Azacitidine with or without eltrombopag for first-line treatment of intermediate- or high-risk MDS with thrombocytopenia

Supplemental information

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Supplemental Table S1. Summary of PFS from investigator assessment and central review (ITT)

	Eltrombopag (N=179)	Placebo (N=177)
Investigator assessment		
Events, n (%)	72 (40)	66 (37)
Death	34 (19)	36 (20)
Disease progression	38 (21)	30 (17)
Censored	107 (60)	111 (63)
Kaplan–Meier estimates (days)*		
First quartile (95% CI)	104 (61, 156)	174 (133, 238)
Median (95% CI)	345 (204, 364)	423 (345, 500)
Third quartile (95% CI)	NA	549 (500, NA)
HR (95% CI)†	1.47 (1.05, 2.07)	
Nominal *P* value	0.060	
Central review		
Events, n (%)	76 (42)	67 (38)
Death	44 (25)	41 (23)
Disease progression	32 (18)	26 (15)
Censored	103 (58)	110 (62)
Kaplan–Meier estimates (days)*		
First quarter (95% CI)	129 (66, 156)	158 (114, 182)
Median (95% CI)	330 (194, 351)	394 (298, 479)
Third quartile (95% CI)	NA	NA
HR (95% CI)†	1.38 (0.99, 1.92)	
Nominal *P* value	0.141	

*CI estimated using the Brookmeyer–Crowley method; †HRs estimated using the Pike estimator. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NA, not assessable; PFS, progression-free survival.

Supplemental Table S2. Summary of time to overall response and response duration

	Eltrombopag (N=179)	Placebo (N=177)	Odds ratio (95% CI)	Nominal *P* value
Investigator assessment				
Overall response, n (%)	36 (20)	62 (35)	0.51 (0.30, 0.86)	0.005
Censored	143 (80)	115 (65)		
Complete response	15 (8)	26 (15)		
Kaplan–Meier estimates for time to response (days)*				
First quartile (95% CI)	167 (156, 184)	159 (155, 165)		
Median (95% CI)	NA (NA, 416)	315 (171, 475)		
Third quartile (95% CI)	NA	NA (NA, 475)		
Kaplan–Meier estimates for duration of response (days)*				
First quartile (95% CI)	NA (NA, 169)	151 (119, 190)		
Median (95% CI)	NA	246 (189, 254)		
Third quartile (95% CI)	NA	NA (NA, 254)		
Central review				
Overall response, n (%)	15 (8)	19 (11)	0.89 (0.41, 1.97)	0.683
Censored	164 (92)	158 (89)		
Complete response	11 (6)	7 (4)		
Kaplan–Meier estimates for time to response (days)*				
First quartile (95% CI)	NA (NA, 328)	NA (NA, 330)		
Median (95% CI)	NA	NA		
Third quartile (95% CI)	NA	NA		
Kaplan–Meier estimates for duration of response (days)*				
First quartile (95% CI)	NA	232 (107, 246)		
Median (95% CI)	NA	NA (NA, 246)		
Third quartile (95% CI)	NA	NA (NA, 246)		

*CI estimated using the Brookmeyer–Crowley method. Overall response = complete response + marrow CR + partial response, according to IWG criteria. CI, confidence interval; IWG, International Working Group; NA, not assessable.

Supplemental Table S3. Summary of hematologic improvements

	Eltrombopag (N=179)	Placebo (N=177)	Odds ratio (95%) for platelets*	Nominal *P* value*
Any improvement, n (%)	58 (32)	59 (33)		
Platelets	56 (31)	57 (32)	0.96 (0.60, 1.54)	0.922
Neutrophils	12 (7)	13 (7)	0.93 (0.40, 2.13)	0.860
Hemoglobin	1 (1)	1 (1)	1.28 (0.11, 14.93)	0.858
Platelets and neutrophils	10 (6)	11 (6)		
Platelets and hemoglobin	1 (1)	1 (1)		
Neutrophils and hemoglobin	1 (1)	1 (1)		
Platelets, neutrophils and hemoglobin	1 (1)	1 (1)		

*CMH test stratified by randomization stratification factors. Logit estimator for odds ratio.

CMH, Cochran–Mantel–Haenszel.

