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ORIGINAL ARTICLE

Pomalidomide, cyclophosphamide, and dexamethasone for relapsed/refractory multiple myeloma patients in a real-life setting: a single-center retrospective study

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Abstract

Pomalidomide dexamethasone is a standard of care for relapsed multiple myeloma (MM) patients who received at least two prior lines of therapy, including both lenalidomide and proteasome inhibitors (PI). We report here a real-life single-center series of 49 consecutive patients with relapsed and refractory MM treated with the triplet pomalidomide cyclophosphamide dexamethasone (PCD) combination. The median of prior lines of therapy was 3 and all patients were previously exposed to proteasome inhibitors and lenalidomide. The overall response rate was 76%, including 27% very good partial response or better. With a median follow-up of 16 months, the median progression-free survival (PFS) was 7.3 months and the median overall survival was not reached. Regarding safety, most frequent toxicity was hematologic, including 37% grade 3–4 cytopenias. Nine patients (18%) discontinued therapy due to adverse event. Our study confirms that PCD combination is feasible and results in favorable response rate and PFS in comparison with pomalidomide dexamethasone alone.

Keywords Multiple myelomas · Pomalidomide · Cyclophosphamide · Dexamethasone · Relapse · PCD

Introduction

The life expectancy of myeloma patients has doubled over the past decades [1]. This outstanding improvement is predominantly due to the widespread use of novel agents, including proteasome inhibitors (PI), immunomodulatory drugs (IMiDs), and more recently monoclonal antibodies. However, the outcome of patients whose disease became refractory to PI and IMiDs remains poor, with a median overall survival (OS) of nearly 1 year [2]. The large phase 3 randomized trial MM-003 lead to the approval of pomalidomide and low-dose dexamethasone (Pd) for the treatment of patients with relapsed and refractory myeloma who have received at least two prior therapies, including both lenalidomide and bortezomib [3]. In this trial, patients randomized in the Pd arm achieved an overall response rate (ORR) of 31% and a median progression-free survival (PFS) of 4 months. Similar results were confirmed in the STRATUS trial (MM-010), a phase 3b study that assessed the safety and efficacy of pomalidomide plus low-dose dexamethasone in a large cohort of 682 patients with relapsed or refractory multiple myeloma, previously exposed to alkylator therapy and who failed treatment with bortezomib and lenalidomide [4]. In order to improve these results, the triplet oral combination pomalidomide cyclophosphamide and dexamethasone (PCD) has been investigated [5–7]. In the present study, we report the safety and efficacy of the PCD combination in 49 patients with relapsed and refractory MM who have received at least two prior therapies, including both lenalidomide and PI.

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Material and methods

Patients

We conducted a retrospective institutional review board–approved analysis of all consecutive patients that fulfilled the following criteria: (i) diagnosis of multiple myeloma according to international criteria [8]; (ii) relapsed and/or refractory to at least two priors therapies, including lenalidomide and PI; and (iii) treated with pomalidomide, cyclophosphamide, and dexamethasone. All patients were treated in our institution (Hematology Department, University Hospital of Nantes, France). For each patient, we collected baseline data at the time of PCD therapy initiation including age, sex, ECOG PS, isotype, renal function, cytogenetic by FISH (i.e., *t*(4;14) and 17p deletion), the presence of extramedullary disease, and prior therapies. Cytogenetic abnormalities were considered to be significant if detected in more than 10% of the cells for fusions, and 20% for number abnormalities.

Treatment

The starting dose of PCD combination was as follows: pomalidomide (4 mg once daily orally on days 1–21 of each 28-day cycle), cyclophosphamide (300 mg/day weekly on days 1, 8, 15, and 22), and dexamethasone (40 mg weekly on days 1, 8, 15, and 22). For patient above 75 years old or patients with recorded grade 3–4 toxicity from prior corticosteroid therapy, the starting dose of dexamethasone was reduced to 20 mg weekly. All patients received deep venous thrombosis (DVT) prophylaxis, either with aspirin or low-molecular-weight heparin, according to their risk factors for thrombosis. PCD was given until disease progression or unacceptable toxicity.

Statistical analysis

Response to treatment was determined according to the international criteria [9]. Progression-free survival (PFS) and OS were calculated using the Kaplan-Meier method and compared by the log-rank test from the first day of PCD therapy.

