Supplemental Data

Ponatinib efficacy and safety in Philadelphia chromosome–positive leukemia: Final 5-year results of the phase 2 PACE trial

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Supplemental Table S1. Treatment-emergent arterial occlusive events (AOEs)* reported in CP-CML patients and all patients

	CP-CML n=270			Total N=449		
	Any grade	**Grade 3/4**	**Grade 5**	**Any grade**	**Grade 3/4**	**Grade 5**
Patients with ≥1 AOE, n (%)	84 (31)	49 (18)	3 (1)	111 (25)	66 (15)	**5 (1)**
Angina pectoris	22 (8)	5 (2)	0	28 (6)	5 (1)	0
Peripheral arterial occlusive disease	18 (7)	10 (4)	0	22 (5)	14 (3)	0
Acute myocardial infarction/myocardial infarction	10 (4)	9 (3)	1 (<1)	18 (4)	15 (3)	1 (<1)
Coronary artery disease	10 (4)	9 (3)	0	14 (3)	11 (2)	0
Cerebrovascular accident	9 (3)	1 (<1)	1 (<1)	11 (2)	2 (<1)	1 (<1)
Intermittent claudication	11 (4)	4 (2)	0	11 (2)	4 (1)	0
Peripheral artery stenosis	10 (4)	8 (3)	0	10 (2)	8 (2)	0
Cerebral infarction	8 (3)	7 (3)	0	8 (2)	7 (2)	0
Acute coronary syndrome	6 (2)	5 (2)	0	7 (2)	5 (1)	0
Carotid artery stenosis	7 (3)	5 (2)	0	7 (2)	5 (1)	0
Peripheral arterial occlusion	7 (3)	6 (2)	0	7 (2)	6 (1)	0
Peripheral ischemia	5 (2)	2 (1)	0	7 (2)	2 (<1)	1 (<1)

Transient ischemic attack	6 (2)	0	0	6 (1)	0	0
Coronary artery occlusion	4 (2)	4 (2)	0	5 (1)	5 (1)	0
Peripheral vascular disorder	3 (1)	1 (<1)	0	5 (1)	2 (<1)	0
Extremity necrosis	3 (1)	1 (<1)	0	4 (1)	2 (<1)	0
Cerebral ischemia	1 (<1)	0	0	3 (1)	1 (<1)	1 (<1)
Coronary artery stenosis	2 (1)	2 (1)	0	3 (1)	2 (<1)	0
Ischemic cardiomyopathy	2 (1)	2 (1)	0	3 (1)	3 (1)	0
Renal artery stenosis	2 (1)	2 (1)	0	3 (1)	3 (1)	0
Unstable angina	2 (1)	2 (1)	0	2 (<1)	2 (<1)	0
Aphasia	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)	0
Carotid artery occlusion	2 (1)	0	0	2 (<1)	0	0
Cerebral artery stenosis	2 (1)	2 (1)	0	2 (<1)	2 (<1)	0
Dry gangrene	2 (1)	1 (<1)	0	2 (<1)	1 (<1)	0
Dysarthria	2 (1)	0	0	2 (<1)	0	0
Myocardial ischemia	2 (1)	1 (<1)	0	2 (<1)	1 (<1)	0
Splenic infarction	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)	0
Vertebral artery stenosis	1 (<1)	0	0	2 (<1)	0	0
Coronary artery arteriosclerosis	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Coronary arteriospasm	1 (<1)	0	0	1 (<1)	0	0

Increased blood creatine phosphokinase	1 (<1)	0	0	1 (<1)	0	0
Cardiac discomfort	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Carotid arteriosclerosis	1 (<1)	0	0	1 (<1)	0	0
Cerebellar infarction	0	0	0	1 (<1)	1 (<1)	0
Cerebral arteriosclerosis	1 (<1)	0	0	1 (<1)	0	0
Cerebrovascular disorder	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Cerebrovascular insufficiency	1 (<1)	0	0	1 (<1)	0	0
Celiac artery occlusion	0	0	0	1 (<1)	1 (<1)	0
Coronary vascular graft occlusion	1 (<1)	0	0	1 (<1)	0	0
Electrocardiogram ST segment depression	1 (<1)	0	0	1 (<1)	0	0
Electrocardiogram T wave inversion	1 (<1)	0	0	1 (<1)	0	0
Arterial embolism	0	0	0	1 (<1)	1 (<1)	0
Hemorrhagic cerebral infarction	1 (<1)	0	1 (<1)	1 (<1)	0	1 (<1)
Hemorrhagic transformation stroke	1 (<1)	0	0	1 (<1)	0	0
Hemiparesis	1 (<1)	0	0	1 (<1)	0	0
Hemiplegia	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Lacunar infarction	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Mesenteric arterial occlusion	0	0	0	1 (<1)	0	1 (<1)
Monoparesis	1 (<1)	0	0	1 (<1)	0	0

