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Gore, Lia; Kearns, Pamela; De Souza, Carmino Antonio; de Martino, Maria Lucia; Bertrand, Yves; Hijiya, Nobuko; Stork, Linda C.; Chung, Nack-Gyun; Cardos, Rocio Cardenas; Saikia, Tapan; Fagioli, Franca ; Seo, Jong Jin; Landman-Parker, Judith; Lancaster, Donna L.; Place, Andrew E.; Rabin, Karen R.; Sacchi, Mariana; Swanink, Rene; Zwaan, C. Michel

DOI:

[10.1200/JCO.2017.75.9597](https://doi.org/10.1200/JCO.2017.75.9597)

[10.1200/JCO.2017.75.9597](https://doi.org/10.1200/JCO.2017.75.9597)

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*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Gore, L, Kearns, P, De Souza, CA, de Martino, ML, Bertrand, Y, Hijiya, N, Stork, LC, Chung, N-G, Cardos, RC, Saikia, T, Fagioli, F, Seo, JJ, Landman-Parker, J, Lancaster, DL, Place, AE, Rabin, KR, Sacchi, M, Swanink, R & Zwaan, CM 2018, 'Dasatinib in Pediatric Patients With Chronic Myeloid Leukemia in Chronic Phase: Results From a Phase II Trial', *Journal of Clinical Oncology* . <https://doi.org/10.1200/JCO.2017.75.9597>, <https://doi.org/10.1200/JCO.2017.75.9597>

[Link to publication on Research at Birmingham portal](#)

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Published in *Journal of Clinical Oncology* on 02/03/2018

DOI: 10.1200/JCO.2017.75.9597

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## Dasatinib in Pediatric Patients With Chronic Myeloid Leukemia in Chronic Phase: Results From a Phase II Trial

Lia Gore, Pamela R. Kearns, Maria Lucia de Martino Lee, Carmino Antonio De Souza, Yves Bertrand, Nobuko Hijiya, Linda C. Stork, Nack-Gyun Chung, Rocio Cardenas Cardos, Tapan Saikia, Franca Fagioli, Jong Jin Seo, Judith Landman-Parker, Donna Lancaster, Andrew E. Place, Karen R. Rabin, Mariana Sacchi, Rene Swanink, and C. Michel Zwaan

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Published at [jco.org](http://jco.org) on March 2, 2018.

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0732-183X/18/3699-1/\$20.00

### A B S T R A C T

#### Purpose

Safe, effective treatments are needed for pediatric patients with chronic myeloid leukemia in chronic phase (CML-CP). Dasatinib is approved for treatment of adults and children with CML-CP. A phase I study determined suitable dosing for children with Philadelphia chromosome–positive (Ph+) leukemias.

#### Methods

CA180-226/NCT00777036 is a phase II, open-label, nonrandomized prospective trial of patients < 18 years of age receiving dasatinib. There are three cohorts: (1) imatinib-resistant/intolerant CML-CP, (2) imatinib-resistant/intolerant CML in accelerated/blast phase or Ph+ acute lymphoblastic leukemia (n = 17), and (3) newly diagnosed CML-CP treated with tablets or powder for oral suspension. Major cytogenetic response > 30% for imatinib-resistant/intolerant patients and complete cytogenetic response (CCyR) > 55% for newly diagnosed patients were of clinical interest.

#### Results

Of 113 patients with CML-CP, 14 (48%) who were imatinib-resistant/intolerant and 61 (73%) who were newly diagnosed remained on treatment at time of analysis. Major cytogenetic response > 30% was reached by 3 months in the imatinib-resistant/intolerant group and CCyR > 55% was reached by 6 months in the newly diagnosed CML-CP group. CCyR and major molecular response by 12 months, respectively, were 76% and 41% in the imatinib-resistant/intolerant group and 92% and 52% in newly diagnosed CML-CP group. Progression-free survival by 48 months was 78% and 93% in the imatinib-resistant/intolerant and newly diagnosed CML-CP groups, respectively. No dasatinib-related pleural or pericardial effusion, pulmonary edema, or pulmonary arterial hypertension were reported. Bone growth and development events were reported in 4% of patients.

#### Conclusion

In the largest prospective trial to date in children with CML-CP, we demonstrate that dasatinib is a safe, effective treatment of pediatric CML-CP. Target responses to first- or second-line dasatinib were met early, and deep molecular responses were observed. Safety of dasatinib in pediatric patients was similar to that observed in adults; however, no cases of pleural or pericardial effusion or pulmonary arterial hypertension were reported.

*J Clin Oncol* 36. © 2018 by American Society of Clinical Oncology

### INTRODUCTION

Although chronic myeloid leukemia (CML) accounts for < 5% of leukemias and < 1% of all cancers in patients < 20 years of age,<sup>1</sup> more aggressive disease characteristics have been observed in pediatric and young adult patients with CML compared with older adults, including higher median white blood cell counts, proportionally

larger spleen size, higher peripheral blasts counts, and lower hemoglobin levels.<sup>2</sup> However, there are conflicting reports about the prognostic relevance of these variables on outcomes in children.<sup>3-5</sup>

The development of safe and effective therapies for pediatric CML is critical for the successful treatment of this patient population. Until recently, the BCR-ABL1–target tyrosine kinase inhibitor (TKI) imatinib was the only TKI approved for front-line treatment of pediatric

#### ASSOCIATED CONTENT



Data Supplement

DOI: <https://doi.org/10.1200/JCO.2017.75.9597>

DOI: <https://doi.org/10.1200/JCO.2017.75.9597>

patients with CML in chronic phase (CML-CP)<sup>6</sup>; however, 25% to 29% discontinued as a result of poor response or toxicity.<sup>7,8</sup> In addition, there were no approved therapies to treat children with imatinib-resistant/intolerant CML-CP. There is also a need for formulations of TKIs for younger patients who are unable to swallow tablets.<sup>9</sup>

Dasatinib is a second-generation TKI that is now approved in tablet formulation for the treatment of pediatric patients with CML-CP.<sup>10</sup> Previously, dosing and safety of dasatinib in pediatric patients were determined in phase I trials.<sup>11,12</sup> Here, we present results from a phase II prospective trial to further evaluate safety and efficacy of dasatinib tablet and powder for oral suspension (PFOS) formulations in pediatric patients with CML-CP.

