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

by Slavisa Ninkovic, Simon J. Harrison, Je-Jung Lee, Nicholas Murphy, Jae Hoon Lee, Jane Estell, Vivien M. Chen, Noemi Horvath, Kihyun Kim, Richard Eek, Bradley M. Augustson, Soo-Mee Bang, Shang-Yi Huang, Rajeev Rajagopal, Ferenc Szabo, Daniel Engeler, Belinda E. Butcher, Peter Mollee, Brian Durie, Wee Joo Chng, and Hang Quach

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Authors:

Slavisa Ninkovic[1,2] Simon J Harrison[3,4] Je-Jung Lee[5, 6] Nick Murphy[7] Jae Hoon Lee[8] Jane Estell[9] Vivien M Chen[9, 10] Noemi Horvath[11] Kihuyn Kim[12] Richard Eek[13] Bradley Augustson[14] Soo-Mee Bang[15] Shang-Yi Huang[16] Rajeev Rajagopal[17] Ferenc Szabo[18] Daniel Engeler[19] Belinda E Butcher[20, 21] Peter Mollee'[22, 23] Brian Durie[24] Wee Joo Chng[25]# Hang Quach[1,2]#

 # WJC and HQ contributed equally as co-joint senior authors

Affiliations:

[1]Department of Haematology, St. Vincent's Hospital Melbourne, Melbourne, Australia
[2]Faculty of Medicine, University of Melbourne, St. Vincent's Hospital Melbourne, Melbourne, Australia
[3]Department of Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia
[4]Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia
[5]Department of Haematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, South Korea
[6]Chonnam National University Medical School, Hwasun, South Korea
[7]Department of Haematology, The Royal Hobart Hospital, Hobart, Australia
[8]Department of Haematology, Gachon University Gil Medical Centre, South Korea
[9]Department of Haematology, Concord Repatriation General Hospital, Concord, Australia
[10]Faculty of Medicine and Health, University of Sydney, Sydney, Australia
[11]Department of Haematology, Royal Adelaide Hospital, Adelaide, Australia
[12]School of Medicine, Samsung Medical Centre, South Korea
[13]Border Medical Oncology Research Unit, Albury Wodonga Regional Cancer Centre, Albury, Australia
[14]Haematology Cancer Care, Sir Charles Gairdner Hospital, Perth, Australia
[15]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea
[16]Department of Medicine, National Taiwan University, Taipei, Taiwan
[17]Department of Haematology, Middlemore Hospital, Auckland, New Zealand
[18]Department of Haematology, Royal Darwin Hospital, Darwin, Australia
[19]Australian Leukaemia and Lymphoma Group, Melbourne, Australia
[20]Biostatistics and Medical Writing, WriteSource Medical Pty Ltd, Sydney, Australia
[21]School of Biomedical Sciences, University of New South Wales, Sydney, Australia
[22]Department of Haematology, Princess Alexandra Hospital, Brisbane, Australia
[23]School of Medicine, University of Queensland Brisbane, Australia
[24]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Outpatient Cancer Centre, Los Angeles, US
[25]Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore

Author Contributions:

WJC, HQ, PM, and BD developed the concept and design of the study. SN, SJH, JJL, NM, JHJ, JE, VMC, NH, KK, RE, BA, SMB, SYH, RR, WJC, and HQ managed patients and participated in the collection of clinical data. DE managed the data collection and assembly. BB performed the statistical analyses. SN and HQ interpreted the data and wrote the manuscript. All authors critically revised the manuscript and reviewed and approved the final version.

Running Head:

Carfilzomib, Thalidomide and Dexamethasone (KTd) in RRMM

Corresponding Author:

Name: Prof Hang Quach
Email: hang.quach@svha.org.au

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ABSTRACT:

This multicentre, phase II study of the Australian Lymphoma and Leukaemia Group (ALLG) and the Asian Myeloma Network (AMN) investigated fixed-duration (18-month) treatment with carfilzomib (K), thalidomide (T), and dexamethasone (d; KTd) in patients with relapsed and/or refractory multiple myeloma and 1-3 prior lines of therapy. Patients received induction with up to twelve 28-day cycles of K [20mg/m^2 IV cycle 1 day 1 and 2, 56mg/m^2 (36mg/m^2 for patients ≥75 years) from day 8 onwards), T 100mg PO nocte and weekly dexamethasone 40mg (20mg for patients ≥75 years). During maintenance T was omitted, while K continued on days 1,2,15,16 with fortnightly dexamethasone. The primary endpoint was progression free survival (PFS). Secondary endpoints were overall response rate, overall survival (OS), duration of response, safety, and tolerability. Ninety-three patients (median age 66.3 years (41.9 – 84.5)) were enrolled with a median follow-up of 26.4 (1.6 – 54.6) months. The median PFS was 22.3 months (95% CI 15.7 – 25.6) with a 46.3% (95% CI 35.1 – 52.8) 2-year PFS. Median OS was not reached and was 73.8% (95% CI 62.9 – 81.9) at 2 years. The overall response rate was 88% (≥ VGPR 73%). There was no difference in the depth of response, PFS or OS comparing Asian and Non-Asian cohorts (p=0.61). The safety profile for KTd was consistent with each individual drug. KTd is well tolerated and effective in patients with RRMM irrespective of Asian or non-Asian ethnicity and provides an alternative option particularly where use of KRd is limited by access, cost, or renal impairment.

