NOVARTIS

# FDA ONCOLOGIC DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT

Panobinostat capsules

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## Table of contents

## List of tables

## List of figures

## List of abbreviations

| | |
|---|---|
| AE | adverse event |
| AML | acute myeloid leukemia |
| ASCT | allogeneic stem cell transplant |
| BTZ | bortezomib |
| CI | confidence interval |
| CML | chronic myeloid leukemia |
| CNAE | clinically notable AE |
| CR | complete response |
| CRAB | Calcium elevation, Renal dysfunction, Anemia, Bone destruction |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTCL | cutaneous T-cell lymphoma |
| DAC | deacetylase |
| Dex | dexamethasone |
| DLT | dose-limiting toxicity |
| DoR | duration of response |
| EBMT | European Society for Blood and Marrow Transplantation |
| ECG | electrocardiogram |
| EORTC | European Organisation for Research and Treatment of Cancer |
| FACT/GOG-Ntx | Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity questionnaire |
| FAS | Full Analysis Set (intent-to-treat) |
| FDA | Food and Drug Administration |
| GI | gastrointestinal |
| HDAC | histone deacetylase |
| HR | hazard ratio |
| IDMC | Independent Data Monitoring Committee |
| IMiD | immunomodulatory drug |
| IMWG | International Myeloma Working Group |
| IRC | Independent Review Committee |
| ISS | International Staging System |
| i.v. | intravenous |
| mEBMT | Modified EBMT |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MM | multiple myeloma |
| MR | minimal response |
| MRR | minimal response rate |
| MTD | maximum tolerated dose |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institutes |
| nCR | near complete response |
| NDA | New Drug Application |

| | |
|---|---|
| ORR | overall response rate |
| OS | overall survival |
| PAN | panobinostat |
| PBO | placebo |
| PD | pharmacodynamics |
| PFS | progression-free survival |
| Pgp | p-glycoprotein |
| PK | pharmacokinetics |
| PR | partial response |
| PRO | patient-reported outcomes |
| QLQ-C30 | Quality of Life Questionnaire-Cancer (30 questions) |
| QLQ-MY20 | Quality of Life Questionnaire-Multiple Myeloma Module (20 questions) |
| QoL | quality of life |
| QW | twice a week |
| RR | response rate |
| SAE | serious AE |
| s.c. | subcutaneous |
| sCR | stringent CR |
| SOC | system organ class |
| TI | toxicity index |
| TIW | three times a week |
| TTP | time to progression |
| TTR | time to response |
| US | United States |
| VGPR | very good partial response |

# 1 Executive summary

This Briefing Document provides background information on the clinical development program for the pan-deacetylase (DAC) inhibitor panobinostat in Multiple Myeloma (MM) and summarizes nonclinical and clinical information included in the New Drug Application (NDA). Novartis is seeking United States (US) Food and Drug Administration (FDA) approval for panobinostat capsule in combination with bortezomib and dexamethasone for the treatment of patients with MM who have received at least 1 prior therapy. This NDA was submitted 24 March 2014 and has been granted a priority review with an expected action date of 24 November 2014.

## 1.1 Relapsed and refractory multiple myeloma

Multiple myeloma is a malignant proliferation of plasma cells which accounts for 10% to 15% of all hematologic malignancies and 20% of deaths related to cancers of the blood and bone marrow in adults. Approximately 24,000 people in the US will receive a new diagnosis of MM in 2014 (Howlader et al 2014). Despite a survival that improved from 45 to 60 months after the introduction of newer therapies (particularly proteasome inhibitors and immunomodulatory drugs, commonly called "IMiDs", often used in combination with dexamethasone), all patients ultimately progress and there is still today no evidence of cure.

Multiple myeloma is characterized by excessive proliferation of plasma cells resulting in production of monoclonal proteins, which can lead to end-organ damage. The hallmarks of MM are bone marrow failure, renal failure, and bone disease. Symptoms related to bone marrow dysfunction include anemia, decreased white blood cells leading to increased susceptibility to infection, and decreased platelet counts leading to increased susceptibility to bleeding. Patients with MM suffer from bone pain and fractures as a result of osteolytic lesions. They also suffer from the symptoms and complications of renal failure which further contribute to worsening anemia. These signs and symptoms are commonly denoted as CRAB (Calcium elevation, Renal dysfunction, Anemia, Bone destruction).

The management of patients with relapsed and refractory disease represents a clinical challenge, as these patients suffer from continuing symptoms, complications of the disease (including renal failure, blood cytopenia or recurrent infections) and decreased quality of life.

These patients typically receive salvage therapy until the next relapse or progression of disease or the development of intolerable toxicity and then go onto the next salvage option. Despite salvage therapy, overall survival (OS) remains poor in this population (in the range of 30 months) and treatment options are limited to only three classes of agents (chemotherapy, IMiDs, and proteasome inhibitors) used in variable permutations and sequences. Depth and duration of response are shorter than for newly-diagnosed patients and decrease with each line of therapy as drug resistance develops. In current clinical practice, there is no single standard of care regimen for patients with relapsed or relapsed and refractory MM. Agents such as thalidomide, lenalidomide and bortezomib are established standards of care and are often used in various doublet or triplet combination regimens (always including dexamethasone), taking into account patient factors (e.g., presence of comorbidities) and response and tolerability to prior regimens (NCCN 2014).

Patients who become refractory to the most active agents bortezomib and lenalidomide is an even greater challenge, as these patients have a very short life expectancy in the range of only 9 months (Kumar et al 2012). Recently, carfilzomib and pomalidomide were approved in the US for this late line setting of more refractory disease. However, both drugs have similar mechanisms of action compared with established agents bortezomib and thalidomide/ lenalidomide, acting either as a new-generation proteasome inhibitor or as a new IMiD. All these regimens are associated with substantial toxicities including myelosuppression, severe infections, peripheral neuropathy, gastrointestinal toxicities, and thromboembolic and cardiovascular events.

In summary, despite the introduction of two new classes of compounds in the past decade, the use of multiple lines of therapy is limited by the overlapping mechanisms of action of the available agents. Based on these considerations, there is a need for new agents with different mechanisms of action for patients with relapsed or relapsed and refractory MM.

## 1.2 Panobinostat

### 1.2.1 Panobinostat as a potent pan-deacetylase inhibitor

Panobinostat (LBH589) belongs to a structurally novel cinnamic hydroxamic acid class of compounds and is a pan-inhibitor of Class I, II, and IV histone (and non-histone) DACs (HDAC) which are epigenetic modulators and important cancer targets due to the dysregulation of these enzymes in many types of tumors. DAC enzymes also target lysine groups on various non-histone proteins such as p53, α-tubulin, Hsp90, and HIF1-α; thus panobinostat is also referred to as a pan-DAC inhibitor.

Through its effects on histone acetylation and gene expression, as well as on the oncogenic function of non-histone proteins such as Hsp90, panobinostat offers a multifaceted approach for the inhibition of cancer cell proliferation and survival. Panobinostat is highly effective at inhibiting the HDAC activity of the majority of class I, IIa, IIb, and IV isoforms at low nanomolar concentrations, and is the most potent pan-HDAC inhibitor developed to date, including those which already received regulatory approval in indications other than MM in select countries, including the US.

### 1.2.2 Rationale for panobinostat in multiple myeloma

In multiple models, panobinostat has been shown to impact several pathways that are critical to the biology of MM. These include the up-regulation of cyclin-dependent kinase inhibitor p21 leading to cell-cycle arrest and apoptosis, the disruption of the signaling pathway between MM cells and bone marrow stromal cells, and the inhibition of the aggresome protein degradation pathway by hyperacetylation of α-tubulin.

It has been demonstrated that panobinostat is effective as a single agent in multiple *in-vitro* and *ex-vivo* experiments, including in cells known to be resistant to standard of care agents. The combination of bortezomib and panobinostat has been shown to be synergistic in *in-vitro* and *in-vivo* models of MM (Ocio et al 2010), which is particularly relevant for this NDA. The combination of these two agents results in a synergistic inhibition of the unfolded protein response pathways (aggresome, proteasome) which are particularly relevant to MM.

### 1.2.3 Panobinostat development program in multiple myeloma and safety database

NDA 205353 is primarily based on data from a large, double-blind, placebo-controlled Phase III study CLBH589D2308 (hereafter D2308, also known as PANORAMA-1 trial) of panobinostat in combination with bortezomib and dexamethasone (PAN arm) compared to placebo in combination with bortezomib and dexamethasone (PBO arm) in 768 relapsed or relapsed and refractory MM patients (excluding bortezomib-refractory patients) with a primary endpoint of progression free survival (PFS).

Additional data include results from a supportive Phase II study CLBH589DUS71 (hereafter DUS71, also known as PANORAMA-2 trial) in 55 relapsed and bortezomib-refractory MM patients who received at least 2 prior lines of therapy including an IMiD, as well as safety and efficacy data from Phase Ib study CLBH589B2207 (hereafter B2207).

These three studies form the NDA foundation for the efficacy analyses and are central to the safety analyses as they were specifically conducted in the indication being sought. In addition, data from 6 completed studies (Studies B2201, B2202, B2203, B2211, B2101 and B2102) which evaluated panobinostat as a single agent in patients with other hematological malignancies and solid tumors provide additional information on the general safety profile at the relevant dose of 20 mg.

The clinical pharmacology and pharmacokinetic profile of panobinostat has been characterized in a total of 14 single-agent clinical trials conducted in patients with various hematologic malignancies and solid tumors.

## 1.3 Efficacy of panobinostat in multiple myeloma

The registration Study D2308, a large, double-blind, placebo-controlled Phase III trial, met its primary objective, demonstrating a statistically significant and clinically important reduction in the risk of progression or death of 37% with PAN+BTZ+Dex over the standard regimen of PBO+BTZ+Dex (hazard ratio [HR] 0.63; 95% Confidence Interval [CI]: 0.52, 0.76; $p < 0.0001$). Of note, PFS is a standard and accepted endpoint for trials in patients with relapsed and/or refractory MM, used to support the historical approvals of both bortezomib and lenalidomide.

This improvement in PFS translated into a prolongation of median PFS of 3.9 months (from a median of 8.1 to 12.0 months) over the standard regimen of bortezomib and dexamethasone. Importantly, the median PFS in the control arm is in line with that seen in recent studies using bortezomib ± dexamethasone in the relapsed setting (Richardson et al 2007, Moreau et al 2011, Kumar et al 2012, Arnulf et al 2012).

This improvement in PFS was robust and clinically relevant for the following reasons:

- It was consistent across all preplanned sensitivity analyses, with HRs ranging between 0.58 and 0.71, all highly statistically significant ($p < 0.0001$). In particular, the PFS benefit was consistent when using various censoring methods, the Independent Review Committee (IRC) assessment, the Per Protocol set, or a Cox model adjusting for baseline covariates. In addition, a similarly high level of consistency was observed in the pre-specified subgroup analyses, demonstrating patient benefit independent of age group

(< and ≥ 65 years), gender, race, prior therapies (i.e., bortezomib, IMiDs, stem cell transplantation), relapsed or relapsed-and-refractory disease, and cytogenetic risk.

- It was associated with an improvement in the quality of the responses. While the overall response rate (ORR) (≥ Partial Response [PR]) was only slightly higher among patients in the PAN arm relative to the PBO arm (60.7% vs. 54.6%), it was associated with a marked increase in the rate of near complete response or complete response (nCR/CR, 27.6% vs. 15.7%), and the duration of responses (DoR) were also longer with PAN. This is particularly relevant given that higher quality responses (>PR) have been shown to be associated with longer PFS and OS in patients with relapsed or refractory MM (Chanan-Kahn and Giralt 2010, Palumbo and Cavallo 2012). Accordingly, in landmark analyses, the achievement of a response >PR was associated with prolonged PFS.
- The improvement in PFS was also associated with a trend towards an improvement in OS. At the second interim OS analysis when 86.5% of the 415 target final OS events had occurred, median OS was 38.24 months and 35.38 months, in the PAN and PBO arms, respectively (HR 0.87; 95% CI: 0.70, 1.07; p=0.18). 342 patients (179 in the PAN arm and 163 in the PBO arm) are still being followed for survival. Importantly, crossover of patients between the treatment arms was not allowed to preserve the integrity of this endpoint.

Consistent benefit was also shown in the Phase II study DUS71 in a more advanced and heavily pre-treated patient population with an ORR of 34.5%.

## 1.4 Safety of panobinostat in multiple myeloma

Patients who received the three drug regimen with panobinostat generally experienced more adverse events (AEs) than patients receiving the two drug regimen of the control arm. This increase in AEs was not unexpected given the overlapping safety profiles of panobinostat and bortezomib, including myelosuppression, fatigue and gastrointestinal (GI) toxicity. At the time of the final PFS analysis of Study D2308, all randomized patients had completed therapy. The median duration of exposure to study treatment was 5.0 months in the PAN arm and 6.1 months in the PBO arm. Altogether, 33.9% and 17.7% of patients discontinued treatment due to an AE in the PAN and PBO arms, respectively. The 3 most frequent severe categories of events were blood disorders, GI toxicities, metabolism disorders and infections and infestations.

- The rate of grade 3/4 thrombocytopenia laboratory abnormalities was higher in the PAN arm (67.4.0% vs. 31.4%). In this context, the rate of grade 3/4 hemorrhage (mostly GI) was low in both arms (4.2% vs. 2.4%). Thrombocytopenia AEs led to discontinuation in 1.6% and 0.5% of patients in the PAN and PBO arms, respectively.
- GI toxicities were more common in the PAN arm than in the PBO arm, mostly due to diarrhea (grade 3/4: 25.5% vs. 8%), nausea (grade 3/4: 5.5% vs. 0.5%), and vomiting (grade 3/4: 7.3% vs. 1.3%). Diarrhea was a reason for treatment discontinuation in 4.5% and 1.6% of patients in the PAN and PBO arms, respectively.
- The rate of grade 3/4 infections was higher in the PAN arm (31.2% vs. 23.9%). These grade 3/4 infections were primarily pneumonia and sepsis. These severe infections were preceded by a severe neutropenia in only 20% of patients. Patients in the PAN arm

experienced more severe neutropenia, but few were grade 4 (6.6% vs. 2.4%). Febrile neutropenia were infrequent (1.0% vs. 0.5%).

- Elderly patients (≥ 65 years) generally had a higher level of toxicity compared to younger patients, in particular for severe (grade 3/4) thrombocytopenia (72.5% vs. 56.6%), diarrhea (31.3% vs. 21.3%) and asthenia/fatigue (48.1% vs. 18.1%).

Thirty patients (7.9%) in the PAN arm died on treatment compared to 18 (4.8%) in the PBO arm. The primary causes of death were disease progression (1.0% vs. 1.6%) and AEs (6.8% vs. 3.2%) in the PAN vs. PBO arms. The main causes of these deaths included infections and hemorrhages. The cases were complex and confounded by the natural history of the disease and concurrent comorbidities (see Section 8.2.2). In both arms, approximately half of on-treatment deaths occurred within two cycles. Altogether, 2.9% of these deaths were considered drug-related by the investigator in the PAN arm vs. 1.9% in the PBO arm. In contrast, there were fewer post-treatment deaths in the PAN arm (36%) in comparison to the PBO arm (45%), mostly related to myeloma.

In a more advanced and heavily pretreated population, the safety data from studies DUS71 and B2207 were consistent with the Phase III Study D2308. In study DUS71, 18% patients discontinued therapy because of an AE, and there was only one (1.8%) on-treatment death due to AE (a multi-organ failure).

Elderly patients have generally a higher frequency of AEs including severe AEs, and require closer patient selection and monitoring as recommended in international MM practice guidelines (Palumbo et al 2011 and Palumbo et al 2014a).

In an attempt to identify the factors which could be potentially associated with a higher toxicity with this regimen, a multivariate analysis including baseline covariates was conducted using the calculation of a toxicity index (TI) integrating on-treatment deaths and most representative clinically notable AEs (any grade) for all patients in the PAN arm as described in Section 6.3. This analysis identified both age ≥ 65 years and a baseline platelet count ≤ $150x10^9$/L, as factors associated with a higher TI. Therefore, when treated with the PAN+BTZ+Dex combination, these patients require more frequent monitoring.

In summary, the safety profile of the combination of panobinostat, bortezomib and dexamethasone is characterized in a large safety database, with the main toxicities being thrombocytopenias, diarrheas, fatigue and infections. These toxicities are not uncommon in patients with relapsed and/or refractory MM treated with current standard of care and require careful patient monitoring, appropriate supportive case and dose adjustment of either agent as appropriate.

## 1.5 Overall benefit-risk

The combination of intravenous (i.v.) bortezomib and dexamethasone is an accepted standard of care for patients with a relapsed or relapsed-and-refractory disease (NCCN 2014), with a median PFS of 8 months and rates of on-treatment deaths and discontinuation for AEs of 7% and 27% in a contemporary Phase III study (Moreau et al 2011).

Against this background, the overall clinical benefit for the combination of panobinostat with bortezomib and dexamethasone compares favorably with that of the standard of care regimen

of bortezomib plus dexamethasone. The addition of panobinostat prolongs the median PFS by 3.9 months to a median of 12 months with a 37% reduction in the risk of progression or death in patients with relapsed or relapsed and refractory MM. Although OS data are still not mature, at the time of the second interim analysis of OS, there was a trend in favor of the panobinostat containing arm with medians of 38.2 vs. 35.4 months (HR=0.87, p=0.18). Follow-up on survival will continue to be assessed in Study D2308.

In the context of the significant clinical benefit observed in this population with limited treatment options and for whom the problem of drug resistance is a challenge, the tolerability of this combination treatment regimen is considered acceptable. The safety profile of PAN+BTZ+Dex consists of manageable thrombocytopenia, neutropenia, and GI toxicity. Importantly, the addition of panobinostat does not aggravate the peripheral neuropathy related to bortezomib. Rates of discontinuations due to AE and on-treatment deaths with PAN+BTZ+Dex were within the spectrum of rates reported with current standard of care regimens (See Table 2-2). Because elderly patients with relapsed or relapsed and refractory MM have frequent comorbidities, these patients require more frequent monitoring in line with recent international practice guidelines (Chng et al 2014, Palumbo et al 2011).

It should be noted that in Phase III study D2308, bortezomib was administered intravenously (i.v.) twice weekly in the first 8 cycles and once weekly from cycle 9 to 12, based on the established dosing schedule and administration route at the start of this trial. In 2012, the US Package Insert of bortezomib was updated to add subcutaneous (s.c.) administration at the same dose and schedule as the i.v. route. The data from a randomized Phase III trial comparing the two modes of administration showed non-inferiority of s.c. route with a better safety profile. In particular, $\geq$ 5% differences were reported for grade $\geq$ 3 AEs of neuralgia (3% s.c. vs. 9% i.v.), peripheral neuropathies (6% s.c. vs. 15% i.v.), neutropenia (13% s.c. vs. 18% i.v.), thrombocytopenia (8% s.c. vs. 16% i.v.) and diarrhea (1% s.c. vs. 4% i.v.) (USPI 2014, Moreau et al 2011). A reduced frequency of i.v. bortezomib has also shown an improved tolerability profile, particularly with less frequent peripheral neuropathies, GI toxicities and thrombocytopenia (Bringhen et al 2010).

In conclusion, the data from the above detailed studies indicate that the regimen of panobinostat in combination with bortezomib and dexamethasone which introduces a new agent with a novel mechanism of action into the therapeutic armamentarium has a favorable benefit-risk profile and would be a valuable option for patients with MM who have received at least one prior therapy.

# 2 Multiple myeloma

Multiple myeloma is a malignant proliferation of plasma cells which accounts for 10%-15% of all hematologic malignancies and 20% of deaths related to cancers of the blood and bone marrow (Laubach et al 2011). The most common presenting symptoms are fatigue and bone pain (Kyle et al 2003a). Osteolytic bone lesions and/or compression fractures are the hallmark of the disease and cause significant morbidity. Anemia occurs in more than 66% of patients at diagnosis and is the primary cause of fatigue. Renal dysfunction occurs in 20% and hypercalcemia in 15-20% of patients at diagnosis.

Myeloma cells are highly dependent upon the bone marrow microenvironment, including the presence of certain cytokines such as interleukin-6, macromolecules in the extracellular matrix, and supportive cells (stromal cells), for their growth and survival (Klein et al 1989, Vidriales and Anderson 1996). Processes that change the bone marrow microenvironment either retard the growth of the tumor or cause myeloma cells to undergo apoptosis.

The diagnosis of MM is based on the International Myeloma Working Group (IMWG) 2003 definitions (Durie et al 2003, Kyle et al 2003b) and considered positive when all three of the following criteria are met:

- Elevated monoclonal immunoglobulin (M component) or ≥ 30% monoclonal bone marrow plasma cells or biopsy-proven plasmacytoma for non-secretory myeloma;
- Bone marrow (clonal) plasma cells ≥ 10% or biopsy proven plasmacytoma;
- Related organ or tissue impairment (CRAB symptoms), hyperviscosity, amyloidosis or recurrent infections.

Although many prognostic markers have been proposed in MM, due to the heterogeneity of the disease, definitive criteria are limited. In a recent consensus meeting of the IMWG (Chng et al 2014), the following factors were described as being of prognostic significance: patient factors, of which age is the most important, with decreasing survival by every increasing 10-year age band, as reported recently (Ludwig et al 2010); and tumor factors, of which cytogenetic aberrations are the most important, with t(4;14) and 17p13 deletion consistently associated with poor survival. Additionally, high-risk cytogenetics seem to have prognostic impact independently of the International Staging System (ISS), as shown in a recent analysis by IMWG demonstrating that a combined model could segregate patients into three risk groups (Avet-Loiseau et al 2013).

An important feature of MM that contributes to disease resistance and relapse is the presence of several competing malignant clones, from initial diagnosis onwards (Keats et al 2012). Therefore, any therapeutic regimen acts as a selection pressure which selects for those clones inherently resistant to a given class of drug. As a result, even the most robust responses to induction therapy only reflect elimination of the dominant clone or clones, while the remaining resistant clones mediate disease relapse (Bahlis 2012). The inherent resistance of these clones explains in large part the shorter duration and lower depth of responses to therapy in the relapsed/refractory setting (Hajek 2013). In order to counteract this biological mechanism, combination therapy using drugs with differing and complementary mechanisms of action are utilized in both the frontline and relapsed/refractory setting.

## 2.1 Current treatment options

The median survival in the pre-chemotherapy era was about 7 months from initial diagnosis of the disease. After the introduction of chemotherapy, prognosis improved significantly with a median survival of 24 to 30 months and a 10-year survival rate of 3%. With the introduction of newer therapies in recent times, median survival has been reported to improve further to 45 to 60 months from the diagnosis of the disease (NCI 2013). Despite marked improvements in patients' outcomes with the introduction of new agents in various combinations or sequences, all patients ultimately progress. There is no evidence of cure with current drug therapies.

