ONLINE-ONLY APPENDIX

Table A1. Prior therapies received (agents received by >5 patients).

	Schedule A, N=27		Schedule B, N=17		
Prior therapy	**MM**	**Lymphoma**	**MM**	**Lymphoma**	**Total**
	n=15	**n=12**	**n=2**	**n=15**	**N=44**
Prior agents, n (%)					
Doxorubicin	11 (73)	12 (100)	1 (50)	14 (93)	38 (86)
Cyclophosphamide	12 (80)	11 (92)	1 (50)	10 (67)	34 (77)
Vincristine	11 (73)	11 (92)	1 (50)	11 (73)	34 (77)
Prednisone[a]	4 (27)	10 (83)	1 (50)	10 (67)	25 (57)
Etoposide	2 (13)	10 (83)	0	12 (80)	24 (55)
Rituximab	1 (7)	11 (92)	0	9 (60)	21 (48)
Dexamethasone	14 (93)	3 (25)	2 (100)	2 (13)	21 (48)
Ifosfamide	0	7 (58)	0	12 (80)	19 (43)
Bortezomib	15 (100)	1 (8)	2 (100)	1 (7)	19 (43)
Carboplatin	0	6 (50)	0	12 (80)	18 (41)
Lenalidomide	11 (73)	0	2 (100)	1 (7)	14 (32)
Melphalan	8 (53)	2 (17)	1 (50)	2 (13)	13 (30)
Gemcitabine	0	5 (42)	0	6 (40)	11 (25)
Thalidomide	11 (73)	0	0	0	11 (25)
Vinorelbine	0	5 (42)	0	6 (40)	11 (25)
Cytarabine	1 (7)	4 (33)	0	3 (20)	8 (18)
Cisplatin	3 (20)	3 (25)	0	1 (7)	7 (16)
Bleomycin	0	2 (17)	0	4 (27)	6 (14)
Fludarabine	0	4 (33)	0	2 (13)	6 (14)

[a]Including prednisolone

Table A2. Summary of pevonedistat plasma pharmacokinetic parameters on days 1 and 9 of cycle 1 on schedule A (administration on days 1, 2, 8, 9 of 21-day cycles).

	Pevonedistat dose, mg/m^2					
Parameter	**25**	**50**	**65**	**83**	**110 (MTD)**	**147**
Day 1, n	**3**	**2**	**3**	**2**	**13**	**3**
C_{max}, ng/mL	272 (25)	637	919 (25)	1285	1502 (33)	2380 (41)
T_{max}, hr	1.1	2.0	1.0	1.2	1.0	1.0
	(1.0–1.5)	(1.0–3.0)	(1.0–1.0)	(1.1–1.4)	(1.0–1.3)	(1.0–1.1)
AUC_{0-24hr}, ng.hr/mL	1367[a]	3329	3562 (21)	4526	4685 (23)	7704 (36)
Day 9, n	**3**	**2**	**2**	**2**	**9**	**2**
C_{max}, ng/mL	281 (24)	794	867	2495	1683 (28)	1734
T_{max}, hr	1.1	1.0	1.2	1.4	1.1	1.0
	(1.1–1.5)	(1.0–1.0)	(1.2–1.2)	(1.0–2.0)	(1.0–1.1)	(1.0–1.1)
AUC_{0-24hr}, ng.hr/mL	1631 (12)	3084	3013	9860[b]	4833 (19)[c]	4774

Data shown as geometric mean (%coefficient of variation) except for T_{max}, which is shown as median (range). [a]n=2, [b]n=1, [c]n=7

Table A3. Summary of pevonedistat plasma pharmacokinetic parameters on days 1 and 4 (or, alternatively, day 11) of cycle 1 on schedule B (administration on days 1, 4, 8, 11 of 21-day cycles).

