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A retrospective study of isatuximab-pomalidomide-dexamethasone in relapsed/refractory systemic AL amyloidosis

Sargam Rachit Vohra[1], Sriram Ravichandran[1], Darren Foard[1], Ana Martinez-Naharro[1], Lucia Venneri[1], Marianna Fontana[1], Carol J Whelan[1], Philip N Hawkins[1], Julian Gillmore[1], Helen J Lachmann[1], Shameem Mahmood[1], Ashutosh D Wechalekar[1]

[1]National Amyloidosis Centre, UCL (Royal Free Campus), London, UK

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Corresponding author:
Professor Ashutosh Wechalekar
National Amyloidosis Centre,
UCL (Royal Free Campus)
Rowland Hill Street,
London NW3 2PF, UK
Email: a.wechalekar@ucl.ac.uk

Systemic AL amyloidosis (AL) is a multi-system disorder caused by over production (by clonal plasma cells or B-cell dyscrasia) and deposition of misfolded immunoglobulin free light chains (FLC) as amyloid fibrils in organs. Outcomes have markedly improved with newer treatments. However, AL remains incurable.[1] Daratumumab-CyBorD became the first licensed treatment for newly diagnosed AL in 2021. [2] Presently, there are no licenced treatments for relapsed AL, and all treatments at relapse are adapted from myeloma.

Isatuximab, an anti-CD38 monoclonal antibody, in combination with Pomalidomide, an immunomodulatory drug, and dexamethasone (Isa-PD), has shown efficacy in myeloma. [3] Single-agent pomalidomide has shown a modest efficacy in relapsed AL with 3% achieving complete response (CR), 23% very good partial response (VGPR) and 44% at least a partial response (PR). [4] A phase II study using single-agent Isatuximab in relapsed AL showed an ORR of 77.1%. [5] There is currently no published data on Isa-PD in AL amyloidosis. Here, we present the UK experience of the Isa-PD in relapsed AL.

We report 28 patients treated with Isa-PD from 2020-2024 at the UK National Amyloidosis Centre (UK-NAC). Diagnosis, organ involvement [6, 7], haematologic (3,6 & 12-months) [8] and organ response (12-months) [8] was as per standard criteria. The suggested regimen was: Isatuximab ,10 mg/kg IV weekly for 1st month, then alternate weeks in a 28-day cycle; Pomalidomide 4mg orally daily on days 1-21, and Dexamethasone 20 mg weekly. Patients received Paracetamol, Chlorphenamine, and Dexamethasone before Isatuximab. Montelukast was used for initial 3 cycles. Haematologic response was the primary endpoint. [8] Toxicity, overall survival (OS), and event free survival (EFS) were secondary endpoints. OS and EFS were calculated from the initiation of Isa-PD to death from any cause and to next treatment or death, respectively. The study was approved by NHS ethics board and patients provided informed consent.

Table I shows the pre-treatment characteristics. The median age at diagnosis was 65 years. 42.9%, 46.4% and 10.7% patients received Isa-PD for inadequate response, haematologic progression, and organ progression, respectively. 20/28 (71.4%) had cardiac involvement

and 12/28 (42.9%) had renal involvement. 11/28 (39.3%) had ≥ Mayo stage 3 disease. The median pre-treatment dFLC, NT-proBNP and creatinine were 74 mg/l, 766 ng/l, and 103 µmol/l, respectively. All patients had received 3 prior lines of treatment before receiving Isa-PD. The median time from diagnosis to start of Isa-PD was 77 months. Patients received a median of 24 cycles. Of the 28 patients, 2 patients progressed and received further different treatment,1 patient progressed and died, 6 patients died whilst on treatment and 19 remain on treatment at the time of this analysis.

Haematologic responses were assessed on an intention to treat basis (ITT). Response data was not available in 4/28, 3/28 and 4/28 patients at 3, 6 & 12 months, respectively; these patients are excluded in the response analysis at those time points. One patient progressed between 3-6 months and 2 progressed between 6-12 months. One patient died between 3-6 months of treatment.