### 2.1.1 Drugs approved for multiple myeloma in the United States

The FDA-approved agents are provided in Table 2-1. Currently available therapies for MM in the US fall into 3 classes: proteasome inhibitors, IMiDs, and chemotherapy. These may broadly be grouped into older agents (cytotoxic agents such as alkylating agents and anthracyclines, and corticosteroids) and the more active "novel" agents (the proteasome inhibitors bortezomib and carfilzomib and the IMiDs lenalidomide and thalidomide). Of note, there are no corticosteroid agents that are approved as monotherapy for myeloma, although they are regularly administered in combination with other agents.

**Table 2-1 Treatments approved for multiple myeloma in the United States**

| 1st line | Relapsed | Refractory MM* |
|---|---|---|
| **Proteasome inhibitors** | | |
| Bortezomib *(Velcade®, 2008)* | Bortezomib *(Velcade®, 2003)* | Carfilzomib *(Kyprolis®, 2012)* |
| **Immunomodulatory agents (IMiDs)** | | |
| Thalidomide *(Thalomid®, 2006)* | Lenalidomide *(Revlimid®, 2006)* | Pomalidomide *(Pomalyst®, 2013)* |
| **Chemotherapy** | | |
| Cyclophosphamide *(Cytoxan®, 1959)* | Liposomal doxorubicin *(Doxil®, 2007)* | |
| Carmustine *(BICNU®, 1977)* | | |
| Melphalan (for "palliative treatment" of MM) (*Alkeran®, 1964*) | | |

*Defined as ≥2 prior lines of therapy including BTZ *and* an IMID (for Kyprolis) or Lenalidomide (for Pomalyst), *and* refractory to the last prior therapy (progressed during therapy or within 60 days of last dose of therapy)

### 2.1.2 Principles of first-line therapy

Treatment for newly diagnosed MM depends on a patient's eligibility for an autologous stem cell transplant (ASCT). For patients under the age of 65 years who do not have substantial heart, lung, renal or liver dysfunction, ASCT should be considered after 3-4 cycles of induction therapy. For older patients or those with coexisting conditions, ASCT with a reduced intensity conditioning regimen should be considered (Palumbo et al 2011). Nowadays, lenalidomide- and bortezomib-containing regimens are extensively used as induction therapies before ASCT (Ludwig et al 2014).

For patients ineligible to undergo ASCT, standard regimens listed in the current NCCN guidelines generally include combinations regimens using a bortezomib or an IMiD backbone with prednisolone or dexamethasone, with or without chemotherapy (usually with melphalan or cyclophosphamide).

Patients with MM who respond to initial therapy receive consolidation and/or maintenance therapy. Maintenance therapy with thalidomide or lenalidomide improved PFS in both younger and elderly patients (Attal et al 2012, Palumbo et al 2010). At present, lenalidomide appears to be the most suitable choice for maintenance, whereas bortezomib is still under evaluation in randomized studies. Despite these initial therapies, the disease ultimately recurs and additional therapy is needed for patients with relapsed or relapsed and refractory disease.

### 2.1.3 Principle of salvage therapy in relapsed patients

Patients with relapsed and/or refractory MM typically receive salvage therapy until progression or toxicity and then go onto the next salvage option (Richardson et al 2014). However, with each treatment failure and subsequent line of treatment, the clinical benefit typically decreases.

The selection of a salvage regimen is highly individualized and guided by several factors that can be broadly divided into disease-related and patient-related variables:

- Disease-related factors include depth and duration of response to initial therapy, usage of maintenance therapy, rapidity of relapse (less than or greater than 6 months), presence of high risk disease elements (del 17p, 4:14), the specific prior therapy and eligibility for autologous transplantation at relapse.
- Patient-related factors include age, performance status, and comorbidities including presence of renal dysfunction, and peripheral neuropathy, all of which influence selection and dosing of various therapeutic regimens.

Patients who achieve deep (≥ Very Good PR [VGPR]/nCR) and long lasting (>6 months) responses to first line therapy can either be retreated with the same regimen or be given a new regimen, depending on predicted patient tolerance and the AE profile of the regimen.

In patients with higher risk features and/or rapid relapses (relapse within 6 months of prior therapy), combination therapy using an alternate drug class from that used for front-line therapy is generally the preferred approach for salvage (Palumbo et al 2014a). For example, a bortezomib-based regimen should be considered for patients having received an IMiD-based regimen in first line, and vice-versa. In fit patients, a second ASCT may be considered, provided the patient responded well to the previous ASCT and had a PFS of more than 12 months (Ludwig et al 2014).

The approved agents listed in Table 2-1 are used in various combination regimens; for relapsed MM in patients who received at least one prior therapy, both bortezomib and lenalidomide combined with dexamethasone are the most commonly administered in the US. The results of the trials leading to regulatory approval of these two agents and additional available publication data are provided in Table 2-2. With a follow-up time similar to the follow-up available in study D2308, the median TTP was 6.2 months in the bortezomib registration trial and 11.1 and 11.3 months in the two lenalidomide registration trials.

**Table 2-2 Efficacy of most frequently used treatments for relapsed MM approved in the United States**

**Bortezomib**

**US Label Indication** VELCADE® (bortezomib for i.v. or s.c. injection) is indicated for the treatment of patients with multiple myeloma.

**Pivotal trial type** Phase III study in 669 relapsed MM patients following 1 to 3 prior therapies randomized to bortezomib vs. high-dose dexamethasone.

Primary endpoint: TTP by EBMT criteria

| | US Label | | Richardson et al (2007) |
|---|---|---|---|
| | **Dexamethasone** | **Bortezomib** | **Bortezomib** |
| | **N=336** | **N=333** | **N=333** |
| Median follow-up | 8.3 months | | 22 months |
| Median prior lines | 2 | 2 | 2 |
| ORR (%) | 18 | 38 | 43 |
| Median DoR – months | 5.6 | 8.0 | 7.8 |
| Median TTP – months | 3.5 | 6.2 | 6.2 |
| Median OS – months | 23.7 | NE | 29.8 |

**Lenalidomide + dexamethasone**

**US Label Indication** REVLIMID® in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.

**Pivotal trial type** Two Phase III studies in 691 MM patients who had received at least one prior treatment randomized to lenalidomide + dexamethasone vs. dexamethasone alone.

Primary endpoint: TTP by EBMT criteria

| | | | | |
|---|---|---|---|---|
| | **Len + dex** | **Dex** | **Len + dex** | **Dex** |
| **US Label** | **N=170** | **N=171** | **N=176** | **N=175** |
| Median follow-up | 20.1 weeks | | 22.3 weeks | |
| Median prior lines | 2 | 2 | 2 | 2 |
| ORR (%) | 53 | 16 | 51 | 19 |
| Median TTP – months | 37.1 weeks | 19.9 weeks | NE | 20 weeks |
| **Updated results in:** | Weber et al (2007) | | Dimopoulos et al (2007) | |
| | **Len + dex** | **Dex** | **Len + dex** | **Dex** |
| | **N=177** | **N=176** | **N=176** | **N=175** |
| Median follow-up | 17.6 months | | 16.4 months | |
| ORR (%) | 61.0 | 19.9 | 60.2 | 24.0 |
| Median DoR – months | 15.8 | 5.1 | 16.5 | 7.9 |
| Median TTP – months | 11.1 | 4.7 | 11.3 | 4.7 |
| Median OS – months | 29.6 | 20.2 | NE | 20.6 |

| Meta-analysis by Dimopoulos et al (2009) | **Lenalidomide + dex N=353** | **Dexamethasone N=351** |
|---|---|---|
| Median follow-up | 48 months | |
| ORR (%) | 60.6 | 21.9 |
| Median DoR – months | 15.8 | 7.0 |
| Median TTP – months | 13.4 | 4.6 |
| Median PFS – months | 11.1 | 4.6 |
| Median OS – months | 38.0 | 31.6 |

The results of these trials need to be interpreted in the context that they were conducted in 2002-2004, at a time when the activity of prior lines of therapy including first line therapy

was modest and primarily based on chemotherapy (Table 2-3). In the bortezomib trial, the most frequently reported prior therapies included chemotherapy (with alkylating agents, anthracyclins or vinca-alkaloids) in more than 92% of patients and thalidomide in 49% of patients. In the lenalidomide trials, the most frequently reported prior therapies included chemotherapy (with melphalan or doxorubicin) in approximately half of the patients, thalidomide in approximately 40% of patients, and bortezomib in only 5-12% of patients.

The panobinostat pivotal Study D2308 was conducted in patients with a median of one prior regimen, with a range of one to three; this corresponds to the setting of relapsed MM where treatment with bortezomib and lenalidomide was approved. The median time between randomization and cutoff dates at the time of final PFS analysis was 28.9 months, and 40.1 months at the time of second OS interim analysis.

**Table 2-3 Prior therapies in bortezomib and lenalidomide registration trials and Study D2308**

| | BTZ pivotal trial | Len+ dex pivotal trials | | D2308 |
|---|---|---|---|---|
| | Richardson et al (2005) | Weber et al (2007) | Dimopoulos et al (2007) | |
| Location | Global | US | EU & Australia | Global |
| Enrollment period | Jun 02 – Oct 03 | Feb 03 – Apr 04 | Sep 03 – Sep 04 | Jan 10 – Feb 12 |
| No. of prior therapies | | | | |
| 1 | 38% | 38% | 32% | 52% |
| ≥ 2 | 62% | 62% | 68% | 48% |
| Type of prior therapy | | | | |
| Bortezomib | 0 | 12% | 5% | 43% |
| Lenalidomide | 0 | 0 | 0 | 20% |
| Thalidomide | 49% | 44% | 34% | 51% |
| Chemotherapy | | | | |
| Alkylating agents | 92% | - | - | - |
| Melphalan | - | 33% | 54% | 80% |
| Anthracyclins | 77% | - | - | - |
| Doxorubicin | - | 53% | 57% | 35% |
| Vinca-alkaloid | 73% | - | - | - |
| Vincristine | - | NR | NR | 30% |
| ASCT | 68% | 60% | 83% | 57% |

NR: Not reported

### 2.1.4 Principle of salvage therapy in relapsed and refractory patients

Recently, carfilzomib and pomalidomide were approved (accelerated approval) in the US for the late line setting of more refractory disease (Table 2-4). Both these drugs belong to the same class of drugs as the established agents bortezomib, thalidomide and lenalidomide, acting as a new generation proteasome inhibitor (carfilzomib, Kuhn et al 2007) or as a new IMiD (pomalidomide, Richardson et al 2002). The pivotal trials for these agents included more advanced bortezomib-refractory and/or IMiD-refractory patients who had received a median of 5 prior regimens, a patient population similar to the Phase II Study DUS71. In this more advanced population, the ORR, median PFS and OS were 23%, 3.7 and 15.6 months with carfilzomib and 32%, 4.2 and 14.7 months with pomalidomide + dexamethasone.

**Table 2-4 Efficacy of treatments for relapsed and refractory MM approved in the United States**

**Pomalidomide + dexamethasone**

**US Label Indication**: POMALYST® is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

**Pivotal trial type**: Phase II, open label study in patients with relapsed MM randomized to pomalidomide + dexamethasone vs. pomalidomide alone.

Primary endpoints: ORR (CR + PR) and duration of response (DOR)

| | US Label | | Richardson et al (2014) | |
|---|---|---|---|---|
| | **Pomalidomide N=108** | **Pom + dex N=113** | **Pomalidomide N=108** | **Pom + dex N=113** |
| Median follow-up | 8.3 months | | 14.2 months | |
| Median prior lines | 5 | 5 | 5 | 5 |
| ORR (%) | 7.4 | 29.2 | 18 | 33 |
| Median DoR – months | 7.4 | NE | 10.7 | 8. 3 |
| Median PFS – months | NA | NA | 2.7 | 4.2 |
| Median OS – months | 13.6 | 14.4 | 13.6 | 16.5 |

Abbreviations: NE – not evaluable; NA- not available

| San Miguel et al (2013) | **Pomalidomide N=153** | **Pom + dex N=302** |
|---|---|---|
| Median follow-up | 10.0 months | |
| Median prior lines | 5 | 5 |
| ORR (%) | 10 | 31 |
| Median DoR – months | 6.1 | 7.0 |
| Median PFS – months | 1.9 | 4.0 |
| Median TTP – months | 2.1 | 4.7 |
| Median OS – months | 7.8 | 11.9 |

**Carfilzomib+ dexamethasone**

**US Label Indication**: KYPROLIS® (carfilzomib for i.v. injection) is indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

**Pivotal trial type**: Open-label, single-arm study of 266 refractory MM patients who received at least 2 prior therapies including bortezomib and an IMiD.

Primary endpoint: ORR (CR+VGPR+PR) by IRC.

| | **US Label Carfilzomib+ dex N=266** |
|---|---|
| Median prior lines | 5 |
| ORR (%) | 22.9 |
| Median DoR – months | 7.8 |
| Median TTP – months | 3.9 |
| Median PFS – months | 3.7 |
| Median OS – months | 15.4 |

### 2.1.5 Toxicities of regimens used in patients with relapsed or relapsed and refractory MM

High rates of morbidity have been reported with currently used treatment regimens in this difficult to treat patient population with MM. In particular, these patients are known to have an increased risk of infection (and particularly pneumonia) in relation to their disease (related to polyclonal hypogammaglobulinemia or cytopenia, or both) and as a consequence of their therapy. This risk increases with the number of prior lines of therapy. Elderly patients are at higher risk of infection, as are patients with renal impairment, with concomitant respiratory disease, or with dexamethasone-induced hyperglycemia (Nucci and Anaissie 2009).

Hemorrhagic complications are also known to occur in MM due to multiple factors such as thrombocytopenia, renal disease, disseminated intravascular coagulation, or related to paraproteins (Augustson et al 2005). The most common sites of hemorrhage include the digestive tract (35%), lung (17%) and intracranium (12%) (Oshima et al 2001).

In addition, on-treatment deaths are not uncommon, with rates ranging from 4-7% with bortezomib (± dexamethasone) (Richardson et al 2005, Moreau et al 2011, Petrucci et al 2013) to 7% with carfilzomib + dexamethasone (Siegel et al 2013) and 9% with lenalidomide + dexamethasone (Hazarika et al 2008). The primary causes of deaths not related to disease progression include infection (mainly pneumonia) (Vesole et al 2012, Nucci and Anaissie 2009, Bringhen et al 2013) and hemorrhage (Kyle et al 2003a, Talamo et al 2010, Augustson et al 2005).

Regimens involving IMiDs (lenalidomide and pomalidomide) are associated with a high incidence of grade 3/4 neutropenia and infections (particularly pneumonia, reported in 30% of patients with pomalidomide), and also with the occurrence of deep vein thrombosis and pulmonary embolism (Richardson et al 2014, Lacy 2013, San Miguel et al 2013, Dimopoulos et al 2007). Lenalidomide has been associated with a small increase in the risk of second malignancies (Palumbo et al 2014b, Pratt 2014).

Treatment with proteasome inhibitors is associated with thrombocytopenia and with diarrhea. Bortezomib is associated with peripheral neuropathy. The recently approved s.c. formulation of bortezomib is associated with a lower frequency and severity of peripheral neuropathy, GI toxicity and thrombocytopenia (Moreau et al 2011). Carfilzomib is associated with a high incidence of cardiac failure and renal failure (Herndon et al 2013).

**Table 2-5 Safety of treatments approved in the United States**

| Approved treatment class | Main toxicities |
|---|---|
| Proteasome inhibitors (bortezomib, carfilzomib) | Peripheral neuropathy (bortezomib), thrombocytopenia, diarrhea, cardiac and renal failure (carfilzomib) |
| Immunomodulatory agents (IMiDs) (thalidomide, lenalidomide, pomalidomide) | Neutropenia and infections, thromboembolic events, second malignancies (lenalidomide) |
| Liposomal doxorubicin | Thrombocytopenia and hemorrhages, neutropenia, diarrhea, hand-foot-syndrome |

Elderly patients are generally at higher risk of treatment-related toxicities (and in particular infections) and have to be monitored closely, with supportive care initiated early as appropriate (e.g., initiation of broad spectrum antibiotics if an infection is suspected, introduction of G-CSF for severe neutropenia, use of loperamide for early signs of diarrhea).

In addition, according to recently published practice guidelines, it is recommended to treat elderly patients with reduced dosage of these agents depending on the level of comorbidities or "frailty" (Palumbo et al 2011, Palumbo et al 2013).

Hence, new compounds with a different mechanism of action offering new treatment options are needed to expand the available choices for those patients who are no longer responding to or tolerating currently approved therapies.

# 3 Panobinostat

## 3.1 Strong rationale for deacetylase inhibition in myeloma

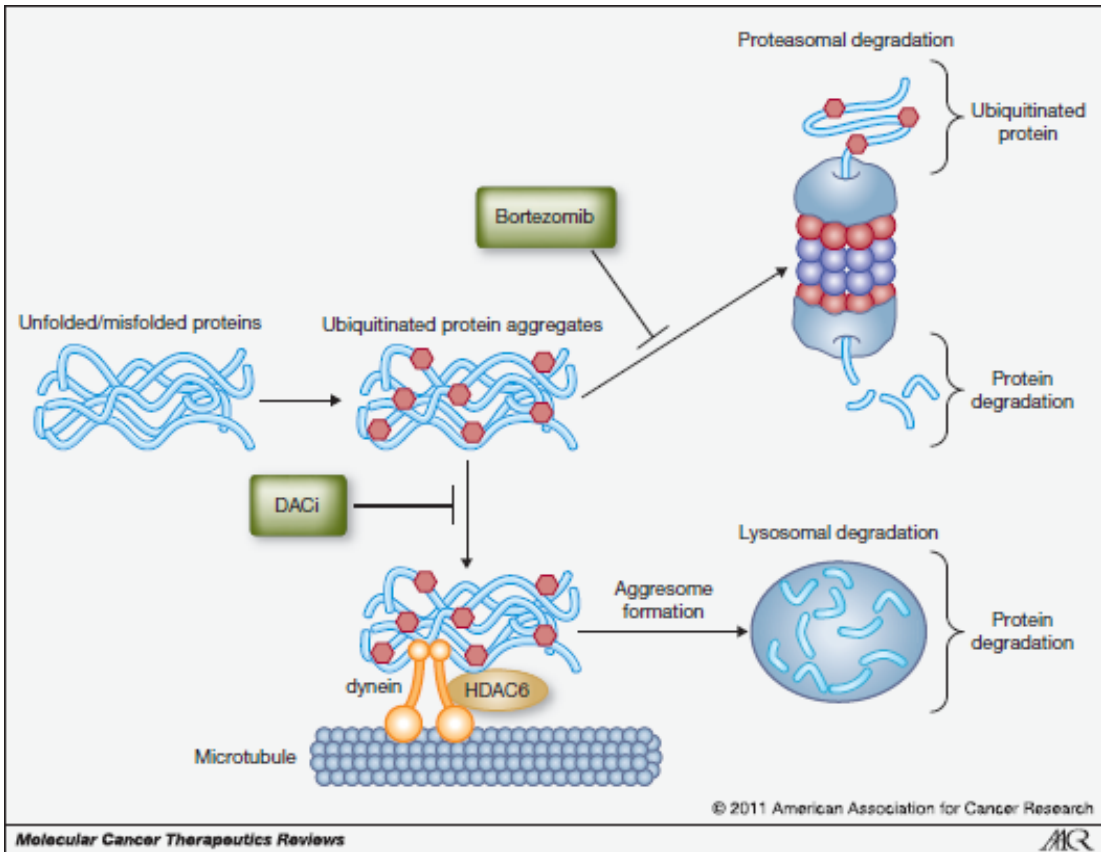
Dysregulated epigenetic regulation by activation of HDAC is a common finding in cancer including MM, leading to decreasing gene transcription (notably of tumor suppressor genes) and modulation of the activity of cellular target proteins implicated in tumorigenesis (including for example p53, α-tubulin and Hsp90). The biological basis for the anti-myeloma activity of DAC inhibitors and panobinostat is related to a number of intracellular effects in MM cells and resulting interactions between the tumor cells and the tumor microenvironment. These include:

- Up-regulation of the tumor suppressor gene p21 leading to cell-cycle arrest followed by apoptosis (Mitsiades et al 2003)
- Disruption of the signaling pathway between MM cells and bone marrow stromal cells (Mitsiades et al 2003)
- Inhibition of the unfolded protein response through inhibition of the aggresome protein degradation pathway by hyperacetylation of α-tubulin and induction of proteasome overload (Catley et al 2006)

The combination of bortezomib and DAC inhibitors resulted in strong synergistic effects seen on apoptosis and growth inhibition in in vitro and in vivo models (Hideshima et al 2011).

Since the activation of the aggresome pathway is one escape mechanism involved in the resistance to proteasome inhibition, these effects may be related to the dual inhibition of the proteasome and aggresome pathways as illustrated in Figure 3-1. Targeting both pathways induces greater accumulation of polyubiquitinated proteins, resulting in increased cellular stress and apoptosis. Therefore, combining bortezomib with a DAC inhibitor represents an attractive strategy for the treatment of patients with MM.

**Figure 3-1 Rationale for the combination of HDAC inhibitors and bortezomib**




## 3.2 Panobinostat in multiple myeloma

Panobinostat is a DAC inhibitor belonging to a structurally novel cinnamic hydroxamic acid class of compounds. Panobinostat is a highly potent pan-inhibitor of Class I, II, and IV histone and non-histone DACs active at low nanomolar concentrations.

The drug substance is panobinostat lactate anhydrous in solid crystalline form:

- Chemical name: (2E)-N-Hydroxy-3-[4-({[2-(2-methyl-1H-indol-3-yl)ethyl]amino} methyl)phenyl]prop-2-enamide 2-hydroxypropanoate (1:1)
- Molecular formula: $C_{21}H_{23}N_3O_2 \cdot C_3H_6O_3$

Panobinostat has shown anti-tumor activity in a range of human myeloma cell lines and fresh cells from MM patients including cells resistant to standard chemotherapeutic agents (Atadja 2009). When tested in animal models, panobinostat demonstrated a robust pharmacodynamic effect and corresponding anti-tumor activity in a broad range of hematological and solid tumor models. Moreover, the combination of bortezomib and panobinostat resulted in strong synergistic effects seen on growth inhibition and apoptosis in both in vitro and in vivo models (Ocio et al 2010).

# 4 Clinical pharmacology

Panobinostat pharmacokinetics (PK) was characterized with data from 581 patients across 14 Phase I/II studies in patients with solid tumors or hematological malignancies receiving oral or i.v. administration of panobinostat.

The key PK characteristics of panobinostat are summarized below:

- Panobinostat exhibits linear PK within the clinically relevant dose range (10-30 mg) and is rapidly absorbed.
- Panobinostat is extensively metabolized through CYP and non-CYP mediated pathways. Metabolites are not active towards the target enzymes. Panobinostat has an effective half-life of approximately 16 hours. Steady-state is achieved after the third dose on a TIW schedule.
- Panobinostat exposure is decreased by 20-50% by the concomitant use of dexamethasone, a mild/moderate CYP3A4 inducer. Furthermore, *in-silico* data showed that systemic panobinostat exposure may be decreased by ~70% in the presence of strong CYP3A4 inducers. Therefore, concomitant use of strong CYP3A4 inducers should be avoided.
- Co-administration of panobinostat with dextromethorphan or ketoconazole resulted in weak drug-drug interactions. Caution and clinical monitoring is recommended when panobinostat is co-administered with strong CYP3A inhibitors. Co-administration with sensitive CYP2D6 substrates that also have a narrow therapeutic index is to be avoided.
- Mild, moderate or severe renal impairment did not alter the plasma exposure of panobinostat in patients with solid tumors.
- Moderate hepatic impairment increased the plasma exposure of panobinostat by 2-fold. Caution should be exercised in patients with hepatic impairment, with close clinical monitoring for AEs, and dose adjustments may be considered.
- The regimen of 20 mg TIW 2 weeks on / 1 week off in combination with bortezomib and dexamethasone does not expose patients to risk of QT prolongation.

