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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 (298, maximum 300)

Background: Panobinostat is a pan-deacetylase inhibitor which in combination with bortezomib and dexamethasone is approved for patients with relapsed multiple myeloma (MM). The MUK six trial investigated panobinostat with bortezomib, thalidomide and dexamethasone (VTD-P) for patients receiving 1-4 previous lines of therapy.

Methods: This multi-centre phase I/II trial aimed to determine the maximum tolerated dose (MTD) and recommended dose (RD) of panobinostat with VTD in an escalation phase, utilising a rolling six design and to estimate the response rate at the RD in an expansion phase. 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. Patients could receive up to 16 cycles of VTD-P then up to one year panobinostat maintenance. www.clinical trials.gov (NCT02145715), ISRCTN59395590.

Findings: 57 patients were enrolled with a median of one prior lines of therapy (80·2% at first relapse). 46 were treated at the RD (intention-to-treat population). One dose limiting toxicity was reported, hence the MTD was not reached and the RD of panobinostat was 20mg. The overall response rate (primary endpoint) was 91·3% (95% CI 79·2%-97·6); CR 3(6·5%), VGPR 18 (39·1%), PR 21 (45·7%), MR 2 (4·3%), SD 2 (3%) and was independent of prior bortezomib. The overall median PFS (secondary endpoint) was 15·6 months (95% CI 13·4-20·47). The regimen was well tolerated with a low number of grade 3-4 toxicities. The majority of AEs were grade 1-2 with low rates of grade 3-4 diarrhoea and fatigue.

Interpretation: This trial demonstrated that VTD-P is a highly efficacious and well tolerated regimen for patients with relapsed MM. The weekly use of sub-cutaneous bortezomib is likely to have improved the tolerability compared with the PANORAMA 1 trial[1].

Funding: Novartis and Myeloma UK

Introduction

Proteasome inhibitor and immunomodulatory (IMiD) agents have become standard therapy for patients with multiple myeloma (MM). 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 a proteasome inhibitor 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 uses 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 MM, and determine the overall response rate within 16 cycles of VTD-P.

Methods

Study Design and Treatment Schedule

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 MM who had received between one and four prior lines of therapy. Patients ≥18 years were eligible with measureable disease, 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 and adequate liver function. 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, Medicines and Healthcare Products Regulatory Agency (MHRA) and registered at www.clinicaltrials.gov (NCT02145715).

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

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 (Table 1). In the absence of disease progression or unacceptable toxicity, patients continued VTD-P for 16 cycles. 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] (Figure 1) was used to determine the 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 RD 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 (see Supplementary material). Response assessment and disease progression was performed locally, by Modified IWG Uniform Response Criteria[6, 8, 9] and also performed by clinicians independently without knowledge of the investigator-reported responses for quality assurance. 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].

Statistical Analysis

For the expansion phase, forty two patients, including six patients from the escalation phase, were deemed sufficient to estimate activity of the RD (≥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]. The lower limit response rate of 63% was based on 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 RD 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 RD). This population was used for all efficacy and compliance endpoints. The RD cohort includes all patients registered to escalation or expansion phases and treated at the RD 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. ASCT patients were censored at time of ASCT for primary PFS analysis and sensitivity analyses performed.

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. 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 2). 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 RD of panobinostat was taken at 20mg.

The ITT population comprised 46 patients treated at the RD, and the evaluable population 39 patients. Baseline demographics are in Table 2. The median number of prior therapies was one (range 1-4) and 64·3% had received prior ASCT, 80·4% had received only one prior therapy. 66·1% of patients had prior bortezomib, 60·7% prior Immunomodulatory agent (IMiD), and 21·4% ≥ two prior lines of therapy including bortezomib and an IMiD (known as the European Medicines Agency (EMA) approval population). 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. 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 MM, 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 RD (ITT population n=46) was 91·3% (95% CI 79·2-97·6); Table 3 shows breakdown by maximum response and 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)), and lower for those in the EMA approval population (≥VGPR 12·5% (n=8) vs 52·6% (n=38). 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).

Progression-free survival curves are displayed in Figure 3. Median PFS was 15·6 months (95% CI 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) and 66·1% for those that did not (n=22, median PFS 14·1 months (95% CI 7·0-16·10)). Median overall survival (OS) was not reached, with a median follow-up of 15·0 months.

For those treated at the RD, the actual mean panobinostat dose administered across all cycles 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 4. 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.