MAIN TEXT

Introduction

Multiple myeloma (MM) is a neoplasm of clonal plasma cells, characterised by a vicious cycle of response and relapse with ultimate development of resistance to therapy in most patients. The steadfast introduction and approval of novel agents including first- and second-generation proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs) and monoclonal antibodies (mAbs), both in the newly diagnosed (ND) and relapsed/refractory (RR) setting, has translated to progressive improvements in survival, especially for the elderly and patients with favourable risk disease.[1-3] We are currently entering an even more promising era of cellular- and immune-based therapies with remarkable responses seen even in heavily pre-treated patients.[4, 5] In parallel, however, the associated healthcare costs are steadily increasing and while treatment-related drug costs account for less than a third of the total, the increased dependency on inpatient and outpatient services required for delivery of novel therapies is expected to further jeopardise their affordability and accessibility for all patients.[2, 6]

The management of relapsed or refractory multiple myeloma (RRMM) is complex, taking into consideration prior drug exposure, response, and toxicity profile, as well as disease- and patient-related factors. The challenge of managing RRMM is compounded by limited access to novel agents outside of clinical trials. In the late 2000s, the combination of lenalidomide and dexamethasone (Rd) was a well-established and utilised standard of care in early RRMM.[7] With contemporary practice however, most patients receive upfront lenalidomide as part of either a triplet or even quadruplet therapy with continuous or maintenance treatment until disease progression.[8] For patients who are non-refractory to lenalidomide, re-treatment at relapse with the Rd backbone in combination with novel agents including carfilzomib (K), ixazomib (Ixa), daratumumab (Dara), or elotuzumab (Elo) is effective, and was instrumental in the registrational approval of these agents.[9-13] Most patients at first relapse will have been exposed to but are not necessarily refractory to bortezomib. However, the ENDEAVOR study demonstrated that for these patients, switching to second-generation PI, carfilzomib, is superior to re-treatment with bortezomib across a variety of subgroups of patients.[14]

The phase III ASPIRE study compared fixed duration KRd followed by Rd against Rd until disease progression in a cohort of patients with 1 to 3 prior lines of therapy, including 20% lenalidomide-exposed patients. The triplet KRd significantly improved overall response rate (ORR; 87.1 vs. 66.7%; $p < 0.001$) and progression free survival (PFS; 26.3 vs. 17.6 months; HR 0.69; 95% confidence interval [CI] 0.57 - 0.83; p=0.0001) compared to Rd alone. At the

time of this study design, in certain jurisdictions including the Asia-Pacific region, thalidomide, a first-generation IMiD, was a more affordable alternative to lenalidomide. This single arm, multicentre, phase II study conducted jointly by the Australasian Leukaemia and Lymphoma Group (ALLG) and the Asian Myeloma Network (AMN) evaluated the safety and efficacy of fixed duration carfilzomib, thalidomide, and dexamethasone (KTd) in patients with relapsed and/or refractory multiple myeloma and 1 to 3 prior lines of therapy (ANZCTR: 12615000818538; NCT03140943).

Methods

Patients. Adults (≥18 years of age from ALLG or ≥21 years of age from AMN) with RRMM, evidence of measurable disease [serum M-protein ≥5g/L, or urine M-protein ≥200mg/24hr or in patients without detectable serum or urine M-protein, serum free light chains >100mg/L (involved light chain) and an abnormal kappa/lambda ratio or for IgA patients whose disease can only be reliably measured with serum quantitative IgA immunoglobulin ≥7.5g/L] and a history of 1 to 3 prior lines of therapy [where induction therapy followed by stem cell transplant and consolidation/maintenance therapy is considered as one line] were eligible. Patients with prior exposure to any IMiD [thalidomide, lenalidomide or pomalidomide] or bortezomib, but not carfilzomib, were eligible. All patients had an ECOG performance status 0 to 2; with adequate haematological [absolute neutrophil count ≥1.0x10^9/L independent of growth factor support for at least 1 week; platelet count ≥50x10^9/L or ≥30x10^9/L if >50% plasma cell burden on bone marrow biopsy] , renal [calculated or measured creatinine clearance of ≥15ml/min], and hepatic [serum bilirubin <1.5 times the upper limit of normal (ULN) and aspartate aminotransferase and alanine aminotransferase <3 times the ULN] function at time of screening. Patients with New York Heart Association class III or IV cardiac failure, or grade 3 or 4 peripheral neuropathy (or grade 2 with pain) were excluded. The study protocol was approved by the relevant Human Research Ethics Committee (HREC) for all participating institutions. All patients provided written informed consent.

Study Design. Patients were treated on a 28-day cycle for a pre-defined period of 18 months, consisting of 12 induction and 6 maintenance cycles, unless prior disease progression, unacceptable adverse events, or withdrawal of consent. The first 10 patients from each of the ALLG and AMN cohorts were treated on a lead-in safety phase. Intravenous carfilzomib was given at 20mg/m^2 on C1D1 and D2 followed by dose escalation to 27mg/m^2 on D8, D9, D15 and D16 (i.e., carfilzomib 20/27mg/m^2). Providing 4 or less patients in each cohort experienced grade 4 treatment emergent adverse events attributed by investigators to carfilzomib exposure during the first two cycles, all subsequent patients

