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Effect of the Tyrosine Kinase Inhibitor Nilotinib in Patients with Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia: Analysis of the Phase 2, Open-Label, Single-Arm A2101 Study

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Abstract

Purpose—Hypereosinophilic syndrome (HES) and chronic eosinophilic leukemia (CEL) are characterized by sustained overproduction of eosinophils and organ dysfunction. CEL involves the presence of clonal genetic markers, such as a fusion of FIP1-like 1 protein and platelet-derived growth factor receptor α (FIP1L1-PDGFR α , or F/P) or PDGFR α -activating mutations.

Methods—Sixteen patients with HES/CEL were enrolled in the phase 2 nilotinib registration trial (NCT00109707) and treated with nilotinib 400 mg twice daily. The median duration of treatment was 95 days (range, 3–1079).

Results—Twelve patients had HES: 1 achieved a complete hematologic response (CHR), 3 achieved stable disease, 3 had progressive disease, and 5 were not evaluable for response. Four patients had CEL: 2 with the F/P fusion and 2 with PDGFR α -activating mutations. Both patients with an F/P fusion achieved a CHR; 1 also achieved a complete molecular response (CMR). Of the

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2 patients with PDGFR α -activating mutations, 1 had stable disease and the other achieved CMR. At 24 months, overall survival in the HES group was 75.0% (95% CI, 50.5–100.0) and no patients in the CEL group died. Median survival was not yet reached after a median follow-up of 32 months. The most common grade 3/4 hematologic laboratory abnormalities were lymphocytopenia (31.3%) and neutropenia (25.0%). The most common drug-related nonhematologic grade 3/4 adverse event was pruritus, which occurred in 2 patients (12.5%).

Conclusions—Nilotinib 400 mg twice daily was effective in some patients with HES/CEL regardless of F/P mutation status, and the safety profile was consistent with other nilotinib studies.

Keywords

Nilotinib; Hypereosinophilic syndrome; Chronic eosinophilic leukemia

Introduction

Hypereosinophilia is defined as a persistent (> 6 months) peripheral blood (PB) eosinophil count greater than 1500/ μ L that is associated with tissue damage. After exclusion of secondary causes of eosinophilia, diagnostic evaluation of eosinophilia relies on a combination of morphologic review of the PB and bone marrow (BM), characterization of organ infiltration, standard cytogenetics and molecular genetics, flow immunocytometry, and T-cell clonality assessment to detect histopathologic or clonal evidence for an acute or chronic myeloid or lymphoproliferative disorder^(Gotlib 2012).

Chronic eosinophilic leukemia (CEL) is distinguished from hypereosinophilic syndrome (HES) by evidence of clonal molecular markers or significantly increased numbers of blasts^(Gotlib 2012). The estimated age-adjusted incidence rate for HES/CEL is 0.036/100,000 person-years (based on Surveillance Epidemiology and End Results data from 2001 to 2005)^(Crane et al. 2010). The median age at HES diagnosis is 52.5 years, with a male-to-female ratio ranging from 1.47 to 9^(Crane et al. 2010; Roufosse et al. 2007). The reported 10-year survival rate for patients with HES is less than 50%^(Verstovsek 2007).

Genetic abnormalities are found in most patients with CEL. The most frequent chromosomal abnormality is a deletion on chromosome 4q12 that creates a fusion of FIP1-like 1 protein with platelet-derived growth factor receptor α (FIP1L1- PDGFR α , or F/P)^(Cools, DeAngelo et al. 2003; Loules et al. 2009). F/P is present in approximately 10% to 20% of all patients with suspected nonreactive eosinophilia and is associated with increased disease severity due to constitutive tyrosine kinase activity of PDGFR α ^(Loules et al. 2009; Helbig et al. 2010; Roche-Lestienne et al. 2005). Recently, several activating mutations in PDGFR α , including Y849S, have been identified in F/P-negative patients^(Elling et al. 2011). Two patients presented in the report of PDGFR α -activating mutations were enrolled in the present study. This set of activating mutations induces clonogenic growth, growth factor-independent cell proliferation and constitutive phosphorylation of PDGFR α and signal transducer and activator of transcription 5 (STAT5), and are thought to play a role in the pathogenesis of CEL. Other genetic abnormalities associated with eosinophilia include fusions of fibroblast growth factor receptor 1 (FGFR1) or PDGFR β , each occurring in < 1% of patients. More than 20 gene fusion partners for

PDGFR β and more than 10 for FGFR1 have been identified^(Gotlib and Cools 2008; Cross and Reiter 2008).

