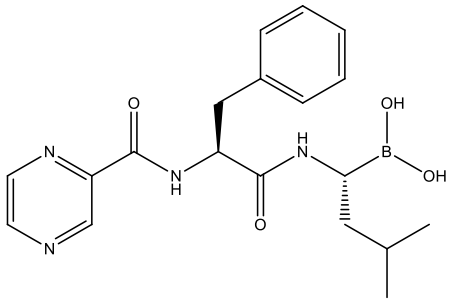
®

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])**
	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**

	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 **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)	0	0

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)
	[redacted]	3 (1)	[redacted]			

	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

	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:

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 ¼ 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