2 (0·5)	0	0
Hernia	0	0	0	0	0	1 (0·2)	0	0
Influenza-like illness	54 (12·3)	0	0	0	49 (11·0)	0	0	0
Malaise	8 (1·8)	0	0	0	7 (1·6)	1 (0·2)	0	0
Medical device site joint pain	0	0	0	0	0	1 (0·2)	0	0
Pain	5 (1·1)	0	0	0	2 (0·5)	1 (0·2)	0	0
Hepatobiliary disorders								
Cholecystitis, acute	0	1 (0·2)	0	0	0	0	0	0
Hepatocelluar injury	0	1 (0·2)	0	0	1 (0·2)	0	0	0
Immune system disorders								
Anaphylactic shock	0	0	1 (0·2)	0	0	0	0	0
Hypogammaglobulinaemia	53 (12·0)	3 (0·7)	0	0	13 (2·9)	3 (0·7)	0	0
Sarcoidosis	0	0	0	0	0	1 (0·2)	0	0
Injury, poisoning, and procedural complications								
Burns, second degree	0	0	0	0	0	1 (0·2)	0	0
Forearm fracture	0	1 (0·2)	0	0	0	0	0	0
Fracture	0	0	0	0	0	1 (0·2)	0	0
Hip fracture	0	1 (0·2)	0	0	0	0	0	0
Humerus fracture	1 (0·2)	1 (0·2)	0	0	2 (0·5)	2 (0·5)	0	0
Lumbar vertebral fracture	0	1 (0·2)	0	0	0	1 (0·2)	0	0
Post-procedural complication	0	1 (0·2)	0	0	0	0	0	0
Spinal fracture	0	0	0	0	1 (0·2)	1 (0·2)	0	0
Tendon rupture	1 (0·2)	0	0	0	0	1 (0·2)	0	0

Thoracic vertebral fracture	0	0	0	0	0	2 (0·5)	0	0
Upper limb fracture	1 (0·2)	1 (0·2)	0	0	1 (0·2)	0	0	0
Wrist fracture	0	1 (0·2)	0	0	0	0	0	0
Investigations								
Alanine aminotransferase increased	3 (0·7)	0	0	0	3 (0·7)	1 (0·2)	0	0
Aspartate aminotransferase increased	3 (0·7)	0	0	0	3 (0·7)	1 (0·2)	0	0
Gamma-glutamyltransferase increased	1 (0·2)	3 (0·7)	0	0	1 (0·2)	0	0	0
Weight decreased	7 (1·6)	0	0	0	1 (0·2)	2 (0·5)	0	0
Weight increased	9 (2·0)	4 (0·9)	0	0	9 (2·0)	2 (0·5)	0	0
Metabolism and nutrition disorders								
Diabetes mellitus	0	1 (0·2)	0	0	0	1 (0·2)	0	0
Hypercalcaemia	2 (0·5)	0	0	0	5 (1·1)	0	1 (0·2)	0
Hyperkalaemia	2 (0·5)	0	0	0	0	1 (0·2)	0	0
Hypokalaemia	2 (0·5)	0	0	0	2 (0·5)	1 (0·2)	1 (0·2)	0
Hypophophataemia	1 (0·2)	0	0	0	1 (0·2)	1 (0·2)	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	50 (11·4)	1 (0·2)	0	0	50 (11·3)	2 (0·5)	0	0
Arthritis	5 (1·1)	1 (0·2)	0	0	1 (0·2)	0	0	0
Back pain	43 (9·8)	2 (0·5)	0	0	59 (13·3)	2 (0·5)	0	0
Bone pain	41 (9·3)	0	0	0	31 (7·0)	1 (0·2)	0	0
Dupuytren’s contracture	0	0	0	0	0	1 (0·2)	0	0
Intervertebral disc protrusion	3 (0·7)	0	0	0	3 (0·7)	1 (0·2)	0	0
Osteoarthritis	10 (2·3)	1 (0·2)	0	0	11 (2·5)	2 (0·5)	0	0
Osteolysis	0	0	0	0	0	1 (0·2)	0	0
Osteonecrosis	1 (0·2)	1 (0·2)	0	0	1 (0·2)	1 (0·2)	0	0
Osteonecrosis of jaw	2 (0·5)	1 (0·2)	0	0	0	0	0	0
Osteopenia	2 (0·5)	0	0	0	1 (0·2)	1 (0·2)	0	0
Pain in jaw	2 (0·5)	1 (0·2)	0	0	0	0	0	0
Rhabdomyolysis	0	0	0	0	0	1 (0·2)	0	0

