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Efficacy of retreatment with immunomodulatory drugs and proteasome inhibitors following daratumumab monotherapy in relapsed and refractory multiple myeloma patients

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Summary

This single-centre retrospective observational study analysed the efficacy of retreatment with immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs) after treatment with daratumumab monotherapy in patients with relapsed and/or refractory multiple myeloma (RRMM). In total 55 patients were treated with daratumumab monotherapy between 2010 and 2017. From this group 29 (53%) IMiD-refractory patients were retreated with an IMiD after daratumumab and 6 (11%) PI-refractory patients were retreated with a PI-based regimen. For the IMiD-refractory patients the overall response rate (ORR) was 52% (15/29 patients, partial response or better) upon IMiD retreatment, whereas the ORR to PI retreatment was 67% (4/6 patients) in the PI-refractory group. The immunomodulatory effects of daratumumab may play a role in these high response rates in previously refractory patients. Due to the >6 month-long persistence of daratumumab in the plasma the subsequent therapies can effectively be considered as combination therapy. Furthermore, the excellent tolerability of daratumumab treatment may enable patients to recover from prior lines of treatment and receive full dosing of subsequent therapies. In conclusion, a high proportion of RRMM patients benefitted from retreatment with IMiDs and PIs after daratumumab treatment. These retreatment options should therefore be explored in RRMM patients progressing on daratumumab monotherapy.

Keywords: multiple myeloma, immunotherapy, antibody therapy, immunomodulatory agents, clinical haematology.

Over the past years many new agents for the treatment of multiple myeloma (MM) have been introduced, significantly increasing survival of MM patients. The next-generation immunomodulatory drug (IMiD), pomalidomide, and proteasome inhibitors (PIs), carfilzomib and ixazomib, have demonstrated superior potency and toxicity profiles in comparison to the older IMiDs (thalidomide and lenalidomide) and PI (bortezomib) respectively (Lacy *et al*, 2010; Siegel *et al*, 2012; Kumar *et al*, 2016a). Also, new classes of drugs, such as the monoclonal antibodies daratumumab (anti-CD38) and elotuzumab (anti-SLAMF7) and the histone deacetylase inhibitor panobinostat have been introduced, and several new agents are under investigation (San-Miguel *et al*, 2014; Lokhorst *et al*, 2015; Lonial *et al*, 2015; Moreau, 2017).

Unfortunately, for patients with relapsed and/or refractory disease (RRMM), responses are generally limited and short-lived and their prognosis remains unfavourable. Median overall survival (OS) in patients who are double refractory to a PI and an IMiD is 9–13 months (Kumar *et al*, 2012, 2017). These patients represent a major clinical challenge as data on optimal treatment regimens in this group are limited and trials of new drugs are often difficult to compare. RRMM patients frequently apply only for experimental therapies, but for a large group of patients these are not readily available (van de Donk *et al*, 2011; Botta *et al*, 2017).

Daratumumab monotherapy has shown encouraging results, with overall response rates (ORR) of around 30%, even in heavily pre-treated and refractory patients, in the GEN501 and SIRIUS trials. Moreover, the agent was well tolerated with only few treatment discontinuations due to toxicity. However, with a median progression-free survival (PFS) in these studies of only 4 months, most patients expectedly

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required subsequent therapy within a short time frame after discontinuation (Lokhorst *et al*, 2015; Lonial *et al*, 2016; Usmani *et al*, 2016). The findings that daratumumab also has immunomodulatory effects by targeting CD38-expressing immune cells other than plasma cells and has prolonged persistence in the patients' blood may help guide the choice of next therapy (Oostendorp *et al*, 2015; Krejcik *et al*, 2016).

In May 2016, daratumumab was approved by the European Medicines Agency for application as monotherapy in patients with RRMM after treatment with an IMiD and a PI and who were refractory to their last line of treatment. In April 2017 this therapeutic indication was extended to combination therapy with either lenalidomide and dexamethasone or bortezomib and dexamethasone in MM patients who have received at least one prior therapy. Nonetheless, considering the high costs daratumumab has only recently become available as monotherapy in the Netherlands and currently there is no reimbursement of the combination therapies.

