A Sequential Cohort Study Comparing KappaMab Alone To KappaMab, Lenalidomide And Low Dose Dexamethasone In Kappa-Restricted Relapsed Refractory (RR) Multiple Myeloma (AMaRC 01-16)

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BACKGROUND & OBJECTIVE

KappaMab is a chimeric IgG1 monoclonal antibody specific for Kappa Myeloma antigen (KMA), a tumour specific cell antigen exclusively expressed on the surface of kappa restricted MM cells. Early safety and efficacy signals seen with single-agent treatment in phase I/II studies in conjunction with observations that IMiD®-treatment upregulates the KMA target and enhances effector cell cytotoxicity, providing rationale for this proof-of principal immune-oncology (IO) approach in a minimally pre-treated MM population.

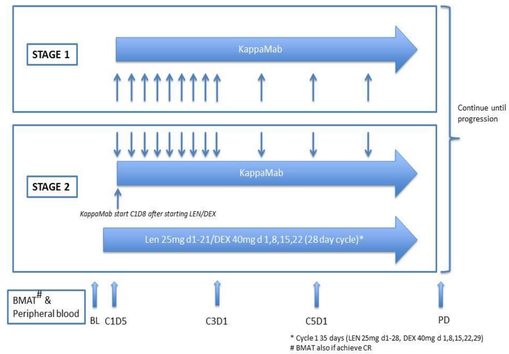
The primary aim of this study was to establish the clinical benefit rate (CBR) of KappaMab alone (Stage 1) and in combination with lenalidomide (LEN) and low dose dexamethasone (DEX) (Stage 2). Secondary aims: to determine the safety of KappaMab in combination with LEN and DEX, in particular, the incidence of immunological adverse events (AEs); and to evaluate the kinetics of response and loss of response (time to response [TTOR], time to disease progression [PFS], overall survival [OS]).

METHODS

Investigator initiated, phase IIb, multi-centre, open label sequential cohort study comparing KappaMab alone to KappaMab in combination with LEN and DEX in RR MM (funded by the Victorian Cancer Agency, Australia). Key inclusion criteria were kappa-restricted myeloma, 1-3 prior lines of therapy but no prior LEN.

Recruitment is planned for 60 patients in total, with an initial intention to treat 30 patients per stage. In Stage 1, patients received KappaMab (10mg/kg IV infusion) weekly for 8/52 (induction), then every 4/52 (maintenance). [One cycle = 28d] For patients in Stage 2, KappaMab dosing was as per stage 1 with the addition of LEN (25mg D1-21) and DEX 40mg weekly. In cycle 1 of Stage 2, LEN and DEX commenced 1/52 prior to KappaMab. [Cycle 1 was of 35 days duration: LEN 25mg D1-28 and DEX 40mg weekly (D1, 8, 15, 22, 29)].

Treatment continued until toxicity/progression. This is a planned interim analysis of the primary endpoint (CBR).



RESULTS & DISCUSSION

59 patients have commenced therapy. Following review by the DMC, recruitment to Stage 1 was terminated early (n=19). 39 of a planned 40 patients for stage 2 have commenced treatment. [One patient who entered Stage 2 received lenalidomide, but did not receive KappaMab]. Patients were recruited between November 2016 and July 2019

Cut-off date for this interim analysis: 31/08/2019.

Of the 60 patients included in this analysis, 27 patients remain on study (Stage 1=0, Stage 2=27).

26 have progressed: (Stage 1=16, Stage 2=10),
- 6 withdrew consent (3 each stage),
- 2 other and
- 5 patients are known to have died (Stage 1=2, Stage 2=3).

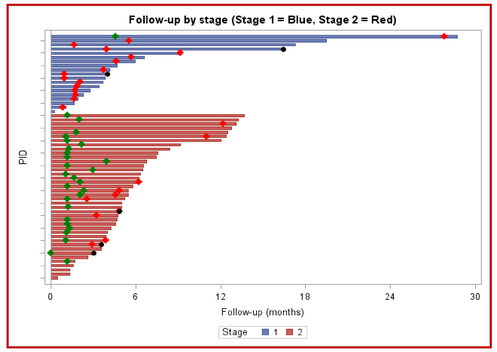
Estimated median potential follow-up was 4.17m in Stage 1 (UQ=9.23m) and 5.49m in Stage 2 (UQ =8.41m).

