Real-world use of pomalidomide and dexamethasone in double refractory multiple myeloma suggests benefit in renal impairment and adverse genetics: a multi-centre UK experience

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Summary

Myeloma patients who become refractory to IMiDs and bortezomib have poor survival, with limited therapeutic options. Pomalidomide has shown improved survival and good tolerability in this patient cohort in clinical trials, but real world data are scarce. We retrospectively analysed all patients treated with pomalidomide at 5 UK centres between 2013 and 2016. Of 85 patients identified, 70 had sufficient information for response assessments. Median age was 66 years [40-89], 96.5% were refractory to IMiDs, 72.9% were refractory to both an IMiD and bortezomib and 92.9% were refractory to their last treatment. Of patients with FISH results (45) 64% had adverse risk, 19 patients (22.4%) had eGFR <45ml/min. Grade ≥3 non-haematological toxicities occurred in 42.4%, and grade ≥3 neutropenia and thrombocytopenia in 38% and 24% respectively, but only 18.8% had dose reductions. The ORR was 52.9%. At a median follow up of 13.2 months, median PFS was 5.2 months (95% CI 4.150 – 6.238), and median OS 13.7 months (95% CI 11.775 – 15.707). No significant difference was seen in response, survival or tolerability by renal function, age or cytogenetic risk. This real-world data support the results seen in published clinical trials.

Keywords: multiple myeloma, myeloma therapy, imids, hematological malignancy, clinical

Introduction

Despite recent improvements in overall survival, myeloma remains an incurable disease with a median overall survival of 7 years. (Kumar *et al*, 2014) The therapeutic options remain limited for patients who relapse after or become refractory to bortezomib and IMiDs (thalidomide or lenalidomide), with a median overall survival (OS) of 9 months and only 3 months if no further treatment is given (Kumar *et al*, 2012).

Such patients have an increasing symptom burden related to advanced disease and prior therapies(Boland *et al*, 2013),(Mols *et al*, 2012) hence the need for therapies providing good disease control while maintaining quality of life. Pomalidomide is a second generation immunomodulatory agent (IMiD), with efficacy demonstrated in end stage multiple myeloma in both phase 1 and 2 clinical trials.(Richardson *et al*, 2013), (Richardson *et al*, 2014) The pivotal MM-003 trial was a large multi-centre randomised trial of 455 patients refractory to both lenalidomide and bortezomib, comparing pomalidomide (4mg OD for 21/28days) plus low dose dexamethasone (40mg weekly) with high dose dexamethasone alone. ORRs were 32% versus 11%. With a median follow up of 15.4 months pomalidomide/dexamethasone demonstrated a significant benefit in PFS (median 4 months vs 1.9 months, $p < 0.0001$) and OS (median 13.1 vs 8.1 months, $p = 0.009$) despite significant crossover in the high dose dexamethasone arm.(San Miguel *et al*, 2013) A recent phase 3b trial (MM-010) confirmed the safety and efficacy of pomalidomide and low dose dexamethasone in these patients.(Dimopoulos *et al*, 2016)

Based primarily on the MM-003 trial results pomalidomide was approved by both the FDA and EMA in 2013 for patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have progressed on their last therapy. Following adoption by the Cancer Drugs Fund, pomalidomide entered clinical use in the UK in this cohort of patients. Unfortunately in February 2015 NICE (NICE 2015.) did not approve pomalidomide for use as per EMA license and it was subsequently removed from the UK Cancer Drugs Fund in September 2015 (Cancer Drug Fund 2015), restricting NHS access to pomalidomide in the UK to the clinical trial setting.

Pomalidomide has been shown to be relatively well tolerated in patients with advanced/end-stage myeloma. Although myelosuppression is common with neutropenia being the most common side effect, febrile neutropenia has been reported to be relatively infrequent.(Lacy *et al*, 2011)

Clinical trial data may not always reflect real world clinical practice and outcomes, particularly when dealing with a cohort of patients with such advanced stage disease, many of whom have significant disease or treatment related co-morbidities, making delivery of recommended treatment challenging. We thus carried out a retrospective analysis of patients receiving pomalidomide in current UK myeloma practice, to describe

the outcomes as well as tolerability of pomalidomide in a real world clinical setting, in comparison with those from current published clinical trials.

Methods

Patients and treatment details

All patients who had received or were currently receiving treatment with pomalidomide at 5 major UK centres between August 2013 and March 2016 were identified from electronic chemotherapy records. Data on patient demographics, side effects and response to treatment were collected using a standardised proforma. To be included in response assessments, patients had to have measurable disease as defined by IMWG guidelines and have completed at least one cycle of pomalidomide with repeat biomarkers performed. Treatment consisted of 28 day cycles of pomalidomide (taken daily on days 1-21) plus dexamethasone (on days 1, 8, 15 and 22), plus or minus a third agent.