Patients with HES or CEL, particularly those with the F/P mutation, are sensitive to treatment with the tyrosine kinase inhibitor (TKI) imatinib^(Novartis Pharmaceuticals Corporation January 2012), which is known to inhibit ABL1 and BCR-ABL1, as well as the discoidin domain receptor (DDR)-1 and -2, colony-stimulating factor 1 receptor (CSF1R), KIT, and PDGFR α and β ^(Buchdunger et al. 2001; Manley et al. 2010). Resistance and intolerance to imatinib develop in some patients, often due to the emergence of clones expressing mutant forms of PDGFR α that are less sensitive to imatinib inhibition.^(Lierman et al. 2006; Cools et al. 2003; Cools et al. 2005) For example, the D842V mutation corresponds to the KIT D816V mutation, found in some patients with systemic mastocytosis or gastrointestinal stromal tumors, which confers resistance to imatinib and results in limited clinical activity of nilotinib and sorafenib^(Metzgeroth et al. 2012). In addition, the T674I mutation is found in some resistant cases of F/P-positive CEL and is analogous to the T315I gatekeeper mutation in BCR-ABL1 that confers resistance to imatinib and second-generation TKIs (dasatinib, nilotinib, and bosutinib) in patients with chronic myeloid leukemia (CML)^(Lierman et al. 2006; Cools et al. 2003; Cools et al. 2005).

Nilotinib is a TKI that inhibits ABL1, BCR-ABL1, DDR, CSF1R, and KIT, as well as PDGFR α and β in vitro^(Verstovsek et al. 2006; Stover et al. 2005; Manley et al. 2010). Follow-up data from a multicenter, phase 2, open-label registration trial demonstrated that nilotinib 400 mg twice daily continued to be safe and effective in patients with CML in chronic phase^(Giles et al. 2013), accelerated phase^(le Coutre et al. 2012), and blast phase^(Giles et al. 2012) who were resistant to or intolerant of previous therapies and had a different adverse-effect profile to that of imatinib.^(Cortes et al. 2011) Nilotinib showed comparable effectiveness to imatinib in a xenograft model of CEL in which mice were injected with F/P-positive human CEL cells^(Wicklein et al. 2012), and nilotinib has demonstrated activity in individual patients with HES/CEL who were intolerant or resistant to imatinib^(Tabouret et al. 2011; Ikezoe et al. 2010). The present analysis evaluated the efficacy and safety of nilotinib 400 mg twice daily in patients with HES/CEL enrolled in the phase 2 nilotinib registration trial (CAMN107A2101, registered at ClinicalTrials.gov as NCT00109707).

Materials and Methods

Patient Population

Eligibility criteria for patients enrolled in the phase 2, multicenter A2101 trial have been previously described^(Kantarjian et al. 2007). Briefly, for the phase 2 portion of the study, adult patients with hematologic malignancies were recruited into 6 parallel treatment arms. Patients who met the standard disease criteria for HES/CEL^(Vandenberghe et al. 2004) and had clinical indications for treatment were recruited into the HES/CEL arm of the study and were assessed for efficacy according to a Simon 2-stage mini-max design. Patients were initially classified as either HES or CEL based on investigator assessment. Subsequently, patients with either an activating mutation in PDGFR α or presence of the F/P fusion protein were classified as CEL and all other patients were classified as HES. Standard disease criteria for all patients in the study included eosinophilia $> 1500/\text{mm}^3$ for at least 6 months;

signs and symptoms of organ involvement; and exclusion of other causes of eosinophilia (eg, clonal or abnormal T-cell populations, reactive eosinophilia).

