Use of Ixazomib, Lenalidomide and Dexamethasone in patients with relapsed AL amyloidosis

Oliver Charles Cohen[1], Faye Sharpley[1], Julian Gillmore[1], Helen Lachmann[1], Sajitha Sachchithanantham[1,2], Shameem Mahmood[1,2], Marianna Fontana[1], Carol Whelan[1], Ana Martinez-Naharro[1], Charalampia Kyriakou[2], Neil Rabin[2], Rakesh Popat[2], Kwee Yong[2], Simon Cheesman[2], Raakhee Shah[2], Philip Hawkins[1] and Ashutosh Wechalekar[1,2]

[1] National Amyloidosis Centre, University College London (Royal Free Campus), London, United Kingdom,

[2] University College London Hospitals NHS Trust, London, United Kingdom

Summary word count: 188

Main text word count: 2450

Tables: 3

Figures: 1

Address for Correspondence:

Professor Ashutosh Wechalekar
National Amyloidosis Centre
UCL (Royal Free Campus)
Rowland Hill Street, London NW32PF
UK
Email: a.wechalekar@ucl.ac.uk

Summary

With improving outcomes in AL amyloidosis, there is a need to study novel agents in this setting. We report outcomes of 40 patients with relapsed AL amyloidosis treated with Ixazomib-lenalidomide-dexamethasone (IRd). Haematological responses were assessed on an intention-to-treat basis at 3 months: complete response (CR) - 8 (20.5%), very good partial response (VGPR) - 8 (20.5%), partial response (PR) - 7 (17.9%) and no response – 16 (41.0%). One patient had missing data. Six patients subsequently improved response. Best responses were: CR - 10 (25.6%), VGPR - 8 (20.5%), PR - 7 (17.9%), NR - 14 (35.9%). Cardiac and renal organ responses occurred in 5.6% and 13.3% respectively. Median PFS was 17.0 months (95% CI 7.3-20.7 months), improving to 28.8 months (95% CI 20.6-37.0 months) in those achieving CR/VGPR. Median OS was 29.1 months (95% CI 24-33 months). Serious adverse events were seen in 14 (35.0%) patients inclusive of 15 admissions due to: infection (6/15, 40.0%), fluid overload (5/15, 33.3%), cardiac arrhythmia (2/15, 13.3%), renal dysfunction (1/15, 6.6%) and anaemia (1/15, 6.6%). In summary, IRd is an oral treatment option with a manageable toxicity profile leading to deep responses in 47% patients with relapsed AL amyloidosis.

Keywords: Ixazomib, Lenalidomide, AL amyloidosis, Chemotherapy, Relapse

Introduction

AL amyloidosis is a systemic disorder characterised by the extracellular deposition of misfolding monoclonal light chains, produced by a small plasma (or B) cell clone, resulting in progressive organ dysfunction (Merlini 2017). The outlook for AL amyloidosis has transformed over the last 40 years with 4-year overall survival (OS) doubling from 21% (1977-1986) to 42% (2003-2006) (Kumar*, et al* 2011); directly coinciding with the remarkable development of novel plasma cell targeting therapies (Joseph and Kaufman 2018) and improved patient selection for autologous stem cell transplantation (ASCT) (Landau*, et al* 2017).

Suppressing production of monoclonal light chains to attain a deep haematological response, without incurring additional organ toxicity over and above that caused by amyloid deposition, remains the keystone of treatment (Muchtar*, et al* 2019). Bortezomib-based regimens are routinely used for upfront treatment with good haematological responses in 60% (Palladini*, et al* 2015) due to enhanced susceptibility of plasma cells in AL amyloidosis to proteasome inhibitor led killing (Oliva*, et al* 2017). **Most** patients eventually relapse after chemotherapy leading to increasing need to study novel agents at relapse. Lenalidomide-dexamethasone is commonly utilised (Mahmood*, et al* 2014b) either alone or in combination with cyclophosphamide (Kumar*, et al* 2012) or melphalan (Dinner*, et al* 2013) leading to haematological response rates of 60% and 58% respectively. Tolerance limits lenalidomide dose and, hence, response.

Ixazomib is an oral proteasome inhibitor (PI), which has been assessed in a phase 1/2 study in relapsed/refractory AL amyloidosis demonstrating a 52% haematological response (Sanchorawala*, et al* 2017). A phase III trial of ixazomib-dexamethasone vs. physician's choice closed early due to failure to meet primary endpoints but has reported a haematological response rate of 53% (Dispenzieri A 2019). Trials assessing the role of single agent ixazomib in AL amyloidosis as maintenance (NCT03618537) and in combination with daratumumab (NCT03283917) and cyclophosphamide (NCT03236792) are currently recruiting/have completed recruitment. The combination of ixazomib-lenalidomide-dexamethasone (IRd) is established in multiple myeloma (MM) and demonstrates

significantly longer PFS than lenalidomide-dexamethasone alone (Moreau*, et al* 2016). We report the real-world use of IRd in patients with relapsed systemic AL amyloidosis, which has not been reported previously.

