Title: Bortezomib, Thalidomide, Dexamethasone plus Panobinostat (VTD-P) for patients with Relapsed Multiple Myeloma: results of the MUK six phase I/II Clinical Trial.

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Panel. Research in context

Evidence before this study

A search of PubMed for the terms “multiple myeloma”, “histone deacetylase inhibitor”” for clinical trials published between 1st July 2006 and 1st January 2013 was performed to provide evidence prior to the study. This revealed seven phase I/II trials specifically for patients with myeloma, including investigation of panobinostat as monotherapy and in combination with melphalan prednisolone and thalidomide. A number of other HDAC inhibitors were also investigated; however, none of them demonstrated clinically significant activity for myeloma. The PANORAMA 2 trial (see below) had commenced before this study started enrolment.

Added value of this study

The MUK-six trial demonstrated the safety and activity of panobinostat in a four drug combination for patients with relapsed myeloma. Since this trial started there had been further publications to that described above. The included the pivotal phase III trial (PANORAMA 2) of bortezomib (Velcade), dexamethasone plus panobinostat (VD-P) versus bortezomib dexamethasone and placebo for relapsed myeloma. A separate publication of the predefined sub-set analysis led to panobinostat approval in the US and Europe. Other published trials included VD-P for newly diagnosed patients which was halted due to a lack of efficacy and increased toxicity (used bi-weekly intravenous bortezomib), a Phase I/II of panobinostat with carfilzomib and dexamethasone and the phase I study to determine the recommended dose of panobinostat for bortezomib combinations. The PANORAMA 1 phase II trial (VD-P) reported the efficacy of VD-P in patients with relapsed and bortezomib refractory myeloma with a response rate of 34·5%. However, the VD-P regimen in the PANORAMA 2 trial was associated with significant gastrointestinal toxicity which was partly attributed to the use of bi-weekly intravenous bortezomib. The MUK-six study incorporated weekly subcutaneous bortezomib plus low dose thalidomide with panobinostat. The results described in this paper demonstrated high efficacy and good tolerability.

Implications of all the available evidence

Panobinostat represents a new class of anti-myeloma therapy that has gained FDA and EMEA approval for patients following two or more prior lines of therapy including bortezomib and an immunomodulatory agent. This was based on the sub-group analysis of the phase III PANORAMA 2 trial. The MUK-six trial predominantly included patients at first relapse and adds to the evidence that a panobinostat and proteasome inhibitor combination can be safely and effectively delivered, particularly earlier in the treatment pathway to that currently indicated.

Abstract

Background: Panobinostat (pan-deacetylase inhibitor) is approved in combination with bortezomib and dexamethasone for patients with relapsed multiple myeloma. The MUK six trial investigated the safety and efficacy of panobinostat with sub-cutaneous weekly bortezomib, thalidomide and dexamethasone (VTD-P).

Methods: This phase I/II trial enrolled patients with relapsed myeloma that were ≥18 years, had an Eastern Cooperative Oncology Group performance status of ≤2 and previously received 1-4 prior lines of therapy. The primary objective was to determine the maximum tolerated dose (MTD), recommended dose of panobinostat with VTD and to estimate the overall response rate within 16 cycles at the recommended dose. A rolling six escalation design was used to determine the MTD and the intention-to-treat population used to derive response rates. Panobinostat was administered days 1, 3, 5, 8, 10 and 12 with bortezomib 1·3mg/m^2 days 1, 8; thalidomide 50-100mg daily and dexamethasone 20mg days 1, 2, 8 and 9 every 21 days for up to 16 cycles then up to one year panobinostat maintenance. Patients were permitted to come off study for autologous stem cell transplant (ASCT). This trial has closed to recruitment and is registered at ClinicalTrials.gov, number NCT02145715.

Findings: 57 patients enrolled with a median of one prior therapy (80·2% at first relapse), 46 at the recommended dose (intention-to-treat population). One dose limiting toxicity was reported, hence the MTD was not reached. The recommended dose of panobinostat was 20mg. The overall response rate (primary endpoint) was 91·3% (80% CI 83·4-96·2); CR 3(6·5%), VGPR 18(39·1%), PR 21(45·7%), MR 2(4·3%), SD 2(3%) and independent of prior bortezomib. Most AEs grade 1-2 with low rates of grade 3-4 diarrhoea/ fatigue. The commonest ≥grade 3 toxicities (safety population) were neutrophil count reduced (15, 26·4%), hypophosphatemia (11, 19·3%), platelet count decreased (8, 14·1%). 46 serious adverse events were reported in 27 patients.

Interpretation: VTD-P is an efficacious and well tolerated regimen for relapsed multiple myeloma and has clinical utility either as re-induction to ASCT or as an alternative schedule for relapsed refractory patients. Weekly sub-cutaneous bortezomib may have improved the tolerability compared with the PANORAMA 1 trial resulting in fewer discontinuations for toxicity.

