REGULAR ARTICLE

blood advances

Dabrafenib, alone or in combination with trametinib, in *BRAF* V600–mutated pediatric Langerhans cell histiocytosis

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Key Points

- Dabrafenib monotherapy or combination with trametinib showed preliminary evidence of clinical efficacy in *BRAF* V600–mutant pediatric LCH.
- The safety profile in pediatric *BRAF* V600–mutant LCH was similar to that observed in solid tumors in adults.

Langerhans cell histiocytosis (LCH) is a rare, heterogenous, neoplastic disorder primarily affecting children. *BRAF* mutations have been reported in >50% of patients with LCH. The selective BRAF inhibitor, dabrafenib, in combination with the MEK1/2 inhibitor, trametinib, has been approved in select *BRAF* V600–mutant solid tumors. Two open-label phase 1/2 studies were conducted in pediatric patients with *BRAF* V600–mutant, recurrent/refractory malignancies treated with dabrafenib monotherapy (CDRB436A2102; NCT01677741) or dabrafenib plus trametinib (CTMT212X2101; NCT02124772). The primary objectives of both studies were to determine safe and tolerable doses that achieve similar exposure to the approved doses for adults. Secondary objectives included safety, tolerability, and preliminary antitumor activity. Thirteen and 12 patients with *BRAF* V600–mutant LCH received dabrafenib monotherapy and in combination with trametinib, respectively. Investigator-assessed objective response rates per Histiocyte Society criteria were 76.9% (95% confidence interval [CI], 46.2-95.0) and 58.3% (95% CI, 27.7-84.8) in the monotherapy and combination studies, respectively. More than 90% of responses were ongoing at study completion. The most common treatment-related adverse events (AEs) were vomiting and increased blood creatinine with monotherapy and pyrexia, diarrhea, dry skin, decreased neutrophil count, and vomiting with combination therapy. Two patients each discontinued treatment with monotherapy and combination therapy because of AEs. Overall, dabrafenib monotherapy or in combination with trametinib demonstrated clinical efficacy and manageable toxicity in relapsed/refractory *BRAF* V600–mutant pediatric LCH, with most responses ongoing. Safety was consistent with that reported in other pediatric and adult conditions treated with dabrafenib plus trametinib.

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Novartis is committed to sharing, with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. Requests are reviewed and approved by an independent review panel based on scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on ClinicalStudyDataRequest.com.

The full-text version of this article contains a data supplement.

Introduction

Langerhans cell histiocytosis (LCH) is a rare neoplastic disorder that primarily affects children. LCH is characterized by inflammatory lesions and excessive multiplication and accumulation of cells with a histologic resemblance to Langerhans cells in bones, skin, and visceral organs, such as the liver, spleen, and lungs.[1] Pediatric LCH affects from 4 to 9 per 1 000 000 children aged <15 years old.[2,3] LCH is heterogenous in its manifestations and clinical behavior. Clinical presentations can range from self-resolving single lesions that have a good prognosis (low risk) to the failure of multiple organ systems, which is associated with a higher risk of recurrent events and poor outcomes (high risk).[2,4,5] Manifestation at a young age is associated with disseminated disease of greater severity.[2] Severe forms of LCH are more commonly reported among children aged <2 years and primarily affect the liver, spleen, lungs, skin, and/or hematopoietic system.[5] Some patients experience long-term complications, including neurodegeneration.[2]

BRAF mutations leading to the activation of the mitogen-activated protein kinase pathway have been identified as key oncogenic drivers in several pediatric malignancies, including pediatric LCH.[6,7] *BRAF* V600 mutations have been reported in >50% of the patients with LCH,[4-8] and this mutation has been associated in some, but not all, studies, with a worse prognosis and a more severe clinical phenotype.[2,5,8] *BRAF* V600E mutations have been observed at a higher frequency among younger patients than among older patients.[5,6,9]

Despite advances in understanding the pathogenesis of LCH, chemotherapy remains the standard treatment for patients with multisystem disease.[2,10] Prednisone plus vinblastine combination therapy has been the most widely used first-line therapy for pediatric LCH because of its efficacy and manageable toxicity profile;[2] however, patients with advanced disease have frequent recurrences and may experience long-term health problems.[10] Cladribine and cytarabine combination therapies[11] and allogeneic hematopoietic cell transplant are treatment strategies that have been successfully used for patients with refractory or relapsed LCH, with 1 study of hematopoietic cell transplant showing a 3-year overall survival of ~70%.[12]

Dabrafenib (a selective mutant BRAF inhibitor), as monotherapy or in combination with trametinib (a MEK inhibitor), has shown clinically meaningful activity with a tolerable safety profile in *BRAF* V600–mutant malignancies among children[13-15] and adults.[16,17] Dabrafenib plus trametinib is now an established standard of care in multiple *BRAF* V600–mutant conditions and has been approved by the US Food and Drug Administration for the treatment of adults with *BRAF* V600–mutant melanoma, nonsmall cell lung cancer, and anaplastic thyroid cancer and, more recently, for the tumor-agnostic treatment of patients aged ≥6 years with relapsed/refractory *BRAF* V600E–mutant solid tumors.[18,19] The established benefits of dabrafenib plus trametinib in adults provided the basis for evaluating their use in children with *BRAF* V600–mutant malignancies,[14] such as pediatric high-grade glioma, low-grade glioma, and LCH.[13,20,21] Appropriate weight-based dosing has now been established and reported for each agent as monotherapy[14,21] and in combination[21] in pediatric patients with recurrent/refractory malignancies in 2 open-label, phase 1/2 studies of dabrafenib monotherapy (CDRB436A2102; NCT01677741)[14] or trametinib ± dabrafenib (CTMT212X2101; NCT02124772).[21] Here, we report the efficacy and safety results from those studies for pediatric patients with *BRAF* V600–mutant LCH.