# 5 Clinical development program

## 5.1 Regulatory consultations

Panobinostat is a new chemical entity and has been in clinical development as an investigational drug for solid and hematological malignancies since April 2003 as an intravenous (i.v.) formulation for injection (IND 67,091) and since June 2004 as an oral capsule (IND 69,862).

Panobinostat has been investigated as a single agent and in combination in hematologic and non-hematologic malignancies. Currently, panobinostat is being developed in combination with bortezomib and dexamethasone in MM.

At a Type C meeting in February 2012, the FDA acknowledged the acceptability of PFS as the primary endpoint and agreed to the statistical analysis plan for the registration study D2308. Following a pre-NDA meeting in February 2014, Panobinostat NDA 205353 was submitted in March 2014 to seek market authorization of panobinostat (in combination with

bortezomib and dexamethasone) for the treatment of patients with MM who have received at least one prior therapy.

The NDA is primarily based on data from the registration study D2308, a multinational, randomized, double-blind, placebo-controlled, parallel group Phase III study comparing progression free survival with PAN+BTZ+Dex to PBO+BTZ+Dex in MM patients with 1 to 3 previous lines of therapy whose disease has recurred or progressed and is not refractory to bortezomib. Supportive data are provided from Phase II study DUS71 in 55 relapsed and bortezomib-refractory MM patients who received at least 2 prior lines of therapy including an IMiD, as well safety and efficacy data from 15 relapsed or relapsed and refractory MM patients in the dose expansion phase of Phase Ib study B2207. Table 5-1 describes the key regulatory milestones in the development of panobinostat in MM and significant interactions with the FDA.

**Table 5-1 US regulatory milestones**

| Date | Milestone |
|---|---|
| June 2004 | IND submitted for oral capsule formulation |
| February 2012 | Type C meeting: FDA acknowledged the acceptability of PFS as the primary endpoint and overall survival as the key secondary endpoint |
| August 2012 | Granted Orphan Drug Designation for panobinostat for the treatment of MM |
| February 2014 | Pre-NDA meeting. |
| March 2014 | Panobinostat NDA submitted |
| May 2014 | Priority review granted |

Abbreviations: IND = investigational new drug; NDA = new drug application

## 5.2 Development of panobinostat in multiple myeloma

The panobinostat clinical development program in MM focuses on panobinostat in combination with bortezomib and dexamethasone, and includes a large, double-blind, placebo-controlled Phase III study, one supportive Phase II study, safety and preliminary efficacy data from the dose expansion phase of a Phase Ib study (Table 6-1).

These three studies form the foundation for the efficacy analyses and are central to the safety analyses as they were specifically conducted in the indication being sought. In addition, data from 6 completed studies (Studies B2201, B2202, B2203, B2211, B2101 and B2102) including patients with other hematological malignancies and solid tumors provide additional information on the general safety profile for panobinostat as a single agent at the relevant dose of 20 mg (Table 6-3).

All studies were conducted in full compliance with Good Clinical Practice. All studies were monitored by Novartis personnel or a contract organization for compliance in accordance to the protocol and the procedures described in it.

## 5.3 Dose-selection rationale

The dose and schedule of panobinostat (20 mg panobinostat, 2 weeks on / 1 week off) used in Study D2308 was selected based on the following rationale and clinical experience in the Phase I/II program.

Single-agent oral panobinostat was first tested in patients with MM in dose-escalation Phase I Study B2102 and in the Phase II Study B2203 in MM. These trials showed tumor responses in cutaneous T-cell lymphoma (CTCL), Hodgkin's Lymphoma, Acute Myeloid Leukemia (AML), myelofibrosis and MM patients at doses of ≥ 20 mg used in various schedules. In addition, these single-agent studies suggested that sustained histone acetylation was achieved in peripheral blood mononuclear cells up to one week after dosing at doses ≥ 20 mg.

The Phase Ib dose-finding Study B2207 was initiated for the combination of panobinostat with bortezomib in patients with relapsed or relapsed and refractory MM, following at least one prior line of therapy. This study determined a Maximum Tolerated Dose (MTD) of 20 mg panobinostat TIW in combination with 1.3 mg/m$^2$ bortezomib:

- Doses of 10 mg to 30 mg panobinostat (TIW, until progression) in combination with 1.0 or 1.3 mg/m$^2$ BTZ i.v. (on days 1, 4, 8 and 11 of a 21-days cycle) were tested.
- The MTD was defined as the highest dose level of panobinostat in combination with bortezomib in the specified dosing schedule that met the overdose control criteria based on Dose Limiting Toxicities (DLT) observed in Cycle 1 and additional safety information.
- Based on 15 evaluable patients, the MTD was declared at 20 mg panobinostat TIW and 1.3 mg/m$^2$ bortezomib.
- Dose limiting toxicities were reported in 3/15 patients (20%) in the MTD cohort. Thrombocytopenia as a dose limiting toxicity (DLT ≥ grade 3) was reported by 1/15 patient (6.7%) in the MTD cohort compared to more than 15% in the cohorts with higher doses of panobinostat. Of note, 4 patients in the MTD cohort (23.5%) received more than 12 months of therapy.
- In the dose-escalation phase of the study, overall response rates were highest in the cohorts using a dose of bortezomib of 1.3 mg/m$^2$ and a dose of panobinostat ≥ 20 mg, ranging from 52.9% to 57.1%.

Subsequently, on the basis of a pooled analysis and a PK-PD modeling of single-agent panobinostat-induced thrombocytopenia suggesting that drug holidays should be effective to allow recovery of platelet counts, a dosing schedule of 2 weeks on / 1 week off at 20 mg panobinostat was introduced into the dose expansion phase of Study B2207 and in D2308 to manage thrombocytopenia and to allow for accelerated platelet recovery (Capdeville et al 2013).

The backbone regimen of intravenous bortezomib with a dose of 1.3 mg/m$^2$ administered on days 1, 4, 8, 15 of 21-days treatment cycles was the standard approved regimen used in 2009 when the Phase III and Phase II studies were initiated.

# 6 General methodological considerations

## 6.1 Trial design and conduct

### 6.1.1 Overview of trials

Key study design features of the three studies which form the foundation for the efficacy analyses are provided in Table 6-1. All studies were conducted in accordance with relevant

current ICH guidelines, and FDA and CHMP guidance documents for the conduct, analysis, and evaluation of anticancer medicinal products in humans.

**Table 6-1 Study design features of studies included in the submission**

| Study | Phase, study design, study objectives, and endpoints | Patients enrolled |
|---|---|---|
| Study D2308 | Pivotal Phase III, international, multi-center, randomized, double-blind, placebo-controlled<br>Efficacy/safety in relapsed or relapsed and refractory MM patients who received 1 to 3 prior lines of therapy and were not refractory to bortezomib.<br>*Primary*: PFS<br>*Secondary*: OS (key), ORR, nCR/CR, TTR, TTP, DoR, safety, QoL, PK in a subset of Japanese patients. | 768 patients<br>(387 to PAN, 381 to PBO) |
| Study DUS71 | Phase II, US multi-center, single-arm, open-label<br>Efficacy/safety in relapsed and bortezomib -refractory MM patients who received at least 2 prior lines of therapy including an IMiD.<br>*Primary*: ORR<br>*Secondary*: MR, TTR, DoR, PFS, TTP, OS, safety and tolerability. | 55 patients |
| Study B2207 [1] dose expansion | Phase Ib, US and EU multi-center, open-label, post dose-escalation<br>MTD/safety and preliminary efficacy of the dose and schedule from the dose-escalation phase in patients with relapsed or relapsed and refractory MM who received at least 1 previous line of therapy and are suitable for (re) treatment with bortezomib.<br>*Primary*: Confirmation of MTD<br>*Secondary*: Safety and tolerability, PK and PD of biomarkers, preliminary efficacy | 62 patients<br>(15 in dose expansion phase) |

[1] Only the cohort of patients treated in the expansion phase is included.

### 6.1.2 Dosing schedule in Phase II and Phase III studies

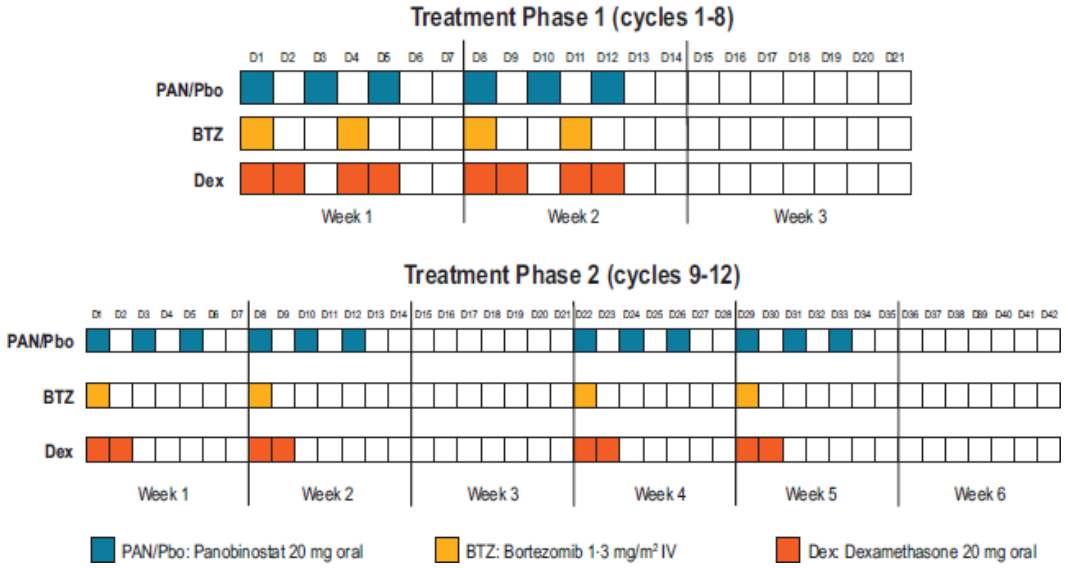
The same dosing schedule was used for the Phase III Study D2308 and the Phase II Study DUS71, and both included 2 treatment phases. In treatment phase 1 (eight 3-week cycles), patients received oral panobinostat (20 mg) (or placebo in Study D2308) administered 3 times a week for the first 2 weeks, and i.v. bortezomib (1.3 mg/m$^2$) administered on Days 1, 4, 8, and 11. Oral dexamethasone (20 mg) was administered on the days of and after bortezomib administration in accordance with current medical practice.

At the end of treatment phase 1, patients with clinical benefit could proceed to treatment phase 2 in which panobinostat was administered on the same schedule, but bortezomib was administered with a decreased frequency of once-weekly during Weeks 1, 2, 4, and 5 and dexamethasone was administered on the days of and after bortezomib (Figure 6-1).

- In the Phase III Study D2308, treatment consisted of a maximum duration of 12 cycles (or 48 weeks): eight 3-week cycles in treatment phase 1 and four 6-week cycles in treatment phase 2.
- In the Phase II Study DUS71, patients with a clinical benefit could continue therapy in treatment phase 2 until progression or unacceptable toxicity.

The dose and schedule of administration of bortezomib corresponds to the approved regimen for patients with relapsed MM which was an established standard at the time of initiation of the trials (NCCN 2008).

**Figure 6-1 Trial dosing schedule**




## 6.1.3 Patient selection

The key patient selection criteria were similar between the Phase II and Phase III trials (Table 6-2), with the exception that patients refractory to bortezomib were excluded from Study D2308 but were eligible for entry to Study DUS71.

**Table 6-2 Key patient selection criteria**

| | Study D2308 | Study DUS71 |
|---|---|---|
| **Inclusion criteria** | | |
| Adult patients >18 years of age | ✓ | ✓ |
| Relapsed, or relapsed and refractory MM, with 1-3 prior treatments | ✓ | — |
| Relapsed and bortezomib-refractory MM with at least 2 prior lines of therapy and had been exposed to an IMiD | — | ✓ |
| Eastern Cooperative Oncology Group Status ≤ 2 | ✓ | ✓ |
| Absolute neutrophil count ≥ 1.5 $\times 10^9$/L | ✓ | — |
| Absolute neutrophil count ≥ 1.0 $\times 10^9$/L | — | ✓ |
| Platelet count ≥ 100 $\times 10^9$/L | ✓ | — |
| Platelet count ≥ 70 $\times 10^9$/L | — | ✓ |
| Adequate liver function | ✓ | ✓ |
| Peripheral neuropathy < grade 2 | ✓ | ✓ |
| **Exclusion criteria** | | |
| Primary refractory myeloma | ✓ | ✓ |
| Bortezomib-refractory myeloma | ✓ | — |

## 6.1.4 D2308 study design

The population in Study D2308 was comprised of adult patients with relapsed or relapsed and refractory MM who had received 1 to 3 prior lines of therapy and was not refractory to prior bortezomib treatment. Primary refractory MM patients were excluded from the study.

For this study, relapsed MM was defined by MM disease that recurred in a patient who responded under a prior therapy by reaching a Major Response (MR) or better, and had not progressed up to 60 days of last dose of this therapy. Relapsed and refractory MM was defined by relapsed MM disease in a patient who at another point in the course of prior therapies experienced refractoriness to a line of therapy.

Patients were randomized into the 2 treatment groups stratified by 2 important factors: the number of prior lines of anti-myeloma therapy (1 versus 2 or 3) and prior use of bortezomib (yes or no). Crossover of patients between the treatment arms was not allowed to preserve the integrity of the key secondary endpoint of OS.

In addition, 6-monthly interim safety analyses were performed by an Independent Data Monitoring Committee (IDMC) which was composed of four oncologists/hematologists (none being an investigator for the study), one cardiologist and one statistician external to Novartis. During the course of the study, the IDMC did not identify safety concerns and after each review advised Novartis to continue the study with no changes.

### 6.1.5 Phase I and Phase II study designs

The primary purpose of the dose-expansion phase of Study B2207 was to evaluate the safety and preliminary efficacy of the recommended MTD with 2 weeks on / 1 week off schedule as concluded from the dose-escalation phase. The study population of Study B2207 was comprised of patients with relapsed or relapsed and refractory MM, following at least one prior line of therapy, and who were suitable for treatment (or re-treatment) with bortezomib.

Study DUS71 was a Phase II, multi-center, single-arm, open-label study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory MM who had received at least 2 prior lines of therapy (which include an IMiD [thalidomide or lenalidomide]). The main purpose of Study DUS71 was to assess whether patients refractory to bortezomib would regain responsiveness to the drug if given in combination with panobinostat. Given that bortezomib is a current standard of care for relapsed/refractory MM, either as a single agent or in combination, the possibility of rescuing a response in patients who have become refractory to bortezomib is of high clinical relevance.

## 6.2 Efficacy endpoints and statistical methodology

### 6.2.1 Phase I Study B2207

The purpose of Study B2207 was to determine the MTD dose for panobinostat in combination with bortezomib, using doses of panobinostat of 10 to 30 mg, and of bortezomib of 1.0 to 1.3 $mg/m^2$. The purpose of the dose-expansion phase was to confirm the safety of the dose identified in the dose-escalation phase. The PK profiles of panobinostat and bortezomib without (in Cycle 1) and with dexamethasone (in Cycle 2) were also evaluated. In this study, efficacy was evaluated using the IMWG response criteria (Durie et al 2006; Kyle and Rajkumar 2009).

### 6.2.2 Phase II Study DUS71

The US Study DUS71 was conducted with the objective of assessing efficacy in terms of ORR (comprising of CR, nCR, and PR) based on modified European Society for Blood and Marrow Transplantation (mEBMT) criteria after 8 cycles. Secondary efficacy endpoints included: MR, TTR, DoR, PFS, TTP, and OS. An additional objective was to characterize the safety and tolerability of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed, bortezomib-refractory MM who had received at least 2 prior lines of therapy and had been exposed to an IMiD (thalidomide or lenalidomide). The sample size was estimated based on a 2-stage design to test the null hypothesis of an ORR $\leq$ 10% vs. an alternative hypothesis of an ORR >10%. Using a 1-sided type-I error rate of 0.05 and 80% power, 47 evaluable patients were required for the study.

### 6.2.3 Phase III Study D2308

#### 6.2.3.1 Primary endpoint

The primary efficacy endpoint in Study D2308 was PFS (defined as the time from randomization to the date of first documented progression of disease or death from any cause) as assessed by the investigator using mEBMT criteria. Modified EBMT response criteria were selected for assessment of the primary endpoint and all response-dependent secondary endpoints because of previous validation in clinical trials as well as the support of regulatory approvals in MM (e.g. bortezomib). The mEBMT criteria use the following assessments to evaluate responses or progression:

- Protein electrophoresis (PEP) for serum M-protein or PEP for urine M-protein
- Evaluation of the presence/absence of soft-tissue plasmacytoma
- Serum calcium levels
- Bone lesion assessment

##### 6.2.3.1.1 Validity of primary endpoint

The statistical evaluation of these data was performed on the Full Analysis Set (FAS, i.e. the intent-to-treat population). PFS has been considered to be a relevant and clinically meaningful endpoint for patients with refractory MM by an ASH/FDA panel on clinical endpoints in MM in 2008 (Anderson et al 2008). From both a patient and physician perspective, preventing or delaying tumor progression represents an important clinical benefit considering that today no cure exists for the disease. PFS as assessed by the investigator was considered a valid measure for the following key reasons:

- The mEBMT criteria use objective measures to assess response or progression. In particular, progression of disease is often associated with serum or urine M-protein changes.
- As defined in the protocol, confirmation of progression was required with 2 repeated assessments based on M-protein.
- Study D2308 was a double-blind randomized trial and with the overlapping adverse event profiles of panobinostat and bortezomib, the blinding was unlikely to be compromised. Per the FDA Guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and

Biologics (May 2007), the use of investigator assessment in this case was considered appropriate.

- The endpoint of PFS as assessed by the investigator was discussed and agreed with FDA (Type-C Meeting on 29-Feb-2012).

#### 6.2.3.1.2 Sensitivity analyses

Several sensitivity analyses pre-specified in the protocol and in the statistical analysis plan were performed on the primary endpoint of PFS to support the robustness and consistency of the primary analysis results:

- Actual event: Analysis of the impact of missing response assessments by using the actual event date of progression, relapse or death as the PFS event date even after ≥ 2 missing adequate assessments
- Backdating date: Analysis of the impact of missing response assessments by backdating the PFS event to the date of the next scheduled response assessment after the last adequate response assessment for events occurring after ≥ 1 missing adequate assessment
- Drop-out: Analysis of the impact of patients who are no longer followed for disease assessment by imputing PFS events when patients discontinued with progressive disease or initiated anticancer treatment without documented disease progression/ relapse/death and disease progression after ≥ 2 missing adequate assessments
- Analysis of the impact of major protocol violations by using the Per Protocol set of patients
- Analysis of the impact of prognostic factors using the multivariate Cox regression model by including treatment group, age group, renal impairment, prior stem cell transplantation, clinical staging according to ISS, sex, race, geographic region and prior use of IMiDs

Prior to database lock, Novartis determined that 177 patients (23%) had at least one disease assessment performed using methodology other than the protocol-specified PEP method to quantify the M-protein (including measurement of globulin fractions, nephelometry or turbidimetry). Therefore, Novartis instituted an IRC to perform a blinded independent response assessment in all patients enrolled in the study. The IRC response assessment was performed without knowledge of the investigator response assessment. The IRC charter required confirmation of progression with 2 repeated assessments based on M-protein, as specified for the primary endpoint; however, the IRC assessed response visit by visit and did not include confirmation after a repeated assessment in their report. As a result, the following 2 PFS sensitivity analyses were conducted (see Section 7.3.2.1.1):

- Using the first report of progression irrespective of the confirmation of PD (IRC without PD confirmation);
- Using the first report of progression with confirmation by at least one repeat assessment or the first report of progression without confirmation if progression was identified due to a reason other than M-protein (IRC with PD confirmation, as per mEBMT criteria).

### 6.2.3.2 Secondary endpoints

The key secondary efficacy endpoint in Study D2308 was OS which was analyzed in a hierarchical testing procedure. OS was to be tested only if the primary endpoint of PFS was

statistically significant. Irrespective of whether OS was tested or not, alpha for OS was spent according to a separate 3-look group sequential plan at each PFS analysis (see Section 6.2.3.3). The first OS interim analysis was performed at the time of the final PFS. The second OS interim analysis was performed when 86.5% of the required final 415 OS events were observed, to provide more mature OS data to assess the efficacy of panobinostat. A final OS analysis will be performed after 415 OS events.

Other secondary efficacy endpoints were ORR, nCR/CR rate, MRR, TTR, DoR and TTP. Also, patient reported outcome (PRO) / quality of life (QoL) assessments were included, based on the self-administered questionnaires European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30), EORTC Multiple Myeloma Module (QLQ-MY20) and Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx).

#### 6.2.3.3 Sample size consideration

In order to calculate the sample size, median PFS of the PBO and PAN arms were assumed to be 7.5 months and 10.2 months, respectively (HR=0.74). This assumption was based on a study comparing bortezomib to dexamethasone in patients with relapsed myeloma with an observed median TTP of 6.2 months (Richardson et al 2005). An improvement of median PFS by 3-4 months was considered clinically meaningful in this patient population by the investigators. Under the above assumption and using a 1:1 randomization to the two arms a total of 460 PFS events were required in Study D2308 corresponding to an estimated 762 patients planned to be randomized.

Per the 3-look group sequential design for PFS, two interim analyses were planned after observing 33% and 80% of the required final number of 460 PFS events. These analyses would have allowed stopping for futility at the first interim analysis of PFS and for efficacy at the second interim analysis of PFS. However, the second interim analysis planned to occur after 80% observed events was not performed due to the time needed to implement protocol amendment 5 and the resulting overlap with the timing of the final PFS analysis. Protocol amendment 5 was required to document the non-protocol-defined methods used for the evaluation of M-protein, to capture the results in the case report form and to introduce disease assessment by IRC (see Section 7.3.2.1.1). Accordingly, the Applicant chose to continue the study until accrual of final number of 460 PFS events. There was no change in the group sequential design for the final analyses of PFS and OS; alpha was spent at each time point that an interim analysis had been planned. After the OS interim analysis conducted at the time of the final PFS analysis, a second OS interim analysis with minimal alpha assigned was performed when 86.5% of the 415 events required for the final OS analysis were observed to provide more mature OS data to assess the efficacy of panobinostat. The group sequential plan for OS was adjusted to ensure strict control of the overall type I error. The final OS analysis will be performed after all 415 OS events have been observed.