Myocardial necrosis	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Poor peripheral circulation	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Retinal artery occlusion	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Stress cardiomyopathy	0	0	0	1 (<1)	1 (<1)	0
Subclavian artery stenosis	0	0	0	1 (<1)	0	0
Increased troponin	1 (<1)	0	0	1 (<1)	0	0

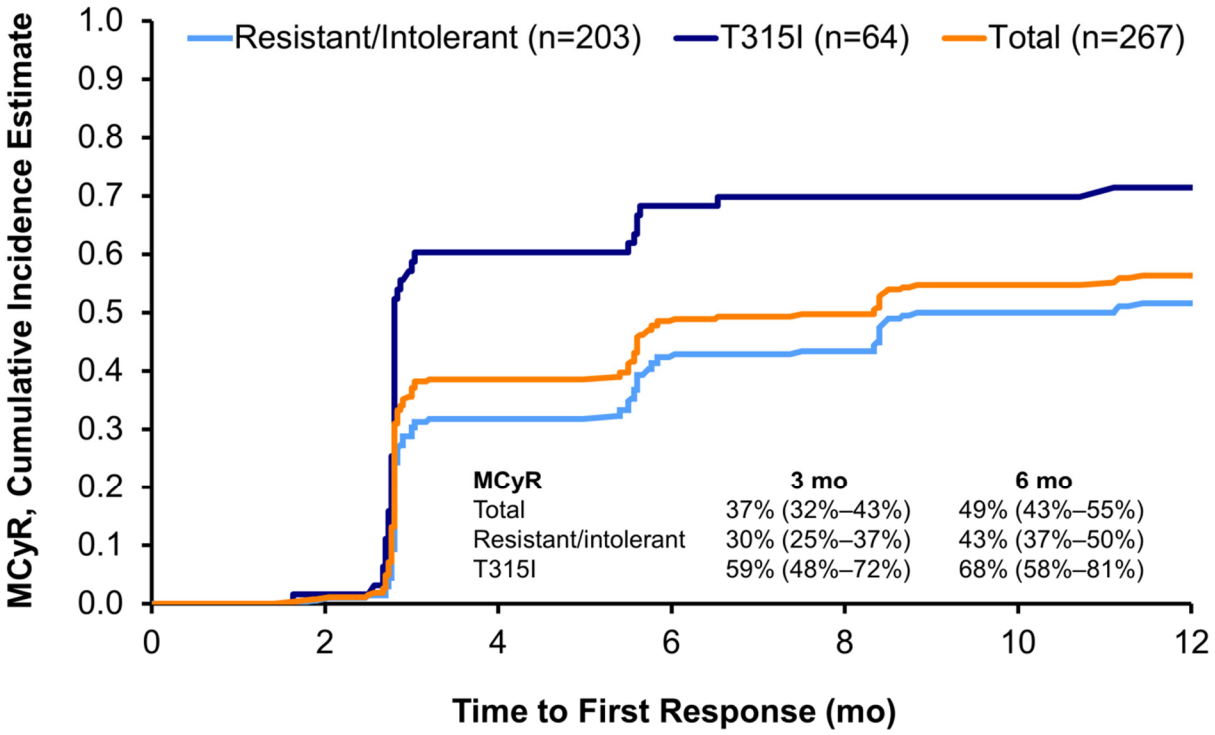
*Categorization of AOEs is based on a broad collection of >300 MedDRA preferred terms related to vascular ischemia or thrombosis.

