TAKE LIFE ON

REFIXIA® ONCE-WEEKLY

prophylaxis[1] giving your patients the confidence to live beyond haemophilia B[2–5]

27%

REFIXIA® ALLOWS FOR MORE AMBITIOUS PROPHYLAXIS, IN LINE WITH THE WFH GUIDELINES:[6]

mean trough FIX levels in adolescents and adults[4]

100%

REFIXIA® PROPHYLAXIS ALLOWS FOR AN ALMOST BLEED-FREE LIFE[4,7–10]

target joint declassification[3] with 0 median annualised spontaneous bleeds[3–5]

50%

REAL-WORLD EVIDENCE DEMONSTRATES

reduction in the mean-intra patient ABR after patients switched from SHL rFIX to Refixia®*,**[11,12]

Leopoldo, 61 years old, is an IT engineer and loves spending time sailing. Leopoldo lives with haemophilia B.

*The CBDR collects real-world data for patients with haemophilia.[11,12] Based on a retrospective study on CBDR patients with haemophilia B receiving prophylactic Refixia® for at least 6 months after switching from either rFIXFc or rFIX. Data set contains 5 patients under the age of 18[12]
**Significant reduction using a binomial regression model[12]

ABR, annualised bleed rate; CBDR, Canadian Bleeding Disorders Registry; FIX, factor IX; rFIX, recombinant factor IX; rFIXFc, recombinant factor IX-Fc fusion protein; SHL, standard half-life; WFH, World Federation of Hemophilia

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Prescribing Information

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CORRESPONDENCE

Clinical associations of *BRAF* and *MAP2K1* mutations in pediatric Langerhans cell histiocytosis: When 1 + 1 = 3

To the Editor:

With great interest, we have read the recent publication by Hélias-Rodzewicz and colleagues describing the molecular and clinicopathologic characterization of 415 children with histiocytoses included in the French national histiocytosis registry, including 366 with Langerhans cell histiocytosis (LCH).[1] Among LCH patients, the authors detected somatic $BRAF^{V600E}$ mutations in 184 cases, *MAP2K1* exon 2 or 3 mutations in 44 cases, *BRAF* exon 12 deletions in 26 cases, and *BRAF* exon 12 insertions in 8 cases. Because the groups of patients with *MAP2K1* or *BRAF* exon 12 alterations encompassed fewer than 50 patients each, the authors stated that the analysis of clinical correlations of these non-$BRAF^{V600E}$ mutations was limited. Although it is certainly possible to gain valuable insights from <50 patients, as illustrated by our recent collaborative study of 39 cases with ALK-positive histiocytosis,[2] we agree with the French authors that larger groups of patients are required to draw more definitive conclusions regarding the clinical impact of recurrent driver mutations beyond $BRAF^{V600E}$. Prior to publication of the study by Hélias-Rodzewicz et al, we reported the findings of an international clinicogenomic study of childhood LCH,[3] which did not involve French patients. We described detailed clinical characteristics and outcomes of 377 children with LCH, including 191 with $BRAF^{V600E}$, 54 with *MAP2K1* exon 2 or 3 mutations, 27 with *BRAF* exon 12 deletions, and 12 with *BRAF* exon 12 insertions. Combining our findings with those from the separate study by Hélias-Rodzewicz et al. provides us the unprecedented opportunity to explore the clinical features of >50 patients with *MAP2K1* mutations or *BRAF* exon 12 deletions — the second and third most common oncogenic drivers of pediatric LCH.[4]