### 6.3 Safety evaluation plan and statistical methodology

The safety of PAN+BTZ+Dex is primarily based upon data from the pivotal Phase III Study D2308 in 381 patients with relapsed or relapsed and refractory MM who received panobinostat at the target dose and schedule, representing the target indication and regimen.

Safety data from the US Phase II Study DUS71 is provided in 55 patients with relapsed, bortezomib-refractory MM who had received at least 2 prior lines of therapy receiving PAN+BTZ+Dex.

In addition, safety data from Study D2308, Study DUS71, and from the dose expansion phase of Study B2207 (N=15) were pooled to provide data on 451 patients with relapsed or relapsed and refractory patients using the same dose and schedule of investigational drug and the same dose and schedule of combination regimen.

To better characterize the contribution of panobinostat to the safety profile of the combination treatment, safety data from 6 completed panobinostat single agent studies including a total of 278 patients with other hematological malignancies and solid tumors were included to provide additional information for single agent panobinostat 20 mg administered once daily TIW, every week or every other week. This pool consisted of patients with AML, chronic myeloid leukemia (CML), CTCL, and MM (Table 6-3). This safety pooling strategy was agreed at a Type C meeting with the FDA.

**Table 6-3 Clinical studies included in the safety pool of single agent panobinostat**

| Study | Phase, Study Design, Study objectives | Patients enrolled | Treatment duration |
|---|---|---|---|
| B2203 | Phase II, Single-arm, three stage, open-label, multi-center<br>*Primary*: RR (CR and PR) | 38 heavily pre-treated patients with MM who were progressing on their last line of therapy | Until progression or unacceptable toxicity<br>Study was terminated after Stage 1 due to insufficient efficacy |
| B2202 | Phase II, single-arm, open-label, multi-center<br>*Primary*: MCyR rate | 29 patients with CML-CP whose disease was resistant following treatment with at least 2 BCR-ABL TKIs | Until progression or unacceptable toxicity |
| B2211 | Phase II, single-arm, open-label, multi-center<br>*Primary*: Hematologic response | 27 patients with accelerated phase or blast phase CML with resistant disease following treatment with at least two BCR-ABL TKIs | Until progression or unacceptable toxicity |
| B2201 | Phase II, open-label, non-randomized, single agent<br>*Primary*: ORR | 139 patients with refractory CTCL whose disease was refractory to or had progressed following at least two treatment regimens | Until progression or unacceptable toxicity |
| B2101 (only 20 mg dose contributing to safety assessment) | Phase Ia, multi-arm, multi-center, dose-escalation<br>*Primary*: MTD and DLT | 36 patients received the 20 mg dose only | Until progression or unacceptable toxicity |
| B2102 (only 20 mg dose contributing to safety assessment) | Phase Ia, 2-arm, multi-center, dose-escalation<br>*Primary*: MTD and DLT | 9 patients with hematologic malignancies received the 20 mg dose only | Until progression or unacceptable toxicity |

The safety of panobinostat was evaluated on the basis of the AE rate, type, severity (graded in accordance with the NCI Common Terminology Criteria for Adverse Events [CTCAE], and causal relationship to treatment. Adverse events were reported using the Medical Dictionary

for Regulatory Activities (MedDRA) (and recoded using MedDRA version 16.0) and arranged by system organ class (SOC).

Seventeen groups of clinically notable AEs (CNAE) consisting of pooled AEs that are similar in nature were identified based on specific clinical interest in connection with the mechanism of action of panobinostat, on non-clinical studies with panobinostat, or on signals observed during the conduct of the clinical development program: QT prolongation, Myelosuppression, Hemorrhage, Severe Infections, Hepatic dysfunction, Renal dysfunction, Diarrhoea, Cardiac Failure, Ischemic Heart Disease, Tachyarrhythmia, Venous thromboembolism, Ischemic colitis, Interstitial lung disease, Hypothyroidism, Pericardial effusion, Acute pancreatitis, and Hepatitis B reactivation. As the focus is on the CNAEs associated with the combination treatment regimen, no data is presented for the single agent pool dataset.

### Toxicity index analysis

To assess the potential baseline risk factors associated with greater AE burden and to discriminate patients on the basis of their toxicity experiences, the methodology proposed by Rogatko et al (2004) was applied. This methodology assigns a toxicity index (TI) to each patient, based on a weighted sum of ordered AE grading using the reported CTCAE grades.

For the analysis in Study D2308, on-treatment deaths and clinically notable AEs (Thrombocytopenia, Neutropenia based on laboratory assessments, Diarrhea, Hemorrhage, Infections and IHD) of any grade were included. These clinically notable AEs were selected as the most representative AEs characterizing panobinostat, bortezomib and dexamethasone. On-treatment deaths were assigned CTCAE grade 5 and hence assigned the highest weight in the toxicity index. A linear regression analysis model based on all patients in the PAN arm was used to model the calculated TI with key baseline characteristics as covariates to predict the TI. This model included baseline demographics, disease characteristics, prior treatment, and baseline laboratory values as covariates. The covariates included in the model were considered to be either factors known to have differential prognosis in the current treatment paradigm of MM such as demographic characteristics or baseline factors considered to have a potential impact on the observed notable clinical AEs (Table 6-4).

**Table 6-4 Covariates included in the Toxicity Index model**

| Covariates | Description |
|---|---|
| Age | <65 years vs. ≥ 65 years |
| Gender | Male vs. Female |
| Race | Asian vs. Caucasian vs. Other |
| ECOG performance status | 0 vs. ≥ 1 |
| Prior stem cell transplant | Yes vs. No |
| Prior lines of multiple myeloma therapy | 1 vs. >1 |
| Baseline platelet counts per liter | ≤ 150 x $10^9$/L vs. >150 x$10^9$/L* |
| Baseline hemoglobin | ≤ 123 g/L vs. >123 g/L* |
| Baseline neutrophil count | ≤ 1.8 x$10^9$/L vs. >1.8 x$10^9$/L* |

* Cut-off is determined based on lower limit of normal (Kratz et al 2004)

Backward elimination (using a nominal two-sided 5% cut-off) was used to determine the most significant contributing risk factors.

In addition, a similar analysis was performed in the PAN arm where TI was computed including on-treatment deaths and grades 3-4 clinically notable AEs.

# 7 Efficacy of panobinostat in multiple myeloma

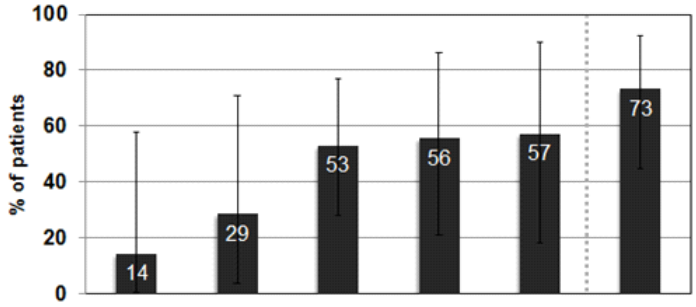
The following section describe first the results of the two supportive studies in heavily pretreated patients including bortezomib-refractory patients (studies B2207 and DUS71), and then the results of the pivotal Phase III study D2308.

## 7.1 Efficacy in the Phase Ib Study B2207

Study B2207 enrolled a total of 62 patients with advanced disease, who had a median age of 62 years (46-83 years), and had received a median of 2 prior lines of therapy (range 1-10). A majority of patients had received prior bortezomib (63%) including 31% patients who were bortezomib-refractory. In addition, 45% of patients had received prior lenalidomide and 53% were relapsed-and-refractory. A total of 47 patients were enrolled in the dose-escalation phase and 15 in the dose-expansion phase.

There was a clear indication of a dose-response relationship in this study, with higher level of responses in the cohorts using a dose of panobinostat ≥ 20 mg and of bortezomib of 1.3 mg/m$^2$ (Figure 7-1).

**Figure 7-1 Best overall response in Study B2207 (IMWG criteria, FAS)**




| | | | | | | |
|---|---|---|---|---|---|---|
| Patients (n) | 7 | 7 | 17 | 9 | 7 | 15 |
| Panobinostat (mg) | 10 | 20 | 20 | 25 | 30 | 20 |
| Bortezomib (mg/m$^2$) | 1.0 | 1.0 | 1.3 | 1.3 | 1.3 | 1.3 |

Shaded bars represent point estimates, vertical lines above them represent the standard deviations

The majority of patients in the expansion phase of Study B2207 responded to treatment with PAN+BTZ+Dex, with 11/15 patients (73.3%) having a response to treatment (Figure 7-1). Three of 15 patients (20.0%) had a VGPR and 8/15 patients (53.3%) had a PR, thus providing preliminary evidence of the activity of panobinostat in combination with bortezomib.

## 7.2 Efficacy in US Study DUS71

The main purpose of Study DUS71 was to assess whether patients refractory to bortezomib would become sensitive when used in combination with panobinostat due to its synergistic activity. Given that bortezomib is a current standard of care for relapsed/refractory MM,

either as a single agent or in combination, the possibility of rescuing a response in patients who have become refractory to bortezomib is of high clinical relevance.

Fifty-five patients with bortezomib-refractory MM were enrolled in Study DUS71. Patients were heavily pretreated and had received a median of 4 prior lines of therapy (Table 7-1). Nearly a third (29.1%) of patients had received 6-8 prior lines. In the most recent prior line, almost half of the patients (49.1%) had received bortezomib. All patients were previously treated with bortezomib and at least one IMiD (lenalidomide: 98.2%, thalidomide: 69.1%). The majority of patients had received prior ASCT (63.6%). The best response of ≥ PR to the last prior line of therapy was 21.8%.

**Table 7-1 Key demographic and baseline characteristics (Study DUS71, FAS)**

| | PAN+BTZ=Dex N=55 |
|---|---|
| Age (years) | |
| Mean (SD) | 61.9 (10.54) |
| Median | 61.0 |
| Minimum – Maximum | 41 – 88 |
| Age category (years) – n (%) | |
| <65 | 34 (61.8) |
| ≥ 65 | 21 (38.2) |
| Time since diagnosis (months) | n=54 |
| Mean (SD) | 59.8 (42.81) |
| Median | 54.8 |
| Minimum – Maximum | 7.5 – 263.6 |
| Clinical staging according to ISS – n (%) | |
| Stage I | 18 (32.7) |
| Stage II | 23 (41.8) |
| Stage III | 13 (23.6) |
| Not assessed | 1 (1.8) |
| Prior lines of antineoplastic therapy | n=767 |
| Median | 4.0 |
| Minimum – Maximum | 2 – 11 |
| Number of prior lines of antineoplastic therapy – n (%) | |
| 0-1 | 0 |
| 2-3 | 18 (32.7) |
| >3 | 37 (67.3) |
| Prior anti-myeloma treatment – n (%) | |
| Bortezomib | 55 (100) |
| Lenalidomide | 54 (98.2) |
| Thalidomide | 38 (69.1) |
| Melphalan | 24 (43.6) |
| Prior stem cell transplantation – n (%) | |
| No | 20 (36.4) |
| Yes | 35 (63.6) |

ISS International Staging System

The ORR per mEBMT 1998 criteria was 34.5% (95% CI: 22.2, 46.7), which was considered a clinically meaningful and relevant improvement for bortezomib-refractory patients (Table 7-2). The median OS was 17.5 months (95% CI: 10.8, 25.2) and the median PFS was 5.4 months (95% CI: 3.5, 6.7).

Of note, the median PFS for patients whose disease progressed on bortezomib (n=40) or within 60 days of last dose (n=15) was 4.2 months and 7.6 months, respectively.

For the 14 patients with high-risk cytogenetics – defined as del(17p), t(4;14), or t(14;16) – ORR was 42.9% and CBR was 71.4%. Of the 8 patients who had del(17p), the ORR was 37.5% and the CBR was 87.5%. Although the number of patients is small, it does not appear that high-risk cytogenetics adversely affected response rates.

**Table 7-2 Efficacy endpoints by investigator assessment (Study DUS71, FAS)**

| Efficacy parameter | Study DUS71 N=55 |
|---|---|
| Best overall response – n (%) | |
| CR | 0 |
| nCR | 1 (1.8) |
| PR | 18 (32.7) |
| MR | 10 (18.2) |
| CR/nCR rate (CR or nCR) – n (%) | 1 (1.8) |
| ORR (CR, nCR, PR) – n (%) | 19 (34.5) |
| 95% CI [1] | 22.2, 46.7 |
| Median DoR – months / days ($25^{th}$-$75^{th}$ percentile) | 6.0 months / 183 days (126, 238) |
| Median PFS – months / days (95% CI) [2] | 5.4 months / 164 days (107, 204) |
| BTZ relapsed (n=40) (95% CI) | 4.2 months / 128 days (78, 176) |
| Progressed within 60D of BTZ (n=15) (95% CI) | 7.6 months / 232 days (204, 295) |
| Median OS (95% CI) [2] | 17.5 months / 534 days (329, 767) |

[1] 95% confidence interval for two-stage Simon's Optimal Design (Simon 1989).
[2] Derived using Kaplan-Meier method and its 95% CI according to Brookmeyer and Crowley (1982).

In summary, these results support the scientific hypothesis of the dual inhibition of the aggresome and proteasome pathway outlined in Section 3.1. The study, conducted in a heavily pretreated and bortezomib-refractory population, demonstrate that panobinostat can overcome resistance by recapturing response to bortezomib, thereby addressing an important unmet medical need for these patients.

## 7.3 Placebo-controlled Study D2308

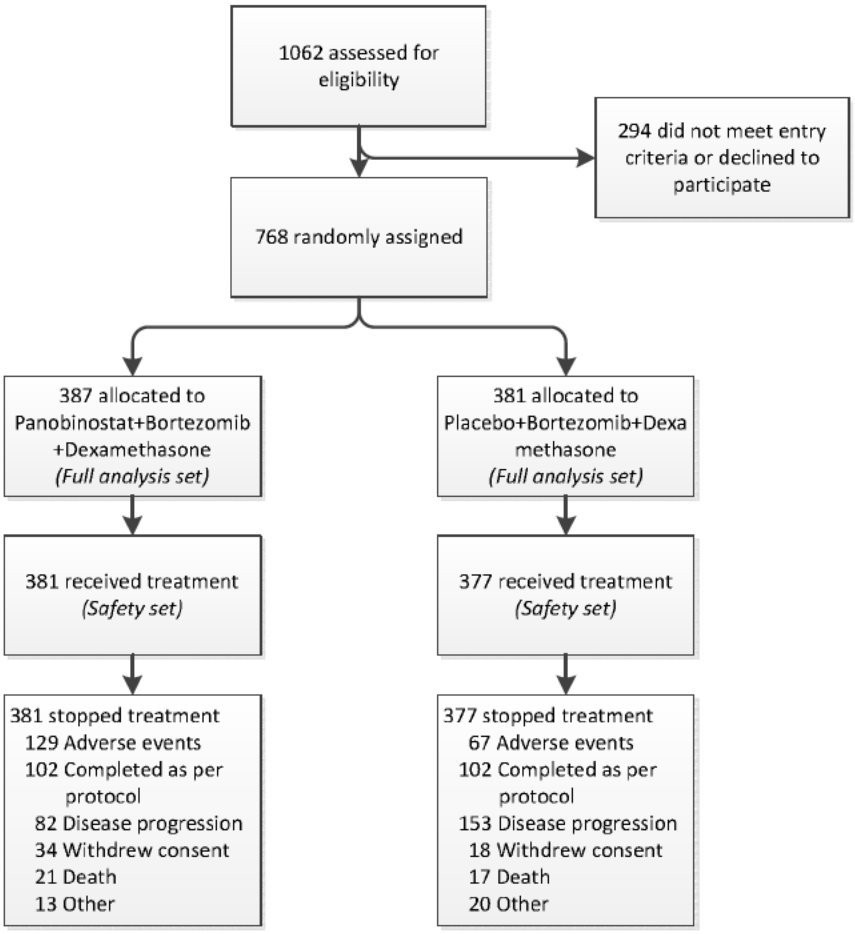
### 7.3.1 Patient population and disposition

The population of adult patients with relapsed or relapsed and refractory MM having received one to three prior lines of therapy and who were not refractory to prior bortezomib examined in the controlled Phase III Study D2308 reflects the target population of patients with relapsed or relapsed and refractory MM.

### 7.3.1.1 Patient disposition

A total of 768 patients with relapsed or relapsed and refractory MM were enrolled in Study D2308, and randomized to receive either PAN+BTZ+Dex (n=387 patients) or PBO+BTZ+Dex (n=381 patients). At the time of the data cut-off on 10-Sep-2013, all patients in both treatment arms had discontinued treatment.

**Figure 7-2 Patient disposition (Study D2308)**




### 7.3.1.2 Patient population

Patient selection criteria were appropriately chosen so that the population in this study reflected the target population of patients with relapsed or relapsed and refractory MM. The median age was 63 years, which is representative of a Phase III trial MM population. The median time since diagnosis was 37.1 and 38.9 months in the PAN and PBO arms, respectively. By ISS stage, 25.5% of all patients were Stage II and 21.2% were Stage III. In this trial, 51.6% of all patients had received one prior line of anti-MM therapy and 48.4% had received 2-3 prior lines, with a mean and median of 1.7 and 1 prior line, respectively. The proportion of patients having received bortezomib as prior antineoplastic therapy (43%) was similar in both treatment arms. Reflecting the medical practice at the time of study conduct, the proportion of patients having received thalidomide as prior antineoplastic therapy (51.2%)

was higher than patients having received lenalidomide (20.4%). More than half of patients had received a prior stem cell transplant. All patients had relapsed disease, and in some cases were also refractory to a prior regimen. The two treatment groups were generally well balanced with regards to all demographics, baseline disease characteristics, and disease/treatment histories providing reassurance with regards to the interpretation of the treatment comparisons and validity of the efficacy and safety conclusions.

**Table 7-3 Key demographics and baseline characteristics (Study D2308, FAS)**

| | PAN+BTZ+Dex N=387 | PBO+BTZ+Dex N=381 | All N=768 |
|---|---|---|---|
| Age (years) | | | |
| Mean (SD) | 62.4 (9.34) | 61.8 (9.43) | 62.1 (9.38) |
| Median | 63.0 | 63.0 | 63.0 |
| Minimum – Maximum | 28 – 84 | 32 – 83 | 28 – 84 |
| Age category (years) – n (%) | | | |
| <65 | 225 (58.1) | 220 (57.7) | 445 (57.9) |
| ≥ 65 | 162 (41.9) | 161 (42.3) | 323 (42.1) |
| Time since diagnosis (months) | n=386 | n=381 | n=767 |
| Mean (SD) | 46.7 (38.02) | 49.0 (34.78) | 47.8 (36.44) |
| Median | 37.1 | 38.9 | 37.9 |
| Minimum – Maximum | 2.4 – 308.1 | 2.4 – 300.2 | 2.4 – 308.1 |
| Clinical staging according to ISS – n (% ) | | | |
| stage I | 156 (40.3) | 152 (39.9) | 308 (40.1) |
| stage II | 104 (26.9) | 92 (24.1) | 196 (25.5) |
| stage III | 77 (19.9) | 86 (22.6) | 163 (21.2) |
| not assessed | 50 (12.9) | 51 (13.4) | 101 (13.2) |
| MM category – n (%) | | | |
| Relapsed | 247 (63.8) | 235 (61.7) | 482 (62.8) |
| Relapsed and refractory | 134 (34.6) | 141 (37.0) | 275 (35.8) |
| Prior lines of antineoplastic therapy | n=386 | n=381 | n=767 |
| Mean (SD) | 1.7 (0.76) | 1.7 (0.78) | 1.7 (0.77) |
| Median | 1.0 | 1.0 | 1.0 |
| Minimum – Maximum | 1 – 4 | 1 – 3 | 1 – 4 |
| Number of prior lines of antineoplastic therapy – n (%) | | | |
| 0-1 | 198 (51.2) | 198 (52.0) | 396 (51.6) |
| ≥ 2 | 189 (48.8) | 183 (48.0) | 372 (48.4) |
| Prior anti-myeloma treatment – n (% ) | | | |
| Thalidomide | 205 (53.0) | 188 (49.3) | 393 (51.2) |
| Bortezomib | 169 (43.7) | 161 (42.3) | 330 (43.0) |
| Lenalidomide | 72 (18.6) | 85 (22.3) | 157 (20.4) |
| Combined bortezomib+dexamethasone | 147 (38.0) | 143 (37.5) | 290 (37.8) |
| Combined bortezomib+IMiDs | 94 (24.3) | 99 (26.0) | 193 (25.1) |
| Combined bortezomib+lenalidomide | 34 (8.8) | 45 (11.8) | 79 (10.3) |

| | PAN+BTZ+Dex N=387 | PBO+BTZ+Dex N=381 | All N=768 |
|---|---|---|---|
| Melphalan | 310 (80.1) | 301 (79.0) | 611 (79.6) |
| Doxorubicin | 129 (33.3) | 138 (36.2) | 267 (34.8) |
| Vincristine | 115 (29.7) | 117 (30.7) | 232 (30.2) |
| Prior stem cell transplantation – n (%) | | | |
| No | 172 (44.4) | 157 (41.2) | 329 (42.8) |
| Yes | 215 (55.6) | 224 (58.8) | 439 (57.2) |
| Cytogenetic risk group – n (%) [1] | n=120 | n=124 | n=244 |
| Normal risk | 79 (65.8) | 88 (71.0) | 167 (68.4) |
| Poor risk | 24 (20.0) | 13 (10.5) | 37 (15.2) |
| Unknown or Missing | 17 (14.2) | 23 (18.5) | 40 (16.4) |

[1] Based on the number of patients who consented for biomarker protocol.

## 7.3.2 Efficacy results

### 7.3.2.1 Primary endpoint – progression-free survival

This large randomized global study met its pre-specified primary endpoint of PFS as assessed by investigator.

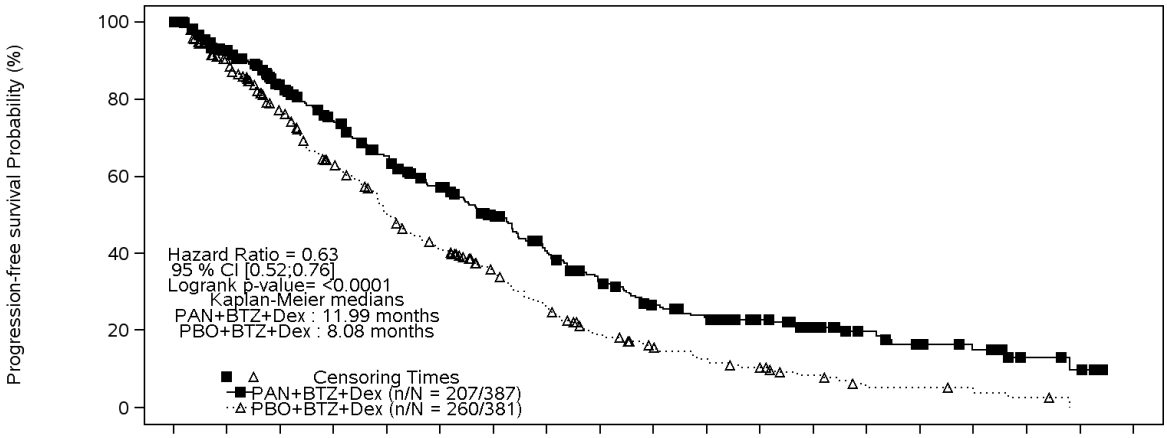
A 37% relative risk reduction in progression, relapse or death in favor of PAN was evident as per investigator assessment; this result was statistically significant (p <0.0001) (Table 7-4). Median PFS was prolonged by a clinically meaningful 3.9 months from 8.1 months for patients receiving PBO to 12.0 months for PAN-treated patients.

