Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors

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Long-term efficacy and safety of bosutinib (≥4 years follow-up from last enrolled patient) were evaluated in an ongoing phase 1/2 study in the advanced leukemia cohort with prior treatment failure (accelerated-phase [AP], n = 79) chronic myeloid leukemia [CML], blast-phase [BP, n = 64] CML, acute lymphoblastic leukemia [ALL, n = 24]). Fourteen AP, 2 BP, and 1 ALL patient remained on bosutinib at 4 years (vs. 38, 8, 1 at 1 year); median (range) treatment durations: 10.2 (0.1–88.6), 2.8 (0.03–55.9), 0.97 (0.3–89.2) months. Among AP and BP patients, 57% and 28% newly attained or maintained baseline overall hematologic response (OHR); 40% and 37% attained/maintained major cytogenetic response (MCyR) by 4 years (most by 12 months). In responders at 1 versus 4 years, Kaplan-Meier (KM) probabilities of maintaining OHR were 78% versus 49% (AP) and 28% versus 19% (BP); KM probabilities of maintaining MCyR were 65% versus 49% (AP) and 21% versus 21% (BP). Most common AEs (AP, BP) were gastrointestinal (96%; 83%), primarily diarrhea (85%; 64%), which was typically low grade (maximum grade 1/2: 81%; 59%) and transient; no patient discontinued due to diarrhea. Serious AEs occurred in 44 (56%) AP and 37 (58%) BP patients, most commonly pneumonia (n = 9) for AP and pyrexia (n = 6) for BP; 11 and 13 died within 30 days of last dose (2 considered bosutinib-related [AP] per investigator). Responses were durable in ~50% AP responders at 4 years (~25% BP patients responded at year 1, suggesting possible bridge-to-transplant role in BP patients); toxicity was manageable.

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considered appropriate treatment options [23,24]. Bosutinib has demonstrated activity and manageable tolerability in a phase I/2 study of patients with CP CML following resistance/intolerance to imatinib or imatinib plus dasatinib and/or nilotinib [25–28]. The current analysis from the same study presents for the first time the durability of response and long-term safety of bosutinib in the fully enrolled advanced leukemia cohort. The data include a long-term follow-up to ≥4 years after the last patients’ first visit.

Methods

Patient characteristics. Eligible patients were aged ≥18 years with diagnosis of AP or BP CML or Ph+ ALL. AP CML was defined by ≥1 of the following: per peripheral blood or bone marrow blasts, ≥30% blasts; ≥30% blasts plus promyelocytes; ≥20% basophils; or <100 x 10^9/L platelets (unrelated to therapy). BP CML and ALL were characterized by ≥30% blasts in blood or bone marrow, or extramedullary disease involvement in organs other than liver/spleen. The most advanced historical CML diagnosis for each patient was considered for cohort allocation.

Eligible patients were resistant/intolerant to prior imatinib, as defined in Supporting Information Table I, and were allowed to have received prior dasatinib and/or nilotinib. Patients also had an Eastern Cooperative Oncology Group Performance Status of 0 to 2, adequate hepatic and renal function, no prior antiproliferative treatment (except hydroxyurea or anagrelide) within 7 days of first dose, and ≥3 months since allo-HSCT (if applicable). Patients with a documented T315I Bcr-Abl mutation were allowed to start bosutinib therapy until a protocol amendment (May 28, 2008) excluded such patients; patients already receiving treatment could remain on study if enrolled before the amendment or if a baseline sample subsequently tested positive for the T315I mutation.

All patients provided written informed consent before study entry. The study protocol was approved by institutional review boards at each site and conducted in accordance with the Declaration of Helsinki. This trial was registered at www.ClinicalTrials.gov (NCT00261846).

Study design. This phase 1/2, open-label, two-part study evaluated oral bosutinib in Ph+ leukemia. Part 1 was a dose-escalation study in primarily imatinib-resistant patients with CP CML, which determined a recommended part 2 starting dose of bosutinib 600 mg/day [25]. Part 2 examined the activity and tolerability of bosutinib in patients with CP CML [25,26,28] and advanced leukemia (AP CML, BP CML, ALL; described herein) with resistance/intolerance to prior imatinib (second-line) and possibly dasatinib and/or nilotinib (≥third-line). Dose escalation to bosutinib 600 mg/day was allowed for lack of efficacy (failure to reach CHR by week 8 or complete cytogenetic response [CCyR] by week 12) if no grade 3/4 bosutinib-related toxicity had occurred. Other concomitant antileukemia therapy was prohibited; however, intrathecal cerebrospinal fluid prophylaxis/treatment was permitted during the treatment phase as clinically indicated.

Efficacy and safety assessments. Bone marrow examinations were performed at weeks 4, 8 (unless patient returned to CP), and 12; every 3 months until 2 years; and thereafter every 6 months. Complete blood count with differential was assessed at weeks 1, 2, 3, 4, 8, and 12; every 3 months until 2 years; and thereafter every 6 months. Disease status was not typically assessed after treatment discontinuation. Central laboratory sequencing was performed to identify Bcr-Abl mutations at baseline and treatment completion; assay sensitivity was 20% in the background of non-mutated cells.

The key endpoint was confirmed overall hematologic response (OHR) by week 48. Other endpoints included safety/tolerability, hematologic and cytogenetic responses, time to and duration of response, response by Bcr-Abl mutational status, time to progressive disease (PD) or death, and overall survival (OS).

Hematologic responses were to be confirmed after ≥4 weeks of duration, with peripheral blood and bone marrow differential documentation and extramedullary disease assessment; for CHR, bone marrow differential documentation was required (Supporting Information Table II). Standard criteria for cytogenetic response were employed [29]. Baseline assessments required ≥20 metaphases. Fluorescence in situ hybridization (FISH) was used for baseline assessment (≥200 cells required) only if the bone marrow sample was inadequate for cytogenetic analysis (i.e., <20 metaphases); responses based on FISH were determined as indicated above except that <1% of positive cells were required for CCyR. To be considered responders, patients must have had improvement from baseline or maintained a baseline response for ≥5 weeks for hematologic response or ≥4 weeks for cytogenetic response.

Progressive disease was defined as any of the following while receiving bosutinib: evolving from AP to BP on 2 consecutive assessments ≥1 week apart; increasing WBC (doubling over ≥1 month, with the second WBC ≥20 x 10^9/L and confirmed ≥1 week after initial loss of confirmed CHR that is confirmed with a subsequent hematologic assessment ≥2 weeks after initial loss; loss of MCyR with Ph+ metaphases increased by ≥30%; and (for ALL) loss of previous hematologic response or complete remission (blasts ≥5% in bone marrow).