Guidelines and reviews on the treatment of relapsed MM generally recommend to switch classes of drugs, proceed to higher-generation agents or add new cytotoxic drugs in doublet, triplet or even quadruplet combination regimens when initiating subsequent lines of treatment, taking previous responses and toxicities into consideration. These recommendations are however based on limited scientific evidence and are mostly prompted by personal experience or theoretic considerations. Data on the efficacy of retreatment with agents to which patients were previously refractory are scarce. It is mostly advised to consider retreatment with a prior agent only if the patient previously responded and relapsed at least 6 months after the drug was stopped (Nooka *et al*, 2015; Harousseau & Attal, 2017; Moreau, 2017). Retreatment with first-line IMiD's and/or PI's could, however, preserve alternative options for later stages of disease and improve cost-efficacy of treatment. Specifically, after daratumumab treatment this could be an effective treatment option due to the altered immune status of the treated patients and the demonstrated long persistence of the antibody in the patients' plasma for more than 6 months.

The aim of this study was to analyse the efficacy of retreatment with IMiDs and PIs after daratumumab treatment in patients who were considered IMiD and/or PI refractory prior to their daratumumab treatment, in a single-centre observational cohort study.

Materials and methods

We retrospectively studied all patients who received daratumumab monotherapy or daratumumab in combination with all-trans retinoic acid (ATRA) for RRMM at the University Medical Centre of Utrecht between 1 October 2010 and 1 August 2017, either within or outside the context of a clinical trial. Data on previous and subsequent treatment with IMiD's and/or PI's were collected. The diagnosis of MM was made by International Myeloma Working Group (IMWG) criteria (Rajkumar *et al*, 2014). A new line of therapy was initiated for progressive disease (PD) according to national and international guidelines (Rajkumar *et al*, 2014; Zweegman *et al*, 2015). The choice of treatment was based on routine clinical practice considering previous treatment responses and toxicities. Relapse was defined as progression of disease after an initial response (minimal response [MR] or better), more than 60 days after cessation of therapy. Refractory disease was defined as having no response (<MR) during treatment or progression of disease during or within 60 days of cessation of therapy. Disease response was assessed according to the IMWG uniform response criteria (Kumar *et al*, 2016b). ORR was defined as partial response (PR) or better (Kumar *et al*, 2016b). This analysis was performed in accordance with the principle of the Helsinki Declaration, participants of the clinical trials signed the appropriate informed consents.

Results

Patients

In the period October 2010 to August 2017, 55 RRMM patients were treated with daratumumab monotherapy ($n = 46$) or daratumumab in combination with ATRA ($n = 9$). They were either included in the GEN501 or DARA-ATRA trials or treated with compassionate use or commercially available daratumumab. Among these 55 patients, 46 were refractory to at least one IMiD, which was lenalidomide in 43 patients, thalidomide in 12 patients and pomalidomide in 9 patients. Two of these IMiD-refractory daratumumab-treated patients were lost to follow-up. Of the 44 remaining patients, 33 were retreated with an IMiD-containing regimen, four of which were subsequently lost to follow-up or follow-up was too short for an evaluation of response resulting in 29 evaluable patients with IMiD retreatment after daratumumab therapy. Nineteen of the 55 daratumumab-treated patients were refractory to a PI, which was bortezomib in 18 cases and carfilzomib in 1 case. One of the PI-refractory patients was lost to follow-up. Of the 18 remaining patients, six were retreated with a PI-based regimen, in this group there was no further loss to follow-up. See Fig 1 for the patient flow diagram.

