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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Abstract

This multicenter, phase II study of the Australasian Lymphoma and Leukemia Group and the Asian Myeloma Network investigated fixed-duration (18-month) treatment with carfilzomib (K), thalidomide (T), and dexamethasone (d) (KTd) in patients with relapsed and/or refractory multiple myeloma who had received one to three prior lines of therapy. Patients received induction with up to 12 28-day cycles of carfilzomib (20 mg/m^2 intravenously in cycle 1 on days 1 and 2, then 56 mg/m^2 [36 mg/m^2 for patients ≥75 years] from day 8 onwards), thalidomide 100 mg orally in the evening and weekly dexamethasone 40 mg (20 mg for patients ≥75 years). During maintenance, thalidomide was omitted, while carfilzomib was continued on days 1, 2, 15, and 16 with fortnightly dexamethasone. The primary endpoint was progression-free survival. Secondary endpoints were overall response rate, overall survival, duration of response, safety, and tolerability. Ninety-three patients (median age 66.3 years [range, 41.9-84.5]) were enrolled and followed up for a median of 26.4 months (range, 1.6-54.6). The median pro-

gression-free survival was 22.3 months (95% confidence interval: 15.7-25.6) and the 2-year progression-free survival was 46.3% (95% confidence interval: 35.1-52.8). The median overall survival was not reached and the 2-year overall survival was 73.8% (95% confidence interval: 62.9-81.9). The overall response rate was 88% (73% had a very good partial response or better). There was no difference in the depth of response, progression-free survival or overall survival comparing Asian and non-Asian cohorts (*P*=0.61). The safety profile of KTd was consistent with that of each individual drug. KTd is well tolerated and effective in patients with relapsed and/or refractory multiple myeloma irrespective of Asian or non-Asian ethnicity and provides an alternative treatment option, particularly in circumstances in which the use of carfilzomib, lenalidomide, and dexamethasone (KRd) is limited by access, cost, or renal impairment.

Introduction

Multiple myeloma is a neoplasm of clonal plasma cells, characterized 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, immunomodulatory drugs and monoclonal antibodies, in both the newly diagnosed and relapsed/refractory settings, has translated into progressive improvements in survival, especially for the elderly and patients with favorable-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 jeopardize 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 utilized 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 not refractory to lenalidomide, re-treatment at relapse with the Rd backbone in combination with novel agents including carfilzomib, ixazomib, daratumumab, or elotuzumab is effective, and was instrumental in the registrational approval of these agents.[9-13] Most patients at first relapse will have been exposed to bortezomib, but are not necessarily refractory to the drug. However, the ENDEAVOR study demonstrated that for these patients, switching to a second-generation proteasome inhibitor, carfilzomib, is superior to re-treatment with bortezomib across a variety of subgroups of patients.[14]

The phase III ASPIRE study compared fixed-duration carfilzomib, lenalidomide, and dexamethasone (KRd) followed by Rd against Rd until disease progression in a cohort of patients who had received one to three prior lines of therapy, including 20% lenalidomide-exposed patients. The triplet KRd significantly improved overall response rate (87.1 *vs.* 66.7%; *P*<0.001) and progression-free survival (PFS; 26.3 *vs.* 17.6 months; hazard ratio [HR]=0.69; 95% confidence interval [95% 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 immunomodulatory drug, was a more affordable alternative to lenalidomide. This single-arm, multicenter, phase II study conducted jointly by the Australasian Leukemia 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 RRMM who had received one to three prior lines of therapy. The study was registered with the Australian New Zealand Clinical Trials Registry (identifier: ACTRN12615000818538) and ClinicalTrials.gov (identifier: NCT03140943)