Method

All patients with AL amyloidosis treated with IRd chemotherapy between 2016–2019 were identified from the database at the UK National Amyloidosis Centre (NAC). In all cases, a diagnosis of amyloidosis was confirmed by Congo red staining of a tissue biopsy with demonstration of characteristic birefringence under cross-polarized light. The amyloid subtype was confirmed by immunohistochemistry with specific antibodies, or by mass spectrometry (Rezk*, et al* 2019). All patients had a detailed baseline assessment including serum free light chains (sFLC), serum protein electrophoresis, imaging and organ assessment including cardiac biomarkers.

Haematological and organ response was assessed using international amyloidosis consensus criteria (Palladini*, et al* 2012). Progression was defined as haematological progression or death. Responses were assessed at 3 months and best response achieved whilst on therapy. Adverse events (AEs) were graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Ixazomib was given at a dose of 4mg orally weekly on days 1, 8 and 15 of a 28-day cycle. Lenalidomide was started at a standard dose of 15mg (Days 1-21) whilst dexamethasone was 40mg weekly.

Statistical analysis was performed using SPSS version 25. Approval for analysis and publication was obtained from the institutional review board at University College London whilst written consent was obtained from all patients in accordance with the Declaration of Helsinki. The primary outcomes were haematological responses and OS. Overall survival was defined as time in months from commencement of IRd therapy to death from any cause whilst PFS was a secondary outcome, calculated from commencement of IRd to haematological progression or death from any cause. All treatment and survival outcomes are reported on an intention-to-treat (ITT) basis.

Results

Forty two patients were identified - 2 patients were excluded (1 declined follow up and 1 commenced treatment prior to review). Forty patients were included and baseline characteristics are detailed in Table I. Median time from diagnosis to IRd was 21 months (5-132 months). The median number of cycles was 7 (range 1-36). Two patients received one treatment cycle (1 death, 1 grade 3 maculopapular rash).

Haematological responses were assessed on an ITT basis; 1 patient with missing data was excluded from response analysis. At 3 months, responses were: complete response (CR) - 8 (20.5%), very good partial response (VGPR) - 8 (20.5%), partial response (PR) - 7 (17.9%) and no response - 16 (41.0%). Six patients subsequently improved their response. Best responses were: CR - 10 (25.6%), VGPR - 8 (20.5%), PR - 7 (17.9%) and NR - 14 (35.9%) (See Figure 1). Median time to any and best response were both 2 months (range 1-9 months). Seventeen out of eighteen (94.1%) patients who achieved VGPR or better reached this response within 2 months. None of the 12 patients who had received lenalidomide previously achieved a CR at 3 months, 58.3% ultimately achieved ≥PR. Three out of the four (75%) patients who were refractory to prior lenalidomide did not respond to IRd. All patients received prior bortezomib. Of 4 patients who were bortezomib-refractory, 2 achieved a PR and 2 failed to respond to IRd. One patient was switched to melphalan-prednisolone after failing to respond to 2 cycles of IRd whilst the remaining three patients died within 8 months of commencing IRd.

Overall median PFS was 17.0 months (95% CI 7.3-20.7 months). The median PFS for patients achieving CR/VGPR was 28.8 months (95% CI 20.6-37.0 months) and for ≤PR was 10.1 months (95% CI 6.0-13.6 months). Median OS for the cohort was 29.1 months (95% CI 24.4-33.8 months), for patients achieving CR/VGPR - 35.3 months (95% CI 32.0-38.6 months) and ≤PR - 25.2 months (95% CI 19.1-31.4 months) (Log rank p=0.103 for the latter two groups) (See Figure 1). In patients achieving any haematological response (CR, VGPR, PR), OS was 32.5 months (95% CI 26.7-38.3 months). In contrast, OS was 16.2 months (95% CI 12.5-20.0 months) in non-responders (p=0.071). There was no significant

difference in PFS (p=0.185) in patients who had received prior lenalidomide when compared with lenalidomide-naïve patients.