## METHODS

### Study Design

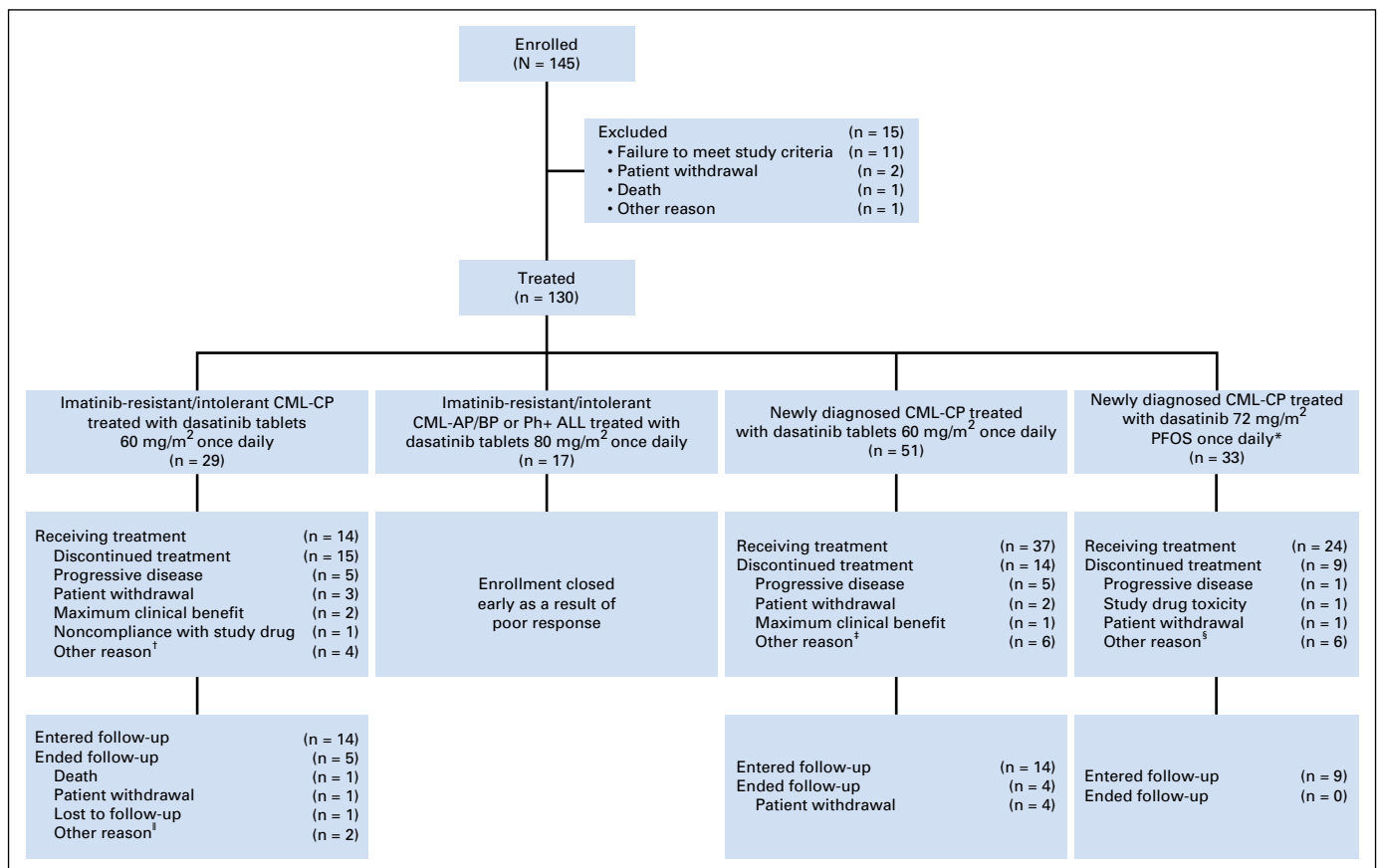
Study CA180-226 is an ongoing phase II, open-label, non-randomized, multicenter trial investigating dasatinib in pediatric patients with Philadelphia chromosome-positive (Ph+) leukemia (ClinicalTrials.gov identifier: NCT00777036). Patients < 18 years of age (the protocol was amended 9 months after enrollment started to change inclusion criteria from < 21 to < 18 years) were enrolled in three cohorts (Fig 1): (1)

patients with CML-CP resistant to or intolerant of imatinib who received dasatinib tablets 60 mg/m<sup>2</sup> once daily; (2) patients with accelerated- or blastic-phase CML (CML-AP/BP) or Ph+ acute lymphoblastic leukemia (ALL) resistant to or intolerant of imatinib who received dasatinib tablets 80 mg/m<sup>2</sup> once daily; and (3) patients with CML-CP newly diagnosed who received either dasatinib tablets 60 mg/m<sup>2</sup> once daily or PFOS 72 mg/m<sup>2</sup> once daily for ≥ 12 months; patients were then allowed to switch to tablets. PFOS dose was increased by 20% (to 72 mg/m<sup>2</sup>) to match the exposure of the 60 mg/m<sup>2</sup> tablet on the basis of bioavailability data in adults. Detailed inclusion and exclusion criteria are listed in the Data Supplement.

Patients could receive dasatinib until disease progression, unacceptable toxicity, or patient/physician preference. Patients who discontinued therapy were followed yearly for survival, effects on growth and development, and effects on bone metabolism up to 5 years after the last dasatinib dose. The protocol was approved by all institutional review boards, ethics committees, and national competent authorities at participating sites. All patients and/or legal guardians gave written informed consent and assent where applicable in accordance with the Declaration of Helsinki and local guidelines.

