A phase 1b dose-escalation study of Carfilzomib in combination with Thalidomide and Dexamethasone in patients with relapsed/refractory systemic immunoglobulin light chain amyloidosis

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Abstract

Introduction: Proteasome inhibitors are the backbone of AL amyloidosis treatment – bortezomib being most widely used. Carfilzomib is a proteasome inhibitor licensed to treat multiple myeloma; autonomic and peripheral neuropathy are uncommon toxicities with carfilzomib. There is limited data on the use of carfilzomib in AL amyloidosis. Here, we report the results of a phase Ib dose-escalation study of Carfilzomib-Thalidomide-Dexamethasone (KTD) in relapsed/refractory AL amyloidosis.

Results: The trial registered 11 patients from 6 UK centres from September 2017- to January 2019; 10 patients received at least one dose of trial treatment. 80 adverse events were reported from 10 patients in the 1st three cycles. One patient experienced dose-limiting toxicity (acute kidney injury) at a dose of 45mg/m^{2,} and another patient had a SAR (fever). Five patients experienced an AE ≥ grade 3. There were no hematologic, infectious, or cardiac AE ≥ grade 3. The overall haematological response rate (ORR) at the end of three cycles of treatment was 60%.

Conclusion: Carfilzomib 45 mg/m^2 weekly can be safely given with thalidomide and dexamethasone. The efficacy and tolerability profile appears comparable to other agents in relapsed AL amyloidosis. These data provide a framework for further studies of carfilzomib combinations in AL amyloidosis.

Introduction

Amyloidosis is a rare protein misfolding disorder where ordinarily soluble proteins are deposited as abnormal, insoluble fibrils leading to progressive disruption of tissue structure and functional impairment. Systemic immunoglobulin light chain amyloidosis (AL) is caused by the deposition of a misfolded immunoglobulin light chain produced by an underlying monoclonal B-cell or plasma cell dyscrasia. [1] AL is a clinically heterogeneous disease; cardiac and renal involvement is commonest, the former a critical prognostic factor at diagnosis.[2] Treatment in AL amyloidosis aims to suppress the underlying clonal disorder with chemotherapy or autologous stem cell transplantation. [3-6] Deep suppression of the amyloidogenic light chains results in superior outcomes. Proteasome inhibitors are very effective in suppressing the light chains due to the marked sensitivity of AL plasma cells to proteasome inhibition. Bortezomib-based regimes are the de-facto standard of care [7,8], and daratumumab combined with cyclophosphamide, bortezomib, dexamethasone was recently the first only formally licensed treatment for AL amyloidosis.[9] Most other treatment and treatment regimens are adapted from those used in multiple myeloma.

Despite the success of bortezomib in AL, its use in AL is not without challenges, mainly due to the risk of neuropathy (autonomic or peripheral), either *de novo* or worsening of pre-existing neuropathy in AL. [10] Additionally, with bortezomib used as a first-line agent in the majority of the cases, an alternative proteasome inhibitor with a different toxicity profile and possible lack of cross-resistance would be a helpful agent in AL treatment paradigm.

Carfilzomib is a distinct proteasome inhibitor that is licensed for the treatment of multiple myeloma. It is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsin-like active site of the 20S proteasome, structurally and mechanistically distinct from bortezomib. Autonomic and peripheral neuropathy are uncommon toxicities with carfilzomib.[11] There is extensive data using carfilzomib combined with immunomodulatory agents (IMiDs) in myeloma treatment. Therefore, it is very appealing to use this agent in AL amyloidosis. However, there are reported cardiac and renal toxicities with carfilzomib in a small number of patients. Hence, it cannot be adopted directly for AL amyloidosis without formal prospective studies. There is limited data on the use of carfilzomib in AL amyloidosis comprising only a single case series and a phase 1 dose-escalation study using Carfilzomib alone.[12,13] There is no data on the safety/efficacy of combination therapy using Carfilzomib.

Here, we report the results of the CATALYST study (NCT02545907), a phase Ib dose-escalation study of carfilzomib-thalidomide-dexamethasone (KTD) in relapsed/refractory AL amyloidosis.