Combining the two study cohorts yielded a virtual cohort of 743 children with LCH genotyped for at least $BRAF^{V600E}$. $BRAF^{V600E}$ was detected in 375/743 (50.5%) patients, with very similar frequencies in both studies (50.3%[1] vs. 50.7%[3]). Among patients without $BRAF^{V600E}$, *MAP2K1* exon 2 or 3 mutations were detected in 98 cases, *BRAF* exon 12 deletions in 53 cases, *BRAF* exon 12 insertions in 20 cases, and *BRAF* exon 15 mutations other than $BRAF^{V600E}$ in 14 cases (Tables S1–S3). As convincingly demonstrated previously,[1,3,5] $BRAF^{V600E}$ is strongly associated with multisystem disease (Figure 1A,B), particularly with involvement of risk organs (liver, spleen, and/or hematopoietic system). Yet, children with this severe disease presentation occasionally had alternative *BRAF* or *MAP2K1* alterations (Figure S1). In addition, $BRAF^{V600E}$ is strongly associated with skin involvement (Figure 1D). In contrast, *MAP2K1* mutations were associated with a higher incidence of bone involvement (Figure 1C), whereas *BRAF* exon 12 deletions appeared to correlate with more lung involvement (Figure 1E), substantiating our previous observations.[3] No significant differences in lymph node, pituitary, or (non-pituitary) central nervous system (CNS) involvement were observed (Figure 1F,G; Table S1), although this may be caused by a lack of power. Notably, 19/19 patients who developed neurodegenerative LCH had $BRAF^{V600E}$ (Table S1), underscoring the intimate relation between $BRAF^{V600E}$ and this devastating clinical condition.[6] Moreover, patients with $BRAF^{V600E}$ received second-line treatment and targeted therapy more frequently than patients with *BRAF* exon 12 or *MAP2K1* mutations (Table S1). However, these outcome data should be interpreted with caution, as we previously showed that this seems (primarily) driven by the association of $BRAF^{V600E}$ with disease extents known for high rates of progression or relapse, including multisystem LCH and single-system multifocal skin disease.[3]

In conclusion, by combining published data from two large cohort studies of pediatric LCH, we present a concise overview of the clinical impact of somatic *BRAF* or *MAP2K1* mutations on LCH presentation during childhood. Although the individual studies convincingly showed the frequency and clinical associations of $BRAF^{V600E}$, the combination of their results allowed a first look into the clinical presentation of >50 children with LCH harboring *BRAF* exon 12 deletions or *MAP2K1* mutations. In the setting of a rare disease like LCH, the combination of research data is often crucial and synergistic. Increasing international collaboration through the Histiocyte Society, the European Consortium for Histiocytosis (ECHO), and the North American Consortium for Histiocytosis (NACHO), as well as prospective molecular analysis of LCH lesions, will further advance our understanding of the pathogenesis of this clinically heterogeneous disorder.