**Table 7-4 Progression-free survival (Study D2308, FAS)**

| | PAN+BTZ+Dex N=387 | | PBO+BTZ+Dex N=381 | |
|---|---|---|---|---|
| PFS events – n (%) | 207 | (53.5) | 260 | (68.2) |
| Disease progression | 164 | (42.4) | 231 | (60.6) |
| Relapse from CR | 20 | (5.2) | 15 | (3.9) |
| Death | 23 | (5.9) | 14 | (3.7) |
| Number censored – n (%) | 180 | (46.5) | 121 | (31.8) |
| Median PFS – months | 11.99 | | 8.08 | |
| 95% CI | 10.32, 12.94 | | 7.56, 9.23 | |
| Hazard ratio (95% CI) | 0.63 (0.52, 0.76) | | | |
| p-value | <0.0001 | | | |

The Kaplan-Meier curves for PFS started to diverge at approximately Month 2 of treatment in favor of the PAN arm, with the progression-free probability remaining higher for the PAN arm than for the PBO arm throughout the time of observation, indicating sustained advantage associated with addition of panobinostat to the combination treatment (Figure 7-3).

**Figure 7-3 Kaplan-Meier plot of PFS by investigator assessment (Study D2308, FAS)**




Number of patients at risk

| Time (months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PAN+BTZ+Dex | 387 | 288 | 241 | 202 | 171 | 143 | 113 | 89 | 69 | 52 | 44 | 35 | 26 | 18 | 13 | 10 | 5 | 3 | 0 |
| PBO+BTZ+Dex | 381 | 296 | 235 | 185 | 143 | 114 | 89 | 64 | 42 | 32 | 24 | 18 | 12 | 5 | 5 | 3 | 2 | 0 | 0 |

### 7.3.2.1.1 Sensitivity analyses

The robustness and consistency of the primary analysis were confirmed by a series of preplanned supportive and sensitivity analyses, with all HRs ranging from 0.58 to 0.71 and statistical significance ($p < 0.0001$) (Table 7-5 and Table 7-6). In a multivariate Cox model adjusting for pre-specified and relevant prognostic factors, PFS was significantly longer in the PAN arm, with a HR of 0.58 (95% CI: 0.48, 0.71, $p < 0.0001$).

**Table 7-5 PFS sensitivity analyses per investigator assessment (Study D2308, FAS)**

| | PAN+BTZ+Dex | | PBO+BTZ+Dex | | | | |
|---|---|---|---|---|---|---|---|
| **Sensitivity analysis** | **Median PFS (95% CI)** | | **Median PFS (95% CI)** | | **HR** | **(95% CI)** | **p-value** |
| **Primary analysis** | 11.99 | (10.32, 12.94) | 8.08 | (7.56, 9.23) | 0.63 | (0.52, 0.76) | <0.0001 |
| **Alternative censoring methods** | | | | | | | |
| Actual event [1] | 11.30 | (9.53 ,12.68) | 7.89 | (7.46 ,8.67) | 0.66 | (0.56,0.79) | <0.0001 |
| Backdating date [2] | 10.25 | (8.31 ,11.30) | 7.43 | (6.37 ,7.98) | 0.68 | (0.58,0.81) | <0.0001 |
| Drop-out [3] | 9.46 | (8.11 ,10.91) | 7.62 | (6.47 ,8.08) | 0.71 | (0.61,0.83) | <0.0001 |
| **Per Protocol Set** | 12.71 | (11.04,14.06) | 8.08 | (7.13 ,9.69) | 0.60 | (0.49,0.75) | <0.0001 |
| **Adjusting for baseline characteristics** [4] | 11.99 | (10.32,12.94) | 8.08 | (7.56,9.23 ) | 0.58 | (0.48,0.71) | <0.0001 |

[1] Includes the event whenever it occurred even after ≥ 2 missing adequate assessments.

[2] Uses the date of next scheduled assessment for events occurring after ≥ 1 missing adequate assessment.

[3] Includes subsequent antineoplastic therapy, reason for end of treatment as disease progression without investigator documentation and disease progression after ≥ 2 missing adequate assessments as events.

[4] Baseline covariates included in the Cox proportional hazard model are treatment group, age group, renal impairment, prior stem cell transplantation, clinical staging according to ISS, sex, race, geographic region and prior use of IMiDs.

Hazard Ratio and 95% CI of PAN+BTZ+Dex vs. PBO+BTZ+Dex are obtained from stratified Cox model.

Two-sided p-value is obtained from the stratified log-rank test.

High rates of concordance were observed between the investigator assessment and the IRC assessment (85% [n=329] for the PAN arm and 83% [n=315] for the PBO arm), although there were cases where the process followed by IRC review differed from investigator review.

Importantly, the sensitivity analysis based on IRC assessment applying the same requirement for confirmation of progression on two successive visits if based on M protein (as done in the primary analysis using the investigator assessment) produced very similar results in terms of HR and median PFS (Figure 7-4).

**Table 7-6 PFS sensitivity analyses per IRC (Study D2308, FAS)**

| | PAN+BTZ+Dex | | PBO+BTZ+Dex | | | | |
|---|---|---|---|---|---|---|---|
| **Sensitivity analysis** | **Median PFS (95% CI)** | | **Median PFS (95% CI)** | | **HR** | **(95% CI)** | **p-value** |
| **Analyses with PD confirmation per mEBMT criteria** | | | | | | | |
| **Primary analysis** (investigator assessment} | 11.99 | (10.32, 12.94) | 8.08 | (7.56, 9.23) | 0.63 | (0.52, 0.76) | <0.0001 |
| IRC assessment with PD confirmation [1] | 11.99 | (10.51, 13.50) | 8.31 | (7.62, 9.92) | 0.63 | (0.52,0.76) | <0.0001 |
| **Analysis without PD confirmation** | | | | | | | |
| IRC assessment without PD confirmation [1] | 9.95 | (8.31 ,11.30) | 7.66 | (6.93 ,8.54) | 0.69 | (0.58,0.83) | <0.0001 |

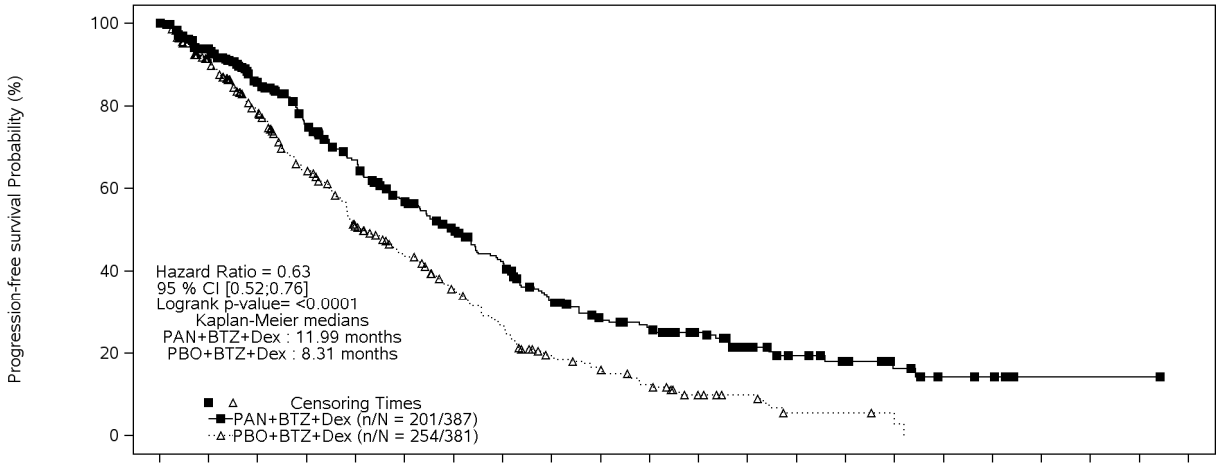
[1] IRC assessment used for all patients.

Hazard Ratio and 95% CI of PAN+BTZ+Dex vs. PBO+BTZ+Dex are obtained from stratified Cox model.

Two-sided p-value is obtained from the stratified log-rank test.

Overall, the sensitivity analyses demonstrated consistency in PFS between investigator assessment, IRC assessment, Per Protocol set, and when including specific dropouts as events or applying alternative censoring rules.

**Figure 7-4 Kaplan-Meier plot of PFS by IRC assessment with PD confirmation (Study D2308, FAS)**




Number of patients at risk

| Time (months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 | 40 | 42 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PAN+BTZ+Dex | 387 | 307 | 251 | 207 | 174 | 142 | 114 | 92 | 67 | 50 | 44 | 36 | 25 | 17 | 13 | 9 | 5 | 4 | 1 | 1 | 1 | 0 |
| PBO+BTZ+Dex | 381 | 308 | 247 | 190 | 141 | 113 | 85 | 63 | 39 | 33 | 23 | 13 | 10 | 3 | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

### 7.3.2.1.2 Stratification factors

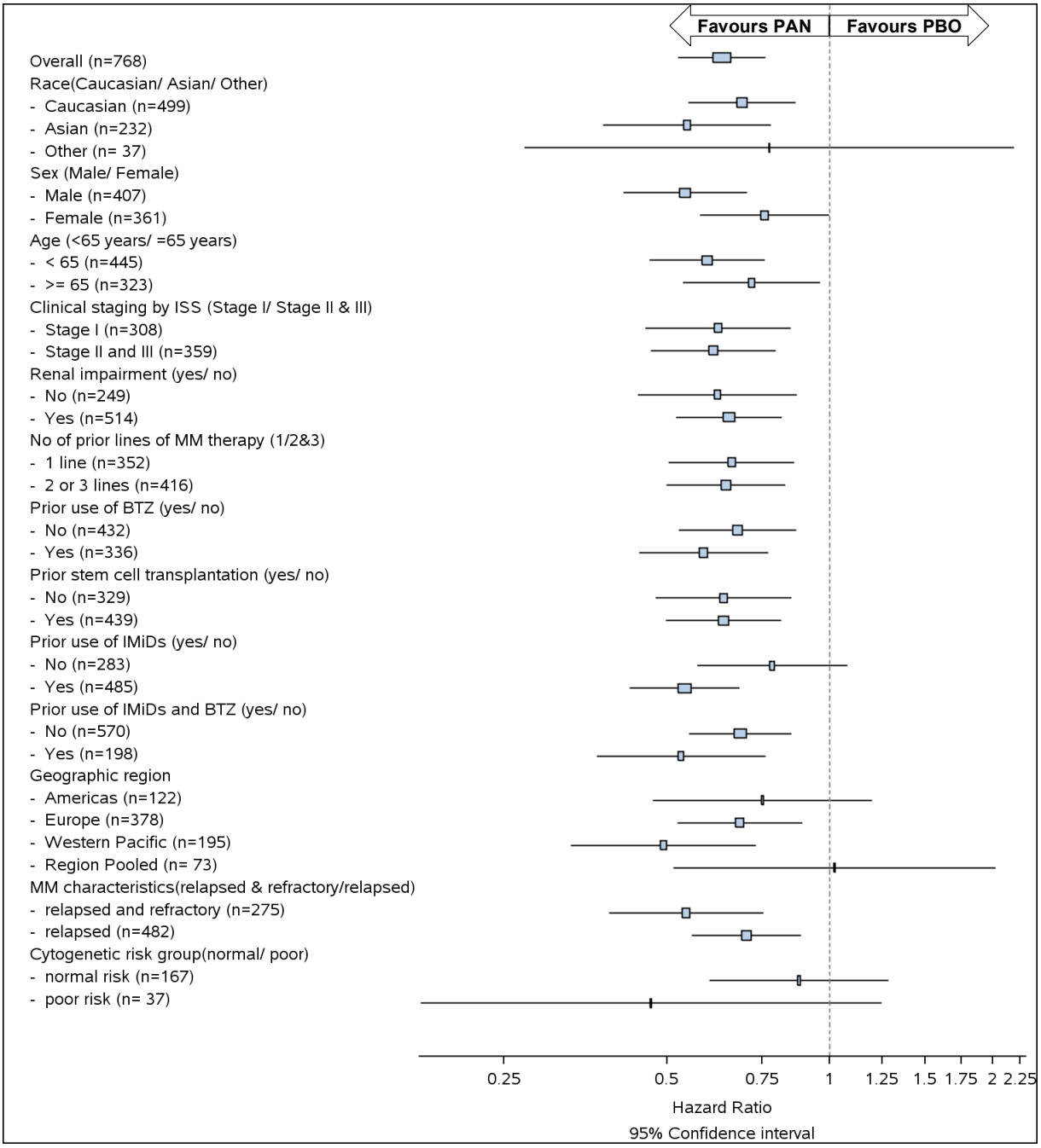
Study D2308 was stratified based on (1) number of prior lines of anti-myeloma therapy: one vs. two or three and (2) prior use of bortezomib: yes vs. no.

The results of the analysis of PFS by randomization stratum further confirmed the robustness of the primary analysis of PFS in all randomization strata, with HRs consistent with the primary analysis, ranging between 0.58 and 0.68 with upper bounds of the 95% CIs separated from and lower than unity. There was a consistent effect in patients with 1 and with 2-3 prior lines of MM therapy, with HRs of 0.66 (95% CI: 0.50, 0.86) and 0.64 (95% CI: 0.50, 0.83), respectively. Prior use of bortezomib had an impact on the improvement in PFS; in patients with prior use of bortezomib, the HR was 0.58 (95% CI: 0.44, 0.77) and in patients without prior use of bortezomib, the HR was 0.68 (95% CI: 0.53, 0.87).

### 7.3.2.1.3 Subgroup analyses

The PFS benefit per investigator assessment was consistent across a series of preplanned analyses in clinically relevant subgroups (Figure 7-5). Hazard ratios within all major subgroups are consistently in favor of the PAN arm, demonstrating patient benefit independent of age, sex, race, prior therapies (i.e., bortezomib, IMiDs, stem cell transplantation), renal impairment, clinical staging by ISS, relapsed or relapsed and refractory disease, and cytogenetic risk. Of note, the percentage of patients with poor cytogenic risk was higher in PAN treatment arm.

**Figure 7-5 Forest plot of PFS subgroup analyses by investigator assessment (Study D2308, FAS)**




Renal impairment – creatinine clearance >60 mL/min (inclusion criteria) and <90 mL/min

### 7.3.2.2 Key secondary endpoint – overall survival

At the first OS interim analysis conducted at the final PFS (based on 68.9% of OS), OS was not statistically different between the two treatments with a lower proportion of deaths reported in the PAN arm (34.6%) as compared to the PBO arm (39.9%). Although the interim data are not yet mature, the median OS in the PAN arm was numerically higher than in the PBO arm (33.6 vs. 30.4 months).

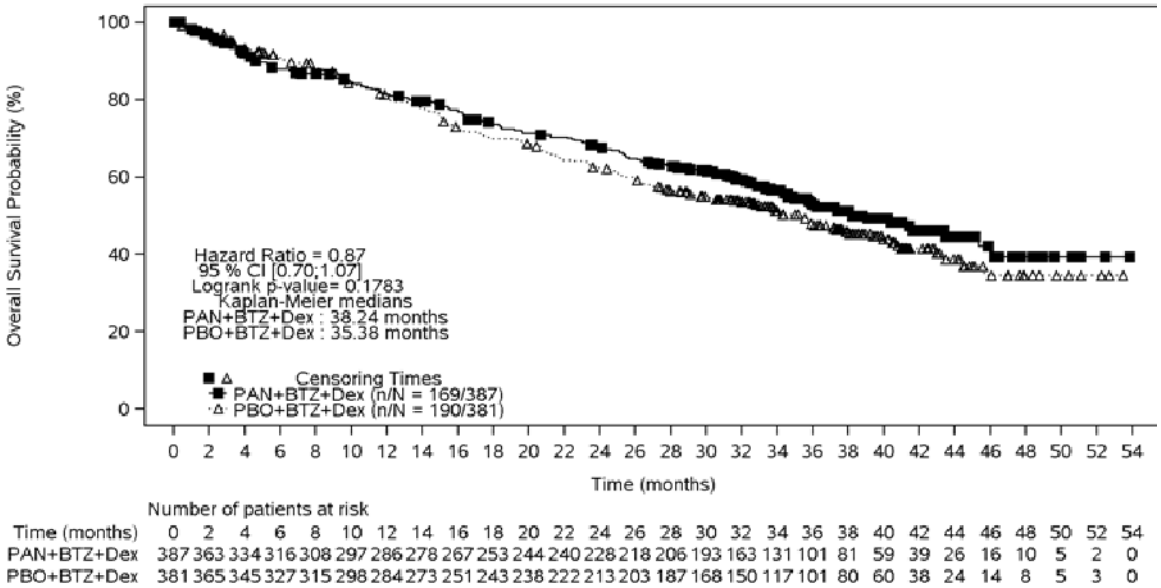
At the second OS interim analysis performed after 359 (86.5%) of the target 415 OS events required for the final OS analysis were observed, OS continued to show a trend towards a benefit for the PAN arm although this did not reach statistical significance (p=0.1783), with a hazard ratio of 0.87 (95% CI: 0.70, 1.07). There were 169 OS events (43.7%) in the PAN+BTZ+Dex arm and 190 (49.9%) in the PBO+BTZ+Dex arm. The median OS was 38.24 months and 35.38 months, respectively (Table 7-7 and Figure 7-6). As of the cut-off date, 342 patients (179 in the PAN arm and 163 in the PBO arm) were still being followed for survival.

**Table 7-7 Overall survival (Study D2308, FAS)**

| | PAN+BTZ+Dex N=387 | | PBO+BTZ+Dex N=381 | | HR | (95% CI) | p-value |
|---|---|---|---|---|---|---|---|
| **Second interim analysis of OS** | | | | | | | |
| Number of OS events – n (%) | 169 | (43.7) | 190 | (49.9) | 0.87 | (0.70,1.07) | 0.1783 |
| Number censored – n (%) | 218 | (56.3) | 191 | (50.1) | | | |
| Kaplan-Meier estimates – months (95% CI): | | | | | | | |
| 25th percentile | 16.49 (14.55, 21.26) | | 15.18 (13.08, 17.48) | | | | |
| Median OS | 38.24 (34.63, 45.37) | | 35.38 (29.37, 39.92) | | | | |
| 75th percentile | not estimable | | not estimable | | | | |

Hazard ratio is obtained from a stratified Cox model. 2-sided p-value is obtained from a stratified log-rank test.

**Figure 7-6 Kaplan-Meier plot of 2nd interim analysis of overall survival (Study D2308, FAS)**



### 7.3.2.3 Other secondary endpoints

Results for other secondary endpoints provide further evidence of efficacy (Table 7-8). Overall response rate (ORR, investigator assessed) was higher in the PAN arm compared to the PBO arm with a higher degree of CRs and nCRs. Of note, the nCR/CR rate was almost two-fold higher in the PAN arm vs. the PBO arm, indicating higher quality responses in the PAN arm.

**Table 7-8 Secondary endpoints by investigator assessment (Study D2308, FAS)**

| Secondary endpoints | PAN+BTZ+Dex N=387 | | PBO+BTZ+Dex N=381 | | p-value [1] |
|---|---|---|---|---|---|
| ORR – n (%) | 235 | (60.7) | 208 | (54.6) | 0.0873 |
| CR | 42 | (10.9) | 22 | (5.8) | |
| nCR | 65 | (16.8) | 38 | (10.0) | |
| PR | 128 | (33.1) | 148 | (38.8) | |
| nCR/CR rate (nCR and CR) – n (%) | 107 | (27.6) | 60 | (15.7) | 0.00006 [3] |
| Median TTR – months (95% CI) [2] | 1.51 | (1.41, 1.64) | 2.00 | (1.61, 2.79) | |
| Median DOR – months (95% CI) [2] | 13.14 | (11.76, 14.92) | 10.87 | (9.23, 11.76) | |
| Median TTP – months (95% CI) [2] | 12.71 | (11.30, 14.06) | 8.54 | (7.66, 9.72) | |

[1] 2-sided p-value that was generated by Cochran-Mantel-Haenszel test and presented for descriptive purposes.
[2] Derived using Kaplan-Meier method and its 95% CI according to Brookmeyer and Crowley (1982).
[3] Post hoc testing.

### 7.3.2.4 Patient-reported outcomes

Health-related quality of life was evaluated in Study D2308 using the general cancer-specific quality of life and functioning questionnaire (EORTC QLQ-C30), the myeloma-specific quality of life module (QLQ-MY20), and the FACT-GOG-Neurotoxicity (Ntx) Subscale to assess treatment-related neurotoxicity. Higher global health status/QoL scores reflect better health-related quality of life (HR-QoL) and higher symptom scores reflect greater presence of symptoms. These questionnaires were administered at screening, on Day 1 of each cycle, and every 6 weeks thereafter until the end-of-treatment visit. At baseline, all domain scores were similar between the 2 arms in the trial, with relatively high completion rates.

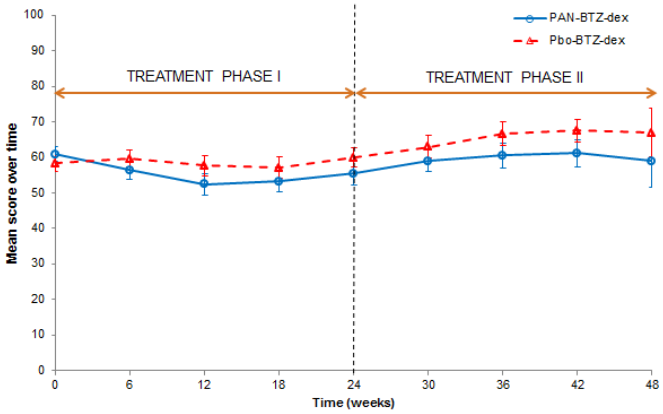
The overall trends within the EORTC QLQ-C30 domain scores were similar between the 2 arms, with overlapping scores in most subscales. During the early treatment cycles, an initial decline in HR-QoL was observed in both arms, which was more pronounced in the PAN arm (Figure 7-7). This initial decline in the PAN arm was mostly driven by the AE fatigue and diarrhea. Subsequently, HR-QoL improved towards baseline from Week 24 onwards (in treatment phase 2).

A similar trend between arms was also observed for the EORTC QLQ MY20, with almost overlapping scores across all domains. The mean disease symptoms scores indicated a trend with improvement from baseline for both treatment arms in the first few weeks that remained stable over time (Figure 7-8).