Assessments

Adverse events were graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) Categories of response and progression were identified using IMWG criteria (Rajkumar *et al*, 2011)

FISH, where performed, was carried out on selected CD138+ plasma cells using standard probes.(Smith *et al*, 2015) High risk FISH was defined as del(17p), 1q gain or t(4;14) in line with IMWG risk stratification in multiple myeloma.(Chng *et al*, 2014)

Statistical analysis

Survival was estimated using Kaplan-Meier method. Data analysis was performed in IBM SPSS for Mac, version 22 (IBM Corp., Armink, NY, USA). Curves were plotted using GraphPad Prism, version 7 (GraphPad Software, La Jolla, CA, USA). Comparisons between groups were estimated using the log rank method. Univariate Cox regression was used to assess the impact of baseline characteristics on PFS and OS. P-values <0.05 were considered statistically significant.

Results

A total of 85 patients who received treatment with pomalidomide were identified. Of these, 70 (82%) were able to be included in response analyses. Of the remaining 15 patients for whom response could not be assessed, 7 did not complete a single cycle of treatment, 5 completed 1 cycle but did not have repeat biomarkers, 2 completed 2 cycles but did not have repeat biomarkers, and the final patient completed 9 cycles but had non-secretory disease.

Baseline patient characteristics, treatment and toxicity data and survival for all 85 patients are reported below. Further data regarding response and sub-group survival analyses are reported for the group of 70 patients in whom response data are available..

Patient Characteristics including previous therapy

Demographic details are given in table I. Median patient age was 66 years (range 40 – 89), 15 (17.6%) patients were over 75 and 48 (56.5%) over 65. Renal function was assessed using estimated glomerular filtration rate (eGFR); 32 patients (37.6%) had eGFR less than 60 ml/min, and 19 patients (22.4%) had eGFR less than 45. Results of fluorescent in situ hybridization (FISH) analysis were available in 45 cases (52.9%). Of these, 29 patients (64%) had adverse cytogenetics, 20 patients (44%) if 1q gain was excluded, and 14 (31%) patients had 17p deletion.

Details of previous treatments and responses are given in table II. It is noteworthy that the majority of patients (96.5%) were refractory to one or more IMiDs, and 72.9% were refractory to both an IMiD and bortezomib. Seventy-nine patients were refractory to their last treatment (92.9%).

Pomalidomide therapy

Details regarding median dose, length of treatment and dose reductions are given in table III.

Seventy patients (82.4%) started therapy on pomalidomide plus dexamethasone (doublet therapy). The remaining 15 patients (17.6%) were started on pomalidomide / dexamethasone plus a third agent (triple therapy). Of those started on doublet therapy, 19 patients had a third agent added during treatment (22.4% of total). The third agent(s) given either up front or added in later were clarithromycin (23), cyclophosphamide (9), carfilzomib (1), and bortezomib (1).

Toxicity and tolerability of pomalidomide therapy

Grade 3 – 4 non-haematological toxicities occurred in 36 out of 85 patients (42.4%): lower respiratory tract infection, 14 (16.5%), neutropenic sepsis, 7 (8.2%), and acute kidney injury, 6 (7.1%), were the most common. Rates of fatigue and venous thromboembolism were low. Grade 3 - 4 neutropenia occurred in 32 patients (38%) and thrombocytopenia in 20 patients (24%) (table IV). Six patients died during the first cycle, 1 with progressive disease and sepsis, 2 with neutropenic sepsis (one had a strangulated hernia), 2 with renal failure in the context of progressive disease, and one from pneumonia. One further patient died on treatment, of lower respiratory tract infection. Of those six patients, 5/6 were male, 4/6 were aged over 70 and 5/6 had a GFR < 45ml/min.

Disease response and survival

The median follow up for the whole group of 85 patients was 13.2 months. Median PFS was 4.5 months (95% CI 2.837 - 6.104) and median OS 9.7 months (95% CI 5.078 - 14.252) Figure 1a). We also analysed outcomes for the group of 70 response assessable patients (median follow up 13.2 months). Of this group, 67 patients had progressed or died (95.7%), 49 of whom had died (70%). Median PFS was 5.2 months (95% CI 4.150 – 6.238), and median OS 13.7 months (95% CI 11.775 – 15.707) See Figure 1b.

