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NCCN Multiple Myeloma Panel: Request for reconsideration of selinexor's safety rating in Multiple Myeloma NCCN Evidence Blocks.

On behalf of Karyopharm Therapeutics, I respectfully request the NCCN Multiple Myeloma Panel members to reconsider the Evidence Blocks safety rating for selinexor and dexamethasone in combination with bortezomib (XVd), pomalidomide (XPd) and daratumumab (XDd) for the treatment of patients with previously treated multiple myeloma (MM).

Suggested Changes: We respectfully ask the NCCN Panel to consider the following:

MYEL-G (EB-3), "Evidence Blocks for Therapy for Previously Treated Multiple Myeloma":

- Under "Other Recommended Regimens":
  - Selinexor/bortezomib/dexamethasone (once weekly): Change safety rating to 3
- Under "Useful in Certain Circumstances":
  - Selinexor/daratumumab/dexamethasone: Change safety rating to 3
  - Selinexor/pomalidomide/dexamethasone: Change safety rating to 3

Clinical Rationale: The once weekly XVd regimen, with selinexor administered at 100 mg once weekly, is better tolerated than the initially approved twice weekly Xd regimen with selinexor administered at a total dose of 160 mg weekly (given 80 mg twice weekly).[1] Analysis of the STORM (Xd), BOSTON (XVd), and STOMP [XPd, XDd and selinexor/carfilzomib/dexamethasone (XKd, recently submitted for NCCN consideration)] trial data demonstrates that gastrointestinal (GI) toxicity is dose-dependent and significantly lower with once weekly selinexor combination regimens.[2-6] Specifically, a 15-20% absolute reduction in GI adverse events (AEs), including nausea, decreased appetite and diarrhea, was observed with once weekly XVd compared to twice weekly Xd, despite the average treatment duration of 10 months on XVd versus ~3 months on Xd (Table 1).[2,3] A significant reduction in hematological AEs, including neutropenia, thrombocytopenia, anemia and leukopenia, was also observed with XVd, again despite the >3-fold longer treatment duration on XVd vs Vd (Table 2).[2,3] In addition, lower rates of overall GI and hematological (particularly Grade 3/4) AEs were observed in patients treated with once weekly XPd, XDd and XKd (Tables 1 and 2).[2,4-6] *Despite the observed improvement in the incidence and severity of AEs associated with XVd, XPd and XDd, Xd was rated as a safer regimen in the NCCN Evidence Blocks.*

Table 1. Selected Gastrointestinal AEs in Patients With Multiple Myeloma Treated With Twice-Weekly Vs Once-Weekly Selinexor Regimens[2-6]

ANY GRADE AE, n (%)	BIW Xd (N=123)	QW XVd (N=195)	QW XKd (N=24)	QW XPd (N=63)	QW XDd (N=34)
Nausea	88 (72)	98 (50)	17 (70.8)	38 (60.3)	24 (71)
Decreased appetite	69 (56)	69 (35)	12 (50.0)	28 (44.4)	12 (35)
Diarrhea	56 (46)	63 (32)	5 (20.8)	18 (28.6)	12 (35)
Vomiting	47 (38)	40 (21)	5 (20.8)	13 (20.6)	10 (29)
GRADE 3/4 AE, n (%)	**BIW Xd (N=123)**	**QW XVd (N=195)**	**QW XKd (N=24)**	**QW XPd (N=63)**	**QW XDd (N=34)**
Nausea	12 (10)	15 (8)	1 (4.2)	1 (1.6)	3 (9)
Decreased appetite	6 (5)	7 (4)	1 (4.2)	1 (1.6)	0
Diarrhea	9 (7)	12 (6)	0	0	1 (3)
Vomiting	4 (3)	8 (4)	1 (4.2)	1 (1.6)	1 (3)

AE, adverse event; BIW, twice weekly; QW, once weekly; Xd, selinexor and dexamethasone; XDd, selinexor, daratumumab, and dexamethasone; XKd, selinexor, carfilzomib, and dexamethasone; XPd, selinexor, pomalidomide, and dexamethasone; XVd, selinexor, bortezomib, and dexamethasone

