History of Erdheim Chester Disease 4/15/2024

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Erdheim Chester Disease

non-Langerhans histiocytosis

History

- First described in 1930 as “lipoid granulomatosis” by Jakob Erdheim and his student William Chester
- Multisystem disorder with common involvement of the long bones
- Inflammatory vs neoplastic process? Now we know…

Epidemiology

- Rare ~ 1000 cases reported but increasingly recognized
- M>F predominance
- Mean age of onset 55 (40-70 yrs)

Image: http://static-content.springer.com

Jakob Erdheim
M.D

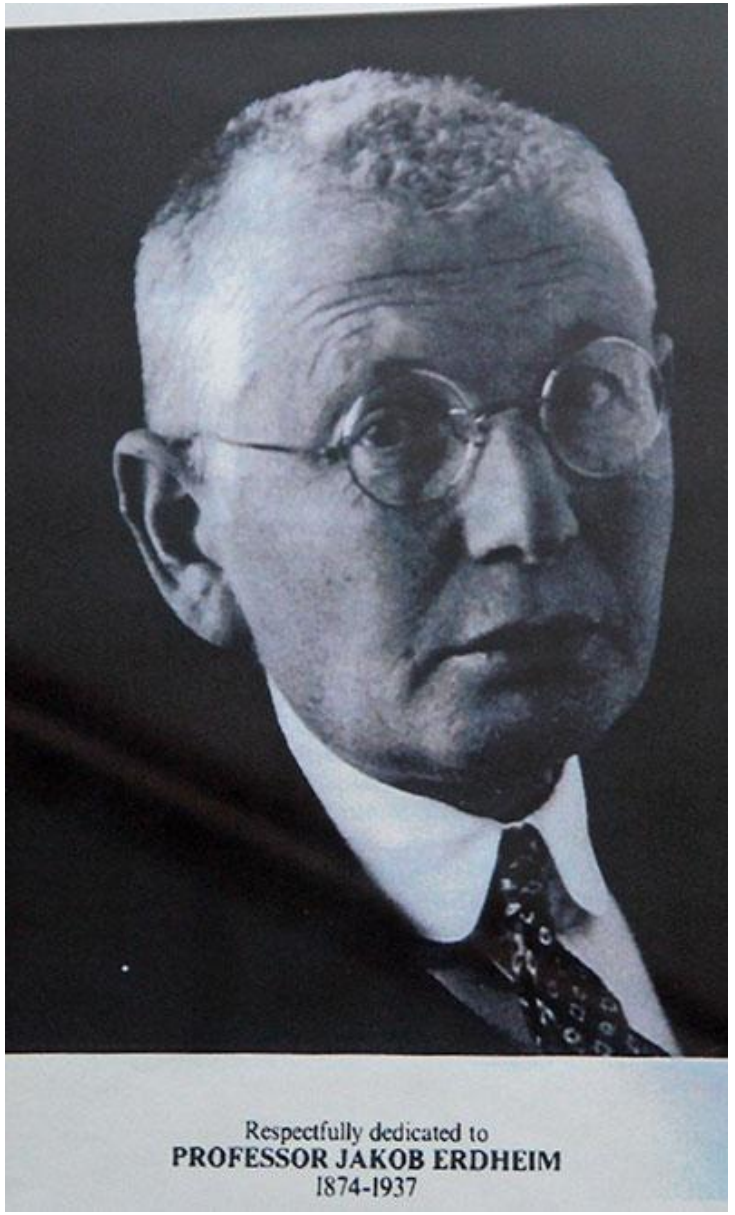
Jakob Erdheim, 1874-1937

- Born in Boryslaw, Galicia, (now part of Ukraine)
- Graduated from the University of Vienna medical school in 1900
- Began career at Pathological-Anatomical Institute of the Vienna General Hospital
- In 1923 he was appointed Chief of the Institute where he worked his entire career
- He perfomed over 2500 autopsies
- Famous as the premier pathologist in Vienna, training over 80 students, including Harvard endocrinologist Fuller Albright
- Known for his research of hyperparathyroidism, acromegaly, Paget’s disease and pituitary gland abnormalities
- Erdheim tumor: a synonym for craniopharyngioma
- Erdheim's syndrome, also known as "Scaglietti-Dagnini syndrome" (cervical spondylosis secondary to acromegaly)
- Erdheim disease: a synonym for cystic medial necrosis
- In 1929 he mentored William Chester, a 26 yo recent MD graduate from NY University

"Erdheim's students were fortunate: Their careers often flourished as a result of Erdheim's generosity. Their names appeared as senior author on papers published in scientific journals, even though Erdheim himself wrote every word of these papers, including the legends for the accompanying illustrations. Anyone reading publications issuing from Erdheim's laboratory could tell that they were not the work of a novice, yet Erdheim was cited only inconspicuously as the director of the institute where the work was done and never as senior scientist."

Romm S. Jakob Erdheim. Eminent pathologist of Vienna.
Am J Dermatopathol. 9(5) 447-450, 1987


MedLink Neurology ♦ www.medlink.com


Respectfully dedicated to
PROFESSOR JAKOB ERDHEIM
1874-1937

Jakob Erdheim photographed at the entrance of the Pathological Institute in Vienna. The Jakob-Erdheim Institute of Pathology and Clinical Bacteriology at the present time

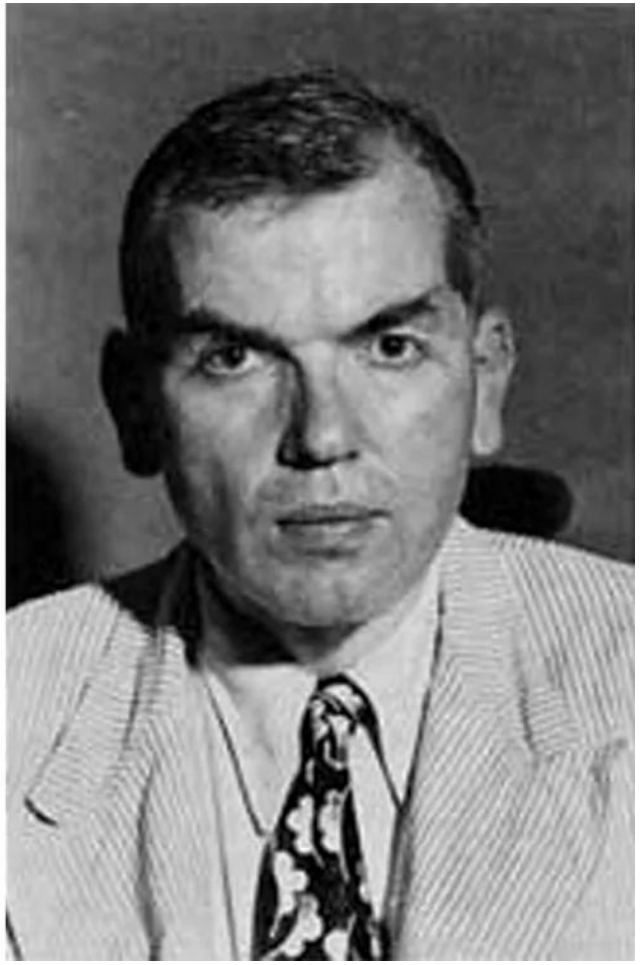
Pascual EM, et al. Virchows Arch (2015) 467:459–469DOI 10.1007/s00428-015-1798-4

The latest anatomical discovery: the parathyroid glands or Glandulae parathyreoideae of Owen-Sandström-Gley

Carlos Ortiz-Hidalgo: Cir Cir. 2022;90(1):140-149. doi: 10.24875/CIRU.20001307.