The pattern of neurotoxicity scores (FACT/GOG-Ntx) was also similar over time and overlapped between arms, with an initial decline before recovering to some extent (Figure 7-

9). Importantly, this pattern is consistent with the frequency of AEs showing no difference in peripheral neuropathy between groups.

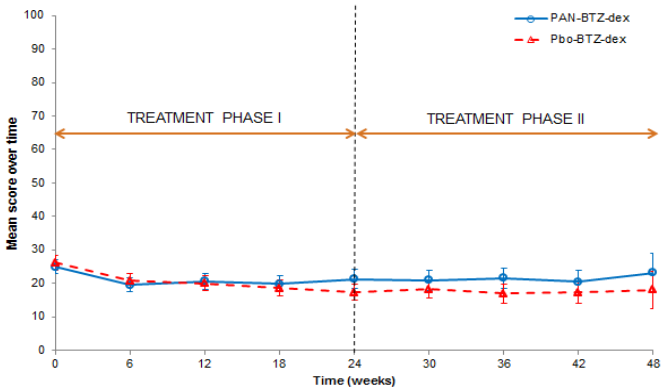
**Figure 7-7 Time course of mean EORTC QLQ-C30 Global Health Status/QoL score by treatment group (Study D2308, FAS)**




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PAN-BTZ-Dex n= 382 | 291 | 217 | 192 | 151 | 145 | 121 | 112 | 38 |
| PBO-BTZ-Dex n= 367 | 306 | 246 | 215 | 181 | 157 | 124 | 114 | 27 |

Mean and 95% CI are provided

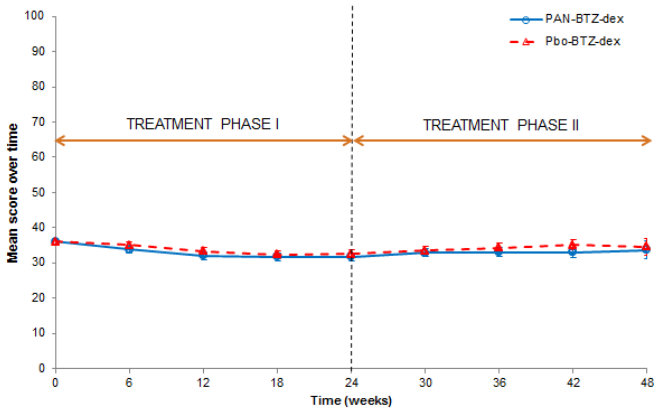
**Figure 7-8 Time course of mean EORTC QLQ-MY20 Disease Symptoms score by treatment group (Study D2308, FAS)**




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PAN-BTZ-Dex n= 379 | 293 | 218 | 193 | 151 | 145 | 122 | 112 | 38 |
| PBO-BTZ-Dex n= 370 | 308 | 248 | 213 | 179 | 157 | 124 | 113 | 27 |

Mean and 95% CI are provided

**Figure 7-9 Time course of mean FACT/GOG-Ntx Neurotoxicity Subscale score by treatment group (Study D2308, FAS)**




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PAN-BTZ-Dex | n= 378 | 288 | 215 | 191 | 149 | 143 | 118 | 108 | 36 |
| PBO-BTZ-Dex | n= 369 | 308 | 244 | 214 | 177 | 155 | 122 | 113 | 26 |

Mean and 95% CI are provided

## 7.4 Efficacy conclusions

Panobinostat in combination with bortezomib and dexamethasone is efficacious in the target population of patients with MM, having received at least one prior therapy. In the large Phase III Study D2308:

- PFS was prolonged by a clinically meaningful 3.9 months (from a median 8.1 to 12.0 months) with a statistically significant 37% risk reduction when adding panobinostat to bortezomib + dexamethasone. This clinical benefit was observed across all subgroups of gender, race, age (<65 and ≥ 65 years), prior therapies (i.e., bortezomib, IMiDs, stem cell transplantation), relapsed or relapsed and refractory disease, and cytogenetic risk. The median PFS in the PBO arm is consistent with that seen in recent studies using bortezomib ± dexamethasone in the relapsed setting (Moreau et al 2011, Kumar et al 2012, Arnulf et al 2012, Richardson et al 2007).
  - All preplanned sensitivity analyses of PFS demonstrated that the observed benefit of panobinostat over placebo is consistent between investigator, independent central assessment by the IRC, PP set, patient drop-out analyses and alternative censoring rules.
  - In addition, in a multivariate Cox model adjusting for pre-specified and relevant prognostic factors, PFS is significantly longer for panobinostat, with a HR of 0.58 (95% CI: 0.48, 0.71, p <0.0001).
- At the interim analysis of OS conducted at the time of the final PFS analysis, a lower proportion of deaths were reported in the PAN arm (34.6%) compared to the PBO arm (39.9%). Although the interim data are not yet mature, median OS in the PAN arm is numerically higher (33.6 months) than in the PBO arm (30.4 months).
- At the planned second interim OS analysis after 359 (86.5%) of the target OS events required for final OS analysis, OS continued to show a trend towards a benefit in the PAN arm although this did not reach statistical significance (p=0.1783) with a hazard ratio of 0.87 (95% CI: 0.70, 1.07). The median OS was 38.24 months in the PAN arm and 35.38

months in the PBO arm. 342 patients (179 in the PAN arm and 163 in the PBO arm) are still being followed for survival.

- The ORR is numerically higher in the PAN arm compared to the PBO arm. Importantly, the depth of response is better with the addition of panobinostat as reflected by the nearly doubled rate of nCR/CR in the PAN arm compared to the PBO arm (27.6% vs. 15.7%).
- The overall trends within the EORTC QLQ-C30 domain scores were relatively similar between the 2 arms, with overlapping scores in most subscales. During the early treatment cycles, an initial decline in HR-QoL was observed in both arms, which was more pronounced in the PAN arm and was mostly driven by the AEs of fatigue and diarrhea. Scores for the QLQ-MY20 and Neurotoxicity subscale of the FACT/GOG-Ntx were similar among patients in both treatment arms.

Results from Study DUS71 conducted in a heavily pretreated and bortezomib-refractory population, demonstrate that panobinostat in combination with bortezomib and dexamethasone can overcome resistance by recapturing response to bortezomib (ORR 35%, OS 17.5 months), thereby addressing an important unmet medical need for these patients.

Results from the dose expansion phase of Study B2207 further support the activity of panobinostat in patients with MM, and show that panobinostat in combination with bortezomib and dexamethasone can recapture responses in heavily pretreated, bortezomib-refractory patients with MM.

# 8 Safety of panobinostat in multiple myeloma

## 8.1 Drug exposure

In Study D2308, the median duration of exposure to study treatment was 5.0 months in the PAN arm and 6.1 months in the PBO arm (Table 8-1). This duration is similar to other trials using a bortezomib backbone regimen (Moreau et al 2011, Orlowski et al 2007, Petrucci et al 2014).

The median daily dose of panobinostat was 20.0 mg with a median relative dose intensity of 80.7% for panobinostat and 95.1% for placebo. The median relative dose intensity of bortezomib was 77.8% in the PAN arm and 86.7% in the PBO arm.

**Table 8-1 Duration of exposure and dose (MM combination studies, safety set)**

| | Study B2207 expansion | Study DUS71 | Study D2308 | | Pooled data |
|---|---|---|---|---|---|
| | PAN+BTZ+Dex | PAN+BTZ+Dex | PAN+BTZ+Dex | PBO+BTZ+Dex | PAN+BTZ+Dex |
| | N=15 | N=55 | N=381 | N=377 | N=451 |
| **Duration of exposure (months)** | | | | | |
| Mean (SD) | 5.9 (3.03) | 5.5 (4.79) | 6.0 (4.13) | 6.4 (3.89) | 6.0 (4.18) |
| Median | 5.2 | 4.6 | 5.0 | 6.1 | 5.0 |
| Minimum – Maximum | 1.5 – 11.6 | 0.1 – 24.1 | 0.1 – 13.5 | 0.1 – 14.6 | 0.1 – 24.1 |

Duration of exposure = [(Last dosing date of any study drug – date of 1st administration of any study drug) + 1]

## 8.2 Adverse events

### 8.2.1 Frequent adverse events

The frequency and severity of AEs were generally higher and more severe for the PAN+BTZ+Dex combination regimen relative to PBO+BTZ+Dex, especially for thrombocytopenia, neutropenia, diarrhea, fatigue, hypokalemia, and pneumonia, and could be due to the overlapping toxicities of the individual agents. AEs were consistent with the known safety and tolerability profiles of panobinostat and bortezomib.

In the more advanced and heavily pretreated patient population enrolled into Study DUS71 (Table 8-2), the safety profile of the panobinostat regimen was similar in both the type and nature of events reported to those observed in Study D2308.

In registration Study D2308, a higher proportion of PAN-treated patients reported the following AEs with a ≥ 10% difference relative to PBO (Table 8-3): diarrhea, thrombocytopenia, fatigue, nausea, decreased appetite, neutropenia, hypokalemia, vomiting, and pyrexia. A higher proportion of PAN-treated patients reported the following grade 3/4 AEs with a ≥ 10% difference relative to PBO: diarrhea, thrombocytopenia, neutropenia, and hypokalemia. The increased frequencies of AEs in general in the PAN vs. the PBO treatment group are not unexpected since both panobinostat and bortezomib share a similar toxicity profile, especially myelosuppression and GI toxicity.

No apparent increase of frequency and severity was observed regarding peripheral neuropathy for the PAN arm, since the all-grade (30.7% vs. 35.3% in the PAN and PBO arms, respectively) and grade 3-4 frequencies (6.8% vs. 5.6%) of peripheral neuropathy were comparable in the PAN and the PBO treatment groups.

The most frequently reported drug-related AEs (≥ 20%) in the PAN arm were thrombocytopenia (50.7%), anemia (25.5%), neutropenia (21.8%), diarrhea (50.9%), nausea (23.4%), and fatigue (31.0%). The most frequently reported drug-related AEs (≥ 20%) in the PBO arm were thrombocytopenia (28.6%), diarrhea (25.2%), and fatigue (21.8%).

**Table 8-2 Adverse events by frequent preferred term (occurring in at least 20% of patients) (Study DUS71, Safety set)**

| | PAN+BTZ+Dex N=55 | |
|---|---|---|
| | Any | Grade 3/4 |
| Preferred term | % | % |
| Diarrhoea | 70.9 | 20.0 |
| Fatigue | 67.3 | 20.0 |
| Thrombocytopenia | 65.5 | 63.6 |
| Nausea | 60.0 | 5.5 |
| Anaemia | 47.3 | 14.5 |
| Decreased appetite | 41.8 | 0 |
| Oedema peripheral | 40.0 | 0 |
| Dizziness | 38.2 | 3.6 |
| Dyspnoea | 36.4 | 3.6 |
| Constipation | 34.5 | 0 |

| | PAN+BTZ+Dex N=55 | |
|---|---|---|
| | Any | Grade 3/4 |
| Preferred term | % | % |
| Upper respiratory tract infection | 32.7 | 0 |
| Vomiting | 29.1 | 1.8 |
| Neuropathy peripheral | 27.3 | 1.8 |
| Hypokalaemia | 23.6 | 9.1 |
| Insomnia | 23.6 | 0 |
| Pyrexia | 21.8 | 1.8 |
| Dysgeusia | 21.8 | 0 |
| Asthenia | 20.0 | 9.1 |
| Hypotension | 20.0 | 9.1 |
| Headache | 20.0 | 0 |

A patient with multiple occurrences of an AE is counted only once in the AE category.

**Table 8-3 Adverse events by frequent preferred term (occurring in at least 20% of patients) (Study D2308, Safety set)**

| | PAN+BTZ+Dex N=381 | | PBO+BTZ+Dex N=377 | |
|---|---|---|---|---|
| | Any | Grade 3/4 | Any | Grade 3/4 |
| Preferred term | % | % | % | % |
| Diarrhoea | 68.2 | 25.5 | 41.6 | 8.0 |
| Thrombocytopenia | 64.6 | 57.0 | 40.8 | 24.9 |
| Anaemia | 41.5 | 16.5 | 33.4 | 15.9 |
| Fatigue | 41.2 | 17.1 | 29.2 | 8.8 |
| Nausea | 36.2 | 5.5 | 20.7 | 0.5 |
| Neuropathy peripheral | 30.7 | 6.8 | 35.3 | 5.6 |
| Neutropenia | 29.9 | 24.1 | 10.6 | 8.0 |
| Oedema peripheral | 28.6 | 2.1 | 19.1 | 0.3 |
| Decreased appetite | 28.1 | 3.1 | 12.5 | 1.1 |
| Hypokalaemia | 27.3 | 19.2 | 14.1 | 6.4 |
| Constipation | 26.8 | 1.0 | 32.6 | 1.1 |
| Pyrexia | 26.0 | 1.3 | 14.9 | 1.9 |
| Vomiting | 25.7 | 7.3 | 13.0 | 1.3 |
| Asthenia | 22.0 | 9.4 | 14.6 | 3.7 |
| Cough | 21.3 | 1.0 | 18.6 | 0 |

A patient with multiple occurrences of an AE is counted only once in the AE category.

Safety analysis for patients entering treatment phase 1 (in which bortezomib was administered twice weekly) compared to treatment phase 2 (in which bortezomib was administered once weekly) demonstrated a higher incidence of AEs in the initial 8 cycles of therapy for both treatment regimens (Table 8-4). Of note, for patients in the PAN+BTZ+Dex arm, the rates of grade 3/4 events for the most common AEs were markedly reduced in treatment phase 2: thrombocytopenia – 56.7% reduced to 6.0%; diarrhea – 24.1% to 7.1%; fatigue – 16.3% to 1.8%. This was also the case in the PBO+BTZ+Dex arm, in which the frequency of grade 3/4 thrombocytopenia, diarrhea and peripheral neuropathy decreased. Although these

observations should be interpreted with caution due to potential patient selection bias, they are particularly interesting in the context of published Phase III data showing that weekly bortezomib is associated with an improved tolerability profile particularly with regards to thrombocytopenia, gastro-intestinal AE and neuropathy in comparison with twice a week regimen (Bringhen et al 2010).

**Table 8-4 Adverse events by frequent preferred term (occurring in at least 20% of patients) and by treatment phase (Study D2308, Safety set)**

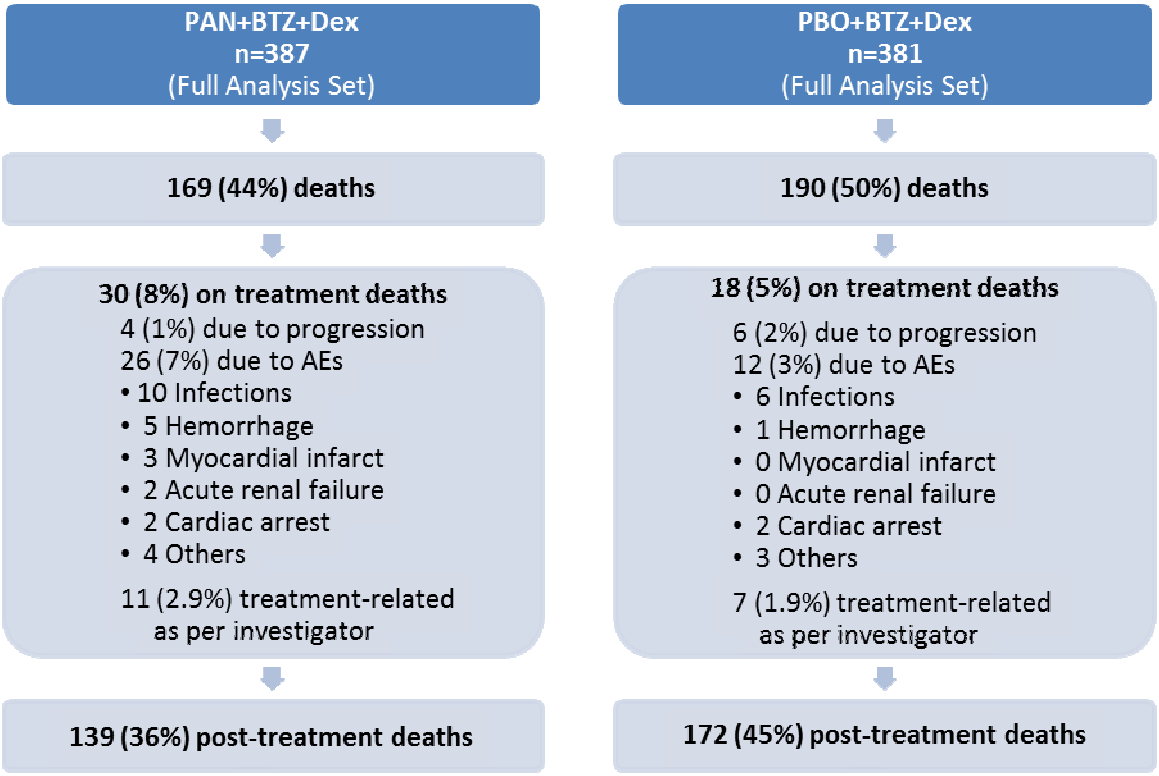
| | Treatment phase 1 (Cycles 1-8) | | | | Treatment phase 2 (Cycles 9-12) | | | |
|---|---|---|---|---|---|---|---|---|
| | PAN+BTZ+Dex N=381 | | PBO+BTZ+Dex N=377 | | PAN+BTZ+Dex N=168 | | PBO+BTZ+Dex N=193 | |
| | Any | Grade 3/4 | Any | Grade 3/4 | Any | Grade 3/4 | Any | Grade 3/4 |
| **Preferred term** | % | % | % | % | % | % | % | % |
| Diarrhoea | 65.9 | 24.1 | 38.2 | 8.0 | 29.8 | 7.1 | 20.2 | 0 |
| Thrombocytopenia | 64.3 | 56.7 | 40.1 | 24.4 | 18.5 | 6.0 | 5.2 | 1.0 |
| Anaemia | 39.9 | 15.5 | 31.8 | 15.1 | 13.7 | 3.0 | 9.3 | 3.6 |
| Fatigue | 39.6 | 16.3 | 28.9 | 8.8 | 8.9 | 1.8 | 4.7 | 0 |
| Nausea | 35.2 | 5.5 | 19.4 | 0.5 | 5.4 | 0 | 4.7 | 0 |
| Neuropathy peripheral | 29.4 | 6.0 | 32.9 | 4.8 | 6.5 | 3.0 | 11.9 | 1.6 |
| Neutropenia | 26.8 | 20.7 | 10.3 | 7.4 | 19.0 | 12.5 | 4.7 | 2.1 |
| Oedema peripheral | 26.5 | 2.1 | 17.0 | 0.3 | 10.7 | 0 | 5.7 | 0 |
| Constipation | 26.0 | 1.0 | 31.8 | 1.1 | 3.6 | 0 | 5.7 | 0 |
| Hypokalaemia | 26.0 | 18.6 | 12.5 | 5.6 | 8.3 | 4.2 | 5.2 | 2.1 |
| Decreased appetite | 25.5 | 3.1 | 11.4 | 1.1 | 10.7 | 0.6 | 3.6 | 0 |
| Vomiting | 24.1 | 6.8 | 11.7 | 1.1 | 6.0 | 1.2 | 3.6 | 0.5 |
| Pyrexia | 22.6 | 1.3 | 11.9 | 1.6 | 12.5 | 0 | 5.7 | 0.5 |
| Asthenia | 20.5 | 8.7 | 14.3 | 3.7 | 8.3 | 3.0 | 2.1 | 0 |

### 8.2.2 On-treatment deaths

In Study D2308, more deaths were reported in the PBO arm (n=172, 45%) than in the PAN arm (n=139, 36%) (Figure 8-1). However, there were more on-treatment deaths in the PAN arm. Thirty patients (7.9%) in the PAN arm died on treatment vs. 18 (4.8%) in the PBO arm. The primary causes of death were disease progression (1.0% vs. 1.6%) and AEs (6.8% vs. 3.2%) in the PAN arm versus PBO arm.

Altogether, 2.9% of these deaths were considered drug-related by the investigator in the PAN arm, vs. 1.9% in the PBO arm.

**Figure 8-1 Overview of deaths (Study D2308, FAS)**




The AEs associated with the on-treatment deaths are presented below.

**Infections**

In the PAN arm, 10 infection-related deaths (2.6%) were reported; the majority (9/10) were associated with lung infection (including 1 pulmonary tuberculosis), and had septic shock or respiratory failure reported as causes of death in most cases. The remaining patient died of sepsis associated with urinary tract infection. One of these patients died of multi-organ failure in the context of pneumonia and disease progression. Only 2 of the 10 deaths were associated with preceding grade 3-4 neutropenia.

In the PBO arm, 6 infection-related deaths (1.6%) were reported, 5 of which were associated with lung infection (pneumonia). The other patient died of necrotizing fasciitis. Only one of these patients had a preceding grade 3-4 neutropenia.

Importantly, nearly half of these infection deaths (4 on PAN arm and 3 on PBO arm) occurred in the first 2 cycles. The management of early infection deaths is recognized as a clinical challenge in managing patients with MM with various therapies, as these patients may have pre-existing infections or risk factors (Nucci et al 2009).

**Hemorrhages**

Five patients (1.3%) in the PAN arm died of events associated with hemorrhage: 2 GI hemorrhages (1 with hemorrhagic shock of GI origin), 2 pulmonary hemorrhages, and 1 cerebral hemorrhage. Three of these patients died in complicated clinical situations. One

patient with pulmonary hemorrhage developed hemoptysis with grade 4 thrombocytopenia and died of acute respiratory failure. The true cause of death in this patient was unknown due to the lack of an autopsy; however, the clinical course of the event could not be fully explained by the pulmonary hemorrhage and pulmonary embolism was one possible cause. The death due to cerebral hemorrhage was associated with MM involvement in the brain (leptomeningeal myelomatosis). The investigator assessed this fatal hemorrhage as not suspected to be related to study drug. A third patient died of a hemorrhagic shock in the context of septic shock. All 5 patients reported thrombocytopenia during the study, which was grade 4 in 2 patients and grade 3 in 3 patients. Two of these patients were receiving concomitant therapy with drugs impairing platelet function (one NSAID, one prostaglandin inhibitor).

In the PBO arm, 1 patient died of a cerebral hemorrhage in cycle 1 in the context of a grade 4 thrombocytopenia.

**Other AEs associated with on-treatment death**

In the PAN arm, 3 patients (0.8%) had a myocardial infarction. Each of these patients had significant underlying risk factors, e.g., history of hypertensive heart disease. Acute renal failures associated with disease progression occurred in 2 patients (0.5%), and cardiac arrest in 2 patients. The remaining causes of death included: 1 overdose with unknown medication, 1 intestinal ischemia related to surgery, 1 pulmonary edema, and 1 cerebrovascular accident.

In the PBO arm, 2 patients had a cardiac arrest, and the remaining causes of deaths included 2 cases of pulmonary failure, and 1 pulmonary embolism.

**On-treatment deaths in Studies B2207 and DUS71**

In Study B2207, 2 patients (3.2%) died on-treatment because of an AE out of the 62 patients enrolled. These two patients were both in the dose-expansion cohort; one patient died because of an injury, and the second with an ischemic stroke. None were considered related to treatment by the investigator.