	Stage 1 (n=19)	Stage 2 (n=40)
Age, years (range	65 (40 - 82)	67 (43 – 86)
Sex (M:F)	11:8	22:18
MM Subtype		
KLC only	4	8
IgG Kappa	14	19
IgA Kappa	1	11
ISS stage (diagnosis)		
1 – 2	13	21
3	6	8
unknown	0	11
Cytogenetics/FISH (diagnosis)		
High risk [+1q21, del17p, t(4;14)]	3/11	9/18
Median Prior lines of therapy (range)	2 (1 – 3)	1 (1 – 3)
Prior thalidomide (refractory)		20 (4)
Prior bortezomib (refractory)		36 (8)
Prior ixazomib (refractory)		4 (2)
Prior carfilzomib (refractory)		3 (0)
Double refractory (PI and thal)		3
Prior ASCT	11	21

Disposition	Stage 1 N=19 n (%)	Stage 2 N=40 n (%)
Number of Cycles of Therapy		
10+ cycles	1 (5.3)	6 (15)
5 - 9	6 (31.6)	13 (32.5)
4 cycles	1 (5.3)	6 (15)
1 - 3 cycles	10 (52.6)	8 (20)
No completed cycles	1 (5.3)	2 (5)
Data not available		5 (12.5)

Swimmer plot (by stage) of the status of patients (n=59) enrolled on the study and included in analysis

- Green diamond - time of achievement of OR (i.e. PR or better)
- Red diamond - time to progression
- Black dot - time to death



Response

Response	Stage 1 (n=19)	Stage 2 (n=21)
IMWG Response – n (%)		
CR	0 (0.0)	1 (2.5)
VGPR	0 (0.0)	6 (15)
PR	1 (5.3)	20(50)
MR	0 (0.0)	4 (10)
< MR	18 (94.7)	9 (22.5)

Observed CBR (Table 3) in Stage 1 was 5.3% (1/19, PR=1) compared to 77.5% in Stage 2 (31/40, CR=1, VGPR=6, PR=20, MR=4). (Response assessments are ongoing). Proof of concept (PoC) criteria were not met for Stage 1 (Table 4a), but were met for Stage 2 (Table 4b): observed CBR ≥ 55%, and the posterior probability (PP) that the true CBR exceeds 35% was > 0.95 (PP=0.999).

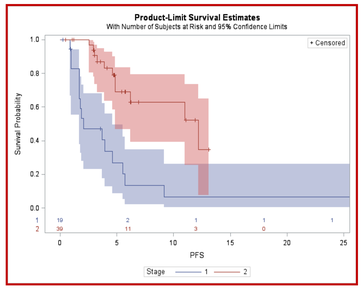
ORR for Stage 1 (Table 5a) was 5.3% (1/19) compared to 67.5% (27/40) for Stage 2. .

Median TTOR was not reached in Stage 1 (95% CI: 4.6m and above), and was 1.64m in Stage 2 (95% CI: 1.18 – 2.17m) (p<0.001).

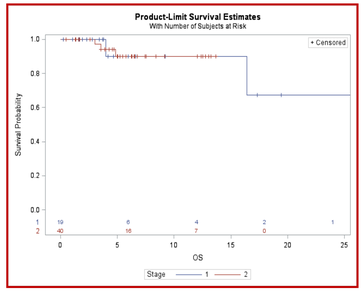
Survival

Median PFS for Stage 1 was 2.07m (95% CI: 1.68 – 4.63m), compared to 12.19m for patients in Stage 2 (95% CI 4.86m – NA) (p<0.001).

Median OS for both stages was not reached: 95% CI 4.0m and above for Stage 1, and 4.9m and above for Stage 2 (p=0.964).



Progression-free survival (PFS) by stage with conventional 95% confidence intervals in months from the date of the first dose of study drug.



Overall survival (OS) by stage in months from the date of the first dose of study drug.

Adverse Events

Infusion related
3/19 patients in Stage 1 had infusion reactions (grade 1=1, grade 2=2), compared to 4/21 patients in Stage 2 (grade 2=4).

Haematologic
There were no haematologic toxicities reported in Stage 1, in comparison to anaemia 5/40 (grade 3=1), neutropenia 8/40 (grade 3=4, grade 4=1), and thrombocytopenia 6/40 (grade 3=1, grade 4=2) reported in Stage 2.

Non Haematologic (regardless of causality > 10% incidence)

	Stage 1 (n=19)	Stage 2 (n=40)
Musculoskeletal pain	5	8
Fatigue	4	6
Infection		
URTI	5	7
LRTI	2 (grade 3 = 1)	6 (grade 5 = 1)
Abdominal pain	0	4

CONCLUSIONS

In a patient population with high prior IMiD (thalidomide) exposure and a median of 1 prior line of therapy, KappaMab combined with LEN and DEX demonstrated an ORR of 67.5% and was well tolerated.

This novel immune-oncology combination may represent a promising new therapeutic option. This trial is ongoing.

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