Jakob Erdheim (1874-1937)

Félix Mandl (1892-1957)



Fuller Albright (1900-1969)

William Chester, MD, 1903-1974

- Parents were Anna Rifkin and Jacob Hasanovich, Jewish immigrants in the late 1800s from the region of Minsk, the capital of Belorussia. As was commonly the practice at the time, Mr. Hasanovich, then 20 years old, changed his last name upon arrival at Ellis Island to the more “American” sounding “Chester.”
- Born in New York City in 1903
- MD from New York University in 1927
- Intern at Mt Sinai Hospital 1928
- Fellowships in Berlin and Vienna 1928-1930
- In Vienna in 1929 he worked with Jakob Erdheim at the Pathological Institute of the University of Vienna.
- Findings were published in 1930
- Internal medicine resident at Montefiore 1931-32, Pathology 1932-35
- Private practice in internal medicine and cardiology in Mamaroneck NY
- Positions included Director of Medicine and Cardiology at United Hospital, Port Chester NY, President of Westchester Heart Association

Rush, WL:WILLIAM CHESTER, M.D., 1903–1974. Dermatopathology: Practical & Conceptual. Jul – Sep 2001 | Vol. 7, No. 3.

Publications of William Chester, MD

- 1.Chester W: Uber Lipogranulomatose. Virchows Arch Pathol Anat 279: 561-602, 1930.
- 2.Chester W, Kugel: Lipoid granulomatosis (Type, Hand-Schuller-Christian). Arch Path, vol 14, no. 5, pp. 595-612, Nov 1932
- 3.Chester W: The Trachea in non-syphilitic disease of the ascending aorta and the aortic arch. Am J Roent. 28: 796-800, Dec 1932
- 4.Chester W: Multiples Myelom und Hypoproteinmie. Zeitschr f. Klin Med 124: 466-477, 1933
- 5.Chester W, and Miller HR: Studies in Oscillometric pressure. Am Heart J 8: 388-399, Feb 1933
- 6.Chester W, and Spiegel L: Hereditary Diabetes Insipidus. JAMA 100: 806-809, March 18, 1933
- 7.Chester W, and Schwartz SP: Cutaneous lesions in rheumatic fever. Am J Dis Child 48: 69-80, July 1934
- 8.Chester W: Patent ductus botalli with subacute bacterial endocarditis and recovery. Am Heart J, 13: 492-4, April, 1937
- 9.Melamed S, and Chester W: Osseus form of Gaucher's disease. Arch Int Med, 61: 798-807, May 1938
- 10.Chester W, and Chester EM: The vertebral column in acromegaly. Am J Roent. 44: 552-557, Oct 1940

VIRCHOWS ARCHIV
FÜR
PATHOLOGISCHE ANATOMIE
UND PHYSIOLOGIE
UND
FÜR KLINISCHE MEDIZIN

HERAUSGEGEBEN
VON
OTTO LUBARSCH

279. BAND
MIT 343 ABBILDUNGEN IM TEXT

BERLIN
VERLAG VON JULIUS SPRINGER
1931

(Aus dem pathologisch-anatomischen Institut des Krankenhauses der Stadt Wien [Vorstand: Prof. Dr. *J. Erdheim*].)

Über Lipoidgranulomatose[1].

Von

Dr. **William Chester**, New-York.

Mit 9 Abbildungen im Text.

(Eingegangen am 29. Mai 1930.)

Inhaltsübersicht.

Einleitung.
1. Die *Hand*sche Krankheit und ihre Geschichte.
2. Die *Niemann-Pick*sche Krankheit.
3. Die verschiedenen Formen der Lipoid- und Kerosinstoffwechselstörung.
4. Eigenes Material.
5. Über das Lipoidgranulom.

Zusammenfassung.

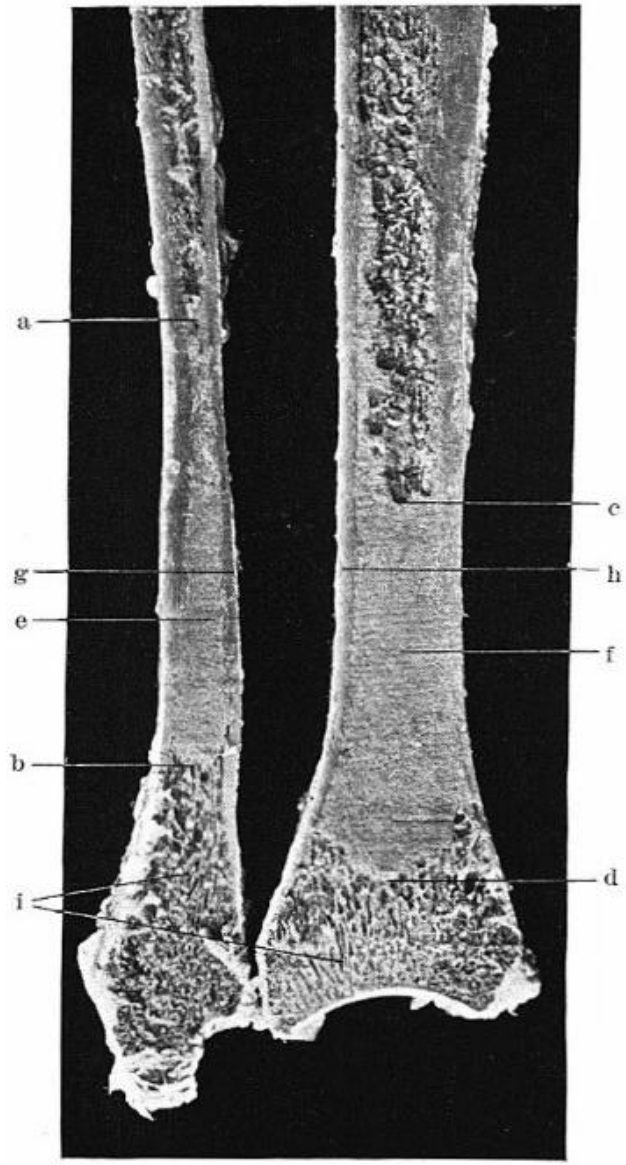


Abb. 1. Osteosklerotische Lipoidgranulomherde der Tibia und Fibula. In der rechten Fibula A und der rechten Tibia B je ein großer osteoplastischer Lipoidgranulomherd a—b, c—d, deren dichtes Knochengewebe e, f, sich gegen die dicke Knochenrinde g h deutlich abhebt. Normale Spongiosa.