<75 years were escalated to 56mg/m^2 from D8 onwards (i.e., carfilzomib 20/56mg/m^2), while those ≥75 years were escalated to 36mg/m^2 from D8 onwards (i.e., carfilzomib 20/36mg/m^2). Additionally, patients not achieving at least a partial response (PR) after the first two cycles during the lead-in safety phase and providing they did not experience ≥ grade 3 carfilzomib-related toxicity, were escalated to either carfilzomib 20/56mg/m^2 (<75 years) or 20/36 mg/m^2 (≥75 years). For comprehensive insights into both haematologic and non-haematologic toxicities necessitating dose adjustments, further details are provided in Supplementary Table 1. Dexamethasone 40mg PO was administered on D 1, 8, 15 and 22 (20mg for patients ≥75 years) together with oral thalidomide 100mg D1-D28. During the maintenance phase of treatment, carfilzomib was administered on D1, 2, 15 and 16, dexamethasone on D1 and 15, while thalidomide was omitted. Concomitant medication and supportive care, including venous thromboembolism prophylaxis, were prescribed at the discretion of investigators, following institutional practices, which included options such low dose aspirin (100mg daily), low molecular weight heparin, direct acting oral anticoagulant or Vitamin K antagonist. Local response assessments were performed in National Association of Testing Authorities (NATA)/Royal College of Pathologists Australasia (RCPA) accredited laboratories prior to day 1 of each treatment cycle, and interpreted, according to the International Myeloma Working Group Uniform Response Criteria, by local investigators with automated sponsor oversight and resolution of discrepancies in response assessment by the co-ordinating principal investigator.[15] Patients were followed up monthly for disease progression and survival until 1 year following the completion of the last patient's last cycle of treatment or induction therapy, whichever occurred earlier. The primary endpoint was to assess the progression free survival (PFS) in patients with RRMM and 1 to 3 prior lines of therapy, when treated with the fixed-duration KTd. The secondary endpoints were overall response rate (ORR), overall survival (OS), duration of response (DOR), time to progression (TTP) and safety and tolerability. Additionally, peripheral blood and bone marrow aspirate and trephine samples were collected at time of screening, after 6 months of KTD and at time of either disease progression or complete response, or both, with view to interrogate changes in the immune system and the bone marrow tumour microenvironment and correlate findings to treatment outcomes. These translational, exploratory endpoints will be reported on at a later date.

Statistical Analysis. The sample size for this study was estimated using a Simon's minmax two stage design, with a minimum of 37 patients per jurisdiction required to have an 80% power with a two-sided alpha of 0.05 to reject the null hypothesis of ≤ 50% PFS at 6.5 months (based on results from the OPTIMUM study), compared to the alternative hypothesis of ≥ 70% PFS at 6.5 months.[16] PFS and OS were defined as the time, in consecutive days

from the from start of treatment (C1D1) to disease progression or death from any cause, whichever came first (PFS) or death from any cause (OS). DOR was defined as the time in consecutive days from date of first response (PR or better) to the date of progression or death from any cause. TTP was defined as the time from C1D1 to the date of progression with deaths due to causes other than progression censored. Time to events analyses were censored by the closeout date or the date of last follow-up for patients lost to follow-up. The influence of prognostic factors (age, cytogenetic abnormalities, lines of prior therapy, previous thalidomide resistance, TTP ≤6 months vs > 6 months; baseline $ß_2$-microglobulin and IPSS at baseline) on PFS, TTP, OS and response were explored using Cox PH regression or multiple logistic regression, as appropriate. Given the sample size, these analyses are considered hypothesis generating. Although not specifically powered, comparisons between ethnically Asian and non-Asian populations were pre-specified post-hoc analyses in the statistical analysis plan which was developed and approved prior to database lock. All hypothesis testing was two sided, with values of $p<0.05$ considered statistically significant. Analyses were conducted using Stata MP for Mac v17 (Statacorp, Texas Station, US).

Results

Patients and Treatment. Between March 2017 and May 2020, 93 patients were screened with three patients ineligible and excluded from the final analysis set (Australia n=49; Asia n=41). Patient disposition is summarised in Figure 1. Baseline characteristics according to ethnic background (Asian (n=44) vs. Non-Asian (n=46)) are presented in Table 1.

Efficacy. The cut-off date for final analysis was 31 May 2022. The median duration of follow-up was 26.4 months (range: 1.6 to 54.6 months) in non-Asian and 26.2 months (0.7 to 52.7 months) in Asians. A total of 64 primary events were recorded with a median PFS of 22.3 months (95% confidence interval [CI] 15.7 to 25.6), a 6.5-month PFS of 80.4% (95% CI 70.4% to 87.3%) and a 2-year PFS of 46.3% (95% CI 35.1% to 56.8%). The median PFS for patients with 1 prior line of therapy (n=48) was 22.3 months (95% CI 12.9% to 26.0%); 20.5 months for patients with 2 prior lines (n=20; 95% CI 5.95% to 27.2%), and 20.0 months for patients with 3 prior lines (n=22; 95% CI 13.9% to 28.6%). A total of 29 deaths occurred with a median OS not reached and a 2-year OS of 73.8% (95% CI 62.9 to 81.9%). The ORR was 88% with 73% patients achieving a VGPR or better and 32% attaining a CR or better. There was no difference in the depth of response (p=0.69), nor PFS (p=0.18) or OS (p=0.61) observed comparing the Asian and Non-Asian cohort of patients (See Table 2). The median

time to first response was 0.92 months (range 0.92 to 0.95) while median time to best response was 3.65 months (range: 2.53 to 4.57). The median duration of response (DOR) for patients achieving a PR or better was 22.6 months (95% CI 18.2 to 25.4) and the median time to progression (TTP) was 23.4 months (95% CI 18.9 to 26.2) with a 2-year TTP of 49.7% (95% CI 37.9 to 60.4%).

Figure 3 shows hazard ratio and 95% CI for PFS in pre-specified subgroups according to baseline characteristics including age (18-64 vs. 65-74 vs. ≥75 years), cytogenetic risk by FISH (high (presence of t(4;14), t(14;16) or del(17p)) vs. standard risk), creatinine clearance (<30 vs. 30-60 vs. ≥ 60 ml/min), serum $ß_2$-microglobulin (≤ 3.5 vs. 3.5 to ≤ 5.5 vs. > 5.5mg/ml), R-ISS at screening (Stage I vs. Stage II vs. Stage III), prior lines of therapy (1 vs. >1), prior bortezomib exposure and prior thalidomide exposure.