Patients and methods

Study Design and Treatment Schedule

CATALYST was a single-arm open-label multi-centre phase Ib dose-escalation study with an expansion phase for patients with relapsed or refractory systematic AL amyloidosis with the exclusion of genetic mutations associated with hereditary amyloidosis and immunohistochemical exclusion of AA and TTR amyloidosis as appropriate. Eligible participants were 18 years or over with measurable clonal disease and life expectancy ≥ 6 months. Participants were required to have an Eastern Cooperative Oncology Group performance status ≤ 2 and meet the following

specified laboratory values: platelet count ≥ 50x109/l, neutrophil count ≥ 1x109/l, haemoglobin ≥ 8g/dL and bilirubin < 2 times or alkaline phosphatase < 4 times the upper limit of normal. Exclusion criteria included: overt symptomatic multiple myeloma, localised AL amyloidosis, trivial or incidental AL amyloid deposits in the absence of a significant amyloid-related organ syndrome and severe peripheral or autonomic neuropathy causing significant functional impairment. A complete list of inclusion criteria is included in the supplementary appendix.

Participants were recruited from the UK National Amyloidosis Centre (UK NAC), and following consent were registered through the University of Leeds Clinical Trials Research Unit. The study was approved by the UK national ethics committee (16/LO/0087), Medicines and Healthcare Products Regulatory Agency (MHRA) and registered on the International Standard Randomized Controlled Trial Number Register (ISRCTN 16308011). All participants provided written informed consent.

The trial was planned in two parts, a dose-escalation phase to determine the maximum tolerated dose (MTD) and subsequently recommended dose (RD) and a dose-expansion phase to further assess the safety and tolerability of KTD at the RD identified in the dose-escalation phase (primary endpoint). Secondary endpoints included clonal response, improvement in amyloidotic organ function and number of progressions and deaths at six months.

Participants received a loading dose of Carfilzomib at 20mg/m² on day 1 of cycle 1 and then at the allocated dose level on day 8 and day 15 of cycle one, and during all subsequent cycles; alongside 20mg of dexamethasone on days 1,8 and 15 and Thalidomide 50mg daily for an initial 3 cycles (Table 1). Following an evaluation after 3 cycles of treatment; if a participant has no

response to treatment, they will stop trial treatment; if a participant has CR or VGPR with plateau, they will complete a further 3 cycles of treatment; if a participant has a PR with or without plateau, they will complete one more cycles, and if there is no incremental response, they will stop trial treatment, and if there is an incremental response, they will continue treatment until maximum response.

A 3+3 design was used to determine the MTD of KTD beginning at dose level 0 and following the schema in Table I. The MTD was defined as the highest dose level at which no more than 1 participant out of six evaluable patients experienced dose-limiting toxicity (DLT). If no more than one participant experienced a DLT at the highest dose level, then this was considered the MTD. DLTs were assessed during the first 28 days of treatment, up to the start of cycle 2. The safety review committee (SRC), comprising all the principal investigators and at least one independent member, reviewed safety data and decided cohort dose escalations. DLTs were defined by any of the following events: any non-haematological toxicity ≥ grade 3 according to NCI CTCAE Version 4.03, which fails to return to ≤ grade 1 or baseline after 7 days; grade 4 neutropenia lasting > 7 days or grade 4 neutropenia with sepsis despite adequate supportive measures; any grade 4 thrombocytopenia which fails to return to grade 2 within 7 days without platelet support; delay of >8 days within cycle 1 or delay of commencement of 2nd cycle by more than 14 days, due to significant toxicity or tolerability issue; any other event which, in the opinion of the SRC, is considered to be clinically significant and related to treatment.

At the recommended dose level identified, a further 20 patients were planned to be recruited to further assess safety and toxicity at the RD. There was no formal sample size calculation for this component.

Assessment of response and disease progression was done using the international society of amyloidosis consensus criteria.[6,14] Toxicities were graded according to the National Cancer Institute CTCAE version 4.03. Response assessments were performed within 3 days before each cycle, day 8 and 15 of each cycle, after 3 cycles of trial treatment and either 6 months post-registration or in patients receiving 6 cycles of treatment, 1 month after the final cycle of treatment.

