Incidence, outcomes, and risk factors of pleural effusion in patients receiving dasatinib therapy for Philadelphia chromosome-positive leukemia

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Online Supplementary Materials

Methods

Pooled population of patients with Ph+ leukemia

Patient listings were available for all trials in this pooled analysis; however, not all data elements were available for all studies. Duration of treatment varied across studies, and was longer in chronic myeloid leukemia in chronic phase (CML-CP) (median 29 months; range 0-93 months) than in accelerated or blast phase CML (CML-AP/BP) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) (median 6 months; range 0-93 months). Treatment duration also was longer in patients with CML-CP treated with first-line dasatinib from DASISION (median 60 months; range 0-73 months) than in CML-CP patients treated following failure of prior imatinib from 034/Dose-optimization (median 30 months; range 0-93 months).

Assessments

Adverse events were graded as follows: Grade 1—asymptomatic; Grade 2—symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated; Grade 3—symptomatic and supplemental oxygen, <2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated; Grade 4—life-threatening, causing hemodynamic instability or ventilatory support indicated; Grade 5—death related to pleural effusion. Confirmed complete cytogenetic response (CCyR) was defined as 0% Ph+ cells in ≥20 metaphases, partial cytogenetic response (CyR) >0% to 35%, minor CyR >35% to 65%, and minimum CyR >65% to 95%. Major molecular response (MMR) was defined by *BCR-ABL1* transcripts ≤0.1% on the International Scale (IS), corresponding to a 3-log reduction from the standardized baseline. MR^4 was defined by *BCR-ABL1* transcripts <0.01% (IS), corresponding to a 4-log reduction from the standardized baseline. $MR^{4.5}$ was defined by *BCR-ABL1* transcripts ≤0.0032% (IS), corresponding to a 4.5-log reduction from the standardized baseline.

Progression was defined broadly in DASISION as any of the following: doubling of white blood cell (WBC) count to >20×10^9/L in the absence of complete hematologic response (CHR); loss of CHR; increase in Ph+ bone marrow metaphases to >35%; transformation to CML-AP/BP; or death from any cause. Patients who discontinued who had not died and agreed to follow-up continued to be followed for transformation and survival on a yearly basis for up to 5 years in DASISION. Progression was defined in 034/Dose-optimization as confirmed CML-AP/BP, loss of a previous CHR or major CyR (MCyR), ≥30% increase in Ph+ metaphases, increasing WBC count (recorded by the investigator as a doubling from lowest value to >20,000/μL or an increase by >50,000/μL on 2 assessments performed at least 2 weeks apart), or death from any cause. Patients were followed for overall survival (OS) for a minimum of 7 years, but were not followed for progression-free survival (PFS), after they had discontinued dasatinib.

Of note, DASISION was the sole study included in this analysis that required routine chest X-rays to assess the presence of pleural effusion, including asymptomatic events.

Statistical analyses

Retrospective multivariate analyses were performed to identify potential factors associated with the incidence of pleural effusion. These included race, sex, region, age, dosing schedule (034/Dose-optimization only), exposure to interferon (034/Dose-optimization only), baseline Euro (Hasford) risk scores (DASISION only), *BCR-ABL1* levels at 3 months, lymphocytosis, timing of lymphocytosis to onset of pleural effusion, colitis, baseline disease status, baseline hypertension, baseline smoking history, prior autoimmune disease, prior skin rash, prior lung disease, MMR at 12 months, line of therapy, average daily dose, duration of prior TKI therapy, and depth of MR at any time.

Rates of PFS and OS were estimated using Kaplan-Meier analysis. For PFS analysis, patients who discontinued without progression were censored at the time of the last on-study hematologic or cytogenetic evaluation. For OS analysis, patients who had not died were censored on the last date the

patient was known to be alive, which included dates after study discontinuation if provided by investigators.

Table S1. Clinical trials included in pooled population of Ph+ leukemia.

