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Sarcomas

Histiocytic and Dendritic Cell Sarcomas of Hematopoietic Origin Share Targetable Genomic Alterations Distinct from Follicular Dendritic Cell Sarcoma

Lucas R. Massoth,[a,†] Yin P. Hung,[a,†] Judith A. Ferry,[a] Robert P. Hasserjian,[a] Valentina Nardi,[a] G. Petur Nielsen,[a] Sam Sadigh,[d] Vinayak Venkataraman,[b,c] Martin Selig,[a] Alison M. Friedmann,[b] Wesley Samore,[a] Jonathan Keith Killian,[e] Riza Milante,[f] Joseph Giessinger,[g] Kathleen Foley-Peres,[h] Chelsea Marcus,[e] Eric Severson,[e] Daniel Duncan,[e] Smruthy Sivakumar,[e] Jeffrey S. Ross,[e,i] Vikram Desphande,[a] Shakti H. Ramkissoon,[e,j] Jo-Anne Vergilio,[e] Abner Louissaint,[a] Lawrence R. Zukerberg,[a,‡] Erik A. Williams[e,k,‡]

Departments of [a]Pathology, [b]Pediatrics, and [c]Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA; [d]Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [e]Foundation Medicine, Inc., Cambridge, Massachusetts, USA; [f]Department of Dermatology, Jose R. Reyes Memorial Medical Center, Manila, Philippines; [g]A.T. Still University School of Osteopathic Medicine, Mesa, Arizona, USA; [h]Department of Biology, Bristol Community College, Fall River, Massachusetts, USA; [i]Department of Pathology, State University of New York Upstate Medical University, Syracuse, New York, USA; [j]Wake Forest Comprehensive Cancer Center and Department of Pathology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; [k]Department of Pathology, Department of Dermatology, UCSF Dermatopathology Service, University of California San Francisco, San Francisco, California, USA

[†]Contributed equally as co-first authors.

[‡]Contributed equally as co-senior authors.

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Malignant histiocytosis • Follicular dendritic cell sarcoma • Histiocytic sarcoma • Interdigitating dendritic cell sarcoma • Targeted therapy

Abstract

Background. Histiocytic and dendritic cell neoplasms are a diverse group of tumors arising from monocytic or dendritic cell lineage. Whereas the genomic features for Langerhans cell histiocytosis and Erdheim-Chester disease have been well described, other less common and often aggressive tumors in this broad category remain poorly characterized, and comparison studies across the World Health Organization diagnostic categories are lacking.

Methods. Tumor samples from a total of 102 patient cases within four major subtypes of malignant histiocytic and dendritic cell neoplasms, including 44 follicular dendritic cell sarcomas (FDCSs), 41 histiocytic sarcomas (HSs), 7 interdigitating dendritic cell sarcomas (IDCSs), and 10 Langerhans cell sarcomas (LCSs), underwent hybridization capture with analysis of up to 406 cancer-related genes.

Results. Among the entire cohort of 102 patients, *CDKN2A* mutations were most frequent across subtypes and made up 32% of cases, followed by *TP53* mutations (22%). Mitogen-activated protein kinase (MAPK) pathway mutations were present and enriched among the malignant histiocytosis (M) group (HS, IDCS, and LCS) but absent in FDCS (72% vs. 0%; $p < .0001$). In contrast, NF-κB pathway mutations were frequent in FDCSs but rare in M group histiocytoses (61% vs. 12%; $p < .0001$). Tumor mutational burden was significantly higher in M group histiocytoses as compared with FDCSs (median 4.0/Mb vs. 2.4/Mb; $p = .012$). We also describe a pediatric patient with recurrent secondary histiocytic sarcoma treated with targeted therapy and interrogated by molecular analysis to identify mechanisms of therapeutic resistance.

Conclusion. A total of 42 patient tumors (41%) harbored pathogenic mutations that were potentially targetable by approved and/or investigative therapies. Our findings highlight the potential value of molecular testing to enable precise tumor classification, identify candidate oncogenic drivers, and define personalized therapeutic options for patients with these aggressive tumors. ***The Oncologist*** 2021;26:e1263–e1272

Correspondence: Erik A. Williams, M.D., Foundation Medicine, Inc., 150 Second Street, Cambridge, Massachusetts 02141, USA. Telephone: 617-245-3403; e-mail: erwilliams@foundationmedicine.com Received December 31, 2020; accepted for publication March 16, 2021; published Online First on May 6, 2021. http://dx.doi.org/10.1002/onco.13801

Implications for Practice: This study presents comprehensive genomic profiling results on 102 patient cases within four major subtypes of malignant histiocytic and dendritic cell neoplasms, including 44 follicular dendritic cell sarcomas (FDCSs), 41 histiocytic sarcomas (HSs), 7 interdigitating dendritic cell sarcomas (IDCSs), and 10 Langerhans cell sarcomas (LCSs). MAPK pathway mutations were present and enriched among the malignant histiocytosis (M) group (HS, IDCS, and LCS) but absent in FDCSs. In contrast, NF-κB pathway mutations were frequent in FDCSs but rare in M group histiocytosis. A total of 42 patient tumors (41%) harbored pathogenic mutations that were potentially targetable by approved and/or investigative therapies.

Introduction

Histiocytic and dendritic cell neoplasms are a diverse group of tumors arising from the monocytic or dendritic cell lineage. They exhibit morphologic, phenotypic, and ultrastructural characteristics that parallel corresponding terminally differentiated hematopoietic cells, from which the World Health Organization (WHO) classification schema is derived [1]. These tumors arise de novo or following clonal evolution from another hematologic malignancy [1]. Although the genomic features for Langerhans cell histiocytosis and Erdheim-Chester disease have been well described [2–4], other less common and often aggressive tumors in this broad category remain poorly characterized, and comparison studies are lacking.