	Pevonedistat dose, mg/m^2					
Parameter	**100**	**110**	**147**	**196 (MTD)**		**261**
Day 1, n	**1**	**2**	**2**	**7**		**4**
C_{max}, ng/mL	1790	1977	2253	4565 (24)		4255 (32)
T_{max}, hr	1.0	1.1	1.0	1.1		1.0
		(1.0–1.1)	(1.0–1.0)	(1.0–1.1)		(1.0–1.3)
AUC_{0-24hr}, ng.hr/mL	5070	5657	5858	10,830 (19)[a]		10,232 (13)
Day 4 or Day 11, n	**Day 4, n=1**	**Day 11, n=2**	**Day 11, n=2**	**Day 4, n=6**	**Day 11, n=2**	**Day 11, n=3**
C_{max}, ng/mL	1790	1479	2141	3751 (53)	3010	5289 (7)
T_{max}, hr	1.0	1.3	1.1	1.0	1.0	1.0
		(1.0–1.5)	(1.1–1.2)	(0.9–1.1)	(1.0–1.1)	(1.0–1.0)
AUC_{0-24hr}, ng.hr/mL	5090	4561	6382	8309 (39)	6950[b]	10,600[c]

Data shown as geometric mean (%coefficient of variation) except for T_{max}, which is shown as median (range). [a]n=6, [b]n=1, [c]n=2.

Table A4. Changes from baseline in gene expression levels for NAE-regulated transcriptional targets on cycle 1, day 1 following pevonedistat administration at the MTDs on schedules A and B

Parameter, median (range)	Schedule A, MTD, 110 mg/m^2, n=12	Schedule B, MTD, 196 mg/m^2, n=6
ATF3		
E_{max}, %	182 (-16.6–3190)	454 (26.9–922)
TE_{max}, hr	9.0 (5.3–24.5)	8.3 (4.9–9.0)
GCLM		
E_{max}, %	47.0 (-6.5–215)	117 (61.4–255)
TE_{max}, hr	7.0 (0–20.9)	5.7 (4.9–8.9)
GSR		
E_{max}, %	158 (33.1–829)	209 (152–341)
TE_{max}, hr	8.0 (0–9.0)	8.4 (6.3–9.0)
MAG1		
E_{max}, %	85.3 (-19.5–870)	145 (64.6–469)
TE_{max}, hr	8.3 (0–20.9)	7.6 (4.9–29.0)
NQO1		
E_{max}, %	494 (121–3580)	655 (564–1090)
TE_{max}, hr	8.3 (5.0–9.0)	6.5 (5.0–9.0)
SLC7A11		
E_{max}, %	1295 (7.6–10,700)	1507 (414–10,900)
TE_{max}, hr	5.3 (5.0–9.1)	7.0 (5.0–9.0)
SRXN1		
E_{max}, %	103.9 (-3.2–211)	126 (44.5–390)

TE_{max}, hr	7.8 (0–23.2)	7.0 (5.0–8.9)
TXNRD1		
E_{max}, %	159.5 (37.8–482)	304 (229–364)
TE_{max}, hr	5.1 (5.0–9.0)	5.0 (4.9–9.0)

E_{max}, observed maximum effect compared to baseline; hr, hours; TE_{max}, time to E_{max}.

Table A5. Patients achieving partial responses

Schedule	Pevonedistat dose	Patient characteristics and disease history	Prior therapy	Response kinetics
A	110 mg/m^2	34-year-old male with relapsed nodular sclerosis HL; diagnosed 31 months before study entry; presented with B symptoms of recurrent drenching night sweats during the previous month	4 lines of prior therapy with: doxorubicin, bleomycin, vinblastine, dacarbazine; ifosfamide, carboplatin, etoposide; carmustine, etoposide, cytarabine, melphalan; and a monoclonal antibody (XmAb2513), with a best response of CR	Steady decrease in tumor burden; achieved PR after 5 cycles; had progressive disease on cycle 7, day 21
B	196 mg/m²	47-year-old male with DLBCL; Ann Arbor stage IV with bone marrow involvement, diagnosed 59 months	3 lines of prior therapy: Rituximab, cyclophosphamide, doxorubicin, vincristine,	PR after 3 cycles; remained on study to cycle 9, day 18, when

		before study entry	prednisone; rituximab, fludarabine, busulphan; tositumomab; with a best response of PR	experienced disease progression
B	196 mg/m^2	65-year-old female with peripheral T-cell lymphoma (not otherwise specified); diagnosed 60 months before study entry	4 lines of prior therapy: Doxorubicin, vincristine, prednisone; cyclophosphamide; belinostat; vorinostat; with a best response of CR	Achieved a PR in cycle 1 (day 21) that lasted 2 cycles until disease progression