Organ responses were assessed at 6 months. The utility of NT-proBNP for assessment of cardiac response whilst on lenalidomide remains unclear; and the cardiac responses here need to be interpreted with this caveat and caution, as they may be markedly under reported due to the paradoxical increase in NT-proBNP during lenalidomide treatment. Of the twenty-six patients (65.0%) with cardiac involvement, 8 were not assessable for response (5 missing data and 3 NT-proBNP <650ng/L). Of the remaining 18 patients, there was only one cardiac responder (5.6%) in the entire cohort who achieved a CR within 1 month. There was cardiac progression in 8 (44.4%) cases – of these 4/8 (50.0%) were on IRd at time of response assessment. The remaining 10 (55.6%) did not respond. Ten patients (25.0%) had liver involvement based on alkaline phosphatase (ALP) of which 7 (70%) were evaluable (2 not reached 6 months, 1 missing data); 4/7 (57.1%) progressed and 3/7 (42.9%) did not respond. Of the patients who demonstrated liver progression, 3 were non-responders and 1 achieved a PR.

Renal involvement was recorded in 28 (70.0%) patients. Across all patients, there was no significant difference in estimated glomerular filtration rate (eGFR) and creatinine levels between baseline and 6 months (p=0.328 and p=0.662 respectively). In patient with renal involvement, 3 month haematological responses were: CR – 8 (28.6%), VGPR – 6 (21.4%), PR – 2 (7.1%) and NR – 12 (42.9%). In this subgroup, the PFS and OS were 17.9 months (95% CI 11.8-24.0 months) and 31.6 months (95% CI 26.8-36.5 months) respectively. In terms of renal response, 13/28 (46.4%) were not evaluable: 3 not reached 6 months, 3 data missing, 4 on dialysis prior to IRd, 2 died and 1 baseline protein <0.5g/24h. Of 15 evaluable patients, 2/15 (13.3%) responded, 7/15 (46.7%) progressed and 6/15 (40.0%) were non-responders. Three patients progressed based on a creatinine increase and four patients based on an increase in proteinuria. One patient with renal progression required dialysis.

Median follow up was 10.5 months (range 2-35 months). During the period of follow up, 8/40 (20.0%) patients died, 14/40 (35.0%) patients have stopped treatment, 17/40 (42.5%) continue on IRd and 1/40 (2.5%) has been lost to follow up. One patient stopped treatment after developing a grade 3 rash following the first dose of ixazomib. Of the remainder, 4/14 stopped due to grade 3/4 toxicity (2 infection, 1 renal, 1 bradyarrythmic cardiac arrest), 2/14 were palliated due to advanced disease with poor quality of life and 7/14 had a suboptimal haematological response. Of these 7 patients, 4 commenced next line therapy (daratumumab x2, melphalan-prednisolone, pomalidomide respectively).

The AEs are detailed in table II. Seven patients had a creatinine increase inclusive of 1 patient who required dialysis, which was classed as a serious adverse event (SAE). During treatment, SAEs were seen in 35.0% of patients - there were 15 admissions in 12/40 (30.0%) patients: infection (6/15, 40.0%), fluid overload (5/15, 33.3%), cardiac arrhythmia (2/15, 13.3%), creatinine increase (1/15, 6.6%) and for a blood transfusion (1/15, 6.6%).

Discussion

Patients with AL amyloidosis often relapse after initial therapy. The treatment of relapsed patients has been studied typically with doublet regimens or doublets combined with alkylators. Novel agent triplets, which are now a standard of care in MM, remain poorly studied – particularly the combination of immunomodulatory agents combined with proteasome inhibitors. We report the efficacy and toxicity of a novel agent triplet combination of an oral PI, ixazomib, in combination with an immunomodulatory drug, lenalidomide, and dexamethasone for the first time in patients with AL amyloidosis. This confirms that the IRd regimen is efficacious in patients previously treated with bortezomib, with the ability to achieve deep clonal responses alongside acceptable tolerability using real world data.

Ixazomib, a next generation PI, appears to show promise as a single agent in AL amyloidosis. Two prior studies demonstrated haematological response rates of 52-53% (Dispenzieri A 2019,