Methods

Clinical study design

CDRB436A2102 (dabrafenib monotherapy). This phase 1/2, 2-part, multicenter, single-arm, open-label study evaluated the safety and efficacy of dabrafenib monotherapy among pediatric patients with relapsed/refractory *BRAF* V600–mutant malignancies (supplemental Figure 1A). The study comprised dose-escalation and disease-specific cohort expansion parts, both of which included patients with pediatric LCH. Efficacy and safety data in patients with *BRAF* V600–mutant LCH are presented here; data from the complete dose-escalation and other disease-specific cohorts have been/will be reported separately.[13,14,20] The clinical trial registry number is NCT01677741, and the study completion/data cutoff date for the analyses presented in this report was 4 December 2020. At study completion, patients who were still deriving clinical benefit per investigator opinion were eligible to continue treatment (at their current regimen and dose) in a rollover study (NCT03975829) for long-term follow-up.

CTMT212X2101 (dabrafenib plus trametinib). This phase 1/2, 4-part, multicenter, open-label study evaluated the safety and efficacy of trametinib monotherapy, or dabrafenib and trametinib combination, in pediatric patients with relapsed/refractory malignancies (supplemental Figure 1B). The study comprised dose-escalation and disease-specific cohort expansion parts for both trametinib monotherapy (not restricted to *BRAF* V600–mutant disease) and dabrafenib plus trametinib (restricted to *BRAF* V600–mutant disease). Efficacy and safety were assessed in patients with *BRAF* V600–mutant LCH treated with dabrafenib plus trametinib in both the dose-escalation and expansion cohorts; no patients with LCH were treated with trametinib monotherapy in this study. Data from the complete dose-escalation and other disease-specific cohorts, including patients receiving trametinib monotherapy, have been/will be reported separately.[21] The clinical trial registry number is NCT02124772, and the study completion/data cutoff date for the analyses presented in this report was 29 December 2020. At study completion, patients who were still deriving clinical benefit per investigator opinion were eligible to continue treatment (at their current regimen and dose) in a rollover study (NCT03975829) for long-term follow-up.

Both studies were sponsored by Novartis, performed in compliance with good clinical practice, and conducted according to the principles of the Declaration of Helsinki. The study protocols were approved by the medical authorities and independent ethics committee/institutional review board in accordance with local laws. Written informed consent was obtained from each patient or their parent/legal guardian.

Study objectives

The primary objective of both studies was to determine safe and tolerable doses for dabrafenib (CDRB436A2102), trametinib (CTMT212X2101), and their combination (CTMT212X2101) in

pediatric patients, that achieve similar exposure to the approved doses for adults. Secondary objectives of relevance for pediatric LCH included characterization of the safety profile and tolerability of dabrafenib monotherapy or dabrafenib plus trametinib, as well as evaluation of the preliminary antitumor activity of dabrafenib monotherapy or dabrafenib plus trametinib, in this disease-specific cohort.

Patients

Both studies enrolled patients with malignancies that had relapsed or were refractory to standard treatments. Other key inclusion criteria of relevance for patients with LCH (CDRB436A2102/dabrafenib monotherapy study; CTMT212X2101/dabrafenib plus trametinib arm of study) included ages from ≥12 months to <18 years, *BRAF* V600–mutant tumors, Karnofsky/Lansky performance status ≥50%, and adequate bone marrow, renal, liver, and cardiac function (described in supplemental Table 1).

Key exclusion criteria of relevance for patients with LCH in both studies included previous treatment with RAF or MEK inhibitors, excluding sorafenib (expansion cohorts), prior or current malignancy apart from that under study, any investigational study treatment within the prior month, cardiovascular risk, and a history of hepatitis B or hepatitis C virus infection. For patients enrolled in the CDRB436A2102 (dabrafenib monotherapy) study, ≥3 weeks should have elapsed since prior chemotherapy or radiation therapy and ≥3 months since an autologous or allogeneic stem cell transplant. For patients enrolled in the CTMT212X2101 (dabrafenib plus trametinib) study, ≥3 weeks should have elapsed since prior chemotherapy, ≥4 weeks since prior radiation therapy to more than 25% of marrow-containing bones, ≥2 weeks since prior local palliative radiation therapy, ≥2 months since autologous transplant, and ≥6 months since prior allogeneic transplant. Previous treatment with an extracellular signal-regulated kinase inhibitor was also not permitted; patients who had received prior BRAF inhibitor monotherapy could enroll if they had prior benefit, as determined by the investigator. In addition, patients receiving medications for left ventricular systolic dysfunction and patients with current liver or biliary disease (except for Gilbert syndrome, asymptomatic gallstones, or liver metastases) were not enrolled. Patients with a history of or current retinal vein occlusion or a history of hepatic sinusoid obstructive syndrome (within 3 months), heparin-induced thrombocytopenia, or interstitial lung disease/pneumonitis were also excluded.

Treatment

CDRB436A2102 (dabrafenib monotherapy). In the dose-escalation part of this study, patients with *BRAF* V600–mutant LCH received dabrafenib monotherapy, administered orally (capsule or oral suspension), at a starting dose of 3.75 mg/kg per day.[14] Patients in the dose-expansion part received dabrafenib at the declared recommended phase 2 dose (RP2D): 5.25 and 4.5 mg/kg per day, divided into 2 equal doses, for patients <12 and ≥12 years of age, respectively. Dose-finding details for dabrafenib monotherapy from this study have been reported previously.[13] Treatment was administered until disease progression, loss to follow-up, or investigator/patient decision.

CTMT212X2101 (dabrafenib plus trametinib). All patients with *BRAF* V600–mutant LCH enrolled in this study received dabrafenib plus trametinib. In the dose-escalation part, trametinib was administered orally (tablet or oral solution) at the declared single-agent RP2D (0.032 and 0.025 mg/kg per day for patients <6 and ≥6 years of age, respectively) combined with 50% or 100% of the RP2D of dabrafenib. Patients in the expansion part received the declared RP2D for the combination, which was the same as the single-agent RP2Ds for both trametinib and dabrafenib: trametinib, 0.032 and 0.025 mg/kg per day for patients <6 and ≥6 years of age, respectively; and dabrafenib, 5.25 and 4.5 mg/kg per day for patients <12 and ≥12 years of age, respectively, divided into 2 equal doses. Dose-finding details for both trametinib monotherapy and dabrafenib plus trametinib combination from this study have been described previously.[21] Treatment was administered until unacceptable toxicity, progressive disease, lack of clinical benefit, or patient/physician decision.