Methods

Patients

Adults (≥18 years of age from the ALLG or ≥21 years of age from the AMN) with RRMM, evidence of measurable disease and a history of one to three prior lines of therapy were eligible. Measurable disease was considered as a serum M-protein ≥5 g/L, or urine M-protein ≥200 mg/24 h or, in patients without detectable serum or urine M-protein, serum free light chains >100 mg/L (involved light chain) and an abnormal κ/λ ratio or for IgA patients, whose disease can only be reliably measured with serum quantitative IgA immunoglobulin, a value ≥7.5 g/L. Induction therapy followed by stem cell transplant and consolidation/maintenance therapy was considered as one line of treatment. Patients with prior exposure to any immunomodulatory drug (thalidomide, lenalidomide or pomalidomide) or bortezomib, but not carfilzomib, were eligible. All patients had an Eastern Cooperative Oncology Group performance status 0 to 2, with adequate hematologic function (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 function (calculated or measured creatinine clearance of ≥15 mL/min), and hepatic function (serum bilirubin <1.5 times the upper limit of normal, aspartate aminotransferase and alanine aminotransferase <3 times the upper limit of normal) at the 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 at 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 six maintenance cycles, unless prior disease progression, unacceptable adverse events, or withdrawal of consent. The first ten patients from each of the ALLG and AMN cohorts were treated on a lead-in safety phase. Intravenous carfilzomib was given at a dose of 20 mg/m^2 in cycle 1 on days 1 and 2, followed by dose escalation to 27 mg/m^2 on days 8, 9, 15, and 16 (i.e., carfilzomib 20/27 mg/m^2). Providing that four or fewer 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 56 mg/m^2 from day 8 onwards (i.e., carfilzomib 20/56 mg/m^2), while those ≥75 years were escalated to 36 mg/m^2 from day 8 onwards (i.e., carfilzomib 20/36 mg/m^2). Additionally, patients not achieving at least a partial response 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 20/56 mg/m^2 (<75 years) or 20/36 mg/m^2 (≥75 years). For comprehensive insights into both hematologic and non-hematologic toxicities necessitating dose adjustments, further details are provided in *Online Supplementary Table S1*. Oral dexamethasone 40 mg was administered on days 1, 8, 15, and 22 (20 mg for patients ≥75 years) together with oral thalidomide 100 mg on day 1 to day 28. During the maintenance phase of treatment, carfilzomib was administered on days 1, 2, 15, and 16, dexamethasone on days 1 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 as low dose aspirin (100 mg daily), low molecular weight heparin, direct acting oral anticoagulants or vitamin K antagonists. 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 coordinating principal investigator.[15] Patients were followed up monthly for disease progression and survival until 1 year after the completion of the last patient's last cycle of treatment or induction therapy, whichever occurred earlier. The primary endpoint was to assess the PFS in patients with RRMM, who had received one to three prior lines of therapy, when treated with the fixed-duration KTd. The secondary endpoints were overall response rate, OS, duration of response, time to progression and safety and tolerability. Additionally, peripheral blood, bone marrow aspirate and trephine samples were collected at the time of screening, after 6 months of KTd and at the time of either disease progression or complete response, or both, with a view to interrogate changes in the immune system and the bone marrow tumor 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 minimax two-stage design, with a minimum of 37 patients per jurisdiction required in order to have an 80% power with a two-sided α 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 overall survival (OS) were defined as the time, in consecutive days from the start of treatment (day 1 of cycle 1) to disease progression or death from any cause, whichever came first (PFS) or death from any cause (OS). Duration of response was defined as the time in consecutive days from date of first response (partial response or better) to the date of progression or death from any cause. Time to progression was defined as the time from day 1 of cycle 1 to the date of progression with deaths due to causes other than progression censored. Time-to-event 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, progression within 6 months *vs*. >6 months, baseline β_2-microglobulin and International Prognostic Scoring System score at baseline) on PFS, time to progression, OS and response were explored using Cox proportional hazard 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, College Station, TX, USA).

Results

Patients and treatment

Between March 2017 and May 2020, 93 patients were screened of whom three patients were ineligible and excluded from the final analysis set (Australia n=49; Asia n=41). The patients' disposition in the study is summarized in Figure 1. The patients' 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 May 31, 2022. The median duration of follow-up was 26.4 months (range, 1.6-54.6 months) for non-Asians and 26.2 months (0.7-52.7 months) for Asians. A total of 64 primary events were recorded with a median PFS of 22.3 months (95% confidence interval [CI] 15.7-25.6) (Figure 2A), a 6.5-month PFS of 80.4% (95% CI: 70.4-87.3%) and a 2-year PFS of 46.3% (95% CI: 35.1-56.8%). The median PFS for patients who had received one prior line of therapy (n=48) was 22.3 months (95% CI: 12.9-26.0%), whereas it was 20.5 months for patients who had received two prior lines (n=20; 95% CI: 5.95-27.2%), and 20.0 months for patients who had received three prior lines (n=22; 95% CI: 13.9-28.6%).

