Supplementary Appendix

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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Inclusion criteria:

Patients with the following characteristics are eligible for this study:

1. Aged 18 years or greater
2. Diagnosis of systemic AL amyloidosis with
    i. exclusion of genetic mutations associated with hereditary amyloidosis and immunohistochemical exclusion of AA and TTR amyloidosis as appropraite
    ii. Amyloid-related organ dysfunction or organ syndrome (see Appendix 2)
3. Measurable clonal disease
4. Clonal relapse after previous chemotherapy or autograft stem cell transplant OR refractory clonal disease to previous chemotherapy or stem cell transplant
5. Capable of providing written, informed consent and willing to follow study protocol
6. Life expectancy ≥ 6 months
7. ECOG performance status of 0-2
8. Platelet count ≥ $50x10^9$/l
9. Neutrophil count ≥ $1x10^9$/l
10. Haemoglobin ≥ 8g/dL
11. Bilirubin <2 times or Alkaline phosphatase <4 times upper limit of normal.
12. Female participants of child-bearing potential must have a negative pregnancy test prior to treatment and agree to use dual methods of contraception for the duration of the study and for 30 days following completion of study. Male participants must also agree to use a barrier method of contraception for the duration of the study and for 90 days following completion of study if sexually active with a female of child-bearing potential. Women who could become pregnant must have taken precautions not to become pregnant for 1 month before the start of

the study. Because of the increased risk of venous thromboembolism in patients, combined oral contraceptive pills are not recommended.

13. Participants must be willing to comply with the Celgene pregnancy prevention programme for Thalidomide

Exclusion Criteria

Patients with the following characteristics are ineligible for this study:

1. Overt symptomatic multiple myeloma
2. Amyloidosis of unknown or non-AL type
3. Localised AL amyloidosis (in which amyloid deposits are limited to a typical single organ, for example the bladder or larynx, in association with a clonal proliferative disorder within that organ)
4. Trivial or incidental AL amyloid deposits in the absence of a significant amyloid-related organ syndrome (e.g., isolated carpal tunnel syndrome)
5. Refractory to or progressive disease with an IMid and proteasome inhibitor combination
6. Allogeneic stem cell transplantation
7. Solid organ transplantation
8. Severe peripheral or autonomic neuropathy causing significant functional impairment that, in the investigator's opinion, may interfere with protocol adherence
9. eGFR <20ml/min
10. Ejection fraction < 40% or NYHA class III or IV heart failure or uncontrolled hypertension that concerns the investigator
11. Severe pulmonary Hypertension that, in the investigator's opinion, may interfere with protocol adherence
12. Advanced Mayo stage III disease as defined by hs-Troponin T>0.07 and NT-proBNP >700 pMol/L OR NT-proBNP >1000 pMol/L OR supine SBP <100 mm of Hg

13. Myocardial infarction in the preceeding 6 months or unstable angina or conduction abnormalities uncontrolled by medication or devices
14. Concurrent active malignancies, except surgically removed basal cell carcinoma of the skin or other in situ carcinomas
15. Pregnant, lactating or unwilling to use adequate contraception
16. Systemic infection unless specific anti-infective therapy is employed
17. Known or suspected HIV infection
18. Contraindication to any of the required concomitant drugs or supportive treatments
19. Any other clinically significant medical disease or condition or psychiatric illness that, in the Investigator's opinion, may interfere with protocol adherence or a participant's ability to give informed consent
20. Previous experimental agents within 3 months before the date of registration
21. Known allergies to Carfilzomib, Thalidomide or Dexamethasone
22. Positive hepatitis B viruses (HBV) test

Table SAI: Dose limiting toxicities

Dose cohort	DLT	DLT description	Is DLT a serious adverse event?
Dose level 1: 45 mg/m^2	Any non-haematological toxicity >= Grade 3	Acute kidney injury on CKD Increased creatinine Reduced urine output	Yes No No
Dose level 1: 45 mg/m^2 After loading dose (20 mg/m^2)	Delay of > 8 days within cycle 1 or delay of 2nd cycle by more than 14 days	Patient admitted to ITU with temperature and hypotension. Discharge followed by slow recovery. Effects due to Carfilzomib as CRP <5. Bilateral Planal Effusions	Yes

Table SAII: List of adverse events experienced by at least one participant

Event	Grade 1- 2	Grade 3
Abdominal Pain	**0 (0%)**	**1 (10%)**
Acute kidney injury	**1 (10%)**	**1 (10%)**
Agitation	1 (10%)	0 (0%)
Alanine aminotransferase increased	1 (10%)	0 (0%)
Alkaline phosphatase increased	1 (10%)	0 (0%)
Alopecia	1 (10%)	0 (0%)
Anemia	3 (30%)	0 (0%)
Anorexia	1 (10%)	0 (0%)
Bladder Infection	1 (10%)	0 (0%)
Bloating	1 (10%)	0 (0%)
Blood Bilirubin Increased	1 (10%)	0 (0%)
Blurred Vision	1 (10%)	0 (0%)
Bronchospasm	1 (10%)	0 (0%)
Chest Infection	2 (20%)	0 (0%)
Cold Feeling Inside Left Ankle	1 (10%)	0 (0%)
Constipation	2 (20%)	0 (0%)
Creatinine increased	**1 (10%)**	**1 (10%)**
Diarrhea	**1 (10%)**	**2 (20%)**
Dizziness	3 (30%)	0 (0%)
Dyspnea	3 (30%)	0 (0%)
Edema face	1 (10%)	0 (0%)
Edema limbs	7 (70%)	0 (0%)
Edema trunk	1 (10%)	0 (0%)
Fatigue	2 (20%)	0 (0%)
Fever	1 (10%)	0 (0%)
Gait disturbance	1 (10%)	0 (0%)
Ggt Increased	**0 (0%)**	**1 (10%)**
Headache	2 (20%)	0 (0%)
Heart failure	2 (20%)	0 (0%)

Hypertension	**1 (10%)**	**1 (10%)**
Hypocalcemia	2 (20%)	0 (0%)
Hypophosphatemia	1 (10%)	0 (0%)
Hypotension	1 (10%)	0 (0%)
Insomnia	1 (10%)	0 (0%)
Lethargy	1 (10%)	0 (0%)
Lupus Flare	1 (10%)	0 (0%)
Mucositis oral	1 (10%)	0 (0%)
Nausea	3 (30%)	0 (0%)
Nervous system disorders - Other, specify	1 (10%)	0 (0%)
Pain in extremity	3 (30%)	0 (0%)
Peripheral sensory neuropathy	**1 (10%)**	**1 (10%)**
Pruritus	1 (10%)	0 (0%)
Rash maculo-papular	2 (20%)	0 (0%)
Renal and urinary disorders - Other, specify	**1 (10%)**	**1 (10%)**
Restlessness	1 (10%)	0 (0%)
Short Temper	1 (10%)	0 (0%)
Sinus tachycardia	1 (10%)	0 (0%)
Skin and subcutaneous tissue disorders - Other, specify	1 (10%)	0 (0%)
Social circumstances - Other, specify	1 (10%)	0 (0%)
Upper Respiratory Infection	2 (20%)	0 (0%)
Urinary Tract Infection	1 (10%)	0 (0%)
Urine output decreased	1 (10%)	0 (0%)
Vaginal infection	1 (10%)	0 (0%)
Vascular access complication	1 (10%)	0 (0%)