Safety. A total of 90 patients received at least one dose of study treatment. The median duration of treatment was 14.2 months (0.2 – 20.6 months). Forty patients (44%) discontinued treatment during the induction phase [most commonly due to PD (n=16; 18%); unacceptable AE (n=7; 8%) and patient decision (n=7; 8%)] while 11 patients (12%) discontinued treatment during the maintenance phase (most commonly due to PD (n=6; 7%), unacceptable AE (n=4, 4%) or unresolved AE (n=1;1%)]. Thirty-nine patients (43%) completed the pre-defined 18 cycles of therapy. The relative dose intensity (RDI), defined as the proportion of the intended carfilzomib dose, decreased significantly with increasing dose levels [20/27mg/m2 dose (n=21) median RDI 98.8% vs. 20/36 mg/m2 dose (n=6) median RDI 93.3%, and 20/56 mg/m2 dose (n=60) median RDI 89.9%; $p < 0.001$] although there was no difference in the median RDI observed between the non-Asian and Asian cohort of patients [91.5% vs. 95.6%; p=0.17]. Almost all patients (99%) experienced at least one adverse event; 74% of patients experienced at least one event attributed to carfilzomib, 66% experienced at least one event related to dexamethasone while 76% of patients reported events related to thalidomide. Carfilzomib related adverse events triggered a dose delay for 42% of patients, dose delay and reduction for 13% and carfilzomib discontinuation in 17% of patients. Thalidomide was discontinued due to adverse events in 21% of patients.

The most common adverse events of any grade are summarised in Table 3 and include dyspnoea (38.9%), upper respiratory tract infection (36.7%), peripheral sensory neuropathy (31.1%), fatigue (26.7%) and peripheral oedema (23.3%). There was no difference observed in the rate of adverse events between Asian and Non-Asian patients. Adverse events of ≥ grade 3 were reported in 76% of patients and at least one serious adverse event was recorded in 61% of patients. The most common haematological adverse events include

neutropenia (11.1%), thrombocytopenia (11.1%), anaemia (8.9%), haemolysis (7.8%) and thrombotic thrombocytopenic purpura (TTP; 2.2%). Haematological adverse events of ≥ grade 3 include neutropenia (8.9%), thrombocytopenia (4.4%), anaemia (2.2%), and TTP (2.2%). Other adverse events of special interest include hypertension (22.2%), muscle weakness (20.0%), thromboembolic event (grouped term; 11.1%), cardiac failure (grouped term; 2.2%) and TTP (2.2%). A total of 29 patients (32%) died during treatment or within 30 days of receiving the last dose of study treatment; 23 deaths (79%) were due to multiple myeloma, 4 due to infective causes including one case of SARS-CoV-2 infection, 1 cardiac death and 1 road traffic incident.

Discussion

The combination of second-generation proteasome inhibitor, carfilzomib, with first-generation immunomodulatory drug, thalidomide, and dexamethasone, irrespective of prior PI or IMiD exposure, is well tolerated and efficacious in patients with relapsed myeloma and 1 to 3 prior lines of therapy. Despite a fixed duration of treatment of 18 months, the combination of KTd leads to a median PFS (mPFS) of 22.3 months. Granted the limitations of cross-trial comparisons, these results for KTd are comparable to that for KRd, with a reported median PFS of 26.3 months in the phase III ASPIRE study, and higher than what was reported with Kd doublet of 18.7 months in the ENDEAVOR study.[10, 14] For patients with only 1 prior line of therapy, the median PFS with KTd is not dissimilar to that reported in the ENDAVOR study; 22.3 months and 22.2 months, while patients with 2 or 3 prior lines treated KTd appear to derive a benefit with a median PFS of 20.5 months and 20.0 months, respectively whereas patients with ≥2 prior lines treated with Kd on the ENDAVOR study had a median PFS of 14.9 months.[17] Considering the notable prevalence of ≥VGPR (73%) and ≥CR (32%) with the KTd combination, there would have been compelling interest in conducting a more comprehensive evaluation of depth of response, although local infrastructure to perform routine minimal residual disease assessment by multiparametric flow cytometry was limited at the time of study setup, representing a limitation of the study.

Carfilzomib was given for 18 months in both our and the ASPIRE study, however, unlike the latter study in which the IMiD backbone (Rd) was continued until disease progression, due to the concern of peripheral neuropathy, thalidomide in our MM018/AMN0002 study was only continued for 12 months. Indeed, the motor neuropathy rate was minimal (6.6% any grade, 2.2% Grade ≥3), in contrast to the more notable sensory neuropathy (31.1% any grade;

11.1% Grade ≥3). Among the 32 patients reporting any-grade sensory or motor neuropathy, only six (18.8%) had pre-existing peripheral neuropathy (grade 1 or 2 without associated pain), likely stemming from prior anti-myeloma therapy, resulting in residual deficits.

Continuous therapy has been shown to improve PFS.[18] A landmark analysis of the ASPIRE study performed at the 18-month mark post randomisation when carfilzomib was discontinued, demonstrated a lower PFS hazard ratio for KRd versus Rd (HR 0.58 (0.46-0.74)) compared to that for the overall study cohort (HR 0.69 (0.57-0.83), begging the question whether PFS to KRd would have been improved further had carfilzomib been continued until PD in the KRd arm.[19] Similarly, in our study we note a sharp drop-off in the PFS curve within months of cessation of carfilzomib-dexamethasone maintenance after the protocol defined 18 months of treatment (Figure 2A). Combined, these observations suggest that carfilzomib ought to be used until disease progression, which has been shown to be safe and effective in the ENDEAVOR study.[14]

Consistent with previous reports on pre-specified subgroup analyses, albeit acknowledging limited patient numbers within these subgroups, the KTd combination appears equally successful irrespective of patient age, or cytogenetic risk group, while R-ISS, prior stem cell transplant or prior bortezomib or thalidomide exposure similarly did not impact outcomes.[20-22] Although 32% of patients had prior thalidomide exposure, with 15% in the Non-Asian and 50% in the Asian study cohorts, this disparity appears to align with regional front-line therapy practices at the time. It's important to note that data regarding refractoriness to prior treatments was not collected in this study, posing a minor limitation in interpreting these sub-group analyses. A less favourable outcome compared to the overall group was still seen in patients with elevated ß2-microglobulin with a trend towards increased efficacy of KTd in patients having second- or third-line therapy, similarly consistent with evidence that carfilzomib remains efficacious whether used early or late in relapse.[23] In our study, patients with poor renal function still did poorly compared to the overall cohort, and while the sample size is too small to make definitive remarks, impaired renal function is known to be an poor prognostic factor in myeloma.[24] Strong evidence already exists that carfilzomib is safe and efficacious irrespective of renal function, with no starting dose adjustments required even in patients with end stage renal failure.[25, 26] Given that thalidomide, as opposed to lenalidomide, is more practical in patients with renal impairment, KTd could be an effective combination when lenalidomide cannot be used.