A total of 29 deaths occurred with a median OS not reached and a 2-year OS of 73.8% (95% CI: 62.9-81.9%) (Figure 2C). The overall response rate was 88% with 73% patients achieving a very good partial response or better and 32% attaining a complete response or better. No differences were seen in the depth of response (P=0.69), PFS (P=0.18) or OS (P=0.61) when comparing the Asian and non-Asian cohorts of patients (Figure 2B, D; Table 1). The median time to first response was 0.92 months (range, 0.92-0.95) while the median time to best response was 3.65 months (range, 2.53-4.57). The median duration of response for patients achieving a partial response or better was 22.6 months (95% CI: 18.2-25.4) and the median time to progression was 23.4 months (95% CI: 18.9-26.2) with a 2-year time to progression of 49.7% (95% CI: 37.9-60.4%).

Figure 3 shows hazard ratios and 95% confidence intervals for PFS in pre-specified subgroups according to baseline characteristics including age (18-64 *vs*. 65-74 *vs*. ≥75 years), cytogenetic risk as determined by fluorescence *in situ* hybridization (high risk denoted by the 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 β_2-microglobulin (≤3.5 *vs*. 3.5-5.5 *vs*. >5.5 mg/mL), Revised International Scoring System stage 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%) discontin-

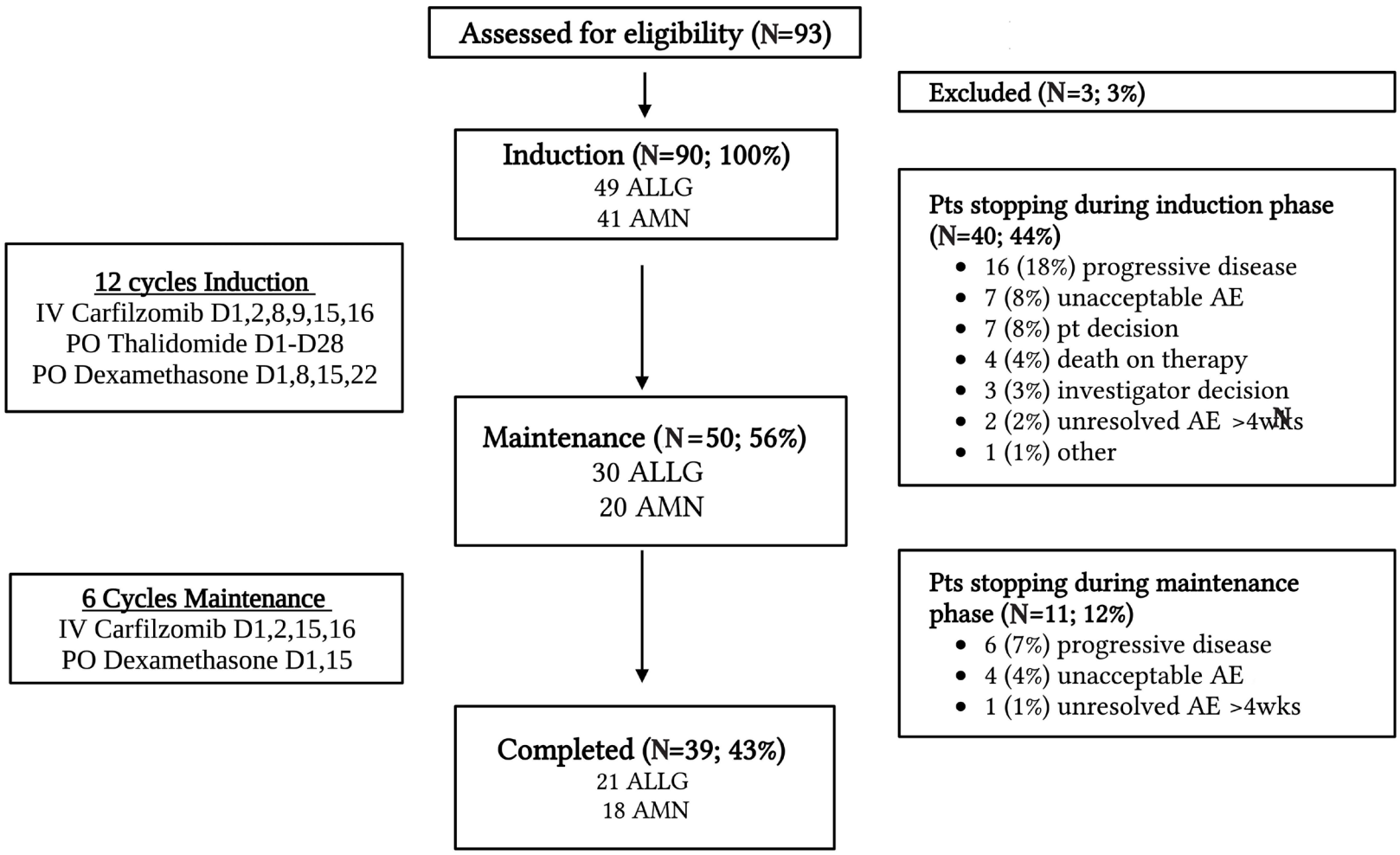

Figure 1. Patients' disposition in the study. ALLG: Australian Lymphoma and Leukemia Group; AMN: Asian Myeloma Network; IV: intravenous; PO: *per os*; D: day; pt: patient; AE: adverse effect; wks: weeks.

