End of Clinical Trial Report

An open label, multi-centre, randomised, parallel group phase II selection trial to identify the optimal starting dose of bendamustine (60 vs 100 mg/m^2) when given in combination with thalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma

1. Trial Summary

EudraCT	2010-021451-12
ISRCTN	ISRCTN90889843
Sponsor No.	HM10/9422
Sponsor	Leeds Teaching Hospitals NHS Trust (Non-commercial sponsor), R&D Department, 34 Hyde Terrace, Leeds, LS2 9NL
Chief Investigator	Dr Steve Schey, Department of Haematology, King's College Hospital, Denmark Hill, London, SE5 9RS
Trial Contact	Debbie Sherratt, Senior Trial Manager, Clinical Trials Research Unit, University of Leeds, Leeds, LS2 9JT
CTA Approval	02/11/2010
Main REC Approval	30/09/2010
Final protocol version and date	v5.0, 4th
Phase of study	II
Investigational Medicinal Products (IMPs)	Bendamustine, thalidomide, dexamethasone
Treatment Groups	60mg/m^2 100mg/m^2
Target number of patients	98
Final number patients recruited	95
Report Date	

Signed: Date: 02/02/15

2. Trial Design

This is a multi-centre, randomised, parallel group, phase II selection trial in patients with relapsed or refractory multiple myeloma (first relapse or later).

Patients will be stratified according to whether they are refractory, or relapsed and responsive, presence or absence of renal or haematological impairment and number of previous treatments.

This is a Bryant and Day two-stage design to assess tolerability and efficacy simultaneously[1]. The trial may be terminated at the end of the first stage due to lack of efficacy or unacceptable tolerability. Assuming at least one of the schedules successfully passes the first stage, a schedule will be deemed worthy of further consideration in a phase III trial at the end of stage two if it is a) acceptably tolerable AND b) sufficiently efficacious.

If both treatment schedules successfully pass stage two, initial selection criteria will be based on progression-free survival rates, following the methodology of Sargent and Goldberg [2].

Assuming tolerance, and in the absence of disease progression, the treatment phase will continue for a minimum of six cycles or until best response plus 2 cycles, up to a maximum of 9 cycles.

After completion of bendamustine, thalidomide and dexamethasone (BTD), the patient may be assessed for eligibility for PBSC mobilisation and harvest and future ASCT. If eligible, they may undergo stem cell harvest at the discretion of the local investigator. Data will be collected to assess the adequacy of the harvest. If there is adequate stem cell harvest, cells will be stored and may be used for ASCT at disease progression, at the discretion of the investigator.

If the patient is not considered by the investigator to be suitable for PBSC harvest, they will proceed to long term follow up.

Follow up will be every 4 weeks until initiation of a new treatment for disease progression, death, or until the end of the trial's follow up period,(1 year post last patient recruited) whichever occurs first. After initiation of a new treatment, trial follow up will be for survival only.

3. Trial Objectives

Primary Objective
The primary objective of this trial is to determine the optimum dose of bendamustine when combined with thalidomide and dexamethasone (BTD) in the treatment of relapsed/refractory multiple myeloma, based on response rates, tolerability and progression-free survival

Secondary Exploratory Objectives
The secondary objectives are:

- To determine maximum and overall response rates
- To determine response duration
- To determine time to next treatment
- To determine safety and toxicity (particularly febrile neutropenia and septicaemia)
- To determine longer term tolerability (ie the proportion of patients successfully receiving six cycles of treatment with bendamustine with no dose reductions or delays)
- To assess the feasibility of stem cell harvest following treatment with bendamustine, thalidomide and dexamethasone (BTD) in eligible patients.
- To determine overall survival

4. Population

Adults with confirmed multiple myeloma requiring therapy for relapsed or refractory disease with a life expectancy of at least 3 months and an ECOG performance score of 0-3. Patients were excluded if they had relapsed on previous bendamustine therapy, or had any of the following within 14 days: platelets <75x109/L (unless attributable to myeloma), neutrophils <1.5x109/L, serum ALT/AST >2.5 times upper limit of normal (ULN), serum bilirubin >2.0 times ULN or calculated or measured creatinine clearance <10 mL/minute, concurrent or previous malignancies, ≥grade 2 peripheral neuropathy, or steroids totalling >160mg dexamethasone or equivalent in 14 days prior to enrolment.