Summary of Chester’s article

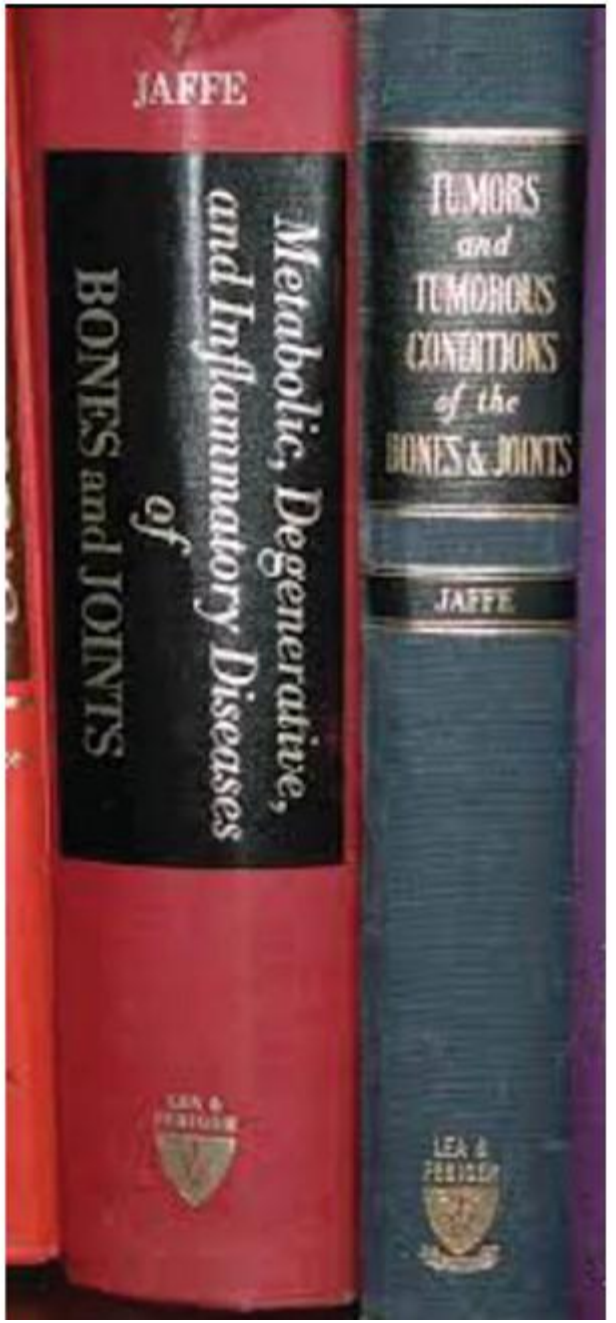
Two separate cases were therefore described in which:

Nothing was clinically noticeable apart from lipoid granuloma on the eyelids but anatomically very widespread lipoid granuloma were present in the skeleton and in one of them also in intestines, in the lungs, in the heart and negligible amounts in the liver. The spleen was unchanged. In one case the bone changes were osteo-plastic in character which has never been described before. The sclerosing-fibrous character affected the entire lung. The change in question in the same case was due to hypertrophy and finally insufficiency of the right heart which was the cause of death as in many cases of Hand's disease.

Dr. Henry L. Jaffe, 1896-1979

- Pioneering authority on pathology of bone diseases
- Chief of Pathology at the Hospital for Joint Diseases, NYC, 1925-1964
- Amassed an important collection of over 3,000 Orthopaedic cases over the course of his career which included the case collections of Dr. Erdheim, who before he died in 1937, was able to have his collection smuggled in a rug out of Vienna, and were delivered to Dr. Jaffe in New York.
- Published book “Metabolic, Degenerative and Inflammatory Diseases of Bones and Joints” 1972,
- In his chapter of this book Jaffe cited the work of Erdheim and Chester, added a case of his own, and proposed that the condition be named Erdheim-Chester disease.

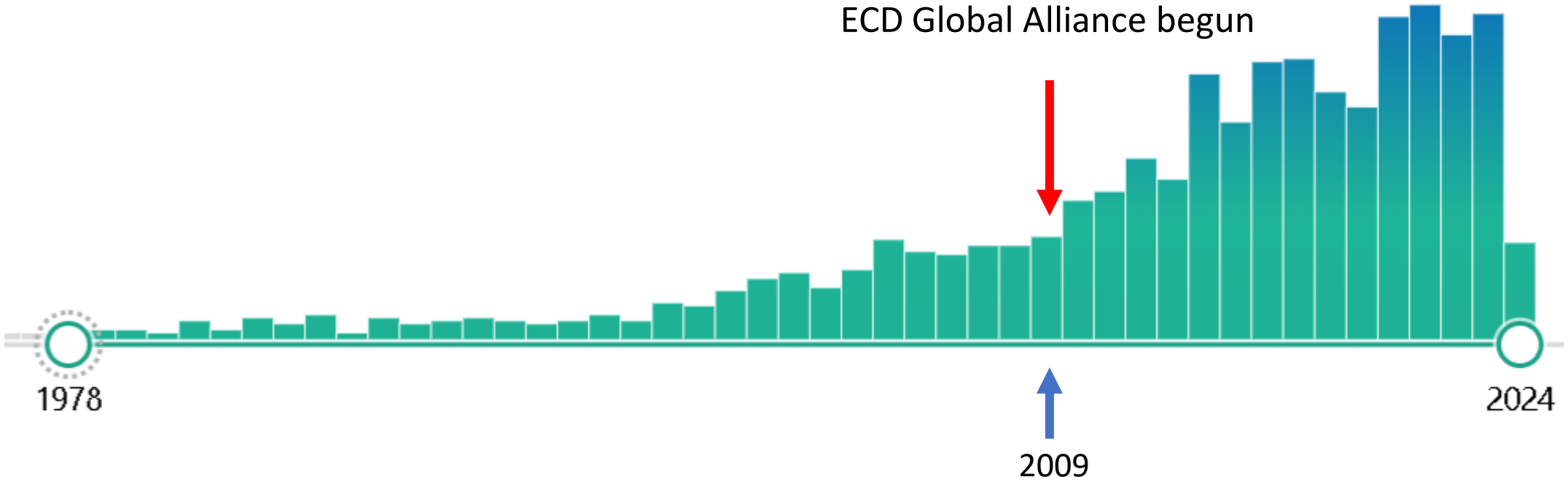
Henry L. Jaffe (1896-1979)
Huvos, AG:Ann Diagn Pathol 3: 260-261, 1999



Jaffe's 1972 Chapter: Gaucher's disease and certain other inborn metabolic disorders: lipid (cholesterol): LIPID (CHOLESTEROL) GRANULOMATOSIS

- "Chester described a pathologic condition which he regarded as distinctive and, in particular, as clearly different from both Niemann-Pick disease and so-called Schuller-Christian disease."
- "The pathologic findings indicated that the granulomatous changes found in the viscera in one case and in the bones in both cases were provoked by the presence of foam cells containing cholesterol."
- Jaffe then described a similar case
- "to keep all such cases distinct from other conditions (such as Schuller-Christian disease and essential familial hypercholesterolemia) in which cholesterol likewise accumulates at various sites, it might not be inappropriate to designate the condition in question here as Erdheim-Chester disease…."

Publications on Erdheim-Chester Disease since 1972: 1310



0025-7974/96/7503-0157$03.00/0
MEDICINE

Vol. 75, No. 3
Printed in U.S.A.

Erdheim-Chester Disease

Clinical and Radiologic Characteristics of 59 Cases

CATHERINE VEYSSIER-BELOT, MD, PATRICE CACOUB, MD, DOMINIQUE CAPARROS-LEFEBVRE, MD, JANINE WECHSLER, MD, BERNARD BRUN, MD, MARTINE REMY, MD, BENOÎT WALLAERT, MD, HENRI PETIT, MD, ANDRÉ GRIMALDI, MD, BERTRAND WECHSLER, MD, AND PIERRE GODEAU, MD.