ued treatment during the induction phase (most commonly due to progressive disease [n=16; 18%]; unacceptable adverse events [n=7; 8%] and patients' decision [n=7; 8%]) while 11 patients (12%) discontinued treatment during the maintenance phase (most commonly due to progressive disease [n=6; 7%], unacceptable adverse events [n=4, 4%] or unresolved adverse events [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 (the median RDI was 98.8% for the 20/27 mg/m^2 dose [n=21] *vs*. 93.3% for the 20/36 mg/m^2 dose [n=6] and 89.9% for the 20/56 mg/m^2 dose [n=60]; *P*<0.001) although there was no difference in the median RDI observed between the non-Asian and Asian cohorts 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 summarized in Table 3 and include dyspnea (38.9%), upper respiratory tract infection (36.7%), peripheral sensory neu-

Table 1. Patients' demographics and disease characteristics at baseline.

Characteristic	Not Asian N=46	Asian N=44	Total N=90
Age in years			
Median	68.8	64.4	66.3
Range	41.9-84.5	42.6-77.1	41.9-84.5
Age distribution, N of patients (%)			
18-64 years old	15 (33)	24 (55)	39 (43)
65-74 years old	19 (41)	19 (43)	38 (42)
≥75 years old	12 (26)	1 (2)	13 (14)
Sex, N of patients (%)			
Female	19 (41)	17 (39)	36 (40)
Male	27 (59)	27 (61)	54 (60)
Race, N of patients (%)			
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, N of patients (%)			
ANZ	46 (100)	3 (7)	49 (54)
Asia	0 (0)	41(93)	41 (46)
ECOG PS, N 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, N of patients (%)			
<30 mL/min	3 (7)	1 (2)	4 (4)
30-60 mL/min	8 (17)	9 (20)	17 (19)
≥60 mL/min	35 (76)	28 (64)	63 (70)
Unknown	0 (0)	6 (14)	6 (7)
Serum ß$_2$-microglobulin, N 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/L	10 (22)	4 (9)	14 (16)
Unknown	1 (2)	4 (9)	5 (6)
Serum albumin, N 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)

