Daratumumab and dexamethasone is safe and effective for triple refractory myeloma patients

IFM2014-04 investigators

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Daratumumab and dexamethasone is safe and effective for triple refractory myeloma patients: final results of the IFM 2014-04 (Etoile du Nord) trial

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Summary

Single agent daratumumab has shown clinical activity in relapsed, refractory multiple myeloma (RRMM). The Intergroupe Francophone du Myélome 2014-04 trial was designed to further investigate daratumumab in combination with dexamethasone in triple RRMM patients. Patients received daratumumab infusions in combination with weekly dexamethasone until disease progression or unacceptable toxicity. Fifty-seven patients were included in the trial and evaluable for response. The overall response rate and the clinical benefit rate were 33% (n = 19) and 48% (n = 27), respectively. Five (8·8%) patients achieved a very good partial response or better. The median time to response was 4 weeks. For responding patients, the median progression-free survival was 6·6 months, compared to 3·7 months (3·0–5·5) for those with a minimal or stable disease. The median overall survival (OS) for all patients was 16·7 months (11·2–24·0). For responding patients, the median OS was 23·23 months, whereas that of patients with progressive disease was 2·97 months. The incidence of infusion-related reactions was 37%; all cases were manageable and did not lead to dose reduction or permanent treatment discontinuation. These data demonstrate that treatment with daratumumab and dexamethasone results in a meaningful long-term benefit with an acceptable safety profile for patients with triple RRMM.

Keywords: myeloma therapy, daratumumab, clinical trial.

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Although novel treatment approaches, including immunomodulatory drugs (IMIDs) and proteasome inhibitors (PI) can prolong the survival of multiple myeloma patients, few, if any, are cured (Röllig *et al*, 2015). Salvage therapies for relapsed disease are equally disappointing, and myeloma patients who fail lenalidomide, bortezomib and pomalidomide have a dire prognosis with estimated median progression-free survival (PFS) and overall survival (OS) of 6–8 and 8–9 months, respectively (Kumar *et al*, 2012; Usmani *et al*, 2017). These patients should therefore be considered for novel treatment approaches.

We report here the effects of daratumumab [Darzalex® (Janssen)], a selective CD38 IgG1κ monoclonal antibody in combination with dexamethasone. CD38 is highly and uniformly expressed on myeloma cells (de Weers *et al*, 2011), making it a suitable target. Daratumumab has previously shown a favourable safety profile as a single agent in patients with relapsed and refractory (RR) multiple myeloma (MM) (Lokhorst *et al*, 2015).

In a phase II study, single agent daratumumab showed activity in 29·2% of patients with advanced myeloma (Lonial *et al*, 2016). In this study, three (2·8%) patients had a stringent complete response (sCR), 10 (9·4%) had a very good partial response (VGPR) and 18 (17·0%) had a partial response (PR).

We hypothesized that adding dexamethasone to daratumumab would have an additive effect and help control early progression. This observation, along with preclinical evidence of antimyeloma activity (Phipps *et al*, 2015), provided the rationale for our open-label phase II study of daratumumab in combination with dexamethasone for heavily pre-treated myeloma patients that had previously failed lenalidomide, pomalidomide and bortezomib and were deemed ineligible for re-treatment with these drugs.

Methods

Patients

Study patients were at least 18 years of age, with RRMM and an expected life expectancy of more than 6 months. Measurable disease was defined as a monoclonal immunoglobulin concentration on serum electrophoresis of at least 10 g/l IgG, 5 g/l IgA or 0·5 g/l IgD or monoclonal light chain urinary excretion of at least 200 mg/24 h. For those without a measurable serum or urine protein, a light chain greater than 100 mg/l and an abnormal free light chain ratio (<0·26 and >1·65) was required.

All patients were refractory to lenalidomide, pomalidomide (defined as a progression within 60 days from last drug dose) and bortezomib (defined as a progression within six months from last dose) or deemed ineligible to receive these agents, and relapsed from their last line of therapy.