Assessments

Regular safety assessments were performed based on physical, dermatologic, and ophthalmologic examinations; Karnofsky/Lansky performance status; vital sign assessment; laboratory parameters; and cardiac assessments. Adverse events (AEs), defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03, were assessed at every visit. Tumor assessments were performed at baseline and on treatment using imaging and/or physical examination. In patients with LCH, response was evaluated using investigator assessment based on the Histiocyte Society Evaluations and Treatment guidelines.[22] Categories of nonactive disease include complete resolution (CR), defined as resolution of all disease signs or symptoms (no evidence of disease), and regressive disease, defined as regressions of disease signs and symptoms without new lesions. Categories of persistent active disease include stable disease (SD), defined as the persistence of signs and symptoms but no new lesions, and progressive disease, defined as the progression of signs or symptoms and/or the appearance of new lesions (supplemental Table 2).

Statistical analysis

All data are descriptively summarized. Safety and efficacy end points were assessed in all patients who received ≥1 dose of the study drug; the response-evaluable population had a predose and ≥1 postdose efficacy assessment. The objective response rates (ORRs) per the Histiocyte Society criteria are summarized with accompanying two-sided exact binomial 95% confidence intervals (CIs). The duration of response (DOR) was measured from the time of response and estimated using the Kaplan-Meier method. For progression-free survival (PFS), measured from the time of study start, survival functions were estimated using the Kaplan-Meier method and displayed graphically; median estimates with 95% CIs are presented.

Results

Patients and treatment

In the CDRB436A2102 (dabrafenib monotherapy) study, 13 patients with *BRAF* V600–mutant LCH were included; 2 patients were enrolled in the dose-escalation part and 11 in the expansion part. In the dose-escalation part, 1 patient with LCH received dabrafenib at 3.75 mg/kg per day, and the other at 4.5 mg/kg per day; in the expansion part, all patients received the RP2D of dabrafenib (supplemental Figure 1A). The median age was 3 years

Table 1. Baseline demographics and prior treatment for patients with *BRAF* V600–mutant LCH

Category	CDRB436A2102 (dabrafenib monotherapy) (n = 13)	CTMT212X2101 (dabrafenib + trametinib) (n = 12)
Age, median (range), y	3 (1-11)	4 (2-13)
<2 y, n (%)	3 (23.1)	0
From 2 to <6 y, n (%)	5 (38.5)	8 (66.7)
From 6 to <12 y, n (%)	5 (38.5)	3 (25.0)
≥12 y, n (%)	0	1 (8.3)
Male, n (%)	8 (61.5)	8 (66.7)
Karnofsky/Lansky PS, n (%)		
100	6 (46.2)	8 (66.7)
90	4 (30.8)	2 (16.7)
80	1 (7.7)	1 (8.3)
70	1 (7.7)	0
<70	1 (7.7)	1 (8.3)
Risk organ involvement, n (%)*	3 (23.1)	N/A
Time since initial diagnosis, median (range), mo	36.3 (1-116)	33.9 (3.8-137)
Prior therapy, n (%)	13 (100)	12 (100)
Chemotherapy	13 (100)	12 (100)
Biologic therapy†	1 (7.7)	0
Immunotherapy‡	1 (7.7)	0
Prior radiotherapy, n (%)		
Yes	0	0
No	9 (69.2)	12 (100)
Missing	4 (30.8)	0
Prior lines of chemotherapy		
0	0	0
1	2 (15.4)	3 (25.0)
2	1 (7.7)	2 (16.7)
≥3	10 (76.9)	7 (58.3)

PS, performance status.

*Liver, spleen, and/or bone marrow involvement at baseline; data not available for CTMT212X2101 (dabrafenib + trametinib).

†,‡The same patient received †prior anti-CD52 monoclonal antibody and ‡prior immunoglobulin.

(range, 1-11 years), and the median time from initial diagnosis was 36.3 months (range, 1-116 months) (Table 1). All patients had prior chemotherapy, including 10 (76.9%) who had received ≥3 prior lines of chemotherapy; 1 patient also had prior immunoglobulin and anti-CD52 monoclonal antibody treatment (Table 1). At study completion, 7 of 13 patients continued treatment in a rollover study, and 6 had withdrawn from the study because of AEs (n = 2; 15.4%), investigator decision (n = 2; 15.4%), investigator and family decision (n = 1; 7.7%), or switch to combination therapy via compassionate use (n = 1; 7.7%; Table 2). The median duration of exposure to dabrafenib was 51 months (range, 7-65 months).

In the CTMT212X2101 (dabrafenib plus trametinib) study, 12 patients with *BRAF* V600–mutant LCH were included; 2 were enrolled in the dose-escalation part and 10 in the disease-specific expansion part. All were treated at the R2PDs for the combination (supplemental Figure 1B). The median age was 4 years (range, 2-13 years), and the median time from initial diagnosis was 33.9 months (range, 3.8-137 months; Table 1). All patients had prior chemotherapy, including 7 (58.3%) who had received ≥3 prior lines of chemotherapy. At study completion, 8 of 12 patients continued treatment in a rollover study, and 4 had withdrawn from the study because of AEs (n = 2; 16.7%), lack of efficacy (n = 1; 8.3%), and long-term CR (n = 1; 8.3%; Table 2). Median duration of exposure to treatment was 22 months (range, 1.8-35.9 months).

Efficacy

Among patients receiving dabrafenib monotherapy (CDRB436A2102), the investigator-assessed ORR was 76.9% (95% CI, 46.2-95.0). Six of 13 patients had CR (46.2%), 4 had regressive disease (30.8%), and 3 had SD (23.1%) (Table 3; Figure 1A); responses were maintained by patients at all dose levels. The median investigator-assessed DOR was not reached (NR; 95% CI, 11.1 months to NR) by the 10 responding patients. One patient treated at the RP2D had a best response of regressive disease but subsequently experienced disease progression after 11.1 months in response (14.7 months since study start); the remaining 9 responders remained in response at study completion. The estimated 12- and 24-month DOR rates were both 90% (95% CI, 40-100). The median PFS was NR (Figure 2A). The estimated 12- and 24-month PFS rates were 100% (95% CI, NR to NR) and 90% (95% CI, 50-100), respectively.