ORR (in response assessable patients) was 52.9%, (5.7% VGPR, 47.1% PR and 38.6% SD) (table V). No patients achieved CR. Median time to best response was 1 month, and median duration of response was 4 months.

All correlates of treatment outcomes are reported for the response assessable group of 70 patients.

Effect of renal impairment

12 patients (17.1%) had eGFR <45 ml/min. Amongst these patients, median starting dose of pomalidomide was 4mg and 5 patients received less than 4mg as a starting dose. In this group of patients, ORR was 50%; 1 patient achieved VGPR, 5 patients achieved PR (41.7%), 4 patients SD and 2 patients had PD. By comparison, amongst patients with eGFR ≥45 (n = 58), ORR was 53.4%, with 3 patients achieving VGPR, and 28 patients (48.3%) achieving PR. Thus, disease responses were similar for both groups of patients.

On univariate analysis, eGFR <45 did not significantly influence PFS or OS. Median PFS in patients with eGFR <45ml/min was 3.7 months, compared with 5.2 months in patients with eGFR ≥45 (HR = 0.952, 95% CI 0.496 – 1.827, p = 0.882). Median OS in patients with eGFR <45ml/min was 7.4 months, compared with 14.1 months in those with for eGFR ≥45ml/min (HR = 1.224, 95% CI 0.592 – 2.531, p = 0.586). (Figure 3) Finally there was no difference in rates of either haematological or non-haematological toxicity between these two groups of patients.

Effect of genetic risk

In the 24 patients with adverse FISH, ORR was 45.8%, (1 VGPR (4.2%), 10 (41.7%) PR, 11 SD (45.8%) and 2 PD (8.3%)). These responses were similar to those in patients with standard risk FISH (n = 14), who had ORR of 50%, with 2 VGPR (14.3%), 5 (35.7%) PR, 5 (35.7%) SD and 2 (14.3%) PD. The presence of adverse FISH did not appear to influence PFS (median PFS 5.1 months in adverse FISH versus 5.2 in standard risk). Similar results were obtained when 1q gain was excluded from the adverse FISH group (median PFS of 6.4 months cf. 5.1 months for standard risk FISH [HR = 0.862, 95% CI 0.444 – 1.675, p = 0.662]). Adverse FISH did not significantly influence OS either (median OS of 10.9 months versus 8.4 months for standard risk, HR = 1.223, 95% CI 0.557 – 2.688, p = 0.616). (Figure 3)

The presence of 17p deletion did not significantly influence PFS, or OS (median PFS of 2.3 months versus 6.2 months for patients without this abnormality, HR 1.194, 95% CI 0.568 – 2.507, p = 0.640, and OS 9.7 months versus 12.9 months, HR = 1.314, 95% CI 0.609 – 2.836, p = 0.486).

Influence of patient age

In patients over the age of 65 (37, 52.9%), ORR was 54.1%, with 2 patients achieving VGPR, and 18 patients (48.6%) PR. In comparison, amongst patients aged 65 or less (n = 33), ORR was 51.5%, 2 patients achieved VGPR, and 15 patients (45.5%) PR. Median

PFS for the over 65 group was 5.5 months versus 4.5 months in younger patients (HR = 1.013, 95% CI 0.624 – 1.643, p = 0.960), and OS was comparable in both groups (Figure 3). Patients over the age of 65 did not seem to experience more toxicities.

Nine patients were aged over 75 (12.9%). Median PFS was 7.2 months for age > 75 versus 5.1 months for age </= 75 (HR = 0.685, 95% CI 0.325 – 1.444, p = 0.321). 7 out of 9 patients aged over 75 were still alive at time of data analysis.

Influence of depth and duration of response

Median PFS was 6.7 months where at least PR was achieved, compared with 4.5 months for SD and 1.4 months for PD, while median OS was 17.7 months where at least PR was achieved, compared with 13.1 months for SD and 3.6 months for PD. More striking was the effect of durability of response. For patients with DOR of at least 4 months, median PFS was 11.7 months and OS 23.0 months. In contrast, in patients whose response lasted less than 4 months or who did not respond, median OS was 9.3 months. (see figure 4)

No other factors were found to significantly influence PFS (sex, increasing age, time from diagnosis to receiving pomalidomide, double versus triple therapy at start of therapy). Increasing time from diagnosis to receiving pomalidomide approached significance (HR 0.908, 95% CI 0.820 – 1.005, p=0.062). No other factors were found to significantly influence OS. (see supplementary table 1)

Outcome of Relapse

Thirty patients went on to receive further treatment after relapse on pomalidomide (42.9%). The most common next treatment was bendamustine / thalidomide / dexamethasone (13 patients, 43.3% of 30). Supplementary table 2 provides further details.