Funding: Novartis, Myeloma UK

Introduction

Proteasome inhibitor and immunomodulatory (IMiD) agents have become standard therapy for patients with multiple myeloma. The combination of these two classes of drugs is highly effective and bortezomib (Velcade), thalidomide and dexamethasone (VTD) is commonly used as induction prior to autologous stem cell transplantation (ASCT)[2, 3], and as an effective salvage regimen at relapse achieving ≥ partial response (PR) rates of 63%[4]. Panobinostat (P), a pan histone deacetylase (HDAC) inhibitor was recently licensed in combination with bortezomib and dexamethasone for patients who have received two or more prior lines of therapy including bortezomib and IMiD, based upon sub-group analysis of the PANORAMA 1 Phase 3 clinical trial[5]. Whilst those treated with panobinostat had a superior response rate (≥PR 58·9% vs 39·2%) and progression-free survival (PFS) (12·5 vs 4·7 months) to those receiving placebo, they also experienced increased toxicities particularly gastrointestinal (grade 3-4: diarrhoea 33% vs 15%, nausea 11% vs 1%) and asthenia (grade 3-4: 26% vs 14%). Notably, the PANORAMA 1 trial[1] utilised intravenous bortezomib administered twice weekly, whereas common practice evolved to use sub-cutaneous bortezomib and many use a weekly schedule.

We therefore designed the MUK six trial to improve the tolerability of the VD-P combination and investigate efficacy by incorporating low dose thalidomide and reducing the frequency of bortezomib administration. The aim of this phase I/II trial was to determine the maximum tolerated dose (MTD) of panobinostat when given with VTD (with subcutaneous bortezomib) in patients with relapsed or relapsed and refractory multiple myeloma, and determine the overall response rate within 16 cycles of VTD-P.

Methods

Study Design and Participants

MUK six was a multi-centre open label phase I/II trial run through the Myeloma UK Clinical Trials Network, for patients with relapsed or relapsed/ refractory multiple myeloma by International Myeloma Working Group (IMWG) criteria[6] who had received between one and four prior lines of therapy.

Patients ≥18 years were eligible with measureable disease (by IMWG consensus criteria[6]), an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, neutrophils ≥1·0 x 10^9/L, platelets ≥100 x 10^9/L, haemoglobin ≥80g/L, serum creatinine ≤2·0 x upper limit of normal, adequate liver function and an anticipated survival of at least 3 months. Exclusion criteria included anti-myeloma therapy within 28 days of treatment (except dexamethasone 160mg >48 hours prior to treatment),

refractory to bortezomib as per consensus criteria (progressed on therapy or <60 days/ achieved <minor response (MR)[6]), peripheral neuropathy >grade 2 or >grade 1 with pain, or significant cardiovascular disease. Following informed consent patients were registered via the University of Leeds Clinical Trials Research Unit. The study was approved by the UK national ethics committee and the Medicines and Healthcare Products Regulatory Agency (MHRA).

Procedures

Patients received bortezomib 1·3mg/m^2 subcutaneously on days 1, 8; thalidomide 100mg orally daily (50mg if baseline peripheral neuropathy), dexamethasone 20mg orally days 1, 2, 8, 9; panobinostat days 1, 3, 5, 8, 10, 12 every 21 days (Appendix Page 1). In the absence of disease progression or unacceptable toxicity, patients continued VTD-P for 16 cycles. This schedule was based upon "Treatment phase 2" of the PANORAMA 1 trial[1]. Those eligible for ASCT were treated to maximum response plus two cycles (minimum six). Those completing 16 cycles of VTD-P could receive panobinostat monotherapy (at the same dose as the current dosing level or escalated to a level deemed safe using the same schedule as induction) for up to one year. Those undergoing ASCT were considered off study and not eligible for maintenance. Supportive care was as per institutional practice.

A rolling six design[7] (Appendix Page 5) was used to determine the maximum tolerated dose (MTD) of panobinostat beginning at dose level 1 and dose limiting toxicities (DLTs) assessed during the first 21 days of VTD-P. The Dose Escalation Review Group (DERG), comprising all principal investigators and at least one independent member, reviewed safety data throughout and decided cohort dose escalations. The recommended dose was the highest dose level at which ≤1 out of six patients experienced a DLT. DLTs were: total bilirubin ≥grade 3 failing to return to grade 1 within 7 days, any other non-haematological toxicity ≥grade 3 failing to return to ≤grade 1 or baseline within seven days (except nausea, vomiting, diarrhoea and electrolyte imbalances), grade 4 neutropenia ≥7 days, grade 4 neutropenia with sepsis, any grade 4 thrombocytopenia failing to return to Grade 2 within seven days, prolongation of QTc ≥Grade 3, and treatment related death. The MTD was defined as the highest dose level at which at least two of up to six patients experienced a DLT during the first cycle.

Dose delays and modifications were as per trial protocol. Response and disease progression assessments were performed locally by Modified IMWG Uniform Response Criteria[6, 8, 9] and also performed by clinicians independently without knowledge of the investigator-reported responses for quality assurance. The primary endpoints were centrally reviewed by the Sponsor.

