ERDHEIM-CHESTER DISEASE: OVERVIEW OF BIOLOGY, CLINCIAL PRESENTATION, AND MANAGEMENT 2023 PATIENT FAMILY GATHERING

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Erdheim-Chester Disease: Overview of Biology, Clinical Presentation, and Management

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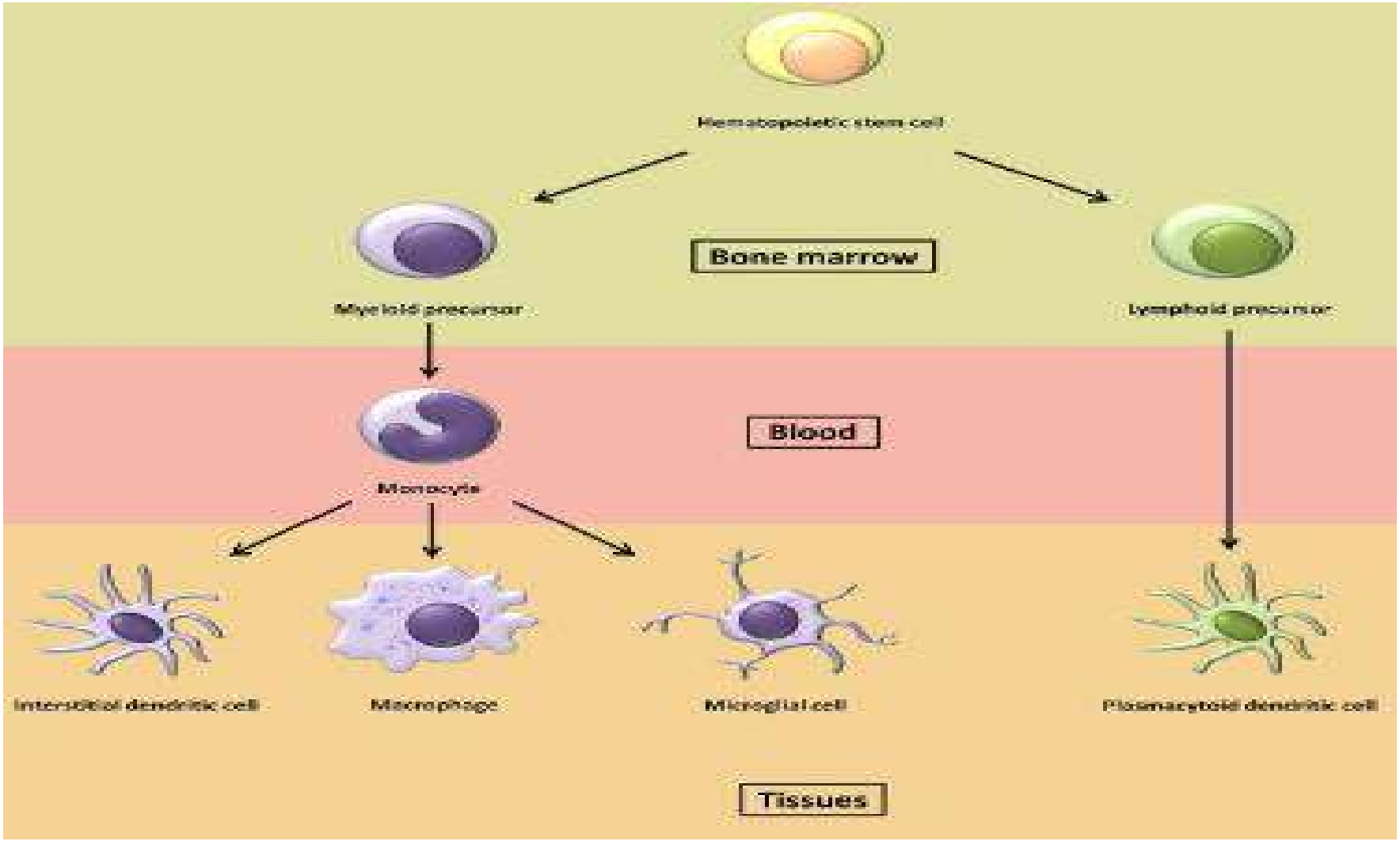
Histiocytosis Background

- Diseases of monocyte-macrophage derivation
- Recurrent mutations have now been identified
- Inflammatory or Neoplastic? Yes

