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# Dabrafenib, Alone or in Combination With Trametinib, in Paediatric Patients With *BRAF* V600 Mutation–Positive Langerhans Cell Histiocytosis

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# Introduction

- Langerhans cell histiocytosis (LCH) is a rare neoplastic disorder that affects 4 to 9 children < 15 years old per 1,000,000[1]
- Chemotherapy is the standard treatment for LCH; however, patients with advanced forms of the disease have frequent recurrences[2]
  - Patients whose treatment failed had long-term complications, such as neurodegeneration[2]
- Oncogenic *BRAF* mutations have been identified in paediatric malignancies, including > 50% LCH tumours[3]
  - Some studies have associated this mutation with worse prognosis and more severe clinical phenotype in LCH[4]
- Dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor, have shown meaningful clinical activity and a tolerable safety profile in patients with *BRAF* V600 mutation–positive paediatric malignancies[5–7]
- This poster presents the safety and efficacy data from two studies, one investigating dabrafenib monotherapy (NCT01677741) and the other looking at dabrafenib in combination with trametinib (NCT02124772) in paediatric patients with previously treated *BRAF* V600–mutation positive LCH (**Figure 1**)

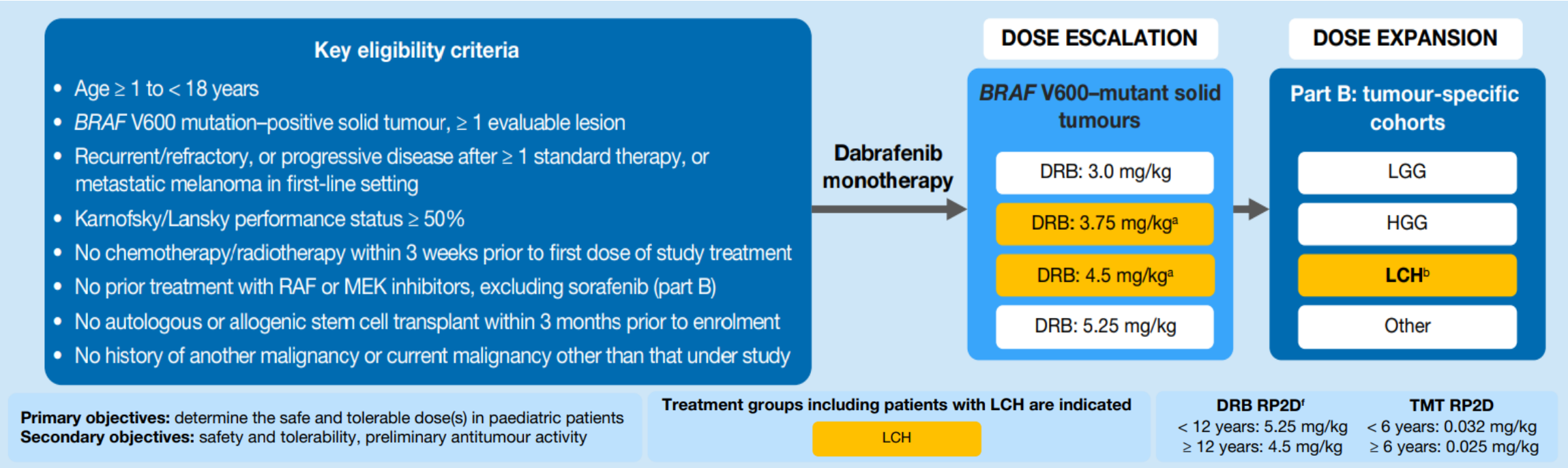
1. Stalemark H, et al. Pediatr Blood Cancer. 2008;51:76-81. 2. Allen CE, et al. N Engl J Med. 2018;379:856-868. 3. Brown NA, et al. Blood. 2014;124:1655-1658. 4. Heritier S, et al. J Clin Oncol. 2016;34:3023-3030. 5. Hargrave DR, et al. Clin Cancer Res. 2019;25:7303-7311. 6. Kieran MW, et al. Clin Cancer Res. 2019;25:7294-7302. 7. Toll SA, et al. Oncotarget. 2019;10:551-557.