Adverse events (AEs) and serious AEs were reported according to National Cancer Institute Common Toxicity Criteria for Adverse Events version 4·0. A 12 lead electrocardiogram was performed on day 1 on each cycle and cytogenetic information obtained from CD138 selected cells according to local practice. Adverse fluorescence in situ hybridization (FISH) was defined as the presence of one or more of: gain(1q), del(p17q), t(4;14), t(14;16) and t(14;20)[10].

Outcomes

The trial had two parts. The primary endpoint in the dose escalation phase was to determine the MTD and recommended dose and in the dose expansion phase to estimate the response rate (≥PR) within 16 cycles at the recommended dose. Secondary objectives included safety profile of VTD-P, to estimate the proportion of participants with each maximum response category within 16 cycles, time to maximal response, PFS, treatment compliance and feasibility of panobinostat maintenance.

Statistical Analysis

For the expansion phase, forty two patients, including six patients from the escalation phase, were deemed sufficient to estimate activity of the recommended dose (≥PR). This gave 80% power to observe at least a 78% response rate and rule out a rate of <63% at the 1-sided 10% significance level using A'Hern's exact single stage design[11]. At least 31/42 responses were required to rule out the lower limit response rate of 63%, which was based upon data for VTD[4] assuming a heterogeneous population with 1-4 prior lines.

Safety data is for all that received at least one dose of any trial treatment (safety population). The primary analysis population to determine the recommended dose of panobinostat was initially defined as patients receiving ≥1 cycle, missing no more than 1 dose of bortezomib, 3 of thalidomide, 1 of dexamethasone or 1 of panobinostat (evaluable population). However this was felt not to reflect an overall realistic estimate of activity in this population. Before analysis and in discussion with the Trial Steering Committee, the primary analysis population was revised to the ITT population (received ≥1 dose of panobinostat at the recommended dose). This population was used for all efficacy and compliance endpoints. The recommended dose cohort included all patients registered to escalation or expansion phases and treated at the recommended dose of panobinostat.

There was no formal statistical testing. Percentages were calculated using the total number of patients in the appropriate population as the denominator. Confidence intervals (CI) were calculated using the Clopper-Pearson method, PFS and time to maximum response used the Kaplan Meier method with patients censored at the point last known to be alive and progression free. ASCT

patients were censored at time of ASCT for analyses including all patients. All statistical analyses were performed with SAS statistical software version 9.4.

This trial was registered as an International Standard Randomised Controlled Trial with ClinicalTrials.gov, number ISRCTN59395590, NCT02145715.

Role of Funding Source

The funder, Myeloma UK, conducted independent review of the study proposal, attended Trial Management Group and DERG meetings. Novartis provided panobinostat, funding to Myeloma UK, attended DERG meetings to provide safety updates on panobinostat, but had no involvement in the design, conduct, analysis or interpretation. The Sponsor had no involvement in the design, conduct, analysis or interpretation of the study. The corresponding author had full access to the data and is responsible for manuscript submission.

Results

The trial registered 67 patients across four sites between 31st January 2013 and 30th October 2014 (Appendix page 2). 57 eligible patients that received ≥ one dose of drug were included in the safety population. Of the ten patients not eligible, nine did not meet the entry criteria and one withdrew consent. The dose escalation phase comprised 16 patients. Seven were registered to the 10mg cohort with six evaluable for DLTs; three patients registered to the 15mg cohort, all evaluable for DLTs; and six patients registered to the 20mg cohort and evaluable for DLTs (Figure 1). There was one DLT of grade 3 hyponatremia (unrelated to study drugs, due to high paraprotein) reported at 20mg of panobinostat and consequently the MTD of panobinostat was not reached. The recommended dose of panobinostat was taken at 20mg.

The ITT population comprised 46 patients treated at the recommended dose, and the evaluable population 39 patients. Baseline demographics are in Table 1. The median number of prior therapies was one (range 1-4) and 59% had received prior ASCT, 80% had received only one prior therapy. 72% of patients had prior bortezomib, 52% prior Immunomodulatory agent (IMiD), and 17% ≥ two prior lines of therapy including bortezomib and an IMiD (population approved for panobinostat in Europe). Patients received a median of 10 cycles of treatment and 24 patients (51·%) came off study following a median of 8 (range 6-16) cycles to proceed to ASCT. Overall, twenty (35·1%) patients completed 16 cycles and 15 (26·3%) received panobinostat maintenance. Nine (15·8%) stopped study treatment due to disease progression, one died on study due to an unrelated event (sickle cell crisis) and 3 (5·3%) withdrew consent due to toxicity. At the time of final analysis six patients had

died: two due to multiple myeloma, two due to unspecified abdominal causes, one due to cerebrovascular disease and another from a secondary malignancy.

