# Selinexor
# (multiple myeloma, ≥ 1 prior therapy)

## Addendum to Project A22-100
## (dossier assessment)[1]

**ADDENDUM**

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## List of abbreviations

| Abbreviation | Meaning |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| CMQ | Customized Medical Dictionary for Regulatory Activities Queries |
| CSR | clinical study report |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| RCT | randomized controlled trial |
| R-ISS | Revised International Staging System |
| SGB | Sozialgesetzbuch (Social Code Book) |

# 1 Background

On 7 February 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments on Commission A22-100 (Selinexor – Benefit Assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the additional data submitted by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [2] as well as in the follow-up to the oral hearing, taking into account the information provided in the dossier [3]:

- Information on prior stem cell transplants and subsequent therapies (for total population)
- Proportion of patients treated with bortezomib for more than 8 cycles
- Analyses of crossover in selected (relevant) subgroups
- Analysis of peripheral neuropathies of any severity grade
- Proportion of patients with peripheral neuropathy (grade 3–4), separated according to study arm, who
  - received > 8 cycles of bortezomib in the BOSTON study,
  - received bortezomib retreatment after < 12 months, and/or
  - already had grade 1–2 peripheral neuropathy before.
- Proportion of patients with cataract who had complete or incomplete resolution of cataract.
- Presentation of the subsequent therapies for the total population separately according to study arms.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

# 2 Assessment

The randomized controlled trial (RCT) BOSTON was used for the benefit assessment of selinexor + bortezomib + dexamethasone. A detailed description of the study can be found in dossier assessment A22-100 [1].

In accordance with the commission, the data subsequently submitted by the company in the commenting procedure and after the oral hearing are assessed below. It is not clear from the subsequently submitted documents of the company which data cut-off the data refer to. The company only described that the data on mortality refer to the data cut-off of 15 February 2021, and the analyses of peripheral neuropathy to the safety data cut-off of 5 June 2022. In deviation from this, the benefit assessment used the data on overall survival at the later data cut-off of 22 March 2022.

## 2.1 Data presented by the company

### Proportion of patients with prior stem cell transplant

The benefit assessment of selinexor + bortezomib + dexamethasone assessed the transferability of the BOSTON study to the German health care context as limited due to the low proportion of patients who had previously received a stem cell transplant [1]. In the commenting procedure, the company provided the patient characteristics separately for patients with or without stem cell transplant. The data presented describe the characteristics of the patients at the start of the BOSTON study and are not suitable for assessing potential eligibility for stem cell therapy in an earlier line of therapy (the present research question refers to patients with ≥ 1 prior therapy). The data presented by the company therefore do not allow for a more extensive assessment compared with the dossier (see Appendix A).

### Proportion of patients treated with bortezomib for more than 8 cycles

According to the approval, bortezomib should be administered in combination with dexamethasone for a maximum of 8 cycles [4]. In the comparator arm of the BOSTON study, treatment with bortezomib + dexamethasone could be administered for more than 8 cycles. At the time of the benefit assessment, no information was available on the proportion of patients who received more than 8 cycles of bortezomib + dexamethasone. These data were subsequently submitted by the company (see Table 1).

Table 1: Patients with more than 8 cycles of bortezomib – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone

| Study | Selinexor + bortezomib + dexamethasone N = 195 | Bortezomib + dexamethasone N = 207 |
|---|---|---|
| **BOSTON** | | |
| Patients with more than 8 cycles of bortezomib, n (%) | 77 (39) | 135 (65)[a] |
| a. The proportion also includes patients with treatment switching to a selinexor-containing therapy. The proportion of patients who received the combination of bortezomib + dexamethasone for more than 8 cycles and did not switch to selinexor-containing therapy is 34%. | | |
| N: number of randomized patients; RCT: randomized controlled trial | | |

The proportion of patients treated with more than 8 cycles was higher in the comparator arm than in the intervention arm. However, these data also include those patients from the comparator arm who switched to bortezomib-containing therapy in the intervention arm (approximately 31% at the data cut-off of 15 February 2021). This means that not only did notably more patients in the comparator arm receive a longer-lasting bortezomib-containing therapy, but almost 1 third of the patients received bortezomib again as subsequent therapy in the context of treatment switching (see also the section on subsequent therapies).