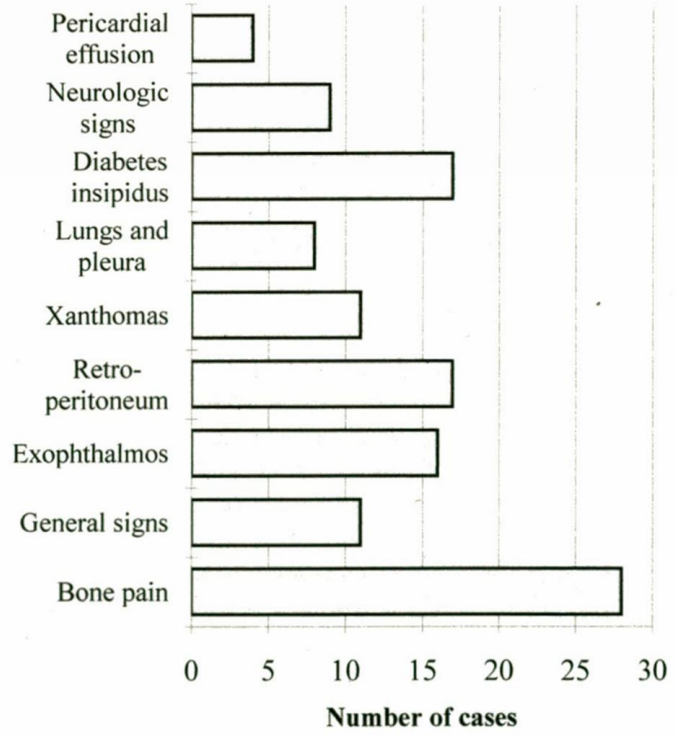


FIG. 5. Clinical signs in 59 patients with Erdheim-Chester disease.

- Rare
- May be confused with Langerhans cell histiocytosis
- Older patients
- No specific therapy
- Poor prognosis, 22 patients died after mean of 32+/-30 months (range 3-120 months

Pathogenesis of ECD, pre 2010

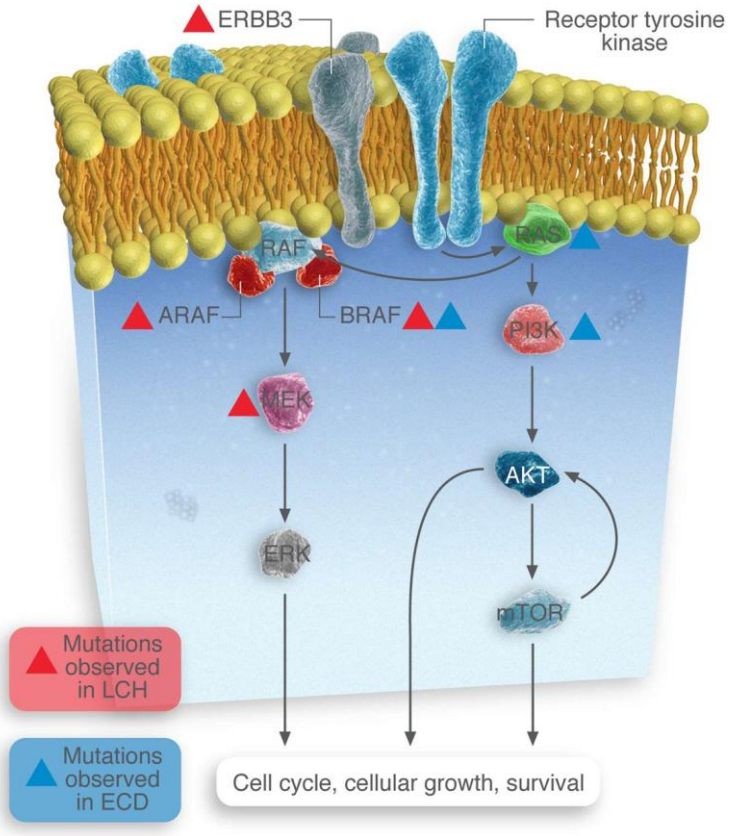
- ECD was considered a disseminated xanthogranulomatous disease of unknown cause with infiltration of various organs and bones with foamy histiocytes.
- Histiocytoses were divided into groups based on immunohistochemical characteristics of cell histiocytes and were classified based on their presumed cell of origin.
- Histiocyte Society Classifications as late as 1998 did not include ECD.

Story of RAF Oncogenes and their role in Cancer

- 1970-80 - Discovery of the cellular origin of retroviral oncogenes and role in human cancer (Varmus and Bishop, Nobel Prize 1989)
- 1986 - RAF oncogenes were described in two different retroviruses. Named RAF for their effect in mice: rapidly accelerated fibrosarcoma (Rapp)
- 1990-2000 -Crucial role of RAF kinases in signaling pathways and the cellular processes they control (Zebisch and Troppmair)
- 2002 – Mutation in BRAFV600E found in melanoma and several other cancers (Davies et al)
- 2008- Identification of a selective inhibitor of BRAFV600E: vemurafenib (Tsai et al)
- Exceptional clinical response to vemurafenib found in treating melanoma – 2010 (Flaherty et al)

MAP Kinases in Erdheim-Chester Disease

- 2002 : *BRAF*V600E discovered in a variety of cancers (Davies)
- 2010 – *BRAF*V600E found in 57% of archived LCH lesions (Badalian-Very et al)
- 2012 - *BRAF*V600E found in >50% of ECD patients (Haroche et al)
- 2014 - ECD patients without BRAFV600E mutations have other activating mutations in the MAPK pathway (Emile et al)
- 2015 – ECD patients with BRAFV600E mutations responsive to vemurafenib (Hyman et al)
- 2016 - Revised classification of histiocytoses (Emile et al)



