Erdheim Chester Disease 2017

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Erdheim-Chester Disease

- Described as “Lipid Granulomatosis” by Jakob Erdheim and William Chester in 1930
  - Lipid-laden macrophages and Touton giant cells
  - CD 68+, FXIII+, CD1a-, S-100-

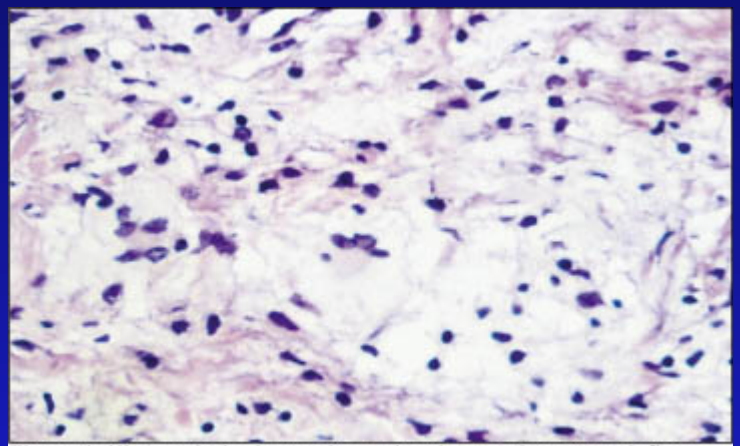
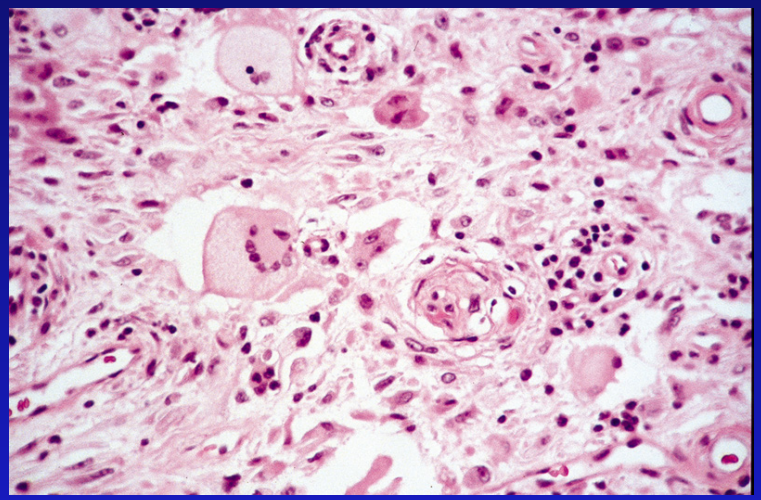
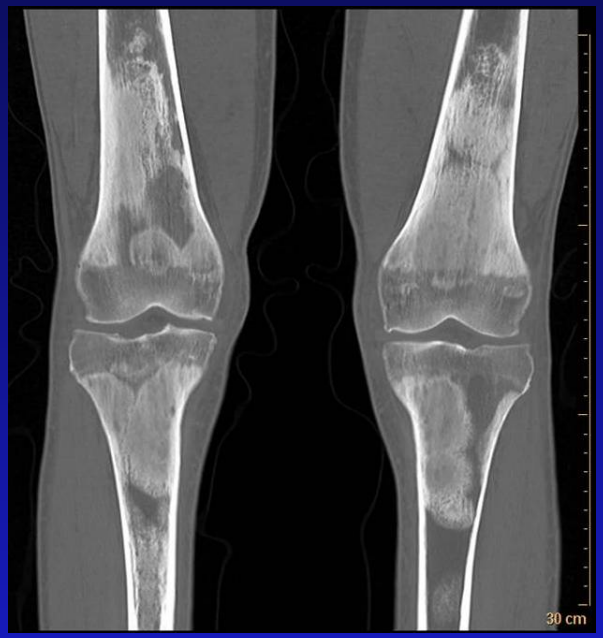


