A phase 1 study of Carfilzomib-Thalidomide-Dexamethasone in patients with relapsed/refractory AL amyloidosis - CATALYST Trial results

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INTRODUCTION

Systemic AL amyloidosis is a rare multisystem disease caused by an underlying plasma cell dyscrasia with amyloid fibril deposition causing progressive organ failure. Treatment of the underlying plasma cell disorder underpins the management of AL amyloidosis with bortezomib based regimes as standard first line treatment. Thalidomide has activity in AL amyloidosis used in low doses in combination with cyclophosphamide and dexamethasone. carfilzomib (Kyprolis™), a second generation irreversible inhibitor of the proteasome, is licenced for treatment of relapsed refractory myeloma. This prospective phase 1 multicentre study was designed to define the maximum tolerated dose (MTD) and recommended dose (RD) of one weekly dose of carfilzomib in combination with a fixed dose of thalidomide and dexamethasone (KTD) in patients with relapsed refractory amyloidosis.

PATIENTS AND METHODS

This was a single arm open label multicentre phase Ib dose escalation study with expansion phases (ISRCTN16308011). Patients received treatment with carfilzomib in escalating dose cohorts along with a fixed dose of dexamethasone and Thalidomide (KTD). The dose escalation phase of the study used a 3+3 dose escalation design. Cohorts of 3-6 participants will be treated with KTD as outlined below. Carfilzomib doses were increased between cohorts until the occurrence of dose limiting toxicities (DLTs) define the MTD. The Safety Review Committee reviewed the safety and ethics of the trial by reviewing interim data after each cohort of treatment during recruitment to the Dose Escalation Cohort.

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

AIMS AND ENDPOINTS

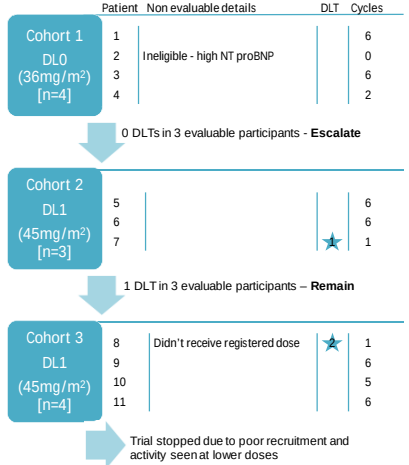
PRIMARY

- **Establish MTD and RD of Carfilzomib in combination with Thalidomide and Dexamethasone:** Dose-Limiting Toxicities (Dose escalation phase), between the time of receiving the first registered dose of Carfilzomib in cycle 1 and day 1 cycle 2.
- **Characterise Safety Profile:** Proportion of patients treated who experience any grade 3 or 4 CTCAE toxicity throughout all treatment cycles

SECONDARY

- **Further Characterise Safety:** Number of SAEs**,** Number of deaths at 6 months.
- **Characterise Efficacy:** Amyloidotic organ response rate within 3m and 6m. Clonal response rate within 3m, at 3m, within 6m and at 6m. Time to amyloidotic organ response. Number of patients progression free at 6 months. Maximum response. Time to maximum response.
- **Treatment Compliance:** Number of patients withdrawing from treatment. Number of patients experiencing dose delays, and compliance profile of KTD. Relative Dose intensity

RESULTS – Dose Finding and Patient Characteristics

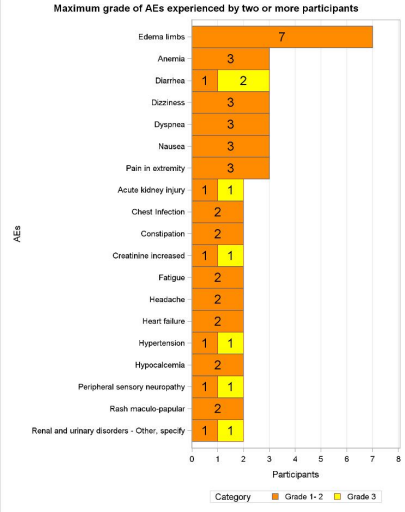


DLT 1: Non Haem toxicity ≥g3 – Acute kidney injury
DLT 2: Delay >8 days cycle 1: admitted to ITU, temperature + hypotension. Patient received 20mg/m² loading dose