Trial designation	Diagnosis for trial enrollment and patient status	Dasatinib-treated patients, n	Study type	Dasatinib starting dose	Median duration of dasatinib treatment, months (range)
DASISION (NCT00481247)	CML-CP newly diagnosed	258	Phase 3; randomized, 2 arms	100 mg QD	60 (0-73)
034/Dose-optimization (NCT00123474)	CML-CP R, I	662	Phase 3; randomized, 4 arms	50 mg BID, 70 mg BID, 100 mg QD, 140 mg QD	30 (0-93)
CA180-035 (NCT00123487)	CML-AP/BP or Ph+ ALL R, I	609	Phase 3; randomized, 2 arms	70 mg BID, 140 mg QD	6 (0-93)
START-A (NCT00101647)	CML-AP R, I	174	Phase 2; non-randomized, single arm	70 mg BID	13 (0-74)
START-B (NCT00101816)	CML-MBP R, I	109	Phase 2; non-randomized, single arm	70 mg BID	4 (0-72)
START-C (NCT00101660)	CML-CP R, I	387	Phase 2; non-randomized, single arm	70 mg BID	25 (0-75)
START-L (NCT00101595)	CML-LBP or Ph+ ALL R, I	94	Phase 2; non-randomized, single arm	70 mg BID	3 (0-31)
START-R (NCT00103844)	CML-CP R	141	Phase 2; randomized, 2 arms	70 mg BID	26 (0-71)
CA180-160 (NCT00529763)	CML or Ph+ ALL R, I	121	Phase 2; non-randomized, single arm	100 mg QD for CML-CP, 70 mg BID for CML-AP/BP and Ph+ ALL	38 (0-62)
CA180-363 (NCT01357655)	CML-CP newly diagnosed	66	Phase 2; randomized, 2 arms	100 mg QD	19 (0-26)
CA180-002 (NCT00103701)	CML or Ph+ ALL R, I	91	Phase 1; non-randomized, single arm	15-240 mg/d	17 (0-91)

ALL: acute lymphoblastic leukemia; AP: accelerated phase; BID: twice daily; BP: blast phase; CML: chronic myeloid leukemia; CP: chronic phase; I: intolerant to imatinib; LBP: lymphoid blast phase; MBP: myeloid blast phase; Ph+: Philadelphia chromosome-positive; QD: once daily; R: resistant to imatinib.

Table S2. Best cytogenetic and molecular responses before and after first drug-related pleural effusion in dasatinib-treated patients with CML-CP in DASISION.

	Treated patients, n					
	Cytogenetic response after first pleural effusion (n=73)					
Cytogenetic response before first pleural effusion	CCyR (n=60)	PCyR (n=1)	Minor CyR (n=0)	Minimum CyR (n=0)	Not evaluated (n=12)	
CCyR (n=65)	53	0	0	0	12	
PCyR (n=3)	2	1	0	0	0	
Minor CyR (n=0)	0	0	0	0	0	
Minimum CyR (n=0)	0	0	0	0	0	
No response (n=5)	5	0	0	0	0	
	Molecular response after first pleural effusion (n=73)					
Molecular response before first pleural effusion	$MR^{4.5}$ (n=34)	MMR (n=24)	*BCR-ABL1* 0.1-≤1% (n=9)	*BCR-ABL1* 1-≤10% (n=2)	*BCR-ABL1* >10% (n=0)	Not evaluated (n=4)
$MR^{4.5}$ (n=12)	9	3	0	0	0	0
MMR (n=35)	19	14	1	0	0	1
BCR-ABL1 0.1-≤1% (n=16)	3	5	5	2	0	1
BCR-ABL1 1-≤10% (n=2)	1	0	1	0	0	0
BCR-ABL1 >10% (n=0)	0	0	0	0	0	0
Not evaluated (n=8)	2	2	2	0	0	2
Improved response		Maintained response		Lost response		

CCyR: complete cytogenetic response; CyR: cytogenetic response; MMR: major molecular response, *BCR-ABL1* transcripts ≤0.1% on the International Scale (IS) corresponding to a 3-log reduction from a standardized baseline; $MR^{4.5}$: *BCR-ABL1* transcripts ≤0.0032% (IS) corresponding to a 4.5-log reduction from a standardized baseline; PCyR: partial cytogenetic response.

Table S3. Best cytogenetic and molecular responses before and after first drug-related pleural effusion in dasatinib-treated patients with CML-CP in 034/Dose-optimization.

	Treated patients, n					
	Cytogenetic response after first pleural effusion (n=218)*					
Cytogenetic response before first pleural effusion	CCyR (n=79)	PCyR (n=17)	Minor CyR (n=5)	Minimum CyR (n=10)	Not evaluated (n=107)	
CCyR (n=116)	45	8	1	0	62	
PCyR (n=21)	7	3	1	4	6	
Minor CyR (n=10)	3	0	2	0	5	
Minimum CyR (n=11)	0	1	1	2	7	
No response (n=60)	24	5	0	4	27	
	Molecular response after first pleural effusion (n=218)*					
Molecular response before first pleural effusion	$MR^{4.5}$ (n=32)	MMR (n=69)	*BCR-ABL1* 0.1-≤1% (n=22)	*BCR-ABL1* 1-≤10% (n=20)	*BCR-ABL1* >10% (n=30)	Not evaluated (n=45)
$MR^{4.5}$ (n=15)	7	5	0	0	0	3
MMR (n=66)	20	34	1	1	1	9
BCR-ABL1 0.1-≤1% (n=42)	1	15	12	3	2	9
BCR-ABL1 1-≤10% (n=38)	3	5	5	12	9	4
BCR-ABL1 >10% (n=31)	0	1	0	4	15	11
Not evaluated (n=26)	1	9	4	0	3	9
Improved response		Maintained response			Lost response	