Supplemental Table S2. Patients with a first arterial occlusive event (AOE) after October 2013 following prospective dose reduction to 15 mg

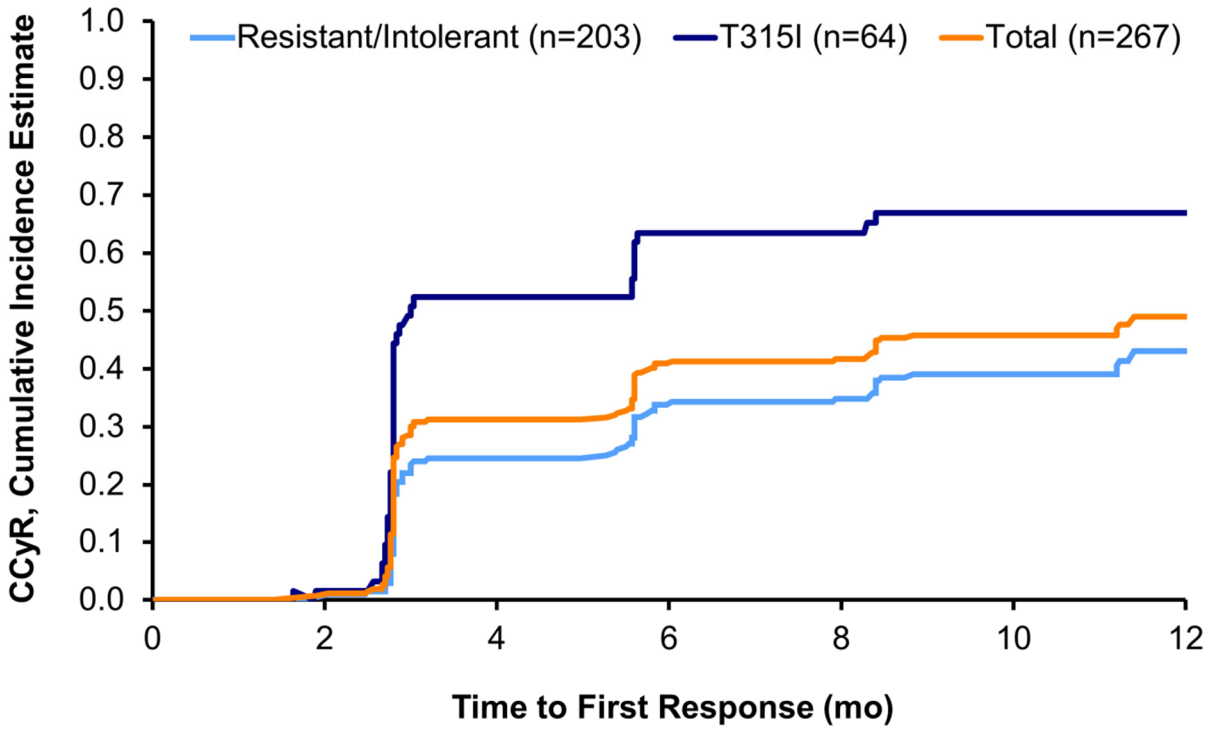
Patient	Time to first AOE following dose reduction (days)	First AOE	Grade	Action taken with study treatment
1	856	Peripheral vascular disorder	1	No dose modification
2	183	Angina pectoris	2	No dose modification
3	53	Cerebral artery stenosis	3	Discontinued treatment
4	239	Peripheral artery occlusion	3	No dose modification
5	70	Carotid arteriosclerosis	1	No dose modification
6	715	Electrocardiogram T wave inversion	1	No dose modification
7	112	Coronary artery occlusion	3	Drug interrupted
8	428	Peripheral vascular disorder	1	No dose modification
9	351	Peripheral artery stenosis	3	Discontinued treatment
10	519	Angina pectoris	2	Dose reduction

Supplemental Figure S1. Time to first response in all evaluable patients with CP-CML, overall and among patients resistant or intolerant to previous treatment with dasatinib or nilotinib or with the BCR-ABL1^{T315I} mutation. (A) Time to first MCyR (12 months), (B) time to first CCyR (12 months), and (C) time to first MMR (up to 5 years). Time to first response for all patients was analyzed using a cumulative incidence function. In (A) and (C), point estimates for cumulative incidence by 3 and 6 months and 95% confidence intervals are shown.

