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ORIGINAL PAPER

A sequential cohort study evaluating single-agent KappaMab and KappaMab combined with lenalidomide and low-dose dexamethasone in relapsed and/or refractory kappa light chain-restricted multiple myeloma (AMaRC 01-16)

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Summary

KappaMab (KM; formerly MDX-1097) is a monoclonal antibody specific for the kappa myeloma antigen (KMA), a cell-surface antigen expressed on malignant plasma cells in kappa-restricted multiple myeloma (κMM), some lymphomas, occasional tonsillar B cells and in vitro activated B cells, but not on normal B cells in bone marrow. Phase I/IIa studies of single-agent KM confirmed a favourable toxicity profile and evidence of anti-myeloma activity. Ex-vivo studies demonstrating upregulation of KMA by lenalidomide, and enhanced effector-cell cytotoxicity provided the rationale for this phase IIb study where KM or KM in combination with lenalidomide and dexamethasone (KM-Rd) was administered in relapsed, refractory κMM patients. In addition, outcomes for a real-world matched case–control cohort from the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR) who received Rd were compared to the KM-Rd cohort. KM-Rd demonstrated an overall response rate of 82.5% which compared favourably to the Rd-MRDR cohort of 45.1%. Both single-agent KM and KM-Rd regimens were well tolerated, with the KM-Rd safety profile similar to patients given only Rd in other clinical settings. Based on the excellent

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safety profile and significant efficacy, further clinical trials escalating the KM dose and pairing KM with other standard-of-care treatments are planned.

KEYWORDS
kappa myeloma antigen, KappaMab, lenalidomide, monoclonal antibodies, multiple myeloma

INTRODUCTION

Despite advances in therapy, multiple myeloma (MM) remains an incurable disease for most patients. However, over the last decade immune-based strategies have resulted in a significant paradigm shift in treating MM, with the monoclonal antibodies daratumumab (DARA) and isatuximab (anti-CD38), and elotuzumab (ELO) (anti-SLAMF7/CD319/CS1) all shown to be effective when used in combination with proteasome inhibitors (PI) and/or immunomodulatory agents (IMiDs).[1–4]

Kappa myeloma antigen (KMA) is a membrane-bound form of free kappa light chain on malignant B cells, in vitro activated B cells and rare tonsillar B cells.[5–7] KappaMab (KM, formerly MDX-1097) is specific for KMA and binds to a unique conformational epitope in the kappa constant region that is presented when kappa free light chain (kFLC) associates with sphingomyelin in the cell membrane.[7,8] KM does not bind to kappa immunoglobulin (Igκ) and it has a fivefold higher affinity for membrane-bound KMA (IC_{50} 4 nM) when compared to serum kFLC (IC_{50} 20 nM).[7] Moreover, in vitro studies demonstrated that KM induces selective antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) of kappa-positive MM cells and that lenalidomide (LEN) exposure upregulates KMA expression on MM cells promoting enhanced KM-induced NK-mediated ADCC.[7]

In a phase I study, 12 patients ($n = 3$/dose level) with persisting but stable disease (SD) who remained on existing therapy received a single infusion of KM at dose levels between 0.3 and 10 mg/kg.[9] Patients with SD were selected as safety of KM was the primary end-point; there was no expectation of efficacy following a single dose. No dose-limiting toxicities were observed and two grade 1 drug-related adverse events (AEs) were reported (infusion-related reactions [IRRs]). A marked reduction in FDG-PET avidity and bone pain was observed in one patient. The mean apparent elimination half-life of KM was 315 h across the dose range. The biologically relevant dose, that is, the single dose level that could safely be administered with measurable levels of KM for 7 days in serum was determined, and a weekly dose of 10.0 mg/kg was selected for the phase IIa study.

A phase IIa open-label multiple dose study of KM monotherapy was conducted on a similar patient population (i.e. relapsed and/or refractory [RR]MM patients who had persisting but stable measurable disease for 3 months prior to study entry).[10] Nineteen patients received 8 weekly 10 mg/kg KM infusions and continued on existing therapy (including two patients receiving LEN). Again, only minor AEs were reported (predominantly grade 1 or 2 IRRs and fatigue). The study was terminated early to expedite this combination trial based on preclinical data gathered in parallel that demonstrated significant synergy of KM combined with lenalidomide to enhance the killing effect of KM.[7]

This phase IIb study was in κRRMM patients with less heavily treated MM, with KM as a single agent and then in combination with LEN and dexamethasone (DEX) in sequential, separate cohorts.

METHODS

Study design and patients

This was a phase IIb, multicentre, open-label sequential cohort study evaluating KM alone (KM, stage 1) followed by KM in combination with lenalidomide (LEN) and dexamethasone (DEX) (KM-Rd, stage 2) in κRRMM. Key inclusion criteria were progressive kappa-restricted MM (as per IMWG criteria[11]), one to three prior lines of therapy and no prior LEN exposure. Patients previously treated with allogeneic stem cell transplant were excluded.