Table 2. Selected Hematologic AEs in Patients With Multiple Myeloma Treated With Twice-Weekly Vs Once-Weekly Selinexor Regimens[2-6]

ANY GRADE AE, n (%)	BIW Xd (N=123)	QW XVd (N=195)	QW XKd (N=24)	QW XPd (N=63)	QW XDd (N=34)
Neutropenia	49 (40)	29 (15)	7 (29.2)	38 (60.3)	17 (50)
Thrombocytopenia	90 (73)	117 (60)	19 (79.2)	34 (54.0)	24 (71)
Anemia	83 (67)	71 (36)	14 (58.3)	34 (54.0)	21 (62)
Leukopenia	41 (33)	-	8 (33.3)	15 (23.8)	16 (47)

GRADE 3/4 AE, n (%)	BIW Xd (N=123)	QW XVd (N=195)	QW XKd (N=24)	QW XPd (N=63)	QW XDd (N=34)
Neutropenia	26 (21)	17 (9)	2 (8.3)	34 (54.0)	9 (27)
Thrombocytopenia	72 (59)	77 (39)	14 (58.3)	20 (31.7)	16 (47)
Anemia	54 (44)	31 (16)	5 (20.8)	21 (33.3)	11 (32)
Leukopenia	17 (14)	-	3 (12.5)	8 (12.7)	11 (32)

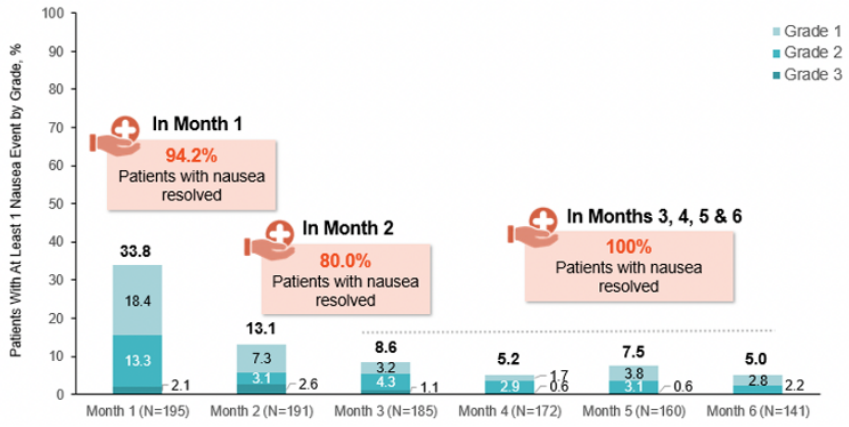
AE, adverse event; BIW, twice weekly; QW, once weekly; Xd, selinexor and dexamethasone; XDd, selinexor, daratumumab, and dexamethasone; XKd, selinexor, carfilzomib, and dexamethasone; XPd, selinexor, pomalidomide, and dexamethasone; XVd, selinexor, bortezomib, and dexamethasone

Once weekly XVd (the only once weekly bortezomib-based regimen approved for relapsed MM) is a more potent regimen than standard twice weekly bortezomib (Vd) based on superior PFS, ORR, and time to next therapy. Furthermore, XVd is associated with significantly less overall (32.3% vs 47.1%, p=0.0010) and grade ≥2 (21.0% vs 34.3%, p=0.0013) peripheral neuropathy (PN).[3] This is the first phase 3 study demonstrating a lower rate of peripheral neuropathy with a triplet Vd regimen versus standard Vd.[7,8] Moreover, treatment with XVd resulted in lower PN-related sensory symptoms and pain.[9] Of note, PN was the most common AE leading to treatment discontinuation in the BOSTON trial on *both* arms of the study (4.6% on XVd vs 7.4% on Vd); discontinuations due to GI toxicity were only 3% (mainly due to nausea) on the XVd arm.[3]