Of interest, both the impressive overall response rate and the benefit to PFS were similarly observed in both the Asian and non-Asian cohort of patients. This is consistent with previous

reports of efficacy of carfilzomib in Asian patients and a subgroup analysis of the ENDEAVOR and A.R.R.O.W trials which specifically reported on outcomes in Asian patients.[27-29] This report, while cognisant of the smaller sample size, highlighted increased rates of grade 3 or higher adverse events, especially grade ≥3 cardiac failure, in the Asian population compared to the overall population of the ENDEAVOR and A.R.R.O.W trials. In our cohort of patients, while dyspnoea was the most commonly reported adverse event of any grade and the most common ≥3 grade event, documented cardiac failure was reported in a single, non-Asian patient. One explanation for the reduced rates of cardiac failure seen in our study may be the benefit of developed clinical experience with carfilzomib at the time of study initiation and routine measures to mitigate risks associated with carfilzomib therapy including: strict monitoring and management of systemic hypertension, fluid balance and symptom-driven carfilzomib dose delays and reductions. Indeed, carfilzomib dose reduction rates in the ENDEAVOR, A.R.R.O.W. and ASPIRE studies were comparable to our study, and while these did not routinely report on carfilzomib dose delay, 42% of our cohort of patients experienced an adverse event triggered carfilzomib dose delay. [10, 14, 30] Another adverse event of special interest, carfilzomib induced TTP, while rare has been reported in association with carfilzomib previously.[31] Both our patients were Asian and developed a non-immune thrombocytopenia with a nadir of $<30x10^9/L$, blood film features of microangiopathic haemolysis with red cell fragmentation, and ADAMTS-13 levels >10%, thus excluding a diagnosis of de novo TTP. Both were on the $56mg/m^2$ dose level, developed features early in treatment (first and third cycle) and responded to immunosuppression and plasma exchange.

In conclusion, KTd demonstrates favourable tolerability with commonly encountered toxicities that require proactive management in routine clinical practice. KTd is efficacious in patients with RRMM irrespective of Asian or non-Asian ethnicity, and irrespective of prior IMIDs or PI exposure in first line MM treatment. This combination may be an alternative to KRd where delivery of lenalidomide is limited by cost, access, or renal impairment. The use of carfilzomib until disease progression may be considered to further improve the PFS as this has been shown to be safe in the ENDEAVOR study.[14]

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TABLES and FIGURES

Table 1: Baseline patient and disease demographics.

Characteristic	Not Asian (n=46)	Asian (n=44)	Total (n=90)
Age			
Median – yrs	68.8	64.4	66.3
Range – yrs	41.9, 84.5	42.6, 77.1	41.9, 84.5
Age distribution – No. of patients (%)			
18-64 yrs	15 (33)	24 (55)	39 (43)
65-74	19 (41)	19 (43)	38 (42)
≥75 yrs	12 (26)	1 (2)	13 (14)
Sex			
Female	19 (41)	17 (39)	36 (40)
Male	27 (59)	27 (61)	54 (60)
Race			
Caucasian	46 (100)	0 (0)	46 (51)
East Asian	0 (0)	24 (55)	24 (27)
South-East Asian	0 (0)	20 (45)	20 (22)
Geographic Region			
ANZ	46 (100)	3 (7)	49 (54)
Asia	0 (0)	41(93)	41 (46)
ECOG performance status – No. of patients (%)			
0	32 (70)	21 (48)	53 (59)
1	9 (20)	12 (27)	21 (23)
2	5 (11)	4 (9)	9 (10)
Missing	0 (0)	7 (16)	7 (8)
CrCl distribution – No. of patients (%)			
< 30ml/min	3 (7)	1 (2)	4 (4)
30 - 60 ml/min	8 (17)	9 (20)	17 (19)
≥ 60ml/min	35 (76)	28 (64)	63 (70)
Unknown	0 (0)	6 (14)	6 (7)
Serum $ß_2$-microglobulin – No. of patients (%)			
≤ 3.5 mg/l	23 (50)	34 (77)	57 (63)
> 3.5 to ≤ 5.5 mg/l	12 (26)	2 (5)	14 (16)
> 5.5 mg/ml	10 (22)	4 (9)	14 (16)
Unknown	1 (2)	4 (9)	5 (6)
Serum Albumin – No. of patients (%)			
< 35 g/L	21 (46)	13 (30)	34 (38)
≥ 35 g/L	24 (52)	31 (70)	55 (61)
Unknown	1 (2)	0 (0)	1 (1)
Serum LDH – No. of patients (%)			
Normal (< ULN)	31 (67)	9 (20)	40 (44)
High (> ULN)	15 (33)	35 (80)	50 (56)
R-ISS			
R-ISS I	6 (13)	4 (9)	10 (11)