Previous imatinib use was permitted, but not required. A washout period of 5 days was required before starting this study. Key inclusion criteria consisted of World Health Organization (WHO) performance status of 2 and levels of potassium, total calcium, and magnesium no lower than the lower limit of normal. Exclusion criteria included disease infiltration into the central nervous system and impaired cardiac function (including a left ventricular ejection fraction < 45%, congenital long QT syndrome, or corrected QT interval using Fredericia's correction (QTcF) > 450 msec).

Dosing

Nilotinib 400 mg twice daily was selected as the study dose based on safety and pharmacokinetic data and preliminary efficacy data from the phase 1 portion of this study^(Kantarjian et al. 2006). One treatment cycle included 28 days of continuous dosing with nilotinib 400 mg twice daily. Patients remained on nilotinib treatment until disease progression or unacceptable toxicity. Patients responding to therapy were allowed to enter an extension study after 24 months of treatment and continued to receive drug. The extension study was ongoing at the time of data cutoff on November 18, 2008.

Dose modifications, including dose reductions and dose interruptions, were allowed for patients who developed intolerance to nilotinib. Patients with treatment interruptions > 21 days were discontinued from the study, except in the case of hematologic toxicity, whereby treatment interruptions > 42 days required discontinuation from the trial. Patients discontinuing due to adverse events (AEs) were followed up until resolution or stabilization of the AE. All patients were followed up for 28 days after the final dose of nilotinib for possible development of AEs.

Study Objectives

The primary efficacy endpoint was the rate of complete hematologic response (CHR), as assessed by the investigator. CHR involved normalization of PB counts, including eosinophil counts, and complete disappearance of all signs and symptoms of disease (ie, normal white blood cell and platelet counts, absence of blasts and promyelocytes in the PB, absence of extramedullary involvement, and < 5% eosinophils and < 5% blasts in the BM). Organ dysfunction was not considered as a response parameter. Partial hematologic response (PHR) was defined as 50% reduction in total white blood cell count and absolute eosinophil count compared with study entry (without normalization of these parameters), and 50% reduction in PB and BM blasts (if > 5% BM and/or PB blasts at study entry) compared with the start of the study. Stable disease included no change in range of peripheral eosinophil counts or any response not meeting CHR, PHR, or progressive disease criteria. Progressive disease was defined as 50% increase over baseline in BM or PB blasts and/or eosinophils, or interval development of extramedullary disease, or in patients who responded to treatment, a return to pretreatment eosinophil counts.

The secondary efficacy endpoint was overall survival, which was estimated using the Kaplan-Meier method. The analysis of overall survival included all deaths occurring during treatment or after discontinuation of study drug.

There is no standardized method to detect F/P transcripts. Biomarker assessment of F/P transcript status was performed using real-time quantitative reverse-transcription polymerase chain reaction (RQ-PCR) and direct sequencing methods^(Metzgeroth et al. 2008; Elling et al. 2011; Metzgeroth et al. 2012). PB or BM samples were collected prior to nilotinib dosing. The rate of hematologic response and overall survival stratified by F/P mutation status at baseline or after baseline was assessed.

Complete molecular response (CMR) was determined in patients with CEL and defined as the loss of clonal markers (F/P or PDGFR α -activating mutations, as determined by RQ-PCR or direct sequencing of PB or BM samples) during the course of treatment. CMR was summarized by mutation status in patients with CEL.

Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0^(National Cancer Institute 2006). Patients were carefully monitored for cardiac changes occurring during the study. AEs and hematologic and nonhematologic laboratory abnormalities were assessed.

Study Ethics

Written informed consent was obtained from all patients according to institutional guidelines. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was reviewed and approved by the ethics board or institutional review board at each participating trial center.