Results

Patient characteristics

From January 2015 to July 2018, 49 consecutive patients with relapsed multiple myeloma previously treated with at least 2 prior lines of therapy including PI and lenalidomide were treated with PCD at our institution. Patient characteristics are summarized in Table 1. The median age was 66 years. Eight patients (16%) were aged above 75 years. Nine (18%) patients had high-risk cytogenetic (*t*(4;14) or 17p deletion). The median time from diagnosis to PCD therapy was 5 years (range, 0.5–17.5 years). The median number of prior therapies was 3 (range, 2–8). All patients were previously treated with lenalidomide and a proteasome inhibitor. Thirty-nine (80%) patients were refractory to lenalidomide. Twenty-eight (57%) patients were refractory to PI including 17 (35%) patients refractory to bortezomib. A double refractory status (lenalidomide and PI) was identified in 21 (43%) patients.

Table 1 Baseline characteristics at time of PCD therapy

	n = 49
Median age, years (range)	66 (46–83)
Age > 75 ans	8 (16%)
Immunoglobulin isotype	
Ig G	31 (63%)
Ig A	8 (16%)
Light chains	10 (21%)
International system staging	
I	14 (29%)
II	26 (53%)
III	9 (18%)
High-risk FISH*	9 (18%)
17p deletion	4 (8%)
(4,14) translocation	5 (10%)
Extramedullary disease	4 (8%)
MDRD clearance < 50 ml/min	11 (22%)
Prior therapies	
Median numbers of prior therapies (range)	3 (2–8)
Refractory to the last therapy	37 (76%)
Prior ASCT	35 (71%)
Prior Btz/refractory to Btz	45 (92%) / 17 (35%)
Prior Len/refractory to Len	49 (100%) / 39 (80%)
Len refractory as last line of therapy	16 (33%)
Prior Carf/refractory to Carf	14 (29%) / 11 (22%)
Double refractory to len and PI	21 (43%)

*Cytogenetic abnormalities were considered to be significant if detected in more than 10% of the analyzed cells for fusions and 20% for number abnormalities

FISH, fluorescence in situ hybridization; *MDRD*, modification of diet in renal disease; *Btz*, bortezomib; *len*, lenalidomide; *Carf*, carfilzomib

Efficacy

Patients received a median number of 7 cycles of PCD (range, 1–32). The overall response rate (ORR) was 76%, including 27% very good partial response. Four patients achieved a negative immunofixation. The median time to best response was 3.6 months. Because bone marrow aspiration was not routinely done in patients achieving a negative immunofixation outside clinical trials, no complete response

has been confirmed. The median follow-up since PCD treatment initiation was 16 months. At the time of analysis (February 2019), thirty-one (63%) patients have discontinued PCD because of disease progression and nine (18%) patients still remain on treatment. The estimated median PFS was 7.3 months (Fig. 1) and the estimated median OS was not reached (Fig. 1b). Patients with high-risk cytogenetic ($n = 9$) were found to have shorter median PFS (3.3 vs 7.9 months, $p = 0.0027$) and shorter median OS (6.5 months vs not reached, $p = 0.003$) in comparison with patients with standard-risk cytogenetic. Non-responder patients ($n = 12$) were found to have shorter median PFS (3 vs 8.4 months, $p < 0.0001$) and shorter median OS (4.2 months vs not reached, $p = 0.0043$) in comparison with patients who achieved at least a partial response. Patients with lenalidomide-refractory disease were found to have similar median PFS and OS than patients who were not refractory to lenalidomide. PFS and OS results for the different subgroups of patients are represented in Fig. 2.

Safety

Nineteen patients (39%) required dose reduction for pomalidomide and 14 patients (29%) required dose reduction for cyclophosphamide due to grade 3 or 4 cytopenias. Dexamethasone dose was decreased in 6 (11%) patients. The most common adverse event was hematologic toxicity, recorded in 24 (49%) patients. Among these patients, 18 (37%) experienced grade 3–4 hematologic toxicity. Despite risk-adapted DVT prophylaxis, 2 (4%) patients developed thrombosis. No death related to toxicity was reported. Overall, 9 (18%) patients stopped PCD therapy because of adverse event: secondary primary malignancy (melanoma ($n = 1$), gastro-intestinal cancer ($n = 1$)), grade 3 fatigue ($n = 1$), and grade 3/4 cytopenia ($n = 6$). Safety and efficacy results are summarized in Table 2.