Eligibility criteria included an Eastern Cooperative Oncology Group performance status (ECOG PS) <3, serum concentration of aspartate aminotransferase or alanine aminotransferase ≤3 times the upper limit of the normal range, a serum total bilirubin concentration ≤34·2 μmol/l, measured or calculated creatinine clearance >30 ml/min, platelet count $\geq 50 \times 10^9$/l, haemoglobin concentration of at least 85 g/l, and an absolute neutrophil count $\geq 1{\cdot}0 \times 10^9$/l. Inclusion deviations regarding low haemoglobin levels were

permitted in cases of high paraprotein levels after discussion with the principal investigator. Patients agreed to use contraception, and women with childbearing potential had a confirmed negative pregnancy test before enrolment.

The trial was approved by the Intergroupe Francophone du Myélome (IFM), the CHRU of Lille Review Board for France, each individual Belgian Centre Review Board in Belgium and the central French drug regulatory agency (ANSM), and was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. All the patients provided written informed consent before any trial-related procedures were performed. An independent data and safety monitoring committee provided oversight throughout the conduct of the trial. This trial was registered at ClinicalTrials.gov and EudraCT as NCT01053949 and 2015-002221-19 respectively.

Study and treatment design

Patients received daratumumab (16 mg/kg) as an intravenous infusion in a 28-day cycle. Daratumumab was administered weekly during the first two 28-day cycles, every other week during Cycles 3–6, and monthly from Cycle 7 until disease progression or unacceptable toxicity, as previously published (Lokhorst *et al*, 2015). Dose reductions were permitted as per protocol. Patients were also assigned to receive 40 mg weekly dexamethasone when aged < 70 years and 20 mg weekly if aged ≥ 70 years. Details may be found in Data S2.

Assessment of efficacy

The primary end point was the overall response rate (ORR) to daratumumab and dexamethasone [including complete response (CR), VGPR and PR]. Secondary end points were time to progression during treatment, duration of response, PFS and OS, safety, clinical benefit rates and quality of life. Responses were assessed centrally according to the criteria of the International Myeloma Working Group (IMWG) (Durie *et al*, 2006) and the European Group for Blood and Marrow Transplantation (EBMT) (Bladé *et al*, 1998).

A sCR was defined by a negative immunofixation test (IFE) alongside classical response criteria (Bladé *et al*, 1998; Durie *et al*, 2006). Patients with insufficient data for an assessment of efficacy were considered to have had a treatment failure. As daratumumab can interfere with both IFE and serum protein electrophoresis (Tang *et al*, 2018), a reflex IFE test using a daratumumab-specific IFE reflex assay (DIRA; van de Donk *et al*, 2016) was performed when daratumumab interference was suspected on serum protein electrophoresis and IFE results. The DIRA test, performed centrally in Nantes, enabled a more reliable evaluation of the depth of clinical response, and was mainly used to trigger bone marrow assessments that would confirm sCR.

Assessment of safety and other secondary endpoints

Adverse events were assessed at each visit and graded according to the National Cancer Institute Common Toxicity Criteria (version 4.0; https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) from the first dose until 30 days after the last dose of daratumumab. Quality of life was assessed with the use of the core quality-of-life questionnaire (QLQ-C30; Aaronson *et al*, 1993), and the modules on multiple myeloma (QLQ-MY20) of the European Organization for Research and Treatment of Cancer (Stead *et al*, 1999) as well as by the EQ5D-3L (Rabin & de Charro, 2001). These assessments were performed on day one of each cycle, as well as at the end of the study. The time to progression during the last course of treatment before study entry was calculated on the basis of the date of relapse recorded by central assessment.