R-ISS II	2 (4)	7 (16)	9 (10)
R-ISS III	26 (57)	21 (48)	47 (52)
Unknown	12 (26)	12 (27)	24 (27)
Time since diagnosis (years)			
Median – No.	4.5	3.5	3.5
Range – No.	0.3 – 15.8	0.3 – 15.5	0.3 – 15.8
Prior lines (PL) of therapy			
Median – No.	1.5	1	1
Range – No.	1 - 3	1 – 3	1 – 3
PL Distribution – No. of patients (%)			
1 PL	23 (50)	25 (57)	48 (53)
2 PL	11 (24)	9 (20)	20 (22)
3 PL	12 (26)	10 (23)	22 (24)
Previous therapies – No. of patients (%)			
Bortezomib	28 (61)	24 (55)	52 (58)
Thalidomide	7 (15)	22 (50)	29 (32)
Lenalidomide	5 (11)	5 (11)	10 (11)
Pomalidomide	1 (2)	0 (0)	1 (1)
Prior AutoSCT	13 (28)	18 (41)	31 (34)
Prior peripheral neuropathy – No. of patients (%)			
Yes	11 (24)	7 (16)	18 (20)
Missing	4 (9)	3 (7)	7 (8)
Left Ventricular Ejection Fraction (%)			
Median	60.0 (n=45)	63.0 (n=29)	61.5 (n=74)
Range	44.0 – 80.0	55.0 – 74.0	44.0 – 80.0

Table 2. Response by ethnicity.

Characteristic	Not Asian (n=46)	Asian (n=44)	p-value
Response by ethnicity			
ORR (n; %)	41 (89)	38 (86)	0.69
≥ VGPR (n; %)	36 (78)	30 (68)	0.28
≥ CR (n; %)	18 (39)	11 (25)	0.15
PFS, months			
Median (95% CI)	20.0 (13.2 – 26.0)	22.5 (14.3 – 26.2)	0.18
2-year PFS	59.8 (45.5 – 74.5)	50.4 (35.6 – 67.4)	
Overall Survival, months			
Median (95% CI)	NR (27.7 – NR)	46.1 (33.6 – NR)	0.61
2-year OS	70.9 (55.2 – 82.0)	76.5 (59.6 – 87.1)	

ORR – overall response rate; VGPR – very good partial response rate; CR – complete response; PFS – progression free survival; OS – overall survival; NR – not reached.

Table 3. Adverse events.

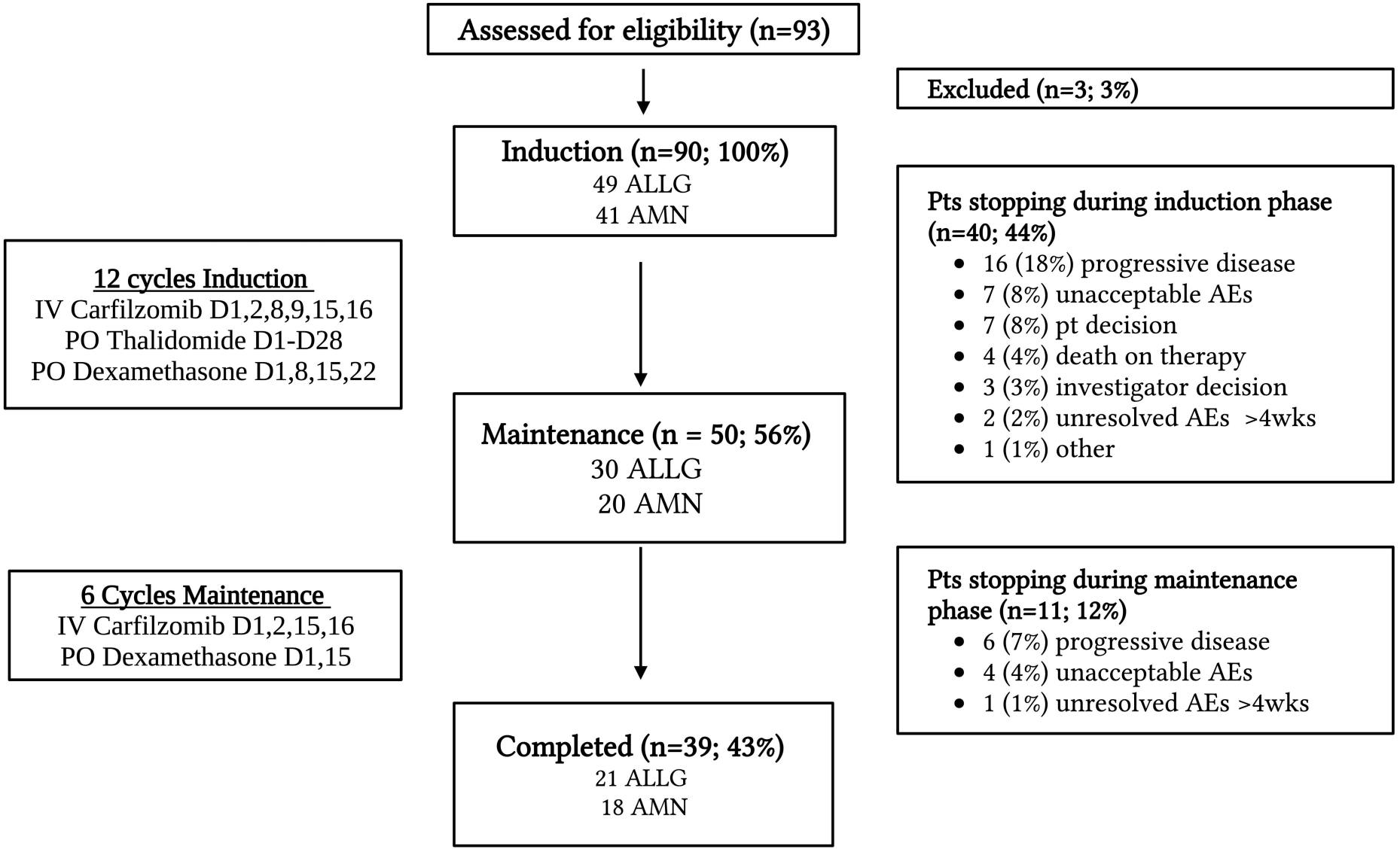
Event	All Grades n (%)	≥ Grade 3 n (%)
Most common non-haematologic adverse events		
Dyspnoea	35 (38.9)	13 (14.4)
Upper Respiratory infection	33 (36.7)	9 (10)
Peripheral sensory neuropathy	28 (31.1)	10 (11.1)
Fatigue	24 (26.7)	5 (5.6)
Peripheral oedema	21 (23.3)	2 (2.2)
Fever	20 (22.2)	6 (6.7)
Hypertension	20 (22.2)	7 (7.8)
Constipation	19 (21.1)	0 (0)
Lung infection	18 (20.0)	12 (13.3)
Muscle weakness	18 (20.0)	2 (2.2)
Insomnia	15 (16.7)	2 (2.2)
Cough	11 (12.2)	1 (1.1)
Diarrhoea	10 (11.1)	1 (1.1)
Other adverse events of special interest		
Thromboembolic event	10 (11.1)	4 (4.4)
Pulmonary hypertension	8 (8.9)	3 (3.3)
Peripheral motor neuropathy	6 (6.7)	2 (2.2)
Pulmonary oedema	2 (2.2)	1 (1.1)
Thrombotic thrombocytopenic purpura	2 (2.2)	2 (2.2)
Cardiac failure	1 (1.1)	1 (1.1)