Results

Baseline Patient Characteristics

A total of 16 patients were enrolled in the HES/CEL arm of the A2101 study: 12 with HES and 4 with CEL. Baseline demographic and disease characteristics are presented in Table 1. The median patient age was 62 years (range, 25–84). Patients in the HES arm were generally older (65 years; range, 42–84) than in the CEL arm (38 years; range, 25–67)]. WHO performance status was 0 or 1 in most patients (93.8%); 1 patient with HES had a WHO performance status of 2. The median time since diagnosis of HES/CEL was 10.7 months (range, 0.2–192.7), with disease duration shorter in the HES arm (7.2 months; range, 0.2–128) than in the CEL arm (19.6 months; range, 2.1–192.7). Five patients (31.3%; 3 with HES and 2 with CEL) had received no previous treatment for HES/CEL.

Extensive molecular analysis was performed using PB or BM at baseline and throughout the study. At baseline, 2 patients were F/P positive, 12 were F/P negative, and 2 had missing data. This included 1 patient with 1 mutational assessment 1 month after starting treatment; this patient was classified as F/P positive at baseline per the definition of CEL (ie, the presence of clonal markers). With subsequent analysis, the 2 patients with missing baseline data were determined to be F/P negative. Activating mutations in PDGFR α were identified

in 2 F/P-negative patients: 1 patient had a Y849S mutation and 1 patient had both Y849S and L507P mutations^(Elling et al. 2011). The CEL population included the 2 patients who were F/P positive and the 2 patients who had PDGFR α -activating mutations; all other patients did not have clonal genetic markers and were allocated to the HES population.

Patient Disposition and Exposure to Drug

At the time of data cutoff, 3 patients (2 with CEL and 1 with HES) had entered the extension study and 13 patients had discontinued treatment (Table 2). Patients received a median of 778 mg of nilotinib per day (range, 193–800) for a median of 95 days (range, 3–1079). This includes 5 patients (31.3%) who were exposed to nilotinib for less than 1 month. The median dose received was close to the planned total daily dose of 800 mg. One-half of patients (50.0%) were treated with nilotinib for a minimum of 3 months, and 31.3% of patients received nilotinib for at least 6 months. Eleven patients (68.8%) had a nilotinib dose reduction and nearly one-third (31.3%) had a dose interruption. Dose interruptions lasted a median of 18 days (range, 2–21). Interruptions constituted a median of 12.7% of total dosing days (range, 1.8–60.0).

Efficacy

Three patients (18.8%) had a CHR to nilotinib 400 mg twice daily, 2 with CEL and 1 with HES (Table 3). None of these 3 had previous treatment with a TKI. No patient had a PHR in this study. Stable disease was observed in 4 patients (25.0%; 3 with HES and 1 with CEL). Three patients (18.8%), all with HES, had disease progression. Six patients (37.5%; 5 with HES and 1 with CEL) were not evaluable for hematologic response.

No patients with CEL died during the study, whereas the deaths of 3 patients with HES were reported. Overall survival at 24 months was 75.0% (95% CI, 50.5–100.0) in patients with HES, with the median overall survival not yet reached after a median follow-up of 32 months (Figure).

Response According to Mutation Status

Response was assessed according to the underlying genetic event in patients with CEL (Table 4). Of the 2 patients with an F/P fusion, both achieved a CHR. One of these 2 patients tested positive for F/P at screening (BM and PB) and after 1 and 2 months of treatment (PB only); this patient then had 2 negative results after 2.5 and 5.5 months of treatment (BM samples), suggesting a CMR. In the other F/P-positive patient, no molecular follow-up data are available. Of the 2 patients with PDGFR α -activating mutations, 1 achieved stable disease and 1 was not evaluable for hematologic response. The patient with stable disease was not evaluable for molecular response. The patient not evaluable for hematologic response achieved a CMR by losing the PDGFR α -activating mutation during the study; the Y849S mutation was found at screening and was absent 1.5 months after starting treatment (both samples from PB).

Safety

All patients reported at least 1 AE. Drug-related AEs of any grade were experienced by 15 patients (93.8%), with grade 3/4 drug-related AEs occurring in 9 patients (56.3%). The most

frequent drug-related nonhematologic AEs of any grade included pruritus (37.5%), rash (31.3%), fatigue (25.0%), and headache (25.0%) (Table 5). The most common grade 3/4 AE was pruritus (12.5%). Gastrointestinal and skin toxicities were consistent with the overall safety profile for nilotinib in other diseases.