*Two patients did not have date of onset of pleural effusion captured and could not be included.
CCyR: complete cytogenetic response; CyR: cytogenetic response; MMR: major molecular response, *BCR-ABL1* transcripts ≤0.1% on the International Scale (IS) corresponding to a 3-log reduction from a standardized baseline; MR4.5: *BCR-ABL1* transcripts ≤0.0032% (IS) corresponding to a 4.5-log reduction from a standardized baseline; PCyR: partial cytogenetic response.

Figure S1

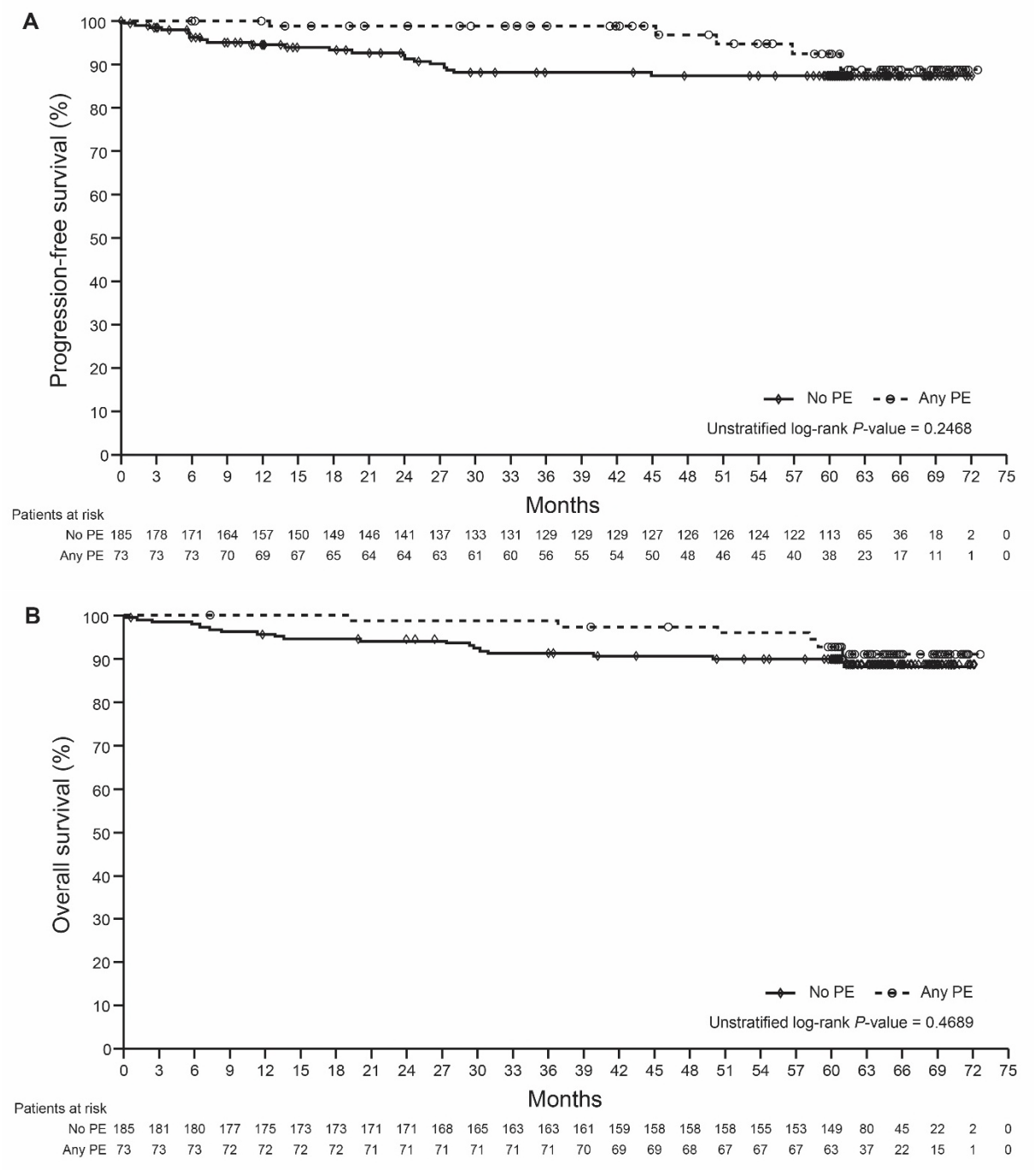

Figure S1. Progression-free survival (A) and overall survival (B) by drug-related PE versus no PE in dasatinib-treated patients in DASISION. PE: pleural effusion.