Legend to Figures

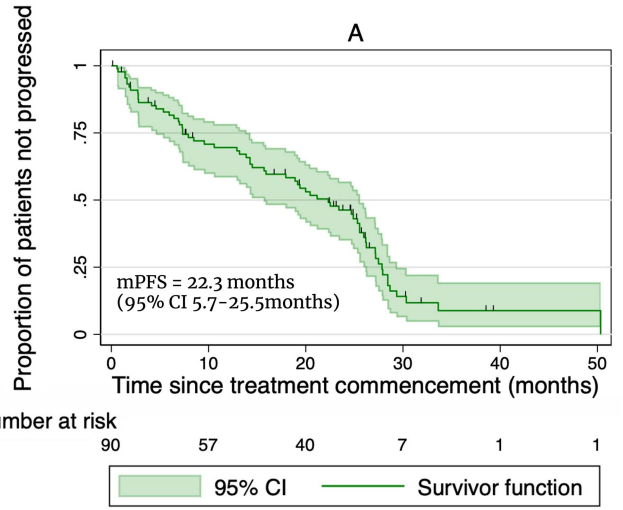
Figure 1: Patient disposition.

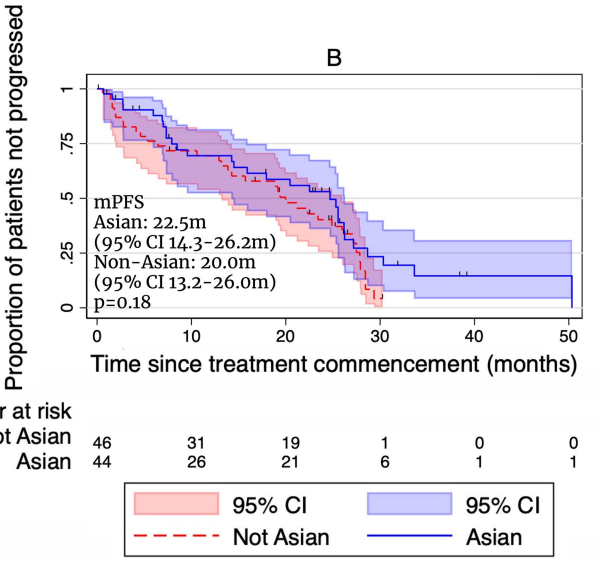
Figure 2. Progression Free Survival (PFS) and Overall Survival (OS). PFS is displayed for the entire cohort (A) and separated by ethnicity (B) [Non-Asian (broken line) vs. Asian (solid line)]. OS is displayed for the entire cohort (C) and separated by ethnicity (D) [Non-Asian (broken line) vs. Asian (solid line)]. *mPFS: median progression free survival, mOS: median overall survival; CI: confidence interval.*

Figure 3. Hazard Ratio and 95% CI for progression free survival in pre-specified subgroups according to baseline characteristics.

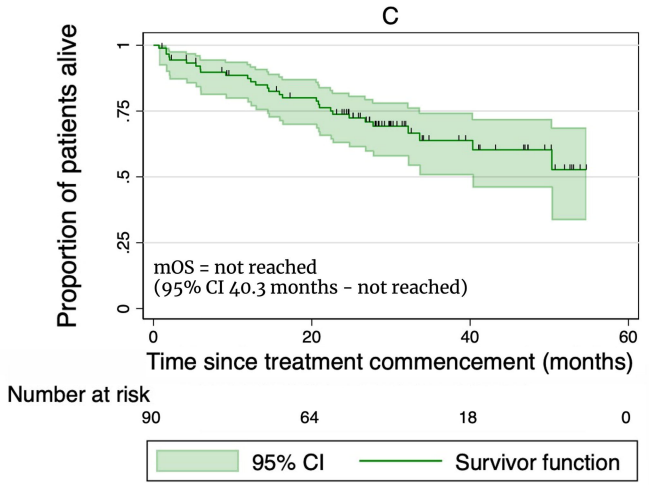

Assessed for eligibility (n=93)
Excluded (n=3; 3%)
Induction (n=90; 100%)
49 ALLG
41 AMN
Pts stopping during induction phase (n=40; 44%)
16 (18%) progressive disease
7 (8%) unacceptable AEs
7 (8%) pt decision
4 (4%) death on therapy
3 (3%) investigator decision
2 (2%) unresolved AEs >4wks
1 (1%) other
12 cycles Induction
IV Carfilzomib D1,2,8,9,15,16
PO Thalidomide D1-D28
PO Dexamethasone D1,8,15,22
Maintenance (n = 50; 56%)
30 ALLG
20 AMN
Pts stopping during maintenance phase (n=11; 12%)
6 (7%) progressive disease
4 (4%) unacceptable AEs
1 (1%) unresolved AEs >4wks
6 Cycles Maintenance
IV Carfilzomib D1,2,15,16
PO Dexamethasone D1,15
Completed (n=39; 43%)
21 ALLG
18 AMN