**Data subsequently submitted with reference to the interpretability of the results on overall survival**

***Subsequent therapies for the total population separately according to study arms***

At the time of the benefit assessment, no information was available on subsequent antineoplastic therapies. In addition to the high proportion of patients who switched from the comparator arm to the intervention arm in the sense of treatment switching, the missing data on subsequent therapies led to uncertainties in the interpretability of the results on overall survival [1]. The company subsequently submitted the data on subsequent therapies for both treatment arms after the oral hearing (see Table 2). However, it is not clear from the data which data cut-off the data subsequently submitted refer to. It is assumed that the data on subsequent therapies, like the mortality data, refer to the data cut-off of 15 February 2021.

Table 2: Data on first subsequent antineoplastic therapy (≥ 2 patients in at least one treatment arm) – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone (BOSTON study)

| **Study** / **Regimen** | **Patients with subsequent therapy n (%)[a]** | |
|---|---|---|
| | **Selinexor + bortezomib + dexamethasone N = 195** | **Bortezomib + dexamethasone N = 207** |
| **BOSTON** | | |
| Total | 87 (44.6) | 129 (62.3) |
| Selinexor + bortezomib + dexamethasone | NA | 64 (30.9)[b] |
| Selinexor + dexamethasone | NA | 13 (6.3) |
| Bendamustine | 2 (1.0) | 0 (0) |
| Cyclophosphamide + dexamethasone | 2 (1.0) | 1 (< 1.0) |
| Chemotherapy | 6 (2.9) | 0 (0) |
| Daratumumab (monotherapy) | 2 (1.0) | 2 (1.0) |
| Daratumumab + pomalidomide + dexamethasone | 2 (1.0) | 2 (1.0) |
| Daratumumab + lenalidomide + dexamethasone | 8 (4.1) | 6 (2.9) |
| Daratumumab + bortezomib + dexamethasone | 2 (1.0) | 2 (1.0) |
| Ixazomib + lenalidomide + dexamethasone | 3 (1.5) | 1 (< 1.0) |
| Carfilzomib + dexamethasone | 4 (2.1) | 1 (< 1.0) |
| Carfilzomib + lenalidomide + dexamethasone | 3 (1.5) | 2 (1.0) |
| Pomalidomide + dexamethasone | 8 (4.1) | 5 (2.4) |
| Lenalidomide | 3 (1.5) | 4 (1.9) |
| Radiotherapy | 3 (1.5) | 0 (0) |
| Lenalidomide + cyclophosphamide + dexamethasone | 2 (1.0) | 1 (< 1.0) |
| Lenalidomide + dexamethasone | 16 (8.2) | 12 (5.8) |
| Thalidomide + cyclophosphamide + dexamethasone | 2 (2.3) | 1 (< 1.0) |
| Bortezomib + cyclophosphamide + dexamethasone | 2 (1.0) | 0 (0) |
| Bortezomib + dexamethasone | 2 (1.0) | 0 (0) |
| Bortezomib + lenalidomide + dexamethasone | 2 (1.0) | 2 (1.0) |

a. Institute's calculation of the percentages related to the randomized patients.
b. The data provided by the company on the first subsequent therapy were supplemented by the treatment switching from the comparator arm to selinexor-containing therapy. This information refers to the data cut-off of 15 February 2021. At the data cut-off of 22 March 2022, 66 (31.9%) patients had switched to selinexor + bortezomib + dexamethasone, and 14 (6.8%) had switched to selinexor + bortezomib.

n: number of patients with subsequent therapy; N: number of randomized patients; NA: not applicable; RCT: randomized controlled trial

In the comparator arm, the majority of patients received selinexor-containing therapy (selinexor + bortezomib + dexamethasone) as the first subsequent therapy due to the high

proportion of treatment switching. In addition, the dual combination of lenalidomide and dexamethasone was the most frequently used first subsequent therapy in both arms. The used treatment regimens mainly corresponded to approved treatment options in recurrence therapy [5].

However, the benefit of switching to a new bortezomib-containing therapy as a direct subsequent therapy after progression under bortezomib is questionable, especially against the background of other available treatment options. This was already discussed in the oral hearing [6].

The uncertainties in the interpretability of the results on overall survival addressed in the benefit assessment are not eliminated by the data on the subsequent therapies subsequently submitted by the company. Rather, the interpretation in the present situation is complicated by the fact that, in connection with the switch to the therapy of the intervention arm, a high proportion of patients in the comparator arm received a bortezomib-containing therapy again after a bortezomib-containing therapy and thus potentially a therapy component that was no longer effective and possibly associated with adverse events. In the intervention arm, in contrast, treatments that did not contain bortezomib were mainly used as subsequent therapy.