Statistical analysis

Time-to-event analysis was performed according to the Kaplan–Meier method. The time to the first response was defined as the time from the initial administration of daratumumab to the first evidence of a response. PFS was defined as the time from the initial administration of daratumumab to disease progression, with censoring of death. The median follow-up at the time of this analysis was 22·8 months (95% CI 20–27·8).

The statistical analysis specified that a lower limit of the two-sided 95% confidence interval (CI) for the ORR that exceeded 20% would be considered to be evidence of significant activity. The sample size was calculated according to a two stages design (Simon clinical trials) with 19 patients in the first stage and 35 in the second stage, thus requiring a total of 54 patients. We performed univariate analyses using Fisher's exact test for categorical factors and logistic regression for continuous factors. All descriptive statistical analyses were performed with the use of R (version 3.4) [The Comprehensive R Archive Network (CRAN), 2018].

Results

Baseline characteristics

From December 2015 to September 2016, 76 patients were enrolled across 30 centres (12 failed screening), of whom 64 received the study treatment and 57 (89%) could be evaluated (seven had a non-inclusion criterion after central review) (Fig 1). Post-selection exclusions were blinded to outcome and based upon central review of the inclusion criteria. Results of the whole treated population may be found in the Supplemental results. The median age was 67 years (range 30–80), and 52% were male. The median time from initial diagnosis was 6·6 years (0·82–22 years). Most (88%) had IgG or IgA myeloma, and 25% had an ECOG PS of 2.

At the time of screening, 21% of patients (n = 10/48) had t (4;14) and 15% (n = 7/48) had del(17p). The International Staging System (ISS) groups at diagnosis were 47%, 30% and 24% for ISS I, II and III, respectively. Patients characteristics are listed in Table I.

Of the 57 patients who could be evaluated, the median number of previous therapies was six (range 3–10) including 63% of patients who had received at least one autologous stem cell transplant. All patients were triple-refractory to lenalidomide, pomalidomide and bortezomib, and 10% had progressed on carfilzomib.

Daratumumab and dexamethasone exert rapid and frequent responses in a heavily pre-treated population

Treatment received. The median number of cycles of daratumumab before progression was four (range 1–31). Sixty percent of patients completed at least four cycles of therapy, and 26% received at least eight cycles. Of the 57 evaluable patients, 49 (86%) discontinued treatment because of progressive disease, and four (7%) discontinued treatment early because of adverse events, 75% of which had not had a response to daratumumab.

Responses to daratumumab and dexamethasone. Among the 57 evaluated patients, the overall response rate was 33% according to the IMWG response criteria (Durie *et al*, 2006). Overall, one (1·8%), four (7%) and 14 (25%) experienced a CR, VGPR and PR respectively. An additional eight (14%) patients had a minimal response (MR) to daratumumab., Treatment with daratumumab lead to stable disease (SD) in an additional 33% of patients (Table II).

The median time to response was four weeks (range: 4–12) and the median time to best response was eight weeks (range: 4–48). The median PFS was 4·17 months (Fig 2A). The median PFS among the 19 patients with a response (CR + VGPR + PR) was 6·6 months (95% CI 3·7–14). Patients with SD or MR had a PFS of 3·7 months (95% CI 3·0–5·5; Fig 2B).

The median OS among the 57 patients was 16·7 months (95% CI 11·2–24·0; Fig 2C). Cause of death was directly related to progressive disease in 83% of deaths. Other causes included Grade 5 infections (9·7%), intracranial haemorrhage (5%) and other causes (7·3%). The median OS among the 19 patients with a PR or better was 23·7 months (95% CI 14·8–not reached), among the 27 patients that achieved a SD or MR it was 17·7 (95% CI 11·7–not reached) and 2·97 months (95% CI 2·03–not reached) among those that progressed (Fig 2D).