Among patients receiving dabrafenib plus trametinib (CTMT212X2101), the investigator-assessed ORR was 58.3% (95% CI, 27.7-84.8). Four of the 12 patients had CR (33.3%), 3 had regressive disease (25.0%), and 3 had SD (25.0%). Two patients discontinued before the first postbaseline assessment because of AEs, and therefore did not have a best overall response recorded (Table 3; Figure 1B); thus, 7 of 10 (70.0%) response-evaluable patients had a response. The median investigator-assessed DOR was NR (95% CI, NR to NR) by the 7 responding patients, and all remained in response at study completion. The estimated 12- and 24-month DOR rates were both 100% (95% CI, NR to NR). The median PFS was NR (Figure 2B), and the estimated 12- and 24-month PFS rates were both 100% (95% CI, NR to NR).

Safety and tolerability

Among patients receiving dabrafenib monotherapy (CDRB436A2102), all 13 patients experienced ≥1 AE, regardless of relationship to study treatment, with 11 (84.6%) patients experiencing grade ≥3 AEs (Table 4). The most common all-cause AEs (≥50% of patients) were pyrexia, vomiting (n = 9 each; 69.2%), and cough (n = 8; 61.5%). All 13 patients experienced ≥1 AE suspected to be related to treatment, with 2 (15.4%) patients experiencing grade ≥3 treatment-related AEs (TRAEs) (supplemental Table 3). The most common TRAEs (≥35% of patients) were vomiting (n = 6; 46.2%) and increased blood creatinine levels (n = 5; 38.5%). AEs of any grade, regardless of study drug relationship, that led to reduction, interruption, or discontinuation of study treatment were reported in 2 (15.4%), 9 (69.2%), and 2 (15.4%) patients, respectively (supplemental Table 4). Among the 9 patients with treatment interruptions/dose reductions, 4 resumed treatments without experiencing a recurrence of the AE that led to the interruption/reduction; pyrexia and

Table 2. Disposition of patients with *BRAF* V600–mutant LCH

	CDRB436A2102 (dabrafenib monotherapy)			CTMT212X2101 (dabrafenib + trametinib)		
Status, n (%)	**Escalation part (n = 2)**	**Expansion part (n = 11)**	**All LCH (n = 13)**	**Escalation part (n = 2)**	**Expansion part (n = 10)**	**All LCH (n = 12)**
Ongoing	0	0	0	0	0	0
Entered rollover study	0	7 (63.6)	7 (53.8)	0	8 (80.0)	8 (66.7)
Withdrawn from study	2 (100)	4 (36.4)	6 (46.2)	2 (100)	2 (20.0)	4 (33.3)
Lack of efficacy	0	0	0	0	1 (10.0)	1 (8.3)
AE	1 (50.0)	1 (9.1)	2 (15.4)	1 (50.0)	1 (10.0)	2 (16.7)
Investigator discretion	1 (50.0)	1 (9.1)	2 (15.4)	0	0	0
Other	0	2 (18.2)	2 (18.2)	1 (50.0)	0	1 (8.3)

vomiting were the most common recurrent AEs leading to multiple dose interruptions (in 2 patients each). Of the 2 patients who permanently discontinued treatment because of AEs, reasons for discontinuation were increased blood creatinine levels (grade 2 TRAE) and Epstein-Barr virus–associated lymphoma (grade 4; not deemed as treatment related by the investigator).

Among patients receiving dabrafenib plus trametinib (CTMT212X2101), all 12 patients experienced ≥1 AE, regardless of relationship to treatment, with 9 patients (75.0%) experiencing grade ≥3 AEs (Table 4). The most common all-cause AEs were pyrexia (n = 10; 83.3%), vomiting (n = 9; 75%), and cough (n = 7; 58.3%). All 12 patients (100%) experienced TRAEs of any grade, of whom 5 patients (41.7%) experienced grade ≥3 TRAEs (supplemental Table 3). The most common TRAEs were pyrexia (n = 7; 58.3%), diarrhea, dry skin, decreased neutrophil count, and vomiting (each n = 5; 41.7%). AEs of any grade, regardless of study drug relationship, that led to dose reduction, interruption, or discontinuation of study treatment were reported in 1 (8.3%), 9 (75.0%), and 2 (16.7%) patients, respectively (supplemental Table 4). Among the 9 patients with treatment interruptions/dose reductions, 5 resumed treatments without experiencing a recurrence of the AE that led to the interruption/reduction; pyrexia was the most common recurrent AE leading to multiple dose interruptions (in 4 patients). Of the 2 patients who permanently discontinued treatment, 1 experienced an increase in both alanine aminotransferase and aspartate aminotransferase (grade 3 TRAEs), and the other patient experienced an increase in alanine aminotransferase (grade 3 TRAE).

Table 3. *BRAF* V600–mutant LCH efficacy summary based on investigator assessment

Category	CDRB436A2102 (dabrafenib monotherapy) (n = 13)	CTMT212X2101 (dabrafenib + trametinib) (n = 12)
Best overall response, n (%)*		
CR	6 (46.2)	4 (33.3)
Regressive disease	4 (30.8)	3 (25.0)
SD	3 (23.1)	3 (25.0)
Progressive disease	0	0
Missing	0	2 (16.7)†
ORR (95% CI), %	76.9 (46.2-95.0)	58.3 (27.7-84.8)
Median DOR (95% CI), mo	NR (11.1 to NR)	NR (NR to NR)
12-month rate (95% CI), %	90 (40-100)	100 (NR to NR)
24-month rate (95% CI), %	90 (40-100)	100 (NR to NR)

*Responses were assessed per the Histiocyte Society criteria. Categories of nonactive disease include CR, which indicates resolution of all disease signs or symptoms (no evidence of disease), and regressive disease, which indicates regressions of disease signs and symptoms with no new lesions. Categories of persistent active disease include SD, which indicates the persistence of signs and symptoms but no new lesions, and progressive disease, which indicates the progression of signs or symptoms and/or the appearance of new lesions.

†Two patients did not have any postbaseline assessments because of early discontinuation and were considered to be nonresponders.