Study stages, dosing and stopping criteria

Recruitment was planned for 60 patients, with an initial intention to treat 30 patients per stage. In stage 1, patients received KM (10 mg/kg IV infusion) weekly for 8 weeks then every 4 weeks as maintenance. In stage 2, KM dosing was as per stage 1 with the addition of LEN, 25 mg days 1–21 of each 28-day cycle and DEX 40 mg weekly, apart from cycle 1 which was 35 days duration as patients commenced LEN and DEX 1 week prior to starting KM (Figure 1). All patients received anti-viral, thromboembolic prophylaxis and osteolytic prophylaxis as per institutional practice. Treatment continued until unacceptable toxicity, progression, death or consent withdrawal consent. In addition, for stage 1, the Trial Management Committee (TMC) periodically assessed response rates and AEs. Based on a Bayesian 'proof of concept' (PoC) approach, if two criteria were not fulfilled: (1) Observed clinical benefit rate (CBR) ≥ clinically determined threshold (of 25%) and (2) Posterior probability that the true CBR is > a futility threshold (of 20%), given the observed data, is > a specified level of proof (of 90%) (see Data S1), then the TMC could recommend stopping stage 1 and starting Stage 2. No patients were permitted to move from stage 1 to stage 2. In stage 2, the following

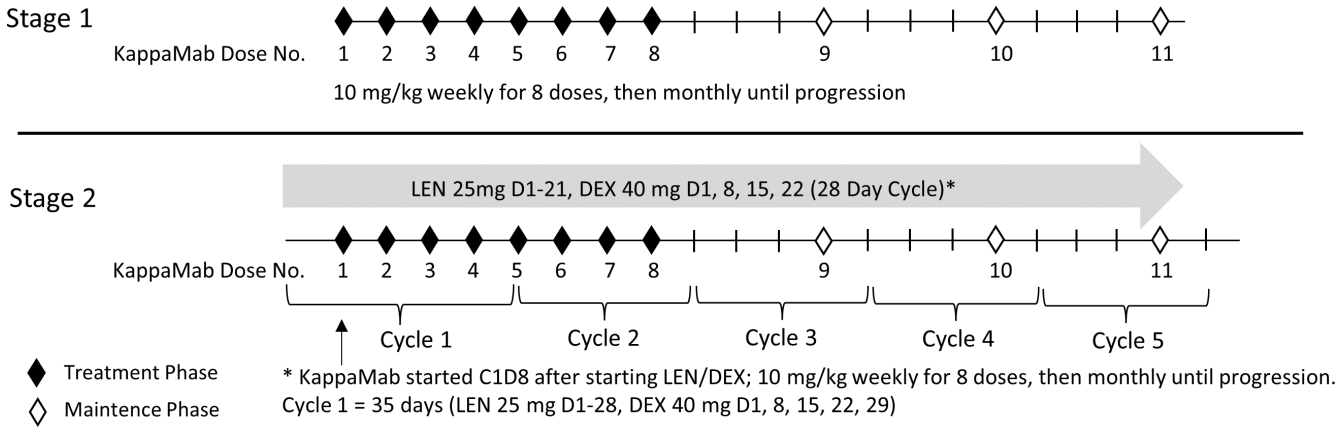

FIGURE 1 Study schema. Stage 1 involved 8 weekly doses of 10 mg/kg KappaMab, followed by monthly dosing until progression. Stage 2 was 8 weekly doses of 10 mg/kg KappaMab, plus 25 mg lenalidomide and 40 mg dexamethasone, followed by monthly dosing of KappaMab plus LEN and DEX until progression. In stage 2, Cycle 1 was 35 days, with a one-week administration of LEN and DEX prior to the first dose of KappaMab. The remaining cycles were 28 days, with KappaMab administration on Day 1 of each Cycle.

criteria were applied: (1) Observed CBR ≥ clinically determined threshold of 55% and (2) posterior probability that the true CBR is > a futility threshold of 35%, given the observed data, is > a specified level of proof of 95%.

Combination KM-Rd cohort compared to matched controls (Rd-MRDR)

The overall response rate (ORR), overall survival (OS) and progression free survival (PFS) of the KM-Rd cohort were compared to a contemporaneous control group of kMM patients who had received Rd for RRMM (Rd-MRDR group), identified via the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR) (https://www.mrdr.net.au/), who were matched for age, gender and prior lines of therapy (Table 1). All controls were eligible to receive KM; there were no contraindications in the control group. They had a similar mix of types of prior therapies, number of prior lines and cytogenetic risk. The KM-Rd group had a higher percentage of patients with baseline ISS stage 2 diagnoses (55%) versus the MRDR cohort (45%) and the KM cohort (22%). Both the KM-Rd and MRDR cohorts had 26% with ISS stage 3 at baseline, while the KM cohort had 33% who were ISS stage 3 at baseline. A limitation of this Rd-MRDR dataset was that patients had their disease status recorded only every 4 months, however, an advantage of this dataset was that OS was regularly cross referenced with the Australian Institutes of Health and Welfare National Death Index (AIHW NDI) (https://www.aihw.gov.au/about-our-data/our-data-collections/national-death-index). Importantly, both the KM-Rd cohort and the Rd-MRDR controls were treated within the same time period and with similar supportive care and access to both reimbursed pomalidomide and carfilzomib but neither CD38 nor BCMA-targeting immune therapies.

Study end-points

The primary end-point for both stage 1 and stage 2 was the CBR.[11] Study end-points are summarised in Table 2. Patients were evaluated every 28 days for OS and PFS. Comparison of CBR, ORR, OS and PFS between KM-Rd and Rd-MRDR groups was performed after the data cut-off (2 June 2021). Assessment of DoR and TTNT was done on 21 March 2022 in the KM-Rd group; these data were not available for the Rd-MRDR group.