Spinal pain	4 (0·9)	2 (0·5)	0	0	6 (1·4)	1 (0·2)	0	0
Nervous system disorders								
Cervicobrachial syndrome	0	1 (0·2)	0	0	1 (0·2)	0	0	0
Headache	15 (3·4)	1 (0·2)	0	0	11 (2·5)	2 (0·5)	0	0
Neuropathy, peripheral	1 (0·2)	1 (0·2)	0	0	1 (0·2)	0	0	0
Paresthesia	35 (8·0)	1 (0·2)	0	0	14 (3·2)	0	0	0
Peripheral sensory neuropathy	65 (14·8)	4 (0·9)	0	0	46 (10·4)	5 (1·1)	0	0
Post herpetic neuralgia	3 (0·7)	1 (0·2)	0	0	9 (2·0)	1 (0·2)	0	0
Presyncope	0	1 (0·2)	0	0	3 (0·7)	0	0	0
Sciatica	9 (2·0)	2 (0·5)	0	0	12 (2·7)	1 (0·2)	1 (0·2)	0
Product issues								
Device breakage	0	0	0	0	1 (0·2)	1 (0·2)	0	0
Psychiatric disorders								
Anxiety	7 (1·6)	0	0	0	7 (1·6)	1 (0·2)	0	0
Burnout syndrome	0	1 (0·2)	0	0	0	0	0	0
Major depression	0	0	1 (0·2)	0	0	0	0	0
Mania	0	1 (0·2)	0	0	0	0	0	0
Suicide attempt	0	1 (0·2)	0	0	0	0	0	0
Renal and urinary disorders								
Renal colic	2 (0·5)	0	0	0	2 (0·5)	2 (0·5)	0	0
Renal failure	0	0	0	0	0	0	1 (0·2)	0
Stress urinary incontinence	0	1 (0·2)	0	0	0	0	0	0
Urinary bladder haemorrhage	0	1 (0·2)	0	0	0	0	0	0
Reproductive system and breast disorders								
Genital prolapse	0	0	0	0	0	1 (0·2)	0	0
Uterine cervical metaplasia	0	0	0	0	0	1 (0·2)	0	0
Respiratory, thoracic, and mediastinal disorders								
Acute pulmonary oedema	0	0	0	0	0	1 (0·2)	0	0
Acute respiratory distress syndrome	0	0	1 (0·2)	0	0	1 (0·2)	1 (0·2)	0

Asthma	3 (0·7)	1 (0·2)	0	0	3 (0·7)	0	0	0
Bronchospasm	6 (1·4)	3 (0·7)	0	0	0	0	0	0
Chronic obstructive pulmonary disease	4 (0·9)	1 (0·2)	0	0	2 (0·5)	0	0	0
Cough	78 (17·7)	1 (0·2)	0	0	40 (9·0)	0	0	0
Dyspnoea	27 (6·1)	2 (0·5)	0	0	6 (1·4)	1 (0·2)	0	0
Eosinophilic pneumonia	0	0	0	0	0	1 (0·2)	0	0
Pleural effusion	0	0	0	0	0	1 (0·2)	0	0
Pulmonary embolism	0	1 (0·2)	0	0	0	1 (0·2)	0	0
Sleep apnoea syndrome	2 (0·5)	0	0	0	2 (0·5)	1 (0·2)	0	0
Skin and subcutaneous tissue disorders								
Rash	24 (5·5)	1 (0·2)	0	0	11 (2·5)	0	0	0
Surgical and medical procedures								
Mammoplasty	0	1 (0·2)	0	0	0	0	0	0
Vascular disorders								
Hypertension	15 (3·4)	13 (3·0)	0	0	10 (2·3)	7 (1·6)	0	0
Hypotension	5 (1·1)	1 (0·2)	0	0	2 (0·5)	0	0	0
Vena cava thrombosis	0	1 (0·2)	0	0	0	0	0	0

*All grade 1 or 2 treatment-emergent adverse events occurring in ≥10% of patients in either treatment group and all grade 3, 4, and 5 treatment-emergent adverse events.
DARA=daratumumab. OBS=observation.