The overall response rate for patients treated at the recommended dose (ITT population n=46) was 91·3% (80% CI 83·4-96·2); Table 2 shows breakdown by maximum response and an exploratory analysis of varying subgroups. The depth of response was higher for those treated at first relapse than those at later stages (≥VGPR: 1 prior line, 54·7% (n=37) vs >1 prior line, 11·1% (n=9)). For those with ≥2 prior lines including bortezomib and IMiD ≥VGPR was 12·5% (n=8). Responses were similar according to prior bortezomib exposure (≥VGPR: 45·5% (n=33) vs 46·2% (n=13)) and slightly lower with prior IMiD exposure (≥ VGPR 37·5% (n=24) vs 54·5% (n=22)). VGPR and above rates were slightly lower for those with one or more adverse FISH lesions[10] (42·9% adverse FISH (n=21) vs 52·2% Standard FISH (n=23)); however the overall response rate was similar. Only two patients had a 17p deletion and both responded (1 PR, 1 VGPR). The independently assessed responses were very similar to the investigator assessed responses. The median time to maximal response was 2·46 months (95% CI 1·91-3·52) with responses deepening with treatment duration (median time to ≥ VGPR 3·71 months; median time to MR/PR 1·84 months).

Median PFS was 15·6 months (95% CI 13·4-20·47; IQR 13·4, 20·47) and 12 month PFS was 75·4% (95% CI 56·7-86·8). PFS at 12 months was 91·3% for those patients who underwent ASCT (n=24, median not yet reached; IQR 17·90, not reached) and 66·1% for those that did not (n=22, median PFS 14·1 months (95% CI 7·0-16·10; IQR 7·0, 18·79)) (figure 2, sub-group demographics shown in Appendix page 3). Median overall survival (OS) was not reached, with a median follow-up of 15·0 months (IQR 10.2, 17.9).

For those treated at the recommended dose, the actual mean panobinostat dose administered (excluding maintenance) was 17·2mg (86·2% of the 20mg planned dose). Nineteen (41·3%) patients required at least one dose reduction and five (10·9%) received at least one cycle without panobinostat. The reasons for dose reductions were: ≥grade 2 non-haematological toxicity (8/19, 42·1%), AST/ALT levels ≥ 5 x upper limit (3/19, 15·8%), grade 3-4 haematological toxicity (5/19, 26·3%), other (10/19, 52·6%). Seven (15·2%) patients received at least one dose reduction due to a GI toxicity. Twenty (43·5%) patients required a dose reduction in thalidomide and this was proportionally more for those starting at 100mg thalidomide (10, 52·6%) compared with those starting at 50mg (10, 37%). Overall, the actual overall dose administered was 79·3% of that intended with those starting at 50mg receiving a mean dose of 41·4mg and those at 100mg received a mean of 72·9mg. Only six (13·3%) patients required a dexamethasone dose reduction with a mean dose of 18·7mg (90·4% of the intended 20mg) administered. Bortezomib compliance was good with only five

(10·9%) patients requiring a dose reduction. A mean of 1·2 mg/m^2 (95·0% of the intended 1·3mg /m^2) was administered.

Adverse events reported in ≥10% of patients irrespective of causality are detailed in Table 3. The commonest ≥grade 3 toxicities in the safety population (n=57) were neutrophil count reduced (26·4%), hypophosphatemia (19·3%), platelet count decreased (14·1%), raised alanine aminotransferase (7·0%), diarrhoea (7·0%, grade 3 only) and upper respiratory tract infection (7·0%). The commonest all grade toxicities were fatigue (89·5%) peripheral sensory neuropathy (77·2%), diarrhoea (66·7%), constipation (63·2%), bone pain (61·4%) and nausea (45·6%); however, these were predominantly grade 1-2. 46 serious adverse events (SAEs) were reported in 27 patients. 7 of the 14 (50%) SAEs suspected to be related to trial medication were gastrointestinal disorders.

Fifteen patients received panobinostat maintenance following completion of 16 cycles of VTD-P, of which four are ongoing at the time of analysis. The mean number of cycles of maintenance received at the time of the analysis was 9·3 (range 3-16). four patients (26·7%) completed one year of maintenance, six stopped due to disease progression and one withdrew consent for further treatment due to predominantly gastrointestinal toxicity. Four patients reduced the panobinostat dose due to diarrhoea; no dose reductions occurred after cycle 4. The mean dose of panobinostat received was 16·5mg.

Discussion

This phase I/II study demonstrated that panobinostat at 20mg can be safely given in combination with VTD for patients with relapsed MM. Response rates were high (ORR 91%, ≥ VGPR 45·6%) and similar by prior bortezomib exposure, showing effectiveness for those that were previously treated with bortezomib. As the trial excluded those refractory to bortezomib, the potential ability of panobinostat to overcome bortezomib resistance cannot be commented upon. Those treated earlier in their disease responded better than those at later relapse (≥VGPR rates: 54·1% (1 prior line) vs 11·1% (≥2 prior lines)). Whilst the numbers in the ≥2 prior lines including bortezomib and IMiD sub-group are small (n=8), it is interesting that 75% achieved ≥PR (PANORAMA 1 trial sub-group analysis ≥PR 58·9% (n=73)[5]). The VGPR rates reported here were high; however the CR rates (8.1% for 1st relapse) were lower than expected (MMVAR-IFM trial 28%[12]). This may be due to many bone marrow biopsies not performed to confirm CR, and a significant proportion of patients completing study early (median cycle 6 out of a possible 16) for ASCT. Of note the MUK-six trial used Modified International Myeloma Working Group Uniform Criteria for response assessment whereas the PANORAMA 1 trial used modified European Group for Blood and Marrow Transplantation criteria.