Responses to IMiD retreatment in IMiD-refractory patients after daratumumab

In the 29 IMiD-refractory patients retreated with an IMiD-based regimen after daratumumab the ORR was 52% (15/29 patients: 13× PR and 2× very good partial response [VGPR]). Nine patients (31%) showed no response and therapy was stopped after a maximum of 3 cycles because of PD, furthermore 1 patient showed stable disease (SD) and 4 patients had a MR. In total 20/29 patients (69%) therefore had an improvement in comparison to the PD upon their previous IMiD

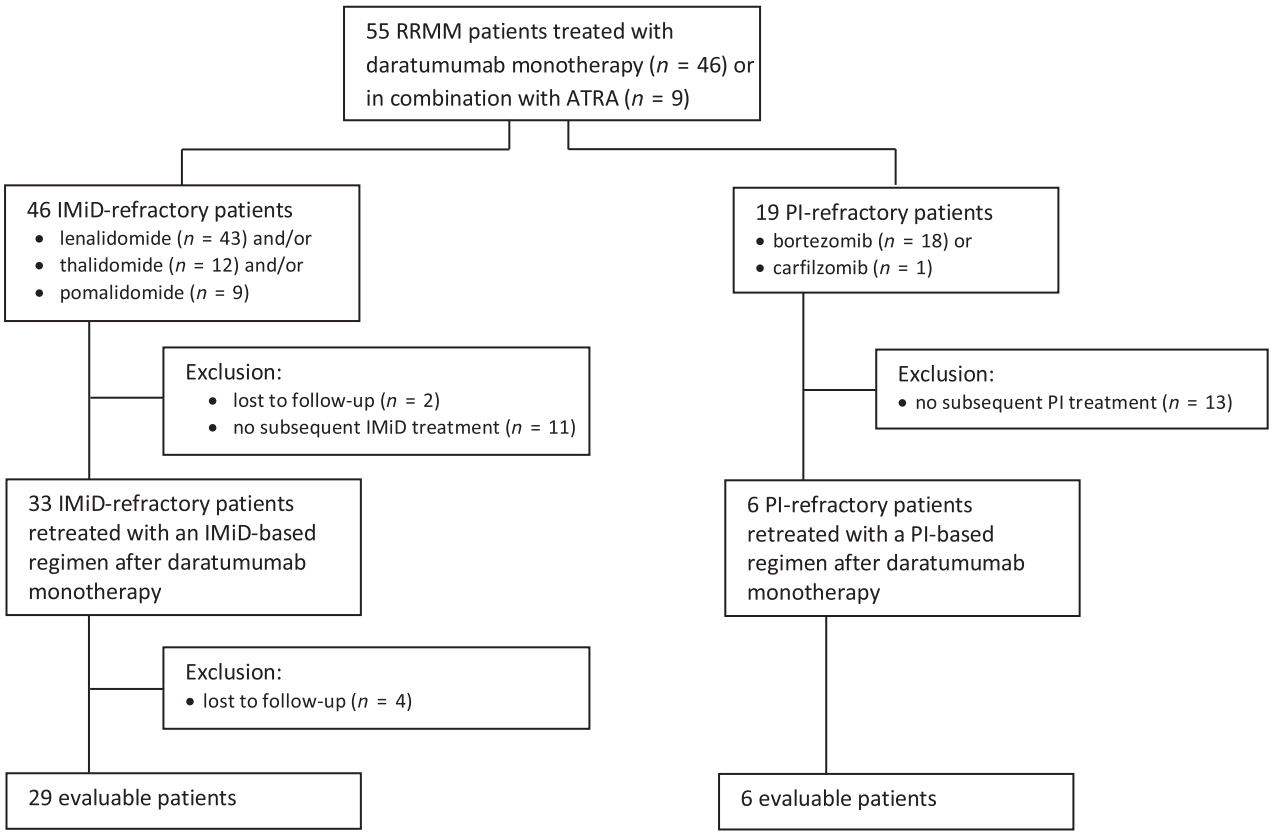

Fig 1. Patient flow diagram. Of 55 RRMM patients treated with daratumumab monotherapy, 29 evaluable IMiD-refractory patients were retreated with an IMiD-based regimen and 6 evaluable PI-refractory patients with a PI-based regimen. ATRA, all *trans* retinoic acid; IMiD, immunomodulatory drug; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma.