***Treatment change in selected (relevant) subgroups***

In the company's dossier, information on the proportion of patients with treatment switching (from the comparator arm to treatment with selinexor) was only available on the basis of the total population, but not for the subgroups. Information on the time point of treatment switching was also not available. The relevant subgroup characteristics presented in the benefit assessment were sex (men/women), age (< 65/≥ 65 years) and Revised International Staging System (R-ISS) stage (stage I and stage II/stage III) [1]. For the subgroup characteristic of age, there was a statistically significant effect modification in overall survival. The benefit assessment rated the results of overall survival on the basis of the total population as not being interpretable with certainty. At the time point of the benefit assessment, it was not possible on the basis of the data available in the dossier to determine whether an effect modification by the characteristic of age could explain existing uncertainties in the interpretability of the data on overall survival, for example the crossing Kaplan-Meier curves.

In the commenting procedure, the company submitted data on the proportion of patients with treatment switching and the median time to treatment switching for various subgroup characteristics. Table 3 shows the data for the total population as well as for the relevant subgroup characteristics of sex, age and R-ISS stage.

Table 3: Subgroups – time to treatment switching in the comparator arm

| Study<br>Outcome<br>Characteristic<br>Subgroup | Treatment switching to selinexor + bortezomib+ dexamethasone<br>N | Median time to treatment switching in months [minimum; maximum]<br>Patients with treatment switching n (%) | Treatment switching to selinexor + dexamethasone<br>N | Median time to treatment switching in months [minimum; maximum]<br>Patients with treatment switching n (%) | Total treatment switching<br>N | Median time to treatment switching in months [minimum; maximum]<br>Patients with treatment switching n (%) |
|---|---|---|---|---|---|---|
| **BOSTON** | | | | | | |
| **Total** | 204 | 7.2 [1.0; 28.9]<br>64 (31.4) | 204 | 9.9 [3.5; 27.9]<br>13 (6.4) | 204 | 7.2 [1.0; 28.9]<br>77 (37.8) |
| Sex | | | | | | |
| Female | 91 | 7.0 [1.7; 28.9]<br>28 (30.8) | 91 | 12.09 [5.3; 27.9]<br>5 (5.5) | 91 | 7.1 [1.7; 28.9]<br>33 (36.3) |
| Male | 113 | 7.3 [1.0; 18.0]<br>36 (31.9) | 113 | 8.20 [3.5; 24.0]<br>8 (7.1) | 113 | 7.33 [1.0; 24.0]<br>44 (38.9) |
| Age | | | | | | |
| < 65 years | 75 | 8.2 [1.0; 28.9]<br>30 (40.0) | 75 | 8.2 [5.3; 17.1]<br>8 (10.7) | 75 | 8.20 [1.0; 28.9]<br>38 (50.7) |
| ≥ 65 years | 129 | 5.5 [1.4; 18.0]<br>34 (26.4) | 129 | 18.9 [3.5; 27.9]<br>5 (3.9) | 129 | 6.47 [1.4; 27.9]<br>39 (30.2) |
| R-ISS | | | | | | |
| I or II | 174 | 6.9 [1.0; 18.0]<br>57 (32.8) | 174 | 8.2 [3.5; 27.9]<br>12 (6.9) | 174 | 6.9 [1.0; 27.9]<br>69 (39.7) |
| III | 16 | 6.6 [4.9; 8.5]<br>4 (25.0) | 16 | –<br>0 | 16 | 6.6 [4.9; 8.5]<br>4 (25.0) |
| Unknown | 14 | 15.7 [11.7; 28.9]<br>3 (21.4) | 14 | 24.0 [–]<br>1 (7.1) | 14 | 19.8 [11.7; 28.9]<br>4 (28.6) |

CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial; R-ISS: Revised International Staging System

The data subsequently submitted show that patients in the total population as well as in the subgroups switched from the comparator arm to the intervention arm already at an early time point. The proportion of patients < 65 years of age who switched to a selinexor-containing therapy is approximately 20 percentage points higher than in the age group of ≥ 65 years. Overall, however, the proportion of patients who switched treatment was high in both age groups and the treatment switching took place at a very early point in time, so that the subgroup results are still not interpretable, especially due to the early treatment switching.