Discussion

This single-center retrospective study investigated the efficacy of PCD in relapsed myeloma patients who received at least 2 prior lines of therapy including lenalidomide and PI. Patients had advanced myeloma with a median number of 3 prior therapies. Most patients (80%) had lenalidomide-refractory disease and the majority of them had PI-refractory disease. In this context, PCD therapy resulted in an ORR of 76% and a median PFS of 7.3 months. These results compared favorably with those obtained with Pd (ORR of 31% and median PFS of 4 months) in a similar population of MM patients [3]. In our study, the benefit of PCD therapy in terms of PFS and OS is mainly observed in patients without high-risk cytogenetic ($t(4;14)$ and/or 17p deletion) and in patients who achieved at least a partial response.

Only a few data investigating the efficacy of PCD in advanced MM patients previously treated with lenalidomide and PI are available. In a phase 2 randomized study, Baz and colleagues reported the efficacy of PCD in 34 patients with relapsed myeloma [5]. The median number of prior therapies was 4 and all patients were refractory to lenalidomide. In this trial, pomalidomide was given at the dose of 4 mg (days 1 to 21 of a 28-day cycle) and cyclophosphamide was given

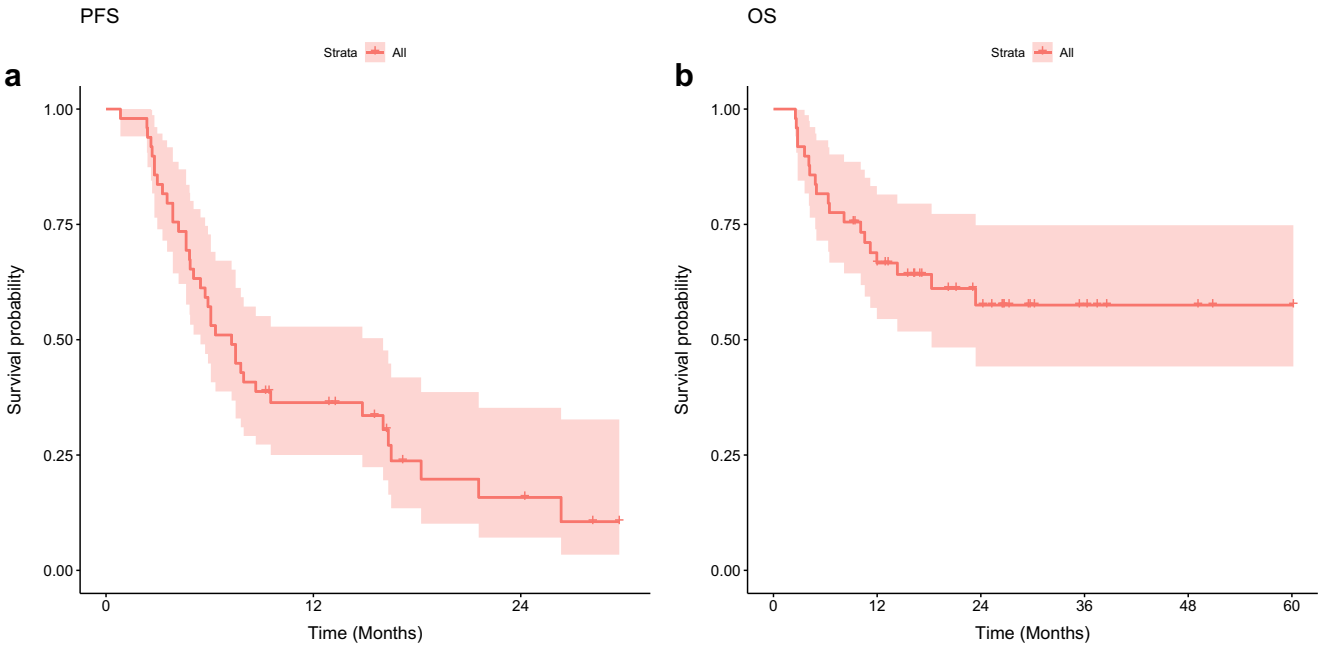

Fig. 1 Progression-free survival and overall survival

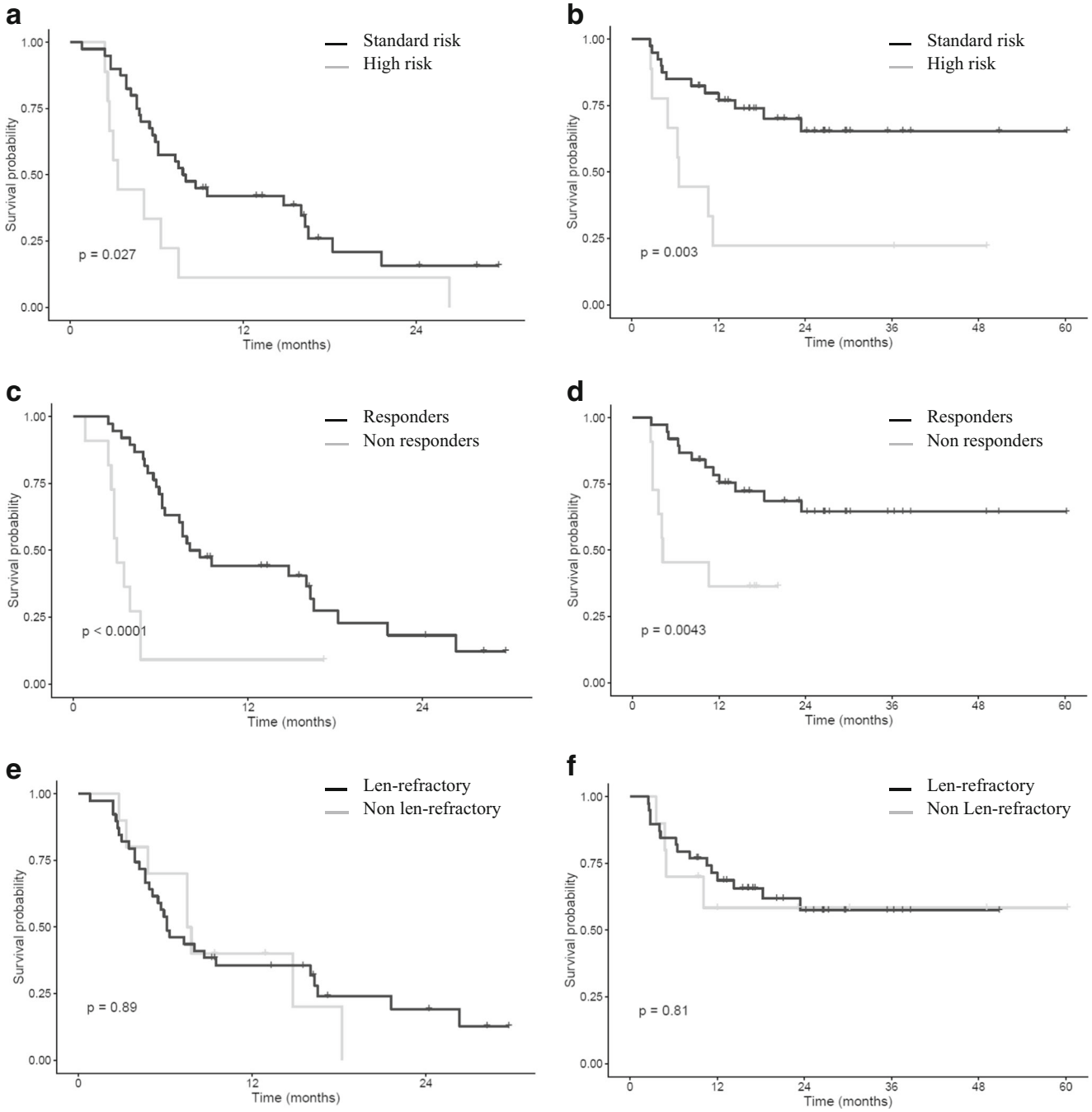

Fig. 2 Outcome according to cytogenetic risk, response, and lenalidomide refractory status. PFS and OS according to cytogenetic risk are represented in (**a**) and (**b**), respectively. PFS and OS according to response to therapy are represented in (**c**) and (**d**), respectively (responder patients are patients who achieved at least a partial response). PFS and OS according to lenalidomide-refractory status are represented in (**e**) and (**f**), respectively. len, lenalidomide