Sanchorawala*, et al* 2017). Lenalidomide has been extensively used in AL amyloidosis in the relapse-refractory setting, typically in combination dexamethasone but also with additional alkylators (Dinner*, et al* 2013, Hegenbart*, et al* 2017, Kumar*, et al* 2012). Haematological response and survival data for other regimens including lenalidomide or ixazomib are documented in Table III. The main challenge of lenalidomide use is the poor tolerance in patients with amyloidosis, especially those with cardiac involvement, for reasons that remain unclear. Additionally, there is potential for worsening renal function with lenalidomide. Full dose lenalidomide can be rarely used in patients with AL amyloidosis. In the current cohort treated with IRd, the overall haematological response rate (65.8%) compared with responses to ixazomib (52-53%)(Dispenzieri A 2019, Sanchorawala*, et al* 2017) and 51% (Kastritis*, et al* 2018a) and 61% (Mahmood*, et al* 2014b) with lenalidomide. There was suggestion that IRd achieved a deep response (CR/VGPR) in nearly half of all the treated patients (47.4%) compared to just less than a third with lenalidomide-dexamethasone (28%). A small phase I study of ixazomib seemed show a good response in 42.9% (Sanchorawala*, et al* 2017). Whilst the studies are not directly comparable, the data is encouraging and suggests that the frequency of deep responses may be more common when the triplet combination is used over the doublets. The clonal responses were rapid with median time to best response was 2 months. It appears that responses deepen with continuing therapy (similar to that documented with IRd in myeloma) (Kumar*, et al* 2019)- 6 patients improved their response beyond 3 months including 2 patients who improved from PR to a CR and VGPR, respectively. Conversely, patients with a poor response at 3 months did not improve their responses significantly with continued therapy; non-response at 3 months should prompt consideration of switching to next line therapy. Encouragingly, patients who had prior exposure to lenalidomide (but not refractory) had good responses whilst three out of four patients in the series refractory to lenalidomide failed to respond. IRd appears to be a useful option of patients relapsing after prior lenalidomide treatment but may have a limited role in lenalidomide refractory patients.

The PFS in this cohort was good at 17.0 months but the PFS for patients responding to IRd was excellent at over 2 years. There is limited data on PFS with Ixazomib alone; in the small phase I cohort,

PFS was 14.8 months (Sanchorawala*, et al* 2017) whilst in the phase 3 trial, in which PI-refractory patients were notably excluded and only 47% of patients had received prior bortezomib, it was 20.1 months (Dispenzieri A 2019). In the present study, the 4 patients who were bortezomib-refractory responded poorly to IRd suggesting possible resistance to both proteasome inhibitors, although numbers are small.

Lenalidomide combinations including cyclophosphamide and melphalan are reported to have a superior PFS of 25.1 (Hegenbart*, et al* 2017) and 28.3 (Kumar*, et al* 2012) months respectively; however, both trialled these therapies in new patients with limited exposure to other novel agent based therapies whereas, in this study, patients had a median of 2 prior lines of chemotherapy. A further study reporting on lenalidomide in combination with melphalan reported significantly worse outcomes (Dinner*, et al* 2013) but did include 92% patients with cardiac involvement, a negative predictor of survival (Wechalekar*, et al* 2013). The OS of our cohort was 29.1 months. However, there was no significant difference in OS between deep responders and those achieving ≤PR (p=0.103) nor between those achieving any response vs. non-responders (p=0.071). The lack of difference in OS can be explained by a relatively short duration of follow up and the availability of effective next line agents such as daratumumab. Further work is required comparing different lenalidomide-containing regimens in comparable patients to ascertain their relative efficacy.

The toxicity of this regimen was manageable but not insignificant. Just over one third of the patients experience serious adverse events – mainly infection and fluid retention. Grade 1-2 thrombocytopenia was common. Details of exact dose reduction from cycle to cycle are unavailable and remain a limitation of this study. These are not dissimilar from the reported grade 3/4 toxicity reported with the individual drugs: 81% with ixazomib (Sanchorawala*, et al* 2017) and 27% with lenalidomide alone (Mahmood*, et al* 2014b). We acknowledge the limitations due to retrospective nature of the study. Lenalidomide has been linked to renal dysfunction in AL amyloidosis (Specter*, et al* 2011) but there are no renal toxicities reported with ixazomib in AL amyloidosis (Dispenzieri A 2019,

Sanchorawala*, et al* 2017). Kastritis and colleagues did report transient increases (to grade 1) in renal failure and 5.5% developed acute renal failure requiring dialysis (Kastritis*, et al* 2018a). In this study, 17.5% of patients developed a creatinine increase inclusive of 1 patient who required dialysis but there was no significant change in the creatinine or eGFR between baseline and 6 month assessments. Furthermore, reported PFS and OS were maintained in patients with renal involvement.

In summary, this real-world data of the use of ixazomib-lenalidomide-dexamethasone gives a first look at outcomes and toxicities in patients with relapsed AL amyloidosis who had received prior bortezomib and lenalidomide showing encouraging deep responses. The regimen has the advantage of an easily deliverable, oral outpatient regimen with less potential for neurotoxicity than bortezomib. Patients achieving CR/VGPR have excellent PFS of 28 months. This study is limited by the small sample size and retrospective data collection. Whilst the place for IRd remains uncertain in the daratumumab era, these results support further larger prospective studies to evaluate either IRd alone or in addition to a monoclonal antibody.