Statistical approach

The demographic and baseline characteristics were compared between the KM-Rd cohort and the Rd-MRDR controls using Chi-square tests of independence, Fisher's exact tests, independent *t*-tests or Mann–Whitney *U* tests as appropriate. CBR and ORR were estimated as simple percentages and 95% credible intervals (CIs) were calculated as specified in the protocol using the pbeta and qbeta functions in R Version 4. A descriptive analysis of each of the time-to-event end-points (DoR, TTNT, OS and PFS) in each stage used the Kaplan–Meier (product-limit) method to estimate the survival functions, with conventional 95% confidence intervals (CIs) for the median times calculated using the Brookmeyer and Crowley method. Median potential follow-up was estimated by reversing the censor indicators in the Kaplan–Meier analyses. TTNT and competing risk of death before a switch to another therapy were investigated by calculating cumulative incidence functions using the cmprsk library (Version 2.2–11) in R Version 4. The time-to-event end-points comparing the KM cohort with KM-Rd cohort, and the KM-Rd cohort with the Rd-MRDR controls were undertaken using log-rank tests and were summarised as hazard ratios with 95% CIs calculated using Cox proportional hazards regression

TABLE 1 Demographics and baseline characteristics.

Factor	Stage 1 KM	Stage 2 KM-Rd	Rd-MRDR controls	*p*-value[a]
N	**19**	**40**	**77**	
Age, years (IQR)	60 (40–82)	68 (63–74)	69 (61–74)	0.92
Time from diagnosis, months (IQR)		34 (18–47)	26 (17–38)	0.15
Gender				
Male	58%	55%	55%	0.96
Female	42%	45%	45%	
International staging system (ISS) at diagnosis				
1	44%	19%	29%	0.56
2	22%	55%	45%	
3	33%	26%	26%	
Paraprotein type				
IgG	74%	50%	70%	<0.001
IgA	5%	25%	29%	
IgD	0%	0%	1%	
Light chain only	21%	25%	0%	
Prior lines of treatment				
1	42%	55%	39%	0.38
2	47%	35%	44%	
3	11%	0%	2%	
4	0%	0%	4%	
5	0%	0%	1%	
Prior therapy				
Proteosome Inhibitor (PI)	100%	93%	97%	0.336
Refractory to PI	5%	18%	21%	0.672
Thalidomide	47%	55%	50%	0.655
Autologous Stem Cell Transplant	53%	53%	47%	0.555
Cytogenetic risk[b]				
Standard	89%	77%	83%	0.461
High	11%	23%	18%	

Abbreviation: IQR, interquartile range.

[a]Stage 2 versus Rd-MRDR controls: Chi-square tests of independence, Fisher's exact tests, independent *t*-tests or Mann–Whitney *U* tests were used as appropriate.

[b]High risk = t(4;14), del17p or t(14;16).

models. These analyses were performed using SPSS v27 and Stata 16.1. A two-tailed *p*-value <0.05 was taken to indicate statistical significance.

RESULTS

Fifty-nine patients were enrolled between November 2016 and July 2019. Demographics and baseline characteristics for stage 1, stage 2 and the Rd-MRDR patients are in Table 1. Following an interim review by the TMC, the posterior probability calculations deemed it futile to continue with KM single-agent therapy (at $N = 16$; the observed CBR for single-agent therapy was only 1/16 [i.e. 6.25%]), and the posterior probability that the true CBR exceeds 20% was only 5.8%; hence the first PoC criterion was not met and posterior predictive probability calculations for CBR indicated that PoC was unlikely to be declared (see Data S1) and stage 1 was closed early ($N = 19$). Recruitment to stage 2 (KM-Rd cohort) was expanded from 30 to 40 patients to obtain more precise estimates of CBR and ORR. At the study censor date (21 March 2022), two patients in stage 2 (5%) remained on study (one patient achieved an initial PR on 9 October 2018 and the other on 3 June 2020). In the other patients, reasons for discontinuation were progression (stage 1 = 16/19 [84%], stage 2 = 31/40 [70%]), withdrawal of consent unrelated to KM toxicity (stage 1 = 3/19 [16%], stage 2 = 4/40 [10%]), and toxicity due to LEN administration (stage 2 = 3/40 [7.5%]). In stage 2, two patients (5%) died on study from causes that were considered by the investigator to be not related to study drug (pneumonia; $n = 1$, cause unknown; $n = 1$).

TABLE 2 Study end-points and definitions.