Table A6. Patients achieving stable disease and receiving at least 5 cycles of pevonedistat

Schedule	Pevonedistat dose	Disease type	Treatment cycles	Duration of SD	Prior therapies	Prior transplant
A	25 mg/m^2	MM	5	3.22	MAbs, bortezomib, lenalidomide, thalidomide	–
	25 mg/m^2	MM	8	5.55	MAbs, cyclophosphamide, dexamethasone (x4), doxorubicin, lenalidomide, thalidomide, bortezomib, vincristine	Autologous
	110 mg/m^2	Lymphoma	5	3.29	Tositumomab, bleomycin, cyclophosphamide (x2), prednisone (x3), doxorubicin, etoposide, fludarabine, cytarabine, chlormethine, mitoxantrone, platinum, procarbazine, rituximab (x3), methylprednisolone, vincristine (x3)	–
	110 mg/m^2	MM	5	3.94	Bortezomib, cyclophosphamide, dexamethasone (x4), lenalidomide, thalidomide	–

Schedule	Pevonedistat dose	Disease type	Treatment cycles	Duration of SD	Prior therapies	Prior transplant
					(x2)	
	110 mg/m^2	MM	5	3.45	Doxorubicin, cyclophosphamide, dexamethasone (x2), melphalan, bortezomib, vincristine	Autologous
	110 mg/m^2	MM	9	6.01	Carfilzomib, cisplatin, cyclophosphamide, dexamethasone (x4), doxorubicin (x3), etoposide, prednisone, lenalidomide, thalidomide (x3), bortezomib (x2), vincristine	Autologous
B	147 mg/m^2	Lymphoma	5	3.25	Carboplatin, cyclophosphamide (x3), doxorubicin (x2), etoposide, gemcitabine, dexamethasone, vincristine (x2), ifosfamide, vinorelbine, prednisolone, rituximab (x2)	Autologous

Schedule	Pevonedistat dose	Disease type	Treatment cycles	Duration of SD	Prior therapies	Prior transplant
	196 mg/m^2	Lymphoma	5	3.25	Doxorubicin, carboplatin, cyclophosphamide, cytarabine, dexamethasone, etoposide, gemcitabine (x2), ifosfamide, vinorelbine (x2), rituximab (x4), vincristine, ibritumomab tiuxetan (x2)	–
	196 mg/m^2	Lymphoma	7	5.32	Bleomycin, carboplatin, dacarbazine, doxorubicin (x2), etoposide, gemcitabine, ifosamide, vinorelbine, vinblastine	Autologous
	196 mg/m^2	Lymphoma	13	9.26	Bendamustine, bleomycin, carboplatin, investigational drug (x2), doxorubicin (x2), etoposide (x3), gemcitabine (x2), ifosfamide, vinorelbine (x2), chlormethine, prednisone,	Allogeneic / Autologous

Schedule	Pevonedistat dose	Disease type	Treatment cycles	Duration of SD	Prior therapies	Prior transplant
					procarbazine, vinblastine, vincristine (x2)	
	196 mg/m^2	Lymphoma	14	9.53	Bendamustine, bortezomib, carboplatin, carmustine, cyclophosphamide (x2), cytarabine, doxorubicin, etoposide (x2), fludarabine, ifosfamide, melphalan, nicotinamide, prednisolone, rituximab (x4), vincristine, vorinostat, ibritumomab tiuxetan	Autologous
	261 mg/m^2	Lymphoma	11	7.52	Carboplatin, cyclophosphamide, doxorubicin, etoposide, ifosfamide, inotuzumab, prednisolone, rituximab (x3), vincristine	–

Figure Legend

Figure A1. Representative images (20 x magnification) of formalin-fixed paraffin-embedded clots prepared from bone marrow aspirates. Samples were collected at screening or post dose (patient treated at 110 mg/m^2) on cycle 1, day 2, and stained on serial sections with either anti-CD138 (panels A and C) or anti-pevonedistat–NEDD8 adduct (panels B and D) on serial sections. The arrows indicate examples of areas containing cells that are positive for both antigens. Scale bar represents 500 μm.