Newly occurring or worsening grade 3/4 hematologic laboratory abnormalities included lymphocytopenia (31.3%), neutropenia (25.0%), increased prothrombin time (international normalized ratio, 7.7%), thrombocytopenia (6.3%), and anemia (6.3%) (Table 5). Newly occurring or worsening grade 3/4 biochemical laboratory abnormalities included increased levels of lipase (20.0%), bilirubin (12.5%), and potassium (6.7%), and decreased levels of serum phosphate (13.3%) and sodium (6.7%).

Patients were monitored for cardiac changes occurring during the study. A QTcF increase > 60 msec from baseline occurred in 1 patient; QTcF in this patient remained normal (413 msec), but this patient subsequently discontinued treatment due to noncardiac myopathy. The investigator did not consider the myopathy or the QT prolongation to be study drug related. No patient had a QTcF > 480 msec.

Five patients (31.3%) discontinued from the study because of 1 AE. The most frequent AEs leading to discontinuation were endocarditis fibroplastica, sepsis, acute pancreatitis, general physical health deterioration, myopathy, asthma, pruritus, and rash, each occurring in 1 patient. One patient died within 28 days of treatment discontinuation. This patient died due to endocarditis fibroplastica and sepsis, which occurred within the 28-day follow-up period; the investigator did not attribute these AEs to the study drug.

Discussion

Patients with HES/CEL can be treated with a variety of modalities, including glucocorticoids, hydroxyurea, interferon- α , allogeneic stem cell transplantation, and TKIs; however, with the exception of TKIs, responses to many of these agents are typically short lived.^(Butterfield and Weiler 2012; Valent et al. 2012) While imatinib has shown high rates of response in patients with CEL with the F/P mutation, the response is less robust in patients with HES without this abnormality^(Butterfield 2009; Vandenberghe et al. 2004; Pardanani and Tefferi 2004; Metzgeroth et al. 2008). Because of the rare responses observed in F/P-negative patients, it is possible that F/P is not the only molecular target of imatinib in patients with HES^(Pardanani and Tefferi 2004). The approval for use of imatinib in patients with HES/CEL was based on an open-label, multicenter phase 2 study (n = 14) as well as 35 published case reports and case series (n = 162)^(Novartis Pharmaceuticals Corporation January 2012). CHR was achieved in 61 of 61 (100%) patients positive for F/P, 12 of 56 (21%) F/P-negative patients and 34 of 59 (58%) patients with unknown F/P status. PHR was achieved in 9 of 56 (16%) F/P-negative patients and 7 of 59 (12%) patients with unknown F/P status. Response duration ranged from 6 weeks to 44 months. Similarly, in a phase 2 study, 13/15 (87%) F/P-positive patients achieved CMR within 12 months of imatinib treatment, whereas CHR was only achieved in 6/15 (40%) of patients without a known mutation.^(Metzgeroth et al. 2008) In another prospective study of patients with HES, 5 of 36 patients without the F/P mutation (14%) achieved CHR, but

response was lost in all cases after 1 to 15 months of treatment (Baccarani et al. 2007). In the same study, 27 of 27 patients with the F/P mutation (100%) achieved both CHR and CMR; both types of response were maintained until last contact (range, 15–60 months).

The recommended starting dose of imatinib for patients with HES is 100 mg daily. Higher doses of imatinib (up to 400 mg daily) are generally required to elicit a response in the absence of the F/P mutation (Cools et al. 2003; Metzgeroth et al. 2008; Butterfield 2009; Roufosse 2009). While the incidence of imatinib resistance is infrequent in patients with HES/CEL, some events have been reported (Gotlib and Cools 2008). Resistance and intolerance to imatinib develop in some patients, often due to the emergence of clones expressing mutant forms of PDGFR α , which are less sensitive to inhibition with imatinib (Gotlib and Cools 2008). PDGFR α T674I is analogous to the T315I mutation in BCR-ABL that confers imatinib resistance in patients with CML (Cools et al. 2003; Lierman et al. 2006; Cools et al. 2005; Metzgeroth et al. 2012). PDGFR α D842V is analogous to the D816V mutation in KIT that confers resistance to several TKIs and is often found in patients with systemic mastocytosis (Metzgeroth et al. 2012).