5. Treatment

Patients were randomised to receive either 60mg/m^2 Bendamustine with thalidomide and dexamethasone (B60TD) or 100mg/m^2 Bendamustine with thalidomide and dexamethasone (B100TD). This was given over a 28 day cycle. Bendamustine given by IV on days 1 and 8, thalidomide given orally continuously, dexamethasone given orally on days 1, 8, 15 and 22. Treatment was given for a minimum of 6 cycles and up to 9 cycles, unless the treatment was not tolerated.

Patients received between 1 and 9 cycles of treatment.

All IMPs were commercial off the shelf supplies.

6. Participants

Between January 2011 and July 2012 a total of 95 patients were entered into the MUK one trial, the flow of patients through the trial is outlined in Appendix 1. Recruitment was temporarily halted in September 2011 to allow the interim analysis to take place. As a result of this analysis all patients recruited from March 2012 were registered to receive 60mg/m^2 Bendamustine with thalidomide and dexamethasone.

A total of 29 patients were registered to receive B100TD and 65 patients to receive B60TD. One further patient was registered to receive B60TD however withdrew prior to receiving any trial treatment. Last follow up was September 2013. Four patients were still in follow up when the decision to close the trial was made.

Participants were recruited from 8 centres open to the trial:

St James University Hospital Leeds; Dr Gordon Cook

Queen Elizabeth Hospital, Birmingham; Dr Mark Cook

St Bartholomews Hospital, London; Dr Jamie Cavenagh

University College Hospital, London; Dr Kwee Yong

Royal Marsden Hospital, London; Dr Faith Davies

Nottingham University Hospital, Nottingham; Dr Cathy Williams

The Christie Hospital, Manchester; Dr Jim Cavet

Kings College Hospital, London; Dr Steve Schey

7. Statistical Methods

The trial was designed with joint primary endpoints of tolerability and activity using the Bryant and Day two-stage design (1). Tolerability was assessed by the proportion of patients successfully receiving both doses of their second cycle of bendamustine at full dose with no more than 2 weeks delay without primary GCSF prophylaxis, as an indicator of initial tolerability and the likelihood of the patient being able to receive the initial prescribed dose. Activity was assessed by the proportion of patients achieving at least a partial response (PR) within six cycles of treatment. Response to treatment was assessed using modified International Myeloma Working Group Uniform response criteria (3), and independently reviewed. Progression-free survival was used to select the optimal dose in the event both doses were deemed sufficiently deliverable and active (2). The study was not powered to directly compare the two arms for statistically significant superiority.

With 90% power and type 1 error rates of 10% for both tolerability and activity, a maximum of 49 patients/arm were required, allowing for 10% drop-out, to detect response and tolerability rates of 50% and 90% respectively, and reject rates of <20% and <75%, respectively. These cut-offs, although challenging, were based on previous IMiD-based studies of relapsed/refractory disease (4,5). A pre-specified interim analysis was scheduled once 20 patients per arm had been followed-up for primary endpoints, with recruitment continuing during follow-up. For an arm to continue onto the second stage at least 16/20 (80%CI [63.9-91.0]) patients were required to tolerate treatment as well as at least 5 patients achieving at least a partial response.

All secondary endpoints were summarised descriptively, with no formal comparisons between the arms.

After the first 20 patients in each arm had received at least 2 cycles of treatment and were therefore evaluable for tolerability, a pre-specified independent Data Monitoring & Ethics Committee (DMEC) analysis was performed (see results section for further detail). At the

recommendation of the DMEC, an amendment to the eligibility criteria was implemented allowing only patients with unsupported platelets >75x109/L and neutrophils >1.5x109/L within 48 hours of registration to be entered into the study, reflecting a change from the initial criteria to exclude patients where cytopaenia was considered by the responsible clinician to be attributable to myeloma; this definition was applied retrospectively to those patients already recruited, and prospectively to patients recruited after the amendment.