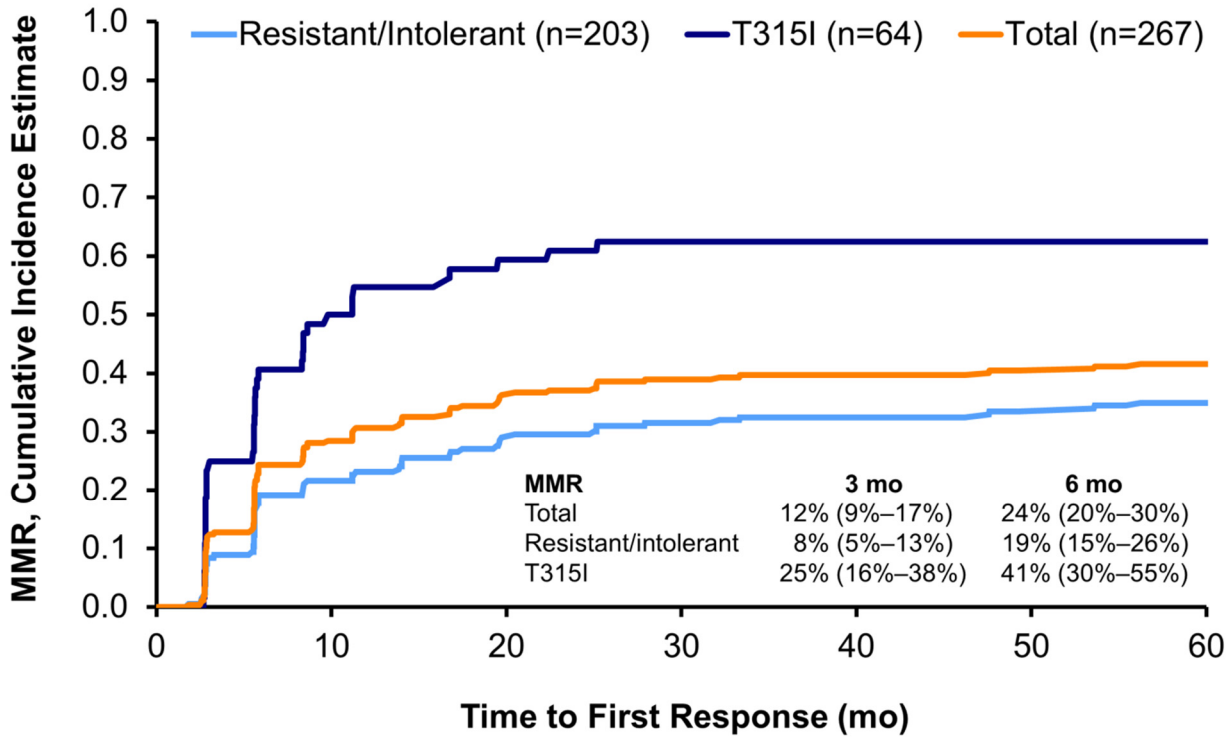
(A) Time to MCyR



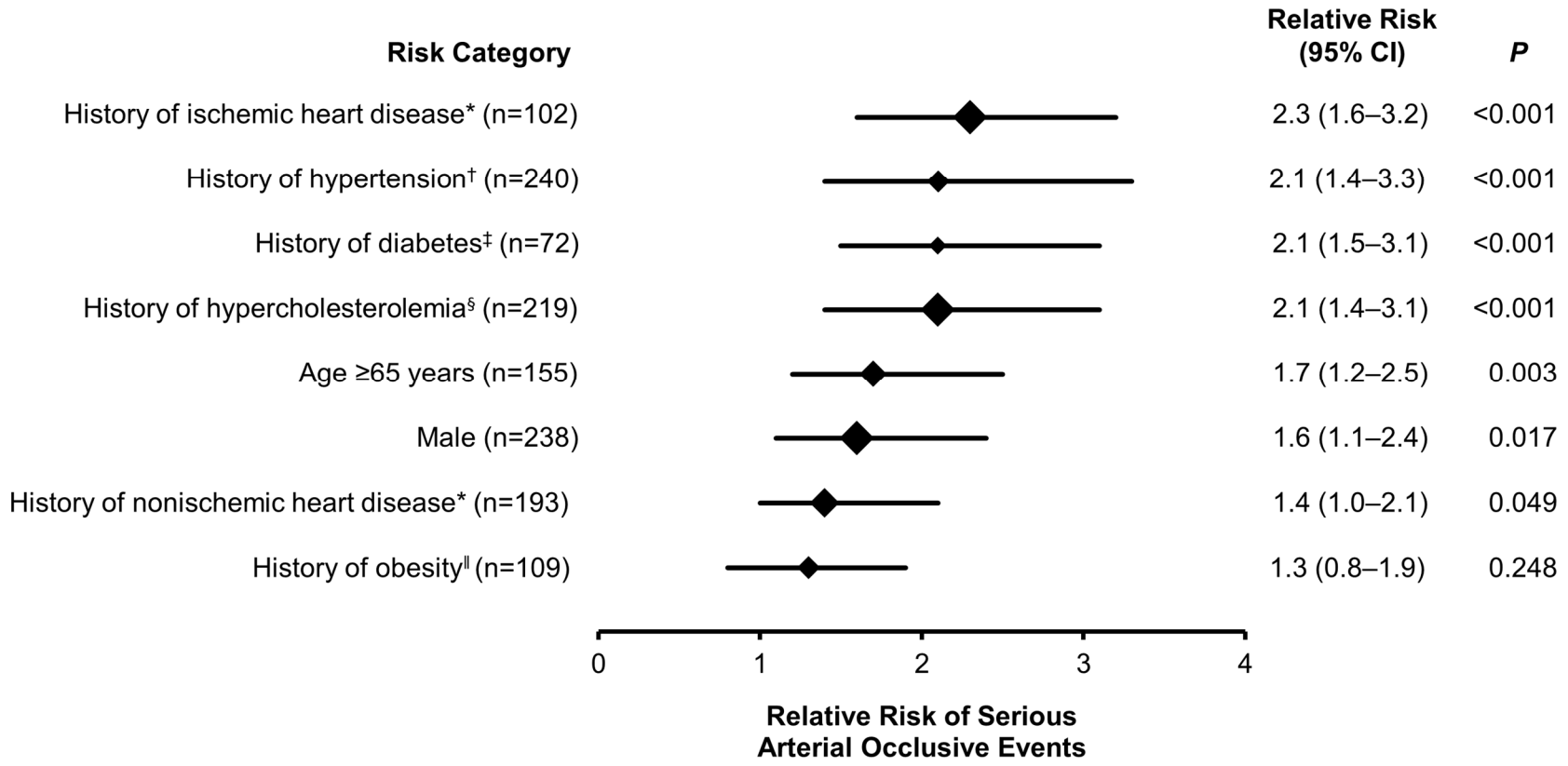
(B) Time to CCyR



(C) Time to MMR


Resistant/Intolerant (n=203)
T315I (n=64)
Total (n=267)
MMR, Cumulative Incidence Estimate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
Time to First Response (mo)
MMR
3 mo
6 mo
Total
12% (9%–17%)
24% (20%–30%)
Resistant/intolerant
8% (5%–13%)
19% (15%–26%)
T315I
25% (16%–38%)
41% (30%–55%)

Supplemental Figure S2. Relative risk of serious arterial occlusive events by risk category (N=449).



To calculate the relative risk of serious arterial occlusive events for each risk category, the frequency of serious arterial occlusive events in patients in the risk category was divided by the frequency in patients not in the risk category. For example, the frequency of serious arterial occlusive events was 27% (64/240) in patients with a history of hypertension and 12% (26/209) in patients without a

history of hypertension (240 + 209 = total N = 449), so the relative risk of serious arterial occlusive events in patients with versus without hypertension was 2.1.

*Includes medical history and/or prior concomitant medication.

†Includes medical history, prior concomitant medication, and/or baseline blood pressure grade ≥2.

‡Includes medical history, prior concomitant medication, and/or baseline glucose grade ≥2.

§Includes medical history, prior concomitant medication, and/or baseline triglycerides grade ≥1.

‖Includes medical history and/or baseline body mass index ≥30 kg/m^2.