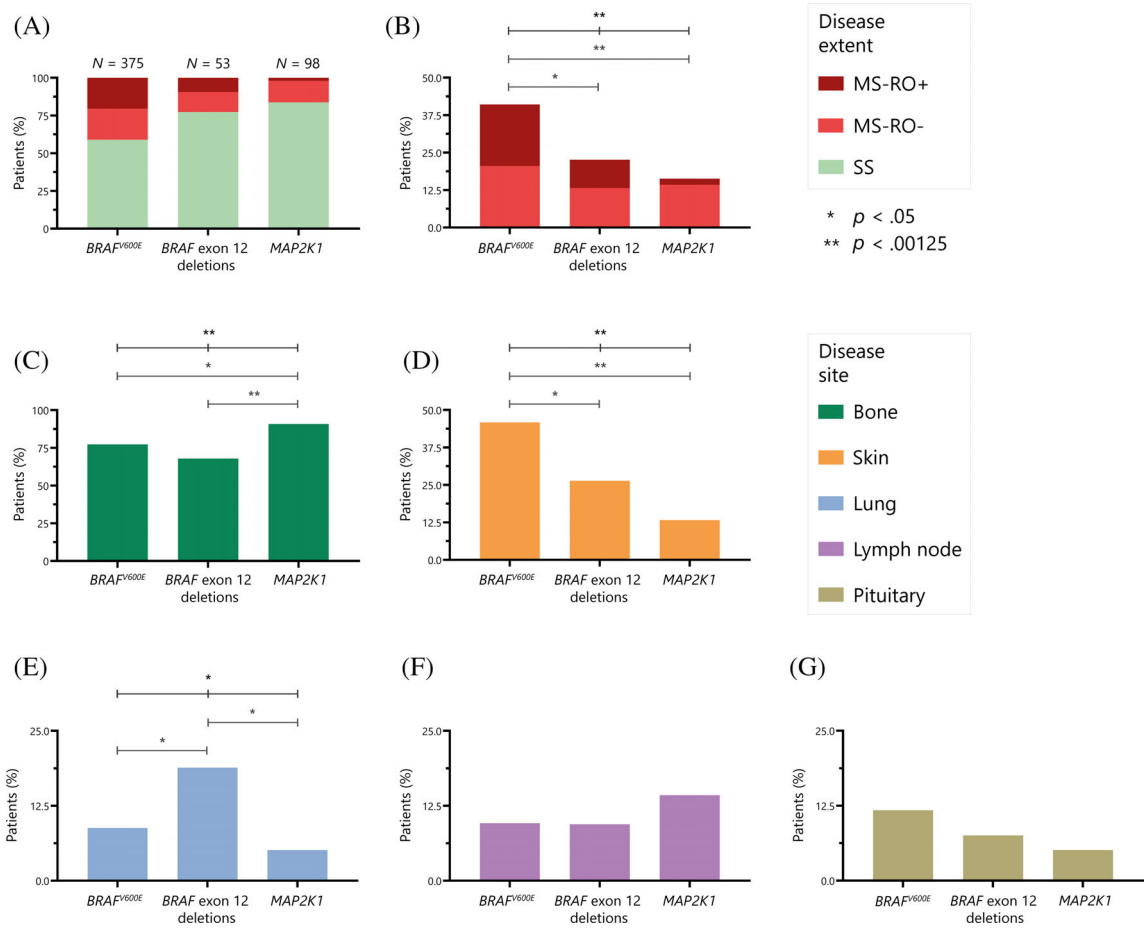

FIGURE 1 (A and B) Bar charts depicting the percentage of patients with *BRAF*^{V600E}, *BRAF* exon 12 deletions, or *MAP2K1* mutations having specific disease extents at LCH diagnosis. Statistical comparisons were performed for multisystem disease in panel B. (C–G) Bar charts depicting the percentage of patients with *BRAF*^{V600E}, *BRAF* exon 12 deletions, or *MAP2K1* mutations having specific disease sites at LCH diagnosis. Statistical tests with *p* values < .05 are depicted. Comparisons of proportions between three subgroups were done with the Fisher–Freeman–Halton exact test; comparisons of proportions between two subgroups were done with the Fisher's exact test. The numbers of patients are provided in Table S1. Precise *p* values are provided in Figure S2. Symbols: $^{**}p < .00125$; $^{*}p < .05$.

AUTHOR CONTRIBUTIONS

Paul G. Kemps analyzed the combined clinicogenomic data, prepared the figures and tables, and drafted the manuscript. Cor van den Bos and Astrid G. S. van Halteren were co-PI's of the original study by Kemps et al.[3] and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

Paul G. Kemps[1,2], Cor van den Bos[2,3], Astrid G. S. van Halteren[1,2,4] on behalf of the International Study Group[†]

[1]*Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands*

[2]*Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands*

[3]*Department of Pediatric Oncology, Emma Children's Hospital, Amsterdam University Medical Centers, Amsterdam, The Netherlands*

[4]*Department of Internal Medicine, Section Clinical Immunology, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands*

Correspondence
Astrid G. S. van Halteren, Department of Internal Medicine/Clinical Immunology, Erasmus Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.
Email: a.vanhalteren@erasmusmc.nl

[†]International LCH Study Group are listed in Appendix 1.

ORCID

Paul G. Kemps https://orcid.org/0000-0001-9793-7032
Cor van den Bos https://orcid.org/0000-0002-6175-6077
Astrid G. S. van Halteren https://orcid.org/0000-0002-0563-4155

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

APPENDIX 1

Timo C. E. Zondag, Helga B. Arnardóttir, Nienke Solleveld-Westerink, Jelske Borst, Eline C. Steenwijk, Demi van Egmond, Joost F. Swennenhuis, Ellen Stelloo, Irene Trambusti, Robert M. Verdijk, Carel J. M. van Noesel, Arjen H. G. Cleven, Marijn A. Scheijde-Vermeulen, Marco J. Koudijs, Lenka Krsková, Cynthia Hawkins, R. Maarten Egeler, Jesper Brok, Tatiana von Bahr Greenwood, Karel Svojgr, Auke Beishuizen, Jan A. M. van Laar, Ulrike Pötschger, Caroline Hutter, Elena Sieni, Milen Minkov, Oussama Abla, Tom van Wezel.