Adverse events (AEs) were assessed from the date of informed consent to 30 days after the last bosutinib dose and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Results

Patients and treatment summary

Among 167 patients with advanced leukemia included in the safety population, all had received prior imatinib, 55 (33%) dasatinib, 27 (16%) nilotinib, and 15 (9%) patients had prior exposure to all three TKIs (Table I).

As of the data cutoff (May 23, 2014) based on an unlocked database for this interim manuscript, 14 (18%) AP CML, 2 (3%) BP CML, and 1 (4%) ALL patient was still receiving bosutinib at 4 years, compared with 38 (48%), 8 (13%), and 1 (4%) patient at 1 year; 1 year = 48 weeks). Time from last enrolled patient’s first dose to the data cutoff for AP CML, BP CML, and ALL cohorts was 49.2, 54.5, and 78.5 months, respectively; median (range) duration of follow-up from bosutinib initiation to last contact was 28.4 (0.3–88.6), 10.4 (0.4–79.9), and 3.6 (0.4–89.2) months. Most permanent treatment discontinuations (72% [n = 120]) occurred within the first year of treatment; fewer patients in the AP CML cohort permanently discontinued (52% [n = 41]) within the first year compared with patients in the BP CML (88% [n = 56]) and ALL (96% [n = 23]) cohorts (Table II). Across cohorts, the most common primary reasons (≥5% of patients) for treatment discontinuation (∇1 year vs. ≥1 to 4 years) for those on-treatment during those years were PD (29% vs. 34%), AEs (13% vs. 13%), unsatisfactory response (8% vs. 6%), symptom deterioration (8% vs. 4%), and death (8% vs. 0%).

The median (range) duration of bosutinib treatment for AP CML, BP CML, and ALL was 10.2 (0.1–88.6), 2.8 (0.03–55.9), and 0.97 (0.3–89.2) months; median treatment duration was longer for second-line patients versus third-line patients (AP, 11.5 vs. 6.9 months; BP, 3.31 vs. 1.8 months). Among AP CML, BP CML, and ALL cohorts, respectively, AEs were managed by treatment interruption (47 [59%], 28 [44%], 10 [42%], respectively) and/or dose reductions (38 [48%], 17 [27%], 1 [4%]); dose escalation to 600 mg/day (due to lack of efficacy) occurred in 14 (18%), 16 (25%), and 5 (21%) patients with initial dose <600 mg/day.

Efficacy

Among 72 evaluable patients with AP CML, confirmed OHR by week 48 (key endpoint) was newly attained or maintained by 41 (57%) patients (Table III), including 32 (44%) with a major hematologic response (MHR) and 22 (31%) with CHR. Among AP CML patients, 41 (57%), 34 (47%), and 24 (33%), respectively, attained/maintained an OHR, MHR, or CHR by 4 years. Among patients without a CHR at baseline (n = 63), 18 (29%) achieved a CHR on...
| Characteristic                              | AP CML | BP CML | Total (n = 79) | AP CML | BP CML | Total (n = 64) | All (n = 24) |
|--------------------------------------------|--------|--------|---------------|--------|--------|---------------|------------|
| Median (range) age (yr)                    | 49 (18–73) | 57 (21–83) | 51 (18–83) | 36.5 (19–75) | 52.5 (22–82) | 47 (19–82) | 59 (24–84) |
| Men, n (%)                                 | 26 (53) | 18 (60) | 44 (56) | 25 (69) | 17 (61) | 42 (66) | 12 (50) |
| ECOG performance status, n (%)             | 0      | 1      | 1      | 16 (44) | 6 (21) | 22 (34) | 9 (38) |
| 0                                          | 30 (61) | 15 (50) | 45 (57) | 11 (31) | 18 (64) | 29 (45) | 10 (42) |
| 1                                          | 18 (37) | 14 (47) | 32 (41) | 9 (25) | 4 (14) | 13 (20) | 5 (21) |
| 2                                          | 1 (2)   | 1 (3)   | 2 (3)   | 1 (3)   | 1 (3)   | 1 (3)   | 1 (3)   |
| Median (range) WBC, 10^9/L                 | 13.0 (2.2–360.1) | 11.5 (0.5–153.0) | 11.6 (0.5–360.1) | 13.0 (0.7–87.5) | 18.8 (2.4–213.7) | 14.1 (0.7–213.7) | 7.9 (0.5–115.0) |
| Median (range) platelet count, 10^9/L       | 309.0 (5.0–1939.0) | 161.5 (8.0–2189.0) | 246.0 (5.0–2189.0) | 68.7 (6.0–455.0) | 61.0 (3.0–1060.0) | 65.5 (3.0–1060.0) | 31.5 (5.0–670.0) |
| Median (range) duration of disease (yr)     | 3.9 (1.1–22.1) | 8.2 (1.5–19.2) | 5.6 (1.1–22.1) | 2.3 (0.4–9.3) | 5.8 (1.1–14.5) | 3.3 (0.4–14.5) | 1.0 (0.1–20.0) |
| No. prior therapies, n (%)                 | 1 (imatinib) | 0      | 29 (37) | 30 (83) | 0      | 30 (47) | 15 (63) |
| 2                                          | 20 (41) | 5 (17)  | 25 (32) | 6 (17)  | 11 (39) | 17 (27) | 8 (33) |
| ≥3                                         | 0      | 25 (83) | 25 (32) | 0      | 17 (61) | 17 (27) | 1 (4)  |
| Prior therapy, n (%)                       | 20 (41) | 21 (70) | 41 (52) | 6 (17)  | 14 (50) | 20 (31) | 1 (4)  |
| Interferon, n (%)                          | 49 (100) | 30 (100) | 79 (100) | 36 (100) | 28 (100) | 64 (100) | 24 (100) |
| Imatinib, n (%)                            | 35.6 (0.8–108.3) | 35.6 (4.1–66.4) | 35.6 (0.8–108.3) | 13.4 (0.9–48.6) | 29.8 (1.0–62.6) | 212 (0.9–62.6) | 7.2 (0.5–55.8) |
| Reason for imatinib discontinuation, n (%) | Adverse event | 5 (10) | 6 (20) | 11 (14) | 4 (11) | 6 (21) | 10 (16) | 2 (8)  |
| Disease progression/ inadequate response   | 44 (90) | 24 (80) | 68 (86) | 32 (89) | 22 (79) | 54 (84) | 22 (92) |
| Dasatinib, n (%)                           | 0      | 25 (83) | 25 (32) | 0      | 22 (79) | 22 (34) | 8 (33) |
| Median (range) duration (mo)               | 6.9 (0.1–30.4) | 6.9 (0.1–30.4) | 6.9 (0.1–30.4) | 7.0 (0.1–14.34) | 7.0 (0.1–14.34) | 7.0 (0.1–14.34) | 7.4 (2.6–32.7) |
| Nilotinib, n (%)                           | 0      | 15 (50) | 15 (19) | 0      | 11 (39) | 11 (17) | 1 (4)  |
| Median (range) duration (mo)               | 4.3 (0.8–34.0) | 4.3 (0.8–34.0) | 4.3 (0.8–34.0) | 1.0 (0.1–19.3) | 1.0 (0.1–19.3) | 0.4 (0.4–0.4) | 3.3 (13) |

