Supplemental Information

Supplemental Table 1. Eligibility criteria related to adequate organ function, as detailed in the protocols for each study (available in Kieran MW, et al. *Clin Cancer Res*. 2019;25:7294-7302 and Bouffet E, et al. *J Clin Oncol*. 2022;JCO2201000.)

CDRB436A2102 (dabrafenib monotherapy)	CTMT212X2101 (dabrafenib + trametinib)
Adequate bone marrow function defined as:	
• Absolute neutrophil count ≥ 1000/μL • Hemoglobin ≥ 8.0 g/dL (may receive red blood cell transfusions) • Platelets ≥ 75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment)	• Absolute neutrophil count ≥ 1000/μL • Hemoglobin ≥8.0 g/dL (may receive red blood cell transfusions) • Platelets ≥75,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment) • PT/INR and PTT ≤ 1.3 x ULN (subjects receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to starting study medication)
Adequate renal and metabolic function defined as:	
• Calculated eGFR (Schwartz formula, http://www.medcalc.com/pedigfr.html), or radioisotope GFR ≥90 mL/min/1.73 m^2, or • Serum creatinine within the institutional reference range upper limit of normal (for age/gender, if available)	• 24-hour creatinine clearance (revised Schwartz formula), or radioisotope GFR ≥ 60 mL/min/1.73 m^2, or • Serum creatinine ≤ ULN for age and gender (as defined in the study protocol)
Adequate liver function defined as:	
• Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x ULN for age • AST and ALT ≤ 2.5 x ULN (AST/ALT may be < 5 x ULN at baseline if disease under treatment involves the liver; requires radiographic confirmation of liver involvement)	• Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x ULN for age • ALT ≤ 2.5 x ULN (for the purposes of enrollment and toxicity monitoring the ULN for ALT will be 45 units/L)
Adequate cardiac function defined as:	
• LVEF of either ≥ 50% by ECHO or greater than institutional LLN by ECHO (while not receiving medications for cardiac function) • Corrected QT (QTcB) interval < 450 msecs	• LVEF ≥ LLN by ECHO • Corrected QT (QTcB) interval < 480 msec

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECHO, echocardiogram; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; ITT, international normalized ratio; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; PT, prothrombin time; PTT, partial thromboplastin time; QTcB, QT correction with Bazett formula; ULN, upper limit of normal.

Supplemental Table 2. Histiocyte Society response assessment guidelines

Nonactive disease	Complete resolution/no evidence of disease	Resolution of all signs or symptoms
	Regressive disease	Regression of signs or symptoms, no new lesions
Active disease	Stable disease	Persistence of signs or symptoms, no new lesions
	Progressive disease	Progression of signs or symptoms and/or appearance of new lesions

Supplemental Table 3. Treatment-related adverse events (≥30% of patients with LCH in either study)

Category, n (%)	CDRB436A2102 (dabrafenib monotherapy) (n=13)		CTMT212X2101 (dabrafenib + trametinib) (n=12)	
	Any grade	Grade ≥3[a]	Any grade	Grade ≥3[b]
Any TRAE	13 (100)	2 (15.4)	12 (100)	6 (50.0)
Vomiting	6 (46.2)	0	5 (41.7)	0
Blood creatinine increased	5 (38.5)	0	2 (16.7)	0
Dry skin	4 (30.8)	0	5 (41.7)	0
Rash	4 (30.8)	0	2 (16.7)	0
Melanocytic naevus	4 (30.8)	0	0	0
Pyrexia	3 (23.1)	0	7 (58.3)	1 (8.3)
Diarrhea	2 (15.4)	0	5 (41.7)	0
Neutrophil count decreased	1 (7.7)	0	5 (41.7)	3 (25.0)
Abdominal pain	1 (7.7)	0	4 (33.3)	0
Maculopapular rash	1 (7.7)	0	4 (33.3)	0

LCH indicates Langerhans cell histiocytosis**;** and TRAE, treatment-related adverse event**.**

[a] Grade ≥3 TRAEs experienced by two patients treated with dabrafenib monotherapy were dental caries (n=1, 7.7%), nausea (n=1, 7.7%) and increased alanine aminotransferase (n=1, 7.7%). [b] Grade ≥3 TRAEs experienced by six patients treated with dabrafenib monotherapy were decreased neutrophil count (n=3, 25.0%), increased alanine aminotransferase (n=2, 16.7%), pyrexia (n=1, 8.3%), increased aspartate aminotransferase (n=1, 8.3%), anemia (n=1, 8.3%), increased gamma-glutamyltransferase (n=1, 8.3%), hypotension (n=1, 8.3%), decreased lymphocyte count (n=1, 8.3%), parotitis (n=1, 8.3%), increased weight (n=1, 8.3%).

