Selinexor (Nexpovio®) in combination with bortezomib and dexamethasone for the treatment of multiple myeloma (MM)

General information

Drug description [1]	Indication [2]
Selinexor (Nexpovio®) is an oral selective inhibitor of the nuclear export protein exportin 1. Bortezomib is a proteasome inhibitor.	Selinexor (Nexpovio®) is indicated in combination with bortezomib and dexamethasone for the treatment of adult patients with MM who have received at least one prior therapy.

Current treatment [3]

- **ESMO recommendations for patients who receive second-line therapy:**
  - Second-line autologous stem cell transplantation is an option for patients who received primary therapy that included an ASCT followed by lenalidomide maintenance and had an initial remission duration of ≥36 months.
  - Patients who had received a bortezomib-based therapy upfront without lenalidomide or daratumumab should receive an Rd-based regimen, i.e. KRd, DaraRd, IRd or EloRd.
  - DaraRd provides the best PFS for these patients, while only KRd and EloRd showed an OS benefit over Rd to date.
  - Patients who are refractory to lenalidomide upfront could receive either PomVD, DaraKd, IsaKd or DaraVd.
  - PomVd is the approved indication with best results, in terms of PFS, as second-line therapy in lenalidomide-refractory patients.
  - DaraKd has given the best reported PFS to date in lenalidomide-refractory patients, but DaraKd is awaiting EMA approval.
  - Similarly, IsaKd and SVd, which are also suitable for this setting, have not yet been approved by the EMA.
  - VenVd is a suitable option for patients with t(11;14) who have failed lenalidomide and are sensitive to proteasome inhibitors, if available.
- **ESMO recommendations for patients at third and subsequent lines of treatment:**
  - For patients who have been exposed or are refractory to both bortezomib and lenalidomide, DaraKd, IsaPd, IsaKd and EloPd are recommended.
  - Patients with t(11;14), who are refractory to lenalidomide and are PI-sensitive may be treated with VenVd, if available.
  - For triple-class refractory patients, Sd or belantamab mafodotin monotherapy is recommended, if available.
  - Results of phase III studies of melflufen, T-cell engagers and chimeric antigen receptor T cells, in triple-class refractory patients are awaited.

Regulatory status

EMA [2]	FDA [4, 5]
Approval status for this indication: On 19 May 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Nexpovio®. The CHMP adopted a new indication: ❖ Nexpovio® is indicated in combination with bortezomib and dexamethasone for the treatment of adult patients with MM who have received at least one prior therapy. **Other indications**: ❖ Nexpovio® is indicated in combination with dexamethasone for the treatment of MM in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. ✓ **Medicine under additional monitoring**	**Approval status for this indication**: On 18 December 2020, the FDA approved selinexor (Xpovio®) in combination with bortezomib and dexamethasone for the treatment of adult patients with MM who have received at least one prior therapy. ✓ Regular review ✓ Orphan drug designation **Other indications**: Xpovio® is indicated: ❖ in combination with dexamethasone for the treatment of adult patients with relapsed or refractory MM who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. ❖ for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy (this indication is approved under accelerated approval based on response rate).

✓ **Medicine received a conditional marketing authorisation[1]**	

Costs

20 Nexpovio® film-coated tablets 20 mg = € 8,890.00 (ex-factory price) [6].

Posology [7]

- The recommended selinexor, bortezomib and dexamethasone doses based on a 35-day cycle are as follows:
  - Selinexor 100 mg taken orally once weekly on Day 1 of each week.
  - The dose of selinexor should not exceed 70 mg/m^2 per dose.
  - Bortezomib 1.3 mg/m^2 administered subcutaneously once weekly on Day 1 of each week for 4 weeks followed by 1 week off.
  - Dexamethasone 20 mg taken orally twice weekly on Days 1 and 2 of each week.
- Treatment with selinexor combined with bortezomib and dexamethasone should be continued until disease progression or unacceptable toxicity.