treatment. In several cases however a different IMiD, and in many cases a different regimen and/or a different dose was used in the post-daratumumab treatment. Table I and Fig 2 provide detailed information on IMiD retreatment in the IMiD-refractory daratumumab-treated patients. The median time interval between the last IMiD prior to daratumumab and daratumumab imitation was 3 months, with a maximum of 23 months. The median time interval between daratumumab cessation and subsequent IMiD treatment was 1 month, in three patients this time interval was longer than 1 year. Some patients were given other therapies between the IMiD and daratumumab treatments.

Four of the PRs were achieved with the use of pomalidomide in pomalidomide-naïve patients and one MR was achieved with pomalidomide in combination with carfilzomib and dexamethasone in a previously pomalidomide/dexamethasone-refractory patient. Of the remaining 15 responding patients, 13 were retreated with lenalidomide (all lenalidomide-refractory) and two with thalidomide (one thalidomide-refractory, one thalidomide-naïve but refractory to both lenalidomide and pomalidomide). Three patients had a response to lenalidomide at the same dose and in a similar or even less potent combination than their previous lenalidomide-treatment. Median PFS after IMiD retreatment was 3 months for the whole group and 5 months in the responding patients (range 0–37 months). Upon their prior IMiD therapy these patients had a median PFS of 5 months with a range of 0–35 months (data not shown).

Responses to PI retreatment in PI-refractory patients after daratumumab

Six PI-refractory patients were retreated with a PI-based regimen after daratumumab treatment, of which one (17%) again showed PD and one patient developed a MR. The ORR was 67% (4/6 patients: 3× PR and 1× VGPR) in this group. In most cases the subsequent treatment consisted of a more potent regimen than the previous combination: one carfilzomib-naïve bortezomib-refractory patient received carfilzomib and 4 patients went from a doublet to a triplet PI-based combination. One patient developed a VGPR with bortezomib-lenalidomide-dexamethasone (VRD) treatment while refractory to VRD plus cyclophosphamide (VRED) treatment before daratumumab therapy with a similar bortezomib dose, however with an increased lenalidomide dose from 10 to 25 mg. Time intervals between prior PI treatment and daratumumab varied from 1 to 12 months, and between daratumumab cessation and subsequent PI treatment from 1

Table I. Characteristics of IMiD treatment before and after daratumumab treatment in IMiD refractory patients.