a Of 64 patients with BP CML, 10 had lymphoid BP, 23 had myeloid BP, and 31 had unspecified BP.

b Includes TKI and interferon therapy.

c Excludes 1 patient with unknown imatinib start and/or stop date.

2L, second-line (prior imatinib only); ≥3L, third-/fourth-line (imatinib followed by dasatinib and/or nilotinib); AP, accelerated phase; CML, chronic myeloid leukemia; BP, blast phase; ALL, acute lymphoblastic leukemia; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cell count.
TABLE II. Reasons for Treatment Discontinuation and Adverse Events Resulting in Dose Modification Over Time

| Reason for treatment discontinuation, a n (%) | Year 1 | Year 2 | Year 3 | Year 4 |
|---------------------------------------------|--------|--------|--------|--------|
| AP CML (n = 79)                             |        |        |        |        |
| BP CML (n = 64)                             |        |        |        |        |
| ALL (n = 24)                                |        |        |        |        |
| Any reason                                  | 41 (52) | 56 (88) | 23 (96) | 19 (50) |
| AE                                          | 16 (20) | 2 (3)  | 3 (13) | 4 (11)  |
| Disease progression                         | 10 (13) | 29 (45) | 10 (42) | 11 (29) |
| Death                                       | 5 (6)   | 6 (9)  | 2 (8)  | 0 (0)   |
| Symptomatic deterioration                   | 5 (6)   | 6 (9)  | 3 (13) | 1 (5)   |
| Unsatisfactory response                     | 3 (4)   | 5 (8)  | 5 (21) | 3 (8)   |
| Subject request                             | 1 (1)   | 3 (5)  | 0 (0)  | 0 (0)   |
| Other                                       | 1 (1)   | 3 (5)  | 0 (0)  | 1 (13)  |
| Investigator request                        | 0 (0)   | 1 (2)  | 0 (0)  | 0 (0)   |
| Lost to follow-up                           | 0 (0)   | 1 (2)  | 0 (0)  | 0 (0)   |
| Protocol violation                          | 0 (0)   | 1 (2)  | 0 (0)  | 0 (0)   |
| Dose interruption                           | 20 (25) | 8 (13) | 0 (0)  | 1 (3)   |
| Thrombocytopenia                            | 2 (3)   | 0 (0)  | 1 (3)  | 0 (0)   |
| Neutropenia                                 | 11 (14)| 6 (9)  | 1 (4)  | 0 (0)   |
| Anemia                                      | 7 (9)   | 3 (5)  | 0 (0)  | 0 (0)   |
| ALT increased                               | 6 (8)   | 1 (2)  | 0 (0)  | 0 (0)   |
| AST increased                               | 5 (6)   | 0 (0)  | 0 (0)  | 0 (0)   |
| Leukopenia                                  | 4 (5)   | 4 (6)  | 1 (4)  | 0 (0)   |
| Vomiting                                    | 4 (5)   | 3 (5)  | 2 (8)  | 0 (0)   |
| Diarrhea                                    | 3 (4)   | 2 (3)  | 1 (4)  | 0 (0)   |
| Nausea                                      | 3 (4)   | 2 (3)  | 0 (0)  | 0 (0)   |
| Pyrexia                                     | 3 (4)   | 1 (2)  | 1 (4)  | 0 (0)   |
| Rash                                        | 4 (5)   | 2 (3)  | 1 (4)  | 0 (0)   |
| Dose reduction                              | 14 (18)| 5 (8)  | 0 (0)  | 0 (0)   |
| Thrombocytopenia                            | 5 (6)   | 2 (3)  | 0 (0)  | 0 (0)   |
| Neutropenia                                 | 3 (4)   | 1 (2)  | 0 (0)  | 1 (3)   |
| Anemia                                      | 3 (4)   | 1 (2)  | 0 (0)  | 0 (0)   |
| Leukopenia                                  | 3 (4)   | 1 (2)  | 0 (0)  | 0 (0)   |
| AST increased                               | 3 (4)   | 0 (0)  | 0 (0)  | 0 (0)   |
| Rash                                        | 3 (4)   | 0 (1)  | 1 (4)  | 0 (0)   |

a n = 48 weeks.
b In ≥2 patients (any cohort).
c In ≥3 patients (any cohort).
AE, adverse event; ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; AP, accelerated phase; AST, aspartate aminotransferase; BP, blast phase.

boasutinib, all within the first 2 years; among patients with a CHR at baseline (n = 9), 6 (67%) maintained a CHR on bosutinib. Median (95% CI) duration of OHR in responders was 119.9 (63.1 – not reached [NR]) weeks, with Kaplan-Meier–estimated probabilities (95% CI) of 78% (59%–89%) for maintaining an OHR at 1 year versus 49% (30%–66%) at 4 years (Fig. 1A). Among evaluable patients without a CCyR at baseline (n = 59), 16 (38%) achieved MCyR and 19 (28%) achieved CCyR by 4 years; the three AP CML patients with a CCyR at baseline maintained CCyR on bosutinib. Median (95% CI) duration of MCyR among responders was 29.1 (11.9–38.3) weeks for patients with BP CML, with Kaplan-Meier–estimated probabilities (95% CI) of maintaining a MCyR of 65% (43%–80%) at 1 year versus 49% (28%–66%) at 4 years (Fig. 1B). Hematologic and cytogenetic response rates appeared higher for the second-line versus ≥third-line BP CML cohort (Table III).