Hence any cross trial comparison is limited. As two doses of s.c. bortezomib were administered per cycle, the tolerability was good and patients remained on study deepening response with time, in fact one patient achieved a VGPR after cycle 11. Treatment was well tolerated with only two patients withdrawing consent due to toxicity (PANORAMA 1, 36% patients discontinued due to adverse events[1]). The majority of AEs were grade 1-2 with low rates of grade 3-4 diarrhoea and fatigue. Panobinostat maintenance was well tolerated and feasible. Fifteen patients commenced maintenance with four ongoing at the time of this report. Four patients completed 16 cycles of maintenance, but the median dose delivered fell with duration (20mg at start of maintenance, 12·5mg at cycle 16) mainly due to diarrhoea. The impact of maintenance cannot be determined due to a lack of comparator.

Whilst the outcomes for patients with relapsed multiple myeloma continue to improve[13], there is a need for new effective classes of drugs. HDAC inhibitors have alternate mechanisms of cytotoxicity to proteasome inhibitors and IMiDs and demonstrate synergy in pre-clinical models[14]. The phase III PANORAMA 1 study demonstrated an improvement in PFS for those treated with panobinostat, particularly patients with two or more prior lines of therapy including a proteasome inhibitor and IMiD[1, 5]. These patients otherwise have a poor prognosis with a median PFS of 4·7 months with VD. However, the tolerability of the VD-P regimen could be improved. This study suggests that the 4 drug combination was tolerable with a lower proportion of grade 3-4 toxicities than the PANORAMA 1 study, particularly diarrhoea and fatigue. It is postulated that the weekly s.c. administration of bortezomib with only 2 doses per 3 weeks improved the overall toxicity profile. The incorporation of low dose thalidomide (≤100mg) is likely to have increased the efficacy and may in fact have reduced the incidence of diarrhoea. The rate of grade 3-4 peripheral neuropathy was low reflecting a low intensity bortezomib and thalidomide schedule.

The primary endpoint was planned to be compared to a study of patients treated with VTD that had at least two prior lines of therapy[4]. This was no longer appropriate as 80% of patients enrolled had one prior line of therapy probably due to evolving practice of panobinostat use earlier in the treatment pathway. The response rates would therefore need to be compared to a more appropriate population such as the MMVAR-IFM 2005-04 trial comparing VTD with TD for patients at first relapse following previous ASCT[12] which reported an ORR for VTD of 87%, ≥VGPR 56%, (MUK six 1st relapse: ORR 94·6%, ≥VGPR 54·1%). However, there were differences in the patient groups: all were bortezomib naïve, none were refractory to therapy, all had received previous ASCT (MUK six: 59% prior ASCT) and received a total of 48 doses of V (MUK six: 32 doses of V).

Panobinostat has also been combined with carfilzomib in a four weekly schedule with a rest week between the two weeks of panobinostat[15]. This schedule was well tolerated and resulted in an ORR of 67% in a more heavily pre-treated population (median of five prior lines). However, whilst the MTD was determined to be 30mg, the authors recommended the 20mg dose should be investigated further. In comparison to many other new treatments, VTD is comparatively cost-effective, therefore the VTD-P regimen is likely to be an attractive treatment option in a real world setting where funding is rationed. Other DACs are also under investigation[16-19]. Vorinostat with bortezomib was investigated in a randomised phase III trial for relapsed multiple myeloma. The improvement in PFS for the combination over bortezomib monotherapy was not clinically relevant[18]. Early data for Ricolinostat (a selective HDAC 6 inhibitor) in combination with bortezomib suggested efficacy and tolerability[19].

As the treatment paradigm for multiple myeloma continues to evolve and new classes of drugs are approved, it remains crucial to maintain long term tolerability with multi-agent regimens. The MUK six trial demonstrated an efficacious and well tolerated four drug schedule for a new class of agent, panobinostat in combination with VTD for patients with relapsed multiple myeloma.

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Declaration of Interests:

RP reports personal fees from Janssen, Novartis outside the submitted work; LF reports grants from Myeloma UK, non-financial support from Novartis, during the conduct of the study; MS has nothing to disclose; AH reports grants from Myeloma UK, non-financial support from Novartis, during the conduct of the study; BK has nothing to disclose; GC reports grants and personal fees from Janssen, grants and personal fees from Celgene, outside the submitted work; EL reports grants from Novartis; WG reports personal fees from Celgene, Janssen, grants from Myeloma UK, non-financial support from Novartis, outside the submitted work; SB reports grants from Myeloma UK, HO reports personal fees and non-financial support from Novartis, Celgene, Janssen, during the conduct of the study; KY reports grants from Celgene outside the submitted work; JC reports personal fees from Janssen, Celgene, Novartis, outside the submitted work; .