	Definition
Primary end-point	
Clinical Benefit Rate (CBR)	Minimal response (MR) or better as per the IMWG uniform response criteria[11]
Secondary end-points	
Overall response rate (ORR)	The proportion of patients who achieved a ≥ partial response [PR] as per the IMWG uniform response criteria[11]
Safety end-points	
Overall survival (OS)	Measured from the date of first dose of study drug until the date of death from any cause
Progression free survival (PFS)	Measured from the date of first dose of study drug until the earliest of the date of relapse, progression or death from any cause
Infusion-related reactions (IRRs)	Symptoms of an IRR can include fever, chills, shakes, itching, rash, hyper- or hypotension, difficulty breathing, vomiting or headache
Adverse events (AEs)	Unintended changes in signs or symptoms of the body; incidence and severity of AEs were assessed using the CTCAE version 4.0
Duration of response (DoR)	Restricted to patients who achieved PR, measured from the date on which a PR or better was first observed; patients who were not known to have progressed or died were censored at the date of their last evaluation
Time to next treatment (TTNT)	Measured from the date of first dose of study drug until the date that next therapy commenced or the date of death if another therapy did not commence, and, censored at the date of last contact

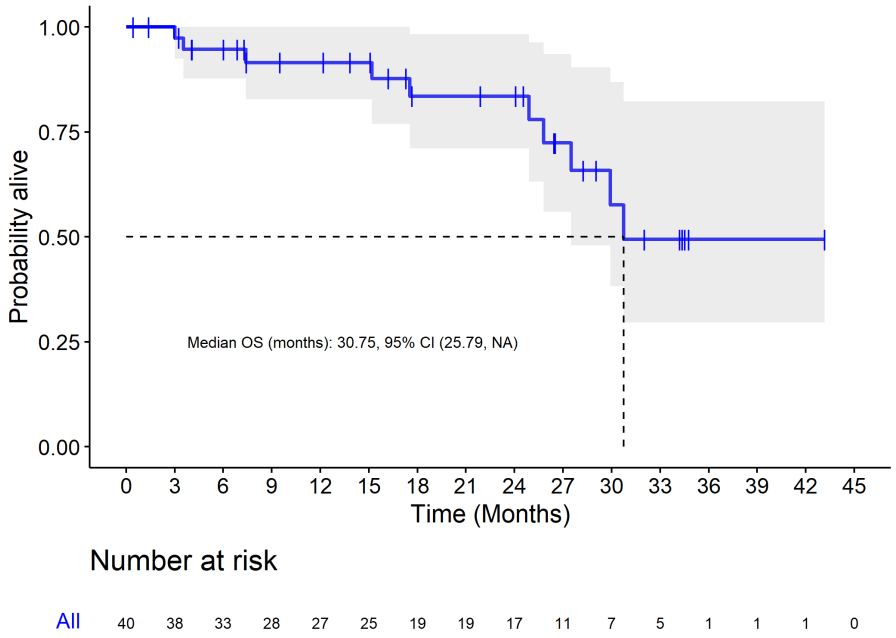

FIGURE 2 Duration of response in stage 2 KM-Rd treated patients. Shaded region indicates the 95% confidence interval for the probability of remaining in response at each time point.

Primary and secondary end-points for stage 1 and stage 2

The CBRs for stage 1 and stage 2 were 5% (95% CI: 0.5%–21.1%) [1/19, PR = 1] and 93% (95% CI: 79.9%–97.3%) [37/40]; CR = 3/37 (8.1%), VGPR = 11/37 (29.7%), PR = 19/37 (51.4%), MR = 4/37 (10.8%), respectively, with ORR 5% (1/19) and 83% (95% CI: 67.7%–91.1%) [33/40] respectively. The posterior probabilities that the true CBR exceeded 20% in stage 1 and 35% in stage 2 were 3.2% and >99.9% respectively. The median PFS for stage 1 was 2.0 months (95% CI: 0.0–4.7 months) and for stage 2 was 12.7 months (95% CI: 6.6–18.8 months) (HR 0.25, 95% CI 0.13–0.47, $p < 0.001$), with median OS not reached for either stage. Median DoR and TTNT in stage 2 were 12.9 months (95% CI: 6.2–19.6 months) (Figure 2) and 21.9 months (95% CI: 12.6–28.3 months) respectively. Moreover, for stage 2 at 12 and 24 months the cumulative incidences of switching to another treatment were 27.5% (95% CI: 13.5%–43.5%) and 55.1% (35.3%–71.1%) respectively and the cumulative incidence of death before a switch to another treatment remained at 8.8% (95% CI: 2.2%–21.6%) from 7.4 to 30.7 months (Figure 3). KM-Rd, within the limits of cross trial comparisons, was found to have similar response