The primary analysis population was therefore planned to include all patients who received at least one dose of bendamustine, and who were evaluable for the primary tolerability and response endpoints, where evaluable patients are defined those patients with neutrophil and platelet counts above 1.5 x109/L and 75 x109/L respectively at baseline and day 1 of cycle 1, and for whom at least one response assessment had been performed. Patients who terminated treatment at the end of cycle 1 due to disease progression and for whom the tolerability endpoint was deemed non-evaluable were not included in the primary analysis population.

Analysis took place in two phases. The first analysis was carried out on all but the survival, time to event (response duration and time to next treatment) and feasibility of stem cell harvest following treatment endpoints, when all patients had response data observed within six cycles of treatment. The survival, time to event and feasibility of stem cell harvest following treatment endpoints were analysed once the last patient recruited had been followed up for 12 months. A full statistical analysis plan was written and signed off prior to the final data download and statistical analysis of the trial. All statistical analyses were performed in SAS version 9.2.

8. Results

After the first 20 patients in each arm had received at least 2 cycles of treatment and were therefore evaluable for tolerability, a pre-specified independent DMEC analysis was performed, at which time a total of 59 patients had been entered into the study. This analysis demonstrated that a prior neutrophil count <1.5 x109/L &/or platelets <75 x109/L led to inability to administer a second cycle of the B100TD treatment without dose modification or ≥2 week delay. This was deemed excessive in the B100TD arm according to the pre-specified stopping criteria, with just 5/10 patients with sufficiently high neutrophil and platelet counts tolerating treatment (80%CI [26.7-73.3]). Thereafter, at the DMEC's recommendation and in accordance with the trial design specification, the B100TD arm was closed to new patient entry and patients were recruited only into the B60TD arm.

The following analysis populations were summarised:
1) per-protocol population (all patients receiving at least one dose of study drug who were eligible for DMEC-revised entry criteria, excluding those patients with progressive disease (PD) during cycle 1) – corresponding to the original primary analysis population.
2) non-evaluable population (patients with either (1) low platelet (≤75 x 109/L) or neutrophil (≤1.5 x 109/L) counts at baseline or on day 1 of cycle 1 or (2) evidence of disease progression prior to commencing cycle 2 of treatment).

3) non-evaluable due to progressive disease population (patients eligible for DMEC-revised entry criteria with evidence of disease progression prior to commencing cycle 2 of treatment).

4) study eligible population (all patients receiving at least one dose of study drug who were eligible for DMEC-revised entry criteria)

Additionally an intention to treat population was also summarised, including all patients who received at least one dose of study drug, regardless of eligibility criteria.

Analyses were initially performed for the per-protocol and non-evaluable populations. However, after further discussion with the Trial Management Group and the Data Monitoring and Ethics Committee, additional analyses were performed for the study eligible and intention to treat populations. For the purpose of publication of the trial results, and as summarised in this report, results focus on the per-protocol and ITT populations for the tolerability endpoint, and on the study eligible and ITT populations for the activity endpoints. The focus on the per-protocol population for tolerability allows assessment of the ability to deliver at least two cycles of treatment without dose-modifications due to BTD-related adverse reactions (ARs) only, i.e. in the absence of disease progression and in the population in which the treatment is intended based on the revised eligibility criteria. The focus on the study eligible and ITT populations for the activity endpoints provides a conservative assessment of the activity of the treatment.

Recruitment and patient characteristics

Between January 2011 and July 2012 a total of 95 patients were entered into the MUK one trial. A total of 66 patients were registered to the B60TD arm (1 patient withdrew prior to any treatment) and 29 to the B100TD arm. Numbers in each population are as follows:
ITT B60TD n=65, B100TD n=29; Study eligible B60TD n=54, B100TD n=20; per-protocol B60TD n=45, B100TD n=14; non-evaluable B60TD n=20, B100TD n=15; non-evaluable due to PD B60TD n=9, B100TD n=6.