Other secondary end points included additional measures of clinical benefit. Among patients with a PR or better, 84% had a maximal haemoglobin increase of at least 10 g/l, and 53% had a maximal haemoglobin increase of at least 20 g/l. Furthermore erythropoietin (EPO) was stopped and

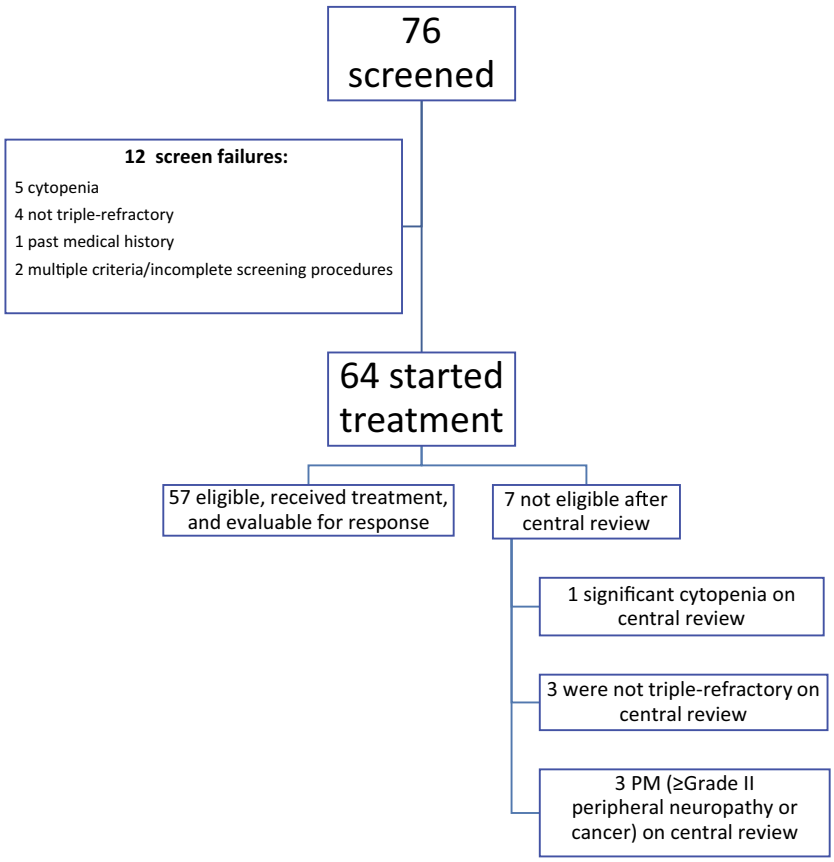

Fig 1. Flow chart summarizing patient selection. GII, grade II; PM, past medical history. [Colour figure can be viewed at wileyonlinelibrary.com]

Table I. Patients characteristics at study entry of all patients recruited on the IFM 2014-04 trial (n = 64).

Feature	
Age at study entry, years; median (range)	67 (30–80)
Male:Female ratio	1:0·96
Isotype	IgA: 21% (n = 12)
	IgG: 66% (n = 38)
	LCO: 13% (n = 7)
ISS at diagnosis (n = 51)	I: 47% (n = 24)
	II: 30% (n = 15)
	III: 24% (n = 12)
ISS at study entry	I: 24% (n = 15)
	II: 41% (n = 27)
	III: 34% (n = 20)
ECOG PS at study entry	0 17% (n = 11)
	1 58% (n = 37)
	2 25% (n = 16)
Cytogenetics at study entry (n = 48)	t(4;14) 21% (n = 10)
	del(17p) 15% (n = 7)
Time from diagnosis, years; median (range)	6·6 (0·82–22)
Number of previous lines; median (range)	6 (3–10)
Previously transplanted	66% (42 patients; 53 transplants)
Median follow-up, months	22·8 (95% CI 20–27·8)

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; LCO, light chain only.

Table II. Efficacy of the daratumumab and dexamethasone combination (n = 57).