- 1 DLT in 6 evaluable patients at Dose level 1 (45mg/m²)
- Recommended dose: 45mg/m² carfilzomib

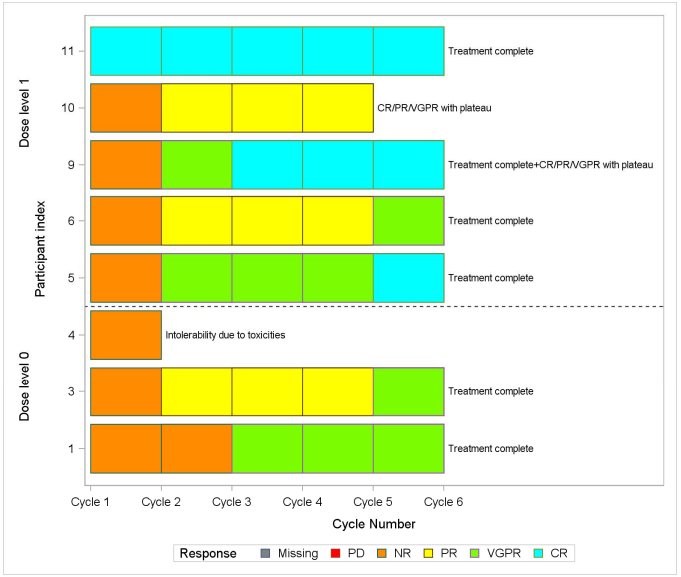
	Overall (n=10)
Participant Sex	
Male	*4 (40.0%)*
Female	*6 (60.0%)*
Age (years)	
Mean (s.d.)	*64.0 (8.76)*
Median (range)	*63.0 (51.0, 75.0)*
Time from original AL amyloidosis diagnosis to baseline (years)	
Mean (s.d.)	*4.6 (3.22)*
Median (range)	*3.7 (0.6, 10.1)*
Time from most recent relapse to baseline (years)	
Median (range)	*0.9 (0.2, 2.0)*
Number of lines of previous therapy	
1	*3 (30.0%)*
2	*4 (40.0%)*
3	*2 (20.0%)*
4	*1 (10.0%)*
Prior treatments for AL amyloidosis	
CTD	*4 (40%)*
CVD	*8 (80%)*
HDMASCT	*3 (30%)*
LenDex	*2 (20%)*
MDex	*1 (10%)*
Other	3 (30%)
Creatinine (umol/L)	
Median (range)	77.0 (50.0, 202)
eGRF (mL/min)	
Median (range)	83.5 (21.0, 90.0)
NT Pro-BNP (pmol/L)	
Median (range)	53.3 (6.8, 220)
dFLC	
Median (range)	77.0 (31.9, 483
Kappa-Lambda Ratio	
Median (range)	0.2 (0.1, 66.2)

RESULTS – Safety



- A total of three patients had SAE's (grade 3 acute kidney injury; pyrexia, hypotension and hypoxia; abdominal pain)
- There were 83 other grade 1 or 2 adverse events reported from 9 participants.
- There were 9 grade 3 adverse events reported from 5 participants.
- There were no grade 4+ adverse events.
- There were no SUSARs or deaths in the study reported to date.
- None of the patients had worsening cardiac function.

RESULTS - Response



- Two participants (7 and 8) experienced DLTs and discontinued treatment without post baseline efficacy assessment.
- The overall response rate at the end of cycle 3 was 60%. Six participants achieved a clonal response of partial response (PR) or above.
- At the end of cycle 6 and within 6 cycles of treatment, the clonal response rate was 70%.
- 7 participants achieved a PR or above. This included: complete response – 3 (30%); VGPR – 3 (30%) and partial response – 1 (10%). One participant (4) had no response by the end of cycle 2 (discontinued due to toxicity)

SUMMARY AND CONCLUSIONS

- This study defined, in combination with thalidomide and dexamethasone, the recommended dose of carfilzomib was 45mg/m² on days 1, 8 and 15.
- The MTD of carfilzomib was not reached.
- Three participants experienced a SAE and a number of participants had grade 1-2 AE's.
- At the end of 3 cycles, 70% of participants achieved a hematologic response with 40% VGPR or better which appears comparable to other studies in relapsed AL amyloidosis.
- KTD is a potentially effective regime that can be considered for further study in relapsed refractory systemic AL amyloidosis.

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