Statistical Analysis

Analysis was performed by the University of Leeds Clinical Trials Research Unit, in which all endpoints were summarised descriptively. A full statistical analysis plan was written before any analyses being undertaken.

Safety data were summarized for all participants who received at least one dose of trial treatment. All efficacy assessments were summarized for the same population. The safety review committee reviewed each DLT and attributed the DLT to the loading dose or the registered dose; any DLT attributed to the loading dose was excluded when determining the MTD. KTD Patients who did not receive one complete cycle due to experiencing a DLT were included in the analysis; patients who did not receive at least one complete cycle for reasons other than toxicity, without experiencing a DLT, and who missed a dose of carfilzomib, more than 14 doses thalidomide or 2 doses of dexamethasone in the first cycle, were replaced.

No formal statistical testing was performed. Percentages were calculated using the total number of patients in the appropriate population as the denominator. Progression-free survival (PFS) and time to maximum response used the Kaplan Meier method with patients censored at the point

last known to be alive and progression-free. Patients were regarded as compliant to treatment where treatment is received as per protocol until withdrawal from treatment and have no more than 1 dose omission of Carfilzomib, 5 of Thalidomide or 1 of Dexamethasone during each cycle. All statistical analyses were performed with SAS statistical software version 9.4.

Results

The trial registered a total of 11 patients from 6 UK centers between September 2017 and January 2019, with 10 patients receiving at least one dose of trial treatment (consort diagram, Figure 1). One patient was ineligible due to a high NT-proBNP level. In agreement with the Trial Management Group, the trial closed to recruitment following the dose-escalation stage without opening the expansion phase due to slow recruitment. Figure 1 shows the CONSORT diagram for the trial.

Table II lists baseline characteristics. The median age was 75 (range 61-75) years and 62 (range 51-73) years in the dose level 0 and dose level 1 cohort, respectively. The median time from original AL amyloidosis diagnosis to baseline was 9.9 (range 3.3-10.1) years and 3.6 (range 0.6-5.70) years, respectively. All patients had received at least one line of treatment previously; Cyclophosphamide-Bortezomib-Dexamethasone (CyBorD) was the most used regimen (n=8/10), followed by CTD (n=3/10), High dose Melphalan autologous stem cell transplant (n=3/10), Lenalidomide-Dexamethasone (n=2/10) and Melphalan + Dexamethasone (n=1/10). One patient had received four lines of treatment before baseline.

Dose-limiting toxicity, maximum tolerated dose, and recommended dose

The first three evaluable patients were recruited at dose level 0 (36 mg/m^2) and none experienced a DLT. As per protocol, the next three patients were recruited at dose level 1 (45 mg/m^2). One patient experienced a DLT (acute kidney injury). The patient with DLT had Mayo stage III cardiac involvement (at diagnosis) and stage II renal disease. A further four patients were recruited at dose level 1: one patient experienced a DLT following the initial dose of 20 mg/m^{2,} this data was not used to evaluate the MTD therefore an additional patient was recruited. This patient did not have cardiac involvement (Mayo stage I) and had stage I renal disease. The data monitoring committee decided that it was not in the patients' interest to proceed to dose level 2 due to evidence of activity at dose level 1 and the potential risk of toxicity at dose level 2. Dose level 1, 45 mg/m^2 weekly was determined as the recommended dose of carfilzomib, with 1/6 patients experiencing a DLT. Table SA1 in the supplementary appendix contains a detailed description of the DLTs.

Safety and tolerability

Three (30%) patients experienced a serious adverse event (SAE). One patient in dose level 1 (45mg/m2) had grade 3 acute kidney injury, which was considered a DLT attributed to carfilzomib at that dose. The acute kidney injury improved at the time of discharge. Another patient in dose level 1 experienced grade 2 fever after the loading dose. Both were classified as serious adverse reactions (SAR) related to carfilzomib. One patient at dose level 0 experienced grade 3 abdominal pain, which was deemed not related to the trial medication. No SUSARs or deaths were reported. No patients withdrew from the study.