We present the molecular characteristics of 102 patient cases within the four major subtypes of malignant histiocytic and dendritic cell neoplasms: follicular dendritic cell sarcoma (FDCS), histiocytic sarcoma (HS), interdigitating dendritic cell sarcoma (IDCS), and Langerhans cell sarcoma (LCS). Our findings demonstrate that the malignant histiocytosis (M) group (HS, IDCS, and LCS, as proposed by Emile et al. [5]), featuring a common hematopoietic origin, share reliance on MAPK pathway alterations. This contrasts with the frequent NF-κB pathway alterations in FDCS, a tumor of mesenchymal origin. Collectively, nearly half of the M group malignant histiocytoses and FDCSs harbor genomic alterations that represent potential therapeutic targets.

Materials and Methods

Cohort and Genomic Analysis

We reviewed the Foundation Medicine, Inc. (Cambridge, MA), database cohort for specimens tested between January 2014 and December 2019. After review of submitted histology via hematoxylin and eosin digital slides by select authors (L.R.Z., J.A.F., R.P.H., Y.P.H., L.R.M., E.A.W.) and immunohistochemistry results from submitted pathology reports, we identified 88 patient tumors classified as FDCS, HS, IDCS, or LCS in accordance with the 2016 WHO classification [1].

Comprehensive genomic profiling (CGP) was performed in a Clinical Laboratory Improvement Amendments–certified, College of American Pathologists–accredited laboratory (Foundation Medicine, Inc.). Approval for this study, including a waiver of informed consent and a Health Insurance Portability and Accountability Act waiver of authorization, was obtained from Western Institutional Review Board (Protocol No. 20152817). Prior to nucleic acid extraction, hematoxylin and eosin–stained slides were reviewed to confirm the presence of tumor. DNA and RNA were extracted from 40-micron sections of formalin-fixed, paraffin-embedded tissue. CGP was performed using FoundationOne Heme (Foundation Medicine, Inc., Cambridge, MA), a clinical-grade, high-throughput, hybridization capture–based next-generation sequencing (NGS) assay that covers all exons of 406 genes with targeted RNA sequencing of 265 genes (supplemental online Table 1) [6–9]. Data were analyzed for genomic alterations including short variant alterations, copy number alterations, and gene rearrangements [6–9]. Tumor mutational burden (mutations/Mb) was determined based on 1.2 Mbp of sequenced DNA [8].

Additionally, 14 patient cases from the Massachusetts General Hospital (MGH) archives (9 HS, 2 IDCS, 3 LCS) from January 2007 to January 2021 underwent targeted DNA sequencing using MGH Heme SNaPshot Assays (V3 and V4; Thermo Fisher Scientific, Waltham, MA) that use ArcherDx platform (ArcherDx, Boulder, CO) and Illumina NextSeq (Illumina, San Diego, CA) to detect variants, insertion/deletions, and copy number alterations (supplemental online Table 2) [10]. Tumor histology and immunohistochemistry were reviewed in all 14 cases by select authors (L.R.Z., J.A.F., R.P.H., Y.P.H., L.R.M.). One patient with histiocytic sarcoma underwent serial biopsies and additional molecular testing, including the initial diagnostic specimen analyzed using MGH Solid Tumor SNaPshot [11], the first recurrence using the National Cancer Institute-Children's Oncology Group Pediatric MATCH Clinical trial [12], and the second recurrence using the hybrid-capture NGS panel OncoPanel POPv3 [13]. Approval for this portion of the study was obtained from Partners Institutional Review Board (Protocol No. 2011P001749). Human investigations were performed after approval by a local Human Investigations Committee and in accordance with an assurance filed with and approved by the Department of Health and Human Services, where appropriate.

Ultraviolet Mutational Signature

Ultraviolet (UV) mutational signature was evaluated in all samples containing at least 20 nondriver somatic missense alterations. Signatures were derived by analysis of the trinucleotide context and profiled using the Sanger COSMIC signatures of mutational processes in human cancer [14]. A positive signature was determined if a sample demonstrated at least 40% fit to a mutational process [14]. UV mutational signature is characterized by recurrent C > T and CC > TT base substitutions at dipyrimidine sites [15].

Results

Clinicopathologic and Molecular Characteristics

The combined cohorts of 102 patients included 44 FDCSs, 41 HSs, 7 IDCSs, and 10 LCSs (Fig. 1). Fifty-three (52%)

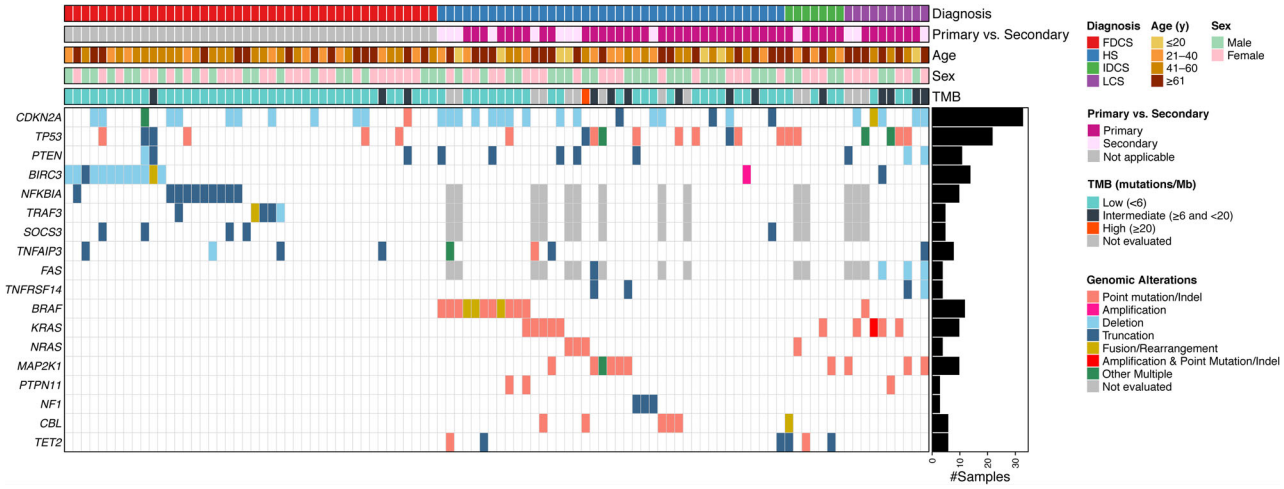


Figure 1. Clinicopathologic features and mutational landscape of histiocytic and dendritic cell sarcomas. Summary tile plot of pathogenic variants identified in FDCS, HS, IDCS, and LCS in 102 patients. Each column represents data (including age, sex, tumor type, and TMB) for an individual patient.
Abbreviations: FDCS, follicular dendritic cell sarcoma; HS, histiocytic sarcoma; IDCS, interdigitating dendritic cell sarcoma; LCS, Langerhans cell sarcoma; TMB, tumor mutation burden.