Discussion

The results presented here demonstrate that treatment with dabrafenib monotherapy or dabrafenib plus trametinib combination therapy was associated with clinical efficacy, including ongoing responses at study completion in most pediatric patients with relapsed or refractory *BRAF* V600–mutant LCH. Dabrafenib monotherapy demonstrated an ORR of 76.9% (95% CI, 46.2-95.0) in 10 of 13 patients, whereas dabrafenib plus trametinib demonstrated an ORR of 58.3% (95% CI, 27.7-84.8) in 7 of 12 patients; all responses were investigator assessed. It is worth noting that variations in patient populations, duration of treatment, and other factors limit the comparison of results across these 2 studies and treatments. However, these rates are consistent with the ORR reported with dabrafenib monotherapy in a retrospective analysis of 20 pediatric patients with *BRAF* V600E–mutant LCH (ORR, 65%).[23] Notable efficacy (ORR, 100%) has also been reported among patients with the *BRAF* V600 mutation treated with vemurafenib monotherapy in an observational study of 54 patients with multisystem refractory disease and in a small cohort of 4 patients enrolled in a phase 2 basket study.[24,25] A retrospective study of 21 pediatric patients with LCH and MAPK pathway mutations also reported an ORR of 86%, with a variety of MAPK-targeted therapies, including BRAF or MEK inhibitor monotherapy or combination, as well as other therapies active in LCH.[26] Variations in the inclusion criteria, treatment, and formulations administered across these studies preclude comparison of the outcomes reported, but collectively these data join the present report in supporting the use of molecularly targeted therapy in patients with relapsed/refractory *BRAF* V600–mutant LCH.

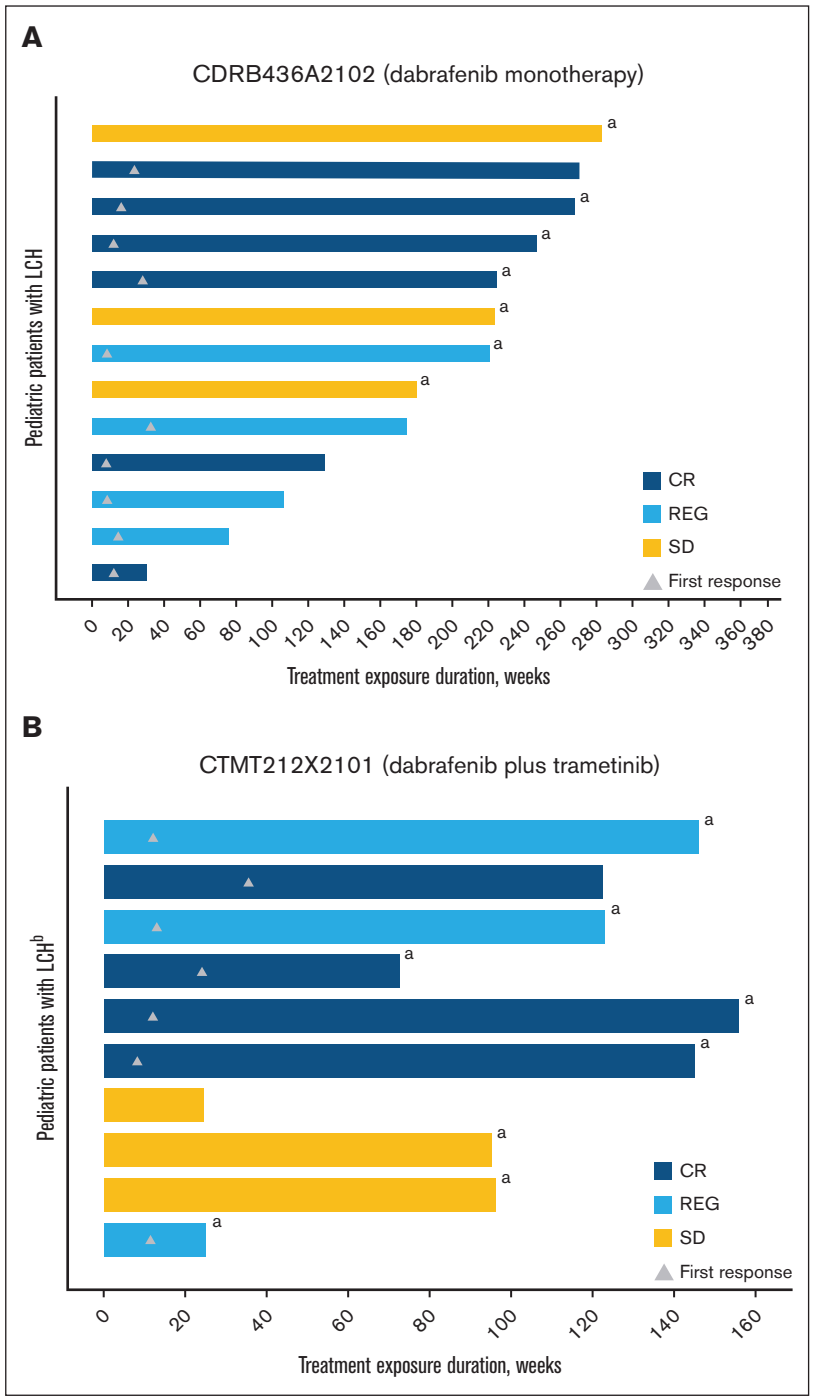

Figure 1. Duration of exposure to study treatment and best overall response (investigator assessment) among patients with *BRAF* V600–mutant LCH. Duration of exposure to dabrafenib monotherapy (A) or dabrafenib plus trametinib (B) in pediatric patients with *BRAF* V600–mutant LCH; best overall response per investigator assessment using the Histiocyte Society response assessment guidelines. Categories of nonactive disease include CR, which indicates resolution of all disease signs or symptoms (no evidence of disease), and regressive disease, which indicates regressions of disease signs and symptoms with no new lesions. Categories of persistent active disease include SD, which indicates the persistence of signs and symptoms but no new lesions, and progressive disease, which indicates the progression of signs or symptoms and/or the appearance of new lesions. [a]indicates patients who have continued therapy on a rollover study, and [b]indicates that 2 patients did not have any postbaseline assessment because of early discontinuation and were considered to be nonresponders. REG, regressive disease.