# Methods

## Figure 1. Study Designs

**A: CDRB436A2102 (dabrafenib monotherapy)**

Phase I/II, 2-part, multicentre, single-arm, open-label study evaluating the safety and efficacy of dabrafenib monotherapy in paediatric patients with relapsed/refractory *BRAF* V600–mutation positive malignancies



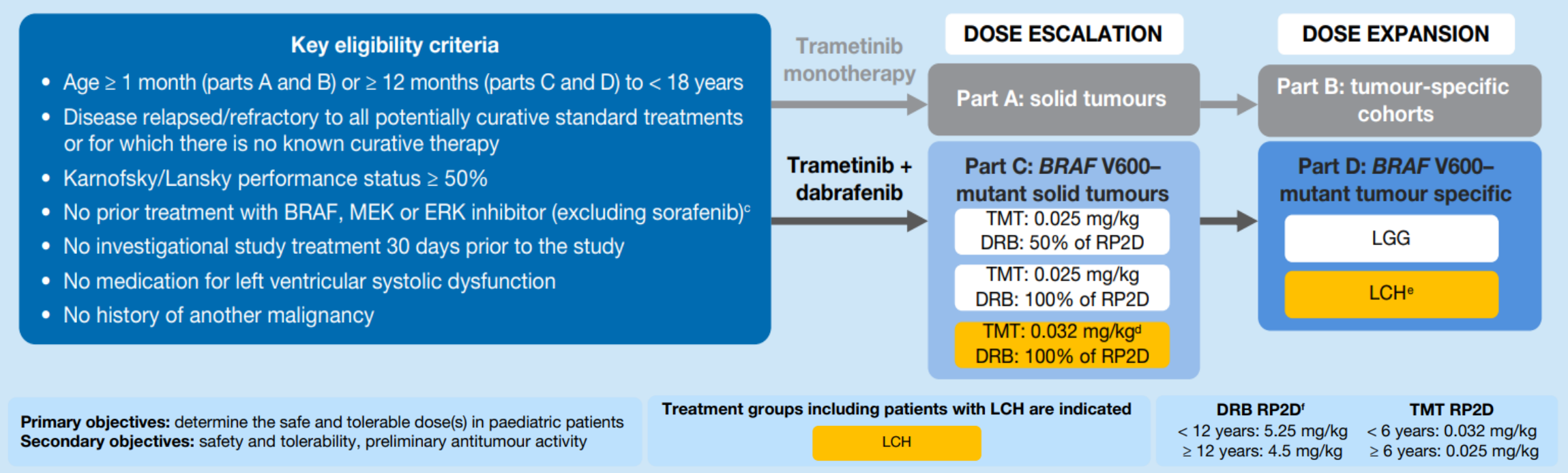

DRB, dabrafenib; HGG, high-grade glioma; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; RP2D, recommended Phase II dose; TMT, trametinib. [a] 1 patient with LCH in this cohort. [b] 11 patients with LCH in this cohort. [c] Patients with prior BRAF monotherapy may enrol if they had benefit as determined by the investigator. [d] 2 patients with LCH in this cohort. [e] 10 patients with LCH in this cohort. [f] The RP2D of dabrafenib for paediatric patients was determined in a prior study [Kieran MW, et al. Clin Cancer Res. 2019;25:7294-7302].

# Methods

## Figure 1. Study Designs

**B: CTMT212X2101 (dabrafenib plus trametinib)**

Phase I/II, 4-part, multicentre, open-label study evaluating the safety and efficacy of trametinib monotherapy, or dabrafenib plus trametinib, in paediatric patients with relapsed/refractory malignancies




DRB, dabrafenib; HGG, high-grade glioma; LCH, Langerhans cell histiocytosis; LGG, low-grade glioma; RP2D, recommended Phase II dose; TMT, trametinib. [a] 1 patient with LCH in this cohort. [b] 11 patients with LCH in this cohort. [c] Patients with prior BRAF monotherapy may enrol if they had benefit as determined by the investigator. [d] 2 patients with LCH in this cohort. [e] 10 patients with LCH in this cohort. [f] The RP2D of dabrafenib for paediatric patients was determined in a prior study [Kieran MW, et al. Clin Cancer Res. 2019;25:7294-7302].