Supplemental Table S4. List of patients who were evaluated as having progression to AML

Patient #	Treatment received eltrombopag/ placebo	AML progression central/local	Time since randomization to AML progression	Male/ female	Race	Baseline values			
						Karyotype	BM blasts, local/ central, %	IPSS risk score	Age, years
1	Placebo	Local	226	Female	White	Normal	1.1/4.0	Int-1	79
2	Placebo	Central	153	Male	White	Int	11.0/10.0	Int-2	67
3	Placebo	Local	86	Male	Asian	Normal	2.0/12.0	Int-1	52
4	Placebo	Central	387	Male	Asian	Poor	12.5/2.0	High	72
5	Placebo	Central and local	85 (central), 141 (local)	Male	Asian	Normal	18.6/14.0	Int-2	72
6	Placebo	Central and local	182	Male	Asian	Normal	11.4/10.0	Int-2	78
7	Placebo	Local	256	Male	White	Poor	15.0/12.5	High	61
8	Placebo	Central and local	262	Female	White	Poor	10.0/13.0	Int-2	76
9	Placebo	Central and local	106 (central), 359 (local)	Male	White	Int	8.0/7.0	Int-1	47
10	Placebo	Local	389	Female	Asian	Poor	19.0/NR	High	68
11	Placebo	Local	114	Male	White	Normal	6.0/32.0	Int-1	59
12	Placebo	Local	279	Male	White	Int	3.0/10.0	Int-1	63
13	Placebo	Central	121	Female	White	Normal	17.0/15.0	Int-2	61
14	Placebo	Central	99	Female	White	Int	9.0/8.0	Int-2	73
15	Placebo	Local	162	Male	White	Normal	14.0/53.0	Int-2	73
16	Placebo	Local	263	Female	White	Poor	15.0/NR	High	66
17	Placebo	Local	143	Male	White	Poor	10.6/15.0	Int-2	62
18	Placebo	Local	162	Male	White	Poor	10.0/14.0	Int-2	69
19	Placebo	Central and local	174	Female	White	Int	8.6/16.0	Int-2	72
20	Placebo	Central and local	33	Male	White	Poor	13.4/43.0	High	67
21	Eltrombopag	Local	183	Female	White	Poor	10.8/2.5	High	58
22	Eltrombopag	Central and local	101	Male	Native Hawaiian or other	Normal	0.6/2.5	Int-1	79

Patient #	Treatment received eltrombopag/ placebo	AML progression central/local	Time since randomization to AML progression	Male/ female	Race	Baseline values			
						Karyotype	BM blasts, local/ central, %	IPSS risk score	Age, years
					Pacific Islander				
23	Eltrombopag	Local	307	Male	White	Normal	5.0/NR	Int-1	72
24	Eltrombopag	Local and central	260	Female	White	Normal	0.2/4.0	Int-1	84
25	Eltrombopag	Local and central	38 (local), 39 (central)	Female	Asian	Poor	10.0/12.5	Int-2	59
26	Eltrombopag	Local and central	197 (local), 225 (central)	Male	White	Normal	14.4/25.0	Int-2	62
27	Eltrombopag	Local and central	56	Male	White	NE	18.6/12.0	High	57
28	Eltrombopag	Local	36	Male	White	Normal	5.0/4.0	Int-1	76
29	Eltrombopag	Central	167	Male	White	Normal	2.0/15.0	Int-1	66
30	Eltrombopag	Local and central	167 (central), 197 (local)	Female	White	Poor	12.0/6.0	High	50
31	Eltrombopag	Local	81	Male	White	Normal	7.3/5.0	Int-1	79
32	Eltrombopag	Local and central	160 (central), 245 (local)	Male	White	Poor	3.0/25.0	Int-1	76
33	Eltrombopag	Local and central	190 (central), 303 (local)	Male	East Asian	Int	4.6/24.0	Int-1	34
34	Eltrombopag	Local	39	Female	White	Poor	8.0/8.0	Int-2	52
35	Eltrombopag	Central	113	Male	Asian	Int	2.8/15.0	High	59
36	Eltrombopag	Central	139	Male	Asian	Poor	17.2/13.0	High	81
37	Eltrombopag	Local and central	60	Male	White	Normal	3.5/11.0	Int-1	85
38	Eltrombopag	Central	92	Male	White	Int	5.2/4.0	Int-2	69
39	Eltrombopag	Local and central	44	Male	White	Normal	17.8/4.0	Int-2	71
40	Eltrombopag	Local	23	Female	White	Normal	11.2/NR	Int-2	49
41	Eltrombopag	Local and central	20	Male	White	Int	14.0/11.0	Int-2	66
42	Eltrombopag	Local and central	163 (central), 236 (local)	Male	White	Poor	12.0/27.0	High	78