400 mg orally on days 1, 8, and 15. Patients received higher dose of dexamethasone during the 4 first cycles (40 mg day 1 to 4 and 40 mg from day 15 to 18) and then 40 mg weekly. PCD resulted here in an ORR of 65% and in a median PFS of 9.5 months. The main toxicity was hematologic, including 51% grade 3–4 neutropenia. Larocca and colleagues reported a phase 1–2 study evaluating the efficacy of pomalidomide (2.5 mg/day) in combination with cyclophosphamide (50 mg every other day) and prednisone (50 mg every other day) in relapsed myeloma patients ($n = 55$) [7]. The median number

Table 2 Safety

	Overall AE, *n* (%)	Grade1/2, *n* (%)	Grade 3/4, *n* (%)
Infection	8 (16%)	3 (6%)	5 (10%)
Neutropenia	22 (45%)	8 (16%)	14 (29%)
Thrombocytopenia	15 (31%)	9 (18%)	6 (12%)
Anemia	17 (35%)	10 (20%)	7 (14%)
Thrombosis	2 (4%)	2 (4%)	0
AE related to corticosteroids	7 (14%)	2 (4%)	5 (10%)

AE, adverse event

of prior therapies was 3, and 67% of patients were refractory to lenalidomide. In this trial, the ORR was 51% and the median PFS was 10 months [6]. Taken together, the present study and the 2 early-phase trial from Baz and Larocca indicate that the addition of cyclophosphamide to pomalidomide improve the ORR and median PFS in comparison with Pd alone in advanced myeloma patients refractory to lenalidomide. In our study, the median PFS (7.3 months) tends to be slightly shorter than those obtained in the studies from Baz and Larocca (9.5 and 10 months, respectively). However, it is difficult to compare clinical data obtained from clinical trials and data from real life. Indeed, real-life studies include more unselected patients (i.e., the presence of renal failure, poor performance status).

Recently, a phase 2 trial from the Intergroupe Francophone du Myélome (IFM) group evaluated the efficacy and safety of PCD in MM patients at first relapse. Forty-nine patients received 8 cycles of PCD (pomalidomide 4 mg days 1–21, cyclophosphamide 300 mg weekly, and dexamethasone 40 mg weekly) followed by Pd given until disease progression. For these patients, the ORR was 84% and the median PFS was 24 months. This promising efficacy results should therefore be interpreted in the context of patients at first relapse, and not refractory to lenalidomide.

In myeloma patients relapsing after bortezomib therapy and refractory to lenalidomide, the addition of carfilzomib to pomalidomide and dexamethasone has been also evaluated [10, 11]. In these two phase 1 studies, carfilzomib was given twice or once weekly with standard pomalidomide and dexamethasone schedule. The overall response rates were 50% and 62%, respectively. The median PFS were 7.2 and 10 months, respectively. No adverse safety signals were reported. For the treatment of relapsed myeloma patients who received at least 2 prior lines of therapy including lenalidomide and PI, the addition of monoclonal antibodies to pomalidomide and dexamethasone has also been reported. A large phase 1b study reported the promising efficacy of pomalidomide dexamethasone and daratumumab (Dara-Pd) in 103 patients with advanced MM (median of 4 prior therapies, 20% refractory to lenalidomide) [12]. The ORR was 60% and the median PFS was 8.8 months. More recently, the randomized trial ELOQUENT-3 demonstrated the superiority of pomalidomide dexamethasone and elotuzumab (Elo-Pd) over Pd alone in 117 patients with relapsed MM refractory to lenalidomide [13]. Patients in the

Table 3 Triplet pomalidomide-based combination for relapsed myeloma patients who received at least 2 prior lines of therapy including lenalidomide and proteasome inhibitor