### Evaluations

Primary objectives were to determine major cytogenetic response (MCyR) for patients with imatinib-resistant/intolerant CML-CP, complete hematologic response (CHR) for patients with imatinib-resistant/intolerant CML-AP/BP or Ph+ ALL, and complete cytogenetic response (CCyR) for



**Fig 1.** CONSORT diagram of study CA180-226. (\*)Patients had the option to switch to dasatinib tablets 60 mg/m<sup>2</sup> once daily after 1 year of receiving PFOS. (†)Other includes bone marrow transplant, allogeneic bone marrow graft, suboptimal response, and patient lost to follow-up. (‡)Other includes T315I mutation, loss of major molecular response, investigator decision, loss of complete cytogenetic response (n = 2), and hematopoietic stem cell transplant (n = 2). (§)Other includes hematopoietic stem cell transplant (n = 2), suboptimal response, second malignancy, and transition to adult hospital (n = 2). (¶)Other includes transfer to adult hospital and bone marrow transplant. CML-AP/BP, chronic myeloid leukemia in accelerated/blast phase; CML-CP, chronic myeloid leukemia in chronic phase; PFOS, powder for oral suspension; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia.

**Table 1.** Baseline Patient Characteristics

Characteristic	Dasatinib-Treated Patients (n = 113)			
	Imatinib-Resistant/Intolerant CML-CP (n = 29)	Newly Diagnosed CML-CP		
		Tablets (n = 51)	PFOS (n = 33)	Total (n = 84)
Age, years, median (range)*	13.77 (1.4-20.1)	12.87 (1.9-17.8)	11.70 (1.8-17.5)	12.33 (1.8-17.8)
Age, years, No. (%)*				
< 2	1 (3)	1 (2)	1 (3)	2 (2)
≥ 2 to < 7	3 (10)	5 (10)	5 (15)	10 (12)
≥ 7 to < 12	6 (21)	16 (31)	12 (36)	28 (33)
≥ 12 to < 18	17 (59)	29 (57)	15 (45)	44 (52)
Sex, No. (%)				
Male	13 (45)	26 (51)	19 (58)	45 (54)
Female	16 (55)	25 (49)	14 (42)	39 (46)
Reason for stopping prior imatinib, No.				
Resistance	25	NA	NA	NA
Intolerance	2	NA	NA	NA
Undetermined†	2	NA	NA	NA
Patients with prior therapy, No. (%)				
Stem cell transplant	1 (3)	0	0	0
Interferon	4 (14)	1 (2)	0	1 (1)
Hydroxyurea or anagrelide	14 (48)	23 (45)	10 (30)	33 (39)
Chemotherapy‡	3 (10)	0	0	0
Median time from initial CML diagnosis to first dasatinib dose, months (range)	27.66 (3.0-33.9)	0.69 (0-3.5)	0.46 (0.1-1.4)	0.61 (0-3.5)

Abbreviations: CML-CP, chronic myeloid leukemia in chronic phase; NA, not applicable; PFOS, powder for oral suspension.

\*Two patients with imatinib-resistant/intolerant CML-CP were ≥ 18 years old and were allowed to continue in study despite not meeting enrollment criteria for age.

†Investigator reported the protocol eligibility criteria with regard to imatinib resistance and/or intolerance were not fully met.

‡Limited to cytostatic and antineoplastic agents.

patients with newly diagnosed CML-CP at any time. MCyR > 30% for imatinib-resistant/intolerant CML-CP, CHR > 15% for imatinib-resistant/intolerant CML-AP/BP or Ph+ ALL, and CCyR > 55% for newly diagnosed CML-CP were considered of clinical interest and align with historic responses in pediatric patients with CML-CP.<sup>7,8</sup> Secondary objectives included assessments of safety and evaluation of best cytogenetic and hematologic response, time to and duration of response, disease-free survival, progression-free survival (PFS), overall survival (OS), complete molecular response (CMR), and major molecular response (MMR). The description of *BCR-ABL1* mutations at baseline (results of which were not available before start of study treatment), progression, treatment failure, or end of treatment, and the exploration of the role of mutations as predictors of response were also secondary objectives. The database lock for this analysis was November 2016. Detailed definitions of efficacy outcomes, safety assessments, mutational analysis, and statistical methodology can be found in the Data Supplement.

## RESULTS

### Patients and Treatments

In total, 145 patients were enrolled between March 2009 and September 2014. Of these, 130 were treated across three cohorts (Fig 1): 29 with imatinib-resistant/intolerant CML-CP, 17 with imatinib-resistant/intolerant CML-AP/BP or Ph+ ALL, and 84 with newly diagnosed CML-CP. Newly diagnosed patients were either treated with dasatinib tablets (n = 51) or PFOS for ≥ 12 months (n = 33). Given the observed poor response of patients with imatinib-resistant/intolerant CML-AP/BP or Ph+ ALL (CHR was achieved at any time by one of eight patients with CML-BP and four of nine patients with Ph+ ALL), and that single-agent TKIs are now considered substandard of care for this pediatric population,

this cohort was closed after 17 patients were enrolled. Discussion of these data are not included in this report.

Baseline characteristics for the cohorts of CML-CP are in Table 1. With ≥ 24 months of follow-up, 14 patients (48%) with CML-CP resistant to or intolerant of imatinib and 61 patients (73%) with newly diagnosed CML-CP were still receiving study treatment. Reasons for exclusion and discontinuation are listed in Fig 1. Most patients received the protocol-recommended daily dose of dasatinib (Table 2). Patients who were initiated on PFOS were allowed to switch to tablets after receiving PFOS for ≥ 1 year. Of the 33 patients receiving PFOS, 22 (67%) switched to tablets because of patient preference. Greater than 38% of patients required at least one dose interruption, primarily because of dosing errors and hematologic toxicity (Table 2). Less than 25% of patients required dose reductions or escalations.