Characteristic	Not Asian N=46	Asian N=44	Total N=90
Serum LDH, N of patients (%)			
Normal, <ULN	31 (67)	9 (20)	40 (44)
High, >ULN	15 (33)	35 (80)	50 (56)
R-ISS stage, N of patients (%)			
I	6 (13)	4 (9)	10 (11)
II	2 (4)	7 (16)	9 (10)
III	26 (57)	21 (48)	47 (52)
Unknown	12 (26)	12 (27)	24 (27)
Time since diagnosis in years			
Median	4.5	3.5	3.5
Range	0.3-15.8	0.3-15.5	0.3-15.8
Prior lines of therapy			
Median	1.5	1	1
Range	1-3	1-3	1-3
Distribution of prior therapy, N of patients (%)			
1 prior line	23 (50)	25 (57)	48 (53)
2 prior lines	11 (24)	9 (20)	20 (22)
3 prior lines	12 (26)	10 (23)	22 (24)
Previous therapies, N 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)
AutoSCT	13 (28)	18 (41)	31 (34)
Prior peripheral neuropathy, N of patients (%)			
Yes	11 (24)	7 (16)	18 (20)
Missing	4 (9)	3 (7)	7 (8)
Left ventricular ejection fraction (%)	N=45	N=29	N=74
Median	60.0	63.0	61.5
Range	44.0-80.0	55.0-74.0	44.0-80.0

ANZ: Australia and New Zealand; ECOG PS: Eastern Cooperative Oncology Group performance status; CrCl: creatinine clearance; LDH: lactate dehydrogenase; ULN: upper limit of normal; R-ISS: Revised International Staging System; AutoSCT: autologous stem cell transplant.