In contrast to PN, a long-term side effect that often persists for the lifetime of the patient and reduces quality of life, GI toxicity is reversible and can be prevented with prophylactic supportive care. In the BOSTON study, only a single anti-nausea agent (typically a 5-HT3 antagonist) was required prior to initiation of XVd.[3] However, based on cumulative experience and similar to NCCN Antiemesis Guidelines, the consensus recommendation is to administer two anti-emetic agents prophylactically (a 5-HT3 antagonist, such as ondansetron) in addition to either an NK1 receptor antagonist such as aprepitant or low-dose olanzapine.[10,11] Therefore, with the use of two anti-emetics, GI side effects can be further prevented and reduced, and it is expected that discontinuations due to GI AEs will be markedly less than the 3% observed on BOSTON.

Furthermore, a post-hoc analysis of the BOSTON study demonstrates that GI sides effects, particularly nausea, improved rapidly over time with each cycle of therapy (Table 3).[12] Nausea was resolved in 100% of patients beyond cycle 2 (after 2 months), indicating that GI side effects experienced in the 1st two cycles of therapy did not impact long-term quality of life. The number of patients experiencing nausea decreased over time due to dose modifications (median selinexor dose of 80 mg once weekly), improved use of standard prophylactic care, and the improvement and resolution of GI side effects.

Table 3. Patients Experiencing Nausea in the First 6 Months of XVd Treatment in the BOSTON Trial[12]



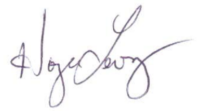
XVd, selinexor, bortezomib and dexamethasone

We also note that once weekly XVd demonstrated a markedly less burdensome AE profile when compared to panobinostat/bortezomib/dexamethasone (FVd), another Vd-containing regimen approved in the 2L+ setting,.[3,13,14] Despite limitations of cross-trial comparisons and differences between study populations, significantly fewer patients experienced

hematological (including thrombocytopenia, neutropenia, and anemia) and non-hematological AEs (including PN, diarrhea, intestinal perforations, vomiting, and fatigue) with XVd compared with FVd in the phase 3 PANOROMA trial (Appendix Table 3). *Despite a comparatively worse AE profile, FVd was rated as a safer regimen than XVd, XPd, and XDd in the NCCN Evidence Blocks.*

Summary: Once weekly oral selinexor in combination with currently approved backbone agents, including XVd, XPd, XDd and XKd, represent novel treatment options with a substantially reduced AE burden in the context of a much longer duration of therapy as compared with the initially approved twice weekly Xd regimen. With standard (dual anti-emetic) prophylaxis, the incidence and severity of GI toxicities may be reduced, and no other prophylaxis is required. Lower rates and severity of PN are associated with XVd, and no clinically significant long-term toxicities have been observed. Furthermore, no significant increases in moderate or serious infections, opportunistic infections, febrile neutropenia, or major organ damage are associated with most of the selinexor combination regimens. Therefore, we respectfully request that these observations warrant reconsideration of the NCCN Evidence Blocks safety ratings for selinexor combination regimens.

Sincerely,



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Appendix

Table 3. Comparison of Select Adverse Events in the BOSTON and PANORAMA Trials[3,14,15]

BOSTON	XVd	Vd
PATIENT CHARACTERISTICS, n	**195**	**207**
Median prior regimens, n (range)	1 (1-3)	2 (1-3)
Number of prior regimens, 1 : 2 : 3, %	51 : 33 : 16	48 : 31 : 21
High-risk chromosomal abnormalities, %	50	46
Creatinine clearance <30 mL/min : 30-60 mL/min, %	2 : 27	5 : 29
Lenalidomide exposed, %	40	37
Bortezomib exposed, %	69	70
Previous PI + IMiD, %	31	31
Previous stem cell transplant, %	39	30
SAFETY, n	**195**	**204**
SAEs, %	52	38
Nausea (%)	50	10
Decreased appetite (%)	35	5
Diarrhea (%)	32	25
Vomiting (%)	21	4
Neutropenia (%)	15	6
Thrombocytopenia (%)	60	27
Anemia (%)	36	23
Peripheral neuropathy (%)	32	47
Fatigue (%)	42	18