### Efficacy

Rates of confirmed CHR (cCHR) achieved at any time on treatment were 93% (95% CI, 77.2 to 99.2) and 96% (95% CI, 89.9 to 99.3) for patients resistant to or intolerant of imatinib or those newly diagnosed, respectively. Median time to cCHR was 0.7 months (95% CI, 0.5 to 1.8) for patients resistant to or intolerant of imatinib and 1.2 months (95% CI, 0.9 to 1.4) for newly diagnosed patients.

The cumulative rate of MCyR > 30% was reached as early as 3 months for patients with imatinib-resistant/intolerant CML-CP, and the cumulative rate of CCyR > 55% was reached as early as 6 months for patients with newly diagnosed CML-CP (Fig 2). Rapid responses were illustrated by a median time to MCyR of 3.1 months (95% CI, 2.8 to 4.1) for those in the imatinib-resistant/intolerant group and 3.0 months (95% CI, 2.9 to 4.3) for newly

**Table 2.** Dasatinib Exposure During Study

Characteristic	Dasatinib-Treated Patients (n = 113)			
	Imatinib-Resistant/Intolerant CML-CP (n = 29)	Newly Diagnosed CML-CP		
		Tablets (n = 51)	PFOS (n = 33)	Total (n = 84)
Average daily dose, mg/m <sup>2</sup> , median (range)	58.18 (35.1-71.7)	58.54 (37.2-77.9)	64.59 (38.3-98.7)	59.84 (37.2-98.7)
Duration of therapy, months, median (range)	49.91 (1.9-90.2)	52.24 (7.6-75.2)	27.40 (0.1-42.0)	42.30 (0.1-75.2)
Relative dose intensity, No. (%)				
50 to < 70	3 (10)	2 (4)	6 (18)	8 (10)
70 to < 90	4 (14)	13 (25)	11 (33)	24 (29)
90 to < 110	19 (66)	33 (65)	15 (45)	48 (57)
≥ 110	3 (10)	3 (6)	1 (3)	4 (5)
Patients with ≥ 1 dose interruption, No. (%)	21 (72)	31 (61)	13 (39)	44 (52)
Dosing error	8 (28)	6 (12)	3 (9)	9 (11)
Hematologic toxicity	5 (17)	13 (25)	6 (18)	19 (23)
Nonhematologic toxicity	6 (21)	9 (18)	4 (12)	13 (15)
Other	2 (7)	3 (6)	0	3 (4)
Duration of first interruption, days, median (range)	8 (2-34)	11 (2-35)	11 (4-19)	11 (2-35)
Patients with ≥ 1 dose reduction, No. (%)	7 (24)	6 (12)	2 (6)	8 (10)
Dosing error	1 (3)	0	0	0
Hematologic toxicity	3 (10)	4 (8)	2 (6)	6 (7)
Nonhematologic toxicity	3 (10)	2 (4)	0	2 (2)
Patients with ≥ 1 dose escalation, No. (%)	7 (24)	9 (18)	5 (15)	14 (17)
Resistance	4 (14)	7 (14)	3 (9)	10 (12)
Other	3 (10)	2 (4)	1 (3)	3 (4)
No change	0	0	1 (3)	1 (1)
Follow-up, months, median (range)	62.4 (8.0-90.9)	54.3 (16.0-76.6)	32.5 (5.2-42.4)	48.4 (5.2-76.6)

Abbreviations: CML-CP, chronic myeloid leukemia in chronic phase; PFOS, powder for oral suspension.

diagnosed patients, and a median time to CCyR of 3.9 months (95% CI, 2.8 to 5.6) for patients in the resistant/intolerant CML-CP group and 5.6 months (95% CI, 5.0 to 6.0) for newly diagnosed patients (Table 3). Cumulative cytogenetic response rates increased over time through 24 months, the minimum follow-up for this analysis (Fig 2). In both cohorts, rates of MCyR increased between 3 and 12 months and were maintained through 24 months. For patients with CML-CP resistant to or intolerant of imatinib, rates of CCyR consistently increased. Median durations of cytogenetic responses were not reached by the time of analysis (Table 3).

Additional assessments were performed to determine the rates of cytogenetic responses at any time, excluding patients with MCyR/CCyR or unknown cytogenetic status at baseline. The results from these assessments were similar to the results calculated using the total number of patients in each cohort (Data Supplement).