The overall haematologic response at 3, 6 and 12 months was 22/24 (91.7%), 23/25 (92%) and 21/24 (87.5%). 15/24 (62.5%), 15/25 (60%) and 15/24 (62.5%) patients achieved ≥VGPR at 3, 6 & 12 months respectively. The best haematological responses at any point were: CR–18 (64.2%), VGPR–6 (21.4%), PR–2 (7.1%). 5/6 patients in VGPR had achieved a FLC-CR. 66% patients achieved their best response within 3 months. Figure 1 shows the change in dFLC at 6 months after starting Isa-PD for each patient. Three previously daratumumab treated patients received Isa-PD at 14, 20, and 36 months post-daratumumab. One patient achieved CR, one achieved VGPR, and one achieved PR.

Eight patients deepened their haematological response with continuing treatment (Figure 2). 6/8 (75%) with < VGPR at 3-months improved to ≥ VGPR with continuing treatment. Two patients with VGPR improved to CR with continued treatment.

9/20 (45%) patients are excluded from the organ response analysis as their pre-treatment NT-proBNP was <650 ng/L. 2/11 (18%) evaluable patients had a cardiac response. Renal responses were not evaluable due to inadequate data.

The median OS and EFS were 53 months (Figure SA 1 in supplementary appendix), and 41 months respectively. The depth of haematologic response did not significantly affect (SA 2 & 3 in supplementary appendix) the OS or EFS. There was no statistically significant difference in OS based on cardiac involvement (p = 0.167).

76 adverse events were reported. Fatigue (11.8%), arrhythmias (10.5%), infections (9.2%), dizziness (6.6%), nausea (5.3%), fluid retention (5.3%), dyspnoea (5.3%), diarrhoea (3.9%) and hypotension (3.9%) were experienced by ≥ patients. Grade 2 neutropenia, grade 2 thrombocytopenia and grade 4 infection were noted in 1 ,1 and 4 patients, respectively. There were no cytopenia > grade 2. No grade 3 or greater infusion-related reactions were reported.

AL is an incurable disease; relapse and further treatment is inevitable. There are no licensed or standardised treatments for relapsed AL. IMiD-based doublets have shown modest efficacy in relapsed AL[9]. Pomalidomide-dexamethasone induced an ORR of 50% in a prospective study in relapsed AL and 77% in a larger multicentre retrospective analysis but with limited CR's. [10, 4] We reported the efficacy of a triplet Ixazomib, Lenalidomide & Dexamethasone. [11] Venetoclax is an excellent option for patients with t (11;14); but has limited global access. Single agent daratumumab in relapsed AL showed excellent response rates in a number of studies.[12] Isatuximab targets a different epitope of the CD38 molecule. A recent phase ll study of single-agent Isatuximab showed a good ORR (77%) in relapsed AL with VGPR in 51% but CR only in 6%.[5] Lately, with the upfront use of daratumumab, the role for single agent anti-CD 38 in the relapsed setting will be limited. Hence, triplet combinations are of interest.

Isa-PD is licensed for the treatment of relapsed myeloma. There is limited data on its efficacy or toxicity in AL. Results of a multicentre, phase II study of Isa-PD in relapsed AL were reported at the American Society of Haematology Meeting 2024. 51% & 80% patients had achieved a CR or ≥VGPR after 6 cycles. This study excluded patients refractory to daratumumab with only two patients exposed to this drug – our current study had 3

daratumumab exposed (but not refractory) patients with responses in 2/3 cases. Deep/rapid clonal responses were achieved within the first few weeks in this study [12]. These results are concordant with our report (≥ VGPR in 85.7 % patients). 66% of our patients achieved their best response within 3 months. We found that responses deepen (8/23) with continuing therapy, even in non-responders. This indicates that tolerability permitting, it is worth persisting with Isa-PD beyond 3 months. We had very few progressions with majority of patients continuing treatment.