Best response	*N* (%)
ORR	
sCR	1 (1·75)
VGPR	4 (7·02)
PR	14 (25)
CBR	
MR	8 (14)
SD	19 (33·3)
PD	11 (19)

CBR, clinical benefit rate; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

transfusion independence reached in five responding patients and the dose of EPO was reduced in an additional patient, indicating improved haematopoiesis. Responses were also associated with increased ECOG PS, which was evident in 58% of patients.

Safety

Sixty-four patients were evaluable for safety analysis, representing 888 daratumumab infusions. The most common adverse events (AEs) were cytopenia and asthenia (Fig 3). Infusion-related symptoms occurred in 35% of cases, 91% of which occurred within the first infusion and were typically mild to moderate. Infusions were interrupted but not aborted and symptoms were manageable with routine support. The most common grade III AEs were anaemia, experienced by 33% of patients, neutropenia (26%), thrombocytopenia (17%) and hypertension (5%). Grade IV AEs were experienced by 33% of patients and included thrombocytopenia (in 14%) and neutropenia (in 7·8%). All other grade IV AEs occurred in ≤2% of the patients.

Overall, 18·5% of patients experienced a grade 3 or greater infection despite receiving prophylaxis for *Pneumocystis carinii* pneumonia (77% of patients) and Varicella zoster virus (86%), 24% received prophylactic antibiotics, and 16% received intravenous or subcutaneous immunoglobulin.

Drug-related adverse events did not lead to discontinuation of daratumumab therapy. Overall, no patients required a reduction of the dose of daratumumab; dose reductions of dexamethasone were seen in 36% of patients following an AE. Thirteen patients (20%) died within 30 days after the last dose of daratumumab, the majority of them from causes related to progressive disease. With the exception of infection, no deaths were directly assessed as possibly related to daratumumab or dexamethasone treatment (Table III).

The QLQ-C30, QLQ-My20 and EQ5Q were used to estimate different aspects of quality of life among patients receiving treatment. There were no signs suggestive of treatment-related AE impacting quality of life, but given the number of missing questionnaires these data need interpreted with caution (Data S1).

Discussion

In this phase II trial, we evaluated the efficacy of daratumumab and dexamethasone in patients with RRMM. The ORR, including CR, was 33%. The median PFS among responders was 6·6 months. Responses were associated with increased haemoglobin levels and improvements in ECOG PS.

The rates of major responses to daratumumab and dexamethasone in patients with advanced, refractory myeloma are noteworthy. Complete responses are rare in populations of patients with multidrug-refractory myeloma (Nooka *et al*, 2015). In addition, the median duration of survival among patients without a response (2·97 months) was within the range that was expected according to the literature (Kumar *et al*, 2012; Usmani *et al*, 2017), and these data were in keeping with previously published trials of single agent daratumumab (Lokhorst *et al*, 2015; Lonial *et al*, 2016; Usmani *et al*, 2016).

Additionally, there appears to be a benefit in terms of OS for patients that achieved either SD or MR, with a median OS of 17·7 months in comparison to an expected 8–9 months (Usmani *et al*, 2016). Although this trial was not