Discussion

We describe a real-world experience of patients receiving pomalidomide for relapsed/refractory MM in the United Kingdom. The characteristics of the patients described in this cohort are broadly similar to those in published clinical trials (San Miguel *et al*, 2013), (Dimopoulos *et al*, 2016). Patients in our cohort were heavily pre-treated; 72.9% were refractory to both an ImiD and bortezomib, and 93% were refractory to their last treatment. In addition, 44% of patients tested had adverse genetics (excluding 1q gain) and 37.6% had an eGFR of <60ml/min.

Disease response in assessable patients (70) in our cohort was 52.9% compared with 31.4% in MM-003 and 32.6% in MM-010. Disease free survival in the same group (5 months) and overall survival (13 months) were remarkably similar to results of published clinical trials. In MM-003 and MM-010, the PFS was 4 and 4.6 months respectively, with OS of 13.1 and 11.9 months respectively. When survival outcomes were analyzed for

the entire cohort of 85 patients, median PFS was 4 months and OS a little shorter at 9 months. This likely reflects the extremely poor outcomes of a minority of patients who do not complete their first cycle of treatment. Of the six patients who died in the first cycle, four died of infection, four were over 70 years, and five had renal impairment. No statistically significant difference in response, survival or tolerability was seen in key patient groups, including those with moderate renal impairment, adverse cytogenetics and of older age. Taken as a whole, our findings are an important addition to the body of evidence for the benefit of pomalidomide therapy in this patient population.

Pomalidomide is metabolised extensively in the liver and only 2% is excreted in the urine (Hoffmann *et al*, 2013). Hence no dose modification for renal failure should be necessary as recently reported from the ongoing MM-013 trial.(Ramasamy *et al*, 2015) The MM-003 trial excluded patients with a creatinine clearance of less than 45ml/min, however, the 31% of patients with a creatinine clearance of less than 60ml/min did not have an inferior PFS or OS and pomalidomide was safe and well tolerated (Weisel *et al*, 2016). A subsequent pooled analysis of patients from 3 trials (MM-003, MM-010 and MM-002) reported comparable response rates and PFS but shorter OS in the 355 patients with creatinine clearance of 30-60ml/min, when compared with patients without renal impairment.(Siegel *et al*, 2016). In our series, median OS was not statistically inferior in those with renal impairment (7.4 vs 14.1mths), although this may be due to small patient numbers. We found no increased toxicity in patients who had eGFR <45ml/min plus response rates and PFS were similar. The final results of on-going MM013 trial examining the safety and pharmacokinetics of pomalidomide in more severe renal impairment are awaited.

Patients with adverse cytogenetic abnormalities generally have poor outcomes, however in the MM-003 trial, PFS and OS benefits of pomalidomide therapy were seen regardless of the cytogenetic risk group.(Dimopoulos *et al*, 2015) In our patient group, 63% of patients with genetic information had adverse FISH features, but this did not appear to influence their outcomes (response, PFS and OS). Some emerging data suggest that Pomalidomide has activity in adverse genetic risk disease. In the phase II study, in combination with dexamethasone, ORR was 74% in high risk patients (del17p, t(4;14) and t(14;16) compared with 63% in the whole group (Lacy *et al*, 2009), while patients with del(17p) in the IFM 2010-2002 study fared well in the pomalidomide arm (Leleu *et al*, 2015). Such observations contribute to our increasing understanding of the interaction of particular drugs with the biology of specific genetic abnormalities, and provide a rationale for further studies investigating the use of pomalidomide earlier in the treatment pathway for patients with high risk disease.

One of the challenges in managing relapsed refractory MM is in the older and more frail patients, however, subgroup analysis of many randomized studies suggest that these patients can also benefit from new drugs. In the MM-003 trial, safety and efficacy benefits of pomalidomide-dexamethasone were not influenced by age(San Miguel *et al*, 2013). Patients in our cohort were of similar age range to that in the MM-

003 study, with 15 patients (17.6%) >75 years and 48 patients (56.5%) > 65 years. We observed no influence of age on response rates, PFS, OS or tolerability.

Depth and sustainability of response were two important predictors of survival benefit in our patient cohort. Achievement of PR or better was associated with a disease-free and overall survival benefit. Importantly patients who achieved SD still appeared to derive a survival benefit with an OS of 13.1 vs 3.6 months in those with progressive disease. Post hoc analysis of the MM-003 trial data has also shown this relationship between depth of response and survival. (Moreau *et al*, 2016), (San Miguel *et al*, 2015) In our cohort, patients with sustained disease response of at least 4 months had an estimated survival of nearly 2 years suggesting that achieving disease stability increases the opportunity to receive further treatment at progression.