Authorship contributions

JC, SB, EL, WG, KY designed the research; RP, JC, BK, MS, KY, GC performed the research and collected data; SB, AH performed statistical analyses; JC, RP, SB, AH, LF reviewed the trial report and interpreted data; LF performed trial and data management; RP, AH, SB wrote the manuscript; All authors reviewed the manuscript.

Table 1: Baseline demographics and treatment characteristics

Demographic	All patients (safety population N=57) n (%)	Intent-to-treat population (N=46) n (%)
Age/ yrs		
Median (IQR)	61 (52, 66)	60·5 (51, 66)
Sex		
Male	34 (60%)	27 (59%)
Female	23 (40%)	19 (41%)
ECOG Performance Status		
0	26 (46%)	22 (48%)
1	26 (46%)	21 (46%)
2	3 (5%)	2 (4%)
Missing	2 (4%)	1 (2%)
ISS		
1	32 (56%)	28 (61%)
2	16 (28%)	13 (28%)
3	6 (11%)	3 (7%)
Missing	3 (5%)	2 (4%)

Prior Lines		
1	43 (75%)	37 (80%)
2	6 (11%)	5 (11%)
3	5 (9%)	1 (2%)
4	3 (5%)	3 (7%)
Prior bortezomib		
No	19 (33%)	13 (28%)
Yes	38 (67%)	33 (72%)
Prior IMiD		
No	23 (40%)	22 (48%)
Yes	34 (60%)	24 (52%)
Received at least 2 prior lines including bortezomib and IMiD		
No	45 (79%)	38 (83%)
Yes	12 (21%)	8 (17%)
Prior autologous stem cell transplant		
No	21 (37%)	19 (41%)
Yes	36 (3%)	27 (9%)
Time from diagnosis to registration		

(months)*		
Median (IQR)	3 (26, 59)	31 (26, 54)
Missing**	10 (18%)	8 (17%)

* data includes partial dates

**For partial dates, the missing days and months were set to 15 and 06 respectively

Table 2: Best Responses

	ORR ≥PR n (%)	≥ VGPR n (%)	CR n (%)	VGPR n (%)	PR n (%)	MR n (%)	SD or NC n (%)
ITT (N=46)	42 (91·3)	21 (45·7)	3 (6·5)	18 (39·1)	21 (45·7)	2 (4·3)	2 (4·3)
1 prior line (N=37)	35 (94·6)	20 (54·1)	3 (8·1)	17 (45·9)	15 (40·5)	0 (0·0)	0 (0·0)
>1 prior lines (n=9)	7 (77·8)	1 (11·1)	0 (0·0)	1 (11·1)	6 (66·7)	2 (22·2)	0 (0·0)
Prior BZ (N=33)	30 (90·9)	15 (45·5)	2 (6·1)	13 (39·4)	15 (45·5)	2 (6·1)	1 (3·0)
BZ naïve (N=13)	12 (92·3)	6 (46·2)	1 (7·7)	5 (38·5)	6 (46·2)	0 (0·0)	1 (7·7)
Prior IMiD (N=24)	21 (87·5)	9 (37·5)	1 (4·2)	8 (33·3)	12 (50·0)	2 (8·3)	1 (4·2)
IMid naïve (N=22)	21 (95·5)	12 (54·5)	2 (9·1)	10 (45·5)	9 (40·9)	0 (0·0)	1 (4·5)
≥2 prior lines including BZ and an IMiD (N=8)	6 (75·0)	1 (12·5)	0 (0·0)	1 (12·5)	5 (62·5)	2 (25·0)	0 (0·0)
Standard FISH (N=23)	21 (91·3)	12 (52·2)	2 (8·7)	10 (43·5)	9 (39·1)	1 (4·3)	1 (4·3)
Adverse FISH	20 (95·2)	9 (42·9)	1 (4·8)	8 (38·1)	11 (52·4)	1 (4·8)	0 (0·0)

(N=21)							

BZ=Bortezomib, ITT=Intention to treat population, IMiD=Immunomodulatory agent; FISH=fluorescence in-situ hybridisation. 80·4% of investigator and independently assigned responses matched exactly. No results differed by more than one response level.

Table 3: Adverse Events (safety population n=57)