Chemotherapy comprising vinblastine plus prednisone is the standard of care for pediatric patients with LCH with de novo multisystem disease; however, challenges with this approach include limited efficacy, as patients often require second, third, or later lines of chemotherapy.[22,27] Recurrences and long-term complications are common in patients with advanced LCH; as such, there is a need for therapies that offer sustained clinical efficacy. In the 2 studies reported here, the responses observed appear to be maintained for patients while on therapy: 9 of 10 patients in the monotherapy group and 7 of 7 in the combination group had ongoing responses at study completion. However, a notable distinction is that chemotherapy is typically administered as a fixed course, whereas targeted therapies, such as dabrafenib ± trametinib, are generally administered continuously as long as clinical benefit and tolerability permit because of the potential for relapse upon discontinuation. Whether it would be possible for patients with *BRAF* V600–mutant LCH to discontinue dabrafenib ± trametinib after an optimized duration of treatment is unclear,

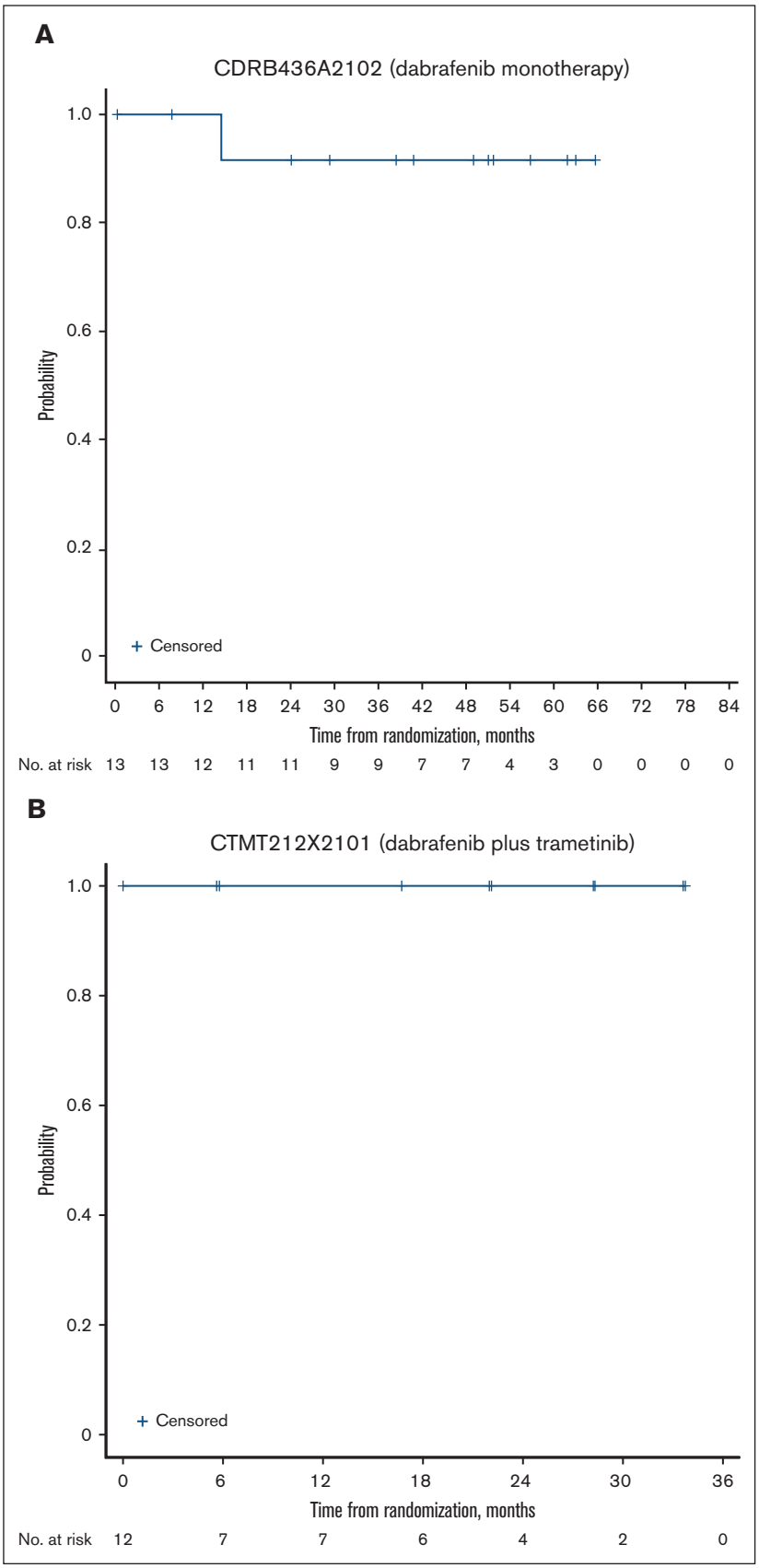

Figure 2. Kaplan-Meier plots for PFS, per investigator assessment, for patients with *BRAF* V600–mutant LCH receiving dabrafenib monotherapy or dabrafenib plus trametinib. Kaplan-Meier plots showing PFS based on investigator assessment among pediatric patients with *BRAF* V600–mutant LCH treated with dabrafenib monotherapy (A) or dabrafenib plus trametinib (B).

Table 4. AEs, regardless of relationship to study treatment (≥30% of patients with *BRAF* V600–mutant LCH in either study)

	CDRB436A2102 (dabrafenib monotherapy) (n = 13)		CTMT212X2101 (dabrafenib + trametinib) (n = 12)	
Category	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any AE, n (%)	13 (100)	11 (84.6)	12 (100)	9 (75.0)
Pyrexia	9 (69.2)	3 (23.1)	10 (83.3)	4 (33.3)
Vomiting	9 (69.2)	0	9 (75.0)	0
Cough	8 (61.5)	0	7 (58.3)	0
Dry skin	6 (42.6)	0	6 (50.0)	0
Upper respiratory tract infection	6 (46.2)	0	6 (50.0)	1 (8.3)
Headache	5 (38.5)	0	2 (16.7)	0
Hypophosphatemia	5 (38.5)	0	3 (25.0)	0
Blood creatinine increased	5 (38.5)	0	3 (25.0)	0
Constipation	5 (38.5)	0	2 (16.7)	0
WBC count decreased	5 (38.5)	0	1 (8.3)	0
Nausea	4 (30.8)	1 (7.7)	3 (25.0)	0
Conjunctivitis	4 (30.8)	1 (7.7)	2 (16.7)	0
Rash	4 (30.8)	0	2 (16.7)	0
Diarrhea	4 (30.8)	0	6 (50.0)	0
Melanocytic naevus	4 (30.8)	0	0	0
Anemia	4 (30.8)	0	2 (16.7)	1 (8.3)
Rhinitis	4 (30.8)	0	0	0
Rhinorrhea	4 (30.8)	0	1 (8.3)	0
Nasal congestion	4 (30.8)	0	4 (33.3)	0
Arthropod bite	4 (30.8)	0	0	0
Maculopapular rash	2 (15.4)	0	6 (50.0)	0
Abdominal pain	2 (15.4)	0	5 (41.7)	0
Neutrophil count decreased	2 (15.4)	1 (7.7)	5 (41.7)	3 (25.0)
AST increased	3 (23.1)	0	4 (33.3)	1 (8.3)
Fatigue	3 (23.1)	0	4 (33.3)	0
Pain in extremities	3 (23.1)	0	4 (33.3)	0