Author Contributions

OCC and AW conceived the study, analysed data and wrote the manuscript. FS, JDG, HL, SS, SM, MF, CW, AMN, CK, NR, RP KY, SC, RS, and PH contributed to the manuscript and provided critical input. All authors reviewed the final version of the manuscript.

Acknowledgements

We would like to thank all the clinical and nursing staff at the National Amyloidosis Centre and the treating hematologists who helped with the clinical care of the patients' involved in this study. We also would like to thank the International Myeloma Society (IMS) for support to present this study at the International Myeloma Workshop 2019.

References

Dinner, S., Witteles, W., Afghahi, A., Witteles, R., Arai, S., Lafayette, R., Schrier, S.L. & Liedtke, M. (2013) Lenalidomide, melphalan and dexamethasone in a population of patients with immunoglobulin light chain amyloidosis with high rates of advanced cardiac involvement. *Haematologica,* **98,** 1593-1599.

Dispenzieri A, K.E., Wechalekar AD, Schonland SO, Kim K, Sanchorawala V, Landau HJ, Kwok F, Suzuki K, Comenzo RL, Berg D, Liu G, Faller DV, Merlini G. (2019) Primary Results from the Phase 3 Tourmaline-AL1 Trial of Ixazomib-Dexamethasone Versus Physician's Choice of Therapy in Patients (Pts) with Relapsed/Refractory Primary Systemic AL Amyloidosis (RRAL). In: *American Society of Haematology* Orlando, FL, USA.

Hegenbart, U., Bochtler, T., Benner, A., Becker, N., Kimmich, C., Kristen, A.V., Beimler, J., Hund, E., Zorn, M., Freiberger, A., Gawlik, M., Goldschmidt, H., Hose, D., Jauch, A., Ho, A.D. & Schonland, S.O. (2017) Lenalidomide/melphalan/dexamethasone in newly diagnosed patients with immunoglobulin light chain amyloidosis: results of a prospective phase 2 study with long-term follow up. *Haematologica,* **102,** 1424-1431.

Joseph, N.S. & Kaufman, J.L. (2018) Novel Approaches for the Management of AL Amyloidosis. *Current Hematologic Malignancy Reports,* **13,** 212-219.

Kastritis, E., Gavriatopoulou, M., Roussou, M., Bagratuni, T., Migkou, M., Fotiou, D., Ziogas, D.C., Kanellias, N., Eleutherakis-Papaiakovou, E., Dialoupi, I., Ntanasis-Stathopoulos, I., Spyropoulou-Vlachou, M., Psimenou, E., Gakiopoulou, H., Marinaki, S., Papadopoulou, E., Ntalianis, A., Terpos, E. & Dimopoulos, M.A. (2018a) Efficacy of lenalidomide as salvage therapy for patients with AL amyloidosis. *Amyloid-Journal of Protein Folding Disorders,* **25,** 234-241.

Kastritis, E., Gavriatopoulou, M., Roussou, M., Bagratuni, T., Migkou, M., Fotiou, D., Ziogas, D.C., Kanellias, N., Eleutherakis-Papaiakovou, E., Dialoupi, I., Ntanasis-Stathopoulos, I., Spyropoulou-Vlachou, M., Psimenou, E., Gakiopoulou, H., Marinaki, S., Papadopoulou, E., Ntalianis, A., Terpos, E. & Dimopoulos, M.A. (2018b) Efficacy of lenalidomide as salvage therapy for patients with AL amyloidosis. *Amyloid,* **25,** 234-241.

Kumar, S., Dispenzieri, A., Lacy, M.Q., Hayman, S.R., Buadi, F.K., Colby, C., Laumann, K., Zeldenrust, S.R., Leung, N., Dingli, D., Greipp, P.R., Lust, J.A., Russell, S.J., Kyle, R.A., Rajkumar, S.V. & Gertz, M.A. (2012) Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol,* **30,** 989-995.

Kumar, S.K., Berdeja, J.G., Niesvizky, R., Lonial, S., Laubach, J.P., Hamadani, M., Stewart, A.K., Hari, P., Roy, V., Vescio, R., Kaufman, J.L., Berg, D., Liao, E., Rajkumar, S.V. & Richardson, P.G. (2019) Ixazomib, lenalidomide, and dexamethasone in patients with newly diagnosed multiple myeloma: long-term follow-up including ixazomib maintenance. *Leukemia,* **33,** 1736-1746.

Kumar, S.K., Gertz, M.A., Lacy, M.Q., Dingli, D., Hayman, S.R., Buadi, F.K., Short-Detweiler, K., Zeldenrust, S.R., Leung, N., Greipp, P.R., Lust, J.A., Russell, S.J., Kyle, R.A., Rajkumar, S.V. & Dispenzieri, A. (2011) Recent Improvements in Survival in Primary Systemic Amyloidosis and the Importance of an Early Mortality Risk Score. *Mayo Clinic Proceedings,* **86,** 12-18.