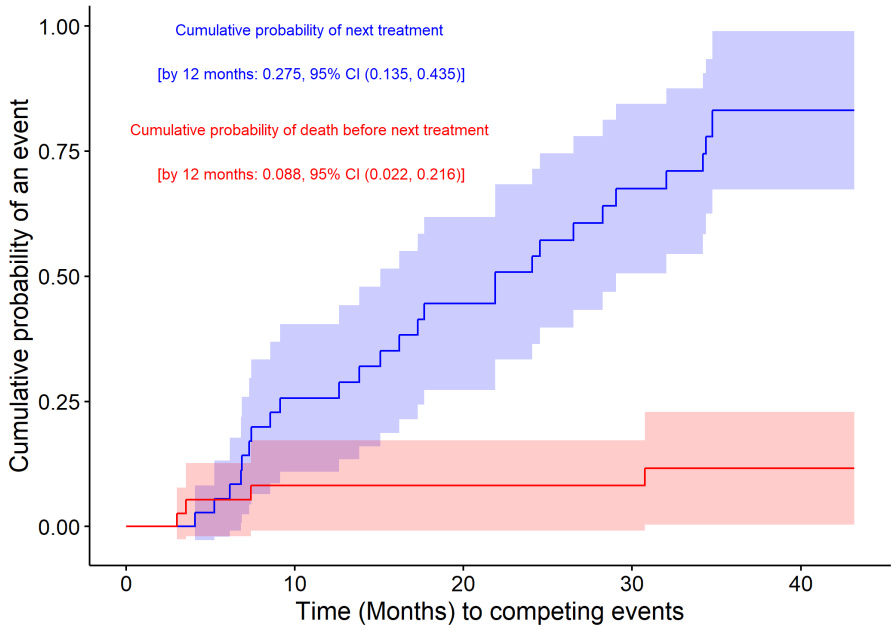

FIGURE 3 Cumulative incidences for the occurrence of the next treatment or the competing event of death before next treatment. Shaded regions indicate the 95% confidence intervals for each type of event at each time point.

rates to other Rd monoclonal antibody combinations (see Table S1).

Comparison of the stage 2 KM-Rd and Rd-MRDR cohorts

While acknowledging the inherent incompleteness of registry data and the inaccuracy that this could potentially create, 51 of 77 patients (66%) in the Rd-MRDR cohort had response data available for both CBR and ORR (Table 3). KM-Rd was superior to Rd-MRDR—93% versus 63% for CBR and 83% versus 45% for ORR respectively, both $p < 0.001$ (Figure 4). Seventy-five of 77 patients in the Rd-MRDR control group had data for survival with no significant difference in PFS between KM-Rd and Rd-MRDR—median PFS 12.7 months versus 10.3 months, 95% CI 6.23–23.57, $p = 0.55$ but with a significant OS advantage—median OS not reached versus 27.8 months, $p = 0.02$, HR 0.46 (95% CI 0.25–0.87) (Figure 5).

M protein and sFLC data observations in stage 1 and 2 patients

Figure 6 shows serum M protein and kFLC data for each stage. Of note in stage 1, a patient showed a disease response based on reduced M protein levels, however, their sFLC increased. This increase was a result of the Freelite assay detecting both circulating light chain and light chain that was bound to KappaMab, as previously described.[9] In addition, one FLC-only MM patient maintained decreased sFLC levels for 31 cycles. In stage 2, the majority of patients responded to KM-Rd. The median per cent change from baseline for sFLC was elevated to cycle 3 (i.e. following nine doses), then reduced and remained below baseline.

TABLE 3 Responses, CBR and ORR—Rd-MRDR Controls versus Stage 2 KM-Rd.

Group	*n*	%	*p*-value	Odds ratio (95% CI)
Overall response rate				
Rd-MRDR $N = 51$	23	45	<0.001	5.7 (2.1–15.4)
Stage 2 (KM-Rd) $N = 40$	33	83		
Clinical benefit rate				
Rd-MRDR $N = 51$	32	63	<0.001	7.3 (2.0–27.0)
Stage 2 (KM-Rd) $N = 40$	37	93		

Safety

KM demonstrated a highly favourable toxicity profile. In stage 1, 3/19 patients (15.8%) experienced an IRR, with one grade 1 and two grade 2 reactions. In stage 2, eight IRRs were observed; six with the first infusion. There was one grade 3 IRR and seven grade 1–2 IRRs, and no patients discontinued treatment because of IRRs. In particular, the patient with the grade 3 IRR recovered following hydrocortisone, salbutamol and loratadine administration in the clinic. There were no haematological toxicities, and in particular no lymphopenias, reported with KM, whereas the rates of anaemia (12.5%), neutropenia (32.5%) and thrombocytopenia (18%) seen in stage 2 with KM-Rd were as expected with Rd administration (Table 4). The most frequently reported non-haematological AEs were fatigue,

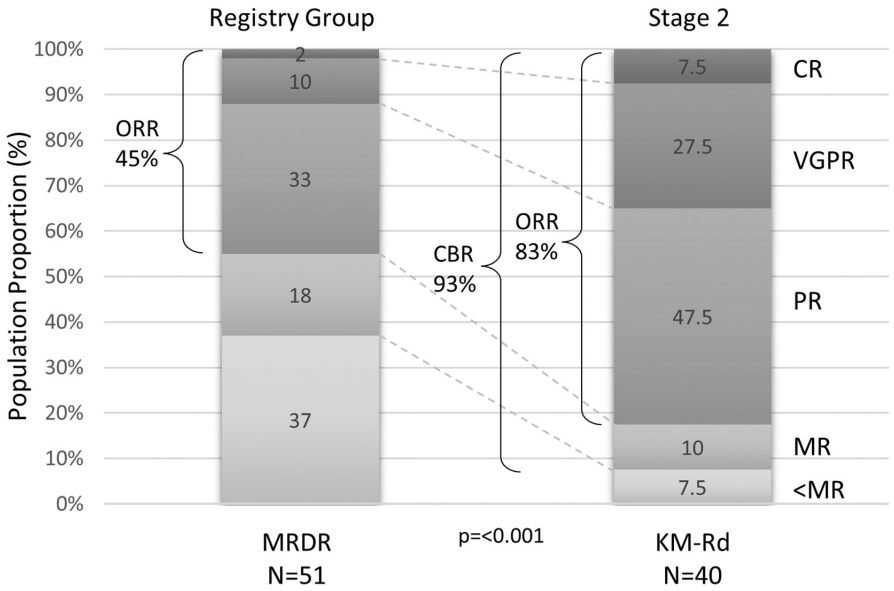

FIGURE 4 ORR and best clinical response rate comparisons between stage 2 KM-Rd and the Rd-MRDR patients.