Patient	IMiD-refractory	Last IMiD before dara	Interval IMiD-dara (months)	Response to dara	First IMiD after dara	Interval dara-IMiD (months)	Response to IMiD after dara	PFS for IMiD after dara (months, reason for discontinuation)	Improved response to IMiD post-dara
1	lena	lena (MPR-R maintenance, 10 mg)	10	PD	lena (len-dex, 25 mg)	1	MR	2 (progression)	yes
2	lena	lena (RAD, 25 mg)	3	SD	lena (REP, 25 mg)	1	MR	16+ (ongoing)	yes (same dose)
3	lena, thal	lena (REP)	1	SD	thal (TAD-bor, 100 mg)	1	MR	2 (progression)	yes
4	lena, thal, poma	poma (pom-dex)	23	PR	poma (pom-carf-dex, dose unknown)	4	MR	3 (progression)	yes
5	lena	lena (len-dex)	1	PD	lena (KRd)	1	PD	0 (progression)	no
6	lena	lena (len-dex)	1	PD	lena (REP)	1	PD	0 (progression)	no
7	lena	lena (len-dex)	2	PD	lena (VRD)	1	PD	0 (progression)	no
8	lena	lena (REP)	1	PR	poma (pom-dex)	1	PD	0 (progression)	no
9	lena	lena (REP)	3	SD	poma (pom-dex)	1	PD	0 (progression)	no
10	lena	lena (RAD)	27	PD	thal (VTD)	2	PD	0 (progression)	no
11	lena	lena (benda-len-dex)	2	PD	thal (VTD)	1	PD	0 (progression)	no
12	lena, thal	lena (REP)	2	SD	lena (len-dex)	1	PD	0 (progression)	no
13	thal	lena (REP)	1	CR	lena (len-dex)	1	PD	0 (progression)	no
14	lena	lena (REP, 10 mg)	16	PD	poma (pom-dex, 4 mg)	1	PR	7 (progression)	yes
15	lena	lena (VRD, 10 mg)	1	SD	lena (len-dex, 25 mg)	19	PR	37 (progression)	yes
16	lena (len-dex, 25 mg)	thal (VTD)	5	PR	lena (REP, 10 mg)	1	PR	1 (death due to infection)	yes
17	lena	lena (len-dex, 15 mg)	4	PD	lena (REP, 15 mg)	1	PR	7 (death due to infection)	yes
18	lena	lena (len-dex, 10 mg)	6	PR	lena (REP, 10 mg)	27	PR	5 (progression)	yes
19	lena	lena (VRD)	2	PR	poma (pom-dex, 4 mg)	13	PR	4 (progression)	yes
20	lena	lena (REP)	2	PR	poma (pom-dex, 4 mg)	1	PR	10 (progression)	yes
21	lena	lena (REP)	3	PR	poma (pom-dex, 4 mg)	2	PR	5 (progression)	yes
22	lena, poma	poma (pom-dex)	n.a.	PD	lena (RAD, dose unknown)	1	PR	8 (progression)	yes
23	lena, poma	poma (pom-dex)	1	PD	thal (VTD, 100 mg)	1	PR	5 (progression)	yes
24	lena, thal	lena (MPR, 15 mg)	3	VGPR	lena (len-dex, 15 mg)	1	PR	9 (progression)	yes (same dose)
25	lena (mono, 10 mg), thal	thal (thal-dex, dose unknown)	5	SD	lena (len-dex, 25 mg)	1	PR	14 (progression)	yes
26	lena, thal	lena (len-dex, 25 mg)	17	PD	lena (REP, 25 mg)	1	PR	3 (death due to infection)	yes
27	lena	lena (REP, 25 mg)	1	PD	lena (len-dex, 25 mg)	1	SD	3 (progression)	yes (same dose)
28	lena	lena (VRED, 10 mg)	2	CR	lena (VRD, 25 mg)	1	VGPR	4 (progression)	yes
29	lena, thal	lena (REP, 15 mg)	10	SD	lena (len-dex, 25 mg)	1	VGPR	12 (progression)	yes

benda, bendamustine; CR, complete remission; dara, daratumumab; dex, dexamethasone; IMiD, immunomodulatory drug; KRd, carfilzomib, lenalidomide, dexamethasone; lena, lenalidomidemono, monotherapy; MPR(-R), melphalan, prednisone, lenalidomide (+rituximab); MR, minimal response; PD, progressive disease; PFS, progression free survival; poma, pomalidomide; PR, partial response; RAD, lenalidomide, adriamycin, dexamethasone; REP, lenalidomide, cyclophosphamide, prednisone; SD, stable disease; TAD, thalidomide, adriamycin, dexamethasone; thal, thalidomide; VGPR, very good partial response; VRD, bortezomib, lenalidomide, dexamethasone; VRED, bortezomib, lenalidomide, cyclophosphamide, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone.