Figure S2

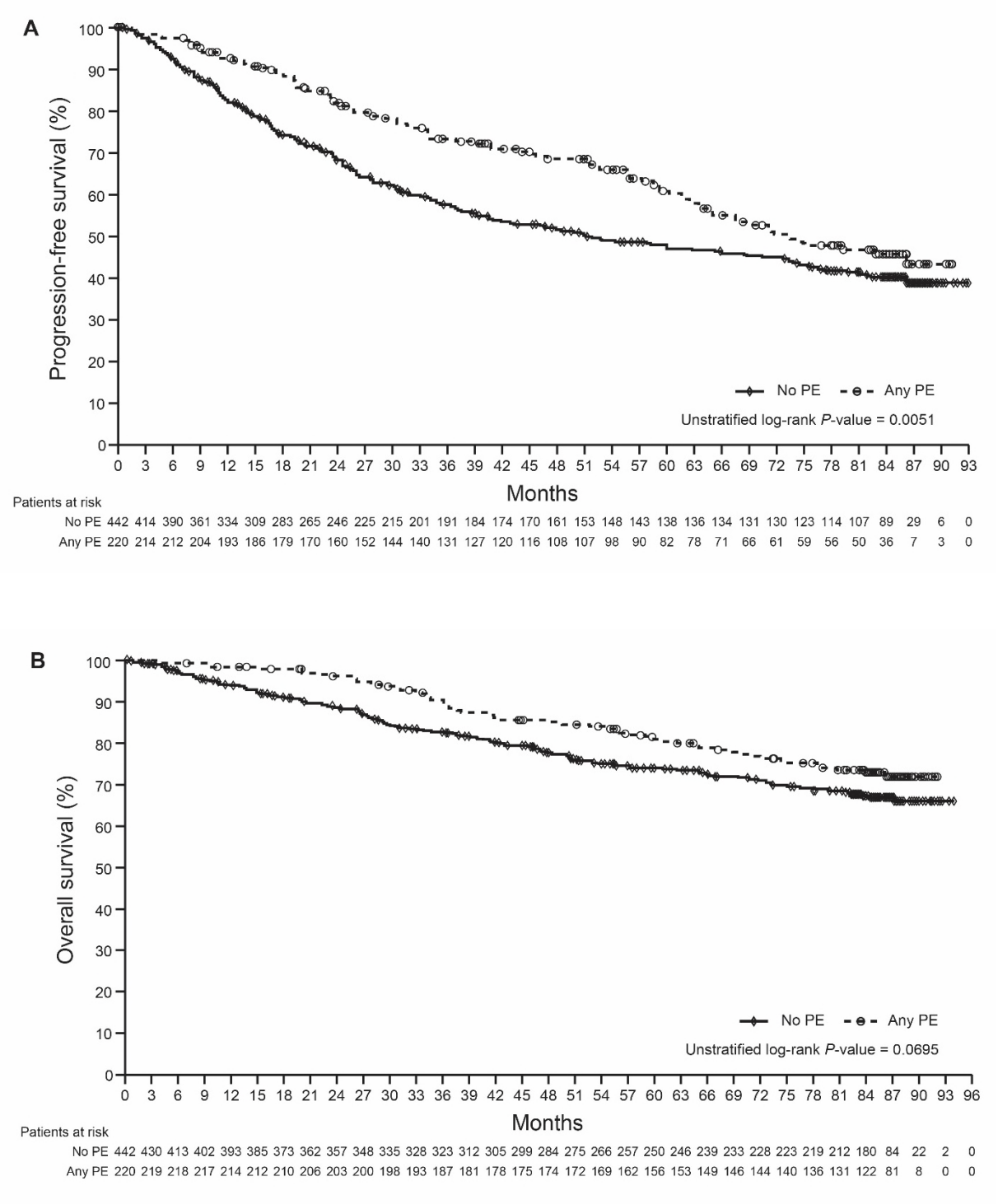

Figure S2. Progression-free survival (A) and overall survival (B) by drug-related PE versus no PE in dasatinib-treated patients in 034/Dose-optimization. PE: pleural effusion.