AST, aspartate aminotransferase; WBC, white blood cell.

and the optimal duration of treatment with cytotoxic chemotherapy is also under investigation by others in patients with molecularly unselected LCH.[10,22,28] The results of our studies presented here provide an early indicator that some patients may be able to remain on dabrafenib ± trametinib and thus continue in response, though additional longer-term follow-up and response evaluations beyond the scope of the studies described here (eg, analysis of circulating tumor DNA)[25,29,30] are needed to determine whether there is an optimal duration of therapy or if discontinuation without disease relapse is achievable.

In these pediatric studies, treatment was generally well tolerated, with toxicities typically managed by dose interruptions; only 2 patients discontinued therapy because of AEs in each of the 2 studies. Similar to previously reported adult[16,31] and pediatric[13,14] study results, pyrexia was the most frequently reported all-cause AE in pediatric patients with *BRAF* V600–mutant LCH after dabrafenib monotherapy (any grade, 69.2% and grade ≥3, 23.1%) and dabrafenib plus trametinib combination therapy (any grade, 83.3% and grade ≥3, 33.3%); pyrexia was managed by dose interruption and did not result in discontinuation for any patient. TRAEs of grade ≥3 were reported in 15.4% and 41.7% of patients treated with monotherapy and combination therapy, respectively; most individual AEs of this severity were uncommon, occurring in only 1 or 2 patients. Moreover, the low rate of discontinuations, the ability of many patients to safely resume therapy, and the high proportion of patients (15 of 25 in total) continuing treatment in a rollover study suggest that this is an acceptable risk/benefit profile in the heavily pretreated (the majority of patients had ≥3 prior lines of chemotherapy) population with *BRAF* V600–mutant LCH in our studies. This is an important consideration because long-term treatment with chemotherapy may be of concern, particularly in young pediatric patients, because of the potential for long-term health and developmental problems, including impaired bone health, growth retardation, and peripheral neuropathy.[27,32] However, the long-term effects of BRAF inhibition, with or without MEK inhibition, are unknown at this time, and risk/benefit assessment

should be evaluated on an individual patient basis given the heterogeneity of LCH presentations and risk organ involvement.

In conclusion, preliminary efficacy and safety signals from these phase 1/2 studies support further investigation of dabrafenib ± trametinib administration for pediatric patients with *BRAF* V600–mutant LCH. A limitation of these studies is that as these *BRAF* V600–mutant LCH cohorts represent a subset of these phase 1/2 studies that enrolled patients with an array of pediatric malignancies to determine the pediatric dosing of dabrafenib ± trametinib, data enabling detailed characterization of the LCH disease types represented, which may be diverse, were not collected. Thus, evaluation in specific subsets of patients with LCH, such as those with newly diagnosed, high-risk/risk organ-involved, or neurodegenerative disease, may be warranted in dedicated studies to enable more thorough characterization of the benefits of dabrafenib ± trametinib in specific LCH disease states. Whether combination therapy has greater benefits in patients with *BRAF* V600–mutant LCH compared with dabrafenib monotherapy also remains unknown because direct comparisons between the 2 studies described here could not be made. However, combination therapy appears to delay resistance, reduce toxicity, and improve outcomes in previously untreated adult and pediatric patients with several types of *BRAF* V600–mutant disease.[13-16,31,33] Given that the present studies are small and were designed only to evaluate preliminary efficacy and safety signals, larger studies could help to evaluate the relative benefits of monotherapy vs combination therapy, explore the optimal duration of treatment with dabrafenib ± trametinib, and elucidate any long-term safety considerations. The ongoing rollover study should also provide valuable insight into some of these remaining questions surrounding dabrafenib and trametinib in *BRAF* V600–mutant pediatric LCH.

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Authorship

Contribution: J.A.W., B.G., D.H., and M. Russo formulated the study design and methodology; J.A.W., B.G., I.J.D., and D.H. were involved with conducting the research and investigations and providing resources; M. Roughton and J.C. were involved in data validation, data curation, formal analysis, and the visualization and presentation of data; M. Russo was involved in leading and overseeing the research activities; and all the authors were involved with the preparation and presentation of the published work and critically reviewed and revised subsequent drafts.

Conflict-of-interest disclosure: J.A.W. reports research funding (to institution) from Novartis, consulting fees/participation in a data safety monitoring board with Pfizer, and consulting fees/participation in advisory boards for Jazz Pharmaceuticals. I.J.D. reports contracts (with institution) from Bristol Myers Squibb, Genentech, and Novartis; payment (to institution) for role as chair of the Pediatric Brain Tumor Consortium; consulting fees/participation in a data safety monitoring board with Celgene/Bristol Myers Squibb; and consulting fees/participation in advisory boards for AstraZeneca, Bristol Myers Squibb, Day One, Fennec, QED, and Roche. J.C. and L.O. report employment with Novartis. M. Russo and M. Roughton report stock/shares in and employment with Novartis. D.H. reports consulting fees from Novartis and participation in a data safety monitoring or advisory board for activities relating to trametinib and dabrafenib. B.G. declares no competing financial interests.