# Results

## Patient Characteristics and Disposition

- Baseline patient demographics and disease characteristics are shown in **Table 1.**

### CDRB436A2102 (dabrafenib monotherapy)

- 13 patients with *BRAF* V600 mutant–LCH received dabrafenib monotherapy; 2 and 11 patients in the dose-escalation and -expansion parts, respectively
  - At the data cutoff date of 4 December 2020, the median duration of exposure (DOE) to treatment with dabrafenib monotherapy was 51 months (range, 7-65 months), with most patients ongoing
- Treatment was discontinued in 6 patients due to investigator decision (n = 3), adverse events (AEs) (n = 2), and patient transferring to combination therapy (n = 1)
  - 7 patients enrolled in a rollover study

### CTMT212X2101 (dabrafenib plus trametinib)

- 12 patients with *BRAF* V600 mutant–LCH received dabrafenib in combination with trametinib; 2 and 10 patients in the dose-escalation and -expansion parts, respectively
  - At the data cutoff date of 29 December 2020, the median DOE to treatment with dabrafenib plus trametinib was 22 months (range, 1.8-35.9 months), with most patients ongoing
- Treatment was discontinued in 4 patients due to AEs (n = 2), lack of efficacy (n = 1), or long-term complete resolution (CR) (n = 1)
  - 8 patients enrolled in a rollover study

# Results

## Table 1. Patient Demographics and Baseline Characteristics

| Category | CDRB436A2102 All LCH (n = 13) | CTMT212X2101 All LCH (n = 12) |
|---|---|---|
| **Age, median (range), years** | 3 (1-11) | 4 (2-13) |
| < 2 years, n (%) | 3 (23.1) | 0 |
| 2 to < 6 years, n (%) | 5 (38.5) | 8 (66.7) |
| 6 to < 12 years, n (%) | 5 (38.5) | 3 (25.0) |
| ≥ 12 years, 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) |
| < 80 | 2 (15.3) | 1 (8.3) |
| **Multisite disease, n (%)** | 3 (23.1) | 0 |
| **Time since initial diagnosis, median (range), months** | 36.3 (1-116) | 33.9 (3.8-136.9) |
| **Prior therapy, n (%)** | 13 (100) | 12 (100) |
| Chemotherapy | 13 (100) | 12 (100) |
| Biologic therapy[a] | 1 (7.7) | 0 |
| Immunotherapy[b] | 1 (7.7) | 0 |
| Targeted therapy | 0 | 0 |
| **Prior surgery, n (%)** | | |
| Yes | 0 | 5 (41.7) |
| No | 9 (69.2) | 7 (58.3) |
| Missing | 4 (30.8) | 0 |

LCH, Langerhans cell histiocytosis; PS, performance status.
The same patient received [a] prior anti-CD52 monoclonal antibody and [b] prior immunoglobulin.

# Results
## Safety and Tolerability

- AEs are summarised in **Table 2**, and treatment-related AEs (TRAEs) are listed in **Table 3**

**CDRB436A2102 (dabrafenib monotherapy)**

- AEs leading to discontinuation included grade 2 increase in blood creatinine and grade ≥ 3 Epstein-Barr virus–associated lymphoma
- Most common grade ≥ 3 AEs reported in patients taking dabrafenib monotherapy were pyrexia (23.1%), neutropenia (15.4%), and syncope (15.4%)
- Most common grade ≥ 3 TRAEs reported in patients taking dabrafenib monotherapy were nausea (7.7%), increased alanine aminotransferase (ALT) (7.7%), and dental caries (7.7%)

**CTMT212X2101 (dabrafenib plus trametinib)**

- AEs leading to discontinuation included grade ≥ 3 increases in ALT and aspartate aminotransferase (AST)
- Most common grade ≥ 3 AEs reported in patients taking dabrafenib plus trametinib were pyrexia (33.3%), decreased neutrophil count (25.0%), and increased ALT (16.7%)
- Most common grade ≥ 3 TRAEs reported in patients taking dabrafenib plus trametinib were decreased neutrophil count (25.0%) and pyrexia (8.3%)

# Results

## Table 2. Safety Summary

| Category, n (%) | CDRB436A2102 All LCH (n = 13) | | CTMT212X2101 All LCH (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 AEs** | 0 | 0 | 0 | 0 |

AE, adverse event; LCH, Langerhans cell histiocytosis.