Table S13: **Additional information regarding patients who experienced a second primary malignancy**

Treatment group	Sex	Age	SPM type	DARA infusions prior to SPM onset*	Medical history
VTd/OBS	F	63	Basal cell carcinoma	NA	Depression; hypertension; sleep apnoea syndrome; urethral operation; Bartonellosis; Dupuytren's contracture; lipoma; bone pain; constipation
VTd/OBS	M	61	Acute myeloid leukaemia	NA	Sleep apnoea syndrome; hypercholesterolaemia; type 2 diabetes mellitus; diabetic neuropathy; spinal fracture; back pain; cementoplasty; anaemia; pneumonia pneumococcal; constipation
VTd/OBS	F	45	Invasive ductal breast carcinoma	NA	Depression
VTd/OBS	F	54	Squamous cell carcinoma of skin	NA	Arthropathy; gastrooesophageal reflux disease; carpal tunnel syndrome; meniscus injury; helicobacter infection
VTd/OBS	M	56	Basal cell carcinoma	NA	Hyperchlorhydria; tendon injury; hypertension; bone pain; anxiety; constipation; hypomagnesaemia; pleural effusion
VTd/OBS	M	59	Malignant melanoma	NA	Tobacco abuse; peritonitis; hypertension; varicose vein operation; hyperthyroidism; bursitis; varicose vein; varicose vein operation; atrial fibrillation; plasmacytoma; bone pain; femur fracture; osteosynthesis
VTd/OBS	M	64	Basal cell carcinoma	NA	Asthenia; carotid arteriosclerosis; ischaemic cardiomyopathy; myocardial infarction; stent placement; anaemia
VTd/DARA	F	55	Non-small cell lung cancer stage IV	14	Polycystic ovaries; spinal operation; pain in extremity; bone pain
VTd/DARA	F	59	Basal cell carcinoma	1	Asthma; osteoporosis; cerebrovascular accident; anxiety; basal cell carcinoma; back pain
VTd/DARA	M	60	Prostate cancer	1	Back pain; anaemia
VTd/DARA	M	53	T-cell lymphoma	3	Foot operation; back pain; anxiety
VTd/DARA	M	65	Basal cell carcinoma	7	Varicose vein operation; deep vein thrombosis; lung disorder; pulmonary embolism; drug hypersensitivity; thrombosis; thrombosis
VTd/DARA	M	56	Hepatocellular carcinoma	14	Femoral neck fracture; gouty arthritis; hepatitis B; intervertebral disc protrusion; hepatitis C; anaemia; arthritis; hyperuricaemia
VTd/DARA	M	61	Prostate cancer	8	Anaemia; appendicectomy; Barrett's oesophagus; hypercholesterolaemia; type 2 diabetes mellitus; large intestinal polypectomy; cataract; bone pain; renal failure
VTd/DARA	F	44	Natural killer-cell lymphoblastic lymphoma	1	Knee operation; constipation; musculoskeletal chest pain; rib fracture; back pain; lumbar vertebral fracture; nausea; vomiting; anxiety

VTd/DARA	F	63	Squamous cell carcinoma of skin	13	Hypertension; thyroidectomy; back pain
VTd/DARA	M	53	Blastic plasmacytoid dendritic cell neoplasia	13	Hypercholesterolaemia; back pain; anxiety; constipation
VTd/DARA	M	54	Squamous cell carcinoma of skin	7	Intervertebral disc protrusion; calculus urinary; back pain; musculoskeletal chest pain
D-VTd/OBS	M	39	Testicular germ cell cancer	16	Orchidopexy; osteomyelitis; testicular torsion; haemorrhoids; cervicobrachial syndrome; intervertebral disc operation; insomnia; asthenia; dyspnoea; gingivitis; oral fungal infection; ear infection
D-VTd/OBS	M	54	Prostate cancer	16	Knee operation; prostatic adenoma; arthralgia; pain in extremity; back pain
D-VTd/OBS	M	63	Lung adenocarcinoma	16	Large intestinal polypectomy; asthenia
D-VTd/OBS	F	64	Invasive ductal breast carcinoma	16	Appendicectomy; breast cyst excision; bunion operation; anaemia
D-VTd/OBS	M	54	Bowen's disease	16	Appendicectomy; dyslipidaemia; hypertension; hypogammaglobulinaemia; intervertebral disc protrusion; joint dislocation; musculoskeletal chest pain; neck pain; rib fracture; herpes zoster; asthenia; gastroenteritis; cervical vertebral fracture; spondylolysis; vertebral lesion
D-VTd/DARA	M	60	Prostate cancer	30	Appendicectomy; benign prostatic hyperplasia; bradycardia; drug hypersensitivity; micturition disorder; migraine; inguinal hernia repair; complex regional pain syndrome; musculoskeletal chest pain; depression
D-VTd/DARA	M	65	Bladder cancer	30	Small intestinal resection; irritable bowel syndrome; atrial fibrillation; benign prostatic hyperplasia; bone pain; alanine aminotransferase increased; lymphopenia
D-VTd/DARA	F	54	Myelodysplastic syndrome	22	Oophorectomy; salpingectomy; bunion operation; hip arthroplasty; sciatica; hysterectomy; uterine leiomyoma; proctitis ulcerative; back pain; anaemia
D-VTd/DARA	F	65	Anaplastic thyroid cancer	26	Blood cholesterol increased; constipation; tonsillectomy; Basedow's disease[$]; ankle fracture; bone pain; asthenia; insomnia
D-VTd/DARA	M	54	Basal cell carcinoma	18	Seasonal allergy; inguinal hernia; bone pain; diverticulitis
D-VTd/DARA	M	61	Squamous cell carcinoma of the tongue	30	Neoplasm; oesophageal carcinoma; oesophageal operation; sciatica; bronchitis; anastomotic stenosis; hepatosplenomegaly; back pain; bone pain; anaemia
D-VTd/DARA	M	46	Papillary thyroid cancer	20	Food allergy; haemorrhoids; drug hypersensitivity; large intestine polyp; thyroid mass; back pain; asthenia; anaemia
D-VTd/DARA	M	64	Prostate cancer	24	Hyperferritinaemia; varicose vein operation; infective tenosynovitis; prostatitis; erectile dysfunction; benign prostatic hyperplasia; rib fracture