Overall, the median number of previous lines of therapy was three (range 1 to 5), with 84% of patients (79/94) receiving ≥3 prior therapies. A total of 85% of patients (80/94) had performance status 0 or 1, and 22% (21/94) were refractory to last therapy. There were 37% of patients (35/94) with International Staging System stage 3 disease at entry, and mean β2-microglobulin level was 5.7 mg/L (range 1.5-22.2). Most patients had previously received thalidomide (90%, 85/94), lenalidomide (74%, 70/94) and bortezomib (84%, 79/94), and 74% (70/94) had received a prior autograft. Over 60% patients received both lenalidomide and bortezomib (66%, 62/94). Median follow-up was 8 months (inter-quartile range 4-11).

Endpoints

Tolerability

B60TD: Two patients were not assessable for tolerability; one patient could not be assessed due to an upper respiratory tract infection, and one through lack of adherence to protocol visits and followup. In the B60TD *per protocol population* 69.8% of patients (30/43, 80% CI [59.1-79.0]) received at least 2 cycles of treatment at full-dose with no more than a 2 week delay in the B60TD arm. The median number of treatment cycles received in the *per-protocol population* was 6 (range 1-9), with 64.4% (29/45) patients receiving at least 6 cycles, and 40.0% (18/45) of patients were able to receive 6 cycles with no dose reductions or delays. In the ITT population 57.1% of patients tolerated therapy according to the pre-specified protocol definition, with the minimum level of tolerability of 75% excluded from the upper limit of the 80% confidence interval [48.3-65.6].

B100TD: In the *per protocol population* (n=14) 71.4% of patients (10/14, 80% CI [50.8-86.9]) tolerated treatment. The median number of treatment cycles was 4 (range 1-9), with 28.6% (4/14) receiving at least 6 cycles and 14.3% (2/14) of patients able to receive 6 cycles with no dose reductions or delays, in the *per protocol population*. In the ITT population 51.7% of patients tolerated therapy according to the pre-specified protocol definition, with the

minimum target level of deliverability of 75% excluded from the upper limit of the 80% confidence interval [38.4-64.9].

Response

B60TD: In the *study eligible population* (n=54), 46.3% of patients (25/54, 80% CI [36.9-55.9]) achieved at least a PR, including 1 complete remission (CR) & 2 very good PR (VGPR); a further 8 patients achieved minimal response (MR). A total of 44/54 patients achieved at least stable disease. Median duration of response (time from PR to PD) in the B60TD *study eligible population* was 8.3 months (95% CI [5.2-11.0]). In the ITT population, 41.5% patients (27/65, 80% CI [33.2, 50.2]) achieved at least a PR.

B100TD*:* In the *study eligible population* (n=20) 25.0% of patients (5/20, 80% CI [12.7-41.5]) achieved at least a PR, including 1 CR. A further 2 patients achieved an MR and overall 11/20 patients achieved at least stable disease. Median duration of response in the B100TD *study eligible population* was 7.5 months (95% CI [3.0- 14.0]). In the ITT population 27.6% patients (8/29, 80% CI [16.8-40.9] achieved at least a PR.

Progression-free survival

Median PFS in the *study eligible population* was 7.5 months (95% CI 5.3-8.7) in the B60TD arm and 2.6 months (95% CI 1.7-5.6) in the B100TD arm (Appendix 2) with 12 months PFS of 18.7% (95% CI 9.1-31.0) and 10.0% (95% CI 1.7-27.2) respectively. In the *ITT population* median PFS was 6.5 months (95% CI 3.5-8.0) in the B60TD arm and 2.4 months (95% CI 2.0-5.2) in the B100TD arm with 12 months PFS of 15.5% (95% CI 7.6-26.1) and 6.9% (95% CI 1.2-19.8) respectively.

Toxicity

Toxicity data are summarised for all patients who received at least one dose of treatment and for whom AR data were received for at least one treatment cycle (B60TD n=64, B100TD n=28).