# Results

## Table 3. TRAEs Occurring in ≥ 20% of Patients

| Category, n (%) | Any Grade | Grade ≥ 3 |
|---|---|---|
| **CDRB436A2102 All LCH (n = 13)** | | |
| **Any TRAE** | 13 (100) | 2 (15.4) |
| Vomiting | 6 (46.2) | 0 |
| Blood creatinine increased | 5 (38.5) | 0 |
| Dry skin | 4 (30.8) | 0 |
| Rash | 4 (30.8) | 0 |
| Melanocytic naevus | 4 (30.8) | 0 |
| Pyrexia | 3 (23.1) | 0 |
| AST increase | 3 (23.1) | 0 |
| Hypophosphatemia | 3 (23.1) | 0 |
| Alopecia | 3 (23.1) | 0 |
| Hair texture abnormal | 3 (23.1) | 0 |
| Constipation | 3 (23.1) | 0 |
| Erythema nodosum | 3 (23.1) | 0 |
| **CTMT212X2101 All LCH (n = 12)** | | |
| **Any TRAE** | 12 (100) | 5 (41.7) |
| Pyrexia | 7 (58.3) | 1 (8.3) |
| Diarrhoea | 5 (41.7) | 0 |
| Dry skin | 5 (41.7) | 0 |
| Neutrophil count decreased | 5 (41.7) | 2 (16.7) |
| Vomiting | 5 (41.7) | 0 |
| Abdominal pain | 4 (33.3) | 0 |
| Maculopapular rash | 4 (33.3) | 0 |
| Cough | 3 (25.0) | 0 |
| Fatigue | 3 (25.0) | 0 |
| Nausea | 3 (25.0) | 0 |
| Pain in extremity | 3 (25.0) | 0 |

AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

# Results
## Efficacy

- Best overall response per Histiocyte Society criteria are reported in **Table 4** and **Figure 2**
- Patients did not progress, and the median progression-free survival was not reached in both studies **(Figure 3)**

**CDRB436A2102 (dabrafenib monotherapy)**

- The investigator-assessed objective response rate (ORR) was 76.9% (95% CI, 46.2%-95.0%) in patients receiving dabrafenib monotherapy

**CTMT212X2101 (dabrafenib plus trametinib)**

- The investigator-assessed ORR was 58.3% (95% CI, 27.7%- 84.8%) in patients taking dabrafenib plus trametinib

# Results

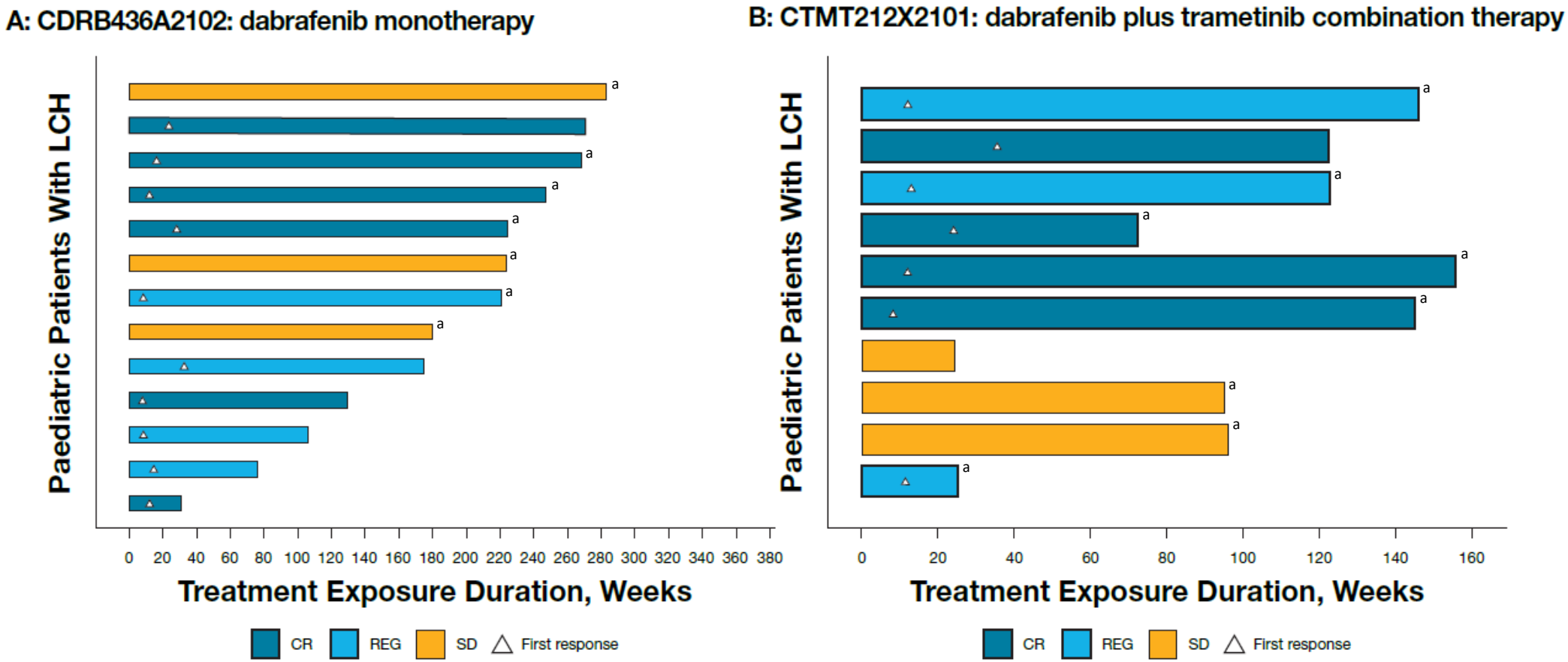
## Table 4. Efficacy by Investigator Assessment