Among 22 evaluable patients with ALL, 2 (9%) newly attained or maintained a confirmed OHR (both CHR) by 4 years (Table III). One of the patients had a CHR at baseline and newly achieved a CHR on bosutinib (duration of response, 3.9 weeks [discontinued treatment due to symptomatic deterioration]). Among patients without a CCyR at baseline (n = 18), three (17%) achieved MCyR (all CCyR); between the two patients
Figure 1. Duration of OHR (A) and MCyR (B). Duration of response was calculated from the first date of response to confirmed loss, treatment discontinuation due to progressive disease or death, or death within 30 days of the last dose of study drug; responders without events were censored at the last follow-up visit. 2L, Second-line (prior imatinib only); ≥3L, third- or fourth-line (imatinib followed by dasatinib and/or nilotinib); ALL, acute lymphoblastic leukemia; AP, accelerated phase; BP, blast phase; CI, confidence interval; CML, chronic myeloid leukemia; MCyR, major cytogenetic response; NR, not reached; NE, not evaluable; OHR, overall hematologic response.
### TABLE III. Response to Therapy by Disease State and Prior Treatment With TKIs

| Response, n (%) | 2L (n = 49) | ≥3L (n = 30) | Total (n = 79) | 2L (n = 36) | ≥3L (n = 28) | Total (n = 64) | ALL (n = 24) |
|----------------|-------------|-------------|---------------|-------------|-------------|---------------|-------------|
| **Week 48 hematologic response**<sup>a</sup> | | | | | | | |
| Evaluable patients<sup>b</sup> | 43 | 29 | 72 | 34 | 26 | 60 | 22 |
| OHR [95% CI] | 29 (67) [52–81] | 12 (41) [24–61] | 41 (57) [45–69] | 13 (38) [22–56] | 4 (15) [4–35] | 17 (28) [18–41] | 1 (5) [1–23] |
| Cumulative hematologic response by 4 yrs<sup>c</sup> | | | | | | | |
| Evaluable patients<sup>a,b</sup> | 43 | 29 | 72 | 34 | 26 | 60 | 22 |
| OHR [95% CI] | 29 (67) [52%–81%] | 12 (41%–61%) | 41 (57%) [45%–69%] | 13 (38%) [22%–56%] | 4 (15%) [4%–35%] | 17 (28%) [18%–41%] | 2 (9%) [1%–29%] |
| CHR | 9 (27) | 2 (8) | 11 (18) | 9 (27) | 1 (4) | 10 (17) | 2 (9) |
| Median [range] time to OHR<sup>c</sup> (wk) | 12.0 [3.7–49.0] | 12.1 [4.0–24.0] | 12.0 [3.7–49.0] | 8.0 [4.0–12.0] | 11.6 [4.1–12.1] | 8.9 [4.0–12.1] | 43.6 [4.0–83.1] |
| Evaluable patients without a CHR at baseline | 39 | 24 | 63 | 32 | 23 | 55 | 21 |
| OHR | 9 (28) | 1 (4) | 10 (18) | 3 (9) | 1 (2) | 4 (7) | 1 (5) |
| Cumulative cytogenetic response by 4 years<sup>d</sup> | | | | | | | |
| Evaluable patients<sup>a,d</sup> | 46 | 26 | 72 | 30 | 24 | 54 | 20 |
| MiCyR | 3 (7) | 0 | 3 (4) | 1 (3) | 1 (4) | 2 (4) | 0 |
| MiCyR [95% CI] | 22 (48%) [33%–63%] | 7 (27%) [12%–48%] | 29 (40%) [29%–53%] | 15 (50%) [31%–69%] | 5 (21%) [7%–42%] | 20 (37%) [24%–51%] | 4 (20%) [6%–44%] |
| CCyR | 16 (33) | 6 (23) | 22 (31) | 11 (37) | 4 (17) | 15 (28) | 4 (20) |
| Median [range] time to CCyR<sup>c</sup> (wk) | 12.3 [3.9–42.0] | 144.7 [4.0–144.7] | 24.0 [3.9–144.7] | 12.1 [3.9–25.1] | NR [41–123] | 12.1 [3.9–25.1] | 9.0 [4.0–12.0] |
| Evaluable patients without a CCyR at baseline | 46 | 23 | 69 | 28 | 22 | 50 | 18 |
| MiCyR | 22 (48) | 4 (17) | 26 (38) | 13 (46) | 3 (14) | 16 (32) | 3 (17) |

<sup>a</sup> To be considered a responder, the patient must have improved from their baseline assessment or maintained their baseline response.

<sup>b</sup> Evaluable patients included those who received ≥1 dose of bosutinib and had a valid baseline hematologic measurement.

<sup>c</sup> Time to response was calculated among responders from first study dosing to the earliest date of response (confirmed response for OHR and unconfirmed response for MiCyR).

<sup>d</sup> Evaluable patients included those who received ≥1 dose of bosutinib and had a valid baseline cytogenetic measurement.

<sup>e</sup> Included four patients with a partial cytogenetic response determined by using FISH instead of cytogenetic analysis.

<sup>f</sup> Included one patient with CCyR determined by using FISH instead of cytogenetic analysis.

2L, second-line (prior imatinib only); ≥3L, third-/fourth-line (imatinib followed by dasatinib and/or nilotinib); AP, accelerated phase; CML, chronic myeloid leukemia; BP, blast phase; ALL, acute lymphoblastic leukemia; OHR, overall hematologic response; CI, confidence interval; CHR, complete hematologic response; MiCyR, minor cytogenetic response; MiCyR, major cytogenetic response; CCyR, complete cytogenetic response.
who had a CCyR at baseline, one had retained a CCyR on bosutinib. The median (95% CI) duration of MCyR among responders was 8.6 (4.4–11.3) weeks for patients with ALL.