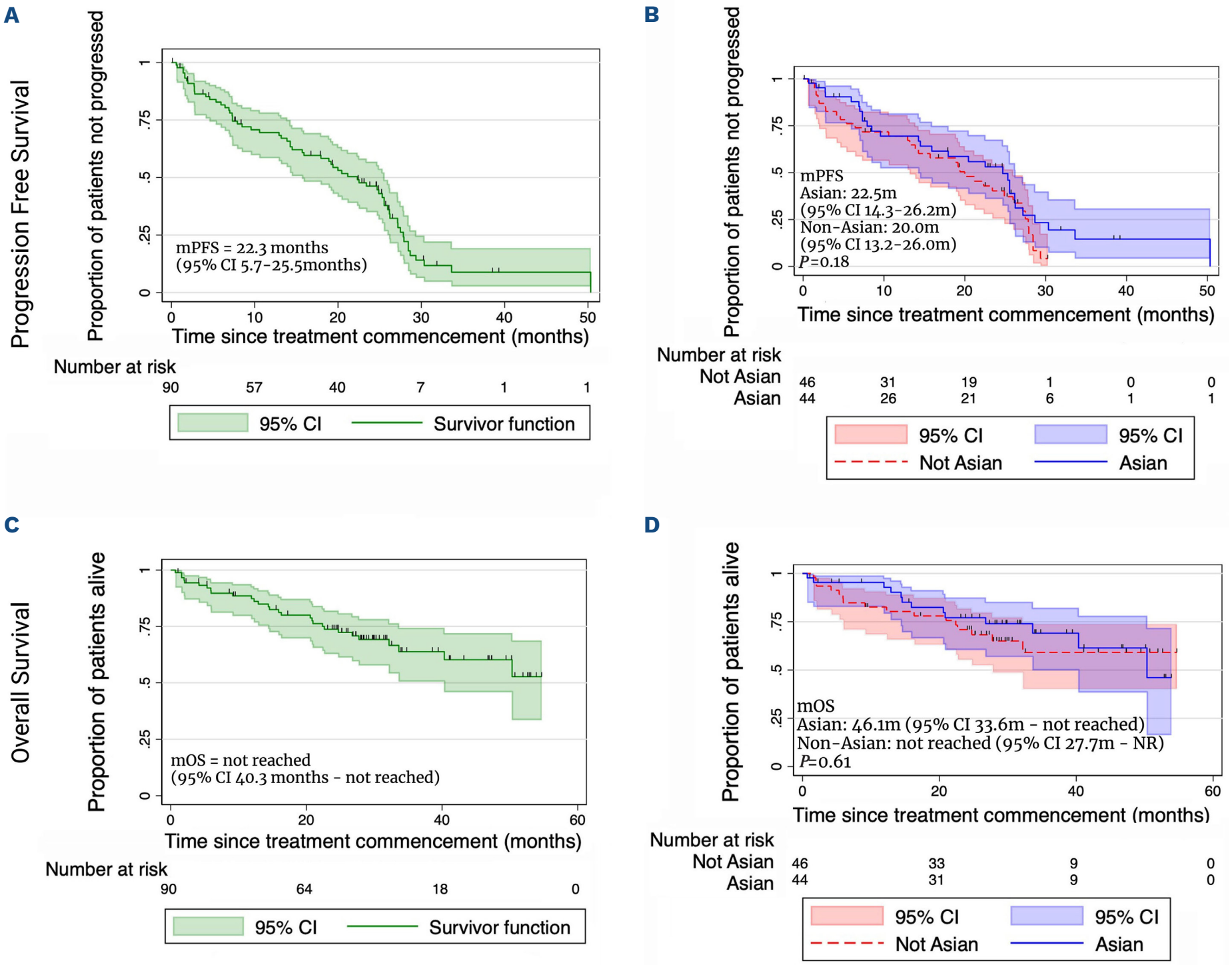

Figure 2. Progression-free survival and overall survival. (A, B) Progression-free survival is displayed for the entire cohort (A) and separated by ethnicity (B). (C, D) Overall survival is displayed for the entire cohort (C) and separated by ethnicity (D). mPFS: median progression-free survival; mOS: median overall survival; 95% CI: 95% confidence interval; NR: not reached.

Table 2. Response by ethnicity.

Characteristic	Not Asian N=46	Asian N=44	*P*
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
Progression-free survival			
Median (95% CI) in months	20.0 (13.2-26.0)	22.5 (14.3-26.2)	0.18
2-year PFS, % (95% CI)	59.8 (45.5-74.5)	50.4 (35.6-67.4)	
Overall survival			
Median (95% CI) in months	NR (27.7-NR)	46.1 (33.6-NR)	0.61
2-year OS, % (95% CI)	70.9 (55.2-82.0)	76.5 (59.6-87.1)	

ORR: overall response rate; VGPR: very good partial response; CR: complete response; PFS: progression-free survival; 95% CI: 95% confidence interval; OS: overall survival; NR: not reached.

ropathy (31.1%), fatigue (26.7%) and peripheral edema (23.3%). No difference was 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 hematologic adverse events were neutropenia (11.1%), thrombocytopenia (11.1%), anemia (8.9%), hemolysis (7.8%) and thrombotic thrombocytopenic purpura (2.2%). Hematologic adverse events of ≥ grade 3 included neutropenia (8.9%), thrombocytopenia (4.4%), anemia (2.2%), and thrombotic thrombocytopenic purpura (2.2%). Other adverse events of special interest were hypertension (22.2%), muscle weakness (20.0%), thromboembolic event (grouped term; 11.1%), cardiac failure (grouped term; 2.2%) and thrombotic thrombocytopenic purpura (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, four were due to infective causes (including one case of severe acute respiratory syndrome coronavirus 2 infection), one was a cardiac death and one was the result of a road traffic incident.