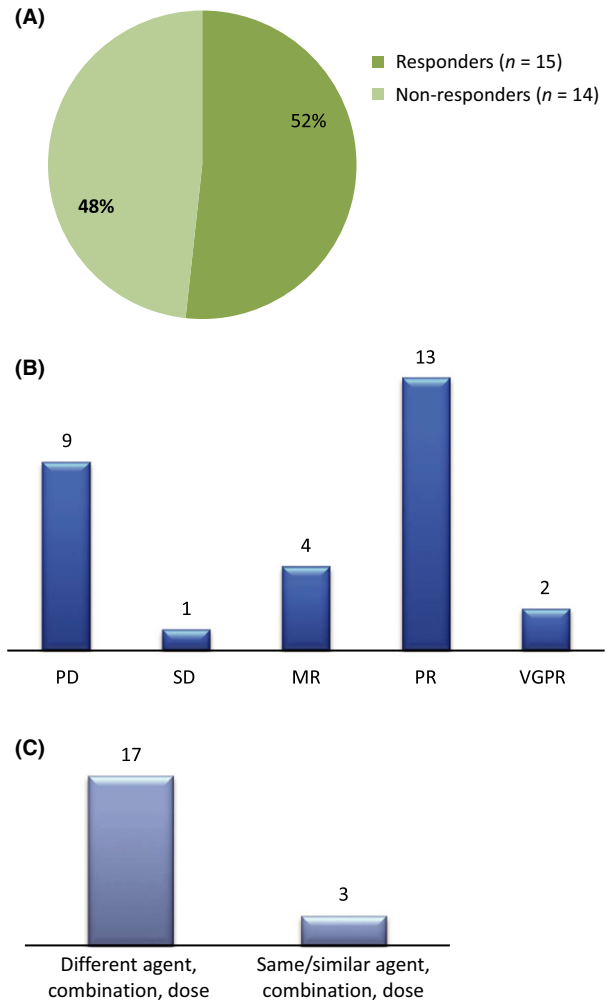

Fig 2. Efficacy of IMiD treatment after daratumumab in IMiD-refractory patients. (A) 29 IMiD-refractory patients were retreated with an IMiD-based regimen, leading to an ORR of 52% (PR or better, 15/29 patients). (B) Distribution of responses in the IMiD-refractory patients. (C) Distribution of variable and comparable treatment combinations and doses in the twenty patients achieving SD or better upon IMiD retreatment.IMiD, immunomodulatory drug; MR, minimal response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response. [Colour figure can be viewed at wileyonlinelibrary.com]

to 24 months, with, in some cases, other therapies in between. The median PFS after PI retreatment was 4 months (range 0–8 months). Table II and Fig 3 provide detailed information of PI retreatment in the PI-refractory daratumumab-treated patients.

Discussion

In this cohort of RRMM patients treated with daratumumab monotherapy, retreatment with IMiDs and/or PIs after prior refractoriness to these agents demonstrated strikingly high ORRs of 52% and 67% respectively, including some VGPRs (7 and 17%, respectively). When the patients achieving MR

Table II. Characteristics of PI treatment before and after daratumumab treatment in PI refractory patients.

Patient	PI-refractory	Last PI before dara	Interval PI-dara (months)	Response to dara	First PI after dara	Interval dara-PI (months)	Response to PI after dara	PFS for PI after dara (months, reason discontinuation)	Improved response PI post-dara
1	bor	bor (MPV, dose unknown)	12	PR	carf (Kd, 56 mg/m^2 biweekly)	6	MR	2 (progression)	yes
2	bor	bor (bor-dex, 1.3 mg/m^2 weekly)	2	PD	bor (VRD, 1.2 mg/m^2 weekly)	1	PD	0 (progression)	no
3	bor	bor (bor-dex, dose unknown)	11	PD	bor (VTD, 1.2 mg/m^2 weekly)	1	PR	4 (progression)	yes
4	bor	bor (bor-dex, 1.3 mg/m^2 biweekly)	1	SD	bor (PAD, 1.3 mg/m^2 biweekly)	24	PR	4 (progression)	yes
5	bor	bor (bor-dex, dose unknown)	6	PD	bor (VTD, 1.6 mg/m^2 weekly)	4	PR	8 (progression)	yes
6	bor	bor (VRED, 1.3 mg/m^2 weekly)	2	CR	bor (VRD, 1.3 mg/m^2 weekly)	1	VGPR	4 (progression)	yes

bor, bortezomib; carf, carfilzomib; CR, complete remission; Kd, carfilzomib, dexamethasone; MPV, melphalan, prednisone, bortezomib; MR, minimal response; PAD, bortezomib, adriamycin, dexamethasone; PD, progressive disease; PFS, progression free survival; PI, proteasome inhibitor; PR, partial response; SD, stable disease; VGPR, very good partial response; VRD, bortezomib, lenalidomide, dexamethasone; VRED, bortezomib, lenalidomide, cyclophosphamide, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone.