A total of 80 adverse events were reported from 10 patients in the 1st three cycles. Table SA2 in the supplementary appendix lists adverse events (AE) by the number of participants experiencing

each and the maximum CTCAE grade experienced. Oedema limbs (70%), anaemia (30%), diarrhoea (30%), dizziness (30%), dyspnoea (30%), pain in extremity (30%), and nausea (30%) were experienced by three or more patients.

Table III lists the AEs of interest. Two patients (20%) in dose level 0 and three patients (30%) in dose level 1 (overall 50%) experienced an AE of CTCAE grade 3 or above at any time during treatment. These included hypertension, diarrhoea, acute kidney injury, creatinine increase, reduced urine output and GGT increase. Three patients experienced an AE above grade 3 in cycle 1.

There was a total of 5 delays from 3 participants, 5 dose modifications from 2 participants and 80 omissions from 6 participants. 6/10 patients overall and 5/7 at dose level 1 were treatment compliant.

Haematologic and amyloidotic organ response

Two patients did not have a post-baseline efficacy assessment- one patient had a DLT, and another had a SAR, therefore, they were non-evaluable for a response. The overall haematological response rate (ORR) within and at the end of three cycles of treatment was 60%. The ORR within and at the end of six cycles of treatment was 70%. 3/10 (30%) had a complete haematological response (CR), and 3/10(30%) had a very good partial response. Figure 2 shows the individual patient's clonal response at the end of each cycle of treatment. The median time to maximum response was 5.3 months. 95% confidence intervals were not calculable due to the small number of events. No patient had progressed at six months post-registration. Two patients

had progressed at 6.3- and 6.6-months post-registration. Median progression-free survival was not reached, and there were no deaths.

Amyloidotic organ response was assessed after three cycles and then after six cycles. There was no organ response throughout treatment or at follow up. Two patients had evidence of organ progression (kidneys), and one patient showed a change in organ function unrelated to amyloidosis. Of the two patients who showed renal progression, one patient was not evaluable, and another patient had no response to treatment.

Discussion

Carfilzomib has been shown to significantly improve outcomes with a favourable risk-benefit profile in relapsed multiple myeloma.[15] However, there is limited data on its use in AL amyloidosis. The primary objective of the present study was to determine the maximum tolerated dose (MTD) and recommended dose (RD)of carfilzomib when used in combination with thalidomide and dexamethasone. Dose escalation successfully reached dose level 1, at which one patient experienced a DLT within the 1st cycle of treatment (grade 3 acute kidney injury). The MTD of carfilzomib was not reached as no further dose escalation occurred. As there was evidence of efficacy at dose level 1 without significant toxicity, 45 mg/m^2 weekly was determined as the RD of carfilzomib in AL amyloidosis.

There were 9 AE's of CTCAE grade 3 or above. Two SARs were deemed related to carfilzomib (AKI and fever). Renal involvement is common in AL amyloidosis. It is common to see worsening renal dysfunction during therapy in AL patients and is probably due to the precarious situation of the kidneys due to disease. In previous studies, Bortezomib has also been known to cause creatinine

increase and fever in a small minority of patients.[16] There were no deaths during the study, and none of the patients withdrew from the study.

To our knowledge, the present study is the only prospective dose-escalation study exploring a carfilzomib triplet in the treatment of AL amyloidosis. We have previously reported our retrospective experience in a small series of five patients with peripheral or autonomic nerve involvement treated upfront with carfilzomib (in combination with lenalidomide or pomalidomide). [12] Another phase I/II study evaluated the MTD of carfilzomib monotherapy (given bi-weekly) in relapsed AL amyloidosis, and the authors concluded that carfilzomib 36 mg/m^2 bi-weekly was feasible and effective in relapsed/refractory AL amyloidosis.[17] However, there was a significant burden of cardiac AEs in the Carfilzomib monotherapy study with Grade 3 or 4 cardiac AEs observed in nearly 1/3 of the patients. Cardiotoxicity is a well-recognized adverse effect of carfilzomib seen in a small number of treated patients as reported in a meta-analysis of published studies, especially in patients with pre-existing cardiovascular disease [18,19]. This study was reassuring from a cardiac safety perspective, with all cardiovascular AEs (five in total) being grade 1 or 2, and none of the patients discontinued treatment due to a cardiac AE. Two out of the 4 patients with cardiac involvement at baseline did not report any cardiac AEs. This is even more striking since thalidomide also is reported to have cardiac AE's in amyloidosis. The key difference to the previous single-agent study by Cohen et al. is with once weekly in the current study compared to bi-weekly in the previous study. Given the current data, any future studies with carfilzomib in AL should explore a once-weekly dosing schedule.