There was a transient rise in NT-proBNP in the phase II multicentre study; a likely Pomalidomide effect and does not suggest cardiac deterioration. The lack of cardiac responses in our cohort (only 2/11 evaluable patients) despite a good proportion of deep haematologic response maybe partly explained by this phenomenon. Cardiac biomarker measurements are typically obtained at 6- to 12-month intervals at the NAC. As a result, we are unable to evaluate changes in these biomarkers on a monthly basis limiting detailed evaluation of a paradoxical increase in biomarkers with pomalidomide. 80.5% patients in the phase II study showed > grade 2 AEs; infections and cytopenias were common. [13] No patient discontinued treatment due to toxicity in our cohort, and we report a lower AE burden. Ours is a retrospective cohort and we acknowledge that AEs may be under reported.

The OS and EFS in this cohort were excellent- 53 & 41 months, respectively. We did not find any significant difference in survival based on the best haematologic response. [14] This may be due to 5/6 patients in VGPR achieving an FLC-CR (thus likely to have outcomes not dis-similar to patients in a true CR) and overall small size of the cohort. Moreover, this is a selected group of patients with good prognosis as documented by more than six years of median survival before starting IPD. A much longer period of follow up is likely to be required show impact on survival. We also lack bone marrow data at response (MRD or otherwise) which may help to stratify patients better for EFS/OS outcomes as previously reported.

We acknowledge some additional limitation of our cohort. Bone marrow plasma cell burden at diagnosis/relapse is only known for a minority of patients. We lack data on dose

intensity/modifications. Mild Grade 1-2 reactions might not have been documented. As part of the National Health service requirement to eligible for Isa-PD, patients could not have been refractory to daratumumab. Hence, we lack data impact of this regime in patient's refractory to daratumumab.

In summary, we show that Isa-PD achieves high, rapid and deep responses and excellent OS and EFS in relapsed AL. It is well tolerated and no patient discontinued treatment due to toxicity. Availability of subcutaneous Isatuximab will make the delivery of this combination easier. Isa-PD is a useful treatment option in relapsed AL amyloidosis.

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Table 1: Baseline characteristics

Gender, N (%)	
Male	16 (57.1%)
Female	12 (42.9%)
Age at diagnosis (years)	65 (49-79)
ECOG, N (%)	
0-2	28 (100%)
>2	0 (0%)
Organ involvement, N (%)	
Heart,	20 (71.4%)
Renal,	12 (42.9%)
Liver,	1 (3.6%)
PNS,	4 (14.3%)
ANS,	3 (10.7%)
Soft Tissue	7 (25.0%)
GI	2 (7.1%)
Number of organs involved	1 (1-4)
Mayo stage, N 9%)	
1	6 (21.4%)
2	11 (39.3%)
3A	9 (32.1%)
3B	2 (7.1%)
LVEF (%)	60 (27-77)
LV septum (mm)	14 (10-19)
NT Pro BNP (ng/L)	766 (50-10051)
Troponin (ng/l)	37 (4-742)
Creatinine (µmol/L)	103 (44-761)
Albumin (g/L)	37 (17-47)
Urine ACR (mg/mmol)	3 (0-430)
dFLC (mg/L)	74 (3-1938)
Monoclonal protein (g/L)	1.5 (0-17)
Bone marrow plasma cell (%)	21(5-90)
Light chain Isotype, N (%)	
Lambda (mgl/L)	24(85.7%)
Kappa (mg/L)	4 (14.3%)
Monoclonal protein Isotype, N (%)	
IgG lambda	12 (44.4%)
IgA lambda	1 (3.7%)
IgG kappa	2 (7.4%)
Kappa	2 (7.4%)
Lambda	10 (37%)
First line treatment, N (%)	
Bortezomib based	17(60.7%)
Carfilzomib	2 (7.1%)
CTD	7(25.0%)
Cyclophosphamide and dexamethasone	1(3.6%)
Lenalidomide	1(3.6%)
Second line treatment, N (%)	
Bortezomib based	11 (39.3%)
Daratumumab based	3 (10.7%)

