Carfilzomib, thalidomide, and dexamethasone are safe and effective in relapsed and/or refractory multiple myeloma: final report of the single-arm, multicenter, phase II ALLG MM018/AMN002 study

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Supplementary Table 1: Carfilzomib dose reduction for haematological and non-haematological toxicities.

Toxicity	Grade	Recommended Actions
HAEMATOLOGICAL Toxicities		
Anaemia		
Anaemia	Any grade	Continue at same dose. Institute supportive measures in accordance with institutional guidelines.
Neutropenia		
First episode ANC ≤0.75 $x10^9/L$	If ANC 0.5-0.75$x10^9/L$	Continue at same dose. GCSF may be used in accordance with institutional guidelines
	If ANC <0.5$x10^9/L$	Withhold dose until ANC returns to ≥0.5$x10^9/L$, then resume at same dose. GCSF may be used in accordance with institutional guidelines.
Subsequent episodes with ANC ≤0.75 $x10^9/L$	If ANC 0.5-0.75$x10^9/L$	Continue at same dose. GCSF may be used and the dose maintained for subsequent cycles at the investigator discretion.
	If ANC <0.5$x10^9/L$	Withhold dose until ANC returns to ≥0.5$x10^9/L$, then resume at 1 dose decrement. GCSF may be used and the dose maintained for subsequent cycles at the investigator discretion.
Neutropenic fever	If ANC <1.0$x10^9/L$ and single temperature >38.3°C OR ANC <1.0$x10^9/L$ and temperature >38°C for more than 1 hour	Withhold dose until ANC returns to baseline grade, then resume at same dose. GCSF may be used and the dose maintained for the next cycle at the investigator discretion.
Thrombocytopenia		
	If platelets 10-30$x10^9/L$ without evidence of bleeding	Continue at same dose

First episode platelets <30x10^9/L	If platelets <10x10^9/L OR evidence of bleeding	Withhold dose until platelets return to ≥10x10^9/L and bleeding is controlled, then resume at same dose
Subsequent episodes with platelets <30x10^9/L	If platelets 10-30x10^9/L without evidence of bleeding	Continue at same dose
	If platelets <10x10^9/L OR evidence of bleeding	Withhold dose until platelets return to ≥10x10^9/L and bleeding is controlled, then resume at 1 dose decrement
NON-HAEMATOLOGICAL toxicity		
For non-haematologic toxicities other than that specified in the table below, study drug should be withheld for ≥ Grade 3 events until resolved to ≤ Grade 2 or return to baseline. After resolution of the event to ≤ Grade 2 or return to baseline, if the adverse event was not treatment-related, subsequent treatment with carfilzomib may resume at the same dose prior to the adverse event. If the event was treatment-related, subsequent treatment with carfilzomib will resume at one level dose reduction. If toxicity continues or recurs, further dose reduction at one level lower is permitted according to the discretion of the investigator. If unacceptable toxicity continues or recurs at the lowest dose level of carfilzomib 15mg/m^2, the subject must be withdrawn from study. If a patient requires a withholding of therapy for more than 4 weeks due to unresolved toxicity, the patient must be withdrawn from the study. Exceptions to this should be discussed with the coordinating investigator. Once a dose reduction has occurred, the patient is to remain on the reduced dose for the remainder of the study.		
Allergic reactions	Grade 2-3	Withhold until ≤Grade 1, re-instate at same dose
	Grade 4	Discontinue carfilzomib
Tumor lysis syndrome	≥3 of the following: - ≥50% increase in creatinine, uric acid or phosphate - ≥30% increase in potassium - ≥ 20% decrease in calcium - ≥2-fold increase in LDH	Withhold carfilzomib until all abnormalities in serum chemistries have resolved. Re-instate at same dose.
Renal impairment	Creatinine clearance < 15ml/min	Withhold carfilzomib until CrCl returns to ≥15ml/min then resume at same dose. If dialysis is required, may resume at maximal dose.

Liver function test abnormalities	≥ Grade 3 elevation in ALT, AST or bilirubin	Withhold carfilzomib until LFTs resolve to baseline. Resume carfilzomib dose at one dose decrement
Infection	≥ Grade 3	Withhold carfilzomib until infection resolves. Resume carfilzomib at same dose if no neutropenia. If neutropenic, follow neutropenia instructions
Congestive cardiac failure	Any subject with symptoms of congestive heart failure, whether or not drug related, must have the dose withheld until resolution or return to baseline, after which treatment may continue at reduced dose. If no resolution after 2 weeks, the subject will be withdrawn from study.	
Any other drug-related non-haematological toxicity	Grade 1-2	Continue at same dose
	≥ Grade 3	For carfilzomib attribution, withhold dose until toxicity has resolved to grade 2 or less or to baseline grade, then resume at same dose. If toxicity returns, withhold dose as noted above, then resume at 1 dose decrement.