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 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 according to prior bortezomib exposure, suggesting effectiveness of this as a "bortezomib re-treat" regimen. As expected, 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 sub-group are small (n=8), it is interesting that 75% of patients achieved ≥PR (PANORAMA 1 trial same sub-group analysis ≥PR 58·9% (n=73)[5]). The VGPR rates reported here were high; however the number of CRs achieved (8.1% for 1st relapse) was lower than expected (MMVAR-IFM trial 28%[12]). This may be due to a low number of bone marrow biopsies performed to confirm CR, and a significant proportion of patients coming off study early (median cycle 6 out of a possible 16) for ASCT. As two doses of s.c. bortezomib were administered per cycle, the tolerability of the regimen 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 MM 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 likely 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 80·4% of patients enrolled had one prior line of therapy. A more appropriate comparator would be 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 this group of patients were better as all were bortezomib naïve, none refractory to therapy, all had received previous ASCT and received a total of 48 doses of V. This compared to 58·7% receiving prior ASCT and a total of 32 doses of V given in MUK six.

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 particularly as bortezomib will soon be off patent. 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. Vorinostat with bortezomib was investigated in a randomised phase III trial for relapsed MM. The improvement in PFS for the combination over bortezomib monotherapy was not clinically relevant[16]. Early data for Ricolinostat (a selective HDAC 6 inhibitor) in combination with bortezomib suggested efficacy and tolerability[17].

As the treatment paradigm for MM 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 MM.

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Declaration of Interests:

RP has received honoraria from Janssen and Novartis,

SB, AH, LF have no conflicts of interest to declare.

Authorship contributions

JC, SB, GM, WG designed the research; RP, JC, BK, MS, KY, GM, 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: Dose escalation and schedule

Dose cohort	**Bortezomib (s/c)** **Days 1 and 8**	**Thalidomide (oral)** **Days 1 - 21**	**Dexamethasone (oral)** **Days 1, 2, 8 and 9**	**Panobinostat (oral)** **Days 1, 3, 5, 8, 10 and 12**
1	1·3 mg/m^2	100 mg/day*	20 mg	10 mg
2	1·3 mg/m^2	100 mg/day*	20 mg	15 mg
3	1·3 mg/m^2	100 mg/day*	20 mg	20 mg

*50mg for those with baseline neuropathy

Table 2 Baseline demographics and treatment characteristics

Demographic	All patients (safety population N=57) n (%)	Intent-to-treat population (N=46) n (%)
Median Age/ yrs		
Median (Range)	61·0 (41·0, 76·0)	60·5 (41·0, 76·0)
Sex		
Male	34 (59·6)	27 (58·7)
Female	23 (40·4)	19 (41·3)
ECOG Performance Status		
0	26 (45·6)	22 (47·8)
1	26 (45·6)	21 (45·7)
2	3 (5·3)	2 (4·3)
Missing	2 (3·5)	1 (2·2)
ISS		
1	32 (56·1)	28 (60·9)
2	16 (28·1)	13 (28·3)
3	6 (10·5)	3 (6·5)
Missing	3 (5·3)	2 (4·3)
Prior Lines		
1	43 (75·4)	37 (80·4)

2	6 (10·5)	5 (10·9)
3	5 (8·8)	1 (2·2)
4	3 (5·3)	3 (6·5)
Prior bortezomib		
No	19 (33·3)	13 (28·3)
Yes	38 (66·7)	33 (71·7)
Prior IMiD		
No	23 (40·4)	22 (47·8)
Yes	34 (59·6)	24 (52·2)
EMA population*		
No	45 (78·9)	38 (82·6)
Yes	12 (21·1)	8 (17·4)
Time from diagnosis to registration (months))include partial dates**		
Mean (SD)	43·8 (28·43)	40·6 (28·36)
Median (Range)	33·2 (11·8, 148·0)	30·8 (11·8, 148·0)
Missing	10	8

* at least 2 prior lines of therapy including bortezomib and an IMiD

** missing days and months are set to 15 and 06 respectively

Table 3: 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)
EMA population (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 (N=21)	20 (95·2)	9 (42·9)	1 (4·8)	8 (38·1)	11 (52·4)	1 (4·8)	0 (0·0)

Table 4: Adverse Events (safety population n=57)