B60TD*:* Overall 33% of patients experienced ≥ grade 3 neutropenia, 31% ≥ grade 3 thrombocytopenia, and 22% ≥ grade 3 anaemia. There were 2 grade 3 neurotoxicities, and no grade 3-4 nausea nor GI disturbance. 39/65 (60%) patients in the B60TD arm experienced at least one serious adverse event. 21% of patients discontinued treatment due to toxicity.

B100TD*:* 64% of patients experienced ≥ grade 3 neutropenia, 43% ≥ grade 3 thrombocytopenia, and 36% ≥ grade 3 anaemia. There were 3 grade 3 neurotoxicities, no grade 3-4 nausea and 1 grade 3 diarrhoea. Thromboembolism rates were 4% overall. 15/29 (52%) patients experienced at least one serious adverse event. 24% of patients discontinued treatment due to toxicity.

Safety

There were no treatment related deaths. Overall there were 80 SAEs reported in 54 patients. 39/65 patients experienced an SAE in the B60TD arm and 15/29 patients experienced an SAE in the B100TD arm.

9. Conclusions

This study demonstrates that bendamustine at a dose of 60mg/m^2 days 1 and 8 is deliverable for repeated cycles in combination with thalidomide and dexamethasone, and active in heavily pre-treated myeloma patients with adequate haematological counts, despite a high proportion previously receiving multiple alkylators, bortezomib, lenalidomide &/or thalidomide. Although not passing strict pre-specified tolerability boundaries at final analysis, B60TD did show a PR rate in excess of 41%, and 12 month PFS rates of 15%,

demonstrating that re-treatment with thalidomide-containing combinations is deliverable & effective in the multiply-relapsed MM patient.

Clinical trials evaluating these combinations at an earlier stage of the disease should be evaluated in the future before myelosuppression limits the use of the combination, to optimise the benefit of this agent.

10. References

(1) Bryant J, Day R. Incorporating toxicity considerations into the design of two-stage phase II clinical trials. *Biometrics* 1995; 51(4):1372-1383.

(2) Sargent DJ, Goldberg RM. A flexible design for multiple armed screening trials. *Statistics in Medicine* 2001;(7):1051-1060.

(3) Durie, B.G., Harousseau, J.L., Miguel, J.S., Blade, J., Barlogie, B., Anderson, K., Gertz, M., Dimopoulos, M., Westin, J., Sonneveld, P., Ludwig, H., Gahrton, G., Beksac, M., Crowley, J., Belch, A., Boccadaro, M., Cavo, M., Turesson, I., Joshua, D., Vesole, D., Kyle, R., Alexanian, R., Tricot, G., Attal, M., Merlini, G., Powles, R., Richardson, P., Shimizu, K., Tosi, P., Morgan, G. & Rajkumar, S.V. International uniform response criteria for multiple myeloma. *Leukemia* 2006; 20, 1467-1473

(4) Dimopoulos, M., Spencer, A., Attal, M., Prince, H.M., Harousseau, J., Dmoszynska, A., San Miguel, J., Hellmann, A., Facon, T., Foa, R., Corso, A., Masliak, Z., Olesnyckyj, M., Yu, Z.N., Patin, J., Zeldis, J.B. & Knight, R.D. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *New England Journal of Medicine* 2007; 357, 2123-2132

(5) Weber, D.M., Chen, C., Niesvizky, R., Wang, M., Belch, A., Stadtmauer, E.A., Siegel, D., Borrello, I., Rajkumar, S.V., Chanan-Khan, A.A., Lonial, S., Yu, Z., Patin, J., Olesnyckyj, M., Zeldis, J.B. & Knight, R.D. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *New England Journal of Medicine*. 2007; 357, 2133-2142.