The toxicity profile in the present study is comparable to previous reports. [15,20]. The incidence of peripheral neuropathy was also comparable to previous reports.

Bortezomib is the current standard of care in AL amyloidosis. Daratumumab, in combination with bortezomib, has shown great promise as upfront treatment and has become the 1st licensed treatment for AL amyloidosis.[21,22] However, treatment of relapsed/refractory patients to bortezomib remains difficult as IMiD doublets are not well tolerated, and deep responses are few. The results of the present study show that the carfilzomib-thalidomide-dexamethasone combination is effective in relapsed AL amyloidosis. Daratumumab-cyclophosphamide-bortezomib-dexamethasone (Dara-CyBorD) has become the first licensed treatment for AL amyloidosis.[9] However, treatment regimens for patients who relapse or progress after Dara-CyBorD remain unclear. A carfilzomib-IMiD triplet would be a potentially attractive option and warrants further study. Even in this small study, we noted an ORR of 70%, even in the setting of exposure to previous proteasome inhibitor therapy. Therefore, the present combination provides a viable option for patients with relapsed/refractory AL amyloidosis after frontline bortezomib. This study also paves the way for studies of carfilzomib with newer IMiDs (especially pomalidomide) which are better tolerated than thalidomide and can be used in the neuropathic setting.

To conclude, the results of the present study show that carfilzomib 45 mg/m^2 weekly can be safely given in combination with thalidomide and dexamethasone. The efficacy and tolerability profile appears comparable with other studies in relapsed AL amyloidosis, although numbers are limited. The MDT of carfilzomib identified in this study can form the basis of further studies of other novel carfilzomib combination with newer IMiDs or monoclonal antibodies in the treatment of AL amyloidosis.

Role of the Funder

The funder, Amgen, conducted an independent review of the study protocol but were not involved in the design, conduct, analysis or interpretation and provided study drug free of charge.

Authorship declaration

SR, AH, AP, JB and SB analysed the data and wrote the manuscript. MJ, MG, BK, HL, JG, and PH reviewed and approved the manuscript. AW supervised the study, reviewed, and approved the manuscript.

Conflict of interests

ADW has received honoraria from Janssen, GSK, Celgene, and Takeda. The other authors do not have any conflict of interest to disclose.

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Table I: Dosing schedule

Dose level	Carfilzomib IV (mg/m²) (Days 1, 8 & 15)	Thalidomide (mg) (Days 1-28)	Dexamethasone (mg) (Days 1, 8 & 15)
-1	27	50	20
0	36	50	20
1	45	50	20
2	56	50	20

Table II: Baseline characteristics

	Dose level 0: 36 mg/m² (n=3)	**Dose level 1: 45 mg/m² (n=7)**	**Total (n=10)**
	N(%)/median(range)	**N(%)/median(range)**	**N(%)/median(range)**
Gender Male Female	 2 (66.7%) 1 (33.3%)	 2 (28.6%) 5 (71.4%)	 4 (40%) 6 (60%)
Age, years	75 (61-75)	62 (51-73)	63 (51-75)
Time from AL amyloidosis diagnosis to baseline, years	9.9 (3.3-10.1)	3.6 (0.6-5.7)	3.7 (0.6-10.1)
Time from most recent relapse to baseline, years *	0.8 (0.8-0.8)	0.9 (0.2-2)	0.9 (0.2-2)
Number of previous lines of therapy			
1	0 (0.0%)	3 (42.9%)	3 (30%)
2	2 (66.7%)	2 (28.6%)	4 (40%)
3	1 (33.3%)	1 (14.3%)	2 (20%)
4	0 (0.0%)	1 (14.3%)	1 (10%)
Prior treatments			
CTD	2 (66.7%)	2 (28.6%)	4 (40%)