patients were women. The median age was 53 (range, <1 to >89) years. Sequenced tumor locations and CGP results are provided in supplemental online Table 3 and 4, respectively. Among the 58 patients with M group malignant histiocytoses (HS, IDCS, and LCS), 13 (22%) had a documented history of hematolymphoid neoplasm. Regarding the entire cohort of 102 patients, *CDKN2A* mutations were most frequent and were identified in 32% of cases, followed by *TP53* mutations (22%). MAPK pathway mutations were present and enriched among the M group histiocytoses but absent in FDCS (72% vs. 0%; $p < .0001$). In contrast, NF-κB pathway mutations were frequent in FDCSs but rare in M group histiocytoses (61% vs. 12%; $p < .0001$). The median tumor mutation burden (TMB) among 88 tested tumors was 3.2 mutations/Mb (range, 0–44; Q1–Q3, 1.6–5.7). TMB was significantly higher in M group histiocytoses as compared with FDCS (median 4.0/Mb vs. 2.4/Mb; $p = .0043$, Mann-Whitney *U* test). A total of 42 (41%) patient tumors harbored 51 pathogenic mutations at initial sequencing that were potentially targetable by approved and/or investigative therapies. These included mutations in *BRAF* ($n = 12$), *PTEN* ($n = 11$), *MAP2K1* ($n = 10$), *ATM* ($n = 4$), *NRAS* ($n = 4$), *NF1* ($n = 3$), *KIT* ($n = 3$), *BRCA2* ($n = 2$), *FGFR3* ($n = 1$), and *NTRK1* ($n = 1$).

Follicular Dendritic Cell Sarcoma

In the 44 patients (median age, 54; range, 22–77 years; 57% female) with FDCS, the most frequently mutated gene was *CDKN2A*, seen in 12 (27%) patients. *TP53* alterations were present in 6 (14%) patients. Alterations in the NF-κB signaling pathway were noted in 27 (61%) patients, including *BIRC3* in 12 (27%), *NFKBIA* in 10 (23%), *TRAF3* in 5 (11%), *SOCS3* in 4 (9%), and *TNFAIP3* in 4 (9%) patients. *CCND2* amplification was present in 4 (9%) cases, whereas alterations in *PTEN* were detected in 3 (7%). Fusions detected included *TYK2-ATPAF2*, *MAP3K1-GCOM1*, and *NTRK1-PDIA3* in one FDCS each. One patient (2%; case 4) had a reported history of Castleman disease. This tumor contained the *PDGFRB* p.N666S alteration, a recurrent mutation in unicentric hyaline vascular Castleman disease, along with *CDKN2A* loss and frameshift alteration of *ATM* [16].

Histiocytic Sarcoma

In the 41 patients (median age, 47; range, <1 to >89 years; 44% female) with HS, a history of lymphoid neoplasm was noted in 9 (22%) patients. *CDKN2A* (16 patients, 39%) and *TP53* (10 patients, 24%) were the most commonly altered genes. Mutations involving at least one gene in the MAPK pathway were identified in 29 (71%) patients, including five patients harboring more than one alteration. Recurrently mutated genes included *BRAF* in 11 (27%, including 4 canonical *BRAF* V600E mutations), *KRAS* in 5 (12%), *MAP2K1* in 6 (15%), *CBL* in 5 (12%), *NF1* in 3 (7%), *NRAS* in 3 (7%), and *PTPN11* in 2 (5%) patients. Additionally, *PTEN* alterations were noted in five (12%) patients with HS who also harbored MAPK pathway alterations. *PIK3CA* amplification was present in one HS without an MAPK-related alteration. Three (7%) patients had in-frame insertion/deletion (indel) of *CSF1R*, all of which co-occurred with MAPK pathway mutations. Fusions detected included *MYC-TRA* (confirmed by cytogenetics and fluorescence in situ hybridization [FISH]), *IGH-BCL2*, *IGH-BCL6*, *BRAF-MBP*, *BRAF-CLIP2*, and *BRAF-NRF1* in one HS each.

Langerhans Cell Sarcoma

In the 10 patients (median age, 62.5; range, 11–78 years; 70% female) with LCS, a history of lymphoma was documented in 3 (30%) patients. Mutations in *CDKN2A* and *TP53* were frequent, found in 5 (50%) and 4 (40%) patients, respectively, and appeared mutually exclusive of each other. Alterations in the MAPK pathway were noted in nine (90%) patients, including four with *KRAS* mutations. *BRAF* V600E mutation was present in one LCS. Three (30%) MAPK pathway–mutated LCSs harbored alterations in *PTEN*, and

an additional LCS contained an in-frame indel of *CSF1R*. *IGH-BCL2* fusion was present in one patient, while another contained *BCL2* rearrangement identified by FISH.

Interdigitating Dendritic Cell Sarcoma

Of the seven patients (median age, 51; range, 22–71 years; 43% female) with IDCS, one had a history of lymphoid neoplasm (B-lymphoblastic leukemia/lymphoma, B-ALL). Four (57%) IDCSs harbored mutations in the MAPK pathway, including *CBL-USP2* fusion in one tumor. One IDCS without MAPK pathway alterations contained a loss-of-function mutation in *FBXW7*, a negative regulator of mTOR signaling. Three (43%) IDCS also harbored mutations in *TET2*, which were rare among other tumor types (7% in HS, 0% in LCS, 0% in FDCS). Alterations in *CDKN2A* were absent in IDCS herein.