11. Publications

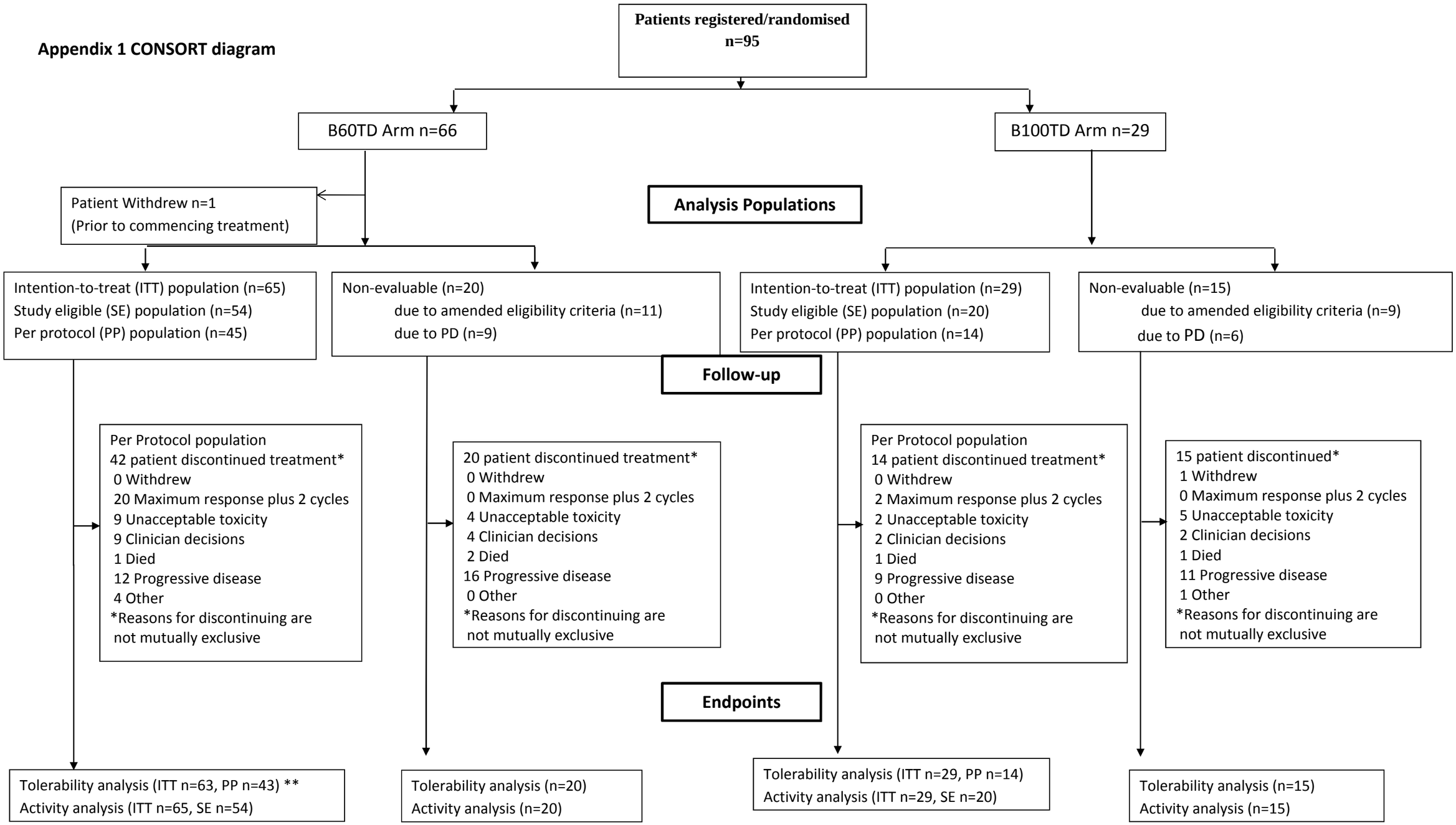
Bendamustine, thalidomide and dexamethasone combination therapy for relapsed/refractory myeloma patients: Results of the MUKone randomised dose selection trial, Steve Schey, Sarah R Brown, Avie-Lee Tillotson, Kwee Yong, Cathy Williams, Faith Davies, Gareth Morgan, Jamie Cavenagh, Gordon Cook, Mark Cook, Guillermo Orti, Curly Morris, Debbie Sherratt, Louise Flanagan, Walter Gregory and James Cavet, on behalf of the Myeloma UK Early Phase Clinical Trial Network. *Submitted to British Journal of Haematology*