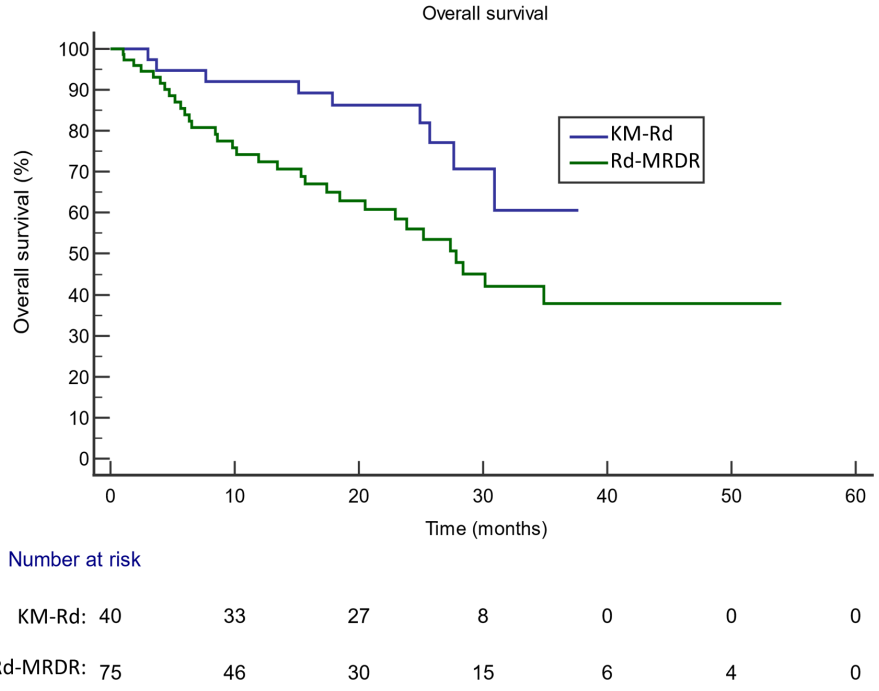

FIGURE 5 Comparisons of the time-to-event overall survival endpoint comparing the KM-Rd group with Rd-MRDR group. The logrank test showed a significance of $p = 0.0163$, and the hazard ratio with 95% confidence interval was HR 0.46, 95% CI (0.2466, 0.8679). Median OS in the Rd-MRDR group was 27.8 months, and median OS was not reached in the KM-Rd group. For mortality data, in the KM-Rd cohort ($n = 40$), 9 patients had evaluable data and 31 patients were censored, while in the Rd-MRDR group ($n = 77$), 32 patients had evaluable data and 45 patients were censored.

insomnia, musculoskeletal pain, peripheral neuropathy and diarrhoea (Table 5).

DISCUSSION

For patients with κRRMM, the combination of KM-Rd demonstrated significant efficacy with an ORR of 82.5%. This response was significantly better than the contemporaneous and matched control group (Rd-MRDR) receiving Rd (45.1%). Moreover, when compared to the controls the KM-Rd cohort also demonstrated a significant OS advantage with a 46% reduction in the risk of death compared to the Rd-MRDR group. Note that the OS data were validated for the Rd-MRDR control cohort via the AIHW NDI as described. Conversely, while KM-Rd demonstrated a numerically superior PFS this was not statistically significant. This is a result that needs to be