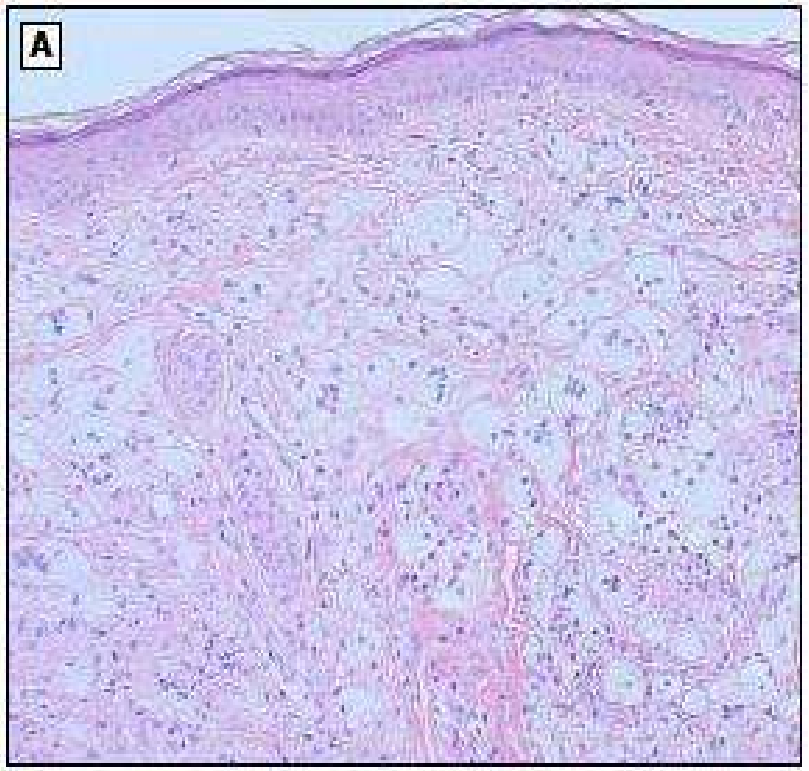
Monocyte-Macrophage Development



Researchgate.net

Erdheim-Chester disease

- Median age of onset: 55
- Men > women (3:1)
- CD68+, CD163+, S100- and CD1a-negative
- "foamy" histiocyte infiltration and multinucleate Teuton giant cells



Okzaya et al, Mod Pathol 2018
Erdheim and Chester, Virchows Arch Pathol Anat Physiol Klin Med 1930

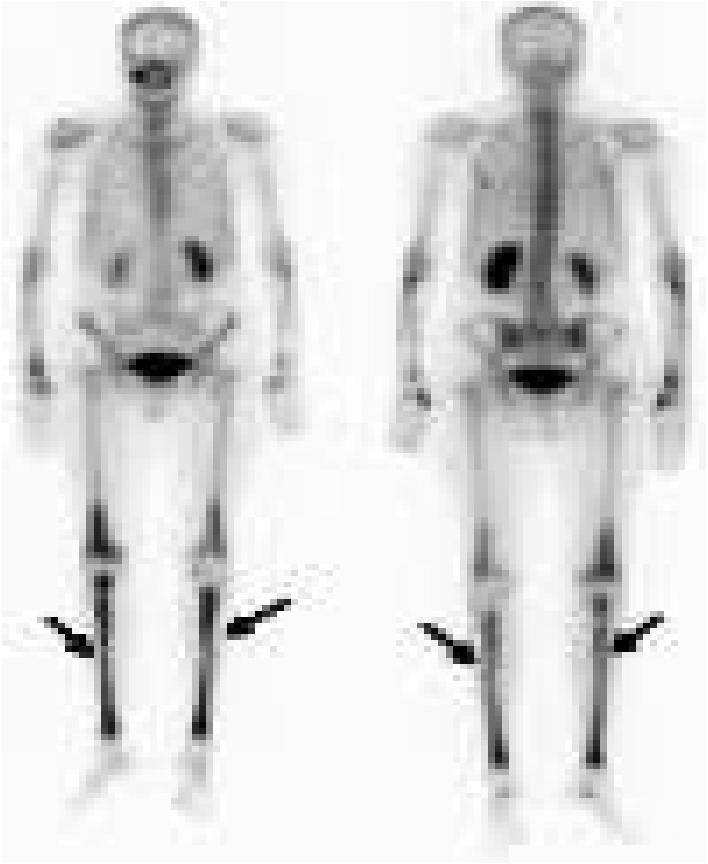
E. Jacobsen, UpToDate 2017
Reproduced with permission from: Kim MS, Kim CH, Choi SJ, et al. Erdheim-Chester disease. Ann Dermatol 2010; 22:439.

Spectrum of ECD

Organ system and clinical findings	NIH patients,* n (%)	Veyssier-Belot et al† (%)	Haroche et al‡ (%)
Bone	57 (95)	NR	96
Kidney	39 (65)	27	68
Periaortic encasement	37 (62)	NR	66
Hypogonadism	36 (60)	NR	NR
Lung	31 (52)	14	43
Bone pain	28 (47)	47	40
Maxilla and mandible§	24 (47)	NR	NR
Diabetes insipidus	28 (47)	29	25
CNS disease infiltration	23 (38)	17	51
Retro-orbital area ± exophthalmos	15 (27)	29	25
Heart (pseudotumor in RA)	22 (37)	NR	19
Xanthelasma	20 (33)	19	28
Skin	15 (25)	10	NR
Pericardial disease	5 (8)	7	42