Lenalidomide based Others	10 (35.7%) 4 (14.3%)
Third line treatment, N (%) Bortezomib based Lenalidomide Others	 4 (14.3%) 15(53.6%) 9 (32.1%)
Stem Cell Transplant, N (%)	4 (14.3%)
Median lines of treatment before Isa-PD	3

LVEF: left ventricular ejection fraction, LV septum: left ventricle septum, NTProBNP: N-Terminal Pro Brain Natriuretic Peptide, Urine ACR: Urine albumin creatinine ratio, dFLC: difference between involved and uninvolved light chain, CTD: Cyclophosphamide, Thalidomide, Dexamethasone

Figure legends

Figure 1: ***Waterfall plot showing the percentage change in difference between involved and uninvolved light chains (dFLC) six months after starting Isa-PD.***

The median decrease in dFLC levels at 6 months was 87.8%. Amongst these patients, 11 achieved a complete response (CR), 4 showed a very good partial response (VGPR), and 7 exhibited a partial response (PR).

Figure 2: ***Deepening haematologic response with continued treatment***

Eight patients improved their haematologic response with continued treatment. 6/8 (75%) patients with < Very Good Partial Response (VGPR) at 3-months improved their response to ≥ VGPR with continued treatment. 2 patients with VGPR improved their response to Complete Response with continued treatment.