Several agents have demonstrated activity against F/P, with or without the T674I mutation. The TKIs ponatinib, sorafenib and dasatinib have demonstrated inhibition of F/P, ponatinib and sorafenib had activity against the T674I mutant, and dasatinib showed activity against F/P without the T674I mutation (Lierman et al. 2006; Baumgartner et al. 2008; Lierman et al. 2012). Nilotinib is not effective against the PDGFR α D842V mutation (Stover et al. 2005) and is not likely to be effective against the T674I mutation because it is also ineffective against the BCR-ABL T315I mutation (Soverini et al. 2007). In a murine model, the multikinase inhibitor midostaurin (PKC412) showed activity against PDGFR α T674I (Cools, Stover et al. 2003). Midostaurin has also shown activity against KIT D816V in patients with mastocytosis (Gotlib et al. 2010; Gotlib et al. 2012) and thus may be a rational alternative therapy in HES/CEL patients with the imatinib-resistant D842V mutation. Clinical studies have shown that monoclonal antibodies directed toward interleukin-5 (eg, mepolizumab and reslizumab) and toward CD52 (eg, alemtuzumab) can be used to treat patients with HES/CEL (Rothenberg et al. 2008; Klion et al. 2004; Verstovsek et al. 2009). Although an initial response (as measured by hematologic improvements or tapering of glucocorticoid doses) was achieved, relapse in eosinophil counts to prebaseline levels occurred after stopping treatment with reslizumab and alemtuzumab.

Nearly one-third of patients (31.3%) were exposed to nilotinib for less than 1 month, which could have contributed to the low response rate observed in this study. Although the rate of response was low, overall survival was more than 80% at 24 months and the median overall survival was not reached after a median follow-up of 32 months. In the CEL group, 4 of 4 patients survived throughout the follow-up period and the 2 patients with the F/P fusion achieved a CHR, with 1 of these patients achieving CMR. While this suggests that nilotinib increases survival in patients with CEL, the small number of patients precludes any definitive conclusions. The reported survival rate for patients with HES is 80% at 5 years (Gotlib et al. 2004) and less than 50% at 10 years (Verstovsek 2007). In a recent study, patients with CEL had a median survival of 22.2 months (range, 2.2–186.2) from diagnosis to death (Helbig et al. 2012). Based on the present study, it is unclear whether nilotinib may prolong survival in patients with HES/CEL. One patient died of endocarditis fibroplastica within 28

days of study treatment, which could be a symptom of progressive disease rather than an adverse event attributable to treatment. Additional long-term studies are warranted to confirm any association of treatment with nilotinib and clinical benefit in this population.

The AE profile of nilotinib in patients with HES/CEL was similar to the known safety profile of nilotinib in other hematologic malignancies^(Kantarjian et al. 2007; Novartis Pharmaceuticals Corporation May 2012). The relatively high rate of grade 3/4 AEs was consistent with a study population that has substantial underlying disease. Given the limitations of the data, it is difficult to draw firm conclusions about the activity of nilotinib in this population relative to the presence or absence of F/P mutations, but it is clear that a CHR or CMR can be achieved in some patients, even in the absence of F/P. Additional studies are needed to determine the potential utility of nilotinib in patients with HES/CEL.

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Figure.
Overall survival (intention-to-treat population). CEL, chronic eosinophilic leukemia; HES, hypereosinophilic syndrome.