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References

1. Haupt R, Minkov M, Astigarraga I, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. *Pediatr Blood Cancer*. 2013;60(2):175-184.
2. Sterlich K, Minkov M. Childhood Langerhans cell histiocytosis: epidemiology, clinical presentations, prognostic factors, and therapeutic approaches. In: Valarmathi MT, ed. *Rare Diseases - Diagnostic and Therapeutic Odyssey*. 2021.
3. Stalemark H, Laurencikas E, Karis J, Gavhed D, Fadeel B, Henter JI. Incidence of Langerhans cell histiocytosis in children: a population-based study. *Pediatr Blood Cancer*. 2008;51(1):76-81.
4. Berres ML, Lim KPH, Peters T, et al. BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. *J Exp Med*. 2014;211(4):669-683.
5. Heritier S, Emile JF, Barkaoui MA, et al. BRAF mutation correlates with high-risk Langerhans cell histiocytosis and increased resistance to first-line therapy. *J Clin Oncol*. 2016;34(25):3023-3030.
6. Badalian-Very G, Vergilio JA, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood*. 2010;116(11):1919-1923.

7. Brown NA, Furtado LV, Betz BL, et al. High prevalence of somatic MAP2K1 mutations in BRAF V600E-negative Langerhans cell histiocytosis. *Blood*. 2014;124(10):1655-1658.
8. Satoh T, Smith A, Sarde A, et al. B-RAF mutant alleles associated with Langerhans cell histiocytosis, a granulomatous pediatric disease. *PLoS One*. 2012;7(4):e33891.
9. Dahiya S, Emnett RJ, Haydon DH, et al. BRAF-V600E mutation in pediatric and adult glioblastoma. *Neuro Oncol*. 2014;16(2):318-319.
10. Allen CE, Merad M, McClain KL. Langerhans-cell histiocytosis. *N Engl J Med*. 2018;379(9):856-868.
11. Donadieu J, Bernard F, van Noesel M, et al. Cladribine and cytarabine in refractory multisystem Langerhans cell histiocytosis: results of an international phase 2 study. *Blood*. 2015;126(12):1415-1423.
12. Veys PA, Nanduri V, Baker KS, et al. Haematopoietic stem cell transplantation for refractory Langerhans cell histiocytosis: outcome by intensity of conditioning. *Br J Haematol*. 2015;169(5):711-718.
13. Hargrave DR, Bouffet E, Tabori U, et al. Efficacy and safety of dabrafenib in pediatric patients with BRAF V600 mutation-positive relapsed or refractory low-grade glioma: results from a phase I/IIa study. *Clin Cancer Res*. 2019;25(24):7303-7311.
14. Kieran MW, Geoerger B, Dunkel IJ, et al. A phase I and pharmacokinetic study of oral dabrafenib in children and adolescent patients with recurrent or refractory BRAF V600 mutation-positive solid tumors. *Clin Cancer Res*. 2019;25(24):7294-7302.
15. Toll SA, Tran HN, Cotter J, et al. Sustained response of three pediatric BRAF(V600E) mutated high-grade gliomas to combined BRAF and MEK inhibitor therapy. *Oncotarget*. 2019;10(4):551-557.
16. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. *J Clin Oncol*. 2018;36(1):7-13.
17. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med*. 2019;381(7):626-636.
18. TAFINLAR (dabrafenib). Package insert. Novartis Pharmaceutical Corporation; 2022.
19. MEKINIST (trametinib). Package insert. Novartis Pharmaceutical Corporation; 2022.
20. Hargrave D, Moreau L, Broniscer A, Bouffet E, Aerts I, Andre N. Dabrafenib in pediatric patients with BRAF V600–positive high-grade glioma (HGG). *ASCO*. 2018. Abstract 10506.
21. Bouffet E, Geoerger B, Moertel CL, et al. Efficacy and safety of trametinib monotherapy or in combination with dabrafenib in pediatric BRAF V600–mutant low-grade glioma. *J Clin Oncol*. 2023;41(3):664-674.
22. Gadner H, Minkov M, Grois N, et al. Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. *Blood*. 2013;121(25):5006-5014.
23. Yang Y, Wang D, Cui L, et al. Effectiveness and safety of dabrafenib in the treatment of 20 Chinese children with BRAFV600E-mutated Langerhans cell histiocytosis. *Cancer Res Treat*. 2021;53(1):261-269.
24. Diamond EL, Subbiah V, Lockhart AC, et al. Vemurafenib for BRAF V600-mutant Erdheim-Chester disease and Langerhans cell histiocytosis: analysis of data from the histology-independent, phase 2, open-label VE-BASKET study. *JAMA Oncol*. 2018;4(3):384-388.
25. Donadieu J, Larabi IA, Tardieu M, et al. Vemurafenib for refractory multisystem Langerhans cell histiocytosis in children: an international observational study. *J Clin Oncol*. 2019;37(31):2857-2865.
26. Eckstein OS, Visser J, Rodriguez-Galindo C, Allen CE; NACHO-LIBRE Study Group. Clinical responses and persistent BRAF V600E(+) blood cells in children with LCH treated with MAPK pathway inhibition. *Blood*. 2019;133(15):1691-1694.
27. Simko SJ, McClain KL, Allen CE. Up-front therapy for LCH: is it time to test an alternative to vinblastine/prednisone? *Br J Haematol*. 2015;169(2):299-301.
28. LCH-IV, International Collaborative Treatment Protocol for children and adolescents with Langerhans cell histiocytosis. Accessed 14 February 2023. https://clinicaltrials.gov/ct2/show/NCT02205762
29. Eder SK, Schwentner R, Ben Soussia P, et al. Vemurafenib acts as a molecular on-off switch governing systemic inflammation in Langerhans cell histiocytosis. *Blood Adv*. 2022;6(3):970-975.
30. Evseev D, Kalinina I, Raykina E, et al. Vemurafenib provides a rapid and robust clinical response in pediatric Langerhans cell histiocytosis with the BRAF V600E mutation but does not eliminate low-level minimal residual disease per ddPCR using cell-free circulating DNA. *Int J Hematol*. 2021;114(6):725-734.
31. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med*. 2014;371(20):1877-1888.
32. Hudson MM, Tyc VL, Srivastava DK, et al. Multi-component behavioral intervention to promote health protective behaviors in childhood cancer survivors: the protect study. *Med Pediatr Oncol*. 2002;39(1):2-1. discussion: 2.
33. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol*. 2017;18(10):1307-1316.