Estrada-Veras et al Blood Adv 2017

Bone Findings in ECD

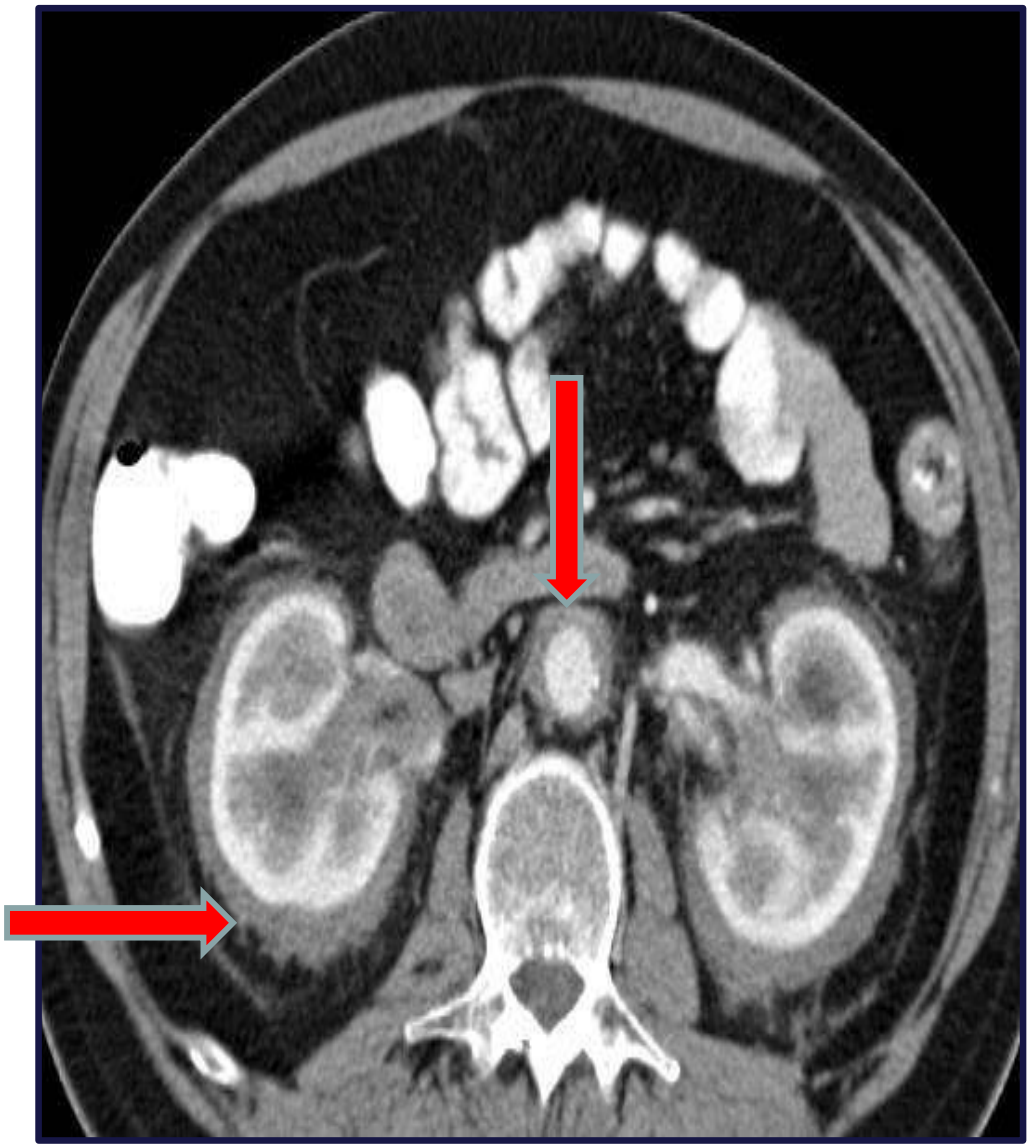


Bilateral, symmetric diaphyseal and metaphyseal osteosclerosis with subchondral sparing in 95%

Antunes et al, Insights imaging 2014

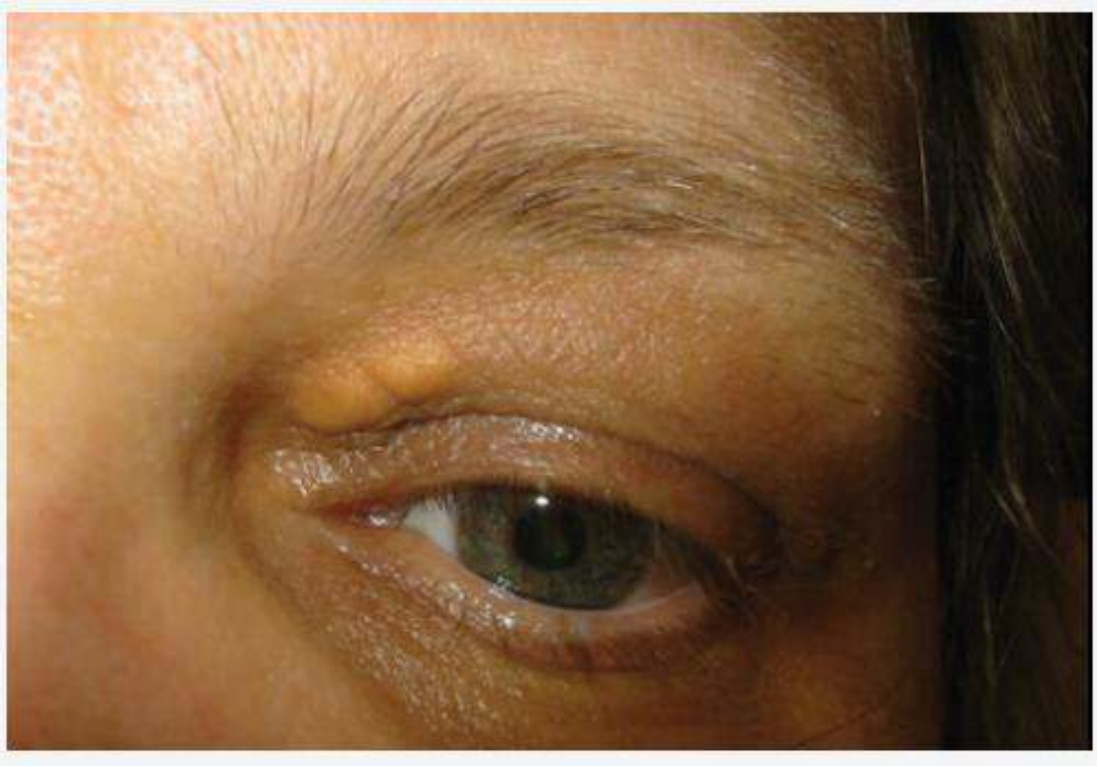
ECD– Retroperitoneal Involvement

- Retroperitoneum: Peri-renal soft tissue with "hairy kidney" appearance
- "coating" of aorta
- DDX:
  - IgG4 related disease
  - Primary retroperitoneal fibrosis
  - Autoimmune causes of aortitis
  - Lymphoma



Lancet Oncol. 2017 Feb;18:e113-e125
Radiology. 2017;284:910-917.