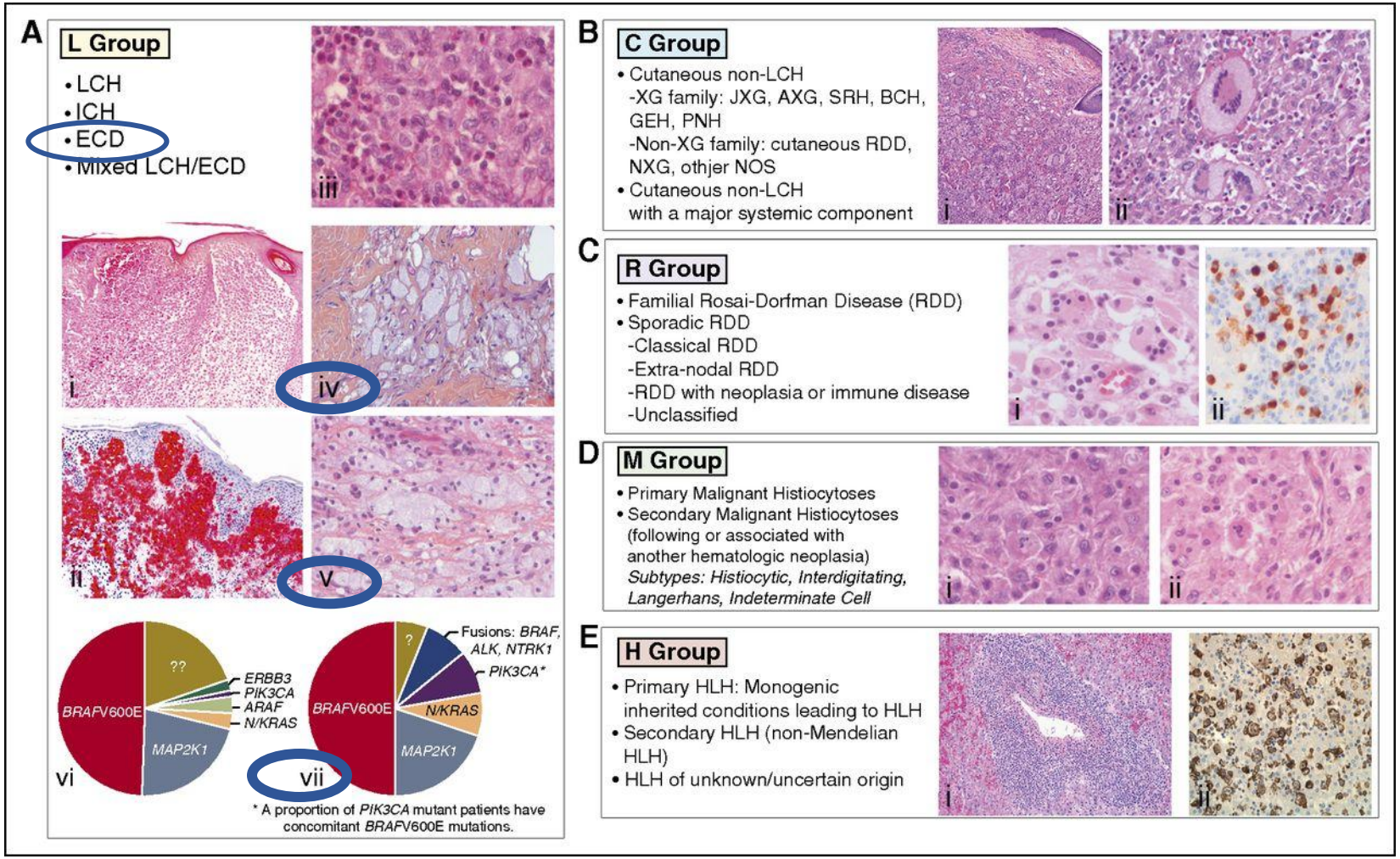
BRAF-RAS-RAF-MEK-ERK pathway

Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

by Jean-François Emile, Oussama Abla, Sylvie Fraitag, Annacarin Horne, Julien Haroche, Jean Donadieu, Luis Requena-Caballero, Michael B. Jordan, Omar Abdel-Wahab, Carl E. Allen, Frédéric Charlotte, Eli L. Diamond, R. Maarten Egeler, Alain Fischer, Juana Gil Herrera, Jan-Inge Henter, Filip Janku, Miriam Merad, Jennifer Picarsic, Carlos Rodriguez-Galindo, Barret J. Rollins, Abdellatif Tazi, Robert Vassallo, and Lawrence M. Weiss

Blood
Volume 127(22):2672-2681
June 2, 2016

Histology and somatic mutations of histiocytoses of group L, C, R, M, and H. (A) L group: Histology of LCH (skin [i-ii] and bone [iii]) and of ECD (perirenal [iv-v]).



Jean-François Emile et al. Blood 2016;127:2672-2681

Summary of entities comprising the L, C, M, R, and H groups in the revised classification of Emile et al for the HS. Professional illustration by Patrick Lane, ScEYEnce Studios.

Group	Entities
L	Langerhans cell histiocytosis (LCH) Indeterminate cell histiocytosis Erdheim-Chester disease (ECD) Mixed ECD and LCH
C	Cutaneous non-LCH histiocytoses Cutaneous non-LCH histiocytoses with a major systemic component
M	Primary malignant histiocytosis Secondary malignant histiocytosis
R	Familial Rosai-Dorfman disease (RDD) Classical (nodal) RDD Extranodal RDD Neoplasia-associated RDD Immune disease–associated RDD Other non-C, non-L, non-M, and non-H histiocytoses
H	Primary HLH: Mendelian-inherited conditions leading to HLH Secondary HLH (apparently non-Mendelian HLH) HLH of unknown/uncertain origin

John L. Frater Blood 2016;127:2655-2656

Current understanding of Erdheim Chester Disease: a multi-system histiocytic neoplasm due to clonal hematopoietic somatic mutation(s) in MAP Kinase genes

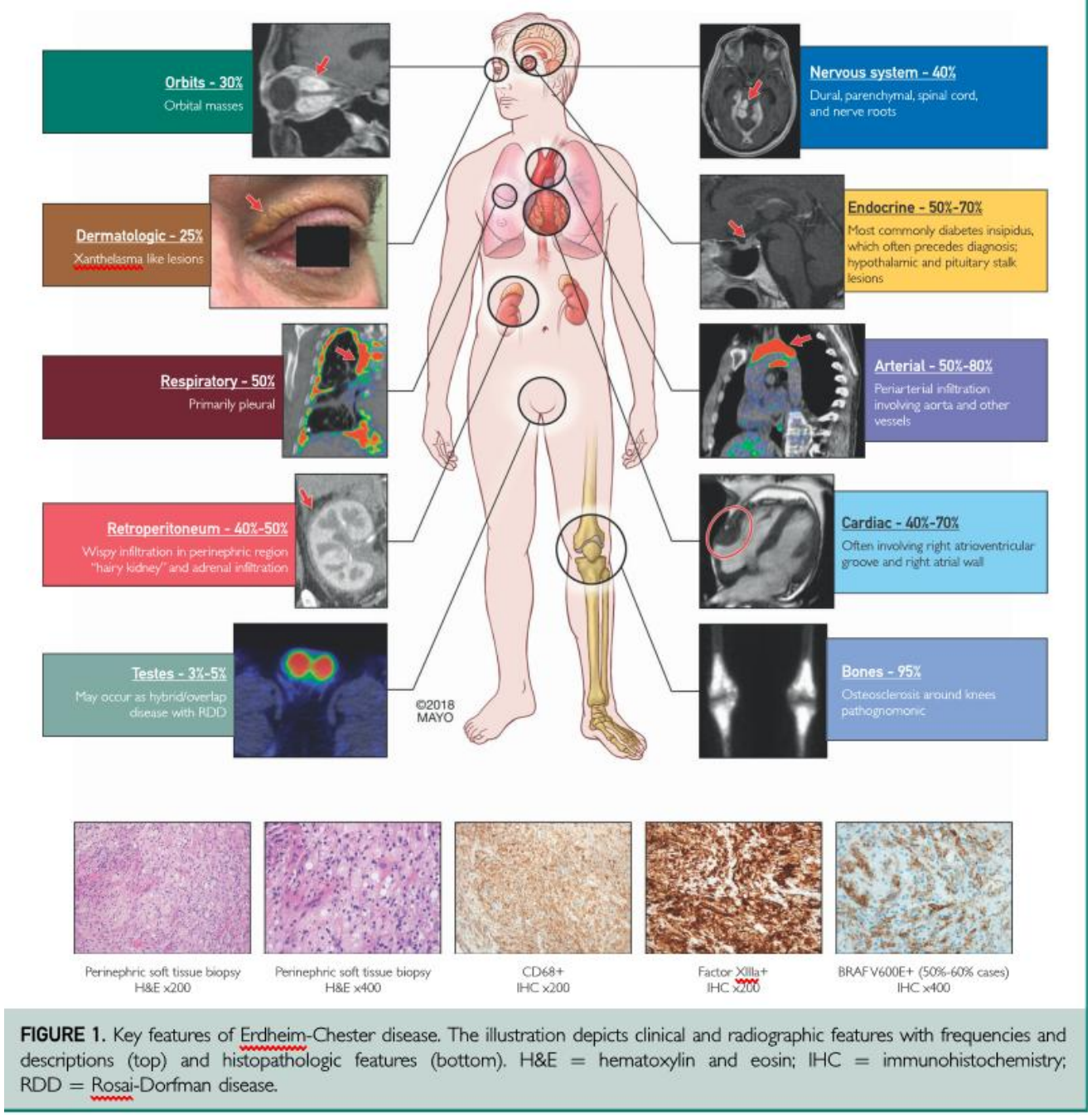
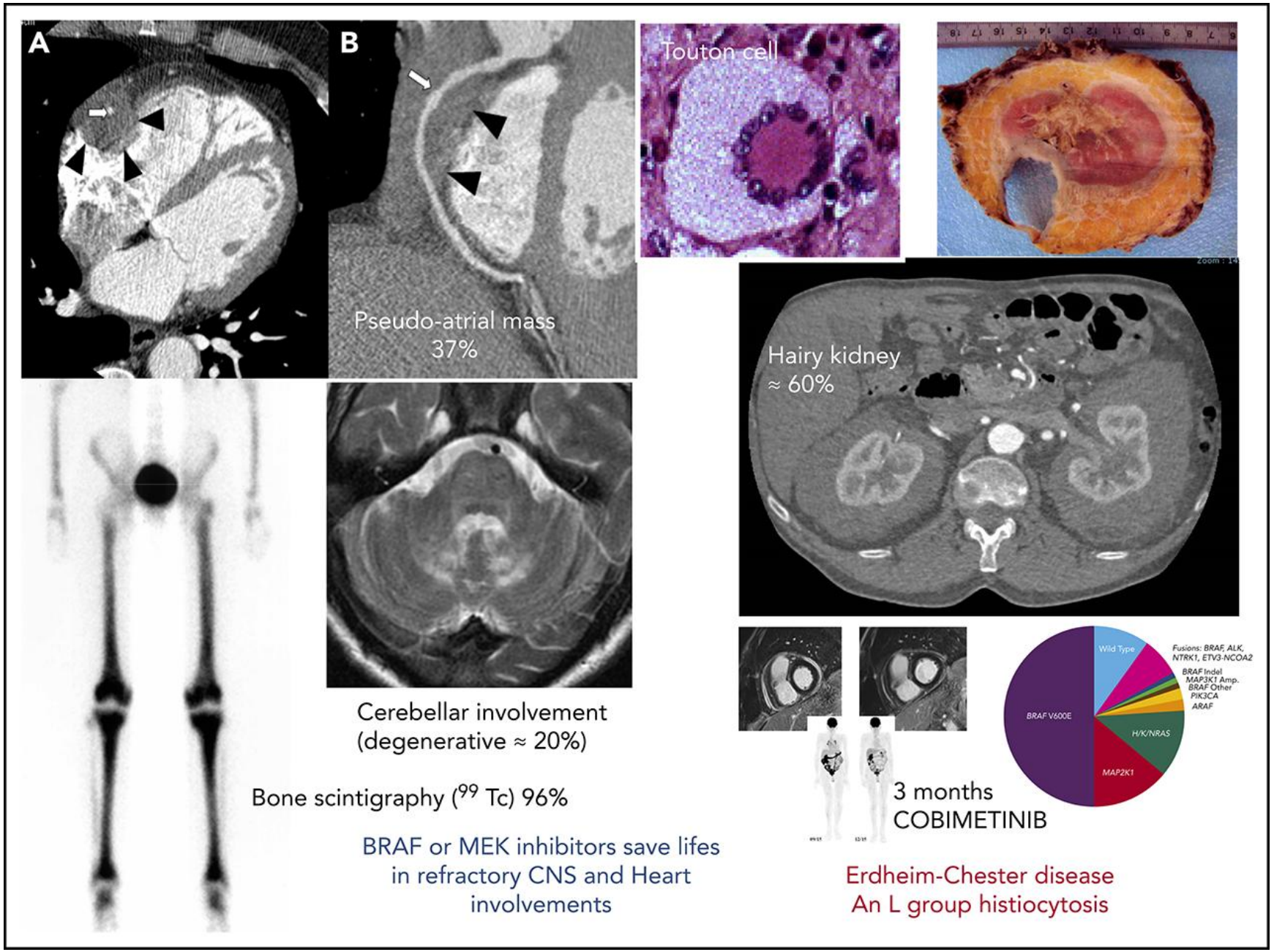