***Summary of the interpretability of overall survival on the basis of the subsequently submitted data***

Also on the basis of the subsequently submitted data, there are still uncertainties in the interpretability of the results on overall survival, both for the total population and for effect modification by the characteristic of age. As stated in the dossier assessment, an effect modification by the characteristic of age might have explained any existing uncertainties in the interpretability of the results on overall survival.

Due to the additional information now available on the already very early treatment switching (median of 7.2 months) from the comparator arm to selinexor-containing treatment, the results on overall survival are still assessed as not interpretable at the level of the total population. For the subgroups, it cannot be ruled out with certainty that the effects by the characteristic of age in the present situation are mainly due to the high proportion of patients with treatment switching. The results of the subgroup analyses are therefore also still assessed as not interpretable.

In addition to the early treatment switching from the comparator arm to a selinexor-containing treatment, switching to another bortezomib-containing treatment as a direct subsequent therapy after progression is also viewed critically. As already described, it is questionable whether patients benefit from bortezomib treatment immediately following a progression under bortezomib.

In summary, the subsequently submitted data cannot resolve the existing uncertainties in the interpretability of the results on overall survival.

**Analyses on peripheral neuropathies**

The benefit assessment described that the results for the adverse event (AE) of peripheral neuropathies (severe AEs) were not interpretable due to incomprehensible discrepancies in event rates between the dossier [3] and the clinical study report (CSR) [7]. The company described in its comments that these discrepancies were due to different operationalizations of the AEs in the CSR and in the dossier. According to the company, the CSR operationalized peripheral neuropathies by a Synonym Recoded Preferred Term, whereas the dossier contained a coding using Dictionary-Derived Terms. The company provided neither a sufficient description of the 2 different methods nor an adequate explanation of why it deviated from the operationalization according to the study documents and decided on a different classification post hoc. Furthermore, it was not possible to compare the event rates in the dossier at the safety data cut-off of 5 June 2022 with data from the CSR because the CSR contained only results of the outcome category of side effects at the data cut-off of 15 February 2021. Irrespective of the aspect of operationalization, the 2 tables provided by the company without further explanation on different so-called subpopulations (proportion of

patients with peripheral neuropathies (grade 3–4) separated by study arm who received > 8 cycles of bortezomib in the BOSTON study, received bortezomib retreatment after < 12 months and/or already had grade 1–2 peripheral neuropathies) are incomprehensible. While the company stated that it presented different subpopulations, it did not provide information on the size of these subpopulations, nor is it possible to recognize the reasons for the differences between the 2 tables. Without further explanation, the results presented in the tables are incomprehensible. The subsequently submitted data on peripheral neuropathies of any severity grade, as well as the tables provided by the company on the subpopulations, are presented as supplementary information in Appendix B.

**Proportion of patients with cataract who had complete or incomplete resolution of cataract**

The AE of cataract (Preferred Term, severe AEs) was presented as a specific AE in the benefit assessment. Following the oral hearing, the company subsequently submitted information on the proportion of patients with complete/incomplete resolution of cataract.

The company did not provide any information on the operationalization or data cut-off of the data presented. It is assumed that these are the event rates of any severity grade at the final safety data cut-off of 5 June 2022. In the data subsequently submitted, 48 patients in the intervention arm had a cataract event, compared with 16 patients in the comparator arm. These event rates differ from those in the dossier at the data cut-off of 5 June 2022 for common AEs of any severity grade (43 versus 14). In addition, Module 4 contains the figures 46 versus 16 for the adverse event of special interest (AESI) operationalized as Customized Medical Dictionary for Regulatory Activities Queries (CMQ). It is not clear from the submitted documents of the company what caused these differences. The analyses presented are shown in Appendix C. Overall, as described in the dossier assessment, there is a hint of greater harm from selinexor for the operationalization of severe cataracts.

## 2.2 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion drawn in dossier assessment A22-100 on the added benefit of selinexor + bortezomib + dexamethasone.

The following Table 4 shows the result of the benefit assessment of selinexor + bortezomib + dexamethasone under consideration of dossier assessment A22-100 and the present addendum.