Adverse Event	Total (n, %)	Grade 1 (n, %)	Grade 2 (n, %)	Grade 3 (n, %)	Grade 4 (n, %)
Fatigue	51 (89·5)	36 (63·2)	13 (22·8)	2 (3·5)	
Peripheral sensory neuropathy	44 (77·2)	41 (71·9)	3 (5·3)		
Diarrhoea	38 (66·7)	26 (45·6)	7 (12·3)	4 (7)	
Constipation	36 (63·2)	30 (52·6)	6 (10·5)		
Bone pain	35 (61·4)	26 (45·6)	7 (12·3)		
Nausea	26 (45·6)	23 (40·4)	3 (5·3)		
Back pain	25 (43·9)	18 (31·6)	7 (12·3)		
Upper respiratory infection	24 (42·1)	16 (28·1)	2 (3·5)	4 (7)	
Edema limbs	23 (40·4)	22 (38·6)	1 (1·8)		
Neutrophil count decreased	22 (38·6)	4 (7)	3 (5·3)	12 (21·1)	3 (5·3)
Tremor	22 (38·6)	19 (33·3)	2 (3·5)	1 (1·8)	
Anemia	21 (36·8)	7 (12·3)	11 (19·3)	3 (5·3)	
Dyspnea	20 (35·1)	15 (26·3)	3 (5·3)	1 (1·8)	
Hypophosphatemia	19 (33·3)	1 (1·8)	7 (12·3)	10 (17·5)	1 (1·8)
Platelet count decreased	19 (33·3)	6 (10·5)	5 (8·8)	3 (5·3)	5 (8·8)
Somnolence	19 (33·3)	19 (33·3)			
Dizziness	18 (31·6)	12 (21·1)	5 (8·8)		
Creatinine increased	16 (28·1)	10 (17·5)	5 (8·8)	1 (1·8)	
Myalgia	15 (26·3)	14 (24·6)	1 (1·8)		
Cough	14 (24·6)	14 (24·6)			
Rash maculo-papular	14 (24·6)	11 (19·3)	3 (5·3)		
Anorexia	12 (21·1)	11 (19·3)	1 (1·8)		
Dysgeusia	11 (19·3)	10 (17·5)	1 (1·8)		

Fever	11 (19·3)	6 (10·5)	3 (5·3)	1 (1·8)	
Hypocalcemia	11 (19·3)	7 (12·3)	4 (7)		
Vomiting	10 (17·5)	5 (8·8)	3 (5·3)	2 (3·5)	