Of note, three patient tumors from the FMI database with submitted diagnoses of IDCS were excluded from this study, as these tumors were of visceral location and contained UV mutational signatures, suggesting that they represented metastatic spindle-cell melanoma rather than bona fide IDCS. UV mutational signature was absent in all remainder of patient tumors in which mutational signatures could be assessed.

Secondary Malignant Histiocytoses

Each of the 13 patients with M group histiocytoses and prior history of lymphoid neoplasm (Table 1) harbored genetic alterations that would be typical of the preceding lymphoid neoplasm. Additionally, all 13 secondary histiocytoses harbored mutations in the MAPK pathway, with 11 of the mutations being uncommon (<10% incidence) in their respective preceding lymphoid neoplasms. The remaining two patients both had a history of B-ALL and both harbored variants in *NRAS* in their malignant histiocytosis, a gene also frequently mutated in B-ALL [17]. Four patient cases underwent genetic testing that confirmed clonality with the preceding disease in all instances; in two, the preceding lymphoid neoplasm contained identical immunoglobulin heavy locus rearrangements to the secondary histiocytosis, although two others shared an identical genetic alteration in both neoplasms (Table 1). Lymphoma-like genetic alterations were not restricted to patients with a documented history of lymphoma. Of the 45 primary M group histiocytoses, 13 (29%) harbored genetic alterations in at least one the following genes that may be present in small B-cell lymphomas: *CREBBP*, *MYD88*, *TNFRSF14*, *TNFAIP3*, *KMT2D*, *ARID1A*, *SETD2*, *EP300*, *SOCS1*, *CARD11*, and/or *NFKBIA*.

Illustrative Patient with Recurrent Secondary Histiocytic Sarcoma Treated by Targeted Therapy

One patient (case 81) in the HS group demonstrated response to two sequential targeted therapies in the course of tumor evolution (Fig. 2). An 18-month-old boy with a history of *MYC*-rearranged T-acute lymphoblastic leukemia (T-ALL; Fig. 2A–2C) in remission presented with fevers and a rapidly enlarging right-sided cranial HS (Fig. 2D). Sequencing studies identified the presence of *BRAF* V600E mutation (allele fraction [AF] 30%) that was absent in the prior T-ALL by similar testing. *MYC* rearrangement was present by FISH, confirming clonality with his *MYC*-rearranged T-ALL (Fig. 2E). After tumor progression during a 5-day treatment of clofarabine and dexamethasone, the patient received MAPK-targeted therapy with oral dabrafenib and trametinib. Abrupt tumor regression was observed within 2–3 days, and the treatment was continued (aspects of this patient's initial care previously published) [18]. Partial tumor recurrence at 2 months led to craniotomy (recurrence 1; Fig. 2H–2K). Sequencing studies of the craniotomy specimen identified a pathogenic *MTOR* variant (p. T1977K; AF 8%) and persistence of *BRAF* V600E (AF 18%). Treatment by dabrafenib and trametinib was continued for 1 year after the resection, as the patient remained disease free. Fourteen months after the craniotomy and 2 months after cessation of dabrafenib and trametinib, a second recurrence was identified within the pleural cavity (recurrence 2; Fig. 2L–2O). Following poor response to reinstitution of MAPK-targeted therapy, molecular testing revealed a persistent *MTOR* mutation with increased AF (25%) and persistence of the *MYC* rearrangement was identified by FISH; *BRAF* V600E alteration was absent, confirmed by next-generation sequencing, polymerase chain reaction testing, and immunohistochemistry (Fig. 2O). mTOR-directed therapy (one dose of temsirolimus and daily oral sirolimus) led to marked improvement of symptoms and radiologic abnormalities (supplemental online Fig. 1). The patient was continued on sirolimus and alive with no symptoms and improved imaging studies at 9 months after recurrence 2 (23 months after initial HS).

Discussion

Our findings illustrated the genomic landscape of malignant histiocytic and dendritic cell neoplasms and identified potentially targetable mutations in 41% of patient cases. This study included a large number of patients affected by these rare tumors and compared the genetic findings across the WHO diagnostic categories of malignant histiocytic and dendritic cell neoplasms. HS, LCS, IDCS, and FDCS are all exceedingly rare, with limited data on optimal treatment. Localized disease is primarily managed by surgical resection, followed by adjuvant radiation and/or chemotherapy [19–22]. Patients with multifocal or multisystem disease often receive intensive chemotherapy regimens, with consideration of allogenic stem cell transplantation [19, 22, 23]. Although isolated nodal disease shows higher survival rates, median overall survival for FDCS after surgical intervention is approximately 3 to 4 years [21, 24]. Outcomes for HS and LCS are dismal, with a median survival of several months for those with disseminated disease [19, 21, 25–27]. The illustrative HS patient case identified a putative genetic event driving transdifferentiation and demonstrated the potential for improved outcomes with targeted therapy.

Malignant histiocytic and dendritic cell sarcomas differ from their benign phenotypic counterparts by the presence of malignant cytomorphology and more aggressive behavior [5]. As there are histologic similarities among tumor subtypes, immunohistochemistry plays a vital role in their classification (Table 2) [1]. In some patients, HS, IDCS, and LCS

Table 1. M group malignant histiocytoses secondary to preceding lymphoid neoplasms