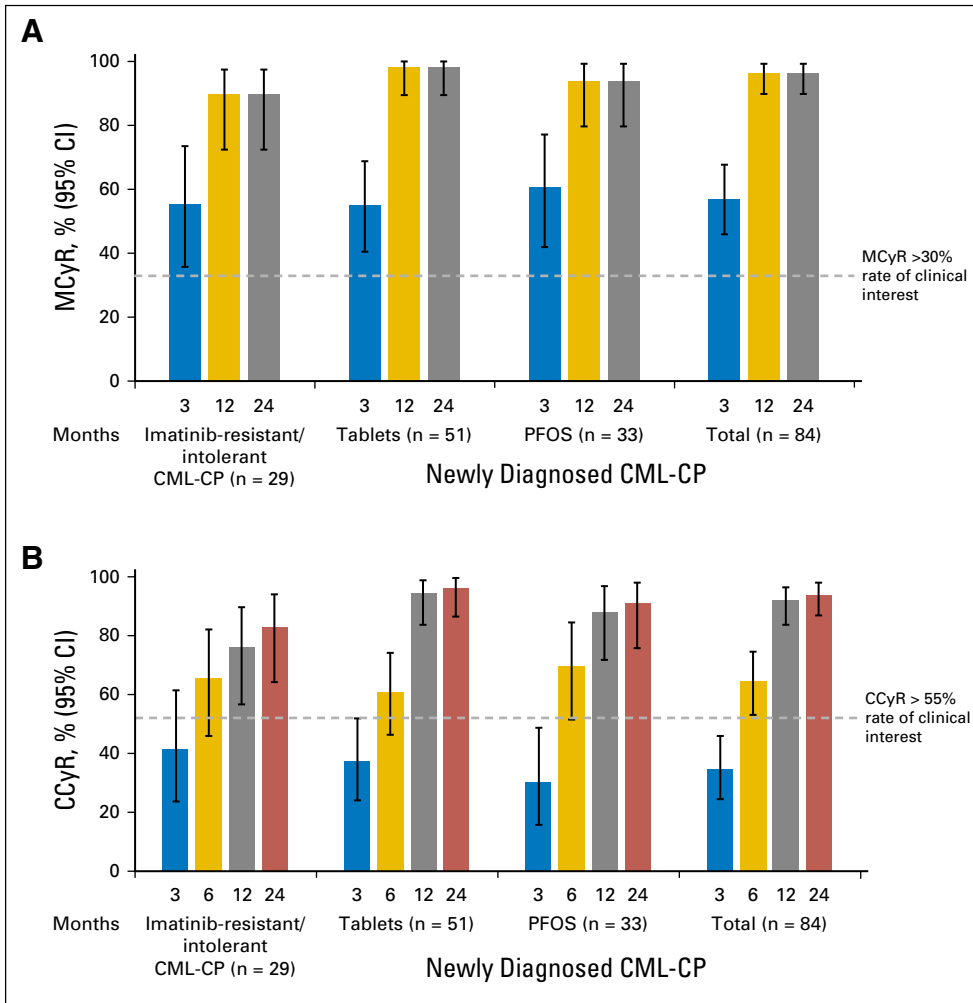
Although they were not focal study end points, the cumulative rates of MMR and CMR were also observed to increase over time in all cohorts (Fig 3). By 12 months, MMR was 41% and CMR was 7% for patients with imatinib-resistant/intolerant CML-CP, and by 24 months, MMR was 55% and CMR was 17% (Figs 3A and 3C). MMR and CMR were 52% and 8%, respectively, by 12 months and 70% and 21%, respectively, by 24 months for the total newly diagnosed patient population (Figs 3B and 3D). Cohorts in this study were not designed to be comparative; however, response rates appeared to be lower for patients taking the PFOS formulation versus tablets. Median time to MMR was 8.9 months (95% CI, 8.1 to 11.7) for newly diagnosed patients and was not calculated for the imatinib-resistant/intolerant cohort.

Median PFS and OS have not been reached in any cohort. Disease is seven of 29 patients (24%) resistant to or intolerant of

imatinib and seven of 84 newly diagnosed patients (8%) had progressed at the time of analyses (Data Supplement). Protocol-defined reasons for progression were loss of MCyR (n = 3 in the imatinib-resistant/intolerant group; n = 4 newly diagnosed patients), loss of CHR (n = 2 in each group), and development of CML-BP (n = 2 in the imatinib-resistant/intolerant group; n = 1 in the newly diagnosed group). Estimated 48-month PFS was 78% and 93% for patients with CML-CP resistant to or intolerant of imatinib and patients with newly diagnosed CML-CP, respectively (Data Supplement). Similar results were observed for disease-free survival (Data Supplement). One death was reported: a patient with CML-CP resistant to or intolerant of imatinib died of gastrointestinal bleeding 1 year after stopping dasatinib. This patient had loss of MCyR before death. There were no deaths reported for patients with newly diagnosed CML-CP. The estimated 48-month OS rate was 96% in the imatinib-resistant/intolerant CML-CP cohort.

A post hoc analysis of the proportion of patients with *BCR-ABL1* ≤ 10% versus > 10% at 3 months was performed for the newly diagnosed cohort. Of the 77 patients with evaluable transcript levels at 3 months, 60 (78%) had *BCR-ABL1* ≤ 10% and 17 (22%) had *BCR-ABL1* > 10%. PFS appeared to be higher for newly diagnosed patients with *BCR-ABL1* ≤ 10% versus those with *BCR-ABL1* > 10% at 3 months (*P* < .001; hazard ratio, 0.10; 95% CI, 0.02 to 0.52); estimated 3-year PFS rates were approximately 97% and 82% for patients with *BCR-ABL1* ≤ 10% or > 10% at 3 months, respectively.

*BCR-ABL1* mutations were assessed at baseline and at the time of disease progression, treatment failure, or end of treatment. In the imatinib-resistant/intolerant cohort, six of 27 patients (22%) evaluated at baseline had a mutation (E255K, F317L, F359V [n = 2], V379I, Y253H); five were in cCHR. Of nine patients with



**Fig 2.** Cytogenetic responses over time for all treated patients. (A) Cumulative rates of MCyR and (B) cumulative rates of CCyR. CCyR, complete cytogenetic response; CML-CP, chronic myeloid leukemia in chronic phase; MCyR, major cytogenetic response; PFOS, powder for oral suspension.

assessments at end of treatment, three had a mutation (E255K, F317L, T315A). The patients with the E255K and F317L mutations had the same mutation at baseline and end of treatment. No patient in this cohort had more than one mutation. Mutations in *BCR-ABL1* at T315, F317, and V299 are now considered resistant to dasatinib,<sup>13</sup> which was not fully understood when this trial began. Of the 78 patients with newly diagnosed CML-CP evaluated at baseline, one had a P58S mutation that was found in leukemia cells

only. This patient was receiving dasatinib tablets and had cCHR. There were no mutations detected in the seven patients newly diagnosed with CML-CP who were evaluated at end of treatment.