BCR-ABL mutations

Sixty-two (78%) AP, 53 (83%) BP, and 13 (54%) ALL patients had mutation assessment at baseline. There were 32 (52%) AP, 28 (53%) BP, and 13 (54%) ALL patients, including 2 (3%) AP and 6 (11%) BP patients who had ≥2 mutations. Mutations occurring in more than five patients (all cohorts) included T315I (AP, n = 3; BP, n = 10; ALL, n = 3), F317L (AP, n = 4; BP, n = 4; ALL, n = 1), G250E (AP, n = 4; BP, n = 2; ALL, n = 1), and Y253H (AP, n = 3; BP, n = 2; ALL, n = 1). In the AP CML cohort, OHR and MCyR rates were 57% (n = 16/28) and 39% (n = 11/28) in patients with ≥1 mutation (62% [n = 16/26] and 44% [n = 11/25], respectively, excluding T315I), versus 62% (n = 18/29) and 43% (n = 12/28) without a mutation. Among the 11 AP patients with ≥1 baseline mutation who had an MCyR, 10 newly attained an MCyR whereas only 1 (with a G321R mutation) maintained an MCyR from baseline while on bosutinib treatment. In the BP CML cohort, OHR and MCyR rates were 27% (n = 7/26) and 17% (n = 4/23) in patients with ≥1 mutation (35% [n = 6/17] and 20% [n = 3/15], respectively, excluding T315I), versus 25% (n = 6/24) and 45% (n = 9/20) without a mutation. None of the seven ALL patients with ≥1 mutation (including the three patients with T315I) achieved an OHR or MCyR, compared with 40% (n = 2/5) and 50% (n = 2/4) of ALL patients without a mutation. Responses were broadly achieved across baseline Bcr-Abl kinase domain mutations for AP and BP CML patients, except for patients with T315I for whom only one response was achieved (Fig. 2).

Among 48 patients who were assessed for mutations at baseline and on-treatment, 14 had an emergent mutation at treatment discontinuation (AP CML, 4/24 [17%]; BP CML, 9/21 [43%]; ALL, 1/3 [33%]). The most frequently detected emergent mutations were T315I (n = 6) and V299L (n = 5); reasons for discontinuation among these patients were PD (n = 7), unsatisfactory response (n = 1 [T315I]), AE (n = 1 [T315I]), and patient request to switch treatment (n = 1 [T315I]). One BP CML patient with an emergent V299L mutation also had a F311L mutation; this patient discontinued treatment due to an AE. F317L emerged in two patients, one of whom also had a G250E mutation and discontinued treatment due to an AE; the other patient discontinued due to PD. An A365G mutation was detected in one patient who discontinued treatment due to PD.

Long-term outcomes

The cumulative incidence of on-treatment PD/death (95% CI) by 1 year versus 4 years in the AP CML, BP CML, and ALL cohorts,
Figure 3. Cumulative incidence of PD/death adjusting for the competing risk of treatment discontinuation without PD/death (A) and overall survival (B). Criteria for PD included transformation to AP/BP CML, increasing white blood cell count (doubling over >1 month with second count >20 \times 10^9/L and confirmed >1 week later, or loss of confirmed CHR or unconfirmed MCyR. OS was calculated from the date of first study dosing to the date of death, with patients without events censored at the last contact, and was evaluated throughout the 2-year follow-up period after treatment discontinuation. The median follow-up was 28.4 (0.3–88.6), 10.4 (0.4–79.9), and 3.6 (0.4–89.2) months for AP, BP, and ALL patients, respectively. 2L, Second-line (prior imatinib only); >3L, third-/fourth-line (imatinib followed by dasatinib and/or nilotinib); ALL, acute lymphoblastic leukemia; AP, accelerated phase; BP, blast phase; CI, confidence interval; CML, chronic myeloid leukemia; NR, not reached; OS, overall survival; Ph+, Philadelphia chromosome-positive; PD, progressive disease.
| Event | AP CML (n = 79) | BP CML (n = 64) | ALL (n = 24) | Total (n = 167) |
|-------|-----------------|---------------|--------------|----------------|
|       | All grades      | Grade 3/4     | All grades   | Grade 3/4     |
| Nonhematologic TEAEs occurring in ≥10% (any grade) of patients (any cohort) | | | | |
| Diarrhea | 3 (4) | 1 (1) | 16 (22) | 7 (4) |
| Nausea | 7 (9) | 0 | 7 (9) | 0 |
| Vomiting | 8 (10) | 0 | 13 (18) | 5 (3) |
| Pyrexia | 8 (10) | 0 | 10 (14) | 1 (1) |
| Constipation | 2 (2) | 0 | 4 (6) | 0 |
| Arthralgia | 4 (5) | 0 | 4 (6) | 0 |
| Pneumonia | 1 (2) | 0 | 2 (3) | 0 |
| Constipation | 1 (1) | 0 | 1 (2) | 0 |
| Anemia | 2 (3) | 0 | 1 (2) | 0 |
| Neutropenia | 2 (3) | 0 | 1 (2) | 0 |
| Leukopenia | 2 (3) | 0 | 1 (2) | 0 |
| Leukocytosis | 2 (3) | 0 | 1 (2) | 0 |
| Thrombocytopenia | 2 (3) | 0 | 1 (2) | 0 |
| Hypertension | 2 (3) | 0 | 1 (2) | 0 |
| Cerebral artery occlusion | 1 (1) | 0 | 1 (2) | 0 |
| Cerebrovascular accident | 1 (1) | 0 | 1 (2) | 0 |
| Intracranial hemorrhage | 1 (1) | 0 | 1 (2) | 0 |
| Intracranial hemorrhage | 1 (1) | 0 | 1 (2) | 0 |
| RHESUS-positive non-HLA transfusion reaction | 1 (1) | 0 | 1 (2) | 0 |

a National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

b Combined with similar MeDRA Preferred Terms from the Investigations System Organ Class (Platelet count decreased, Hemoglobin decreased, Neutrophil count decreased, White blood cell count decreased).

c See Supporting Information Table III for definition of vascular TEAEs.
respectively, were 24% (16%–36%) versus 38% (29%–50%), 58% (47%–71%) versus 61% (50%–74%), and 54% (38%–78%) versus 54% (38%–78%), respectively; 44%, 36%, and 42% discontinued without on-treatment PD/death before year 4 (Fig. 3A). The cumulative incidence (95% CI) of on-treatment transformation to BP CML in the AP CML cohort was 4% (1%–12%); 79% discontinued without on-treatment transformation before year 4. Three AP CML patients had on-treatment transformation to BP CML (two patients with second-line and one with third-line bosutinib), which occurred 164, 315, and 744 days after treatment initiation.