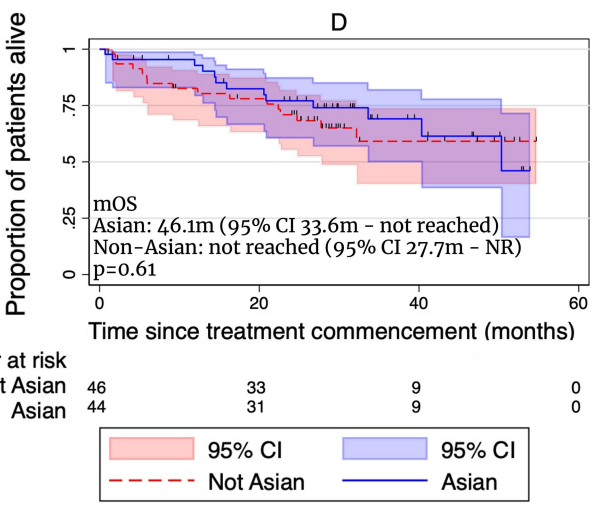
Progression Free Survival



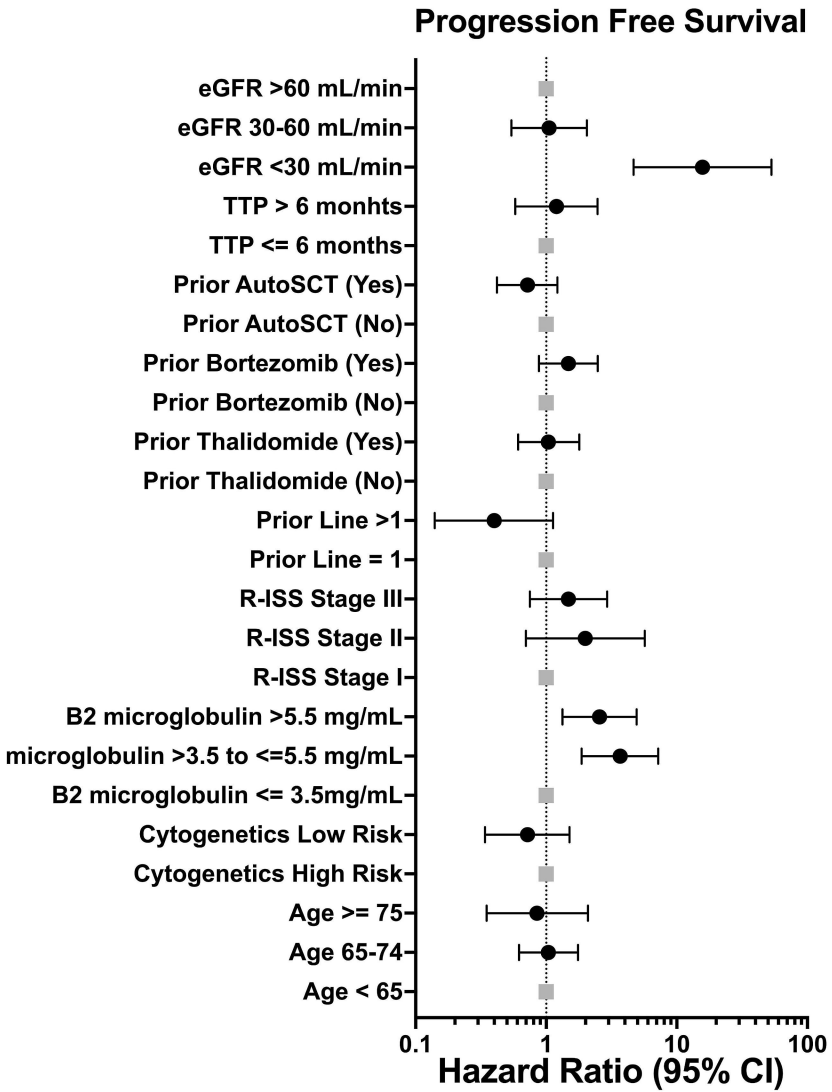


Overall Survival





Characteristic	HR	95% CI	p-value
Age			
18-64 yrs (n=39)	Ref		0.908
65-74 yrs (n=38)	1.04	0.62-1.75	
≥75 yrs (n=13)	0.85	0.35-2.09	
Cytogenetic risk by FISH			
High risk (n=10)	Ref		0.379
Standard risk (n=80)	0.72	0.34-1.51	
Creatine clearance			
< 30 ml/min (n=4)	15.8	4.67-53.1	<0.001
30-60 ml/min (n=11)	1.05	0.54-2.05	
≥ 60 ml/min (n=63)	Ref		
Serum ß₂-microglobulin			
≤ 3.5 mg/ml (n=57)	Ref		<0.001
3.5 to ≤ 5.5 mg/ml (n=14)	3.68	1.87-7.21	
> 5.5mg/m (n=14)	2.56	1.33-4.93	
R-ISS			
Stage I (n=10)	Ref		0.349
Stage II (n=9)	1.99	0.70-5.69	
Stage III (n=47)	1.48	0.75-2.93	
Prior lines of therapy			
1 PL (n=48)	Ref		0.073
> 1 PL (n=42)	0.40	0.14-1.13	
Prior thalidomide exposure			
Yes (n=29)	1.04	0.61-1.79	0,883
No (n=60)	Ref		
Prior bortezomib exposure			
Yes (n=52)	1.48	0.88-2.48	0.138
No (n=37)	Ref		
Prior AutoSCT			
Yes (n=31)	0.72	0.42-1.22	0.22
No (n=58)	Ref		
Time to progression			
≤ 6 months (n=12)	Ref		0.616
> 6 months (n=77)	1.2	0.58-2.47	



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.