Landau, H., Smith, M., Landry, C., Chou, J.F., Devlin, S.M., Hassoun, H., Bello, C., Giralt, S. & Comenzo, R.L. (2017) Long-term event-free and overall survival after risk-adapted melphalan and SCT for systemic light chain amyloidosis. *Leukemia,* **31,** 136-142.

Mahmood, S., Venner, C.P., Sachchithanantham, S., Lane, T., Rannigan, L., Foard, D., Pinney, J.H., Gibbs, S.D., Whelan, C.J., Lachmann, H.J., Gillmore, J.D., Hawkins, P.N. & Wechalekar, A.D. (2014a) Lenalidomide and dexamethasone for systemic AL amyloidosis following prior treatment with thalidomide or bortezomib regimens. *Br J Haematol,* **166,** 842-848.

Mahmood, S., Venner, C.P., Sachchithanantham, S., Lane, T., Rannigan, L., Foard, D., Pinney, J.H., Gibbs, S.D.J., Whelan, C.J., Lachmann, H.J., Gillmore, J.D., Hawkins, P.N. & Wechalekar, A.D.

(2014b) Lenalidomide and dexamethasone for systemic AL amyloidosis following prior treatment with thalidomide or bortezomib regimens. *British Journal of Haematology,* **166,** 842-848.

Merlini, G. (2017) AL amyloidosis: from molecular mechanisms to targeted therapies. *Hematology-American Society of Hematology Education Program***,** 1-12.

Moreau, P., Masszi, T., Grzasko, N., Bahlis, N.J., Hansson, M., Pour, L., Sandhu, I., Ganly, P., Baker, B.W., Jackson, S.R., Stoppa, A.M., Simpson, D.R., Gimsing, P., Palumbo, A., Garderet, L., Cavo, M., Kumar, S., Touzeau, C., Buadi, F.K., Laubach, J.P., Berg, D.T., Lin, J., Di Bacco, A., Hui, A.M., van de Velde, H., Richardson, P.G. & Grp, T.-M.S. (2016) Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *New England Journal of Medicine,* **374,** 1621-1634.

Muchtar, E., Dispenzieri, A., Leung, N., Lacy, M.Q., Buadi, F.K., Dingli, D., Hayman, S.R., Kapoor, P., Hwa, Y.L., Fonder, A., Hobbs, M., Gonsalves, W., Kourelis, T.V., Warsame, R., Russell, S.J., Lust, J.A., Lin, Y., Go, R.S., Zeldenrust, S.R., Kyle, R.A., Rajkumar, S.V., Kumar, S.K. & Gertz, M.A. (2019) Optimizing deep response assessment for AL amyloidosis using involved free light chain level at end of therapy: failure of the serum free light chain ratio. *Leukemia,* **33,** 527-531.

Oliva, L., Orfanelli, U., Resnati, M., Raimondi, A., Orsi, A., Milan, E., Palladini, G., Milani, P., Cerruti, F., Cascio, P., Casarini, S., Rognoni, P., Touvier, T., Marcatti, M., Ciceri, F., Mangiacavalli, S., Corso, A., Merlini, G. & Cenci, S. (2017) The amyloidogenic light chain is a stressor that sensitizes plasma cells to proteasome inhibitor toxicity. *Blood,* **129,** 2132-2142.

Palladini, G., Dispenzieri, A., Gertz, M.A., Kumar, S., Wechalekar, A., Hawkins, P.N., Schonland, S., Hegenbart, U., Comenzo, R., Kastritis, E., Dimopoulos, M.A., Jaccard, A., Klersy, C. & Merlini, G. (2012) New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. *J Clin Oncol,* **30,** 4541-4549.

Palladini, G., Sachchithanantham, S., Milani, P., Gillmore, J., Foli, A., Lachmann, H., Basset, M., Hawkins, P., Merlini, G. & Wechalekar, A.D. (2015) A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. *Blood,* **126,** 612-615.

Rezk, T., Gilbertson, J.A., Mangione, P.P., Rowczenio, D., Rendell, N., Canetti, D., Lachmann, H.J., Wechalekar, A.D., Bass, P., Hawkins, P.N., Bellotti, V., Taylor, G.W. & Gillmore, J.D. (2019) The complementary role of histology and proteomics for diagnosis and typing of systemic amyloidosis. *J Pathol Clin Res*.

