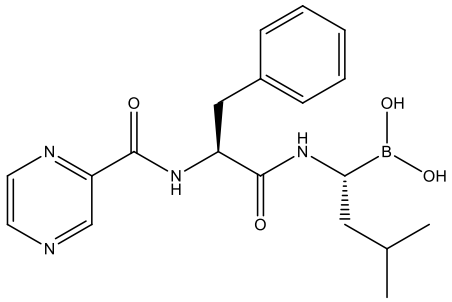
®

2017 11 21
2018 03 09
2018 06 28
2020 11 05

Bortezomib for Injection
Zhusheyong Pengtizuomi

[(1R)-3- -1-[[(2S)-1- -3- -2-[( )]]]]



$C_{19}H_{25}BN_4O_4$
384.24

MP

1.0mg

3~5 6 1
9 1~4 2 1 4 8 11 22 25 29 32
5~9 1 1 8 22 29 72

1

2 1~4											
	1				**2**		**3**	**4**		**5**	**6**
(1.3mg/m^2)	1	--	--	4	8	11		22	25	29	32	
(9mg/m^2) (60mg/m^2)	1	2	3	4	--	--		--	--	--	--	
5~9											
	1				**2**		**3**	**4**		**5**	**6**
(1.3mg/m^2)	1	--	--	--	8			22		29	
(9mg/m^2) (60mg/m^2)	1	2	3	4	--			--		--	

- ≥70×10^9/L ANC ≥1.0×10^9/L
- 1

2

4	
* NCI CTCAE v 4.0 ** ADL *** ADL	

6 6

2

3 1 1 375 mg/m^2 750 mg/m^2 50 mg/m^2 1 2 3 4 5 100 mg/m^2

1

- 100 10^9/L ANC 1.5 10^9/L
- 8 g/dL 4.96 mmol/L
-

		SGOT (AST)	1.3 mg/m^2 2
	≤ 1.0x ULN	> ULN	
	> 1.0x 1.5x ULN		
	> 1.5x 3x ULN		0.7 mg/m^2 1.0 mg/m^2 0.5 mg/m^2
	> 3x ULN		
: SGOT = AST = ULN =			

3~5

0.9%

1.3 mg/m^2

III M34101-039 669 1~3

II 202 2

M34100-025 - II

1.0 mg/m^2 1.3 mg/m^2 M34100-024

6 II III

MedDRA		
	M34100-039 (N=331)	**M34100-024/025 (N=228[a])**
	115 (35%)	97 (43%)
	87 (26%)	74 (32%)
	62 (19%)	55 (24%)
	24 (7%)	15 (7%)
	15 (5%)	11 (5%)
	2 (<1%)	6 (3%)
	1 (<1%)	1 (<1%)
	4 (1%)	2 (<1%)
	9 (3%)	17 (7%)
	6 (2%)	2 (<1%)

MedDRA		
	M34100-039 (N=331)	**M34100-024/025 (N=228[a])**
	5 (2%)	4 (2%)
	7 (2%)	8 (4%)
	6 (2%)	3 (1%)
[b]	1 (<1%)	-
	1 (<1%)	-
	1 (<1%)	-
	3 (<1%)	1 (<1%)
	1 (<1%)	1 (<1%)
	9 (3%)	25 (11%)
	14 (4%)	7 (3%)
	140 (42%)	97 (43%)
	190 (57%)	116 (51%)
	190 (57%)	145 (64%)
	117 (35%)	82 (36%)
	80 (24%)	48 (21%)
	32 (10%)	30 (13%)
	25 (8%)	19 (8%)
	10 (3%)	1 (<1%)
	2 (<1%)	4 (2%)
	14 (4%)	13 (6%)
	24 (7%)	10 (4%)
	4 (1%)	5 (2%)
( )b	7 (2%)	3 (1%)
( )	7 (2%)	3 (1%)
	2 (<1%)	1 (<1%)
	3 (<1%)	2 (<1%)
	1 (<1%)	-
	1 (<1%)	-
	3 (<1%)	-
	1 (<1%)	2 (<1%)
	201 (61%)	149 (65%)
-	40 (12%)	44 (19%)
-	140 (42%)	118 (52%)
-	12 (4%)	9 (4%)
-	13 (4%)	22 (10%)
	116 (35%)	82 (36%)
	37 (11%)	27 (12%)