Study	Treatment	*n*	Prior lines (median)	Lenalidomide refractory (%)	Previously exposed to PI (Btz/Carf) (%)	ORR (%)	PFS (months)
Present study	PCD	54	3	81	93/27	72	6.5
Baz et al.	PCD	34	4	100	71/38	65	9.5
Larocca et al.	PCPred	55	3	67	84/0	51	10.4
Shah et al.	KPD	32	6	100	97/0	50	7.2
Bringhen et al.	KPD	57	2	100	96/0	62	10.3
Dimopoulos et al.	Elo-Pd	60	3	90	100/15	53	10.3
Chari et al.	Dara-Pd	103	4	20	98/33	60	8.8

Btz, bortezomib; *Carf*, carfilzomib; *ORR*, overall response rate; *PFS*, progression-free survival; *PCD*, pomalidomide cyclophosphamide dexamethasone; *PCPred*, pomalidomide cyclophosphamide prednisone; *Elo-Pd*, elotuzumab pomalidomide dexamethasone; *Dara-Pd*, daratumumab pomalidomide dexamethasone

Elo-Pd arm had an improved ORR (53% vs 26%) and an improved PFS (median 10.3 versus 4.7 months). Studies evaluating the efficacy of triplet pomalidomide-based combination in relapsed myeloma patients who received at least 2 prior lines of therapy including lenalidomide and PI are summarized in Table 3.

To the best of our knowledge, this study is the first report evaluating the efficacy of the triplet PCD combination in MM patients in a "real-life" setting. In relapsed MM patients who received at least 2 prior lines of therapy including lenalidomide and PI, the addition of cyclophosphamide to pomalidomide and dexamethasone compared favorably to Pd alone in terms of ORR and PFS. Even if triplet pomalidomide-based combinations with monoclonal antibodies are promising, such combinations are not yet approved. PCD is therefore a manageable, cost-effective, and oral triplet combination for relapsed MM patients eligible to Pd.

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Authorship CT, PM, and ST designed the study. ST collected the data. ST and BT performed statistical analysis. CT and ST wrote the manuscript. All authors treated patients and critically reviewed the manuscript and gave the final approval.