Sanchorawala, V., Palladini, G., Kukreti, V., Zonder, J.A., Cohen, A.D., Seldin, D.C., Dispenzieri, A., Jaccard, A., Schonland, S.O., Berg, D., Yang, H.Y., Gupta, N., Hui, A.M., Comenzo, R.L. & Merlini, G. (2017) A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. *Blood,* **130,** 597-605.

Specter, R., Sanchorawala, V., Seldin, D.C., Shelton, A., Fennessey, S., Finn, K.T., Zeldis, J.B. & Dember, L.M. (2011) Kidney dysfunction during lenalidomide treatment for AL amyloidosis. *Nephrol Dial Transplant,* **26,** 881-886.

Wechalekar, A.D., Schonland, S.O., Kastritis, E., Gillmore, J.D., Dimopoulos, M.A., Lane, T., Foli, A., Foard, D., Milani, P., Rannigan, L., Hegenbart, U., Hawkins, P.N., Merlini, G. & Palladini, G. (2013) A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. *Blood,* **121,** 3420-3427.

Table I. Patient Characteristics

	N(%)/Median(range)
Age, median (range)	66, 42-80 years
Male, N (%)	24 (60.0)
Disease Isotype	
IgG	18 (45.0)
Light Chain Only	15 (37.5)
IgA	5 (12.5)
IgM	2 (5.0)
Light chain isotype Lambda	31 (77.5)
dFLC (mg/L)	51.5 (0-100)
Mayo Stage at Presentation	
1	9 (22.5)
2	14 (35.0)
3A	14 (35.0)
3B	3 (7.5)
Organ Involvement	
Renal	28 (70.0)
Cardiac	26 (65.0)
Liver	11 (27.5)
Peripheral Nerve	1 (2.5)
Autonomic Nerve	6 (15.0)
Soft Tissue	12 (30.0)
Gastrointestinal	1 (2.5)
Baseline Organ Function	
Median eGFR ml/min per 1.73m^2	56 (>90-<15)
Proteinuria, g per 24h,	2.35 (0.1-16.4)
NT-proBNP, ng/L, median (range)	2445 (50-51661)
ALP, IU/L, median (range)	91.5 (13-1203)
Albumin, g/L, median (range)	35.5 (16.0-49.0)
Prior Lines of Therapy	
Median (range)	2 (1-4)
Bortezomib	40 (100.0)
Lenalidomide	12 (30.0)
ASCT	10 (25.0)
Lenalidomide refractory, N (%)	4 (10.0)

Baseline demographics and disease characteristics. dFLC: difference between involved and uninvolved light chains; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro hormone brain natriuretic peptide; ALP: alkaline phosphatase; ASCT: autologous stem cell transplantation.