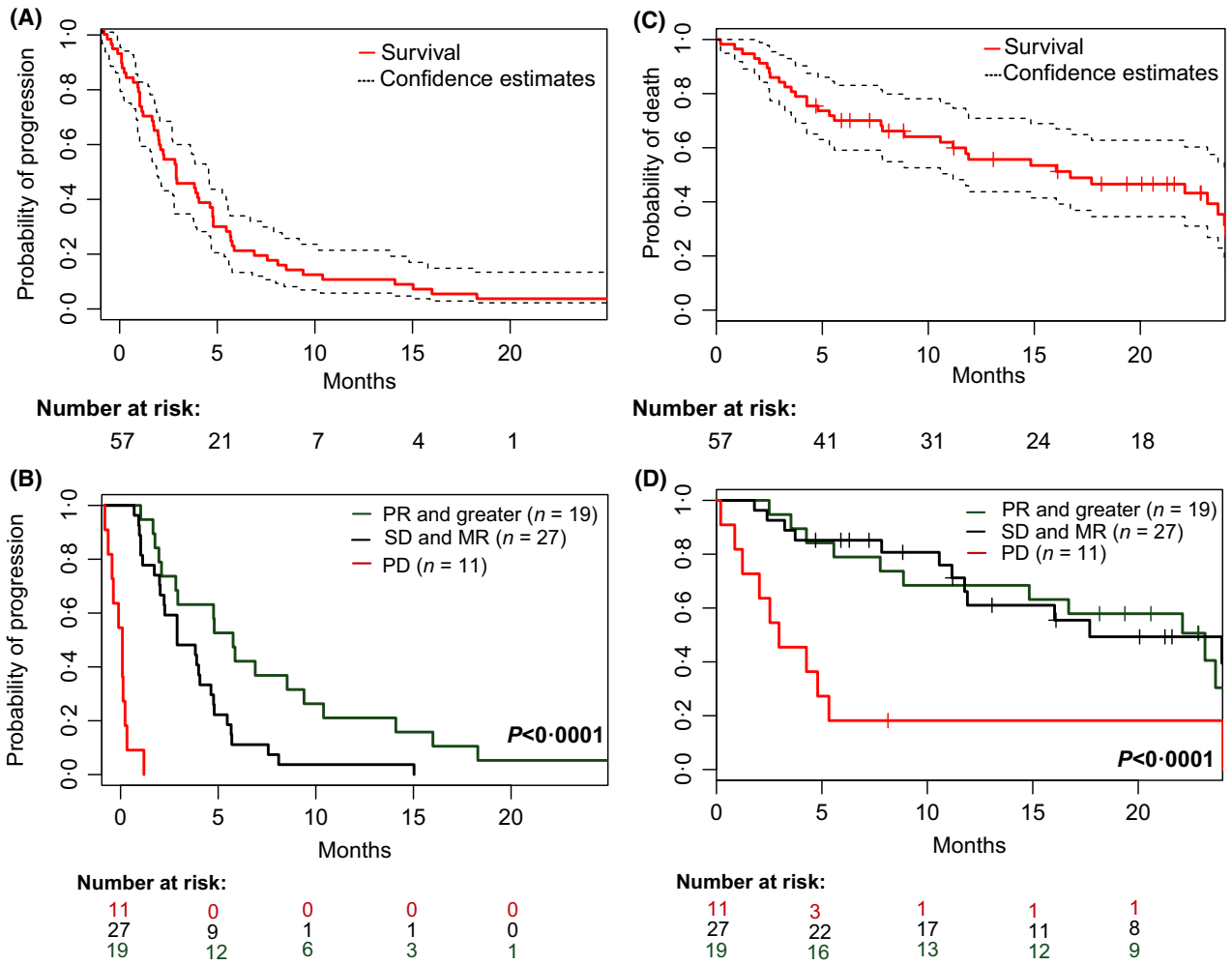

Fig 2. Survival analysis. (A) Progression-free survival; (B) progression free-survival according to response; (C) overall survival; (D) overall survival according to response. MR, minimal response; PD, progressive disease; PR, partial response; SD, stable disease.

powered to answer this question, these data may suggest that perhaps daratumumab improves responses to future lines of therapy by modifying the immune environment (Krejcik *et al*, 2016; Chatterjee *et al*, 2018) and interaction with bone-marrow stromal cells (Marlein *et al*, 2019). Nevertheless, an important confounding factor may be the availability of other drugs (including compassionate carfilzomib) for these patients.