As of the data cutoff, a total of 30 (38%) treated patients with AP CML had died (11 within 30 days of the last bosutinib dose); median OS had not yet been reached; Kaplan-Meier–estimated OS (95% CI) was 78% (67%–86%) at 1 year and 59% (46%–69%) at 4 years with 38% censored before year 4 (Fig. 3B). Among treated patients with BP CML, 44 (69%) had died (13 within 30 days of the last dose), with a median OS (95% CI) of 10.9 (8.7–19.7) months; Kaplan-Meier–estimated OS (95% CI) was 42% (30%–54%) at 1 year and 23% (10%–39%) at 4 years with 28% censored before year 4. Among treated patients with ALL, 22 (92%) had died (8 within 30 days of the last dose), with a median OS (95% CI) of 3.6 (1.3–7.6) months; Kaplan-Meier–estimated OS (95% CI) at 4 years was 8.3% (1%–23%) with one patient censored before year 4. Across cohorts, 32 (19%) patients died within 30 days of their last bosutinib dose; reasons included disease progression (n = 19), AE unrelated to treatment (n = 11), and AE considered to be related to bosutinib (n = 2; myocardial infarction and acidosis, both occurring in year 1). Among the 11 patients who died within 30 days of their last bosutinib dose due to AEs considered unrelated to treatment, 6 deaths were due to cardiac or vascular AEs, including left intraventricular hemorrhage (BP CML), posterior cerebral artery distribution infarct (ALL), congestive heart failure (BP CML), cerebral hemorrhage (ALL), coronary artery disease (AP CML), and brain vascular accident (BP CML).

**Safety and tolerability**

The most common treatment-emergent adverse events (TEAEs) occurring in ≥30% of all advanced leukemia patients were gastrointestinal TEAEs, which were primarily of low grade (diarrhea [any grade, 74%; maximum grade 1/2, 69%], nausea [48%; 46%], and vomiting [44%; 40%]; Table IV). Other frequently occurring TEAEs (any grade; grade 3/4) were thrombocytopenia (45%; 40%), anemia (39%; 26%), pyrexia (38%; 2%), and rash (31%; 4%). No notable differences in TEAE incidence were observed between cohorts (Table IV), and there was no clear pattern of differences in the incidences of TEAEs according to prior treatment (data not shown).

Overall, serious AEs (SAEs) occurred in 59% (99/167) of patients; the most frequently occurring individual SAEs (≥5% of patients overall) included pneumonia (10%), pyrexia (7%), febrile neutropenia (6%), thrombocytopenia (6%), disease progression (5%), headache (5%), and pleural effusion (5%). Most newly occurring SAEs (i.e., those not experienced by the same patient in previous years for patients on-treatment during that specific year) were most common in year 1 (91/167 [55%]; incidences in years 2, 3, and 4 were 11/40 (28%), 4/23 (17%), and 5/18 (28%), respectively (Table V). The only newly occurring individual SAE reported in more than two patients within year 2, 3, or 4 was pneumonia (three patients with events in year 2).

Across the cohorts (n = 167), patients with bosutinib toxicities were frequently managed with dose interruption (51% [n = 85]) and/or dose reduction (34% [n = 56]); some variability was observed across cohorts. In general, most dose interruptions and reductions due to AEs occurred during the first year of treatment (Table II). Thrombocytopenia was the most common TEAE leading to dose reduction (n = 29 [17%] in total; n = 28/167 [17%] in year 1) or dose reduction (n = 19 [11%] in total; n = 19 [11%] in year 1). Adverse events as the primary reason for discontinuation occurred more frequently in AP CML (30% [n = 24]) versus the BP CML (6% [n = 4]) and ALL (13% [n = 3]) patients including discontinuations after year 4. Across the cohorts, the most common AE leading to treatment discontinuation was thrombocytopenia (n = 6); in general, most discontinuations due to AEs occurred during the first year of treatment (Table II).

Diarrhea AEs (defined in Supporting Information Table III) were typically of mild severity (maximum grade 1/2 severity in 69% of patients [AP: 81%; BP: 59%; ALL: 58%]), with first events occurring early (median [range] time to first event, 2 [1–209] days), and transient (median [range] any grade event duration, 2 [1–910] days). Diarrhea was primarily managed with concurrent medication (62% of affected patients used loperamide or similar medication) and less

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**TABLE V. Incidence of Newly Occurring Serious AEs, any Causality Over Timea**

| Year 1 | Year 2 | Year 3 | Year 4 |
|--------|--------|--------|--------|
|        | AP CML | BP CML | ALL |
|        | (n = 79) | (n = 64) | (n = 24) |
|        | AP CML | BP CML | ALL |
|        | (n = 34) | (n = 5) | (n = 1) |
|        | AP CML | BP CML | ALL |
|        | (n = 19) | (n = 3) | (n = 1) |
|        | AP CML | BP CML | ALL |
|        | (n = 16) | (n = 2) | (n = 1) |

| Incidence of Newly Occurring Serious AEs, any Causality Over Timea |
|---------------------------------------------------------------|
| Occurrence (%)                                               |
| Any AE, n (%) a,b                                              |
| Thrombocytopenia                                              |
| General physical health deterioration                          |
| Anemia                                                        |
| Febrile neutropenia                                           |
| Leukocytosis                                                  |
| Nausea                                                       |
| Vomiting                                                      |
| Disease progression                                           |
| Pyrexia                                                       |
| Pneumonia                                                     |
| Headache                                                     |
| Pleural effusion                                              |
| Respiratory failure                                           |

a Newly occurring serious AEs refers to those not experienced by the same patient in previous years for patients on-treatment during that specific year (1 year = 365.25 days).

b In ≥5 patients in the safety population (n = 167) in year 1, or in ≥2 patients in years 2, 3, or 4.

AE, adverse event; AP, accelerated phase; CML, chronic myeloid leukemia; BP, blast phase; ALL, acute lymphoblastic leukemia.
frequently with dose interruption (n = 7 [6% of patients with events]) or dose reduction (n = 3 [2% of patients with events]). Most nausea cases were mild (maximum grade 1/2 severity in 46% of patients), with first event occurring early (median [range] time to first event, 4.0 [1–1113] days), and had limited duration (median [range] any grade event duration, 7.0 [1–274] days). No newly occurring AEs of diarrhea were reported after year 1; newly occurring nausea was reported in only two patients after year 1 (1 BP patient in year 2 and 1 AP patient in year 4). No patient discontinued bosutinib due to either of these AEs, underscoring the manageability of these common toxicities.