Ocular Findings in ECD

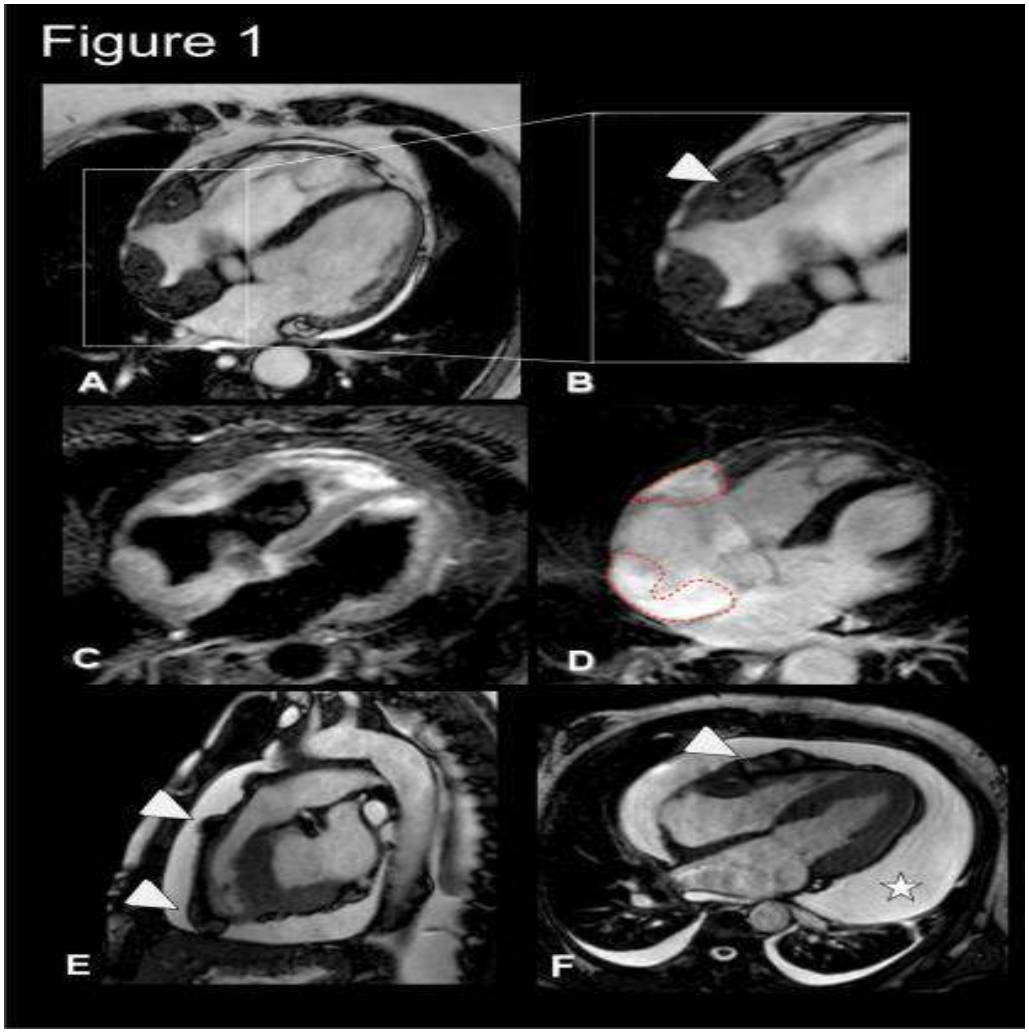


Xanthelasma

Exophthalmos

Medicinenet.com

Cardiac imaging findings in ECD

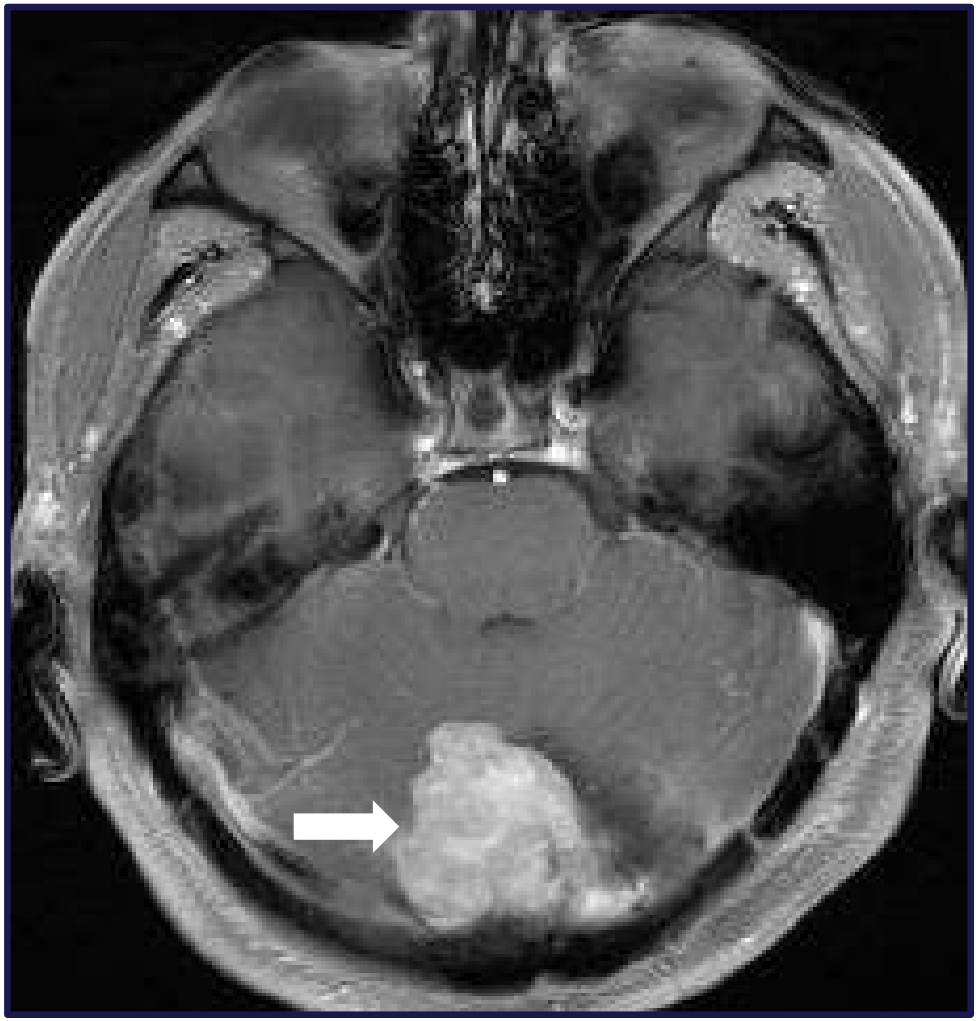


Gianfreda et al Blood 2016

- Right atrium
- Pericardium
- Coronary arteries
- Valves

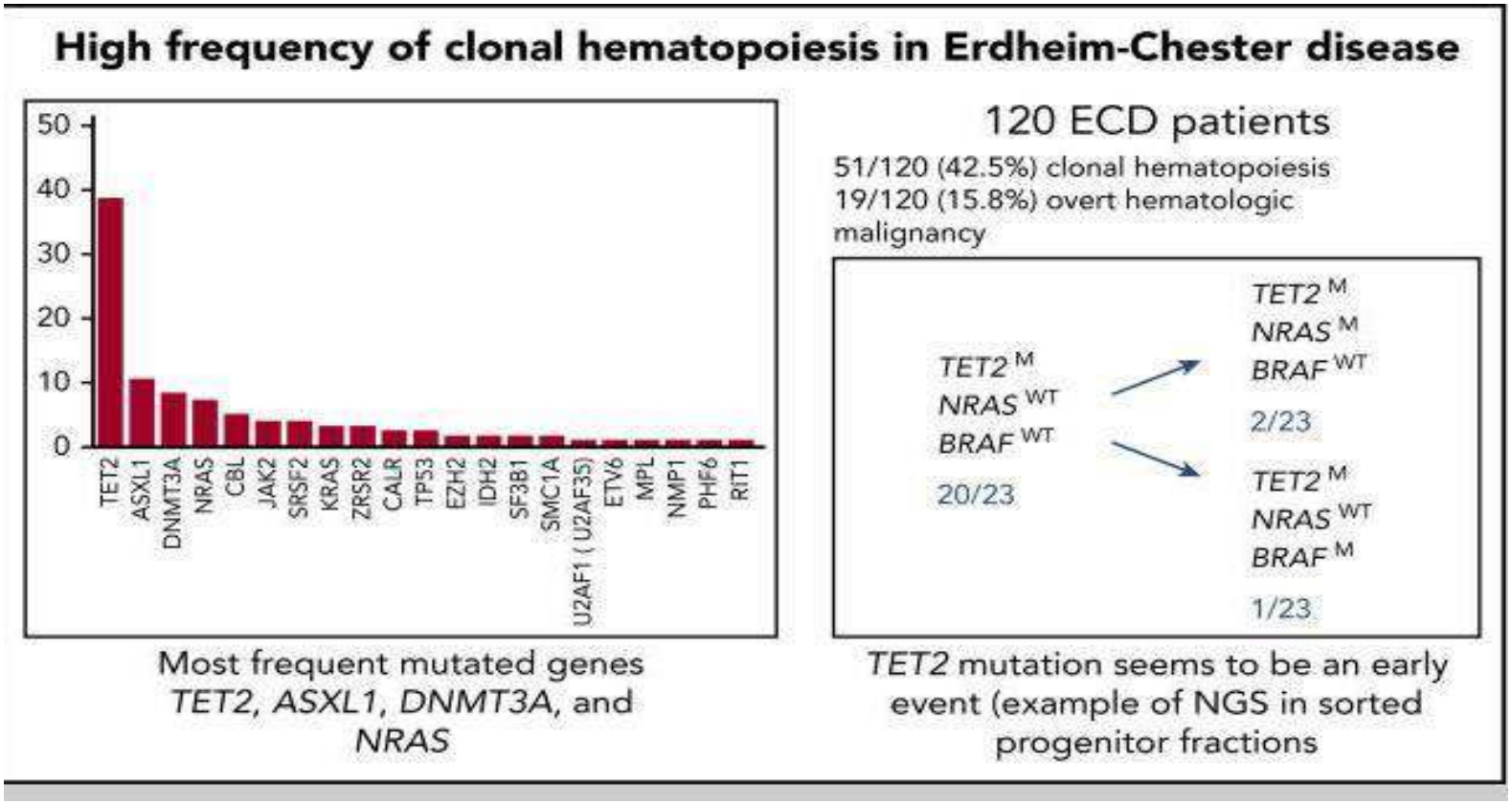