FIGURE 1. Key features of Erdheim-Chester disease. The illustration depicts clinical and radiographic features with frequencies and descriptions (top) and histopathologic features (bottom). H&E = hematoxylin and eosin; IHC = immunohistochemistry; RDD = Rosai-Dorfman disease.

Goyal G, et al. Mayo Clin Proc 2019

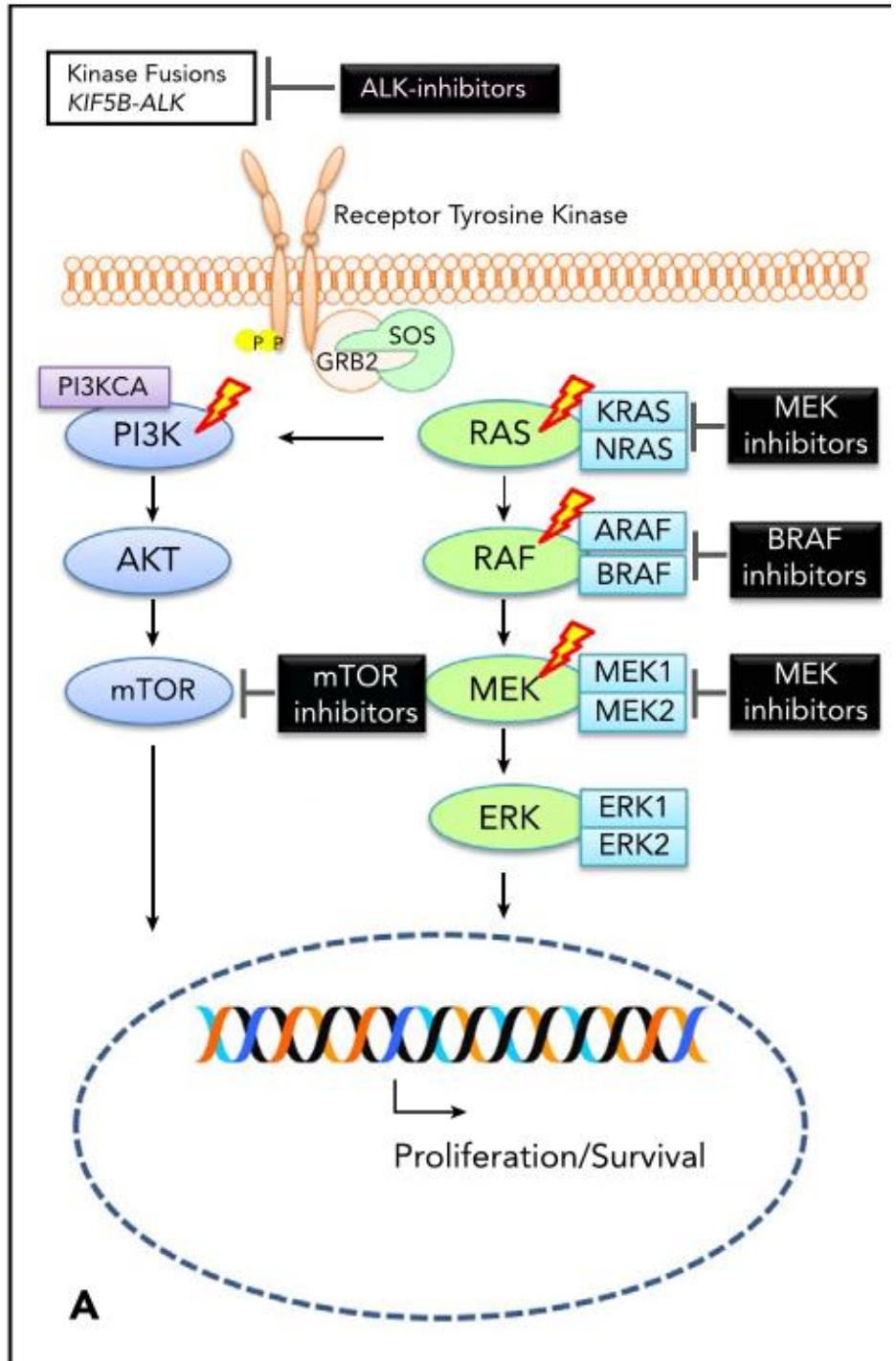
Haroche J et al. Erdheim-Chester disease
Blood (2020) 135 (16): 1311–1318.