Figure 1: Rolling 6 design

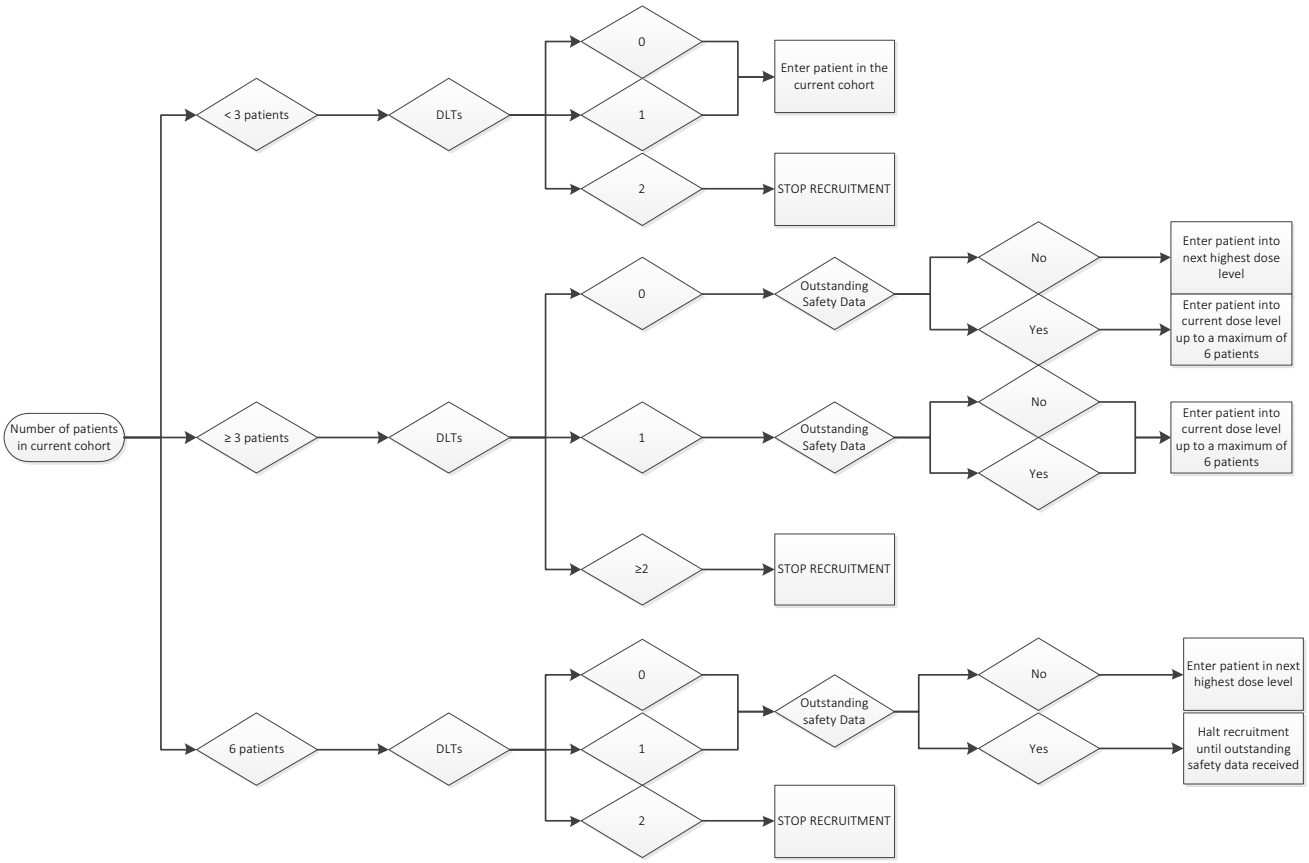


Figure 2: consort diagram

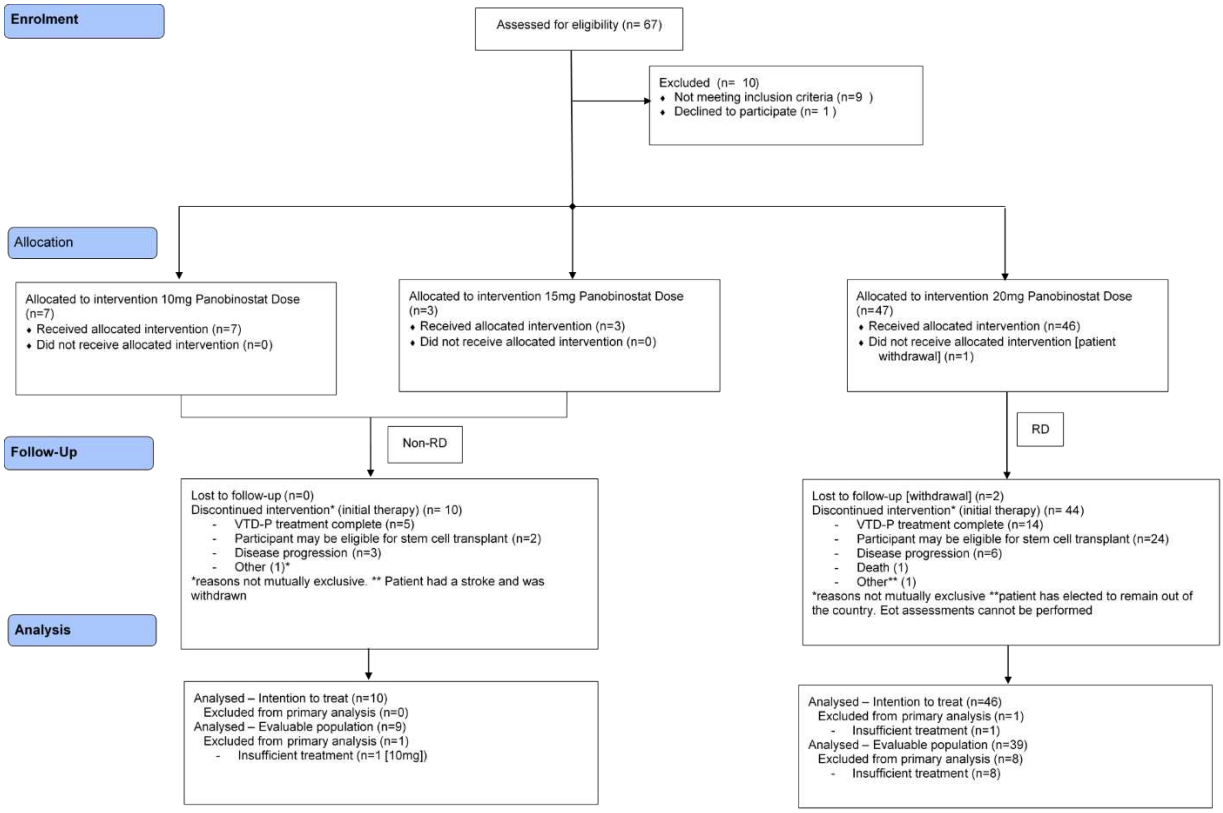
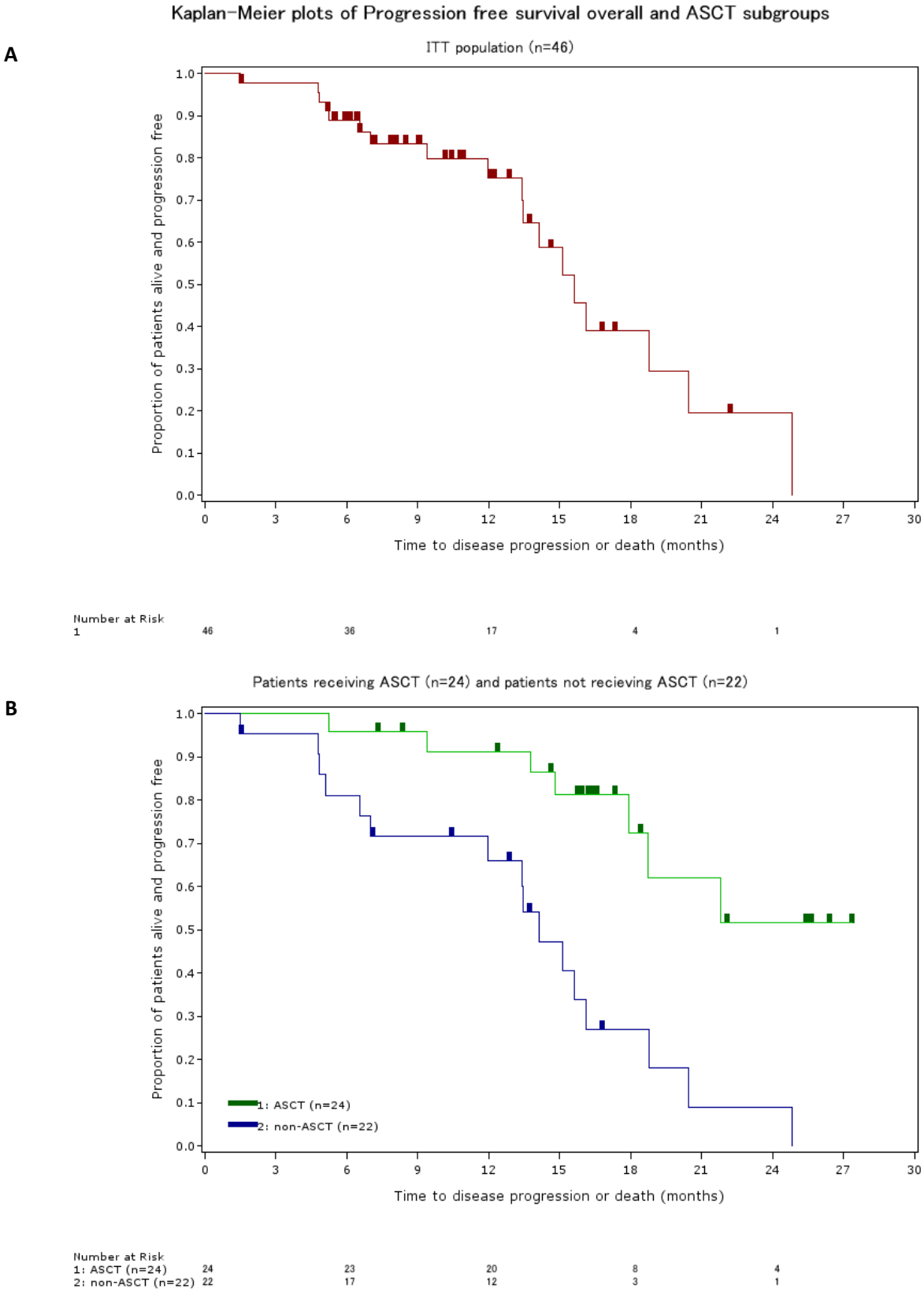


Figure 3: Kaplan-Meier plots of PFS for (A) ITT population, (B) split according to recieved ASCT or not



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