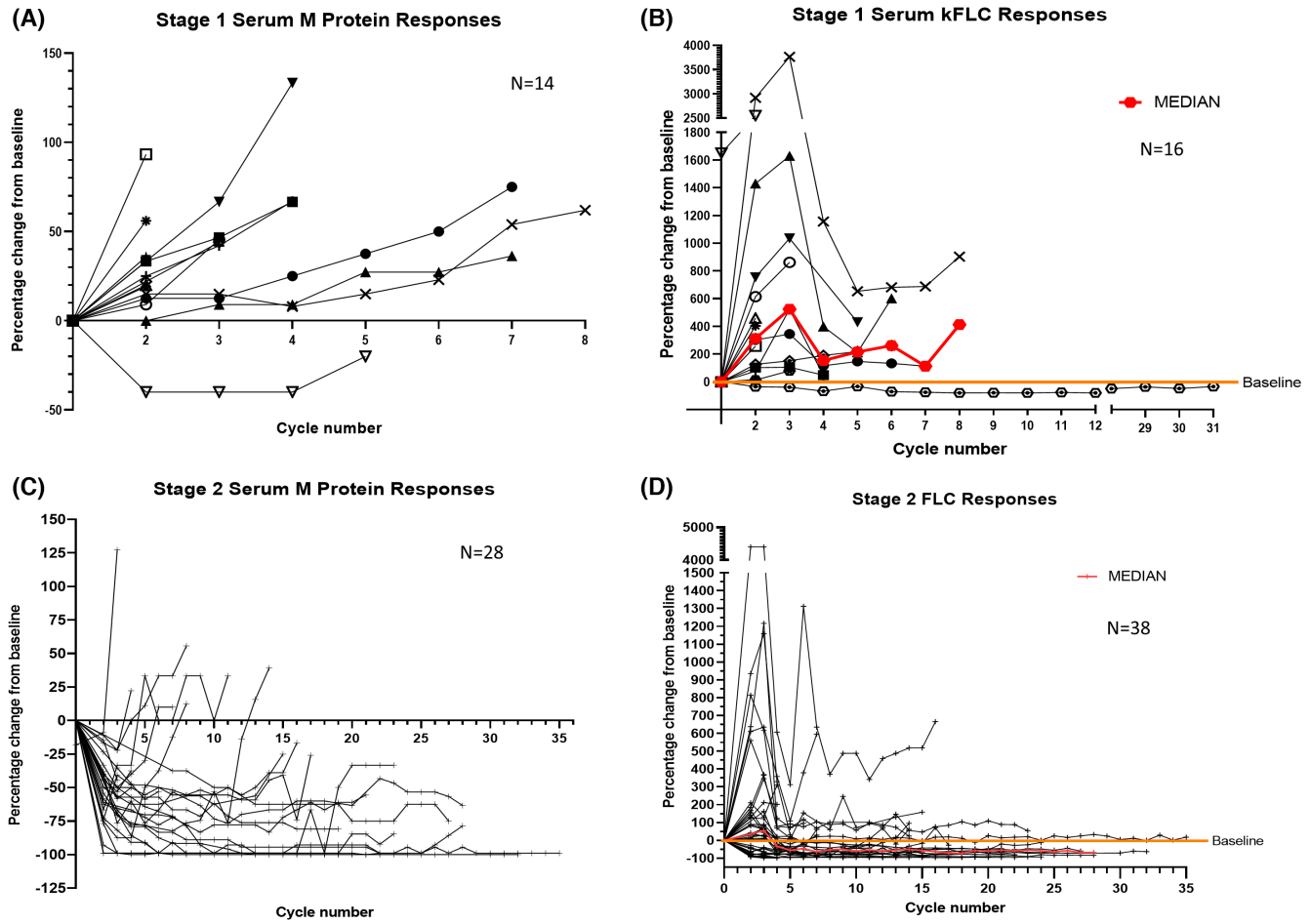

FIGURE 6 Serial M protein and FLC levels for stage 1 (A, B) and stage 2 (C, D). In stage 1, M protein levels decreased below baseline for 1 patient (A, open upside-down triangles), but FLC increased for this patient (B). In stage 1, one FLC-only MM patient showed decreased sFLC levels ranging between −36% and −80% from baseline for 31 cycles of treatment (B, open dotted circles). In stage 2, the majority of patients responded to KM-Rd (C). Median % change from baseline for FLC was elevated to Cycle 3 (i.e., after 9 doses of KM), then it reduced and remained below baseline (D, red line). This was not observed in the stage 1 patients, where median FLC fell between Cycles 3 and 4, then generally elevated followed Cycle 4 (B, red line).

TABLE 4 Stage 2 haematological AEs ($N = 40$).

	Grade, *N* (%)				
	1	2	3	4	Total, *N* (%)
Neutropenia	2 (5%)	3 (7.5%)	6 (15%)	2 (5%)	13 (32.5%)
Anaemia	1 (2.5%)	1 (2.5%)	3 (7.5%)	0 (0%)	5 (12.5%)
Thrombocytopenia	1 (2.5%)	1 (2.5%)	2 (5%)	3 (7.5%)	7 (18%)

interpreted with caution based on the critical differences in PFS attribution between the Rd-MRDR and this phase 2 clinical trial; disease status for the registry cohort was recorded every 4 months in contrast to the trial where this was done every 4 weeks, which can lead to an element of bias with overestimation of PFS in the registry cohort. The modest median PFS with KM-Rd and the absence of identifiable dose-limiting toxicities in prior studies of KM at 10 mg/kg strongly supports evaluation of higher doses of KM in combination treatment. Other limitations were the inability of the Freelite Assay to differentiate between FLC bound to KappaMab and unbound FLC.[9] Hence, some of the increases in sFLC were not necessarily an indication of disease progression. In future studies sFLC will not be used to measure progression (Figure 6).

KM monotherapy has limited anti-MM activity, as was observed with single-agent ELO, where SD (27% of patients) was the best response observed.[12] In contrast, DARA monotherapy demonstrated an ORR of 36% in heavily pretreated RRMM patients with durable responses in patients receiving 16 mg/kg.[13] Importantly, the escalation of DARA from 8 mg/kg to 16 mg/kg was associated with a substantial increase in response rate, from 10% to 36%; a further argument for exploring KM at higher

TABLE 5 Treatment-emergent non-haematological AEs (≥10%) in stages 1 and 2.