Table 4: Selinexor + bortezomib + dexamethasone – probability and extent of added benefit

| **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|
| Adult patients with multiple myeloma who have received at least one previous treatment[b, c] | ▪ Bortezomib in combination with pegylated liposomal doxorubicin<br>or<br>▪ **bortezomib in combination with dexamethasone**<br>or<br>▪ lenalidomide in combination with dexamethasone<br>or<br>▪ elotuzumab in combination with lenalidomide and dexamethasone<br>or<br>▪ carfilzomib in combination with lenalidomide and dexamethasone<br>or<br>▪ carfilzomib in combination with dexamethasone<br>or<br>▪ daratumumab in combination with lenalidomide and dexamethasone<br>or<br>▪ daratumumab in combination with bortezomib and dexamethasone | Added benefit not proven |

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. It is assumed that high-dose chemotherapy with stem cell transplantation is not an option for the patients at the time point of their current treatment.
c. It is assumed that the special situation of refractory patients is taken into account when choosing the ACT.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

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## Appendix A Characteristics of patients with and without stem cell transplant at baseline

Table 5: Characteristics of patients with and without stem cell transplant at baseline

| Study Characteristic Category | No prior stem cell transplant (N = 263) | Prior stem cell transplant (N = 139) | Total (N = 402) |
|---|---|---|---|
| **BOSTON** | | | |
| Age [years], mean (SD) | 68 (10) | 62 (8) | 66 (9) |
| Sex [F/M], % | 45/55 | 38/62 | 43/57 |
| ECOG PS, n (%) | | | |
| 0 | 79 (30) | 67 (48) | 146 (36) |
| 1 | 151 (57) | 69 (50) | 220 (55) |
| 2 | 33 (13) | 3 (2) | 36 (9) |
| R-ISS stage, n (%) | | | |
| I | 109 (41) | 90 (65) | 199 (50) |
| II | 101 (38) | 38 (27) | 139 (35) |
| III | 53 (20) | 11 (8) | 64 (16) |
| Chromosomal abnormalities, n (%) | | | |
| High risk | 124 (47) | 68 (49) | 192 (48) |
| Standard risk | 139 (53) | 71 (51) | 210 (52) |
| Frailty, n (%) | | | |
| Frail | 114 (43) | 16 (12) | 130 (32) |
| No frail | 149 (57) | 123 (88) | 272 (68) |
| Prior therapies, n (%) | | | |
| 1 | 136 (52) | 62 (45) | 198 (49) |
| 2 | 73 (28) | 56 (40) | 129 (32) |
| 3 | 54 (21) | 21 (15) | 75 (19) |
| Type of prior therapy, n (%) | | | |
| Prior PI | 191 (73) | 116 (84) | 307 (76) |
| Prior bortezomib | 171 (65) | 108 (78) | 279 (69) |
| Prior lenalidomide | 89 (34) | 65 (47) | 154 (38) |
| Lenalidomide refractory | 63 (24) | 43 (31) | 106 (26) |

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; PI: proteasome inhibitor; RCT: randomized controlled trial; R-ISS: Revised International Staging System; SD: standard deviation

## Appendix B Supplementary presentation on peripheral neuropathies

Table 6: Peripheral neuropathies of any severity grade – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone

| Study<br>Characteristic<br>Category | Selinexor + bortezomib + dexamethasone<br>N = 195 | Bortezomib + dexamethasone<br>N = 204 | Selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone |
|---|---|---|---|
| | Patients with event<br>n (%) | | RR [95% CI];<br>p-value[a] |
| **BOSTON** | | | |
| **Synonym Recoded Preferred Term** | | | |
| Neuropathy peripheral | 66 (33.8) | 99 (48.5) | 0.70 [0.55; 0.89]; 0.003 |
| **Dictionary-Derived Term** | | | |
| Neuropathy peripheral | 38 (19.5) | 61 (29.9) | 0.65 [0.46; 0.9]; 0.017 |
| Peripheral motor neuropathy | 1 (0.5) | 0 (0) | 3.14 [0.13; 76.59]; 0.367 |
| Peripheral sensorimotor neuropathy | 0 (0) | 1 (0.5) | 0.35 [0.01; 8.51]; 0.515 |
| Peripheral sensory neuropathy | 19 (9.7) | 26 (12.7) | 0.76 [0.44; 1.34]; 0.530 |
| Polyneuropathy | 12 (6.2) | 14 (6.9) | 0.90 [0.43; 1.89]; 0.815 |
| Toxic neuropathy | 0 (0) | 1 (0.5) | 0.35 [0.01; 8.51]; 0.515 |

a. Institute's calculation, effect estimate RR and 95% CI asymptotic; p-value unconditional exact test, (CSZ method according to [8]).

CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients in the category; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk

Table 7: Data provided by the company on different subpopulations on peripheral neuropathies (Table 1 from subsequently submitted data)

| **Table: Number and proportion of patients with peripheral neuropathy (grade 3-4) in subpopulations; bortezomib retreatment is operationalized as prior bortezomib therapy < 12 months (prior bortezomib therapy with less than 365 days to study start)** | | | | | |
|---|---|---|---|---|---|
| | | **SVd (N = 195)** | | **VD (N = 204)** | |
| **Peripheral neuropathy (PN), (grade 3-4)** | | **n** | **%** | **n** | **%** |
| PN Synonym Recoded Preferred Term (corresponding to CSR presentation) | Grade 3-4 | 9 | 100 | 18 | 100 |
| | Thereof > 8 cycles of bortezomib received | 4 | 44.4 | 10 | 55.6 |
| | Thereof prior bortezomib therapy < 12 months | 0 | 0 | 1 | 5.6 |
| | Thereof PN grade 1-2 at baseline | 1 | 11.1 | 2 | 11.1 |
| | Thereof > 8 cycles of bortezomib received OR prior bortezomib therapy < 12 months OR PN grade 1-2 at baseline | 4 | 44.4 | 11 | 61.1 |
| PN Dictionary-Derived Term (corresponding to dossier presentation) | Grade 3-4 | 6 | 100 | 13 | 100 |
| | Thereof > 8 cycles of bortezomib received | 3 | 50 | 7 | 53.8 |
| | Thereof prior bortezomib therapy < 12 months | 0 | 0 | 1 | 7.7 |
| | Thereof PN grade 1-2 at baseline | 0 | 0 | 1 | 7.7 |
| | Thereof > 8 cycles of bortezomib received OR prior bortezomib therapy < 12 months OR PN grade 1-2 at baseline | 3 | 50 | 7 | 53.8 |

Table 8: Data provided by the company on different subpopulations on peripheral neuropathies (Table 2 from subsequently submitted data)

| **Table: Number and proportion of patients with peripheral neuropathy (grade 3-4) in subpopulations; bortezomib retreatment is operationalized as subsequent bortezomib therapy, without consideration of crossover; previous PN grade 1-2 are PN that started at least 1 day before PN grade 3-4** | | | | | |
|---|---|---|---|---|---|
| | | **SVd (N = 195)** | | **VD (N = 204)** | |
| **Peripheral neuropathy (PN), (grade 3-4)** | | **n** | **%** | **n** | **%** |
| PN Synonym Recoded Preferred Term (corresponding to CSR presentation) | Grade 3-4 | 9 | 100 | 18 | 100 |
| | Thereof > 8 cycles of bortezomib received | 4 | 44.4 | 10 | 55.6 |
| | Thereof bortezomib retreatment after < 12 months | 0 | 0 | 0 | 0 |
| | Thereof PN grade 1-2 | 8 | 88.9 | 14 | 77.8 |
| | Thereof > 8 cycles of bortezomib received OR bortezomib treatment after < 12 months OR previous PN grade 1-2 | 8 | 88.9 | 15 | 83.3 |
| PN Dictionary-Derived Term (corresponding to dossier presentation) | Grade 3-4 | 6 | 100 | 13 | 100 |
| | Thereof > 8 cycles of bortezomib received | 3 | 50 | 7 | 53.8 |
| | Thereof bortezomib retreatment after < 12 months | 0 | 0 | 0 | 0 |
| | Thereof PN grade 1-2 | 6 | 100 | 9 | 69.2 |
| | Thereof > 8 cycles of bortezomib received OR bortezomib treatment after < 12 months OR previous PN grade 1-2 | 6 | 100 | 10 | 76.9 |

## Appendix C Complete/incomplete resolution of a cataract

Table 9: Cataract – RCT, direct comparison: selinexor + bortezomib + dexamethasone vs. bortezomib + dexamethasone

| Study | Patients with event n (%) | |
|---|---|---|
| | Selinexor + bortezomib + dexamethasone N = 195 | Bortezomib + dexamethasone N = 204 |
| **BOSTON** | | |
| Total | 48 (100) | 16 (100) |
| Complete resolution | 33 (68.8) | 10 (62.5) |
| Incomplete resolution | 15 (31.3) | 6 (37.5) |

n: number of patients in the category; N: number of analysed patients; RCT: randomized controlled trial