CNS Involvement with ECD

- Posterior fossa
- Brain stem
- Results in substantial morbidity



Arnaud et al Blood 2011

ECD Associated With Other Myeloid Diseases



Aubart et al, Blood 2021

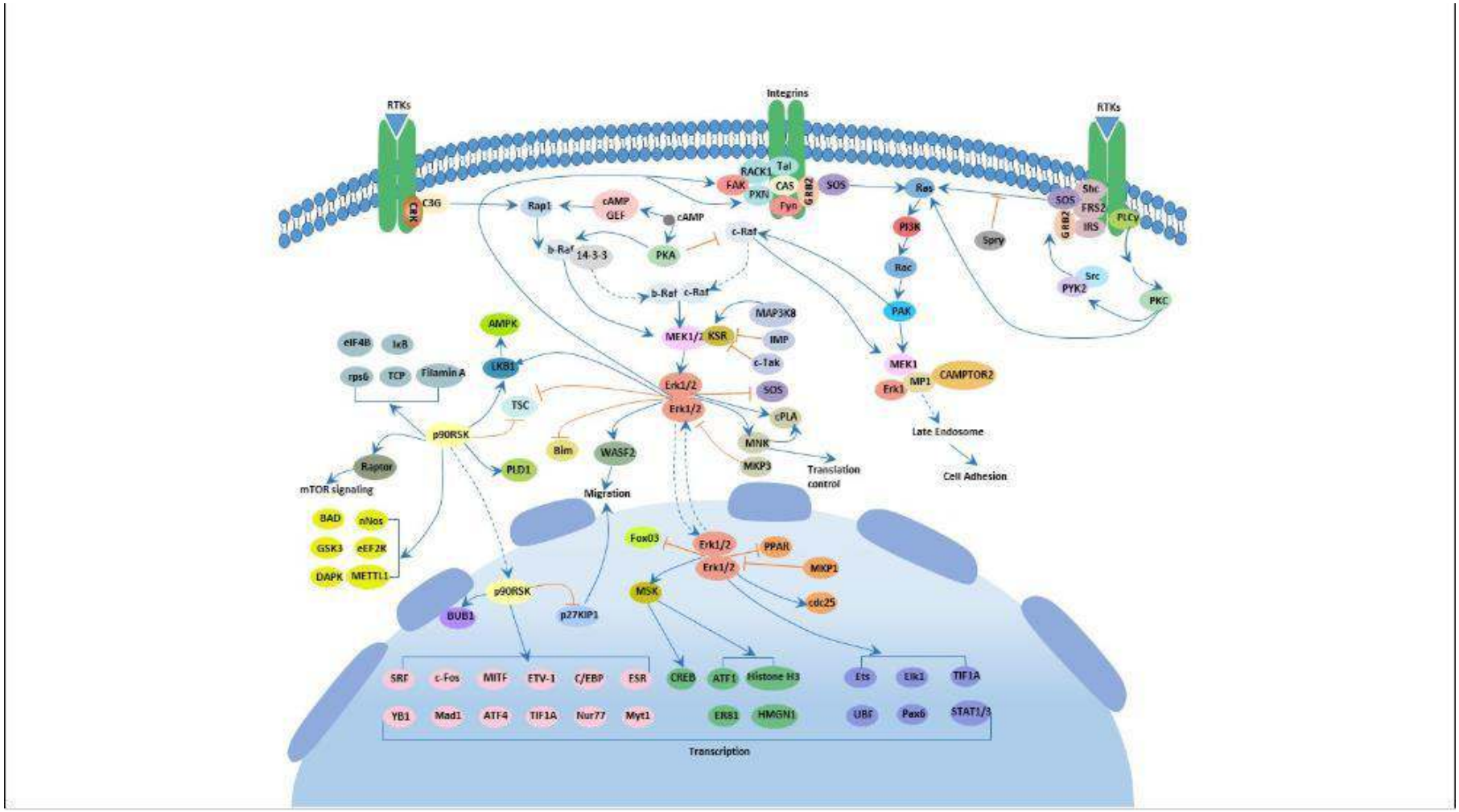
ECD Associated With Autoimmune Disease

Autoimmune disease, n (%)	23 (12%)
Autoimmune thyroiditis	8 (4%)
Systemic lupus erythematosus	3 (1.5%)
Primary Sjogren syndrome	3 (1.5%)
Autoimmune biology, n (%)	
ANA>1/80	50 (26%)
AntidsDNA +	10 (5%)
AntiSS-A +	9 (5%)
AntiSS-B +	1 (0.5%)
APL biology*	36 (18%)
LA	5 (3%)
Anticardiolipid +	31 (16%)
Antiβ2GP1 +	7 (4%)