Pomalidomide plus dexamethasone was well tolerated in this heavily pre-treated population. Haematological toxicities were relatively infrequent, as were infections, including neutropenic sepsis (8%).These rates compare favorably with reported adverse events in the pomalidomide arm of MM-003, and in the MM-010 study (San Miguel *et al*, 2013), (Dimopoulos *et al*, 2016). It is important to highlight however that although overall rates of infection were low, four out of six patient deaths during the first cycle were related to sepsis. This real life data further adds to the published evidence that pomalidomide has a good safety profile and is well tolerated. The low incidence of gastro-intestinal toxicity is particularly notable in an oral agent, and would support testing of combinations of pomalidomide with other anti-myeloma agents.

Several studies of pomalidomide in triplet combinations in the relapsed refractory setting have reported higher overall response rates with acceptable toxicity (Allan *et al*, 2013) , for example in combination with cyclophosphamide (Larocca *et al*, 2013), (Baz *et al*, 2016) and carfilzomib (Shah *et al*, 2015). In our series, addition of a third agent, either at start of therapy or during treatment, was not associated with superior outcomes, but results are likely to be influenced by patient bias and selection in this small series, and the results of prospective randomized studies are awaited. Other combinations being explored in clinical trials include those with marizomib (Richardson *et al*, 2016), bortezomib (Lacy *et al*, 2014), ricolinostat (Raje *et al*, 2015) and daratumumab. (Chari *et al*, 2015)
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Therapeutic options for patients at this late stage of the treatment pathway continue to expand. Newer agents recently licensed for this patient group include HDAC inhibitors such as panobinostat, in combination with bortezomib, and monoclonal antibodies like the first-in-class anti-CD38 antibody, daratumumab plus other agents like elotuzumab, ixazomib and carfilzomib (Nooka *et al*, 2015), (Lonial *et al*, 2016). Across the board, ORRs to these new agents are around 30-40%, with disease free survival of 3-4 months (Siegel *et al*, 2012), (Lonial *et al*, 2016). It is clear however, that despite the overall dismal outlook for this patient group, the subset who are able to respond to a new

drug fare remarkably well. This is borne out by the recently published results of the SIRIUS study with daratumumab, where patients achieving PR had an estimated survival that was not reached, at a median follow up of 14 months(Lonial *et al*, 2016). We urgently need better biomarkers in order to identify which patients are likely to respond to specific therapies, leading to improved utilization of limited healthcare resources, and minimization of treatment-related toxicities for our patients.

In summary, we report our real-world experience of patients receiving pomalidomide for relapsed refractory myeloma, with outcomes (response, survival, tolerability) similar to those in published clinical trials. Importantly, although patient numbers are small, benefit is seen in those with moderate renal impairment, adverse cytogenetics and older age. Recently a small retrospective analysis of 39 patients treated with pomalidomide was published, reporting remarkably similar outcomes to our own, including good tolerability (Sriskandarajah *et al*, 2016). Our data provide confirmatory support for exploring pomalidomide based combination therapy both in the relapsed setting, and more upfront, especially in patients with adverse genetics.

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Bibliography

Allan, J.N., Boyer, A., Rossi, A.C., Pearse, R.N., Zafar, F., Pekle, K., Tegnestam, L., Jayabalan, D., Coleman, M. & Niesvizky, R. (2013) Sequence Impact Of Pomalidomide and Carfilzomib On Treatment Response In Relapsed Multiple Myeloma. *Blood,* **122,** 1954–1954.

Baz, R.C., Martin, T.G., Lin, H.-Y., Zhao, X., Shain, K.H., Cho, H.J., Wolf, J.L., Mahindra, A., Chari, A., Sullivan, D.M., Nardelli, L.A., Lau, K., Alsina, M. & Jagannath, S. (2016) Randomized multicenter phase II study of pomalidomide, cyclophosphamide, and dexamethasone in relapsed refractory myeloma. *Blood***,** blood–2015–11–682518.

Boland, E., Eiser, C., Ezaydi, Y., Greenfield, D.M., Ahmedzai, S.H. & Snowden, J.A. (2013) Living With Advanced But Stable Multiple Myeloma: A Study of the Symptom Burden and Cumulative Effects of Disease and Intensive (Hematopoietic Stem Cell Transplant-Based) Treatment on Health-Related Quality of Life. *Journal of Pain and Symptom Management*, **46,** 671–680.