MedDRA		
	M34100-039 (N=331)	**M34100-024/025 (N=228[a])**
	35 (11%)	27 (12%)
	21 (6%)	5 (2%)
	26 (8%)	16 (7%)
	1 (<1%)	1 (<1%)
	1 (<1%)	1 (<1%)
	1 (<1%)	-
	3 (<1%)	2 (<1%)
	2 (<1%) M34101-040 [c]	-
	1 (<1%)	1 (<1%)
	26 (8%)	41 (18%)
	45 (14%)	17 (7%)
	48 (15%)	29 (13%)
[b]	21 (6%)	23 (10%)
	42 (13%)	26 (11%)
	25 (8%)	13 (6%)
	26 (8%)	6 (3%)
	4 (1%)	1 (<1%)
	14 (4%)	15 (7%)
	6 (2%)	2 (<1%)
	6 (2%)	3 (1%)
	13 (4%)	14 (6%)

MedDRA		
	M34100-039 (N=331)	**M34100-024/025 (N=228[a])**
	8 (2%)	18 (8%)
	50 (15%)	59 (26%)
	39 (12%)	32 (14%)
	45 (14%)	60 (26%)
	2 (<1%) M34101-040 [c]	-
[d]	120 (36%)	84 (37%)
	91 (27%)	53 (23%)
	45 (14%)	48 (21%)
	85 (26%)	63 (28%)
	17 (5%)	29 (13%)
	9 (3%)	1 (<1%)
	8 (2%)	17 (7%)
	4 (1%)	-
	2 (<1%)	-
	2 (<1%)	-
	31 (9%)	32 (14%)
	21 (6%)	21 (9%)
	2 (1%)	3 (1%)
	5 (2%)	4 (2%)
	21 (6%)	23 (10%)
	70 (21%)	39 (17%)
	65 (20%)	50 (22%)
	21 (6%)	18 (8%)
	4 (1%)	9 (4%)
	4 (1%)	14 (6%)
	3 (<1%)	2 (<1%)
	61 (18%)	47 (21%)
	7 (2%)	5 (2%)
	20 (6%)	27 (12%)
/	14 (4%)	8 (4%)

MedDRA		
	M34100-039 (N=331)	**M34100-024/025 (N=228[a])**
	6 (2%)	7 (3%)
[b]	1 (<1%)	-

[a] 228 1.3mg/m^2

[b]

[c] 1.3mg/m^2 4

M34101-039

[d] MedDRA HLT

III 1.3 mg/m^2

222

7 **III** **≥10%**

	N=74			**N=147**		
MedDRA		, n %			, n %	
	n %	3	≥ 4	n %	3	≥ 4
	26 35	6 8	0	53 36	14 10	4 3
	16 22	4 5	1 1	29 20	9 6	0
	20 27	10 14	3 4	42 29	22 15	4 3
	27 36	8 11	6 8	52 35	12 8	7 5
	8 11	0	0	5 3	1 1	0
	8 11	0	0	3 2	0	0
	11 15	1 1	0	21 14	1 1	0
	27 36	3 4	1 1	35 24	2 1	1 1
	14 19	0	0	27 18	0	0
	12 16	0	1 1	17 12	3 2	0
	14 19	4 5	0	23 16	3 2	0
	15 20	3 4	0	17 12	3 2	0
	12 16	0	0	28 19	0	0
	7 9	1 1	0	16 11	2 1	0
	7 9	0	0	14 10	0	0
	8 11	2 3	0	8 5	1 1	0

	8 11	0	0	5 3	0	0
	17 23 36 49	7 9 10	0	35 24	5 3	0

10%

MMY-2036

9 ≥10% **MMY-2036**

	(MMY-2036)		
		3	≥4
	130		
n (%)	126 (97)		
MedDRA			
	71 (55)	19 (15)	14 (11)
	48 (37)	5 (4)	1 (1)
	23 (18)	9 (7)	0
	20 (15)	5 (4)	0
	45 (35)	9 (7)	0
	36 (28)	0	0
	14 (11)	0	0
	31 (24)	2 (2)	0
	29 (22)	6 (5)	0
	21 (16)	0	0
	15 (12)	48 (37)	5 (4)