D-VTd/DARA	M	51	T-cell lymphoma	17	Haemorrhoids; hypercholesterolaemia; spinal laminectomy
D-VTd/DARA	M	57	Transitional cell carcinoma	30	Atrial fibrillation; hip arthroplasty; hypercholesterolaemia; hypertension; tobacco user; coronary arterial stent insertion; myocardial infarction; hyperthyroidism; vitamin d deficiency; alcohol use; asthenia; back pain; cough; drug hypersensitivity
D-VTd/DARA	M	65	Squamous cell carcinoma of skin	29	Hypercholesterolaemia; hypertension; arthralgia; chest pain; fatigue; musculoskeletal chest pain; diaphragmatic hernia; gastrooesophageal reflux disease
D-VTd/DARA	M	40	Testicular seminoma (pure)	26	Asthma
D-VTd/DARA	F	58	Basal cell carcinoma	18	Female sterilisation; insomnia; dyspepsia; depression; radius fracture; pneumothorax; rib fracture; osteopenia

*includes the DARA infusion from first randomisation. †Graves' disease.
DARA=daratumumab. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. OBS=observation. SPM=second primary malignancy. VTd=bortezomib, thalidomide, and dexamethasone.

Table S14: **Second primary malignancies by induction/consolidation and maintenance treatment in the maintenance-specific safety population**

	D-VTd		VTd	
Patients, n (%)	**DARA N=229**	**OBS N=229**	**DARA N=211**	**OBS N=215**
Second primary malignancies	13 (5·7)	5 (2·2)	11 (5·2)	7 (3·3)
Non-cutaneous	8 (3·5)	4 (1·7)	4 (1·9)	1 (0·5)
Invasive ductal breast carcinoma*	0	1 (0·4)	0	1 (0·5)
Lung adenocarcinoma*	0	1 (0·4)	0	0
Prostate cancer*	2 (0·9)	1 (0·4)	2 (0·9)	0
Testicular germ cell cancer*	0	1 (0·4)	0	0
Anaplastic thyroid cancer*	1 (0·4)	0	0	0
Bladder cancer recurrent*	1 (0·4)	0	0	0
Bladder cancer*	1 (0·4)	0	0	0
Hepatocellular carcinoma*	0	0	1 (0·5)	0
Non-small cell lung cancer stage IV*	0	0	1 (0·5)	0
Papillary thyroid cancer*	1 (0·4)	0	0	0
Squamous cell carcinoma of the tongue*	1 (0·4)	0	0	0

Testicular seminoma (pure)*	1 (0·4)	0	0	0
Transitional cell carcinoma*	1 (0·4)	0	0	0
Cutaneous	3 (1·3)	1 (0·4)	4 (1·9)	5 (2·3)
Bowen's disease	0	1 (0·4)	0	0
Basal cell carcinoma	2 (0·9)	0	2 (0·9)	3 (1·4)
Malignant melanoma*	0	0	0	1 (0·5)
Squamous cell carcinoma of skin	1 (0·4)	0	2 (0·9)	1 (0·5)
Haematologic	2 (0·9)	0	3 (1·4)	1 (0·5)
Acute myeloid leukaemia*	0	0	0	1 (0·5)
Blastic plasmacytoid dendritic cell neoplasia*	0	0	1 (0·5)	0
Myelodysplastic syndrome*	1 (0·4)	0	0	0
Natural killer-cell lymphoblastic lymphoma*	0	0	1 (0·5)	0
T-cell lymphoma*	1 (0·4)	0	1 (0·5)	0

*Invasive second primary malignancy. DARA=daratumumab. D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. OBS=observation. VTd=bortezomib, thalidomide, and dexamethasone.

Supplementary References

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