Compliance with ethical standards

Conflict of interest CT and PM are advisory board member and received honoraria from Celgene.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Zeldenrust SR, Dingli D, Russell SJ, Lust JA, Greipp PR, Kyle RA, Gertz MA (2008) Improved survival in multiple myeloma and the impact of novel therapies. Blood 111:2516–2520. https://doi.org/10.1182/blood-2007-10-116129
2. Kumar SK, Dimopoulos MA, Kastritis E, Terpos E, Nahi H, Goldschmidt H, Hillengass J, Leleu X, Beksac M, Alsina M, Oriol A, Cavo M, Ocio EM, Mateos MV, O'Donnell EK, Vij R, Lokhorst HM, van de Donk NWCJ, Min C, Mark T, Turesson I, Hansson M, Ludwig H, Jagannath S, Delforge M, Kyriakou C, Hari P, Mellqvist U, Usmani SZ, Dytfeld D, Badros AZ, Moreau P, Kim K, Otero PR, Lee JH, Shustik C, Waller D, Chng WJ, Ozaki S, Lee JJ, de la Rubia J, Eom HS, Rosinol L, Lahuerta JJ, Sureda A, Kim JS, Durie BGM (2017) Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. Leukemia 31:2443–2448. https://doi.org/10.1038/leu.2017.138
3. San Miguel J, Weisel K, Moreau P et al (2013) Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol 14:1055–1066. https://doi.org/10.1016/S1470-2045(13)70380-2
4. Dimopoulos MA, Palumbo A, Corradini P, Cavo M, Delforge M, di Raimondo F, Weisel KC, Oriol A, Hansson M, Vacca A, Blanchard MJ, Goldschmidt H, Doyen C, Kaiser M, Petrini M, Anttila P, Cafro AM, Raymakers R, San-Miguel J, de Arriba F, Knop S, Rollig C, Ocio EM, Morgan G, Miller N, Simcock M, Peluso T, Herring J, Sternas L, Zaki MH, Moreau P (2016) Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUSTM (MM-010): a phase 3b study in refractory multiple myeloma. Blood. 128:497–503. https://doi.org/10.1182/blood-2016-02-700872
5. Baz RC, Martin TG, Lin H-Y et al (2016) Randomized multicenter phase II study of pomalidomide, cyclophosphamide, and dexamethasone in relapsed refractory myeloma. Blood. 127:2561–2568. https://doi.org/10.1182/blood-2015-11-682518
6. Garderet L, Kuhnowski F, Berge B, Roussel M, Escoffre-Barbe M, Lafon I, Facon T, Leleu X, Karlin L, Perrot A, Moreau P, Marit G, Stoppa AM, Royer B, Chaleteix C, Tiab M, Araujo C, Lenain P, Macro M, Voog E, Benboubker L, Allangba O, Jourdan E, Orsini-Piocelle F, Brechignac S, Eveillard JR, Belhadj K, Wetterwald M, Pegourie B, Jaccard A, Eisenmann JC, Glaisner S, Mohty M, Hulin C, Loiseau HA, Mathiot C, Attal M (2018) Pomalidomide, cyclophosphamide, and dexamethasone for relapsed multiple myeloma. Blood. 132:2555–2563. https://doi.org/10.1182/blood-2018-07-863829
7. Larocca A, Montefusco V, Bringhen S, Rossi D, Crippa C, Mina R, Galli M, Marcatti M, la Verde G, Giuliani N, Magarotto V, Guglielmelli T, Rota-Scalabrini D, Omede P, Santagostino A, Baldi I, Carella AM, Boccadoro M, Corradini P, Palumbo A (2013) Pomalidomide, cyclophosphamide, and prednisone for relapsed/refractory multiple myeloma: a multicenter phase 1/2 open-label study. Blood 122:2799–2806. https://doi.org/10.1182/blood-2013-03-488676
8. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O, Paiva B, Dispenzieri A, Weiss B, LeLeu X, Zweegman S, Lonial S, Rosinol L, Zamagni E, Jagannath S, Sezer O, Kristinsson SY, Caers J, Usmani SZ, Lahuerta JJ, Johnsen HE, Beksac M, Cavo M, Goldschmidt H, Terpos E, Kyle RA, Anderson KC, Durie BGM, Miguel JFS (2014) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 15:e538–e548. https://doi.org/10.1016/S1470-2045(14)70442-5
9. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, Munshi N, Lonial S, Bladé J, Mateos MV, Dimopoulos M, Kastritis E, Boccadoro M, Orlowski R, Goldschmidt H, Spencer A, Hou J, Chng WJ, Usmani SZ, Zamagni E, Shimizu K, Jagannath S, Johnsen HE, Terpos E, Reiman A, Kyle RA, Sonneveld P, Richardson PG, McCarthy P, Ludwig H, Chen W, Cavo M, Harousseau JL, Lentzsch S, Hillengass J, Palumbo A, Orfao A, Rajkumar SV, Miguel JS, Avet-Loiseau H (2016) International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 17:e328–e346. https://doi.org/10.1016/S1470-2045(16)30206-6
10. Shah JJ, Stadtmauer EA, Abonour R, Cohen AD, Bensinger WI, Gasparetto C, Kaufman JL, Lentzsch S, Vogl DT, Gomes CL, Pascucci N, Smith DD, Orlowski RZ, Durie BGM (2015) Carfilzomib, pomalidomide, and dexamethasone for relapsed or

refractory myeloma. Blood 126:2284–2290. https://doi.org/10.1182/blood-2015-05-643320

11. Bringhen S, Mina R, Cafro AM, Liberati AM, Spada S, Belotti A, Gaidano G, Patriarca F, Troia R, Fanin R, de Paoli L, Rossi G, Lombardo A, Bertazzoni P, Palumbo A, Sonneveld P, Boccadoro M (2018) Once-weekly carfilzomib, pomalidomide, and low-dose dexamethasone for relapsed/refractory myeloma: a phase I/II study. Leukemia 32:1803–1807. https://doi.org/10.1038/s41375-018-0024-1
12. Chari A, Lonial S, Suvannasankha A et al (2015) Open-label, multicenter, phase 1b study of Daratumumab in combination with Pomalidomide and dexamethasone in patients with at least 2 lines of prior therapy and relapsed or relapsed and refractory multiple myeloma. Blood 126:508–508
13. Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M, Leleu X, LeBlanc R, Suzuki K, Raab MS, Richardson PG, Popa McKiver M, Jou YM, Shelat SG, Robbins M, Rafferty B, San-Miguel J (2018) Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. N Engl J Med 379:1811–1822. https://doi.org/10.1056/NEJMoa1805762