10 **10%**

DOXIL-MMY-3001 **MMY-2045**

			+		+	
	n (%)	≥3 n (%)	n (%)	≥3 n (%)	n (%)	≥3 n (%)
	318		318		163	
	301 (95)		314 (99)		154 (94)	
MedDRA						
	124 (39)	16 (5)	145 (46)	23 (7)	51 (31)	7 (4)
	126 (40)	3 (1)	154 (48)	8 (3)	20 (12)	1 (1)
	98 (31)	2 (1)	99 (31)	3 (1)	50 (31)	9 (6)
	69 (22)	3 (1)				

			+		+	
	n (%)	≥3 n (%)	n (%)	≥3 n (%)	n (%)	≥3 n (%)
	28 (9)	10 (3)	34 (11)	3 (1)	13 (8)	3 (2)

	MP (n=340)			**MP (n=337)**		
MedDRA		n (%)			n (%)	
	n (%)	3	≥4	n (%)	3	≥4
	156 (46)	42 (12)	2 (1)	4 (1)	0	0
	117 (34)	27 (8)	2 (1)	1 (<1)	0	0
	42 (12)	6 (2)	0	4 (1)	0	0
	85 (25)	19 (6)	2 (1)	48 (14)	4 (1)	0
	54 (16)	18 (5)	0	23 (7)	3 (1)	0
	53 (16)	4 (1)	0	19 (6)	1 (<1)	1 (<1)
	39 (11)	11 (3)	0	9 (3)	4 (1)	0
	64 (19)	6 (2)	0	19 (6)	0	0
	38 (11)	2 (1)	0	7 (2)	0	0
	35 (10)	1 (<1)	0	21 (6)	0	0

III

MP MP

4% 14% MP 26%

17% 3%

1.3 mg/m^2

MMY-3003 410

411

IFM2005-01 239 239

MMY-3010 130

126

	242 (31)	89 (11)	10 (1)	214 (28)	67 (9)	8 (1)
	215 (28)	71 (9)	22 (3)	206 (27)	77 (10)	9 (1)
	133 (17)	29 (4)	23 (3)	110 (14)	26 (3)	6 (1)
	95 (12)	30 (4)	18 (2)	87 (11)	35 (5)	6 (1)
	147 (19)	53 (7)	20 (3)	54 (7)	11 (1)	4 (1)
	101 (13)	24 (3)	11 (1)	80 (10)	15 (2)	2 (<1)
	101 (13)	41 (5)	19 (2)	55 (7)	13 (2)	1 (<1)
	64 (8)	23 (3)	4 (1)	76 (10)	23 (3)	1 (<1)
	158 (20)	50 (6)	21 (3)	161 (21)	68 (9)	21 (3)
	153 (20)	56 (7)	25 (3)	159 (20)	40 (5)	36 (5)
	110 (14)	33 (4)	16 (2)	91 (12)	33 (4)	10 (1)
	239 (31)	54 (7)	63 (8)	171 (22)	27 (3)	27 (3)

	0	2 1	1 5	10 3
	0	28 8	1 5	73 21
	9 43	185 55	18 90	262 77
	8 38	199 59	16 80	239 70
	2 10	27 8	5 25	31 9
	1 5	6 2	0	5 1
	10 48	182 54	13 65	234 69
	0	40 12	0	40 12
	2 10	21 6	1 5	32 9
	6 29	124 37	10 50	159 47
	5 24	151 45	7 35	172 51
( )	0	4 1	0	7 2
	4 19	122 36	13 65	253 74
	4 19	76 23	0	112 33
	4 19	62 18	2 10	54 16
	1 5	15 4	1 5	21 6
	5 24	123 36	8 40	133 39
	1 5	80 24	8 40	140 41
	0	3 1	0	7 2
	1 5	69 20	6 30	112 33

II M34103-053 155
1.3 mg/m^2

14 240
1.3 mg/m^2 375 mg/m^2 750 mg/m^2 50 mg/m^2 100 mg/m^2 VcR-CAP
3 VcR-CAP 4 R-CHOP 3 VcR-CAP 3
VcR-CAP 31% R-CHOP 23%
VcR-CAP 8% R-CHOP 5%
VcR-CAP R-CHOP 4.6% 0.8%