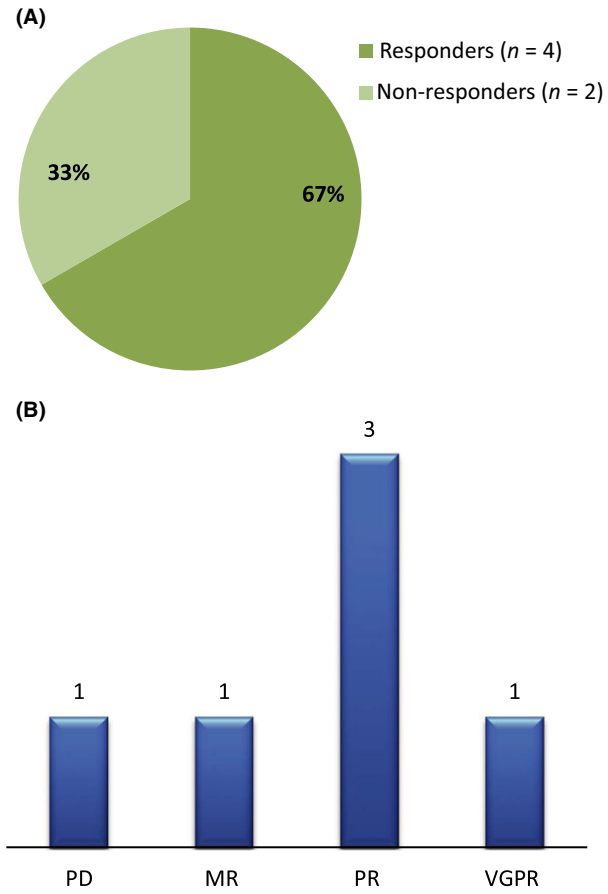

Fig 3. Efficacy of PI treatment after daratumumab in PI-refractory patients. (A) 6 PI-refractory patients were retreated with a PI-based regimen, leading to an ORR of 67% (PR or better, 4/6 patients). (B) Distribution of responses in the PI-refractory patients. MR, minimal response; PD, progressive disease; PR, partial response; VGPR, very good partial response. [Colour figure can be viewed at wileyonlinelibrary.com]

or SD were also included, up to 69% and 83% respectively benefitted from IMiD or PI retreatment. This finding suggests an additional late beneficial effect of daratumumab treatment in this unfavourable group. These data also fit the previously reported observation that even though the median PFS of daratumumab is comparable to pomalidomide and carfilzomib in RRMM, OS is significantly prolonged (20.1 months vs. 13.9 months for pomalidomide and 15.9 months for carfilzomib) (Lacy *et al*, 2010; Siegel *et al*, 2012; Usmani *et al*, 2016). Although our data are single centre and retrospectively analysed, there is currently scarce information available to guide the clinician in the choice of treatment after progression on daratumumab monotherapy.

An exact comparison between the previous and subsequent IMiD- or PI-based treatments is, in many of the analysed cases, difficult as the applied regimens often differed. A more potent combination therapy, consisting of next-generation agents or triplet or quadruplet therapy in contrast to doublet therapy, was chosen for subsequent treatment after daratumumab in the majority of patients. Moreover, IMiDs were frequently administered in a higher dose in the post-daratumumab combinations. Nevertheless, three patients did receive an identical IMiD dose and regimen and still demonstrated an improvement in response compared to their pre-daratumumab IMiD therapy.