"Visual Abstract"



Molecular alterations in ECD.

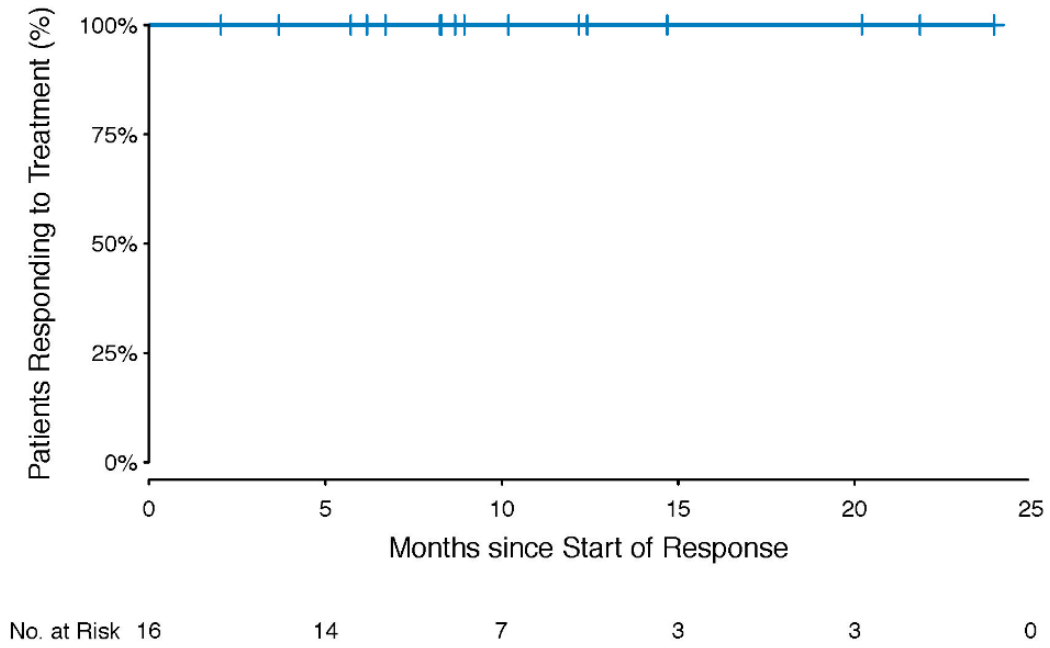
Goyal G, et al. Blood. 2020



Efficacy of MEK Inhibition in Patients with Histiocytic Neoplasms
Diamond EL, et al. Nature 2019

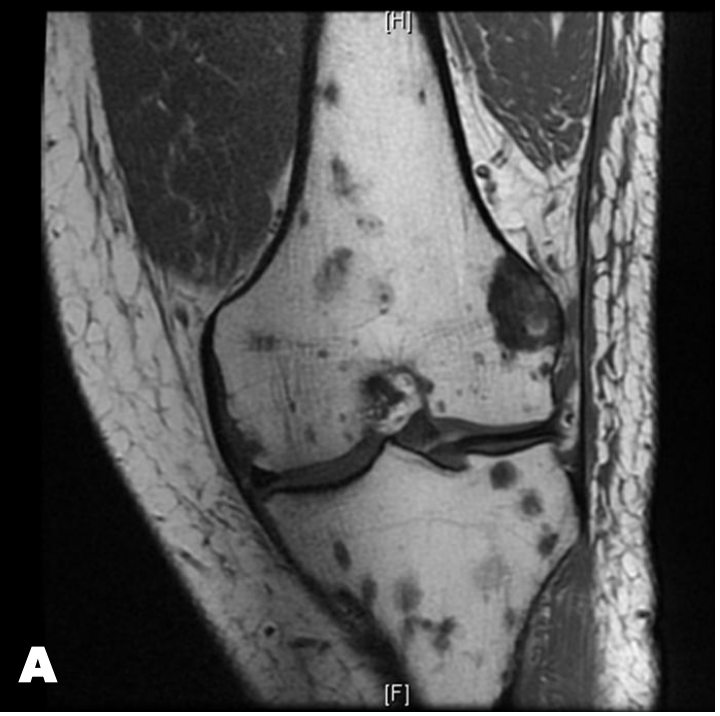
- For histiocytosis patients with BRAFV600-mutations, RAF inhibition is highly efficacious.
- No standard therapy for the remaining 50% of patients lacking BRAFV600-mutations.
- Are all histiocytic neoplasms ERK dependent?
- This trial tested effect of the oral MEK1/2 inhibitor cobimetinib in patients with histiocytoses regardless of tumor genotype.
- In 18 treated patients, the overall response rate (ORR) was 89%. Responses were durable, with no acquired resistance to date.
- Efficacy was observed regardless of genotype.

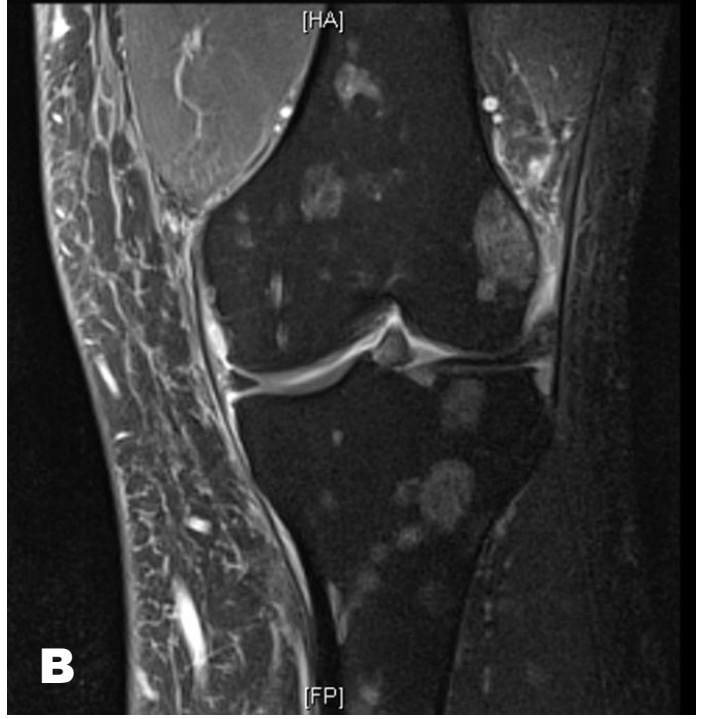
Response of Histiocytic Disorders to MAPK Inhibitor Cobimetinib



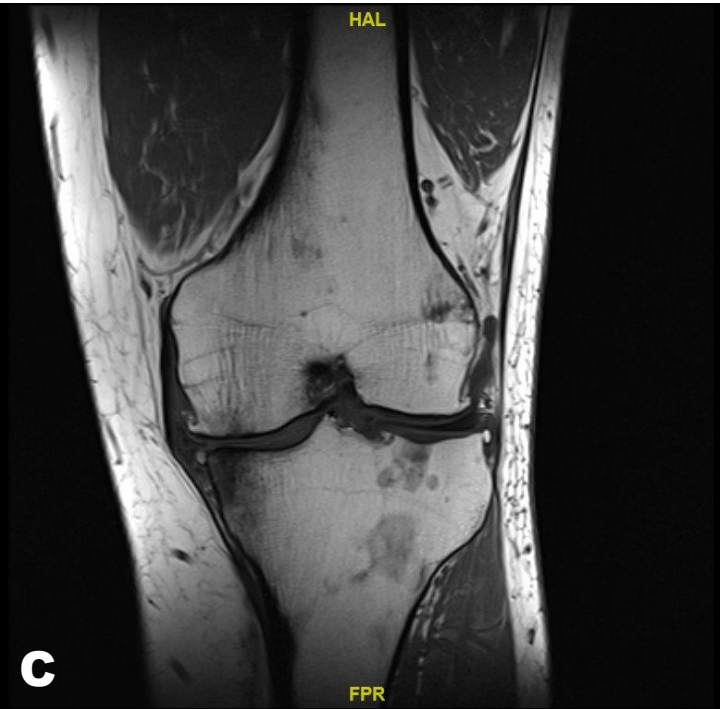
Extended Data Figure 2. PET-Defined Duration of Response (N=16).
Depicts the duration of response according to PET criteria in the 16 responding patients, beginning with date of initial response.