Table 1

Baseline Characteristics

Baseline Characteristic	HES (n = 12)	CEL (n = 4)	Total (N = 16)
Median age, years (range)	65 (42–84)	38 (25–67)	62 (25–84)
Male, n (%)	9 (75.0)	4 (100)	13 (81.3)
WHO performance status, n (%)			
Grade 0	6 (50.0)	3 (75.0)	9 (56.3)
Grade 1	5 (41.7)	1 (25.0)	6 (37.5)
Grade 2	1 (8.3)	0	1 (6.3)
Median time since diagnosis of			
HES/CEL, months (range)	7.2 (0.2–128.0)	19.6 (2.1–192.7)	10.7 (0.2–192.7)
< 6 months, n (%)	4 (33.3)	1 (25.0)	5 (31.3)
6 months to < 1 year, n (%)	3 (25.0)	0	3 (18.8)
1 year to < 2 years, n (%)	1 (8.3)	2 (50.0)	3 (18.8)
2 years to < 5 years, n (%)	3 (25.0)	0	3 (18.8)
5 years, n (%)	1 (8.3)	1 (25.0)	2 (12.5)
No previous treatment, n (%)	3 (25.0)	2 (50.0)	5 (31.3)
FIP1L1-PDGFRα fusion, n (%)			
Yes	0	2 (50.0) ^a	2 (12.5)
No	10 (83.3)	2 (50.0)	12 (75.0)
Missing	2 (16.7) ^b	0	2 (12.5)
PDGFRα-activating mutations, n (%)	0	2 (50.0)	2 (12.5)

CEL, chronic eosinophilic leukemia; FIP1L1-PDGFRα, fusion of FIP1-like 1 and platelet-derived growth factor receptor α; HES, hypereosinophilic syndrome; WHO, World Health Organization.

^aOne of these 2 patients was FIP1L-PDGFRα positive 1.5 months after starting treatment (the only mutational assessment available). Based on the definition of CEL used in this study (ie, the presence of clonal markers), this patient was considered FIP1L-PDGFRα positive at baseline.

^bThe 2 patients with missing baseline mutation data subsequently tested negative for the FIP1L-PDGFRα fusion.

Table 2

Patient Disposition

Disposition	HES (n = 12)	CEL (n = 4)	Total (N = 16)
Total patients treated	12 (100.0)	4 (100.0)	16 (100.0)
Entered extension study ^a	1 (8.3)	2 (50.0)	3 (18.8)
Discontinued core treatment	11 (91.7)	2 (50.0)	13 (81.3)
Adverse event(s)	4 (33.3)	1 (25.0)	5 (31.3)
Disease progression	4 (33.3)	1 (25.0)	5 (31.3)
Administrative reasons ^b	2 (16.7)	0	2 (12.5)
Withdrew consent	1 (8.3)	0	1 (6.3)

CEL, chronic eosinophilic leukemia; HES, hypereosinophilic syndrome.

^aEnrolled in the ongoing extension portion of the study at the time of data cutoff.

^bTwo patients were discontinued under the category “administrative reasons” and were reported as having an unsatisfactory therapy effect (no response).

Table 3

Best Responses and Overall Survival After a Median Follow-up of 32 Months (ITT Population)

	HES (n = 12)	CEL (n = 4)	Total (N = 16)
Best hematologic response			
Overall response, n (%; 95% CI)	1 (8.3; 0.2–38.5)	2 (50.0; 6.8–93.2)	3 (18.8; 4.0–45.6)
CR	1 (8.3)	2 (50.0)	3 (18.8)
PR	0	0	0
Absence of response, n (%)			
SD	3 (25.0)	1 (25.0)	4 (25.0)
PD	3 (25.0)	0	3 (18.8)
NE	5 (41.7)	1 (25.0)	6 (37.5)
Overall survival, % (95% CI)			
6 months	83.3 (62.3–100)	100 (100–100)	87.5 (71.3–100)
12 months	75.0 (50.5–99.5)	100 (100–100)	81.3 (62.1–100)
18 months	75.0 (55.5–99.5)	100 (100–100)	81.3 (62.1–100)
24 months	75.0 (50.5–99.5)	100 (100–100)	81.3 (62.1–100)

CEL, chronic eosinophilic leukemia; CHR, complete hematologic response; HES, hypereosinophilic syndrome; ITT, intention to treat; NE, not evaluable; PD, progressive disease; PHR, partial hematologic response; SD, stable disease.