Most of the available literature recommends to switch classes of anti-myeloma agents to increase the potency of subsequent therapies at each new line of treatment, but data on retreatment with previously administered drugs are limited. Retreatment with bortezomib was shown to have a response rate of 40–50% in patients who previously responded to bortezomib and relapsed at least 6 months after cessation of the drug (Petrucci *et al*, 2013; Mateos *et al*, 2016). These studies however did not include data on the efficacy of PI retreatment in PI-refractory patients. In patients previously treated with thalidomide or lenalidomide, response rates of subsequent treatment with lenalidomide were 48% and 54% respectively, although the majority of patients were, however, not refractory to IMiD treatment. A response rate of 33% was reported in a subgroup of patients refractory to lenalidomide (defined as an initial response of SD or worse) (Madan *et al*, 2011). Our observation of effective retreatment in refractory patients after daratumumab treatment confirms a previous report in which clinical responses (PR or better) were observed in 29% (9/31) of bortezomib-refractory patients upon retreatment with bortezomib after daratumumab (Usmani *et al*, 2016).

Daratumumab may also target CD38-expressing immune cells other than plasma cells, thereby exerting an immunomodulatory effect that possibly persists into subsequent lines of therapy. Due to the high CD38 expression on mainly regulatory B cells, certain regulatory T cells and myeloid-derived suppressor cells (MDSCs) these are depleted upon daratumumab treatment, while counts of both $CD4^+$ and $CD8^+$ T cells are increased and also the T-cell receptor repertoire is influenced. This altered balance between immunosuppressive cells and effector cells may lead to an improved adaptive immune response, which was most prominent in patients responding to daratumumab, but is also observed in patients without clinical responses (Krejcik *et al*, 2016; Feng *et al*, 2017). Furthermore data on the interference of anti-CD38 antibodies with blood compatibility testing suggest that daratumumab can persist in the patients' plasma for up to at least 6 months after the last infusion (Oostendorp *et al*, 2015; van de Donk *et al*, 2016). In large phase 3 clinical trials daratumumab was demonstrated to be very effective as ≥second line of therapy both in combination with lenalidomide and dexamethasone as well as bortezomib with dexamethasone, with ORRs of 92.9% and 82.9% respectively and 12-month PFS rates of 83.2% and 60.7% respectively (Dimopoulos *et al*, 2016; Palumbo *et al*, 2016). The subsequent therapy after cessation of daratumumab could effectively be considered as a combination therapy with a potential synergy between the daratumumab still circulating in the patient and the subsequently administered IMiD or PI. In our cohort,

three patients achieved a PR to a subsequent IMiD-based regimen started more than 12 months after cessation of daratumumab (13, 19 and 27 months interval), which could reflect an even longer persistence of daratumumab in the plasma. An alternative explanation for the regained sensitivity to IMiDs and PIs after daratumumab treatment and the observed improved OS could be that daratumumab is so well tolerated that patients can recover from toxicities of prior therapies and can be treated with subsequent therapies at higher dose levels or in more aggressive combinations.

In conclusion, we analysed for the first time IMiD and PI retreatment responses after daratumumab monotherapy in RRMM patients. Fifty-two percent of IMiD-refractory patients regained a response (PR or better) upon IMiD retreatment after daratumumab therapy and this was demonstrated for 67% of PI-refractory patients when retreated with a PI. These improved responses may have contributed to the significantly improved OS reported for daratumumab treatment in RRMM patients. Possibly, immunomodulatory effects of daratumumab treatment leading to an altered balance between immunosuppressive cell subsets and effector T cells play a role, but also the prolonged half life time and the tolerability of daratumumab may contribute to these responses and enable patients to receive full dosing of subsequent therapies. This finding may contribute to increased treatment options and improved cost-efficacy in this unfavourable patient group. We therefore propose that IMiD and PI retreatment should be taken into consideration in MM patients progressing on daratumumab monotherapy, even in refractory patients.

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Contributions of the authors: RO designed the research, collected and analysed the data and wrote the paper, MJ analysed the data and wrote the paper, RM analysed the data, RR analysed the data, MM designed the research, analysed the data and wrote the paper.

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