Cy-Bor-D	3 (100%)	5 (71.4%)	8 (80%)
High dose melphalan ASCT	0 (0%)	3 (42.9%)	3 (30%)
Lenalidomide-Dexamethasone	1 (33.3%)	1 (14.3%)	2 (20%)
Melphalan-Dexamethasone	1 (33.3%)	0 (0.0%)	1 (10%)
Others	0 (0.0%)	3 (42.9%)	3 (30%)
ECOG performance status 0 1 2	 0 (0%) 3 (100%) 0 (0%)	 2 (28.6%) 4 (57.1%) 1 (14.3%)	 2 (20%) 7 (70%) 1 (10%)
Cardiac Involvement	0 (0%)	4 (57.1%)	4 (40%)
Mayo Stage at diagnosis (European modification) **Stage I** **Stage II** **Stage III** **Stage IIIb**	 3 (100%) 0 (0%) 0 (0%) 0 (0%)	 3 (43%) 1 (14%) 3 (43%) 0 (0%)	 6 (60%) 1 (10%) 3 (30%) 0 (0%)
Renal involvement	3 (100%)	3 (42.8)	6 (60%)
Renal stage at time of entry into the trial **Stage I** **Stage II** **Stage III**	 2 (66.7%) 1 (33.3%) 0 (0%)	 4 (57%) 3 (43%) 0 (0%)	 6 (60%) 4 (40%) 0 (0%)
Nerve involvement	0 (0%)	1 (14.2%)	1 (10%)
Median creatinine, µmol/l, (range)	86 (74-145)	64 (50-202)	77 (50-202)
Median eGFR, ml/min, (range)	79 (33-90)	88 (21-90)	83.5 (21-90)

Median NT-proBNP, pmol/l, (range)	26.6 (9.8-53.3)	56.3 (6.8-220)	53.3 (6.8-220)
Median dFLC, (range)	78.2 (31.9-196)	75.7 (44.8-483)	77 (31.9-483)

* There are 4 (2 at dose level 0, 2 at dose level 1) participants with refractory disease, thus time from most recent relapse is not applicable to these patients.

Table III: AEs of interest (Renal/Cardiac/Fluid Overload/Grade 3 or above)

System organ class	Grade 1-2	Grade 3
Renal		
Acute kidney injury	1 (10%)	1 (10%)
Creatinine increased	1 (10%)	1 (10%)
Cardiac		
Dyspnoea	3 (30%)	
Edema limbs	7 (70%)	
Heart failure	2 (20%)	
Hypertension	1 (10%)	1 (10%)
Gastrointestinal		
Abdominal pain		1 (10%)
Mucositis oral	1 (10%)	
Diarrhoea	1 (10%)	2 (20%)
Nausea	3 (30%)	
Infections	5 (50%) {1 x bladder infection, chest infection, upper respiratory infection, urinary tract infection and vaginal infection}	
Nervous system		
Dizziness	3 (30%)	

Pain in extremity	3 (30%)	
Peripheral sensory neuropathy	1 (10%)	1 (10%)
Investigations		
Anaemia	3 (30%)	
GGT increased		1 (10%)

Figure Legends

Figure 1: Consort diagram of the CATALYST Trial. Eleven patients were assessed for eligibility, ten were found eligible. Three patients received dose level 0 and another seven patients received dose level 1. One patient in dose level 1 discontinued treatment due to toxicity. Two patients in dose level 1 discontinued treatment due to toxicity. The total number of evaluable patients were eight.

Figure 2: Shows individual patient clonal response in the evaluable patients. The overall response rate (ORR) at the end of three & six cycles of treatment was 60% & 70%, respectively. 3/10 (30%) had a complete response (CR) and 3/10(30%) had very good partial response. One patient had a partial response. The median time to maximum response was 5.3 months. No patient had progressed at six months post-registration.