Discussion

The combination of a second-generation proteasome inhibitor, carfilzomib, with a first-generation immunomodulatory drug, thalidomide, and dexamethasone, irrespective of prior exposure to proteasome inhibitors or immunomodulatory drugs, is well tolerated and efficacious in patients with relapsed myeloma who have received one to three prior lines of therapy. Despite a fixed duration of treatment of 18 months, the combination of KTd led to a median PFS of 22.3 months. Granted the limitations of cross-trial comparisons, these results for KTd are comparable to those for KRd, with a reported median PFS of 26.3 months in the phase III ASPIRE study, and better than the 18.7 months that was reported for the Kd doublet in the ENDEAVOR study.[10,14] For patients who had received only one prior line of therapy, the median PFS with KTd was not dissimilar to that reported in the ENDEAVOR study; 22.3 months and 22.2 months, while patients who had received two or three prior lines who were treated with KTd appear to have derived a benefit with a median PFS of 20.5 months and 20.0 months, respectively, whereas patients who had received two or more prior lines treated with Kd on the ENDEAVOR study had a median PFS of 14.9 months.[17] Considering the notable prevalence of very good partial responses or better (73%) and complete responses or better (32%) with the KTd combination, there would have been compelling interest in conducting a more comprehensive evaluation of depth of response; however, 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 study and the ASPIRE study; however, unlike the latter study in which the backbone of immunomodulatory drugs (Rd) was continued until disease progression, due to concern about 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 having resulted 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 after randomization, when carfilzomib was discontinued, demonstrated a lower PFS hazard ratio for KRd *versus* Rd (HR=0.58 [95% CI: 0.46-0.74]) compared to that for the overall study cohort (HR=0.69 [95% CI: 0.57-0.83]), begging the question of whether PFS would have been improved further had carfilzomib been continued until progressive disease in the KRd arm.[19] Similarly, in our study we noted a sharp drop-off in the PFS curve within months of cessation of carfilzomib-dexamethasone maintenance after the protocol-defined 18 months of treatment

Table 3. Adverse events.

Event	All grades N (%)	≥ Grade 3 N (%)
Most common non-hematologic adverse events		
Dyspnea	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 edema	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)
Diarrhea	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 edema	2 (2.2)	1 (1.1)
Thrombotic thrombocytopenic purpura	2 (2.2)	2 (2.2)
Cardiac failure	1 (1.1)	1 (1.1)

(Figure 2A). Combined, these observations suggest that carfilzomib ought to be used until disease progression, a strategy which was shown to be safe and effective in the ENDEAVOR study.[14]

Consistent with previous reports on pre-specified sub-group analyses, albeit acknowledging limited numbers of patients within these subgroups, the KTd combination appears equally successful irrespective of age or cytogenetic risk group of the patients. Similarly, Revised International Staging System score, prior stem cell transplant or prior exposure to bortezomib or thalidomide did not have an impact on outcomes.[20-22] Although 32% of patients had previously been treated with thalidomide, with exposure rates of 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 is important to note that data regarding refractoriness to prior treatments were not collected in this study, posing a minor limitation in interpreting the results of these sub-group analyses. A less favorable outcome compared to that of the overall group was still seen in patients with elevated β_2-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 a 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 cohorts 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 cognizant of the smaller sample size, highlighted increased rates of ≥ grade 3 adverse events, especially grade ≥3 cardiac failure, in the Asian pop-

Characteristic	HR	95% CI	*P*
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	