Adverse event	**Total (n, %)**	**Grade 1-2 (n, %)**	**Grade 3 (n, %)**	**Grade 4 (n, %)**	**Grade 5 (n, %)**
Fatigue	51 (89·5)	49 (86·)	2 (3·5)		
Peripheral sensory neuropathy	44 (77·2)	44 (77·2)			
Diarrhea	38 (66·7)	33 (57·9)	4 (7·0)		
Constipation	36 (63·2)	36 (63·2)			
Bone pain	35 (61·4)	33 (57·9)			
Nausea	26 (45·6)	26 (45·6)			
Back pain	25 (43·9)	25 (43·9)			
Upper respiratory infection	24 (42·1)	18 (31·6)	4 (7·0)		
Edema limbs	23 (40·4)	23 (40·4)			
Neutrophil count decreased	22 (38·6)	7 (12·3)	12 (21·1)	3 (5·3)	
Tremor	22 (38·6)	21 (36·8)	1 (1·8)		
Anemia	21 (36·8)	18 (31·6)	3 (5·3)		
Dyspnea	20 (35·1)	18 (31·6)	1 (1·8)		
Hypophosphatemia	19 (33·3)	8 (14·0)	10 (17·5)	1 (1·8)	
Platelet count decreased	19 (33·3)	11 (19·3)	3 (5·3)	5 (8·8)	
Somnolence	19 (33·3)	19 (33·3)			
Dizziness	18 (31·6)	17 (29·8)			
Creatinine increased	16 (28·1)	15 (26·3)	1 (1·8)		
Myalgia	15 (26·3)	15 (26·3)			
Cough	14 (24·6)	14 (24·6)			
Rash maculo-papular	14 (24·6)	14 (24·6)			
Anorexia	12 (21·1)	12 (21·1)			
Dysgeusia	11 (19·3)	11 (19·3)			
Fever	11 (19·3)	9 (15·8)	1 (1·8)		
Hypocalcemia	11 (19·3)	11 (19·3)			
Vomiting	10 (17·5)	8 (14·0)	2 (3·5)		
Sinus bradycardia	9 (15·8)	9 (15·8)			
Abdominal pain	8 (14·0)	6 (10·5)			1 (1·8)
Alanine aminotransferase increased	8 (14·0)	4 (7·0)	2 (3·5)	2 (3·5)	
Insomnia	8 (14·0)	8 (14·0)			
Hypomagnesemia	7 (12·3)	7 (12·3)			
Weight loss	7 (12·3)	7 (12·3)			

Adverse event	Total (n, %)	Grade 1-2 (n, %)	Grade 3 (n, %)	Grade 4 (n, %)	Grade 5 (n, %)
White blood cell decreased	7 (12·3)	7 (12·3)			
Agitation	6 (10·5)	6 (10·5)			
Alopecia	6 (10·5)	6 (10·5)			
Dyspepsia	6 (10·5)	5 (8·8)			

*Includes patients where AE reported but grade unobtainable, hence the numbers reported as grade 1-4 do not necessarily add up to the total.