12. Presentations

1. Identifying an optimally effective but tolerable dose of bendamustine in combination with thalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma S Schey, K Yong, C Williams, F Davies, G Morgan, J Cavenagh, G Cook, M Cook, AL Coney, S Brown, L Flanagan, W Gregory, J Cavet, on behalf of the Myeloma UK Early Phase Clinical Trial Network. Presented at the American Society of Hematology Annual Meeting 2013, New Orleans, USA

2. Identifying an optimally effective but tolerable dose of bendamustine in combination with thalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma
S Schey, K Yong, C Williams, F Davies, G Morgan, J Cavenagh, G Cook, M Cook, C Morris, AL Tillotson, S Brown, L Flanagan, W Gregory, J Cavet, on behalf of the Myeloma UK Early Phase Clinical Trial Network. Presented at the National Cancer Research Institute Cancer Conference 2014, Liverpool, UK

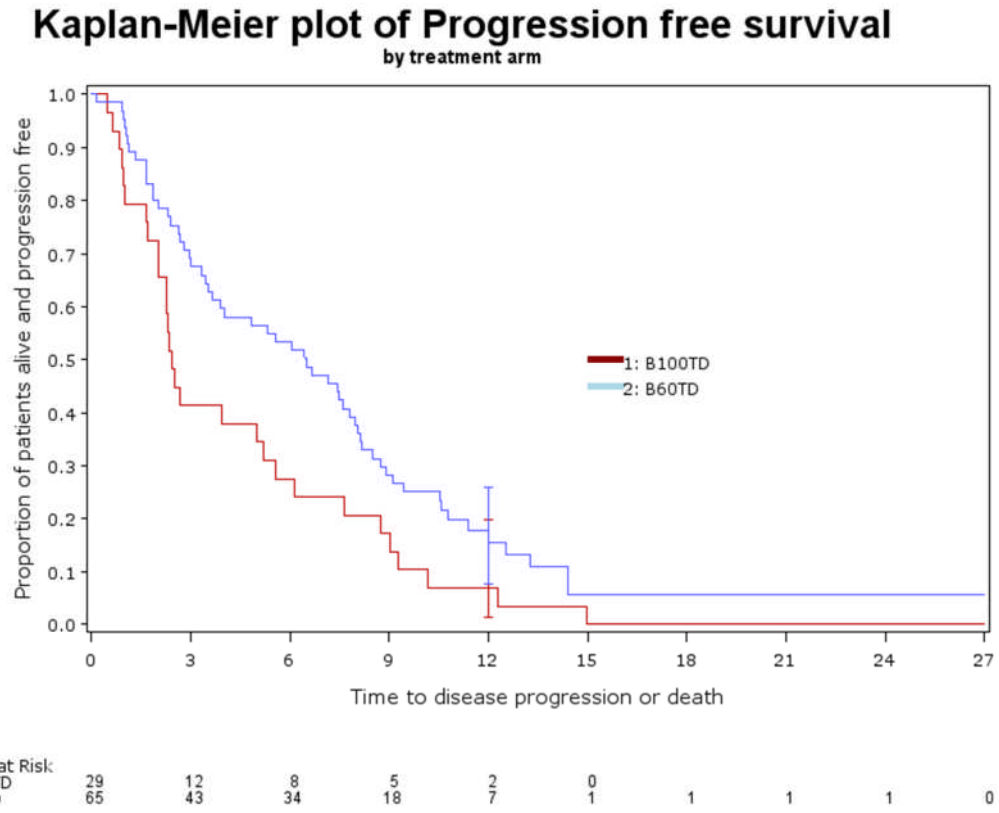
Appendix 1 CONSORT diagram



****There were 2 patients excluded from the primary deliverability analysis: One due to non-compliance to protocol, one due to a non-treatment related AE.**

Appendix 2 Progression free survival

a) ITT population



b) Study eligible population