14 VcR-CAP R-CHOP LYM-3002 N=482
5% 3 4

	VcR-CAP n=240	R-CHOP n=242

3 ≥4

	VcR-CAP n=240			R-CHOP n=242		
		3	≥4		3	4
	n %	n %	n %	n %	n %	n %
	15 6	1 1	0	3 1	0	0
	16 7	1 1	0	8 3	0	0

R-CHOP=

VcR-CAP=

15

(1/10) (1/100 <1/10) (1/1000 <1/100) (1/10000 <1/1000) (<1/10000)

15:

	/
	*
	-
	Sweet’s syndrome

* John Cunningham JC

8

III

40%

16 ≥3

5% 4%

16 **III**

*	**N=331 ****	**<10000/µL %**	**10000/µL 25000/µL %**
≥75000/µL	309	8 3%	36 (12%)
≥50000/µL <75000/µL	14	2 14%	11 (79%)
≥10000/µL <50000/µL	7	1 14%	5 (71%)
* 50000/µL **1			

VcR-CAP VcR-CAP ≥4

32% R-CHOP 2% VcR-CAP

R-CHOP ≥3 1.7% 4 1.2% 3

VcR-CAP CNS R-

CHOP 1 CNS VcR-CAP R-CHOP 23% 3%

VcR-CAP R-CHOP ≥4 70% 52% VcR-CAP

R-CHOP ≥4 5% 6% 78% 61%

-

/

-

-

-

-

0.075 mg/kg 0.5 mg/m^2 0.05 mg/kg 0.6 mg/m^2
1.3 mg/m^2

0.05 mg/kg 0.6 mg/m^2
1.3 mg/m^2

669 245 37% ≥65 125 38%
120 36% ≥65
5.5 4.3 8.0 4.9
≥65 40% n=46 CR+PR 18% n=21
≤50 51~64 ≥65 3 4 64% 78% 75%
≥65

P450 CYP 1A2 2C9 2C19 2D6 3A4
CYP2D6 7% CYP2D6

CYP3A4
12 AUC 35% CYP3A4

CYP2C19
17
CYP3A4 6
AUC 45% CYP3A4
CYP3A4
CYP3A4 7

mg/m^2 2~3

QT 3.0 mg/m^2

2 1 12~14

2

/

26S 26S

-

26S

1 mg/m^2 1.3 mg/m^2 n=12 20S

5 1 mg/m^2 1.3 mg/m^2 20S

1 mg/m^2 1.3 mg/m^2 70% 84% 73% 83%

2 2

2

12 14 1.2 mg/m^2

Ames

6

≥0.3 mg/m^2 1/4 1.2 mg/m^2

11 1.0 mg/m^2 1.3 mg/m^2 1
57 112 ng/ml 67
106 ng/ml 1.0 mg/m^2 89 120 ng/ml 1.3 mg/m^2
40~193 1.0mg/m^2
1.3mg/m^2 102 112L/h 1.0 mg/m^2 1.3 mg/m^2
15~32 L/h
III PK/PD 1.3mg/m^2
n = 14 n = 17 AUC_{last}
(20.4ng/mL) 223 ng/ml AUC_{last} 0.99 90%
80.18% ~ 122.80%

1.0mg/m^2 1.3mg/m^2
489~1884 L/m^2 100~1000 ng/ml
83%

cDNA P450
P450 3A4 2C19 1A2 2D6 2C9
2
26S 8 10 30

104 (2~16) 2 1.3mg/m^2

%CV 7.79 25% L/hr/m^2 834 39% L/m^2 100 44%

60
0.5 1.3mg/m^2 AUC
AUC 60%

CrCL CrCL
≥60 ml/ /1.73 m^2 n=12 CrCL=40 59 ml/ /1.73 m^2 n=10 CrCL=20 39
ml/ /1.73 m^2 n=9 CrCL < 20 ml/ /1.73 m^2 n=3
8 0.7 1.3 mg/m^2 2
(AUC)

1 /

24

YBH12392020

H20173306

5

222069

4008285227 9:00-17:00

http://www.hansoh.cn

25 8

8 8

30

5%

0.9%

	1 mg	3.5 mg
0.9%	1.0 ml	3.5 ml
mg/ml	1.0 mg/ml	1.0 mg/ml