Sequenced tumor diagnosis (case)	Age, yr (sex)	Reported prior malignancy	MAPK alteration	Identified mutations associated with prior malignancy	Mutations uncommon in prior malignancy	Confirmed clonality
Histiocytic sarcoma (69)	4 (M)	T-ALL	*KRAS*	*ARID1A, PTEN, CDKN2A, CDKN2B*		Prior not tested
Histiocytic sarcoma (47)	25 (M)	T-ALL	*BRAF*	*NOTCH1, PTEN, CDKN2A, CDKN2B*		Prior not tested
Histiocytic sarcoma (81)	1 (M)	T-ALL	*BRAF*	*MYC* (rearrangement), *CDKN2A*		Shared *MYC* rearrangement
Histiocytic sarcoma (57)	38 (M)	B-ALL	*NF1*	*SETD2, PAX5, CDKN2A, CDKN2B*		Prior not tested
Histiocytic sarcoma (85)	14 (M)	B-ALL	*NRAS*	*NRAS*[a]		Shared *NRAS* variant
Histiocytic sarcoma (80)	78 (F)	Diffuse large B-cell lymphoma	*BRAF*	*TNFAIP3, TET2, CARD11, CDKN2A, CXCR4*		Prior not tested
Histiocytic sarcoma (83)	70 (F)	Diffuse large B-cell lymphoma	*NRAS*	*CREBBP, EP300, STAT3, CDKN2A, PTEN*	*CUX1*[b]	Prior not tested
Histiocytic sarcoma (60)	62 (F)	Follicular lymphoma	*BRAF*	*IGH/BCL2* (rearrangement), *CREBBP, KMT2D, ARID1A*	*PTEN, SMARCA4, CDKN2A, CDKN2B, ASXL2, DNMT3A*	Shared clonal IgH rearrangement
Histiocytic sarcoma (78)	66 (F)	Follicular lymphoma	*KRAS*	*TNFAIP3*	*DNMT3A, CEBPA*	Prior not tested
Interdigitating dendritic cell sarcoma (92)	22 (M)	B-ALL	*NRAS*	*NRAS*,[a] *TP53*		Shared clonal IgH rearrangement
Langerhans cell sarcoma (99)	66 (F)	B-cell lymphoma (NOS)	*MAP2K1*	*IGH/BCL2* (rearrangement), *CARD11, SF3B1, TNFAIP3, HIST1HD, TNFRSF14, FAS*	*CDKN2A, CDKN2B, PTEN*	Prior not tested
Langerhans cell sarcoma (100)	71 (F)	Small B-cell lymphoma[c]	*KRAS*	*CREBBP, KLF2, KMT2D*	*CDKN2A, FBXW7*	Prior not tested
Langerhans cell sarcoma (102)	65 (F)	Follicular lymphoma	*MAP2K1*	*KMT2D, CARD11, CREBBP, BCL2* (rearrangement)	*PTEN*	Prior not tested

Variants of undetermined significance are not shown.
[a]*NRAS* gain-of-function mutations are common in B-ALL.
[b]*CUX1* loss; diffuse large B-cell lymphoma may show *CUX1* gain of copy alterations.
[c]The patient's submitted history was lymphoplasmacytic lymphoma; however, the presence of a *KLF2* mutation and absence of *MYD88* mutation in the patient's LCS would favor a preceding splenic marginal zone lymphoma.
Abbreviations: B-ALL, B-lymphoblastic leukemia/lymphoma; F, female; M, male; T-ALL, T-acute lymphoblastic leukemia.

can share morphologic and immunophenotypic overlap, rendering precise classification challenging. Tumors with hybrid histomorphology or showing changes on subsequent biopsies that, in isolation, would be classified differently from the original tumor have been documented [28–32].

A recently revised classification schema for histiocytic and dendritic cell neoplasms addresses some of the diagnostic challenges aforementioned by grouping HS, LCS, and IDCS together as M group histiocytoses with additional subclassifiers [5]. Our molecular findings offer support for such classification, as HS, LCS, and IDCS harbor similar alterations with recurrent alterations in the MAPK pathway and frequent *CDKN2A* and *TP53* mutations. Although MAPK pathway alterations are prevalent in M group histiocytoses and other more indolent histiocytic entities (including Langerhans cell histiocytosis, Erdheim-Chester disease, and Rosai-Dorfman disease/sinus histiocytosis with massive lymphadenopathy) [4, 33–38], mutations in *CDKN2A* and *TP53* appear rare in the latter group [34] and may help account for the more aggressive clinicopathologic features in M group histiocytoses.

This study demonstrates that FDCS harbors frequent alterations in the NF-κB pathway, consistent with prior studies [39, 40], and genetically appears distinct from the M group histiocytoses. Although normal follicular dendritic cells play an integral role in hematolymphoid tissues, they arise from a mesenchymal stem cell precursor, in contrast to a common hematopoietic/myeloid progenitor among other macrophage/dendritic cell lineages [41–44]. In FDCS, mutations in *BIRC3*,