Cancer Drug Fund. Summary of decision on Pomalidomide as at least 3rd line treatment for patients with relapsed myeloma Available at: https://www.england.nhs.uk/wp-content/uploads/2015/09/cdf-decision-summ-pomalidomide-3rdline-multiple-myeloma.pdf [Accessed July 24, 2016].

Chng, W.J., Dispenzieri, A., Chim, C.-S., Fonseca, R., Goldschmidt, H., Lentzsch, S., Munshi, N., Palumbo, A., Miguel, J.S., Sonneveld, P., Cavo, M., Usmani, S., Durie, B.G. & Avet-Loiseau, H. (2014) IMWG consensus on risk stratification in multiple myeloma. *Leukemia*, **28,** 269–277.

Dimopoulos, M.A., Palumbo, A., Corradini, P., Cavo, M., Delforge, M., Di Raimondo, F., Weisel, K.C., Oriol, A., Hansson, M., Vacca, A., Blanchard, M.J., Goldschmidt, H., Doyen, C., Kaiser, M., Petrini, M., Anttila, P., Cafro, A.M., Raymakers, R., San Miguel, J., de Arriba, F., et al (2016) Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUSTM (MM-010): a phase 3b study in refractory multiple myeloma. *Blood* Available at: http://www.bloodjournal.org/cgi/doi/10.1182/blood-2016-02-700872 [Accessed July 24, 2016].

Dimopoulos, M.A., Weisel, K.C., Song, K.W., Delforge, M., Karlin, L., Goldschmidt, H., Moreau, P., Banos, A., Oriol, A., Garderet, L., Cavo, M., Ivanova, V., Alegre, A., Martinez-Lopez, J., Chen, C., Spencer, A., Knop, S., Bahlis, N.J., Renner, C., Yu, X., et al (2015) Cytogenetics and long-term survival of patients with refractory or relapsed and refractory multiple myeloma treated with pomalidomide and low-dose dexamethasone. *Haematologica*, **100,** 1327–1333.

Hoffmann, M., Kasserra, C., Reyes, J., Schafer, P., Kosek, J., Capone, L., Parton, A., Kim-Kang, H., Surapaneni, S. & Kumar, G. (2013) Absorption, metabolism and excretion of [14C]pomalidomide in humans following oral administration. *Cancer Chemotherapy and Pharmacology*, **71,** 489–501.

Kumar, S.K., Dispenzieri, A., Lacy, M.Q., Gertz, M.A., Buadi, F.K., Pandey, S., Kapoor, P., Dingli, D., Hayman, S.R., Leung, N., Lust, J., McCurdy, A., Russell, S.J., Zeldenrust, S.R., Kyle, R.A. & Rajkumar, S.V. (2014) Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia*, **28,** 1122–1128.

Kumar, S.K., Lee, J.H., Lahuerta, J.J., Morgan, G., Richardson, P.G., Crowley, J., Haessler, J., Feather, J., Hoering, A., Moreau, P., LeLeu, X., Hulin, C., Klein, S.K., Sonneveld, P., Siegel, D., Bladé, J., Goldschmidt, H., Jagannath, S., Miguel, J.S., Orlowski, R., et al (2012) Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: A multicenter international myeloma working group study. *Leukemia*, **26,** 149–157.

Lacy, M.Q., Allred, J.B., Gertz, M.A., Hayman, S.R., Short, K.D., Buadi, F., Dispenzieri, A., Kumar, S., Greipp, P.R., Lust, J.A., Russell, S.J., Dingli, D., Zeldenrust, S., Fonseca, R., Bergsagel, P.L., Roy, V., Stewart, A.K., Laumann, K., Mandrekar, S.J., Reeder, C., et al (2011) Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. *Blood*, **118,** 2970–2975.

Lacy, M.Q., Hayman, S.R., Gertz, M.A., Dispenzieri, A., Buadi, F., Kumar, S., Greipp, P.R., Lust, J.A., Russell, S.J., Dingli, D., Kyle, R.A., Fonseca, R., Bergsagel, P.L., Roy, V., Mikhael, J.R., Stewart, A.K., Laumann, K., Allred, J.B., Mandrekar, S.J. & Rajkumar, S.V. (2009) Pomalidomide (CC4047) Plus Low-Dose Dexamethasone As Therapy for Relapsed Multiple Myeloma. *Journal of Clinical Oncology*, **27,** 5008–5014.