Although it is impossible to determine the contribution of each individual agent, the activity of this combination mirrors the preclinical data and warrants further investigations. Bearing in mind the absence of direct comparison, toxicity, or inversely, tolerance, was not increased in comparison to previous single agent daratumumab trials (Lokhorst *et al*, 2015; Lonial *et al*, 2016; Usmani *et al*, 2016). There was no evidence that dexamethasone interfered with the immune response to daratumumab. Unlike data presented by Dimopoulos (2018), regarding isatuximab, another antibody directed against CD38, we did not see any significant synergistic effect between daratumumab and dexamethasone.

Most adverse events could be managed with the use of standard approaches; the incidence of grade IV adverse events was relatively low, and was mostly attributed to disease progression. Infusion-related reactions (IRR) were rare and mild in grade. They did not recur after the first infusion and no patient discontinued treatment permanently due to an IRR in this study. IRRs were reported in approximately half of all patients treated with daratumumab, with most occurring during the first infusion (Lokhorst *et al*, 2015; Lonial *et al*, 2016; Chari *et al*, 2017). Severe myelosuppression was uncommon, and grade IV neutropenia, related febrile neutropenia and sepsis were rare, and related to disease progression in most cases. Overall, 18·5% of patients experienced a grade 3 or higher infection despite prophylaxis. This was directly associated with mortality in 5% of cases, therefore highlighting the importance of the burden of infection