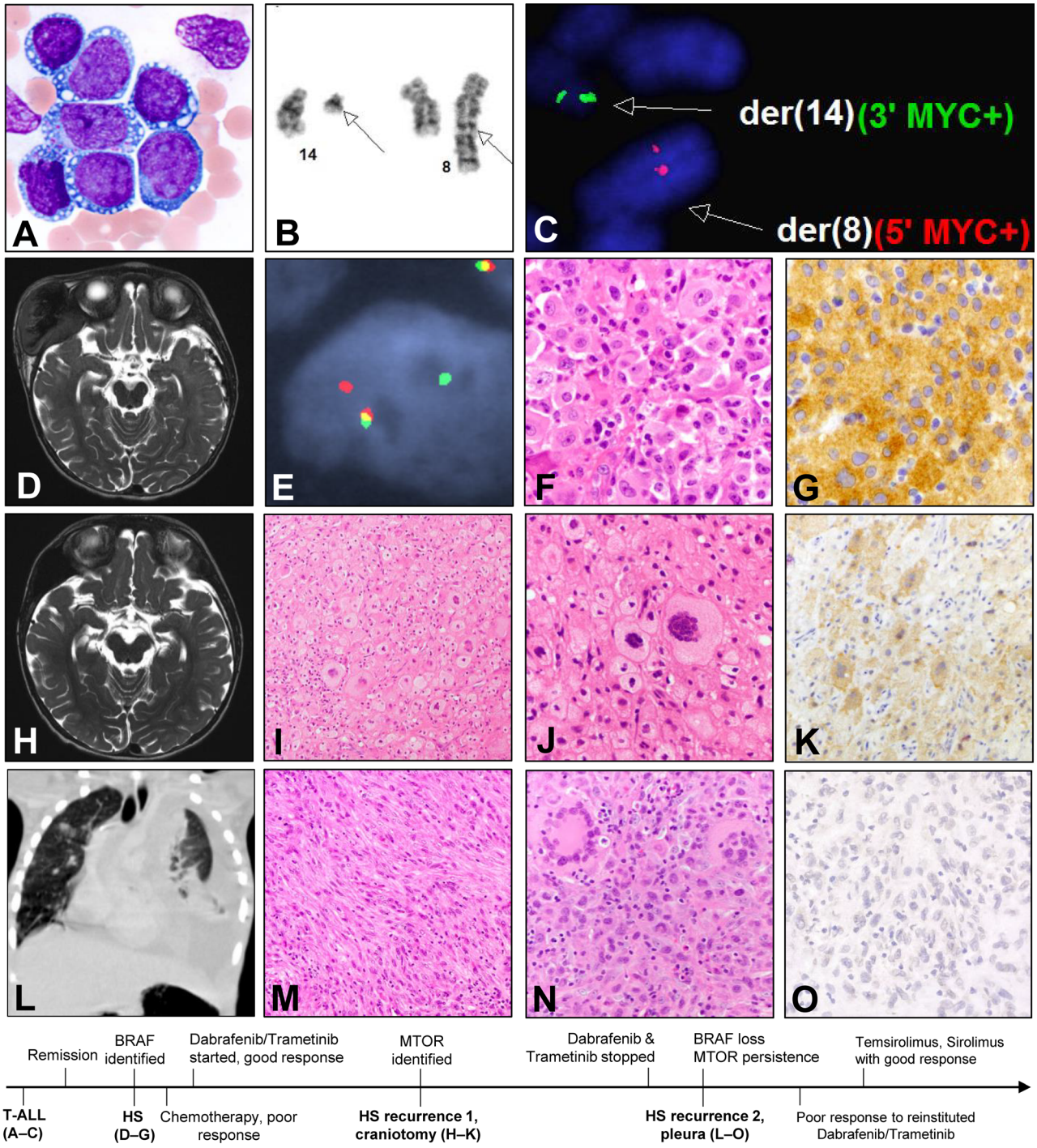
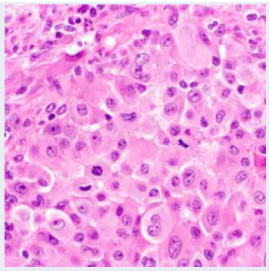
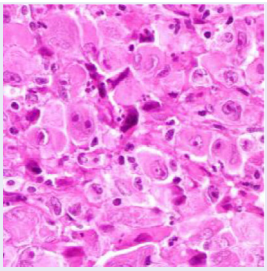
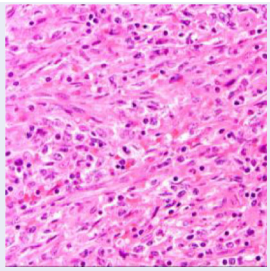
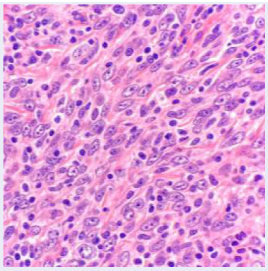
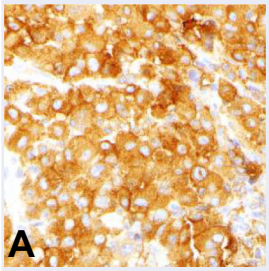
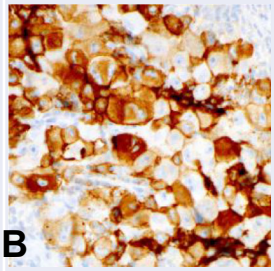
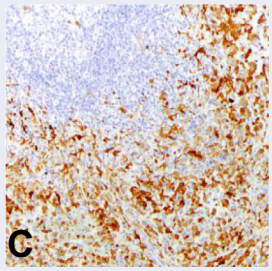
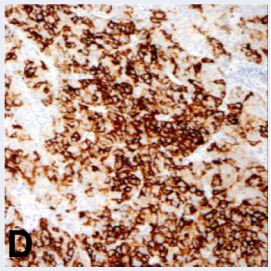
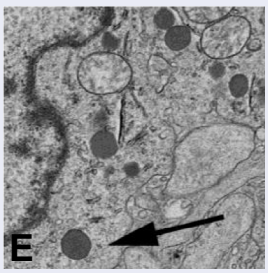
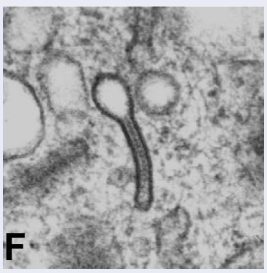
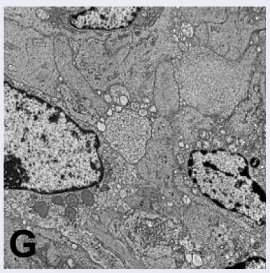
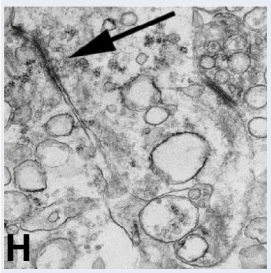


Figure 2. Illustrative patient case of secondary histiocytic sarcoma after T-ALL. The patient's initial T-ALL is characterized histologically by cytoplasmic vacuolization **(A)** and cytogenetically by t(8;14)(q24;q11) **(B)**, indicative of *TRA/MYC* rearrangement as confirmed by *MYC* fluorescence in situ hybridization (FISH) **(C)**. Magnetic resonance imaging (MRI) at initial diagnosis of histiocytic sarcoma shows a large mass destroying right temporal skull with intracranial extension **(D)**. This histiocytic sarcoma harbors *MYC* rearrangement as confirmed by *MYC* FISH **(E)**. Histopathologic examination shows large discohesive histiocytic cells with abundant eosinophilic cytoplasm **(F)**. Immunohistochemistry (IHC) for *BRAF* V600E is strongly positive **(G)**. MRI at recurrence 1 **(H)** shows partial regrowth that is amenable to surgical resection. The resected tumor displays extensive foamy changes, smaller nuclei, condensed chromatin, and multinucleated giant cell forms, with an appearance reminiscent of Erdheim-Chester disease **(I, J)**. *BRAF* V600E expression by IHC is reduced **(K)**. Chest computed tomography at recurrence 2 shows marked consolidation of the left pleural cavity **(L)**. Histopathologic examination shows prominent spindled morphology **(M)** and frequent multinucleated giant cells **(N)**. IHC for *BRAF* V600E at recurrence 2 is negative **(O)**. The history timeline below is not drawn to scale.
Abbreviations: HS, histiocytic sarcoma; T-ALL, T-acute lymphoblastic leukemia.