Figure 1: Consort diagram of the CATALYST Trial

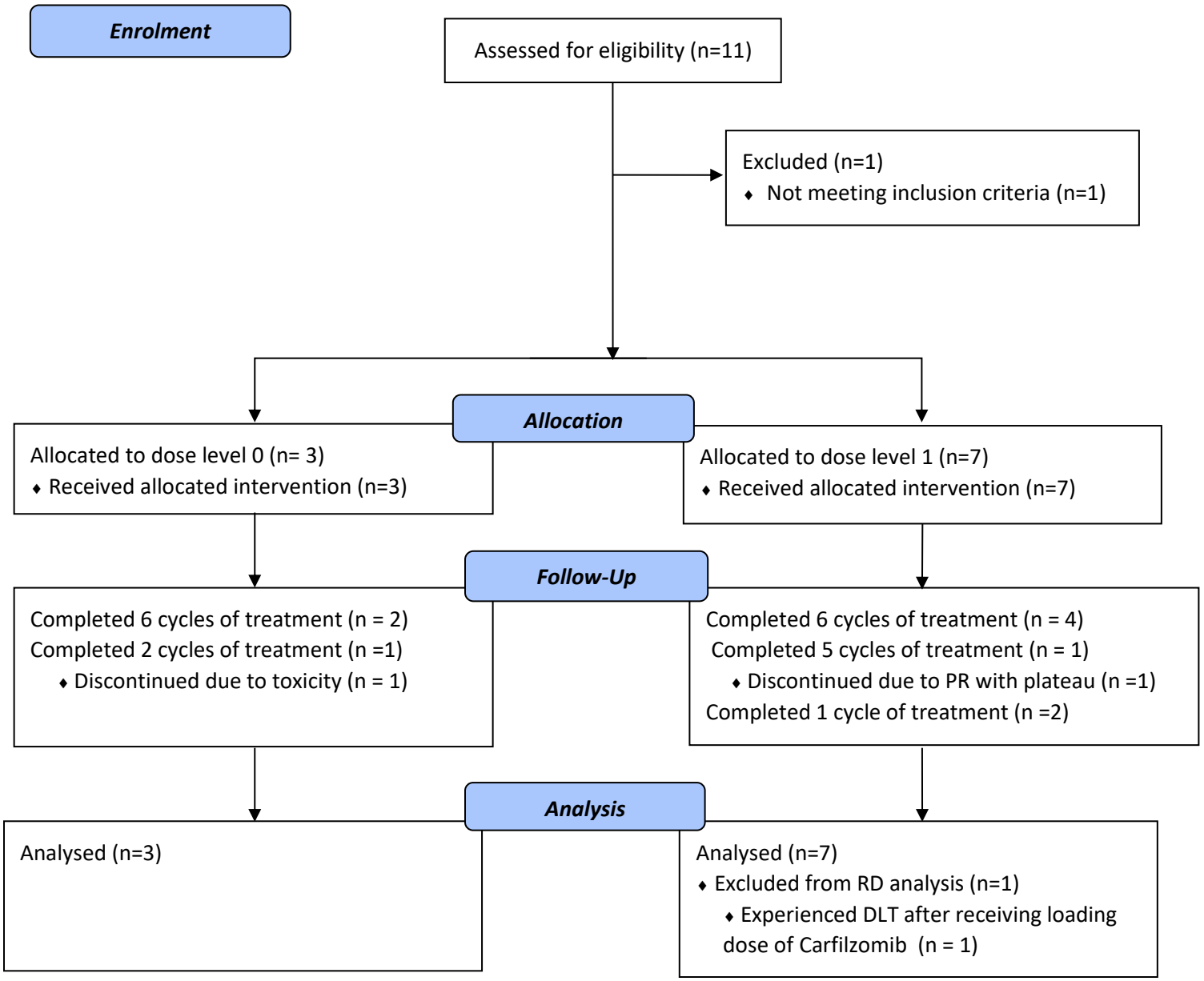

Figure 2: Listing of individual participant clonal responses and reasons for stopping treatment