Roeser, Haematologica 2019

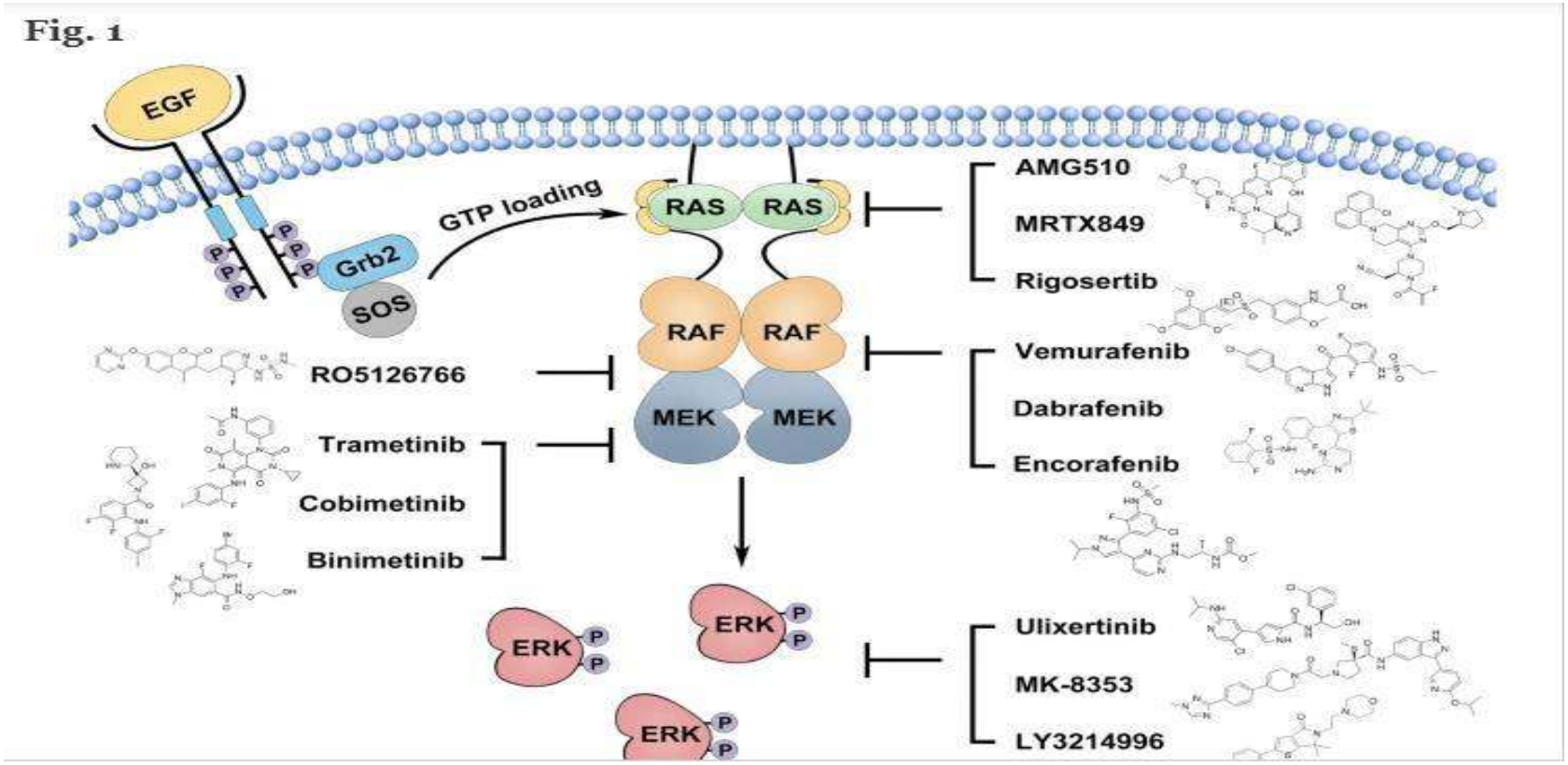
Novel genomic discoveries and clinical application in histiocytosis

MAPkinase-ERK signaling pathway



Cusabio.com

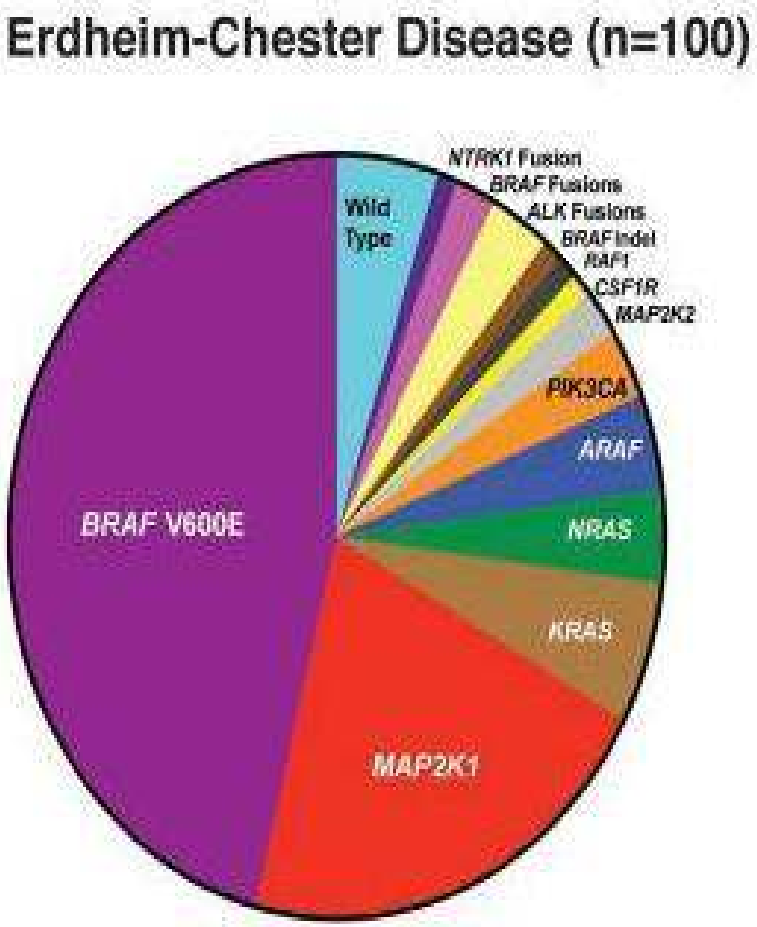
RAS/RAF/MEK/ERK pathway



Yuan, J Hematol Oncol 2020

Mutational Landscape of ECD

- **$BRAF^{V600E}$** 50–60%
- **MAP2K1 mutations** 30%
- **NRAS and KRAS mutations** 27%