Figure 1: Percentage change in dFLC 6 months after starting IPD treatment

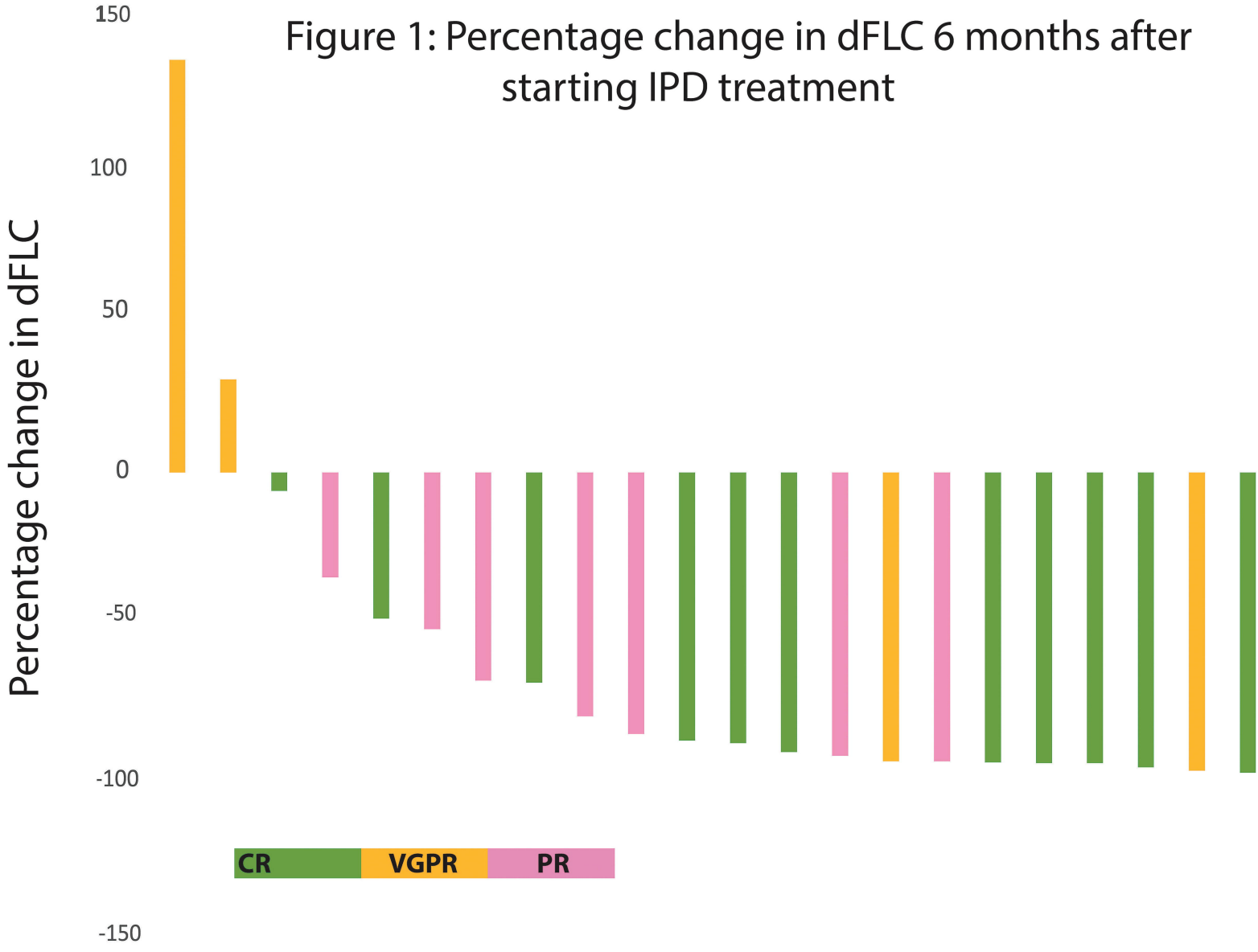
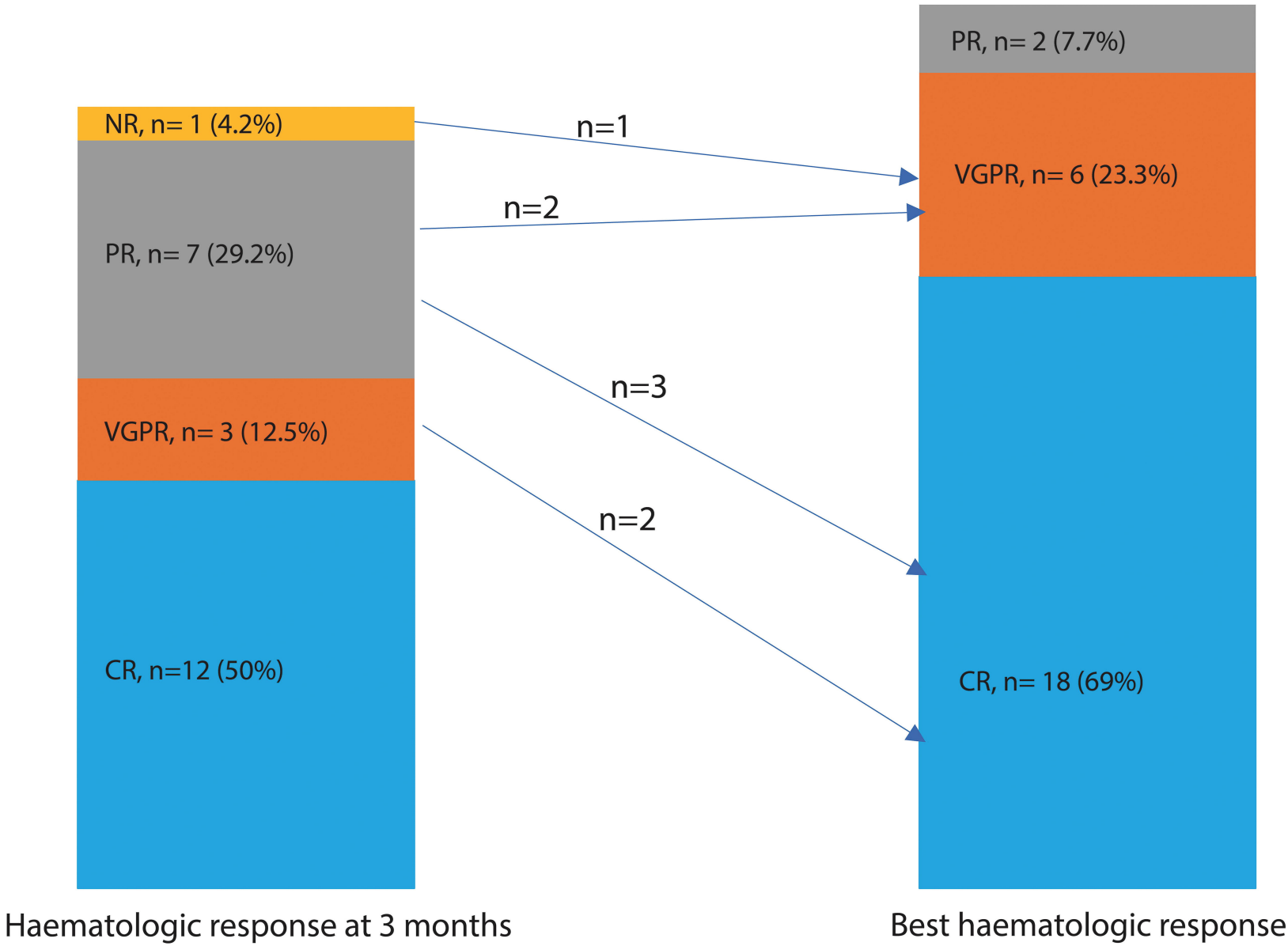


