Supplementary File

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)

Statistical analyses of the primary endpoint

The primary endpoint for each stage of the trial was achievement of at least an MR i.e., MR, PR, VGPR, CR or sCR at any time on study and summarized as the Clinical Benefit Rate (CBR).

In each stage, Proof-of-Concept (PoC) could be claimed if two criteria were fulfilled:

(1) Observed CBR ≥ clinically determined threshold
(2) Posterior probability that the true CBR is > a futility threshold, given the observed data, is > a specified level of proof (LoP).

The calculation of the posterior probability, at any time during a stage, was based on the observed CBR at the time of the calculation and a minimally informative prior probability distribution for the true CBR with a median equal to the futility threshold.

In Stage I of the trial, the following PoC criteria for the investigation of single agent therapy with KappaMab were applied:

(1) Observed CBR ≥ 25%
(2) Posterior probability that the true CBR is > 20%, given the observed data, is > 90%

Calculation of the posterior probability used a minimally informative prior distribution for the true CBR, namely Beta(a=0.43068, b=1) for which the median CBR is 20% and the amount of prior information is equivalent to approximately 1.43 (=a+b) patients. The posterior probability for a true CBR > 20% given “x” defined responses out of “n” patients is given by the right tail (from p=0.2 to p=1.0) of the Beta(a+x, b+n-x) distribution.

For one look based on n=30 patients and a true CBR of 35%, the probability of declaring efficacy in Stage 1, based on this approach, is 0.65 and when the true CBR is 40% the probability of declaring efficacy is 0.82.

In Stage 2 of the trial, the following criteria, including a more stringent LoP for the investigation of combination therapy with KappaMab and lenalidomide, were applied:

(1) Observed CBR ≥ 55%
(2) Posterior probability that the true CBR is > 35%, given the observed data, is > 95%

Calculation of the posterior probability used a minimally informative prior distribution for the true CBR, namely Beta(a=0.66025, b=1) for which the median CBR is 35% and the amount of prior information is equivalent to approximately 1.66 (=a+b) patients. The posterior probability for a true CBR > 35% given “x” defined responses out of “n” patients is given by the right tail (from p=0.35 to p=1.0) of the Beta(a+x, b+n-x) distribution.

For exactly n=30 patients and a true CBR of 60%, the probability of declaring efficacy in Stage 2, based on this approach, is 0.71 and when the true CBR is 65% the probability of declaring efficacy is 0.87.

The trial was overseen by a Trial Management Committee (TMC). The purpose of the TMC was:

1. To provide detailed monitoring of the conduct of each stage of the trial, in particular close review of toxicities and decisions in relation to the PoC criteria.
2. To make recommendations to the Sponsor and provide advice to the Principal Investigator (PI) as required.
3. To inform The Alfred Human Research Ethics Committee (HREC) and HRECs at participating sites on a regular basis, of the status of the trial and its recommendations.

Patient entry in each stage was to continue until 30 patients had been enrolled in the stage.

The TMC evaluated the first 16 patients in Stage 1 at which time the observed CBR for single agent therapy was 1/16 (i.e., 6.25%), and the posterior probability that the true CBR exceeds 20% was 5.8%. If recruitment in Stage 1 was to continue to the target of 30 patients, then the first PoC criterion required at least 8/30 patients to achieve MR or better. If the response status of the first 16 patients did not improve, achievement of the first criterion required at least 7 out of the 14 new patients to achieve MR or better. The predictive probability for this was estimated to be 0.4% so, achievement of the first PoC criterion was considered to be very unlikely.

While no formal futility analysis was described in the protocol, the TMC had broad scope (see above) to make recommendations to the Sponsor and the PI, and formed the opinion, on the basis of the posterior probability calculations that it was futile to continue with single agent therapy and accordingly recommended that the 1st Stage of the trial should be closed and the 2nd Stage should be opened. At the time that the recommendation was made, 19 patients had been enrolled in Stage 1. After follow-up only 1/19 patients in Stage 1 achieved MR or better.

Comparison of response and haematological toxicities in other clinical trials

Supplementary Table 1. Previous Phase I/II clinical trials using monoclonal antibodies plus lenalidomide and dexamethasone show similar response rates and potentially reduced haematological toxicities. Patients in all studies had up to 3 previous lines of therapy.

	KM-Rd	**Daratumumab-Rd[1]**	**Elotuzumab-Rd[2]**	**Elotuzumab-Rd[3]**
Patient numbers	N=40	N=32	N=73 • 36 at 10 mg/kg • 37 at 20 mg/kg	N=33
Previous lenalidomide exposure?	Len naïve	34.4% previous len and 28.1% previous bort + len	Len naïve	Subset had prior len (n=9; 27%)
PFS (months)	12.7 (95% CI 6.6-18.8)	72.1% (95% CI:51.7-85.0)*	Not reported	Not reported
ORR (%)	82.5%	81.3% (95% CI:63.6-92.8)	84% (92% at 10 mg/kg and 76% at 20 mg/kg)	61% (95% CI: 42-77; 20 of 33)
CBR (%)	92.5%	87.5%**	MRs not reported	Not reported
OS (months)	Not reached	90.4% (95% CI:73.1-96.8)*	Not reported	Not reported
Neutropenia: Grade 3-4	8 of 40; 20%	25 of 32; 78%	14 of 73; 19%	6 of 33; 9%
Lymphopenia: Grade 3-4	None observed	Not reported (in ≥25% of patients)	15 of 73; 21%	Not reported (in ≥15% of patients)

Thrombocytopenia Grade 3-4	5 of 40; 12.5%	4 of 32; 12.5%	13 of 73; 18%	Not reported (in ≥15% of patients)

*PFS and OS given as 18-month rates. **N=2 MRs reported.

[1]Plesner, T, Arkenau, HT, Gimsing, P, et al. Phase 1/2 study of daratumumab, lenalidomide, and dexamethasone for relapsed multiple myeloma. *Blood*. 2016; **128**(14):1821-1828.

[2]Richardson PG, Jagannath S, Moreau P, et al. Elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma: final phase 2 results from the randomised, open-label, phase 1b-2 dose-escalation study. *Lancet Haematol*. 2015;**2**(12):e516-527.

[3]Berenson J, Manges R, Badarinath S, et al. A phase 2 safety study of accelerated elotuzumab infusion, over less than 1 h, in combination with lenalidomide and dexamethasone, in patients with multiple myeloma. *Am J Hematol*. 2017;**92**(5):460-466.