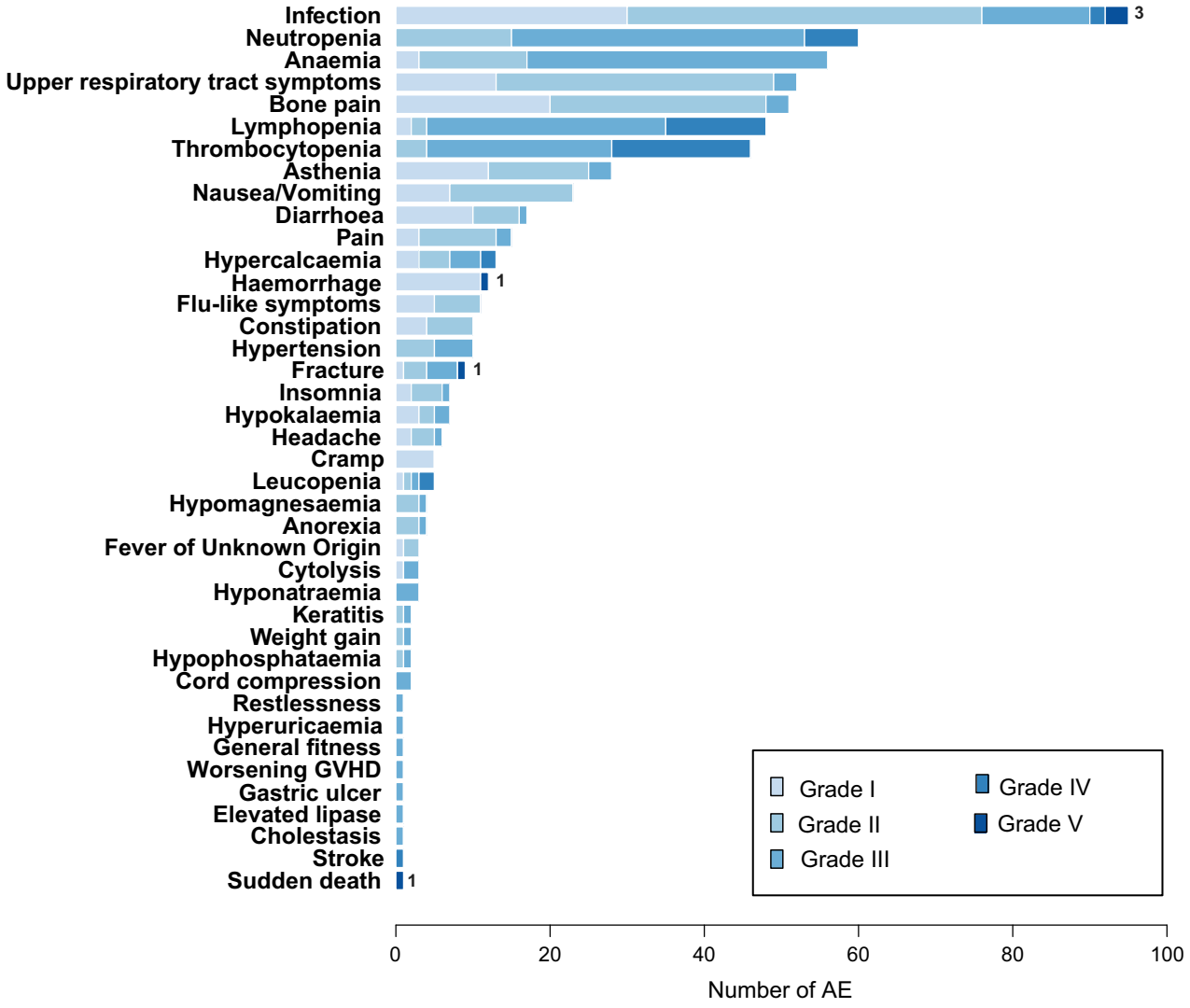

Fig 3. Number of adverse events reported by at least 10% of patients and all Grade 3 or 4 events regardless of relationship to daratumumab. AE, adverse event; GVHD, graft-versus-host- disease.

in this population that not only is responsible for severe morbidity-mortality but may also hinder future drug developments in this setting.

Given this favourable efficacy and toxicity profile, daratumumab was approved by the American Food and Drug Administration in 2015 (U S Food and Drug Administration Home Page, 2015) and the European Medicine Agency approved daratumumab as a single agent in relapsed and RRMM patients previously exposed to lenalidomide, pomalidomide and bortezomib.

In conclusion, the combination of daratumumab and dexamethasone induces clinically significant responses with manageable toxic effects in patients with RRMM, for whom there was, until now, no approved treatment option. The results of this trial and other randomized, multicentre phase III combination studies should provide clinical guidance regarding the use of this agent in earlier-stage disease.

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Table III. Safety: drug-related adverse events reported by at least 10% of patients and all Grade 4 or 5 events regardless of relationship to daratumumab (n = 64).

	Adverse event	Percentage of patients
Grade I/II	Upper respiratory tract symptoms	46·9
	Infection	26·6
	Fatigue	28·13
	Anaemia	20·31
Grade III	Anaemia	32·81
	Lymphopenia	31·25
	Neutropenia	26·56
	Infection	12·5
	Thrombocytopenia	17·2
	Hypercalcaemia	6·25
	Hypertension	4·69
	Fatigue	4·69
	Upper respiratory tract symptoms	4·69
	Increase lipase	1·56
	Increase ALT/AST	1·56
	Duodenal ulcer	1·56
	Worsening GVHD	1·56
	Cholestasis	1·56
	Anorexia	1·56
Grade IV	Lymphopenia	15·6
	Thrombocytopenia	14·0
	Neutropenia	7·81
	Infection	1·56
	Hypercalcaemia	3·13
	Stroke	1·56
Grade V	Infection	4·69
	Subdural haematoma	1·56
	Hip fracture	1·56
	Sudden death	1·56

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GVHD, graft-versus-host-disease.

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Author contributions

Conception and design: EMB, XL, TF. Collection and assembly of data: all authors. Study and CRF conception, Administrative support, Study Coordinator: MOP. Cytogenetic data: HAL. Central laboratory: SS, HC, TD. Data analysis and interpretation: EMB, CPW, TF. Manuscript writing: EMB. Manuscript reviewing and approval: all authors.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supplemental results.

Data S2. A Multicentre Open label Phase II study of Daratumumab in Combination with Dexamethasone in Multiple Myeloma resistant or refractory to Bortezomib and Lenalidomide and Pomalidomide – the IFM 2014-04 study.

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