	Stage 1		Stage 2	
Adverse event	All grade, %	Grade 3, %	All grade, %	Grade 3, %
Rash	16	–	10	–
Hyperglycaemia	–	–	10	–
Fatigue	32	–	30	3
Abdominal pain	5	–	10	3
Constipation	–	–	10	–
Diarrhoea	5	–	13	–
Nausea	–	–	10	–
Hypophosphatemia	–	–	10	–
Infusion-related reaction	16	–	13	3
Peripheral neuropathy	–	–	15	3
Insomnia	–	–	23	6
Cramps	–	–	10	–
Pain	5	–	20	–
URTI	5	–	20	–
Pneumonia	–	–	8	8
Cellulitis	10	5	10	–

doses. Subsequently, DARA combined with either LEN[2] or bortezomib[1] in RRMM resulted in enhanced ORRs of 92.9% and 83.8% respectively. These data informed the evaluation of DARA in newly diagnosed MM patients[14,15] and the emerging adoption of CD38 targeting approaches as a new treatment paradigm for newly diagnosed MM and less heavily pretreated RRMM.[16]

We have shown in this study and the previous phase I/IIa studies that both the single-agent KM and KM-Rd regimens were very well tolerated, with the KM-Rd safety profile essentially recapitulating that seen with Rd[17,18] and with only infrequent (14%) and low-grade KM-related IRRs. This rate of IRRs being similar to that seen with ELO-Rd (10%), again with the majority being grade 1 or 2,[3] but in contrast to DARA-Rd where 47% of patients on the POLLUX trial experienced IRRs.[2] While neutropenia occurred in 32.5% (20%, grade 3/4) of patients receiving KM-Rd, the rate of grade 3 or higher infections was only 7.5% and with a median time on KM-Rd of 12 months there was no evidence of an excess of treatment-emergent infections. These results compare favourably with the published phase III Rd clinical trials, with grade 3/4 neutropenia rates of 29.5%–41.2% and grade 3/4 infection rates of 11.3%–21.5%.[17,18] The lack of increase in neutropenia and infection rates in the KM-Rd cohort likely reflects the highly restricted pattern of KMA expression, with KMA being found only on malignant plasma cells and limited numbers of tonsillar B cells.[5,6]

The efficacy of targeting CD38 in early phase MM notwithstanding, it is evident that resistance emerges in a significant proportion of patients over time.[19,20] This highlights the need for alternative non-CD38 I-O targets in MM. In this context a variety of MM-restricted target antigens are under evaluation[21] with B-cell maturation antigen (BCMA) emerging as a leading candidate deployed using antibody drug conjugates (ADCs), and bi-specific T-cell engager and CAR-T cell technologies currently under investigation.[22] Results have been mixed. The lead BCMA ADC candidate, belantamab mafodotin, while having demonstrable anti-MM activity is associated with very high rates of payload-related keratopathy, which makes its use particularly challenging.[23,24] The picture with CAR-T is less clear. While two anti-BCMA CAR-T products have been approved for use as fourth-line therapy and beyond by the FDA (idecabtagene vicleucel and ciltacabtagene autoleucel) there is a variation in response rates and durability and a not insignificant rate of neurotoxicity.[25,26] Of potentially greater concern is the recently described delayed form of neurotoxicity,[26] an undifferentiated movement and neurocognitive disorder, with recent evidence of BCMA expression within the central nervous system data suggesting this may be an on-target toxicity and best prevented by improved disease control prior to CAR-T infusion.[27] This experience highlights the critical importance of target specificity and the careful monitoring of patients for unexpected on-target toxicities.

CONCLUSIONS

In the context of the more widespread and earlier use of CD38-targeting monoclonal antibodies, alternative specific targets for anti-MM I-O therapeutics are needed. This study validates KMA as a highly specific target and reaffirms the favourable toxicity profile of KM and the ability to safely deliver KM in combination with LEN. Further studies escalating the dose of KM beyond 10 mg/kg in combinatorial studies are planned in κRRMM patients.

AUTHOR CONTRIBUTIONS

Andrew Spencer, Rosanne Dunn, Jake Shortt, John Reynolds and Anna Kalff designed the study. Andrew Spencer, Anna Kalff, John Reynolds, Rosanne Dunn and Jake Shortt acquired the funding and collected and interpreted the data. Andrew Spencer and Anna Kalff wrote the original manuscript draft, Jake Shortt, Rosanne Dunn and Andrew Spencer reviewed and edited the manuscript. John Reynolds and Cameron Wellard performed the statistical analysis and produced figures. All other authors were involved in data collection and final review of the manuscript. All authors approved the manuscript. Editorial assistance was provided to the authors during preparation of this manuscript by Rhonda Oshanek, a medical writer employed by HaemaLogiX Ltd.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest declared for AK, JS, HQ, CWG, PW, CW and JR. RD is an employee of HaemaLogiX Ltd, owns shares in the company, and holds patent rights for KappaMab. AS and SH are members of the Scientific Advisory Board at HaemaLogiX Ltd. JS, HQ and SH have received research funding and participated in Advisory Boards for BMS/Celgene.

DATA AVAILABILITY STATEMENT

Individual participant data and supporting documents for this trial will not be made publicly available. Please contact the corresponding author directly for any data-related queries.

ETHICS STATEMENT

The protocol was approved by the Alfred Hospital Human Research and Ethics Committee. HREC reference: REC/16/Alfred/116, Project Number: 398/16, Initial approval: 19 September 2016, First amendment: 24 February 2017.

PATIENT CONSENT

All patients provided written informed consent in accordance with the Declaration of Helsinki. This study was conducted under Good Clinical Practice (GCP) guidelines.

CLINICAL TRIAL REGISTRATION

This trial was registered on the Australian New Zealand Clinical Trials Registry at www.anzctr.org.au (ACTRN12616001164482).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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