Lacy, M.Q., LaPlant, B.R., Laumann, K.M., Kumar, S., Gertz, M.A., Hayman, S.R., Buadi, F., Dispenzieri, A., Lust, J.A., Kapoor, P., Leung, N., Russell, S.J., Dingli, D., Gonsalves, W.I., Fonseca, R., Bergsagel, P.L., Roy, V., Sher, T., Ailawadhi, S., Chanan-Khan, A., et al (2014) Pomalidomide, Bortezomib and Dexamethasone (PVD) for Patients with Relapsed Lenalidomide Refractory Multiple Myeloma (MM). *Blood*, **124,** 304–304.

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, A.M., 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.

Leleu, X., Karlin, L., Macro, M., Hulin, C., Garderet, L., Roussel, M., Arnulf, B., Pegourie, B., Kolb, B., Stoppa, A.M. & others (2015) Pomalidomide plus low-dose dexamethasone in multiple myeloma with deletion 17p and/or translocation (4; 14): IFM 2010-02 trial results. *Blood*, **125,** 1411–1417.

Lonial, S., Weiss, B.M., Usmani, S.Z., Singhal, S., Chari, A., Bahlis, N.J., Belch, A., Krishnan, A., Vescio, R.A., Mateos, M.V. & others (2016) Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *The Lancet*, **387,** 1551–1560.

Mols, F., Oerlemans, S., Vos, A.H., Koster, A., Verelst, S., Sonneveld, P. & Poll-Franse, L.V. (2012) Health-related quality of life and disease-specific complaints among multiple myeloma patients up to 10 yr after diagnosis: results from a population-based study using the PROFILES registry. *European Journal of Haematology*, **89,** 311–319.

Moreau, P., Weisel, K.C., Song, K.W., Gibson, C.J., Saunders, O., Sternas, L.A., Hong, K., Zaki, M.H. & Dimopoulos, M.A. (2016) Relationship of response and survival in patients with relapsed and refractory multiple myeloma treated with pomalidomide plus low-dose dexamethasone in the MM-003 trial randomized phase III trial (NIMBUS). *Leukemia & Lymphoma*, 1–8.

National Institute For Health And Care Excellence. Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib: final appraisal determination. Available at: https://www.nice.org.uk/guidance/ta338/resources/pomalidomide-for-relapsed-and-refractory-multiple-myeloma-previously-treated-with-lenalidomide-and-bortezomib-82602554094277 [Accessed July 24, 2016].

Nooka, A.K., Kastritis, E., Dimopoulos, M.A. & Lonial, S. (2015) Treatment options for relapsed and refractory multiple myeloma. *Blood*, blood–2014.

Raje, N.S., Bensinger, W., Cole, C.E., Lonial, S., Jagannath, S., Arce-Lara, C.E., Valent, J., Rosko, A.E., Harb, W.A., Sandhu, I., Bahlis, N.J., Reece, D., Terpos, E., Supko, J., Tamang, D., Jones, S.S., Wheeler, C., Markelewicz, R.J. & Richardson, P.G. (2015) Ricolinostat (ACY-1215), the First Selective HDAC6 Inhibitor, Combines Safely with Pomalidomide and Dexamethasone and Shows Promosing Early Results in Relapsed-and-Refractory Myeloma (ACE-MM-102 Study). *Blood*, **126,** 4228–4228.

Rajkumar, S.V., Harousseau, J.-L., Durie, B., Anderson, K.C., Dimopoulos, M., Kyle, R., Blade, J., Richardson, P., Orlowski, R., Siegel, D. & others (2011) Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood*, **117,** 4691–4695.

Ramasamy, K., Dimopoulos, M.A., Donk, N.W.C.J. van de, Gamberi, B., Bridoux, F., Streetly, M., Kueenburg, E., Rosettani, B., Collins, S., Lersch, F., Bacon, P., Weisel, K.C. & Sonneveld, P. (2015) Safety of Treatment (Tx) with Pomalidomide (POM) and Low-Dose Dexamethasone (LoDEX) in Patients (Pts) with Relapsed or Refractory Multiple Myeloma (RRMM) and Renal Impairment (RI), Including Those on Dialysis. *Blood*, **126,** 374–374.

Richardson, P.G., Siegel, D., Baz, R., Kelley, S.L., Munshi, N.C., Laubach, J., Sullivan, D., Alsina, M., Schlossman, R., Ghobrial, I.M. & others (2013) Phase 1 study of pomalidomide MTD, safety, and efficacy in patients with refractory multiple myeloma who have received lenalidomide and bortezomib. *Blood*, **121,** 1961–1967.