In Study DUS71 in a more advanced population, there were 4 on-treatment deaths (7.3%), but only one (1.8%) due to an AE, a multi-organ failure associated with sepsis.

### 8.2.3 Other serious or clinically significant adverse events

In Study D2308, SAEs were reported more frequently in patients in the PAN arm relative to the PBO arm (59.8% vs. 41.6%). SAEs occurring more commonly ($\geq$ 5%) in the PAN arm were thrombocytopenia (7.3% vs. 2.1%), diarrhea (11.3% vs. 2.4%), and pneumonia (14.7% vs. 10.6%).

### 8.2.4 Adverse events leading to treatment discontinuation

In Study D2308, study treatment discontinuation due to AEs was higher in the PAN arm (138 patients, 36.2%) than in the PBO arm (77 patients, 20.4%, Table 8-5). Of note, the rate of discontinuation for AE in prior bortezomib trials ranged from 21% (Petrucci et al 2014) to 24-27% (Orlowski et al 2007, Moreau et al 2012) and 37% in the registration APEX trial (Richardson et al 2005).

The most frequent AEs leading to treatment discontinuation in the PAN arm included diarrhea (4.5% vs. 1.6% for PBO), peripheral neuropathy (3.7% vs. 1.9% for PBO), asthenia (2.9% vs. 0% for PBO), fatigue (2.9% for both treatment groups), and pneumonia (1.3% vs. 2.1% for PBO). Of note, thrombocytopenia was a cause of treatment discontinuation in 1.6% in the PAN arm and 0.5% in the PBO arm.

In the Phase II study DUS71, 18.2% of patients discontinued due to an AE.

**Table 8-5 Adverse events leading to treatment discontinuation by frequent preferred term (occurring in at least 1% of patients) (Studies DUS71 and D2308, Safety set)**

| | Study DUS71 | Study D2308 | |
|---|---|---|---|
| | PAN+BTZ+Dex | PAN+BTZ+Dex | PBO+BTZ+Dex |
| | N=55 | N=381 | N=377 |
| **Preferred term** | **%** | **%** | **%** |
| **Any AE leading to discontinuation** | **18.2** | **36.2** | **20.4** |
| Fatigue | 7.3 | 2.9 | 2.9 |
| Diarrhoea | 3.6 | 4.5 | 1.6 |
| Asthenia | 3.6 | 2.9 | 0 |
| Pneumonia | 3.6 | 1.3 | 2.1 |
| Neuropathy peripheral | 1.8 | 3.7 | 1.9 |
| Thrombocytopenia | 0 | 1.6 | 0.5 |

A patient with multiple occurrences of an AE is counted only once in the AE category.

### 8.2.5 Clinically notable adverse events

Clinically notable AEs (CNAE) are pre-specified categories of risks consisting of pooled AEs that are similar in nature and for which there is a specific clinical interest in connection with the mechanism of action of panobinostat, non-clinical studies and signals observed during the conduct of the clinical development program. Based on these criteria, 17 groups of CNAEs were identified (Section 6.3) and analyzed (Table 8-6).

The most frequently observed CNAEs were diarrhea, leukopenia and thrombocytopenia. These frequent CNAEs associated with the use of panobinostat are discussed in the following sections.

**Table 8-6 Clinically notable adverse events (Studies DUS71 and D2308, Safety set)**

| | Study DUS71 PAN+BTZ+Dex N=55 | | Study D2308 PAN+BTZ+Dex N=381 | | Study D2308 PBO+BTZ+Dex N=377 | |
|---|---|---|---|---|---|---|
| | All grades % | Grade 3/4 % | All grades % | Grade 3/4 % | All grades % | Grade 3/4 % |
| Myelosuppression | | | | | | |
| Thrombocytopenia | 65.5 | 63.6 | 72.7 | 63.3 | 44.6 | 28.1 |
| Anemia | 47.3 | 14.5 | 44.6 | 18.6 | 37.1 | 18.6 |
| Leukopenia | 21.8 | 16.4 | 45.9 | 38.6 | 24.1 | 18.6 |
| Cytopenia | 1.8 | 1.8 | 1.3 | 0.8 | 0.5 | 0.5 |
| Severe infections | | | | | | |
| Pneumonia | 18.2 | 18.2 | 23.9 | 15.7 | 18.6 | 12.7 |
| Sepsis | 14.5 | 14.5 | 6.6 | 6.6 | 4.0 | 3.7 |
| Diarrhoea | 70.9 | 20.0 | 68.2 | 25.5 | 41.6 | 8.2 |
| Hemorrhage | 25.5 | 1.8 | 20.7 | 4.2 | 11.7 | 2.4 |
| Renal dysfunction | 18.2 | 1.8 | 18.9 | 5.0 | 10.9 | 4.5 |
| Hepatic dysfunction | 9.1 | 3.6 | 16.5 | 4.2 | 12.2 | 3.4 |
| Tachyarrhythmia | 12.7 | 0 | 12.1 | 1.8 | 4.8 | 1.1 |
| QT prolongation | 9.1 | 9.1 | 10.5 | 5.2 | 6.1 | 2.9 |
| Venous thromboembolism [1] | 7.3 | 3.6 | 5.2 | 2.4 | 4.0 | 1.6 |
| Ischemic colitis | 5.5 | 1.8 | 4.5 | 1.8 | 1.6 | 1.1 |
| Ischemic heart disease | 0 | 0 | 3.7 | 2.1 | 1.3 | 0.3 |
| Hypothyroidism | 3.6 | 0 | 2.1 | 0 | 1.1 | 0 |
| Cardiac failure | 0 | 0 | 2.1 | 0.8 | 2.1 | 1.3 |
| Interstitial lung disease | 3.6 | 3.6 | 1.3 | 0.8 | 2.1 | 1.1 |
| Acute pancreatitis | 1.8 | 0 | 1.3 | 0.5 | 1.3 | 0.5 |
| Hepatitis B reactivation | 0 | 0 | 0.8 | 0.3 | 0.3 | 0 |
| Pericardial effusion | 0 | 0 | 0.3 | 0.3 | 0.3 | 0 |

[1] One event [Patient D2308-0425-00004] of pulmonary embolism (unsuspected) per narrative was coded as "PT-embolism" in a patient treated with PAN+BTZ+Dex and as such was not captured in the search for venous thromboembolism. The adjusted total number (all grades) for Study D2308 should be 21 (5.5%) for the category under PAN+BTZ+Dex and 26 (5.8%) for the pooled data based on medical review.

### 8.2.5.1 Thrombocytopenia and hemorrhage

In pre-clinical toxicology and human studies conducted prior to initiation of Study D2308, myelosuppression has been commonly detected. Platelets had been the primary lineage affected in humans. Thrombocytopenia observed during treatment with panobinostat in patients seemed to be due to a platelet production or release defect rather than myeloablation or direct platelet apoptosis. In contrast to chemotherapy-induced thrombocytopenia, there is little or no cytotoxicity on the megakaryocytes and thrombocytopenia is rapidly responsive after treatment interruption (often with a rebound effect in mice).

In Study D2308, thrombocytopenia was a common safety finding in both treatment arms (64.6% all grades, 57.0% grade 3/4 in the PAN arm; 40.8% all grades, 24.9% grade 3/4 in the PBO arm) (Table 8-3). The median time to recovery to grade 0, 1, or 2 from first reported

grade 3 or 4 thrombocytopenia was the same (12 days or 0.39 months) for the two treatment groups.

The incidence of thrombocytopenia as an AE leading to discontinuation was low; 1.6% in the PAN arm and 0.5% in the PBO arm (Table 8-5). In Study D2308, 127 patients (33.3%) in the PAN arm and 39 patients (10.3%) in the PBO arm had at least one platelet transfusion.

The higher frequencies of thrombocytopenia requiring dose adjustment or interruption in the PAN arm (31.0% vs. 10.9% for PBO), coupled with much lower frequencies of such AEs leading to study discontinuation suggest that dose adjustment or interruption and platelet transfusions are effective ways to manage AEs for the PAN+BTZ+Dex regimen.

Hemorrhages were observed in both treatment arms in Study D2308. The rate of hemorrhages of any grade was 20.7% for patients in the PAN arm and 11.7% for patients in the PBO arm. Grade 3/4 hemorrhages were infrequent in both treatment groups (4.2% vs. 2.4%) (Table 8-6).

The occurrence of hemorrhage was closely related to thrombocytopenia preceding a bleed, as the majority of patients with all grade and grade 3/4 hemorrhages also reported thrombocytopenia preceding the hemorrhage event within 30 days.

### 8.2.5.2 Severe infections

Infection in general is a known risk for patients with MM as a result of myeloma-associated immunosuppression and has been recognized as the most frequent cause of death in these patients. Myelosuppression associated with both panobinostat and bortezomib as well as the immunosuppressive effect of dexamethasone may likely further contribute to the risk (Nucci and Anaissie 2009).

In Study D2308, the incidence of severe infections in PAN-treated patients was higher than in PBO-treated patients (27.6% vs. 21.5%). Incidence of grade 3/4 events was 20.5% vs. 15.6%.

#### 8.2.5.2.1 Pneumonia and sepsis

Consistent with what has been reported for patients with MM (Augustson et al 2005), pneumonia was the most frequently reported infection in Study D2308.

The most frequently occurring AEs (≥ 1%) in the PAN arm of Study D2308 for the grouping of pneumonia were pneumonia (17.1%), lower respiratory tract infection (3.1%), and lung infection (1.3%). The most frequently occurring AEs (≥ 1%) in the PBO arm were almost identical with pneumonia (12.7%), lower respiratory tract infection (2.1%), lung infection (1.9%), and pneumonitis (1.3%). The frequency and severity of pneumonia and sepsis were similar in Study DUS71.

Pneumonia and sepsis often required hospitalization in both treatment arms of Study D2308 (17.1% of patients with at least one SAE of pneumonia or sepsis in the PAN arm vs. 12.5% in the PBO arm). However, they seldom required treatment discontinuation (5.0% of patients with at least one event of infection of any grade leading to study drug discontinuation in the PAN arm vs. 3.7% in the PBO arm). Ten and six patients in the PAN and PBO arms, respectively, died due to infections. The majority of the fatal infection events were associated with myelosuppression.

#### 8.2.5.2.2 Neutropenia

Neutropenia was frequently reported in patients treated with PAN+BTZ+Dex in Study D2308 with 75.0% of patients having reported at least one event of any grade based on laboratory data (34.5% with at least one grade 3/4 event). However, most neutropenia were grade 3 and only 6.6% of patients experienced more clinically relevant grade 4 neutropenia.

However, whereas the frequency of the most clinically relevant grade 4 neutropenia was 6.6% (vs. 2.4% in the PBO arm) as per laboratory evaluations, febrile neutropenia as a grade 3/4 AE was only reported in 1.0% for PAN and 0.5% for PBO. Of note, granulocyte colony stimulating factors were used in 13.1% and 4.2% of patients in the PAN and PBO arms, respectively.

### 8.2.5.3 Diarrhea

In Study D2308, grade 3-4 diarrhea was reported in 25.5% of patients in the PAN arm compared to 8.2% in the PBO arm. No hemorrhagic diarrhea was reported in the PAN arm. No patient died due to diarrhea-related causes. Electrolyte disturbances were often associated with diarrhea.

Grade 1 or 2 diarrheas were managed with concomitant medication in 50%-60% of patients and dose adjustment in 20% of patients with grade 2 diarrhea. Grade 3 or 4 diarrheas were managed with dose adjustment (for approximately 30% of patients) and concomitant medication (in approximately 40% of patients). Overall, 4.5% of patients with diarrhea discontinued treatment.

Of note, in the dose escalation phase of Study B2207, severe diarrheas occurred only in the cohorts with a dose of bortezomib of 1.3 mg/m$^2$ (vs. 1.0 mg/m$^2$), regardless of the combined dose of panobinostat (20, 25, or 30 mg/day).

### 8.2.5.4 Cardiac-related events

#### 8.2.5.4.1 QTc prolongation

Non-clinical reports and literature from clinical studies with other DAC inhibitors proposed QTc prolongation and changes in the ST segment or T waves as class effects of DAC inhibitors (Subramanian et al 2011, Molife et al 2007). Based on this and the cumulative clinical experience to date, QTc prolongation has been attributed to patients treated with panobinostat. QTc prolongation appeared to be dose dependent and more commonly observed with higher dose levels. Therefore, all trials included an extensive schedule of ECG monitoring.

In Study D2308, the overall incidence of QTcF interval prolongation was similar between treatment arms. No patient had a QTcF interval >500 ms in the PAN arm compared to 2 patients (0.5%) in the PBO arm. A >60 ms change from baseline in QTcF interval or an absolute QTcF >480 ms and ≤ 500 ms was observed in 3 patients (0.8%) and 5 patients (1.3%), respectively, in the PAN arm, compared to 4 (1.1%) and 0 patients, respectively, in the PBO arm.

In conclusion, while panobinostat may cause QTc prolongation, the frequency appears to be low with mild to moderate severity.

#### 8.2.5.4.2 Ischemic heart disease

In Study D2308, ischemic heart disease was reported in 14 patients (3.7%) in the PAN arm and in 5 patients (1.3%) in the PBO arm. For 8 patients (2.1%) in the PAN arm and 1 patient (0.3%) in the PBO arm, this was a grade 3/4 event (Table 8-6).

The number of patients who reported angina pectoris was balanced between the treatment arms (6 including 1 associated with coronary artery arteriosclerosis in the PAN arm vs. 5 in the PBO arm). Half of these patients (3/6 in PAN and 3/5 in PBO) had a history of angina at study entry.

Additional cardiac events were reported in the PAN arm and included myocardial infarction (3 patients, all with a fatal outcome), myocardial ischemia (3 patients, including 1 associated with elevated troponin T), and acute coronary syndrome (2 patients). Most of these events occurred in elderly patients (median age: 62 years; range: 58 to 77 years) with a time to onset ranging from 1 to 391 days.

All cases were associated with significant confounding factors, including relevant cardiovascular history (mostly hypertension) and diabetes. More patients had a reported medical history of hypertension in the PAN+BTZ+Dex arm (42.6% for PAN vs. 36.5% for PBO+BTZ+Dex), which could partially explain the higher incidence observed for the PAN+BTZ+Dex arm regarding the cardiac ischemic events.

In conclusion, there is insufficient evidence to suggest that panobinostat may increase the risk of ischemic heart disease in patients with MM.

## 8.3 Clinical chemistry and hematology

### 8.3.1 Clinical chemistry abnormalities

#### 8.3.1.1 Biochemistry abnormalities

The grade 3-4 electrolytes abnormalities which were more frequent in the PAN+BTZ+Dex arm included hypophosphatemia (20.3% vs. 12.2%), hypokalemia (18.2% vs. 6.9%) and hyponatremia (13.5% vs. 6.9%). These observations are in line with data from the supportive studies. Very few patients required dose adjustments or interruptions due to such abnormalities: hypocalcemia (0%), hypophosphatemia (1.3%), hypokalemia (5.0%), and hyponatremia (1.0%). Except for hypokalemia for which 0.8% of patients required discontinuation from the study, no other electrolyte disturbances led to treatment discontinuation.

Electrolyte disturbances were common among patients treated with PAN+BTZ+Dex, which most often did not require dose modification. Since electrolyte disturbances were often associated with patients reporting diarrhea, it is possible that diarrhea may have contributed to the development of this finding.

### 8.3.1.2 Liver and renal function abnormalities

There was no difference in the frequency of grade 3-4 liver enzyme or bilirubin elevation or grade 3-4 renal dysfunction, which were low in both arms of study D2308. Except for one patient (0.3%) who discontinued the study due to increased ALT/AST, no other patients discontinued the study due to liver or renal dysfunction in the PAN arm. One case met the liver function test criteria (ALT or AST >3× upper limit of normal [ULN] and total bilirubin >2× ULN and alkaline phosphatase ≤ 2× ULN) to qualify for a potential Hy's law case, however, confounding factors for the elevated liver function tests were identified.

## 8.3.2 Hematology abnormalities

Hematologic parameters were the most frequently reported laboratory abnormalities in Study D2308. Cytopenia known to be associated with panobinostat treatment includes thrombocytopenia, neutropenia, lymphopenia, and anemia. Hematologic abnormalities of any grade or grade 3/4 severity were more commonly reported in patients in the PAN arm compared to those in the PBO arm.

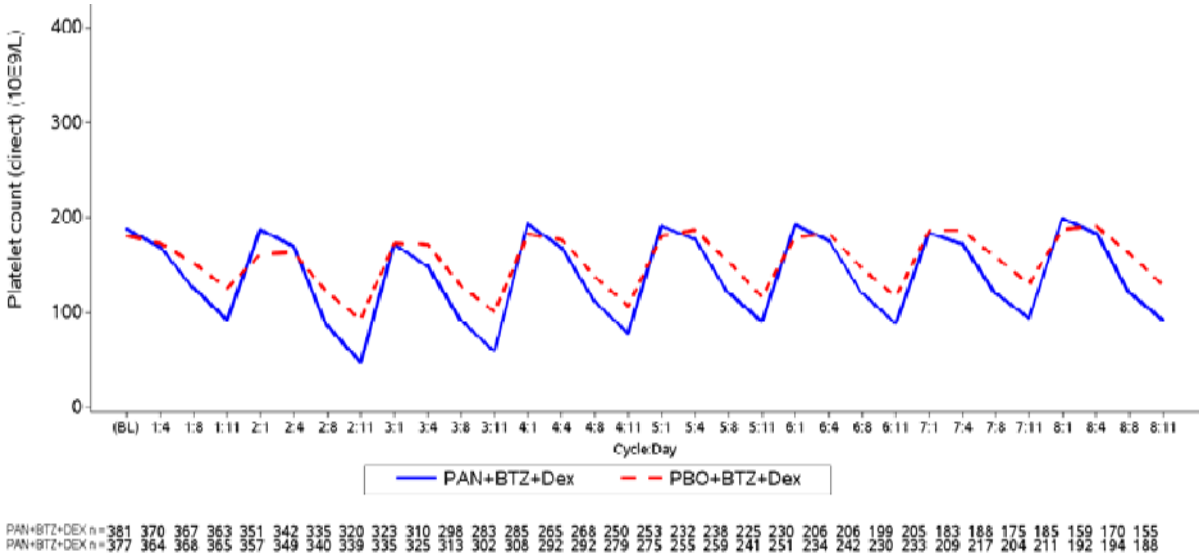
**Table 8-7 Newly occurring or worsening hematologic abnormalities (Study D2308, safety set)**

| | PAN+BTZ+Dex N=381 | | | PBO+BTZ+Dex N=377 | | |
|---|---|---|---|---|---|---|
| | | Any grade | Grade 3/4 | | Any grade | Grade 3/4 |
| Parameter | N | % | % | N | % | % |
| Platelet count (direct) | 380 | 97.6 | 67.4 | 376 | 83.5 | 31.4 |
| Absolute lymphocytes | 380 | 82.6 | 53.2 | 377 | 73.7 | 39.8 |
| WBC (total) | 380 | 81.1 | 23.2 | 377 | 47.7 | 8.2 |
| Absolute neutrophils | 380 | 75.0 | 34.5 | 377 | 35.5 | 11.4 |
| Hemoglobin | 379 | 62.0 | 17.7 | 377 | 52.3 | 19.1 |

Total = no. patients with missing or less than grade x at baseline and with at least one post-baseline value.
n = no. patients with missing or less than grade x at baseline, and worsened to grade x post-baseline.
Patients are counted only for the worst grade observed post-baseline.

Following an initial decrease in platelet median levels during the first 2 weeks of treatment, platelet levels returned to baseline by day 1 of the subsequent cycle (Figure 8-2). These data show that decrease in platelets is reversible and not cumulative.

**Figure 8-2** **Median platelet count in treatment phase I by treatment group (Study D2308, Safety Set)**




## 8.4 Special populations

### 8.4.1 Elderly patients

In Study D2308, 42% of patients were older than 65 years. The subgroups of patients younger and older than 65 years were comparable with regards to baseline disease characteristics and prior therapies for MM, with the exception of a higher percentage of patients with renal impairment in the older group (52% vs. 86%), and –as expected with standard medical practice– a higher percentage of patients having received a prior ASCT in the younger group (71% vs. 37%).

Table 8-8 shows the relative risks of the PAN vs. PBO arm for a number of safety risks. The relative risks overall for grade 3-4 AEs and for infections were similar in both age groups. In contrast, there was a trend for higher relative risks for on-treatment deaths in elderly patients, as well as for grade 3/4 AEs of hemorrhage, thrombocytopenia, diarrhea, and fatigue.

**Table 8-8** **Safety summary by age (Study D2308, Safety Set)**

| | <65 years | | | | ≥ 65 years | | | |
|---|---|---|---|---|---|---|---|---|
| | PAN N=221 % | PBO N=217 % | RR | 95% CI | PAN N=160 % | PBO N=160 % | RR | 95% CI |
| All AEs | 100 | 99.5 | 1.00 | (1.00 – 1.01) | 99.4 | 100 | 0.99 | (0.98 – 1.01) |
| SAEs | 52.9 | 37.8 | 1.40 | (1.13 – 1.73) | 69.4 | 46.9 | 1.48 | (1.22 – 1.80) |
| AEs leading to disc. | 29.9 | 16.6 | 1.80 | (1.26 – 2.58) | 45.0 | 25.6 | 1.76 | (1.28 – 2.41) |
| On treatment deaths | 5.9 | 4.1 | 1.42 | (0.62 – 3.25) | 10.6 | 5.6 | 1.89 | (0.87 – 4.11) |
| Grade 3/4 AE | 95.0 | 77.9 | 1.22 | (1.13 – 1.32) | 96.3 | 88.1 | 1.09 | (1.02 – 1.17) |
| Thrombocytopenia | 60.0 | 33.6 | 1.78 | (1.44 – 2.21) | 77.5 | 28.3 | 2.74 | (2.11 – 3.56) |
| Infection (pneumonia) | 16.3 | 12.4 | 1.31 | (0.82 – 2.08) | 15.0 | 13.1 | 1.14 | (0.66 – 1.97) |
| Infection (sepsis) | 6.8 | 3.7 | 1.84 | (0.80 – 4.25) | 6.3 | 3.8 | 1.67 | (0.62 – 4.48) |

| | <65 years | | | | ≥ 65 years | | | |
|---|---|---|---|---|---|---|---|---|
| | PAN N=221 % | PBO N=217 % | RR | 95% CI | PAN N=160 % | PBO N=160 % | RR | 95% CI |
| Diarrhea | 21.3 | 7.4 | 2.88 | (1.69 – 4.93) | 31.3 | 9.4 | 3.33 | (1.95 – 5.68) |
| Fatigue | 18.1 | 11.5 | 1.57 | (0.99 – 2.50) | 31.9 | 12.5 | 2.55 | (1.60 – 4.07) |
| Hemorrhage | 2.7 | 1.8 | 1.47 | (0.42 – 5.15) | 6.3 | 3.1 | 2.00 | (0.70 – 5.72) |

RR: relative risk in PAN vs. PBO arm. Values >1 indicate a higher risk in the PAN arm relative to the PBO arm

### 8.4.2 Renal impairment

Renal impairment was defined as having a creatinine clearance <90 mL/min at baseline which corresponds to a mild impairment. Patients with a creatinine clearance of <60 mL/min at baseline have been excluded from the trial. In the PAN arm of Study D2308, 262 of the 263 patients with renal impairment and all 118 patients with no renal impairment experienced an AE. In the PBO arm, the number and frequency of AEs in patients with renal impairment and patients with no renal impairment was 100% and 138/139 (99.3%), respectively. In general the incidence of AEs tended to be lower in the patients with no renal impairment. The following AEs showed notable differences in frequency in the PAN arm of Study D2308 for renal impairment vs. no renal impairment, respectively: thrombocytopenia (67.7% vs. 57.6%), diarrhea (70.0% vs. 64.4%) and fatigue (39.5% vs. 44.9%).