Table 4

Hematologic and Molecular Response by Clonal Marker Present at Baseline in Patients With CEL

CEL Patient No.	Clonal Marker at Baseline	Best Hematologic Response	Molecular Response
1	FIP1L1-PDGFR α	CR	NE (no subsequent mutation analysis)
2	FIP1L1-PDGFR α	CR	CMR (F/P not detected after 2.5 and 5.5 months of treatment)
3	PDGFR α activating (L507P, Y849S)	SD	NE (no subsequent mutation analysis)
4	PDGFR α activating (Y849S)	NE	CMR (mutation not detected after 1.5 months of treatment)

CEL, chronic eosinophilic leukemia; CMR, complete molecular response; CR, complete response; FIP1L1-PDGFR α , fusion of FIP1-like 1 and platelet-derived growth factor receptor α ; NE, not evaluable; PDGFR α , platelet-derived growth factor receptor α ; SD, stable disease.

Table 5

Most Common Study Drug–Related Nonhematologic AEs (Occurring in 2 Patients) and Newly Occurring or Worsening Grade 3/4 Laboratory Abnormalities

	HES (n = 12)		CEL (n = 4)		Total (N = 16)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Nonhematologic AEs occurring in > 10% of patients, n (%)						
Pruritus	5 (41.7)	2 (16.7)	1 (25.0)	0	6 (37.5)	2 (12.5)
Rash	4 (33.3)	1 (8.3)	1 (25.0)	0	5 (31.3)	1 (6.3)
Fatigue	4 (33.3)	0	0	0	4 (25.0)	0
Headache	3 (25.0)	0	1 (25.0)	0	4 (25.0)	0
Diarrhea	3 (25.0)	0	0	0	3 (18.8)	0
Nausea	2 (16.7)	0	1 (25.0)	0	3 (18.8)	0
Peripheral edema	2 (16.7)	0	1 (25.0)	0	3 (18.8)	0
Arthralgia	2 (16.7)	1 (8.3)	0	0	2 (12.5)	1 (6.3)
Dyspepsia	2 (16.7)	0	0	0	2 (12.5)	0
Papule	2 (16.7)	0	0	0	2 (12.5)	0
Abdominal pain	1 (8.3)	0	1 (25.0)	1 (25.0)	2 (12.5)	1 (6.3)
Angina pectoris	1 (8.3)	0	1 (25.0)	0	2 (12.5)	0
Bone pain	1 (8.3)	0	1 (25.0)	0	2 (12.5)	0
Myalgia	1 (8.3)	1 (8.3)	1 (25.0)	0	2 (12.5)	1 (6.3)
Laboratory abnormality, n/N ^a (%)						
Hematologic	HES		CEL		Total	
Lymphocytopenia	3/12 (25.0)		2/4 (50.0)		5/16 (31.3)	
Neutropenia	2/12 (16.7)		2/4 (50.0)		4/16 (25.0)	
Prothrombin time (INR)	1/10 (10.0)		0/3		1/13 (7.7)	
Thrombocytopenia	1/12 (8.3)		0/4		1/16 (6.3)	
Anemia	1/12 (8.3)		0/4		1/16 (6.3)	
Nonhematologic, n/N ^a (%)						
Increased serum lipase	1/11 (9.1)		2/4 (50.0)		3/15 (20.0)	

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	HES (n = 12)		CEL (n = 4)		Total (N = 16)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Decreased serum phosphate	1/11 (9.1)		2/4 (50.0)		2/15 (13.3)	
Increased serum bilirubin (total)	2/12 (16.7)		0/4		2/16 (12.5)	
Decreased sodium	1/11 (9.1)		0/4		1/15 (6.7)	
Increased potassium	0/11		1/4 (25.0)		1/15 (6.7)	

AEs, adverse events; CEL, chronic eosinophilic leukemia; HES, hypereosinophilic syndrome; INR, international normalized ratio.

^an/N, where n is the number of patients experiencing the event and N is the number of patients who had < grade 4 at baseline and were evaluable post baseline.