Table 2. Pathologic characteristics of M group malignant histiocytoses and follicular dendritic cell sarcoma

	"M" group malignant histiocytoses			Follicular dendritic cell sarcoma
Subtype	**Histiocytic sarcoma**	**Langerhans Cell sarcoma**	**Interdigitating dendritic cell sarcoma**	**(no subtype)**
Usual Cell Morphology	Epithelioid	Epitheloid	Spindled to ovoid	Spindled to epithelioid
				
IHC	"M" group: Variable staining of CD45, CD68, CD163, Lysozyme, PU.1, CD4			
	CD68, CD163 (A) or lysozyme required; S100 usually not prominent, CD1a & Langerin negative	CD1a (B) & Langerin (at least one); S100	S100 (C) prominent/diffuse; Langerin & CD1a negative	CD21, CD23 (D) & CD35 (at least one); D2-40
				
EM	Lysosomes (E, arrow); lack Birbeck granules & cellular junctions	Birbeck granules (F)	Complex interdigitating cell processes (G)	Cytoplasmic processes with scattered desmosome-like junctions (H, arrow)
				
Common Molecular Findings	*TP53* or *CDKN2A* alterations, MAPK pathway alterations; less frequent PI3K/AKT/MTOR pathway alterations			*TP53* or *CDKN2A* alterations, NF-kB pathway alterations

Abbreviations: IHC, immunohistochemistry; EM, electron microscopy; M group, malignant histiocytosis group.

NFKBIA, and *TRAF3* often occurred exclusive of one another. Alterations in the NF-κB regulatory gene *CYLD* have been described in FDCS [39, 40] but were not examined in this study. Although *BRAF* V600E mutations have been rarely reported in FDCS [45], no recurrent alterations in MAPK pathway genes were identified in this large cohort. One FDCS patient case with a history of Castleman disease demonstrated *PDGFRB* N666S, a recurrent mutation in hyaline vascular Castleman disease [16]. To our knowledge, this is the first description of this variant in FDCS following Castleman disease.

Frequent alterations in the MAPK pathway were identified in the M group histiocytoses, consistent with recent reports on the molecular features of HS [13, 46, 47]. We identified activating mutations in the PI3K/AKT/mTOR pathway in six (15%) HSs, one (14%) IDCS, and three (30%) LCSs; these alterations were described in a subset of HS [13] and often co-occurred with mutations in the MAPK pathway. In-frame indels of *CSF1R*, a recurrent mutation in histiocytic neoplasms [4, 27], were present in four M group histiocytoses (3 HSs and 1 LCS; 9% of the 44 tumors with *CSF1R* coverage). They co-occurred with MAPK alterations and appeared exclusive of PI3K/AKT/mTOR pathway alterations. *CSF1R* encodes the receptor tyrosine kinase CSF-1R, a regulator of both the PI3K/AKT/mTOR and MAPK pathways. Activating *CSF1R* mutations in histiocytic neoplasms have also been shown to lead to ERK1/2 phosphorylation and augment MAPK pathway activity [4].

Mutations in *PTPN11* ($n = 2$) or *NF1* ($n = 3$) were noted in five (12%) patients with HS, with four representing primary HS. One study of primary HS showed predilection for the gastrointestinal tract in *PTPN11*- and/or *NF1*-mutated tumors and frequent *SETD2* alterations [46]. Only one (25%) such present case involved the abdomen; however, the possibility of subsequent gastrointestinal involvement cannot be excluded owing to limited follow-up. In two patients with primary HS affecting the central nervous system, both contained *PTPN11* alterations that co-occurred with other mutations in the MAPK pathway aside from *NF1*. Although the *NF1*-mutated secondary HS had a *SETD2* alteration, the four primary HS cases lacked *SETD2* mutations.

Both LCS and IDCS are rare and poorly characterized. Mutations in the MAPK pathway, as reported in case reports, were identified in a subset of tumors herein [48–54]. Our findings also highlight the diagnostic challenge of IDCS and its distinction from spindle-cell melanoma, given their histologic and immunophenotypic overlap [55]. In difficult cases, analysis of mutation signature by NGS may be helpful in distinguishing metastatic melanoma from IDCS.

We explored the molecular mechanisms of the so-called "transdifferentiation" phenomenon, in which the histiocytic/dendritic cell tumor arises from a shared progenitor or a subclone of a preceding/concurrent hematologic neoplasm [50, 53, 56–58]. Secondary M-type histiocytoses harbored mutations that would be expected in the preceding lymphoid neoplasms, along with additional MAPK alterations that would be unusual for the preceding disease. In the illustrative HS patient case, acquisition of *BRAF* V600E mutation coincided with transformation from T-ALL to histiocytic sarcoma. We also noted a second *BRAF* V600E-mutated HS following T-ALL likely arising in a similar fashion herein. Although some reports similarly show the absence of MAPK alterations in clonally related malignancies, others have noted their presence in the preceding neoplasms [47, 50, 59]. Similarly, we confirmed the presence of an *NRAS* mutation within the preceding B-ALL of one secondary histiocytic sarcoma. Transdifferentiation may require multiple genetic events, with the number and sequence depending on the genomic state of the preceding neoplastic clone. Alterations in *CDKN2A* and *TP53* have been implicated in the transformation of both follicular lymphoma and chronic lymphocytic leukemia into diffuse large B-cell lymphoma [60, 61]; we hypothesize that temporally acquired mutations of the MAPK pathway may play a role in the diversion to histiocytic phenotype instead. Consistent with other descriptions [13], mutations seen in small B-cell lymphomas could be identified in a subset of primary histiocytic and dendritic cell malignancies without a documented history of lymphoid neoplasm.