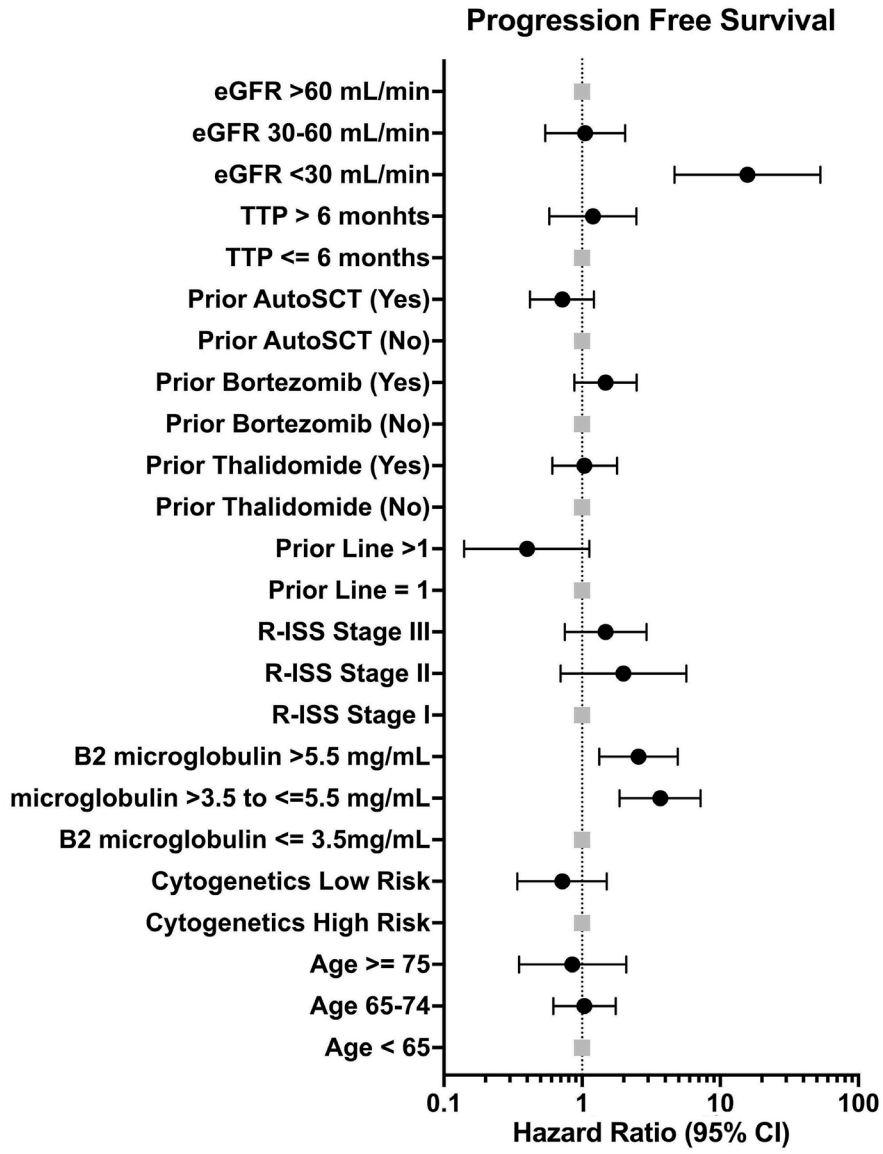

Figure 3. Hazard ratios and 95% confidence intervals for progression-free survival in pre-specified subgroups according to baseline characteristics. HR: hazard ratio; 95% CI: 95% confidence interval; yrs: years; FISH: fluorescence *in situ* hybridization; R-ISS: Revised International Staging System; PL: prior line; autoSCT: autologous stem cell transplant; eGFR: estimated glomerular filtration rate; TTP: thrombotic thrombocytopenic purpura.

ulation compared to the overall population of the ENDEAVOR and A.R.R.O.W. trials. In our cohort of patients, while dyspnea 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 those in 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 thrombotic thrombocytopenic purpura, while rare has been reported in association with carfilzomib previously.[31] Both of our patients who developed this adverse event were Asian and developed a non-immune thrombocytopenia with a nadir platelet count of $<30x10^9$/L, blood film features of microangiopathic hemolysis with red cell fragmentation, and ADAMTS-13 levels >10%, thus excluding a diagnosis of *de novo* thrombotic thrombocytopenic purpura. Both were on the 56 mg/m^2 dose, developed features early in treatment (first and third cycle) and responded to immunosuppression and plasma exchange.

In conclusion, KTd demonstrates favorable 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 exposure to immunomodulatory drugs or proteasome inhibitors in first-line treatment of multiple myeloma. This combination may be an alternative to KRd in circumstances in which 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]

Disclosures

SJH reports consulting or advisory roles for Celgene, Hoffman-La Roche AG, Genetech USA, HaemaLogiX, Janssen Global Services, and Novartis and research support from HaemaLogiX and Janssen Global Services. HQ reports consulting or advisory roles for Amgen, Antengene, Bristol-Myers Squibb/Celgene, Celgene, GSK, Janssen-Cilag, Karyopharm Therapeutics, Pfizer, Roche, and Sanofi and research support from Amgen, Bristol-Myers Squibb/Celgene, Celgene, GSK, Karyopharm Therapeutics and Sanofi. All other authors have no conflicts of interest to disclose.

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.

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Data-sharing statement

Original data and protocols may be obtained upon written request.

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