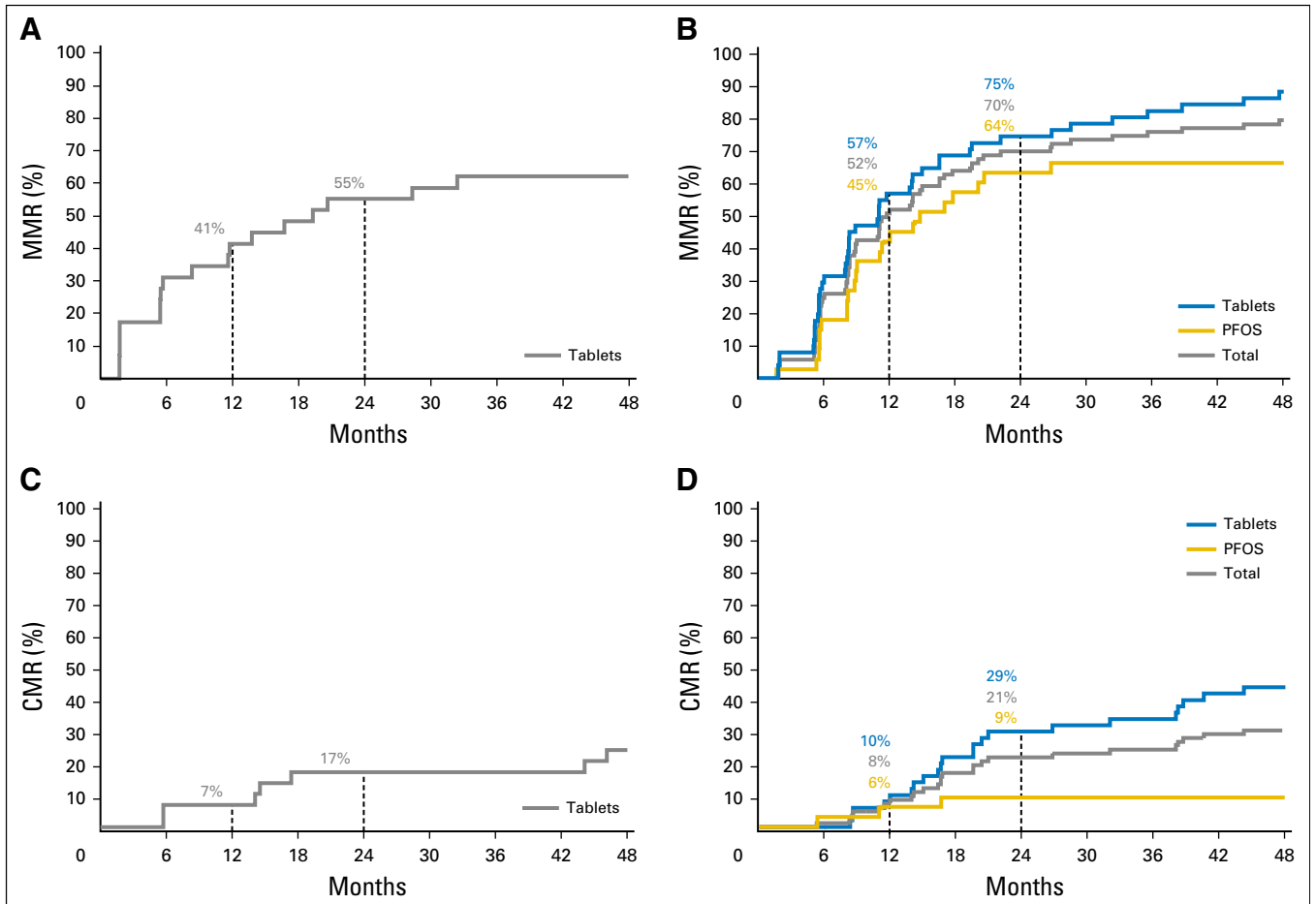
**Safety**

The dasatinib-related adverse events (AEs) of special interest reported in this study are listed in Table 4. There were no occurrences

**Table 3.** Time To and Duration of Response in Patients Treated With Dasatinib

Patient Group	Median Time to Response*		Median Duration of Response*	
	MCyR	CCyR	MCyR	CCyR
Imatinib-resistant/intolerant CML-CP (n = 29)	3.1 (2.8 to 4.1)	3.9 (2.8 to 5.6)	NE (54.9 to NE)	NE (54.9 to NE)
Newly diagnosed CML-CP				
Tablets (n = 51)	3.3 (2.9 to 5.6)	5.7 (3.7 to 6.2)	NE (52.7 to NE)	NE (49.9 to NE)
PFOS (n = 33)	3.0 (2.8 to 5.0)	5.6 (3.1 to 6.0)	NE (NE to NE)	NE (NE to NE)
Total (n = 84)	3.0 (2.9 to 4.3)	5.6 (5.0 to 6.0)	NE (52.7 to NE)	NE (49.9 to NE)

NOTE. Values are months (95% CI). Abbreviations: CCyR, complete cytogenetic response; CML-CP, chronic myeloid leukemia in chronic phase; MCyR, major cytogenetic response, NE, not estimable, median not reached; PFOS, powder for oral suspension. \*For patients who had a best response of CCyR or MCyR.



**Fig 3.** Cumulative rates of molecular responses over time for all treated patients. (A, B) MMR for (A) patients with CML-CP resistant to or intolerant of imatinib and (B) patients with newly diagnosed CML-CP. (C, D) CMR for (C) patients with CML-CP resistant to or intolerant of imatinib and (D) patients with newly diagnosed CML-CP. Cohorts were not designed to be comparative. There are numerical differences between MMR and CMR in newly diagnosed patients with CML-CP treated with dasatinib tablets or PFOS, but CIs overlap. CML-CP, chronic myeloid leukemia in chronic phase; CMR, complete molecular response; MMR, major molecular response; PFOS, powder for oral suspension.

of pleural effusion, pericardial effusion, pulmonary edema, pulmonary hypertension, or pulmonary arterial hypertension related to dasatinib in pediatric patients with CML-CP. In patients with imatinib-resistant/intolerant CML-CP and newly diagnosed patients, any-grade myalgia or arthralgia occurred in 17% and 10%, respectively, and fatigue occurred in 14% and 11%, respectively. Dasatinib-related pediatric bone growth and development AEs were grouped together for reporting purposes. Grade 1/2 events were reported in five of 113 patients (4%) with CML-CP. Data on growth and development continue to be collected and will be reported once mature.