Warnings and precautions [4, 7]

- **Recommended concomitant treatments**
  - Patients should be advised to maintain adequate fluid and caloric intake throughout treatment. Intravenous hydration should be considered for patients at risk of dehydration.
  - Prophylactic concomitant treatment with a 5-HT$_3$ antagonist and/or other anti-nausea agents should be provided prior to and during treatment with Nexpovio®.
- **Thrombocytopenia**
  - Monitor platelet counts throughout treatment.
  - Manage with dose interruption and/or reduction and supportive care.
- **Neutropenia**
  - Monitor neutrophil counts throughout treatment.
  - Manage with dose interruption and/or reduction and granulocyte colony-stimulating factors.
- **Gastrointestinal toxicity**
  - Nausea, vomiting, diarrhoea, anorexia, and weight loss may occur.
  - Provide antiemetic prophylaxis.
  - Manage with dose interruption and/or reduction, antiemetics, and supportive care.
- **Hyponatremia**
  - Monitor serum sodium levels throughout treatment.
  - Correct for concurrent hyperglycaemia and high serum paraprotein levels.
  - Manage with dose interruption, reduction, or discontinuation, and supportive care.
- **Serious infection**
  - Monitor for infection and treat promptly.
- **Neurological toxicity**
  - Advise patients to refrain from driving and engaging in hazardous occupations or activities until neurological toxicity resolves.
  - Optimize hydration status and concomitant medications to avoid dizziness or mental status changes.
- **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise females of reproductive potential and males with a female partner of reproductive potential, of the potential risk to a foetus and use of effective contraception
- **Cataract**
  - Cataracts may develop or progress. Treatment of cataracts usually requires surgical removal of the cataract.
- **Tumour lysis syndrome (TLS)**
  - TLS has been reported in patients receiving therapy with selinexor.
  - Patients at a high risk for TLS should be monitored closely. Treat TLS promptly in accordance with institutional guidelines.

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

❖ **Excipients**

- This medicinal product contains less than 1 mmol sodium (23 mg) per 20 mg tablet, that is to say essentially 'sodium-free'.

Study characteristics [1, 8, 9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
BOSTON NCT03110562	402 (1:1)	**selinexor** (100 mg once per week), **bortezomib** (1.3 mg/m² once per week), and **dexamethasone** (20 mg twice per week	**bortezomib** (1.3 mg/m² twice per week for the first 24 weeks and once per week thereafter) and **dexamethasone** (20 mg four times per week for the first 24 weeks and twice per week thereafter)	PFS in the ITT-population	**ongoing**[2], randomised, open-label, phase 3 trial	-	Karyopharm Therapeutics	[1]

Efficacy (I vs. C)

Median PFS: 13.93 months (95% CI 11.73–not evaluable) vs. 9.46 months (8.11–10.78); HR 0.70 (95% CI 0.53–0.93), p=0.0075
ORR: 76.4% (95% CI 69.8–82.2) vs. 62.3% (55.3–68.9); odds ratio 1.96 (95% CI 1.3–3.1), p=0.0012
Patients with a very good partial response or better (i.e., a ≥90% reduction in MM markers): 44.6% (95% CI 37.5–51.9) vs. 32.4% (26.0–39.2); odds ratio1.66 (1.1–2.5), p=0.0082
Patients who had stable disease or progressive disease as their best response: 13.3% (95% CI 8.9–18.9) vs. 24.2% (18.5–30.6)
Median time to first response in patients with a partial response or better: 1.1 months (IQR 0.8–1.6) vs. 1.4 months (0.8–1.6)
Median duration of response: 20.3 months (95% CI 12.5–not evaluable) vs. 12.9 months (9.3–15.8); HR 0.81 (95% CI 0.56–1.17), p=0.1364
Median time to next anti-MM treatment: 16.1 months (13.9–not evaluable) vs. 10.8 months (9.8–13.4); 0.66 (0.50–0.86), p=0.0012
Deaths (as of the data cu-toff date): 24% vs. 30%
Median OS: not reached (median follow-up 17.3 months; IQR 12.9–20.3) vs. 25 months (95% CI 23.5–not evaluable; median follow-up 17.5 months; 14.4–20.5); HR 0.84 (0.57–1.23), p=0.1852

Cross-over:

- ❖ Of the 207 patients in C group, 54% had disease progression and 30% of these patients crossed over to I group treatment.
- ❖ The median age in this population was 65 years and13% of patients were ≥75 years. Median number of prior therapies was 3; 29% of patients received four previous lines.
- ❖ PFS was 3.91 months (95% CI 3.48-6.93).
- ❖ The ORR was 19.0% (95% CI 10.2-30.9).