PANORAMA	FVd	Vd
PATIENT CHARACTERISTICS, n	**387**	**381**
Median prior regimens, n (range)	-	-
Previous treatment lines 1 : 2 : 3, %	51 : 32 : 17	52 : 28 : 20
Cytogenic risk high, %	-	-
Creatinine clearance 60-89 mL/min : ≥90 mL/min, %	68 : 31	65 : 34
Previous lenalidomide, %	19	22
Previous bortezomib, %	44	42
Previous bortezomib + IMiD, %	24	26
Previous stem cell transplant, %	56	59
SAFETY, n	**381**	**377**
SAEs, %	60	42
Nausea (%)	36	21
Decreased appetite (%)	28	12
Diarrhea (%)	68	42
Vomiting (%)	26	13
Neutropenia (%)	75	36
Thrombocytopenia (%)	98	84
Anemia (%)	62	52
Peripheral neuropathy (%)	61	67
Fatigue (%)	57	18

FVd, panobinostat, bortezomib, and dexamethasone; IMiD, immunomodulatory drug; PI, protease inhibitor; SAE, severe adverse event; Xd, selinexor and dexamethasone; XVd, selinexor, bortezomib, and dexamethasone

References (enclosed):

1. XPOVIO® [package insert]. Newton, MA: Karyopharm Therapeutics, Inc.; 2021.
2. Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. N Engl J Med 2019; 381:727–38.
3. Grosicki S, Simonova M, Spicka I, et al. Once-Weekly Selinexor, bortezomib, and dexamethasone versus twice-weekly bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomized open-label, phase 3 trial. Lancet 2020;396:1563-1573.
4. Chen CI, Bahlis N, Gasparetto C, et al. Selinexor, pomalidomide, and dexamethasone (SPd) in patients with relapsed or refractory multiple myeloma. Presented at: American Society of Hematology Annual Meeting. December 5-8, 2020. Abstract 726.
5. Gasparetto C, Lentzsch, Schiller GJ, et al. Selinexor, daratumumab, and dexamethasone in patients with relapsed or refractory multiple myeloma. eJHaem 8 November 2020;1-10. https://doi.org/10.1002/jha2.122
6. Gasparetto, C, Lipe B, Tuchman SA, et al. Selinexor in combination with carfilzomib and dexamethasone, all once weekly (SKd), for patients with relapsed/refractory multiple myeloma. Presented at: American Society of Hematology Annual Meeting. December 5-8, 2020. Abstract 1366.
7. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. New England Journal of Medicine 2016;375(8):754–66.
8. Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. The Lancet Oncology 2019;20(6):781–94.
9. Sanchez L, Leleu X, Beaumont J, et al. Peripheral neuropathy symptoms, pain and functioning in relapsed or refractory multiple myeloma patients treated with selinexor, bortezomib, and dexamethasone. Presented at: American Society of Hematology Annual Meeting. December 5-8, 2020. Abstract 3489.
10. Mikhael J, Noonan KR, Faiman B, et al. Consensus recommendations for the clinical management of patients with multiple myeloma treated with selinexor. Clin Lymphoma Myeloma Leuk 2020;20(6):351-57.
11. NCCN® Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis. Version 1.2021. National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed April 27, 2021.
12. Data on file. Karyopharm Therapuetics, 2021.
13. San-Miguel JF, Hungria VT, Yoon S-S, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomized, double-blind phase 3 trial. Lancet Oncol 2014;15(11):1195-206.
14. San-Miguel JF, Hungria FT, Yoon S-S, et al. Overall survival of patients with relapsed multiple myeloma treated with Panobinostat or placebo plus bortezomib and dexamethasone (the PANORAMA 1 trial): a randomized, placebo-controlled, phase 3 trial. Lancet Haematol 206;3(11):e506-e515.