Plural effusions of any grade were observed in 15 (9%) patients (grade 3/4 in seven [4%] patients; five considered treatment-related by the investigator). Ten of the 15 patients experienced pleural effusion in year 1; newly occurring AEs of plural effusion after year 1 were reported in five AP CML patients (1 in year 2, 3 in year 3, and 1 in year 4). One AP CML patient discontinued bosutinib due to plural and pericardial effusion TEAEs. Of the 15 patients with a plural effusion on bosutinib, 6 had received prior dasatinib (representing 11% of all patients with prior dasatinib exposure); all 6 patients had a history of plural effusion, and for 3 of these patients, plural effusion was indicated as the reason for dasatinib intolerance. Pneumonia was reported as a TEAE by 22 (13%) patients (n = 19/167 [11%] in year 1; n = 3/40 [8%] newly occurring in year 2) and was the most common nonhematologic grade 3/4 TEAE (n = 17 [10%]; 3 [2%] treatment-related pneumonia); three patients experienced concurrent plural effusion and grade 3/4 pneumonia.

Lever-related TEAEs (defined in Supporting Information Table III) occurred in 35 (21%) patients, with similar incidences across cohorts (AP, 23% [n = 18]; BP, 20% [n = 13]; ALL, 17% [n = 4]); most newly occurring lever-related AEs were reported in year 1 (n = 34/167 [20%] in year 1; n = 3/40 [8%] in year 2). Lever-related TEAEs most commonly included alanine aminotransferase elevation (ALT, n = 18 [11%]; all initially reported in year 1) and aspartate aminotransferase elevation (AST, n = 17 [10%] in total; n = 15 [9%] in year 1); 11 of these patients experienced both ALT and AST elevations. Seventeen

### TABLE VI. Incidence of Laboratory Abnormalities, any Causality

| Event,a n (%) | AP CML (n = 79) | BP CML (n = 64) | ALL (n = 24) | Total (n = 167) |
|---------------|----------------|----------------|-------------|----------------|
| Hematologic laboratory abnormalitiesa | | | | |
| Anemia | 78 (99) | 28 (35) | 60 (94) | 25 (39) | 22 (92) | 7 (29) | 160 (96) | 30 (36) |
| Thrombocytopenia | 64 (81) | 39 (49) | 50 (78) | 42 (66) | 20 (83) | 18 (75) | 134 (80) | 99 (59) |
| Neutropenia | 50 (63) | 18 (23) | 44 (69) | 37 (58) | 20 (83) | 12 (50) | 114 (69) | 67 (40) |
| Lymphopenia | 39 (48) | 11 (14) | 42 (66) | 28 (44) | 16 (67) | 9 (38) | 97 (58) | 48 (29) |
| Hemoglobin | 38 (48) | 12 (15) | 39 (61) | 18 (28) | 12 (50) | 11 (46) | 89 (53) | 41 (25) |
| Other laboratory abnormalities occurring in ≥30% of patients, any cohort | | | | |
| Hypocalcemia | 32 (41) | 4 (5) | 35 (55) | 3 (5) | 9 (38) | 1 (4) | 76 (46) | 8 (5) |
| Elevated alkaline phosphatase | 30 (38) | 1 (1) | 25 (39) | 1 (2) | 15 (63) | 0 | 70 (42) | 2 (1) |
| Hyperglycemia | 30 (38) | 7 (9) | 26 (41) | 2 (3) | 13 (54) | 1 (4) | 69 (43) | 10 (6) |
| Elevated INR | 31 (39) | 2 (3) | 30 (47) | 0 | 10 (42) | 1 (4) | 71 (43) | 3 (2) |
| Elevated ALT | 36 (46) | 7 (9) | 20 (31) | 1 (2) | 11 (46) | 0 | 67 (40) | 8 (5) |
| Elevated AST | 34 (43) | 4 (5) | 19 (30) | 1 (2) | 5 (21) | 0 | 58 (35) | 5 (3) |
| Elevated creatinine | 25 (32) | 0 | 22 (34) | 1 (2) | 9 (38) | 0 | 56 (34) | 1 (1) |
| Hypophosphatemia | 30 (38) | 6 (8) | 17 (27) | 4 (6) | 9 (38) | 3 (13) | 56 (34) | 13 (8) |
| Elevated PTT | 26 (33) | 2 (3) | 21 (33) | 2 (3) | 5 (21) | 0 | 52 (33) | 4 (2) |
| Hypokalemia | 18 (22) | 1 (1) | 25 (39) | 1 (2) | 15 (63) | 0 | 70 (43) | 2 (1) |
| Elevated prothombin time | 23 (29) | 2 (3) | 20 (31) | 0 | 3 (13) | 0 | 46 (28) | 2 (1) |
| Hypoalbuminemia | 16 (20) | 3 (4) | 22 (34) | 6 (9) | 5 (21) | 1 (4) | 43 (26) | 10 (6) |
| Hypoalbuminemia | 18 (23) | 0 | 24 (38) | 2 (3) | 5 (21) | 1 (4) | 47 (28) | 3 (2) |

a Many patients had cytopenias when they started the study. AP, accelerated phase; CML, chronic myeloid leukemia; BP, blast phase; ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; INR, international normalized ratio; AST, aspartate aminotransferase; PTT, partial thromboplastin time.
Peripheral blood documentation. It is also possible that the relatively lower CHR rate might have reflected residual cytopenia and an inadequate level of Ph-negative hematopoiesis, which has been reported previously with dasatinib treatment in BP CML patients [30].

Although differences in designs, patient populations, response definitions, and follow-up durations limit direct comparison with other studies, the MHR rate by 4 years in AP CML patients receiving second-line bosutinib observed here (54%) is comparable with that reported for dasatinib (66% [median follow-up, 15 months] [14]) or nilotinib (55% by 2 years [31]). The MCyR rate in AP CML patients was 39% with dasatinib [14] and 32% with nilotinib [31] after imatinib failure compared with 48% with bosutinib in this study. Kaplan-Meier estimated 2-year OS rates observed previously among patients with AP CML receiving second-line dasatinib (63%) [14] or nilotinib (70%) [31] were each comparable to the 2-year rate observed here for second-line bosutinib (73%); the OS rate for second-line bosutinib continued to be relatively high at 4 years (66%).

The MHR rate reported here among patients with BP CML receiving second-line bosutinib (27%) was lower than that previously reported among patients receiving second-line dasatinib (34% [myeloid BP] and 35% [lymphoid BP] after median follow-up of 3.4 months [32]), whereas the MCyR rate reported here (50%) was comparable to that reported with dasatinib (33% [myeloid BP] and 52% [lymphoid BP] [32]). Median OS also appeared comparable between bosutinib as second-line therapy (11.2 months) and dasatinib (11.8 months [myeloid BP] and 5.3 months [lymphoid BP] [32]). The lack of analyses by myeloid versus lymphoid BP in the current study prevents closer comparison.