Emile et al, Blood 2014

Durham et al, Nat Med 2019

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Histiocytic Neoplasms

NCCN Guidelines Index
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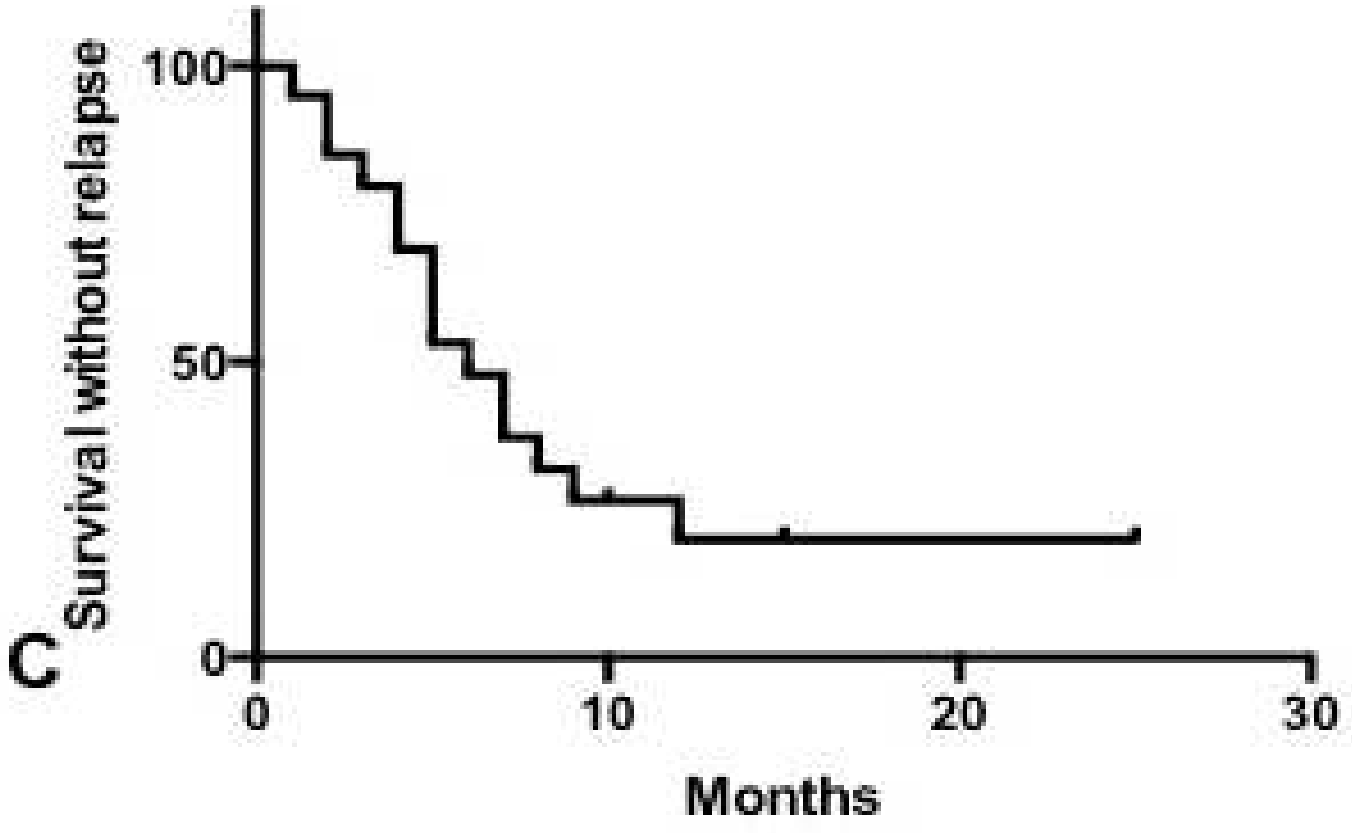
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Erdheim-Chester Disease
- Regimens may be used in the first- or subsequent-line setting

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
***BRAF* V600E mutated disease** • Vemurafenib[a,b,1,30] **MAP kinase pathway mutation, or no detectable mutation, or testing not available** • Cobimetinib[a,b,31] **Irrespective of mutation** • Cladribine[32] • Pegylated interferon alpha-2a and alpha-2b[33]	***BRAF* V600E mutated disease** • Dabrafenib[a,b,31,34] **MAP kinase pathway mutation, or no detectable mutation, or testing not available** • Trametinib[a,b,14,35] **Irrespective of mutation** • Sirolimus + prednisone[36] • Methotrexate (oral)[37] • Anakinra[a,b,38,39]	**Targeted therapy** • Crizotinib for *ALK* fusion[21] • Alectinib for *ALK* fusion[40] • Brigatinib for *ALK* fusion[40] • Ceritinib for *ALK* fusion[40] • Lorlatinib for *ALK* fusion[40] • Pexidartinib for *CSF1R* mutation[21] • Larotrectinib for *NTRK* gene fusion[22,23] • Entrectinib for *NTRK* gene fusion[22,24] • Sirolimus or everolimus for *PIK3CA* mutation[25,26] • Selpercatinib for *RET* fusion[21]

Outcome after vemurafenib discontinuation



20 patients, median treatment time 20 months

Cohen-Aubert et al, Blood 2017

A (short) list of key questions

- Causes
- Does everyone need to be treated?
- Optimal treatment
  - BRAF inhibitor, MEK inhibitor, both, neither?
- Time-limited vs indefinite treatment? Optimal dose?
  - Lessons from other diseases
- Special survivorship considerations