Dasatinib-related serious AEs were reported in five patients (17%) with imatinib-resistant/intolerant CML-CP and eight patients (10%) with newly diagnosed CML-CP (Table 4). No suspected, unexpected serious adverse reactions were reported. There was one dasatinib-related AE leading to discontinuation (grade 3 drug hypersensitivity, which resolved when the drug was discontinued). Safety assessment of the 17 pediatric patients with CML-AP/BP or Ph+ ALL was consistent with the known safety profile in adults with advanced Ph+ leukemias.<sup>14-16</sup>

## DISCUSSION

CA180-226 is the largest prospective, registrational trial to date in pediatric patients diagnosed with CML. With  $\geq 24$  months of follow-up, high response rates and a favorable safety profile for dasatinib were demonstrated in patient with imatinib-resistant/intolerant CML-CP and those newly diagnosed with CML-CP.

This study was designed to explore the most clinically relevant end points for patients with CML at the time the protocol was developed in 2008: MCyR and CCyR. Overall, the efficacy of dasatinib in pediatric patients in this trial was similar to or higher than that historically observed in adults. In a phase III dose-optimization trial of adults with imatinib-resistant/intolerant CML-CP, 2-year MCyR was 63%<sup>17</sup>; in pediatric patients treated in this study, the MCyR rate by 2 years was 90%. Estimated PFS rates at 2 years were similar in adults and pediatric patients with CML-CP resistant to or intolerant of imatinib (80% and 82%, respectively). In adults with newly diagnosed CML-CP from the phase III Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients (DASISION), the cumulative

**Table 4.** Dasatinib-Related Adverse Events of Special Interest During This Study

Dasatinib-Related AEs	Dasatinib-Treated Patients (n = 113)							
	Imatinib-Resistant/ Intolerant CML-CP (n = 29)		Newly Diagnosed CML-CP					
			Tablets (n = 51)		PFOS (n = 33)		Total (n = 84)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
All AEs	26 (90)	11 (38)	41 (80)	20 (39)	28 (85)	12 (36)	69 (82)	32 (38)
AEs of special interest								
Nausea and/or vomiting	9 (31)	0	9 (18)	0	8 (24)	0	17 (20)	0
Myalgia or arthralgia	5 (17)	1 (3)	3 (6)	0	5 (15)	0	8 (10)	0
Fatigue	4 (14)	0	3 (6)	0	6 (18)	0	9 (11)	0
Rash	4 (14)	0	11 (22)	0	5 (15)	0	16 (19)	0
Diarrhea	4 (14)	0	11 (22)	0	4 (12)	0	15 (18)	0
Hemorrhage	3 (10)	0	7 (14)	1 (2)	1 (3)	0	8 (10)	1 (1)
Pediatric bone growth and development	3 (10)	0	1 (2)	0	1 (3)	0	2 (2)	0
Shortness of breath	3 (10)	0	1 (2)	0	1 (3)	0	2 (2)	0
Superficial edema	1 (3)	0	3 (6)	0	3 (9)	0	6 (7)	0
Congestive heart failure or cardiac dysfunction	1 (3)	0	2 (4)	0	0	0	2 (2)	0
Generalized edema	0	0	2 (4)	0	0	0	2 (2)	0
Cardiac disorders	0	0	1 (2)	0	0	0	1 (1)	0
Chest pain	0	0	0	0	1 (3)	0	1 (1)	0
SAEs*	5 (17)	5 (17)	6 (12)	5 (10)	2 (6)	1 (3)	8 (10)	6 (7)
Neutropenia	2 (7)	2 (7)	—	—	—	—	—	—
Anemia	1 (3)	1 (3)	—	—	—	—	2 (2)	2 (2)
Left ventricular dysfunction	1 (3)	0	—	—	—	—	—	—
Abnormal hepatic function	1 (3)	1 (3)	—	—	—	—	—	—
Infection	1 (3)	1 (3)	—	—	—	—	—	—
Overdose	1 (3)	0	—	—	—	—	1 (1)†	0
Febrile neutropenia	—	—	—	—	—	—	1 (1)	1 (1)
Hematochezia	—	—	—	—	—	—	1 (1)	1 (1)
Peripheral edema	—	—	—	—	—	—	1 (1)	0
Drug hypersensitivity	—	—	—	—	—	—	1 (1)	1 (1)
Periorbital cellulitis	—	—	—	—	—	—	1 (1)	1 (1)
Decreased white blood cell count	—	—	—	—	—	—	1 (1)	0
Recurrent leukemia	—	—	—	—	—	—	1 (1)	0
Uterine hemorrhage	—	—	—	—	—	—	1 (1)	0
AEs leading to discontinuation	0	0	0	0	1 (3)‡	1 (3)‡	1 (1)‡	1 (1)‡

NOTE. Values are No. (%).  
Abbreviations: dash, no data; AE, adverse event; CML-CP, chronic myeloid leukemia in chronic phase; PFOS, powder for oral suspension; SAE, serious adverse event.  
\*Patients may have had more than one SAE.  
†Grade unknown.  
‡Drug hypersensitivity.

CCyR rate by 2 years was 86%<sup>18</sup>; the rate in newly diagnosed pediatric patients treated in the present study was 94%. Estimated 2-year PFS rates were similar in newly diagnosed adults and pediatric patients (94% and 95%, respectively).

The results described here in patients treated with first-line dasatinib are promising compared with results previously reported in pediatric patients treated with first-line imatinib. The French National Phase IV Trial (n = 44), a prospective study of newly diagnosed pediatric patients with CML-CP treated with imatinib 260 mg/m<sup>2</sup> daily, reported CCyR and MMR rates at 12 months of 61% and 31%, respectively.<sup>7</sup> In a study of patients < 18 years of age and treated with high-dose imatinib (340 mg/m<sup>2</sup> daily), 51% achieved CCyR and 30% achieved MMR at 12 months.<sup>8</sup> CCyR by 12 months was reported to be 72% in newly diagnosed patients < 22 years of age receiving imatinib 340 mg/m<sup>2</sup> daily.<sup>19</sup> Newly diagnosed pediatric patients treated with dasatinib in this study had CCyR and MMR rates by 12 months of 92% and 52%, respectively. MMR is currently considered a more relevant objective of CML therapy, and findings in this trial support that deep and durable molecular remissions are achievable at high levels in pediatric patients with CML-CP treated with dasatinib.