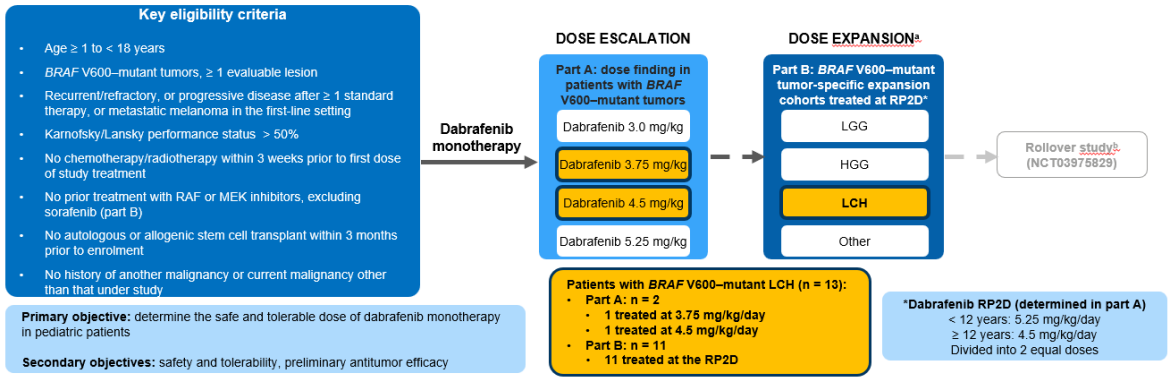
Supplemental Table 4. Safety summary in patients with LCH

Category, n (%)	CDRB436A2102 (dabrafenib monotherapy) (n=13)		CTMT212X2101 (dabrafenib + trametinib) (n=12)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	13 (100)	11 (84.6)	12 (100)	9 (75.0)
Treatment related	13 (100)	2 (15.4)	12 (100)	5 (41.7)
AEs leading to dose reduction	2 (15.4)	0	1 (8.3)	1 (8.3)
AEs leading to dose interruption	9 (69.2)	4 (30.2)	9 (75.0)	5 (41.7)
AEs leading to discontinuation	2 (15.4)	1 (7.7)	2 (16.7)	2 (16.7)
Serious AEs	7 (53.8)	4 (30.8)	7 (58.3)	6 (50.0)
Treatment related	2 (15.4)	0	3 (25.0)	2 (16.7)
Fatal	0	0	0	0

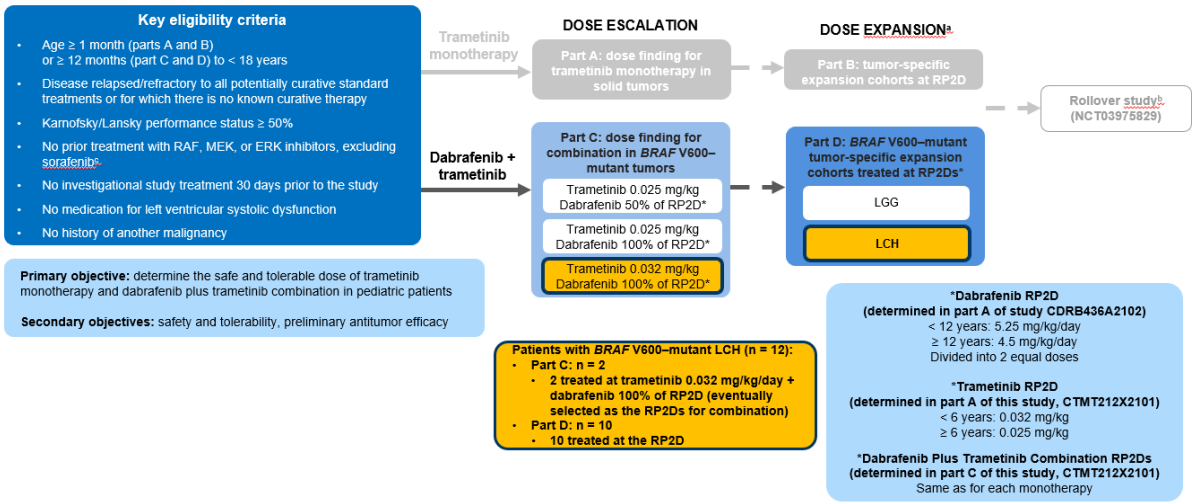
AE indicates adverse event; and LCH, Langerhans cell histiocytosis

Supplemental Figure 1. Study designs

A. CDRB436A2102 (NCT01677741; dabrafenib monotherapy)



B. CTMT212X2101 (NCT02124772; dabrafenib plus trametinib combination)



HGG, high-grade glioma; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; RP2D, recommended phase 2 dose.

[a] After selection of the RP2D of dabrafenib monotherapy (in the dose escalation part A of study CDRB436A2102), or trametinib monotherapy or in combination with dabrafenib (in the dose escalation parts A and C of study CTMT212X2101), tumor-specific expansion cohorts were opened for evaluation of preliminary efficacy and safety at the RP2Ds. The dose escalation and expansion parts of these studies were distinct (ie, patients did not roll over from escalation to expansion); [b] At study completion, if patients were continuing to derive clinical benefit from treatment in the opinion of the investigator, they were eligible to continue treatment (with the same regimen and dose they were currently receiving) in a rollover study. Results of the rollover study are not included in the present report, but 15 of 25 patients with LCH enrolled across the 2 studies reported here continued on to the rollover; [c] Patients with prior BRAF inhibitor monotherapy were eligible to enroll if they had clinical benefit per investigator.