Responses to bosutinib were observed in AP and BP CML patients across a wide range of Bcr-Abl mutations, except T315I, supporting preclinical investigations [33,34]. The more frequent emergence of T315I and V299L at treatment discontinuation in patients with disease progression or unsatisfactory response is also consistent with preclinical investigations [33,34]. Response to bosutinib among patients with F317L (associated with dasatinib resistance [35]) at baseline was lower among patients with advanced CML (two of eight evaluable patients had CHR; zero of six had MCyR) compared with CP CML patients receiving third-line bosutinib (four of eight evaluable patients had CHR; one of seven had MCyR) [28]. This observation reflects the higher degree of tumor heterogeneity that emerges with increasing disease duration and exposure to several treatments, and is intricately driven by the multiple resistance mechanisms underlying the molecular pathogenesis of advanced leukemia.

The observed safety profile of bosutinib in patients with advanced disease is consistent with that reported for patients with CP CML receiving second-line bosutinib [25–27]. In the retrospective evaluation of cross-intolerance (i.e., discontinuation of bosutinib and prior TKI due to the same AE), 4 (18%), 1 (5%), and 0/4 patients experienced cross-intolerance to bosutinib and prior imatinib, dasatinib, or nilotinib, respectively. The incidence of newly occurring AEs generally decreased after the first year of treatment, as did discontinuations due to AEs. These observations emphasize the importance of early AE management and monitoring. Despite the frequent occurrence of diarrhea, these events were of low grade, of short duration, and none led to discontinuation. Similarly, although liver-related AEs were common, few patients discontinued due to these AEs. Bosutinib was also associated with no grade 3/4 QTcF interval prolongation or LVEF across advanced leukemia cohorts. Myelosuppression is part of the natural history of leukemia, especially in advanced disease [6,36,37] and appears common among TKI therapies [6,11,13–15,32,37,38]; consistent with this, the incidence of cytopenias was high across all cohorts at baseline and during treatment. The report of two deaths due to SAEs considered to be related to bosutinib treatment should be

| TABLE VII. Shifts From Baseline in Myelosuppression Laboratory Abnormalities |
|-----------------------------|--------|--------|--------|--------|--------|
| Baseline severity          | n      | Normal | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Anemia (n)                 |        | Normal | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Normal                     | 31     | 5      | 12      | 10      | 4       | 0       |
| Grade 1                    | 60     | 0      | 21      | 24      | 12      | 3       |
| Grade 2                    | 61     | 0      | 4       | 27      | 22      | 6       |
| Grade 3                    | 12     | 0      | 1       | 1       | 4       | 6       |
| Grade 4                    | 3      | 0      | 0       | 0       | 0       | 3       |
| Total                      | 167    | 5      | 38      | 62      | 42      | 18      |
| Neutropenia* (n)           |        | Normal | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Normal                     | 83     | 43     | 16      | 10      | 10      | 4       |
| Grade 1                    | 44     | 4      | 10      | 4       | 10      | 14      |
| Grade 2                    | 17     | 2      | 3       | 1       | 3       | 6       |
| Grade 3                    | 9      | 0      | 0       | 3       | 1       | 5       |
| Grade 4                    | 13     | 0      | 0       | 0       | 3       | 10      |
| Total                      | 167    | 49     | 29      | 18      | 27      | 40      |
| Thrombocytopenia (n)       |        | Normal | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Normal                     | 72     | 28     | 17      | 6       | 12      | 8       |
| Grade 1                    | 29     | 3      | 8       | 1       | 8       | 8       |
| Grade 2                    | 10     | 0      | 0       | 6       | 4       |         |
| Grade 3                    | 25     | 0      | 3       | 4       | 18      |         |
| Grade 4                    | 31     | 0      | 0       | 0       | 1       | 30      |
| Total                      | 167    | 31     | 28      | 7       | 31      | 68      |

* Severity based on National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
One patient had missing baseline absolute neutrophil count data.

**Discussion**

Patients with advanced Ph+ leukemia have a more rapid disease course, worse prognosis, and increased likelihood of developing imatinib resistance than those with CP disease. This 4-year follow-up of an ongoing phase 1/2 study demonstrates durable responses to bosutinib among patients with AP CML and high response rates among patients with CP CML after prior TKI treatment, with some responses also observed among patients with ALL. The higher observed rate of MCyR versus CHR (AP CML, 40% vs. 33%; BP CML, 37% vs. 17%; ALL, 20% vs. 9%) may be due to the requirement for bone marrow differential documentation to achieve a confirmed CHR, potentially excluding some patients who would have achieved a CHR based on
interacted in the context of advanced leukemia patients, for whom AEs can occur due to different causes, and for whom the assessment of a causal relationship between AE and treatment is always more problematic than for patients with chronic disease. Although findings from this analysis and other studies show benefit of TKI treatment in patients with advanced CML, allo-HSCT remains the only curative treatment option for some patients with advanced phase CML, albeit with a lower cure potential compared with those transplanted in chronic phase [18]. Certain factors have been shown to increase the risk of poor treatment outcomes with allo-HSCT, including increased age and increased disease burden at the time of allo-HSCT [39,40]. The promising clinical activity of bosutinib reported herein suggests that bosutinib treatment may facilitate allo-HSCT by in reducing disease burden in these patients. Similar observations have been made with other TKIs, including dasatinib and nilotinib [41].

In summary, bosutinib demonstrates a durable response, with ~50% of AP responders maintaining a response at 4 years. Moreover, ~25% of BP responders maintained response to treatment at 1 year, for whom bosutinib may be considered to be a bridge to stem cell transplantation. Responses were also observed among some ALL patients; however, the analysis of these data was limited by the small number of enrolled ALL patients. Bosutinib toxicities were manageable with long-term treatment. Based on the current treatment landscape, bosutinib represents a long-term treatment option for patients with advanced Ph+ leukemias following failure of prior TKI therapy.

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**Author Contributions**

The study was created/designer by C.G.P., H.J.K., and J.E.C. C.G.P., H.M.K., D.W.K., H.J.K., A.G.T., T.H.B., and J.E.C. collected and assembled the data. C.G.P., H.M.K., D.W.K., H.J.K., A.G.T., T.H.B., E.M., N.B.B., M.S., K.T., E.L., and J.E.C. provided analysis and/or interpretation of the data and provided study materials and/or enrolled patients in the study. J.E.C. performed statistical analyses. All authors assisted in the writing and/or critical review of the manuscript, and all authors approved the final version of the manuscript for submission.

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