Achieving early molecular response (EMR) has been associated with improved long-term outcomes in adults and pediatric patients with CML treated with TKIs.<sup>5,20</sup> For newly diagnosed pediatric patients treated with dasatinib in this study, 78% achieved *BCR-ABL1* ≤ 10% at 3 months. In the French National Phase IV Trial, 63% achieved this same milestone with imatinib.<sup>21</sup> This comparison is consistent with results observed in newly diagnosed adults treated with dasatinib versus imatinib (84% v 64%, respectively).<sup>22</sup> Such observed differences between dasatinib and imatinib may be relevant given the emerging evidence that early, deep response is of clinical relevance in CML. In newly diagnosed patient populations treated with dasatinib or imatinib, a significant association between EMR and PFS was observed.<sup>21,22</sup> In contrast, EMR was not correlated with improved outcomes in pediatric patients treated with high-dose imatinib.<sup>23</sup>

In adults, more patients receiving dasatinib achieved EMR than those receiving imatinib; EMR has been shown to predict improved long-term survival outcomes and deep molecular responses, currently a requirement for consideration in TKI discontinuation and discontinuation trials.<sup>20</sup> Our data suggest a possible role for front-line



dasatinib in achieving earlier and deeper responses in pediatric patients, although long-term studies would be needed to prove superiority in survival. Permanent discontinuation of TKIs is a key unmet, and currently unstudied, need in the treatment of pediatric CML. Efficacy of dasatinib in patients with imatinib-resistant/intolerant CML-CP in our study is of particular interest because all but two patients were resistant to imatinib. Long-term data from this trial and others, as well as randomized trials, are needed to confirm the best front-line TKI for pediatric patients.

TKI cost should also be considered when choosing a front-line TKI. With the introduction of generic imatinib in the United States, imatinib is expected to have a lower initial cost than dasatinib.<sup>24</sup> However, the total cost of dasatinib versus imatinib over a patient's life may be less. Our data and data from other reports suggest that patients receiving dasatinib are more likely to achieve early and deep responses and may be eligible for TKI discontinuation.<sup>20</sup> Additionally, nonadherence is associated with increased health care costs,<sup>25</sup> and complex treatment regimens have been shown to decrease adherence.<sup>26</sup>

Dasatinib has been shown to be better tolerated than imatinib in adults with CML-CP,<sup>22</sup> and there is some evidence, including results described here, that suggest better tolerability of dasatinib versus imatinib in children.<sup>7</sup> There were no reported pleural effusion or pulmonary hypertension events in pediatric patients from this trial or from the phase I study.<sup>12</sup> In contrast, dasatinib-related pleural effusion was reported in 28% of adults with newly diagnosed and imatinib-resistant/intolerant CML-CP, and dasatinib-related pulmonary hypertension was reported in 5% of newly diagnosed adults and 2% adults with imatinib-resistant/intolerant CML-CP.<sup>22,27</sup> It is possible that the pediatric patients in this study had fewer or no cardiopulmonary comorbidities that would predispose them to the events seen in adults. It is also important to investigate potential effects of dasatinib on growth and development in pediatric patients. Follow-up is ongoing to characterize the safety of chronic dasatinib use, because pediatric patients may live for many decades with CML. This will include assessment of growth and puberty, once the data are more mature. Long-term follow-up is essential, considering late toxicities of TKIs have been observed in case reports.<sup>2,5,28</sup>

A bioequivalence study conducted in adults demonstrated that the bioavailability of dasatinib PFOS was 19% lower than that of dasatinib tablets,<sup>29</sup> which led to the use of 72 mg/m<sup>2</sup> dasatinib PFOS in this study. Results reported here were similar between

tablets and PFOS; however, this trial was not designed to compare cohorts. A population pharmacokinetic analysis is ongoing to evaluate dasatinib PFOS exposure in pediatric patients. Dasatinib was shown to be safe and well tolerated in pediatric patients at doses up to 120 mg/m<sup>2</sup>, with no maximum tolerated dose identified in a phase I study.<sup>12</sup>

This trial was not designed to compare results between cohorts, dasatinib treatment in children versus adults, or dasatinib versus imatinib in pediatric patients. Similarities and differences described here were based on data from separate trials with differences in methodology, patient population, and geographic distribution, which limit interpretation.

Overall, dasatinib treatment produced early, deep, and durable responses of clinical importance in this largest prospective trial of pediatric patients with CML-CP to date. Target responses were met as early as 3 and 6 months for patients with imatinib-resistant/intolerant CML-CP or newly diagnosed CML-CP, respectively. Safety of dasatinib was consistent with that reported in adults, except that no cases of pleural or pericardial effusion or pulmonary arterial hypertension were observed in pediatric patients. These results support dasatinib as a safe and effective first- or second-line option for the treatment of pediatric CML-CP.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [jco.org](http://jco.org).

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### Support

Supported by Bristol-Myers Squibb.

### Prior Presentation

Presented in part at the ASCO Annual Meeting, Chicago, IL, June 2-6, 2017; and the European Hematology Association 22nd Congress, Madrid, Spain, June 22-25, 2017.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

## Dasatinib in Pediatric Patients With Chronic Myeloid Leukemia in Chronic Phase: Results From a Phase II Trial

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**Patents, Royalties, Other Intellectual Property:** Patent held for diagnostic discovery and treatment response methodology tools in the use of MR spectroscopy for leukemia.

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***Acknowledgment***

We thank the patients who participated in this study and the clinical study teams. We thank Dr. Yousif Matloub for his work developing this study and Eric Bleickardt for clinical development contributions to this study. Medical writing and editorial support were provided by Samantha L. Dwyer and Andrea Lockett of StemScientific, an Ashfield Company (Lyndhurst, NJ), and were funded by Bristol-Myers Squibb.