Safety (I vs. C, safety population n=399)

Serious AEs: n=101/195 (52%) vs. n=77/204 (38%)
Grade 3–4 peripheral neuropathy: 4.6% vs. 8.8%
Discontinuation of study treatment due to treatment-emergent AEs: n=41/195 (21%) vs. n=32/204 (16%)
Median time to discontinuation of study treatment: 194 days vs.184 days
Infections: 69% vs. 58%
Serious AEs: 52% vs. 38%
Deaths due to adverse events: n=12/195[3] (6%) vs. n=11[4] (5%)

[2] The BOSTON trial is currently ongoing; estimated study completion date is 09/2023.
[3] Of which 8 [67%] were deemed to be unrelated to treatment. The most common treatment-emergent adverse events leading to death were pneumonia (3 [2%]) and sepsis (3 [2%]) in the selinexor, bortezomib, and dexamethasone group.
[4] 10 [91%] unrelated to treatment. The most common treatment-emergent adverse events leading to death were pneumonia (3 [2%]) in the bortezomib and dexamethasone group.

Patient-reported peripheral neuropathy as measured by the QLQ-CIPN20

- Patient scores on the sensory scale of the QLQ-CIPN20 showed a smaller mean change from baseline in the selinexor, bortezomib, and dexamethasone group than in the bortezomib and dexamethasone group, with an estimated mean between-group difference in weekly score change of –0.12 (SE 0.04; 95% CI –0.20 to –0.04, p=0.0038).
- The differences were most pronounced during the first 169 days of the study, when patients in the bortezomib and dexamethasone group received twice-per-week bortezomib, in contrast to the once-per-week bortezomib regimen in the selinexor, bortezomib, and dexamethasone group.
- Mean changes from baseline were similar in each group on the QLQ-CIPN20 motor scale (–0.06; 0.04; –0.14 to 0.02, p=0.1497) and autonomic scale (0.09; 0.06; –0.02 to 0.20, p=0.1228).
- Together, these findings indicate substantially lower rates of sensory peripheral neuropathy with once-per-week selinexor, bortezomib, and dexamethasone than with twice-per-week bortezomib and dexamethasone, consistent with the mostly sensory nature of bortezomib-induced peripheral neuropathy.

UPDATE: Efficacy results assessed by independent review committee (median follow-up 22.1 months) [7]:
Median PFS: 13.2 months (95% CI, 11.7-23.4) vs. 9.5 months (95% CI, 8.1-10.8); HR 0.71 (95% CI, 0.54-0.93)
ORR: 76.9 (95% CI, 70.4-82.6) vs. 63.3 (95% CI, 56.3-69.9)
sCR: 10% vs. 13%
CR: 14% vs. 4%
VGPR: 28% vs. 22%
PR: 32% vs. 31%
Time to response: 1.4 months (95% CI, 1.4-1.5) vs. 1.6 months (95% CI, 1.5-2.1)
Median duration of response: 17.3 months (95% CI, 12.6-26.3) vs. 12.9 months (95%CI, 9.3-15.8)
Median OS (median follow-up 28.7 months): 36.7 months (95% CI, 30.2-not reached) vs. 32.8 months (27.8-not reached); HR 0.88 (95% CI, 0.63-1.2)

Risk of bias (RCT) [10]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	-	no, open-label	unclear[5]	yes[6]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, DaraRd=daratumumab/lenalidomide/dexamethasone, Elo=elotuzumab, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, Int.=intention, IRd=ixazomib/lenalidomide/dexamethasone, Isa=isatuximab, Kd=carfilzomib/dexamethasone, KRd=carfilzomib, lenalidomide and dexamethasone, MG=median gain, n=number of patients, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PomVD=pomalidomide/bortezomib/dexamethasone, PR=partial response, QLQ-CIPN20=Quality of Life–Chemotherapy-induced peripheral neuropathy questionnaire, QoL=quality of life, Rd=lenalidomide/dexamethasone, SAE=serious adverse event, sCR=stringent complete response, Sd=selinexor/dexamethasone, ST=standard treatment, SVd=Selinexor, bortezomib, dexamethasone, TLS=tumour lysis syndrome, Vd=bortezomib, dexamethasone, Ven=venetoclax, VGPR= very good partial response

[5] The BOSTON trial is currently ongoing.
[6] The funder of the trial was involved in trial design, data collection, data analysis, data interpretation, and writing of the report.

References:

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