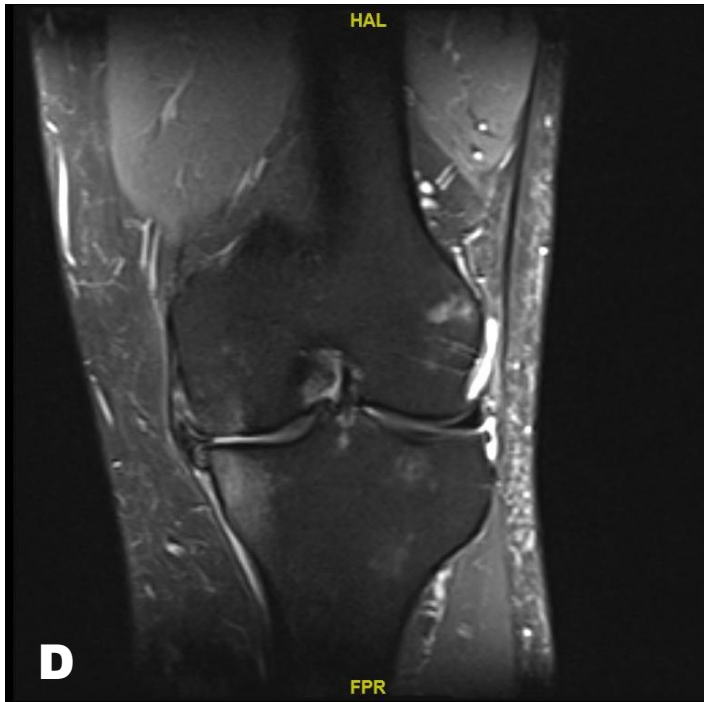
- At one year, 100% of responses were ongoing, and 94% of patients remained progression-free.
- These data demonstrate that histiocytic neoplasms (including ECD) are characterized by remarkable dependence on MAPK signaling and, consequently, responsiveness to MEK inhibition.





ECD patient MRI OF Knee March 2017





Same patient October 2018 after 18 months of cobimetinib

Additional ECD Milestones

- 2009 – ECD Alliance founded. Over $1.2M raised for research
- 2017 - Mutated histiocytes are myeloid (Durham et al)
- 2019 – risk of myeloid malignancies 10% (Papo et al)
- FDA approvals: vemurafenib for ECD: 2017; cobimetinib for histiocytic neoplasms: 2022
- 2020 - Erdheim-Chester Disease: Consensus Recommendations for Evaluation, Diagnosis, and Treatment in the Molecular Era (Goyal et al)
- 2021 – NCCN Clinical Practice Guidelines published for histiocytic neoplasms (Go et al)

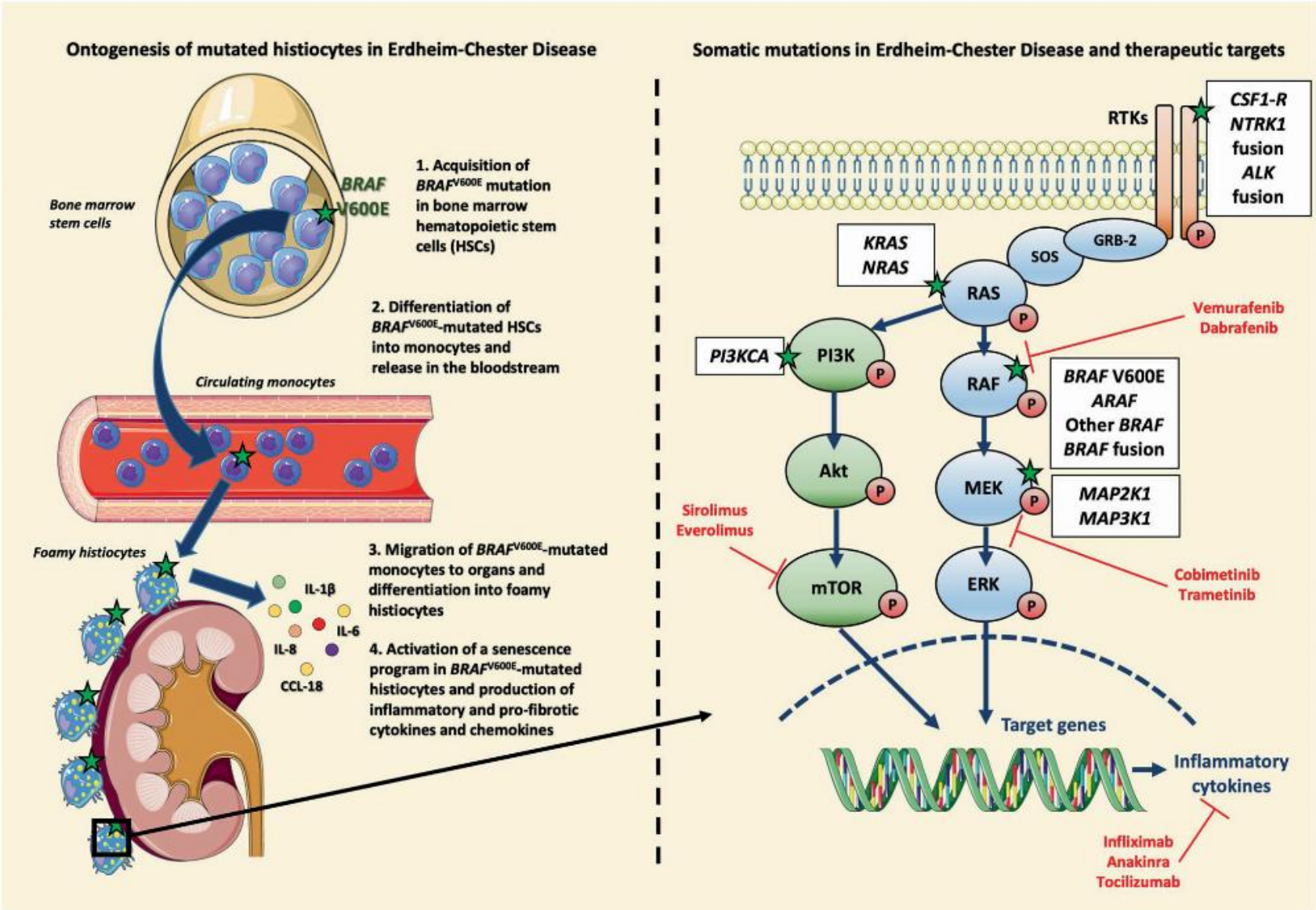


Fig. 2 Pathogenesis. Left panel: pathogenetic mechanisms involved in the development of ECD, from the acquisition of the *BRAF*^{V600E} mutation in the bone marrow to the tissue infiltration by foamy histiocytes and fibro-inflammation. Right panel: MAP-kinase pathway signalling alterations in ECD and relative therapeutic targets. The green stars indicate the most frequently altered genes in ECD.