Table II: Toxicity of Ixazomib-Lenalidomide-Dexamethasone

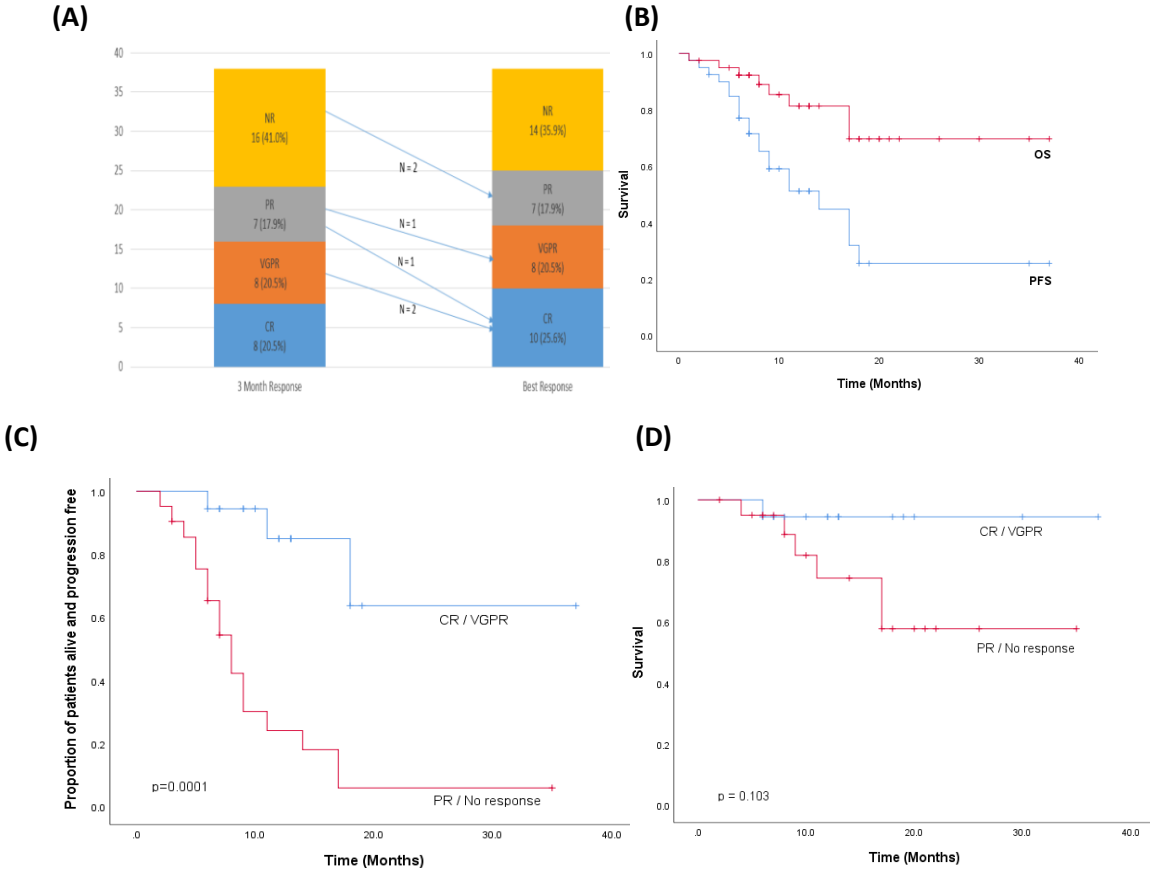
Toxicity	**Total adverse events – n(%)**	**Grade 3-4 events – n(%)**
Thrombocytopenia	17 (42.5)	1 (2.5)
Fatigue	15 (37.5)	-
Constipation	10 (25.0)	-
Infection	9 (22.5)	6 (15.0)
Anaemia	9 (22.5)	2 (5.0)
Oedema	9 (22.5)	5 (12.5)
Neutropenia	9 (22.5)	-
Creatinine increased	**7 (17.5)**	**1 (2.5)**
Diarrhoea	6 (15.0)	-
Muscle / Bone Pain	6 (15.0)	-
Peripheral neuropathy	3 (7.5)	-
Nausea	3 (7.5)	-
Rash	2 (5.0)	1 (2.5)
Cardiac arrhythmia	2 (5.0)	2 (5.0)
Blurred vision	2 (5.0)	-
Insomnia	1 (2.5)	-

Table III: Review of ixazomib or lenalidomide containing treatment regimens

Study	Chemotherapy	Patient No.	Haematological response (CR)	Median PFS	Median OS
Current study*	Ixazomib-Lenalidomide-Dexamethasone	40	66% (26.3%)	17.0m	29.1m
(Sanchorawala*, et al* 2017)	Ixazomib-Dexamethasone	27	52% (10%)	14.8m	85% (1 yr)
(Dispenzieri A 2019)	**Ixazomib-Dexamethasone**	**85**	**53% (26%)**	**20.1m**	**NE**
(Mahmood*, et al* 2014a)	Lenalidomide-dexamethasone	84	61% (20%)	73% (2 yr)	84% (2 yr)
(Kastritis*, et al* 2018b)	Lenalidomide-dexamethasone	55	51% (6%)		25m
(Kumar*, et al* 2012)	Cyclophosphamide-lenalidomide-dexamethasone	35	60% (11%)	28.3m	37.8m
(Dinner*, et al* 2013)	Lenalidomide-melphalan-dexamethasone	25	58% (8%)	3.1m	58% (1 yr), Median NR
(Hegenbart*, et al* 2017)	Lenalidomide-melphalan-dexamethasone	50	68% (18%)	25.1m	67.5m

*A 28-day cycle was used. Ixazomib was given at a dose of 4mg on days 1, 8 and 15. Lenalidomide was given at a dose of 15mg on days 1-21. Dexamethasone was given at a dose of 40mg weekly. Calculation of median progression-free survival (PFS) and median overall survival (OS) were not uniform and have been reported in either months of percentage (%) survival.CR: complete response; NR: not reached; NE: not estimable.

Figure 1: Haematological response and survival



(A) Haematological remission at 3 months and best response at any time after commencement of ixazomib-lenalidomide-dexamethasone. Demonstrates deepening of response in 6 patients. NR: no response; PR: partial response; VGPR: very good partial response; CR: complete response.

(B) Survival of patients with ixazomib-lenalidomide-dexamethasone. Progression-free survival (PFS) and overall survival (OS).

(C) Estimated progression-free survival in relation to the haematological response. CR: complete response; VGPR: very good partial response; PR: partial response.

(D) Estimated overall survival (OS) in relation to the haematological response. CR: complete response; VGPR: very good partial response; PR: partial response.