Figure 1: CONSORT diagram

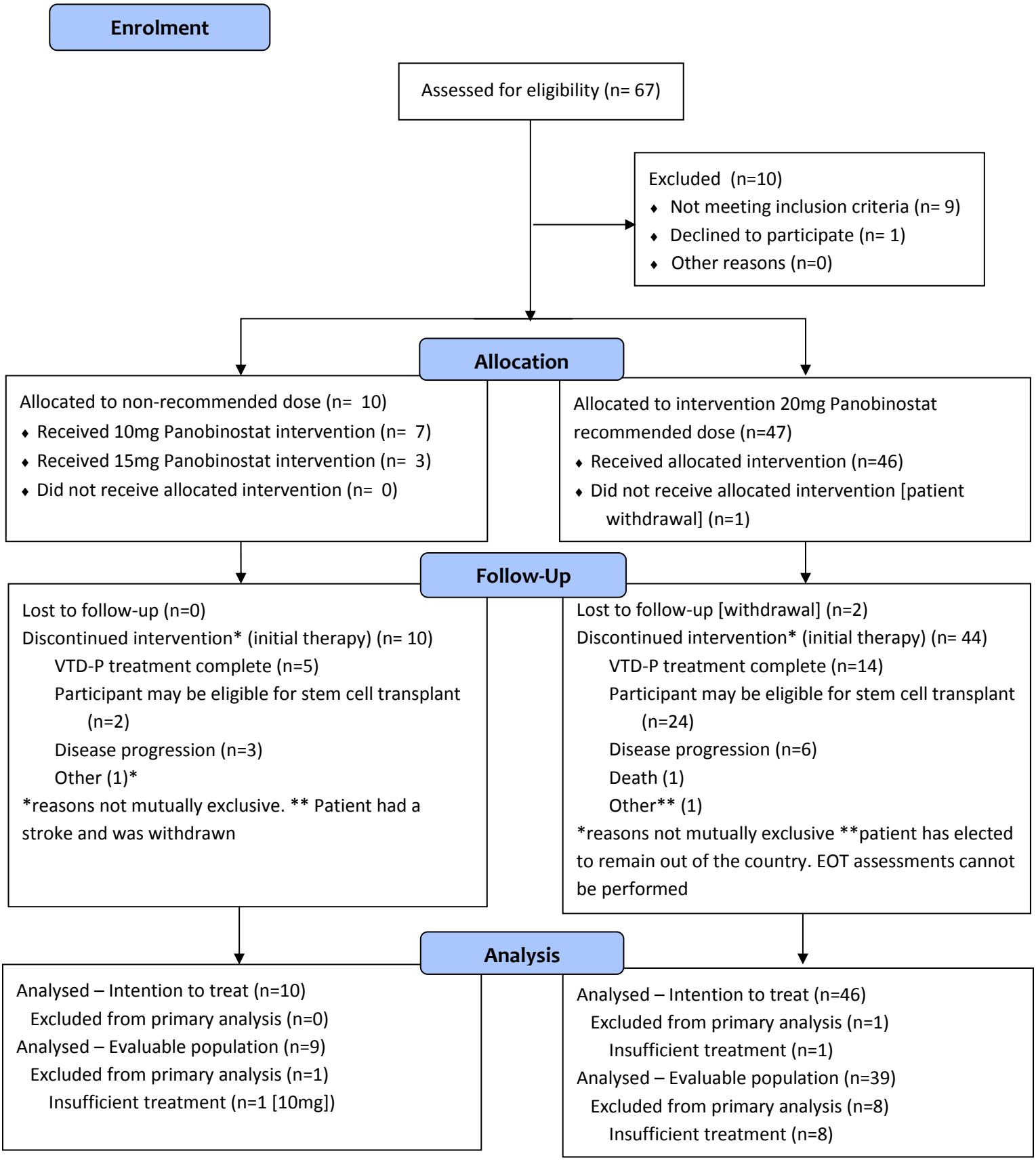
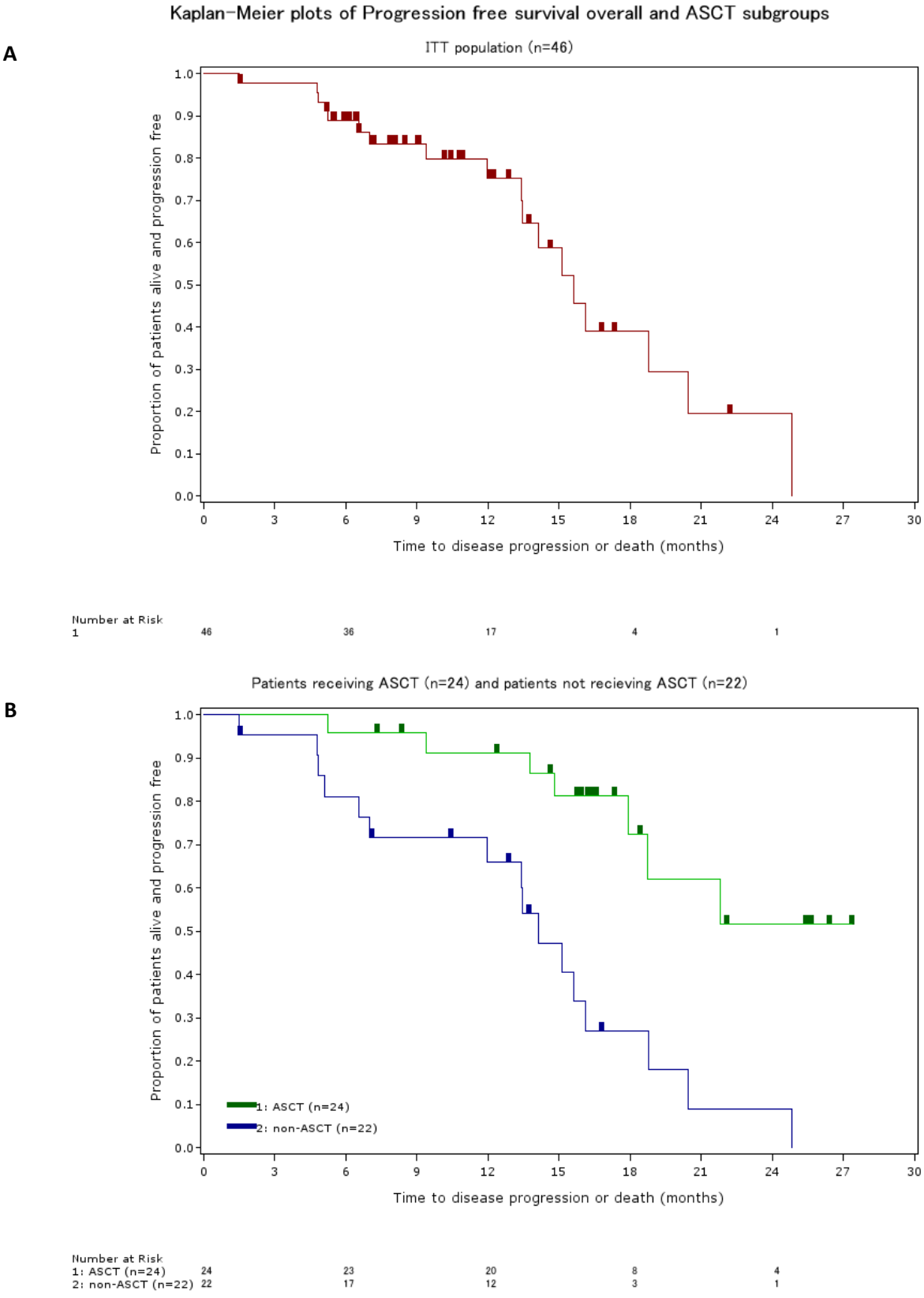


Figure 2: Kaplan-Meier plots of PFS for (A) ITT population, (B) split according to recieved ASCT or not



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