Our detailed clinical, histologic, and comprehensive molecular analysis of one pediatric patient with HS [18] demonstrated the potential for targeted therapy and uncovered genetic alterations that account for therapeutic resistance. The first HS recurrence coincided with the identification of a pathogenic *MTOR* mutation, followed by loss of *BRAF* V600E mutation in the second recurrence when it was unresponsive to MAPK-directed therapy. Although NGS testing of the T-ALL lacked *MTOR* coverage, *MTOR* gene mutations are rare in T-ALL but have been described in HS; it is likely a small *MTOR*-mutant subclone was selected for during targeted therapy [13]. Initiation of mTOR-directed therapy led to prompt regression of this second recurrence, indicating reliance on aberrant mTOR signaling. The presence of frequent aberrations in both the MAPK and PI3K/AKT/mTOR pathway in a subset of M group histiocytoses (including the aforementioned patient) suggests that combination therapies to target these pathways may be valuable. Overall, the identification of targetable alterations in 41% of malignant histiocytic and dendritic cell tumors highlights the value of genomic profiling to identify potential targets in these rare aggressive tumors.

Limitations of this study include the possibility of incomplete medical history/follow-up from the pathology reports in the FMI cohort. For example, one patient with HS with no documented history of lymphoid neoplasm contained an *IGH-BCL6* fusion, which may have arisen from a subclinical B-cell lymphoma of germinal center origin. Additionally, immunohistochemistry results in the FMI cohort were available by pathology report only, and the database itself is enriched for aggressive and/or advanced diseases in which genetic testing is desired for targeted therapy.

Conclusion

We described the genomic features of a large cohort of malignant histiocytic and dendritic cell sarcomas, with identification of frequent alterations in the MAPK pathway among M group malignant histiocytoses (HS, IDCS, and LCS), alterations in the NF-κB pathway in FDCS, and mutations in *CDKN2A* and *TP53* in a subset of both. Our findings highlight the potential value of molecular testing to identify oncogenic drivers and treatment targets and define personalized therapeutic options for patients with these rare aggressive tumors.

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Author Contributions

Conception/design: Lucas R. Massoth, Erik A. Williams

Provision of study material or patients: Lucas R. Massoth, Yin P. Hung, Judith A. Ferry, Robert P. Hasserjian, Valentina Nardi, Jeffrey S. Ross, Shakti H. Ramkissoon, Jo-Anne Vergilio, Abner Louissaint, Lawrence R. Zukerberg, Erik A. Williams

Collection and/or assembly of data: Lucas R. Massoth, Yin P. Hung, Judith A. Ferry, Robert P. Hasserjian, Valentina Nardi, Martin Selig, Jonathan Keith Killian, Chelsea Marcus, Eric Severson, Daniel Duncan, Smruthy Sivakumar, Jeffrey S. Ross, Shakti H. Ramkissoon, Jo-Anne Vergilio, Abner Louissaint, Lawrence R. Zukerberg, Erik A. Williams

Data analysis and interpretation: Lucas R. Massoth, Yin P. Hung, Judith A. Ferry, Robert P. Hasserjian, Valentina Nardi, G. Petur Nielsen, Sam Sadigh, Vinayak Venkataraman, Martin Selig, Alison M. Friedmann, Wesley Samore, Jonathan Keith Killian, Riza Milante, Joseph Giessinger, Kathleen Foley-Peres, Chelsea Marcus, Eric Severson, Daniel Duncan, Julia A. Elvin, Smruthy Sivakumar, Jeffrey S. Ross, Vikram Desphande, Shakti H. Ramkissoon, Jo-Anne Vergilio, Abner Louissaint, Lawrence R. Zukerberg, Erik A. Williams

Manuscript writing: Lucas R. Massoth, Yin P. Hung, Judith A. Ferry, Robert P. Hasserjian, Valentina Nardi, G. Petur Nielsen, Sam Sadigh, Vinayak Venkataraman, Martin Selig, Alison M. Friedmann, Wesley Samore, Jonathan Keith Killian, Riza Milante, Joseph Giessinger, Kathleen Foley-Peres, Chelsea Marcus, Eric Severson, Daniel Duncan, Julia A. Elvin, Smruthy Sivakumar, Jeffrey S. Ross, Vikram Desphande, Shakti H. Ramkissoon, Jo-Anne Vergilio, Abner Louissaint, Lawrence R Zukerberg, Erik A. Williams

Final approval of manuscript: Lucas R. Massoth, Yin P. Hung, Judith A. Ferry, Robert P. Hasserjian, Valentina Nardi, G. Petur Nielsen, Sam Sadigh, Vinayak Venkataraman, Martin Selig, Alison M. Friedmann, Wesley Samore, Jonathan Keith Killian, Riza Milante, Joseph Giessinger, Kathleen Foley-Peres, Chelsea Marcus, Eric Severson, Daniel Duncan, Julia A. Elvin, Smruthy Sivakumar, Jeffrey S. Ross, Vikram Desphande, Shakti H. Ramkissoon, Jo-Anne Vergilio, Abner Louissaint, Lawrence R. Zukerberg, Erik A. Williams

Disclosures

Jonathan Keith Killian: Foundation Medicine, Inc. (E), Foundation Medicine, Inc., Roche (OI); **Chelsea Marcus:** Foundation Medicine, Inc. (E), Foundation Medicine, Inc., Roche (OI); **Eric Severson:** Foundation Medicine, Inc. (E), Foundation Medicine, Inc., Roche (OI); **Daniel Duncan:** Foundation Medicine, Inc. (E), Foundation Medicine, Inc., Roche (OI); **Smruthy Sivakumar:** Foundation Medicine, Inc. (E), Foundation Medicine, Inc., Roche (OI); **Jeffrey S. Ross:** Foundation Medicine, Inc. (E), Foundation Medicine, Inc., Roche (OI); **Shakti H. Ramkissoon:** Foundation Medicine, Inc. (E), Foundation Medicine, Inc., Roche (OI); **Jo-Anne Vergilio:** Foundation Medicine, Inc. (E), Foundation Medicine, Inc., Roche (OI); **Erik A. Williams:** Foundation Medicine, Inc. (E), Foundation Medicine, Inc., Roche (OI).

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