| Category | CDRB436A2102 All LCH (n = 13) | CTMT212X2101 All LCH (n = 12) |
|---|---|---|
| **Best overall response, n (%)** | | |
| Complete resolution | 6 (46.2) | 4 (33.3) |
| Regressive disease | 4 (30.8) | 3 (25.0) |
| Stable disease | 3 (23.1) | 3 (25.0) |
| Progressive disease | 0 | 0 |
| Missing | 0 | 2 (16.7) |
| **Objective response rate (95% CI), %** | 76.9 (46.2-95.0) | 58.3 (27.7-84.8) |
| **Median duration of response (95% CI), months** | NR (11.1-NR) | NR (NR-NR) |
| 12-month rate (95% CI), % | 90 (40-100) | 100 (NR-NR) |
| 24-month rate (95% CI), % | 90 (40-100) | 100 (NR-NR) |
| **Median progression-free survival (95% CI), months** | NR | NR |
| 12-month rate (95% CI), % | 100 (NR-NR) | 100 (NR-NR) |
| 24-month rate (95% CI), % | 90 (50-100) | 100 (NR-NR) |

CI, confidence interval; LCH, Langerhans cell histiocytosis; NR, not reached.

# Results

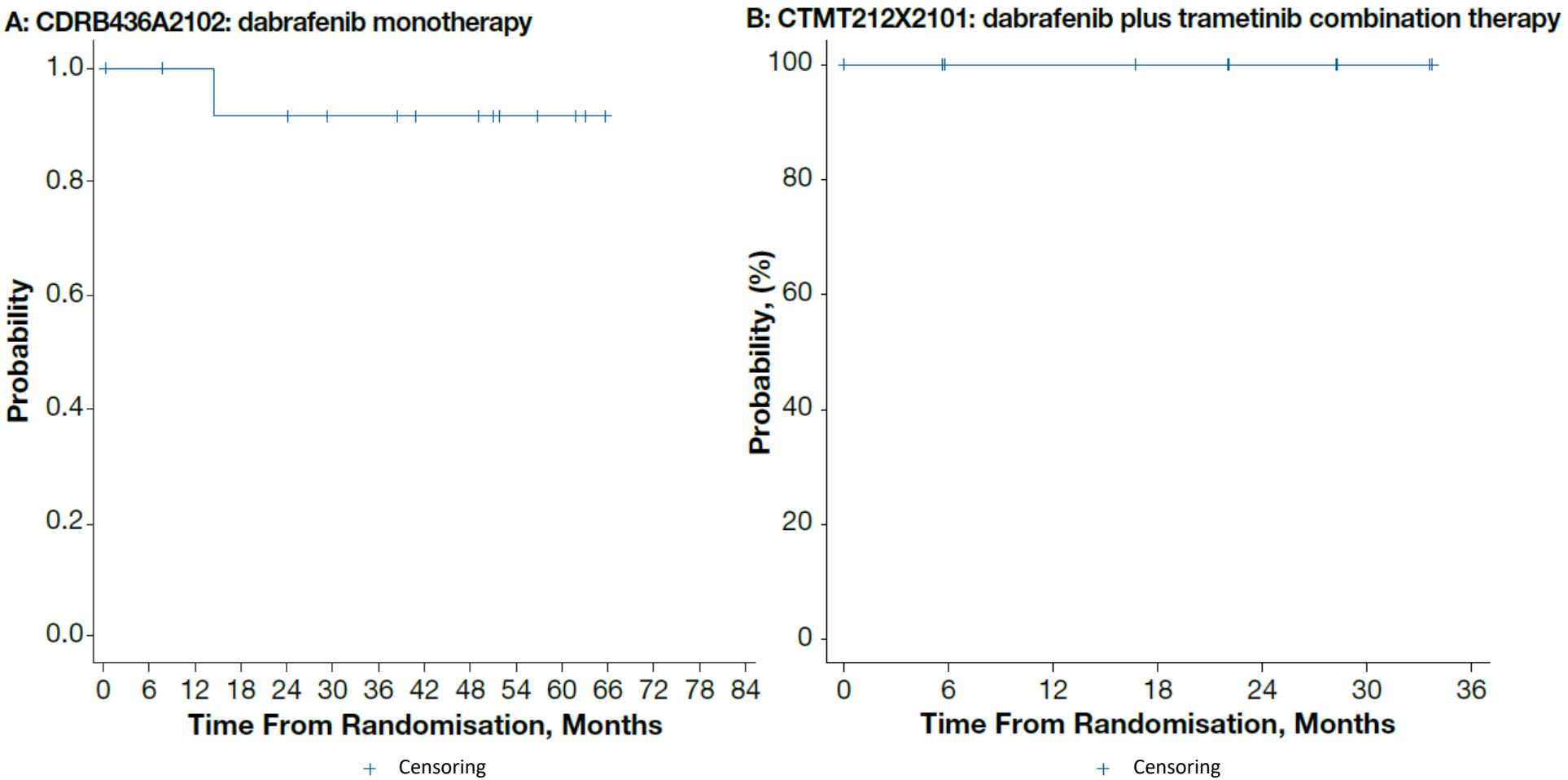
## Figure 2. Duration of Exposure to Study Treatment




CR, complete resolution; LCH, Langerhans cell histiocytosis; REG, regressive disease; SD, stable disease. [a] Patients who have continued therapy on a rollover study.

# Results

## Figure 3. Progression-Free Survival



# Key Findings & Conclusions

- In paediatric patients with relapsed/refractory *BRAF* V600E mutation–positive LCH, dabrafenib monotherapy and in combination with trametinib demonstrated frequent and durable efficacy
  - 90%-100% of patients had responses ongoing at 24 months, and 0 patients had disease progression
  - Response rates compared favourably with what has been seen with standard-of-care vinblastine plus prednisone[1]