Richardson, P.G., Siegel, D.S., Vij, R., Hofmeister, C.C., Baz, R., Jagannath, S., Chen, C., Lonial, S., Jakubowiak, A., Bahlis, N., Song, K., Belch, A., Raje, N., Shustik, C., Lentzsch, S., Lacy, M., Mikhael, J., Matous, J., Vesole, D., Chen, M., et al (2014) Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. *Blood*, **123,** 1826–1832.

Richardson, P.G., Zimmerman, T.M., Hofmeister, C.C., Talpaz, M., Chanan-Khan, A.A., Kaufman, J.L., Laubach, J.P., Chauhan, D., Jakubowiak, A.J., Reich, S., Trikha, M. & Anderson, K.C. (2016) Phase 1 study of marizomib in relapsed or relapsed and refractory multiple myeloma: NPI-0052-101 Part 1. *Blood*, **127,** 2693–2700.

San Miguel, J.F., Weisel, K.C., Song, K.W., Delforge, M., Karlin, L., Goldschmidt, H., Moreau, P., Banos, A., Oriol, A., Garderet, L., Cavo, M., Ivanova, V., Alegre, A., Martinez-Lopez, J., Chen, C., Renner, C., Bahlis, N.J., Yu, X., Teasdale, T., Sternas, L., et al (2015) Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. *Haematologica*, **100,** 1334–1339.

San Miguel, J., Weisel, K., Moreau, P., Lacy, M., Song, K., Delforge, M., Karlin, L., Goldschmidt, H., Banos, A., Oriol, A. & others (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. *The lancet oncology*, **14,** 1055–1066.

512 Shah, J.J., Stadtmauer, E.A., Abonour, R., Cohen, A.D., Bensinger, W.I., Gasparetto, C., Kaufman,
513 J.L., Lentzsch, S., Vogl, D.T., Gomes, C.L. & others (2015) Carfilzomib, pomalidomide,
514 and dexamethasone for relapsed or refractory myeloma. *Blood*, **126,** 2284–2290.

515 Siegel, D.S., Martin, T., Wang, M., Vij, R., Jakubowiak, A.J., Lonial, S., Trudel, S., Kukreti, V.,
516 Bahlis, N., Alsina, M., Chanan-Khan, A., Buadi, F., Reu, F.J., Somlo, G., Zonder, J., Song,
517 K., Stewart, A.K., Stadtmauer, E., Kunkel, L., Wear, S., et al (2012) A phase 2 study of
518 single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory
519 multiple myeloma. *Blood*, **120,** 2817–2825.

520 Siegel, D.S., Weisel, K.C., Dimopoulos, M.A., Baz, R., Richardson, P., Delforge, M., Song, K.W.,
521 San Miguel, J.F., Moreau, P., Goldschmidt, H., Cavo, M., Jagannath, S., Yu, X., Hong, K.,
522 Sternas, L., Zaki, M. & Palumbo, A. (2016) Pomalidomide plus low-dose
523 dexamethasone in patients with relapsed/refractory multiple myeloma and
524 moderate renal impairment: a pooled analysis of three clinical trials. *Leukemia &*
525 *Lymphoma***,** 1–6.

526 Smith, D., Stephenson, C., Percy, L., Lach, A., Chatters, S., Kempski, H. & Yong, K. (2015)
527 Cohort analysis of FISH testing of CD138+ cells in relapsed multiple myeloma:
528 implications for prognosis and choice of therapy. *British journal of haematology*, **171,**
529 881–883.

530 Sriskandarajah, P., Pawlyn, C., Mohammed, K., Dearden, C.E., Davies, F.E., Morgan, G.J., Boyd,
531 K.D. & Kaiser, M.F. (2016) The efficacy and tolerability of pomalidomide in
532 relapsed/refractory myeloma patients in a 'real-world' study: the Royal Marsden
533 Hospital experience. *Leukemia & Lymphoma***,** 1–4.

534 Weisel, K.C., Dimopoulos, M.A., Moreau, P., Lacy, M.Q., Song, K.W., Delforge, M., Karlin, L.,
535 Goldschmidt, H., Banos, A., Oriol, A., Alegre, A., Chen, C., Cavo, M., Garderet, L.,
536 Ivanova, V., Martinez-Lopez, J., Knop, S., Yu, X., Hong, K., Sternas, L., et al (2016)
537 Analysis of renal impairment in MM-003, a phase III study of pomalidomide + low -
538 dose dexamethasone versus high - dose dexamethasone in refractory or relapsed and
539 refractory multiple myeloma. *Haematologica*, **101,** 872–878.

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