Patient #	Treatment received eltrombopag/ placebo	AML progression central/local	Time since randomization to AML progression	Male/ female	Race	Baseline values			
						Karyotype	BM blasts, local/ central, %	IPSS risk score	Age, years
43	Eltrombopag	Local	30	Male	White	Poor	4.0/12.5	Int-2	66
44	Eltrombopag	Local	39	Male	White	Normal	12.0/9.0	Int-2	86
45	Eltrombopag	Local	29	Male	White	Poor	18.0/39.0	High	64
46	Eltrombopag	Local and central	29 (central), 30 (local)	Female	White	Int	10.3/NR	Int-2	69
47	Eltrombopag	Local and central	33 (central), 112 (local)	Male	White	Normal	1.4/18.0	Int-1	77
48	Eltrombopag	Local	31	Male	White	Int	1.0/8.0	Int-1	68
49	Eltrombopag	Local	176	Female	White	Normal	11.0/NR	Int-2	59
50	Eltrombopag	Central	1	Male	White	Normal	3.8/16.0	Int-1	65
51	Eltrombopag	Central	183	Male	White	Int	17.0/29.0	High	87
52	Eltrombopag	Local and central	160	Female	White	Int	2.0/7.0	Int-1	72
53	Eltrombopag	Local	26	Female	White	Int	14.0/11.0	High	79

Good = normal karyotype, Y alone, del(5q) alone, or del(20q) alone; Int, intermediate = other abnormalities; Poor = abnormalities involving chromosome 7 or those with a complex karyotype (≥3 unassociated abnormalities). AML, acute myeloid leukemia; BM, bone marrow; Int-1, intermediate-1 (risk); Int-2, intermediate-2 (risk); IPSS, International Prognostic Scoring System; NE, not evaluable (absence of mitosis); NR, not reported.

Supplemental Table S5. Proportion of patients who were evaluated as having progression to AML or with disease progression according to baseline blast count and IPSS risk category

	Eltrombopag (N=179)	Placebo (N=177)	Odds ratio (95% CI)	Nominal *P* value
Progression to AML				
Baseline BM blast count, central assessment				
<5%, n (%)	4/36 (11)	1/34 (3)	1.95 (0.32, 11.76)	0.268
5–20, n (%)	10/74 (14)	8/80 (10)	1.09 (0.36, 3.31)	0.817
>20%, n (%)	6/33 (18)	1/23 (4)	2.33 (0.45, 12.18)	0.145
Missing, n (%)	1/36 (3)	0/40 (0)		
Baseline BM blast count, investigator assessment				
<5%, n (%)	9/56 (16)	3/50 (6)		
5–20, n (%)	18/99 (18)	12/116 (10)		
>20%, n (%)	0/12 (0)	0/8 (0)		
Missing, n (%)	0/12 (0)	1/3 (33)		
IPSS risk category, central assessment				
Int-1	9/64 (14)	1/61 (2)		
Int-2/high	12/115 (10)	9/116 (8)		
IPSS risk category, investigator assessment				
Int-1	11/64 (17)	5/61 (8)		
Int-2/high	16/115 (14)	11/116 (9)		
Disease progression				
Baseline BM blast count, central assessment				
<5%, n (%)	10/36 (28)	6/34 (18)	0.89 (0.40, 1.97)	0.942
5–20, n (%)	13/74 (18)	17/80 (21)	1.23 (0.75, 2.01)	0.678
>20%, n (%)	6/33 (18)	2/23 (9)	1.91 (0.86, 4.26)	0.195
Missing, n (%)	3/36 (8)	1/40 (3)		
Baseline BM blast count, investigator assessment				
<5%, n (%)	13/56 (23)	7/50 (14)		
5–20, n (%)	24/99 (24)	20/116 (17)		
>20%, n (%)	1/12 (8)	2/8 (25)		
Missing, n (%)	0/12 (0)	1/3 (33)		
IPSS risk category, central assessment				
Int-1	17/64 (27)	10/61 (16)		
Int-2/high	15/115 (13)	16/116 (14)		
IPSS risk category, investigator assessment				
Int-1	14/64 (22)	7/61 (11)		
Int-2/high	24/115 (21)	23/116 (20)		

AML, acute myeloid leukemia; BM, bone marrow; Int-1, intermediate-1 (risk); Int-2, intermediate-2 (risk); IPSS, International Prognostic Scoring System.

Supplemental Figure S1. Number of azacitidine cycles completed (safety population)