Figure 2: Haematologic response at three months and best response at any time after commencement of Isatuximab, Pomalidomide, dexamethasone



Supplementary Appendix

A retrospective study of Isatuximab-Pomalidomide-Dexamethasone in relapsed/refractory systemic immunoglobulin light chain amyloidosis

Figure SA 1: Shows the overall survival of patients from the start of IPD. The Median OS of the entire cohort was 53 months.

Fig SA1

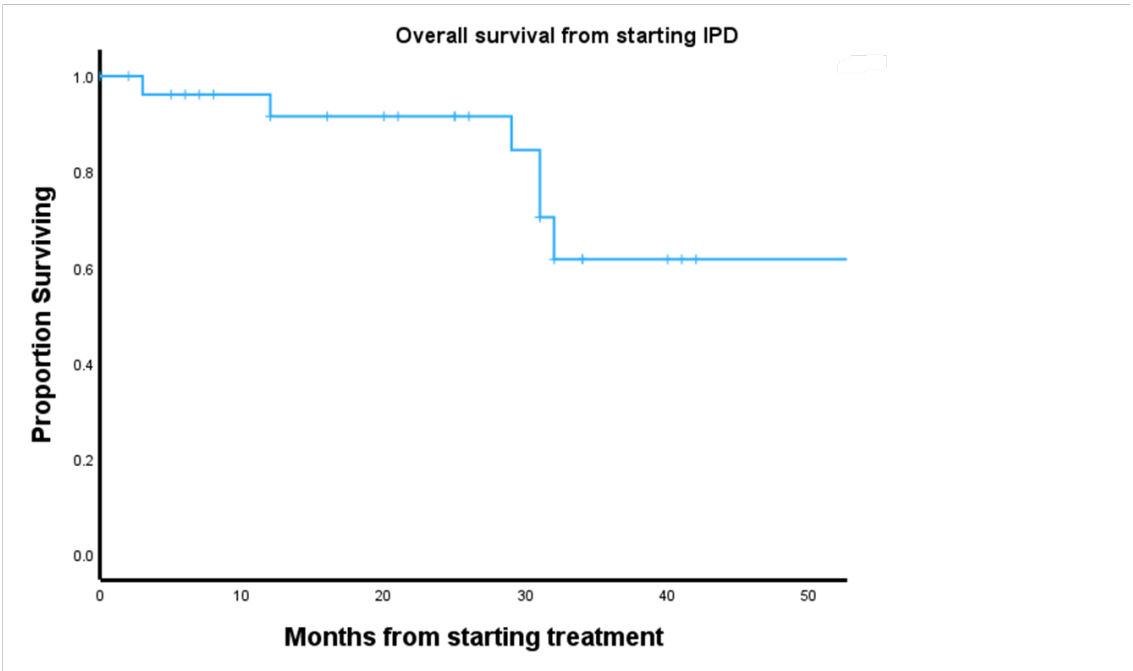


Figure SA 2: Shows the overall survival from start if IPD, stratified by the 12-month haematologic response. The median survival of patients who achieved CR, VGPR and PR/NR/PD was 25 (Range 0-51.29 months), 26 (Range 18.79-33.20 months) and 34 (Range 15.66-52.33 months) months, respectively. There was no difference in survival based on the haematologic response, p value = 0.322.

Fig SA2

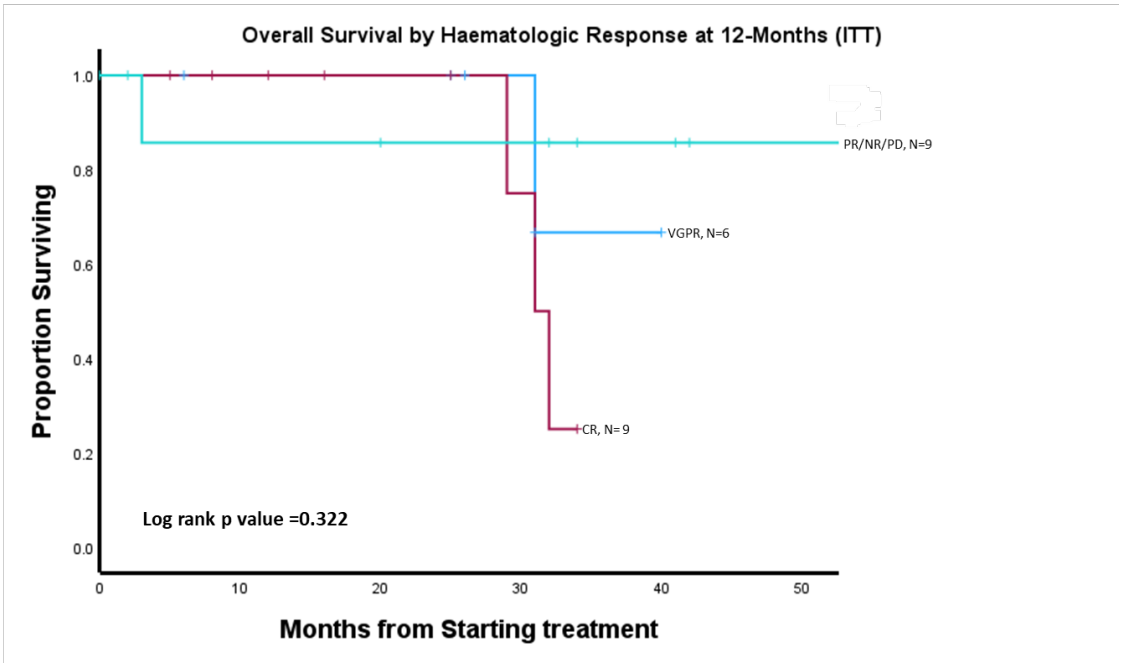


Figure SA 3: Shows the event-free survival from start if IPD, stratified by the 12-month haematologic response. The median survival of patients who achieved CR, & VGPR/PR/NR/PD was 31 months (Range 28.06-33.94 months), and 53 months, respectively. There was no difference in survival based on the haematologic response, p value = 0.145.

Fig SA3