## 8.5 Analysis of risk factors for toxicity

Based on regression analysis of notable AEs of any grade in the PAN arm with baseline covariates, the factors age ≥ 65 years and baseline platelet count ≤ 150 x$10^9$/L were associated with a higher TI. In the second model of notable AEs of grade 3 and 4 in the PAN arm, age ≥ 65 years, baseline platelet count ≤ 150 x$10^9$/L and race (Asian) were associated with a higher TI. Table 8-9 and Table 8-10 provide the summary statistics of TI for each model by the categories of the significant covariates.

**Table 8-9 Toxicity index for the model including any grade notable AEs and on-treatment deaths by significant covariates (PAN arm)**

| Covariates | N | TI mean score (SD) |
|---|---|---|
| Age | | |
| <65 years | 221 | 4.07 (1.00) |
| ≥ 65 years | 160 | 4.37 (0.90) |
| Baseline platelet count | | |
| ≤ 150 x$10^9$/L* | 101 | 4.45 (0.92) |
| >150 x$10^9$/L | 280 | 4.10 (0.97) |

* Cut-off is determined based on lower limit of normal (Kratz et al 2004)

**Table 8-10 Toxicity index for the model including grade 3-4 notable AEs and on-treatment deaths by significant covariates (PAN arm)**

| Covariates | N | TI mean score (SD) |
|---|---|---|
| Age | | |
| <65 years | 221 | 3.51 (1.78) |
| ≥ 65 years | 160 | 4.01 (1.55) |
| Baseline platelet count | | |
| ≤ 150 x$10^9$/L | 101 | 4.26 (1.27) |
| >150 x$10^9$/L | 280 | 3.53 (1.80) |
| Race | | |
| Asian | 127 | 4.06 (1.42) |
| Caucasian | 244 | 3.55 (1.83) |
| Other | 10 | 3.43 (1.33) |

* Cut-off is determined based on lower limit of normal (Kratz et al 2004)

## 8.6 Safety conclusions

The data presented establish that the safety of panobinostat has been evaluated following appropriate patient exposure, and that the safety assessments made were appropriate to this evaluation.

- The most frequent AEs included thrombocytopenia and neutropenia, GI toxicities (primarily diarrhea, nausea and vomiting), and constitutional disorders such as fatigue/asthenia.
- There were more on-treatment deaths in the PAN arm; 30 patients (7.9%) vs. 18 patients (4.7%) in the PBO arm, mostly associated with infections (mainly pneumonia) and hemorrhage.
- A higher rate of treatment discontinuation was observed in the PAN arm (36.2%) compared to the PBO arm (20.4%). Individual AEs represented a low percentage of AEs leading to discontinuation (no more than 5% of patients discontinued due to a single AE).
- The rate of grade 3/4 thrombocytopenia was higher in the PAN arm than the PBO arm (57.0% vs. 24.9%); however the rate of overall grade 3/4 hemorrhages was low (4.2% vs. 2.4%). Thrombocytopenia could be managed in the majority of patients with dose and/or schedule modifications. Thrombocytopenia led to discontinuation in 1.6% and 0.5% of patients in the PAN and PBO arms, respectively.
- GI toxicities were the most commonly reported organ toxicities in the PAN arm of Study D2308, mostly due to AEs of diarrhea (all grades: 68.2%; grade 3/4: 25.5%), nausea (all grades: 36.2%; grade 3/4: 5.5%), and vomiting (all grades: 25.7%; grade 3/4: 7.3%). Few patients with a GI disorder discontinued treatment (4.5% due to diarrhea, 0.5% due to nausea and to vomiting), suggesting that these AEs could be effectively managed by interventions such as dose adjustments or interruptions with antidiarrheal or antiemetic medications when needed.
- Panobinostat did not increase or worsen bortezomib-related peripheral neuropathy when used in combination with bortezomib + dexamethasone (all grades: 30.7% vs. 35.3%; grade 3/4: 6.8% vs. 5.6% for the PAN and PBO arms, respectively).

- Elderly patients generally had a higher incidence of AEs and grade 3/4 AEs in both arms. The relative risks of overall grade 3/4 AEs and infections were similar in both age groups. In contrast, there was a trend for slightly higher relative risks in elderly patients for on-treatment deaths and for grade 3/4 AEs of hemorrhage, thrombocytopenia, diarrhea, and fatigue. In a multivariate analysis of baseline risk factors associated with on-treatment deaths and clinically notable AEs of any grade, age ≥ 65 years and baseline platelet count ≤ 150 x$10^9$/L were associated with higher toxicity (see Section 8.5).

# 9 Benefit-risk evaluation

## 9.1 Summary of benefits

### 9.1.1 Patients with relapsed and/or refractory MM (Phase III population)

The registration Study D2308, a large, double-blind, placebo-controlled Phase III trial, met its objective in demonstrating a highly significant and clinically important reduction in the risk of progression or death of 37% with PAN+BTZ+Dex over the standard regimen of bortezomib and dexamethasone (HR 0.63; 95% CI 0.52, 0.76; p <0.0001). Of note, PFS is a standard endpoint for trials in patients with relapsed and/or refractory MM, used to support the historical approvals of both bortezomib and lenalidomide.

This improvement in PFS translated into a prolongation of median PFS of 3.9 months (from a median of 8.1 to 12.0 months) over the standard regimen of bortezomib and dexamethasone. Importantly, the median PFS in the control arm is in line with that seen in recent studies using bortezomib ± dexamethasone in the relapsed setting (Richardson et al 2007, Moreau et al 2011, Kumar et al 2012, Arnulf et al 2012).

This improvement in PFS was robust and clinically relevant for the following reasons:

- It was consistent across all preplanned sensitivity analyses showing very consistent results, with HRs ranging between 0.58 and 0.71, all highly statistically significant (p <0.0001). In particular, the PFS benefit was consistent when using various censoring methods, the IRC assessment, the Per Protocol set, or a Cox model adjusting for baseline covariates. In addition, a similarly high level of consistency was observed in the pre-specified subgroup analyses, demonstrating patient benefit independent of age group (< and ≥ 65 years), gender, race, prior therapies (i.e., bortezomib, IMiDs, stem cell transplantation), relapsed or relapsed-and-refractory disease, and cytogenetic risk.
- It was associated with an improvement in the quality of the responses. While the ORR (≥ PR) was only slightly higher among patients in the PAN arm relative to the PBO arm (60.7% vs. 54.6%), it was associated with a marked increase in the rate of nCR/CR (27.6% vs. 15.7%), and the duration of responses were also longer in the PAN arm. This is particularly relevant given that higher quality responses (>PR) have been shown to be associated with longer PFS and OS in patients with relapsed or refractory MM (Chanan-Kahn and Giralt 2010, Palumbo and Cavallo 2012). Accordingly, in landmark analyses, the achievement of a response >PR was associated with prolonged PFS.
- The improvement in PFS was also associated with a trend towards an improvement in OS. At the second interim OS analysis at a time when 46.7% of patients had died, median OS

was 38.24 months and 35.38 months, in the PAN and PBO arms, respectively (HR=0.87; 95% CI: 0.70, 1.07; p-value=0.18). 342 patients (179 in the PAN arm and 163 in the PBO arm) are still being followed for survival. Importantly, crossover of patients between the treatment arms was not allowed to preserve the integrity of this endpoint.

Interpretation of the results from the Phase III study has to take into account the following considerations:

- The median PFS of 12 months with PAN+BTZ+Dex cannot be directly compared with the median TTP reported in the registration trials with bortezomib (6.2 months) and lenalidomide (11.1 and 11.3 months for each of the 2 trials) with similar follow-up times (Table 2-2). These results need to be interpreted in the context that the bortezomib and lenalidomide trials were conducted in 2002-2004, at a time when the activity of first-line therapies (based primarily on chemotherapy and, in some patients, thalidomide) was modest. In contrast, Study D2308 enrolled patients between 2010 and 2012 who had received more active agents in prior lines, including, in addition to chemotherapy, bortezomib (43%), lenalidomide (20%), and thalidomide (51%) (Table 7-3).
- This trial used an active control arm with the combination of bortezomib and dexamethasone, in contrast to the registration Phase III trials for bortezomib and lenalidomide, which both included a control arm with dexamethasone only (Richardson et al 2007, Dimopoulos et al 2007, Weber et al 2007). The only registration Phase III study employing an active bortezomib-containing control arm is the trial of bortezomib with or without pegylated liposomal doxorubicin (TTP primary endpoint, HR=1.82, median PFS of 6.5 months with bortezomib and 9.3 months with bortezomib+liposomal doxorubicin) (Orlowski et al 2007).

### 9.1.2 Patients with refractory disease (Phase Ib and II studies)

The results of the Phase III study also support the hypothesis raised by the results of the Phase II Study DUS71 in patients refractory to bortezomib, i.e. that panobinostat can contribute to overcome resistance to bortezomib. These results which are particularly relevant for patients with refractory disease are discussed in more detail below.

The results from the two uncontrolled studies (Study DUS71 and the dose expansion phase of Study B2207) further support the activity of panobinostat in overcoming resistance to bortezomib in refractory patients. In the Phase Ib study B2207 in more advanced patients, there was a consistent evidence of dose-response relationship as the doses of panobinostat and bortezomib were increased in successive cohorts, with a rate of response of 73% in the MTD dose-expansion cohort using the same dose & schedule as in the Phase II and Phase III trials.

Patients with MM who are refractory to other therapeutic agents including bortezomib have a poorer prognosis. Therefore, overcoming resistance to currently used agents such as bortezomib is of primary importance, particularly in patients with relapsed or refractory MM.

In Study DUS71 conducted in heavily pretreated patients (median of 4 prior treatments) who were bortezomib-refractory and 98% of whom had also progressed on prior lenalidomide, a clinically relevant ORR (≥ PR) of 34.5% was achieved exceeding the 21.8% best response (≥ PR) to the prior treatment in this study. This response rate compares favorably with the best overall response of 24% in a similar bortezomib-refractory and IMiD refractory patient

population with a median of 4 prior treatments (Kumar et al 2012). In this population, the median OS was 9 to 12 months depending on the number of subsequent study treatments received (including bortezomib, IMiDs, cyclophosphamide, doxorubicin, melphalan, etoposide and cisplatin). In other trials using the recently approved drugs carfilzomib or pomalidomide in a similar patient population with refractory MM, the median OS was around 15 months. Taken together, the data from study DUS71 indicate that panobinostat combined with bortezomib and dexamethasone can recapture responses and is associated with a favorable overall survival in heavily pretreated, bortezomib-refractory patients with MM.

### 9.1.3 Conclusion on benefits

Collectively, in patients with MM who progressed on at least one line of prior therapy, the results of Study D2308 and Study DUS71 demonstrate the efficacy of the PAN+BTZ+Dex; the data from Study D2308 demonstrate superiority of the PAN+BTZ+Dex combination compared to PBO+BTZ+Dex in all efficacy endpoints, in all sensitivity analyses and in all subgroup analyses.

These robust and consistent results provide clinical validation of the strong scientific rationale for this combination, i.e. that the combined use of bortezomib and panobinostat could lead to the simultaneous blockage of all known pathways of misfolded cytotoxic protein clearance from MM cells including the proteasome, aggresome degradation (tubulin) and reticulum-protein internalization/refolding (Hsp90).

The magnitude of the improvement in PFS observed in Study D2308 represents a clinically relevant advance for patients with MM having progressed on at least one prior line of therapy. The PAN+BTZ+Dex regimen has therefore the potential for offering an effective treatment alternative. This new combination introduces a drug with a novel mechanism of action into the therapeutic armamentarium for relapsed MM. The efficacy results of the PAN+BTZ+DEX regimen reported in both the randomized study D2308 and in study DUS71 appear to be higher than that of the available alternative therapies, and in the randomized study D2308, the PAN+BTZ+DXM regimen was superior to the appropriate alternative therapy.

## 9.2 Summary of risks

The nature and pattern of AEs in Study D2308 were largely consistent with the overlapping safety profiles of panobinostat and bortezomib, which include nausea, diarrhea, transient thrombocytopenia, anemia and fatigue. Peripheral neuropathy that has been frequently reported for bortezomib is not an established risk for panobinostat based on single agent data.

The key safety findings with this combination regimen primarily involved GI disorders (including diarrhea and nausea), thrombocytopenia/ hemorrhage, infection/ neutropenia, and fatigue/ asthenia. In contrast, adding panobinostat to bortezomib + dexamethasone did not increase the risk for patients regarding peripheral neuropathy. More specifically:

- Severe diarrheas were more frequent in the PAN arm, leading to treatment discontinuation in 4.5% of patients. The first episode of diarrhea typically occurs in the first 2 to 3 cycles.
- The rate of grade 3/4 thrombocytopenia was higher in the PAN arm in Study D2308. However, the rate of grade 3/4 hemorrhages (primarily GI) was low. Platelet counts

usually recovered during the week off therapy and by the start of the next treatment cycle, and there was no evidence of cumulative toxicity over time.

- Infections of grade 3/4 were observed more frequently in the PAN arm (31.2% vs. 23.9%), and included primarily pneumonias and sepsis. Patients in the PAN arm experienced more severe neutropenia, but only a small proportion were grade 4 (6.6% vs. 2.4%). Febrile neutropenia was infrequent and similar in the two arms (1.0% for PAN vs 0.5% for PBO).
- Fatigue and asthenia are common AEs in MM patients and are well characterized AEs of DAC inhibitors. In Study D2308, severe fatigue or asthenia was more frequently reported in the PAN arm compared to the PBO arm.
- There was no difference in the rates of secondary malignancies between the two treatment arms (1.8% in PAN arm vs. 2.9% in PBO arm).
- Global health status/QoL mean scores initially declined, which may have been driven by toxicity (diarrhea and fatigue), before returning to baseline in both treatment arms of Study D2308. This observation is consistent with the results from the bortezomib + dexamethasone control arm of a randomized Phase III study vs. thalidomide + dexamethasone (Hjorth et al 2012). Myeloma disease symptom scores indicated trending improvement from baseline in both treatment arms, whereas the neurotoxicity subscale initially worsened in both treatment arms but recovered to some extent over time. However, no difference in these two scores was observed between treatment arms.
- A higher rate of treatment discontinuation due to AEs was observed in the PAN arm (36.2%) compared to the PBO arm (20.4%) in Study D2308. Consistent with the above safety data, the most frequent single AE leading to discontinuations included diarrhea and fatigue (in the PAN arm), and peripheral neuropathy (in both arms). In the Phase II study DUS71 in a more heavily pretreated population, the rate of treatment discontinuation due to AE was 18%.
- A higher proportion of on-treatment deaths not related to disease progression were observed in the PAN arm compared to the PBO arm (6.8% vs. 3.2%). Altogether, 2.9% of these deaths were considered drug-related by the investigator in the PAN arm vs. 1.9% in the PBO arm. Consistent with the safety profile summarized above, the most frequent causes of these deaths included infection (mostly pneumonias) and hemorrhages (mostly gastro-intestinal). In the Phase II study DUS71 in a more heavily pretreated population, there was only one on-treatment deaths (1.8%) related to an AE.
- In comparison with younger patients, elderly patients had a similar benefit in terms of PFS and responses, but were at an increased risk of thrombocytopenia, diarrhea and fatigue which translated into a higher frequency of treatment discontinuations due to AEs and of on-treatment deaths. In this study, elderly patients did not have an increased risk of infection.

A multivariate analysis including baseline covariates was conducted using the calculation of a TI integrating on-treatment deaths and most representative clinically notable AEs (any grade) for all patients in the PAN arm as described in Section 6.3. This analysis identified both age $\geq 65$ years and a baseline platelet count $\leq 150 \times 10^9$/L, as factors associated with a higher TI. Therefore, when treated with the PAN+BTZ+Dex combination, these patients require more frequent monitoring.

The interpretation of the safety profile of this combination of the three drugs panobinostat, bortezomib and dexamethasone has to take into account the population of patients being treated (relapsed and refractory MM), their prior lines of therapy (including highly active agents as mentioned above) and their comorbidities. In addition, the most important safety findings include thrombocytopenia (and hemorrhages), infections (associated in some cases with severe neutropenia), diarrhea and fatigue, all AEs commonly reported in relapsed and refractory MM patients treated with current standard regimens including regimens based on IMiDs and bortezomib as described in Section 2.1.5.

## Summary and management of risks

Consistent with the safety profile reported in panobinostat single agent studies, the major toxicities associated with PAN+BTZ+Dex involved thrombocytopenia with complications of hemorrhage, neutropenia with complication of infection, common GI toxicity such as diarrhea, nausea and vomiting, and constitutional disorders such as fatigue/asthenia. Overlapping toxicity was apparent with respect to frequency and severity.

In general, the toxicities are clinically predictable with adequate patient information and rigorous clinical and laboratory monitoring (including for example frequent blood counts). When the first evidence of these toxicities occurs, patients should be managed with prompt intervention including supportive care and adjustment (or interruption) of the dose of panobinostat and/or bortezomib as appropriate.

More specifically, the management of diarrhea requires proactive patient information, early introduction of loperamide and adequate fluid intake at first loose stool (Andreyev et al 2014) and dose adjustment of panobinostat and/or bortezomib.

Based on the cumulative experience up to date, the risk of thrombocytopenia can be appropriately managed following established clinical guidelines including frequent blood counts, platelet transfusions, and dosing modification or interruption of panobinostat and bortezomib as necessary.

The management of the risk of infection should include a close monitoring of patients at risk (elderly, prior history of infections, prior ASCT, baseline renal impairment), the clinical assessment of patients suspect for infections, proactive management of neutropenia with dose adjustment ± G-CSF, and administration of broad spectrum antibiotics as appropriate.

The management of elderly patients requires particular attention and should follow established recent practice guidelines (Palumbo et al 2011, Palumbo et al 2014a). These patients are at higher risk of toxicity and should be monitored more frequently at initiation of therapy to allow early intervention with dose adjustment of panobinostat and/or bortezomib and/or dexamethasone or supportive care as appropriate. This monitoring should pay particular attention to signs of infections (which may require initiation of broad spectrum antibiotics and prompt management of neutropenia), decreasing platelet count (which may require dose adjustment and/or platelet transfusions), and GI upset including diarrhea and nausea/vomiting requiring prompt initiation of loperamide, adequate fluid intake, and dose adjustments (Andreyev et al 2014).

## 9.3 Recommended use and overall benefit/risk relation

### 9.3.1 Recommended use

Panobinostat, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with MM, who received at least 1 prior therapy.

The starting dose of panobinostat is 20 mg, taken orally once a day, on Days 1, 3, 5, 8, 10 and 12 of a 21-day cycle, followed by individualized dose titration depending on tolerability. Patients should be treated for eight cycles (24 weeks). It is recommended that patients with clinical benefit continue the treatment for eight additional cycles (each cycle consisting of 3 weeks, 2 weeks on / 1 week off). The total duration of treatment is up to 48 weeks. The recommended dose of bortezomib is 1.3 $mg/m^2$ given as an injection on Days 1, 4, 8 and 11 of a 21-day cycle for the first 8 cycles as recommended in its label. For extended treatment of more than 8 cycles, bortezomib is administered once weekly on days 1 and 8 (2 weeks on, 1 week off). The recommended dose of dexamethasone is 20 mg taken orally once a day the same day of bortezomib administration and the day after.

Treatment emergent hematologic toxicities included thrombocytopenia, anemia, neutropenia and lymphopenia. The recommendation is to frequently monitor blood counts and perform complete blood count before initiating any cycle of treatment. For thrombocytopenia, the platelet count should be $\geq 100\times10^9$/L prior to initiation of treatment. Thrombocytopenia is generally reversible with median platelet count recovery time of 12 days. Panobinostat may need to be temporarily withheld and the subsequent dose may need to be reduced. Platelet transfusions may be required, if clinically indicated. The absolute neutrophil count should be $\geq 1.0\times10^9$/L prior to initiation of treatment. In case of grade 3 or grade 4 neutropenia it is recommended to omit dosing and restart at the same (for grade 3) or reduced (for grade 4) dose upon recovery to grade 2. Physicians should also consider the use of growth factors (e.g., G-CSF) according to local guidelines.

The most common non-hematologic adverse reactions reported in patients treated with panobinostat were related to gastrointestinal disorders and include diarrhea, nausea and vomiting. Patients who experience diarrhea and nausea or vomiting may require temporary dose discontinuation or dose reduction of panobinostat and/or bortezomib depending on the severity and duration of the GI toxicities. Fluid and electrolyte blood levels, especially potassium, magnesium and phosphate, should be monitored periodically during therapy and corrected as clinically indicated to prevent potential dehydration and electrolyte disturbances. Antidiarrheal therapy should be instituted at the first sign of loose stools.

In addition, elderly patients treated with this regimen require more frequent monitoring and in presence of toxicities prompt introduction of supportive care and/or dose adjustments of panobinostat and/or bortezomib as appropriate.

### 9.3.2 Overall benefit-risk assessment

Treatment with PAN+BTZ+Dex results in the clinical benefit of a prolongation of the median PFS by approximately 4 months, an improvement in the quality of responses (with a longer duration and a higher rate of CR/nCR) and a trend for a longer OS. The overall clinical benefit compares favorably with that of current standard-of-care regimens in this patient population

and with that of the alternative therapies that may be offered to patients with relapsed or refractory MM. For patients for whom a bortezomib-based regimen is indicated, the addition of panobinostat improves the PFS benefit seen with the approved standard regimen of bortezomib + dexamethasone in the relapsed MM setting. For more advanced patients who are refractory to prior bortezomib, the combination with panobinostat provides an important alternative to manage drug resistance by recapturing responses to bortezomib.

The safety profile of PAN+BTZ+Dex includes essentially a higher risk of thrombocytopenia, diarrhea, and infections. Importantly, the risk of peripheral neuropathy (a well-known AE with bortezomib) was not increased with the addition of panobinostat. These risks must be managed proactively with frequent patient monitoring and prompt introduction of supportive care and/or dose adjustment of panobinostat and/or bortezomib as appropriate.

The PAN+BTZ+Dex regimen introduces a new agent with a novel mechanism of action into the therapeutic armamentarium for patients with MM who received at least one prior therapy and who are candidates for receiving a bortezomib-containing regimen.

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