- Treatment was associated with acceptable tolerability and had a manageable toxicity profile
  - AEs leading to treatment reduction, interruption, or discontinuation were relatively infrequent in both studies
- Safety profile was comparable with that observed in other paediatric[2,3] and adult[4,5] studies
  - Pyrexia was the most common AE reported, consistent with previous studies[2-5]
- This therapy is promising in paediatric patients with *BRAF* V600E mutation–positive LCH, a higher-risk form of LCH, and offers targeted therapy in this defined group of patients with LCH

1. Simko SJ, et al. Br J Haematol. 2015;169:299-301. 2. Hargrave DR, et al. Clin Cancer Res. 2019;25:7303-7311. 3. Kieran MW, et al. Clin Cancer Res. 2019;25:7294-7302. 4. Subbiah V, et al. J Clin Oncol. 2018;36:7-13. 5. Long GV, et al. N Engl J Med. 2014;371:1877-1888.

# Acknowledgments


- D.H. is supported by funding from the NIHR Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health
- We thank the patients and their families for their participation. We also thank the physicians, nurses, research coordinators, and other staff at each site who assisted with the study
- This study was sponsored by Novartis Pharmaceuticals Corporation. Editorial assistance was provided by Sivanjaa Manoj, PhD, from ArticulateScience, LLC, and was funded by Novartis Pharmaceuticals Corporation


# Disclosures

- James A. Whitlock reports consultancy for Sobi Pharmaceuticals, research funding from Novartis, and honoraria from Amgen and Jazz Pharmaceuticals