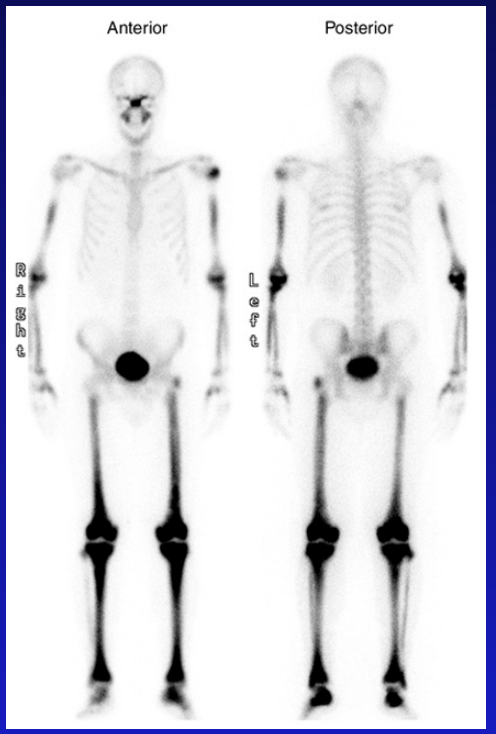
Figure 4 - Histopathologic specimen showing xanthomatous inflammatory infiltrates with Touton giant cells



Erdheim-Chester Disease

- Xanthogranulomas with bony lesions
  - "Radio-pathologic" diagnosis



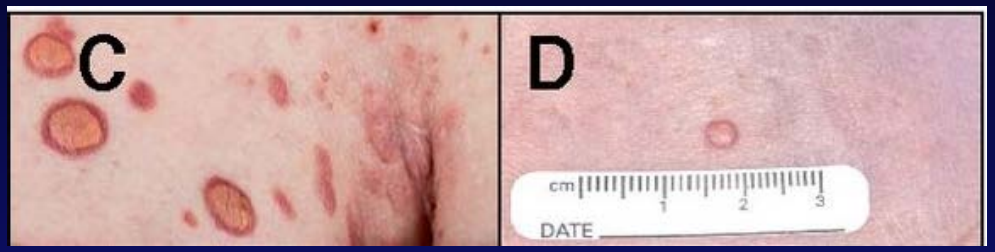


ECD Epidemiology

- Median age of onset: 53 yo
  - Range 7-84 years
- Equal male:female incidence
- Fewer than 1000 cases to date
- No known familial incidence
- No known infectious or exposure association

Common ECD Symptoms

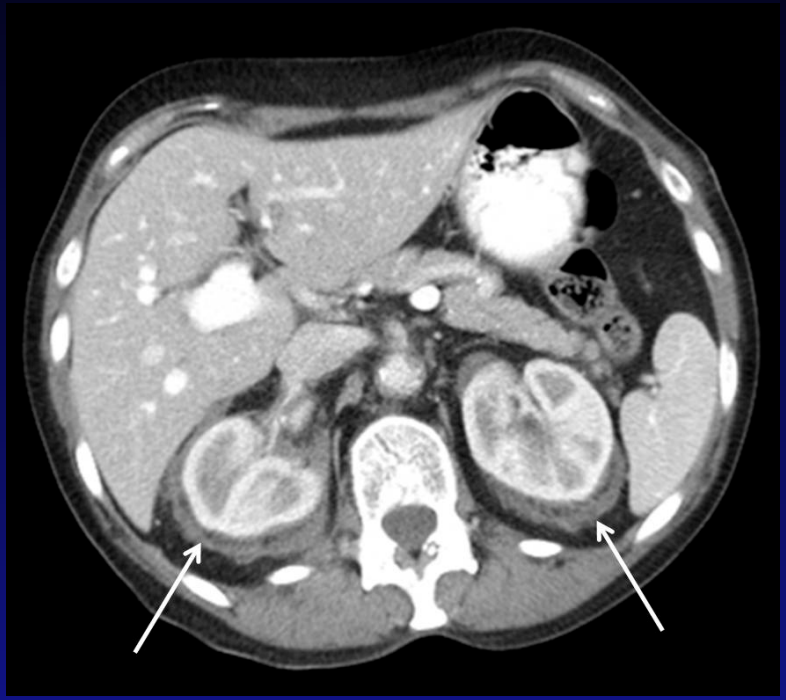
- Bone pain
- Fatigue
- Neurologic
  - Loss of balance
  - Change in personality
  - Decreased alertness
- Shortness of breath
- Increased thirst and urination
- Abdominal pain
- Rash
- Bulging eyes



Estrada-Veras et al Blood Adv 1:357, 2017

Organ Systems Affected by ECD

- Large arteries
- Bones
- Kidneys
- Heart and Heart Lining
- Skin
- Brain
- Lungs
- Endocrine



Hairy Kidneys

Haroche J et al Curr Rheumatol Rep 16:412, 2014

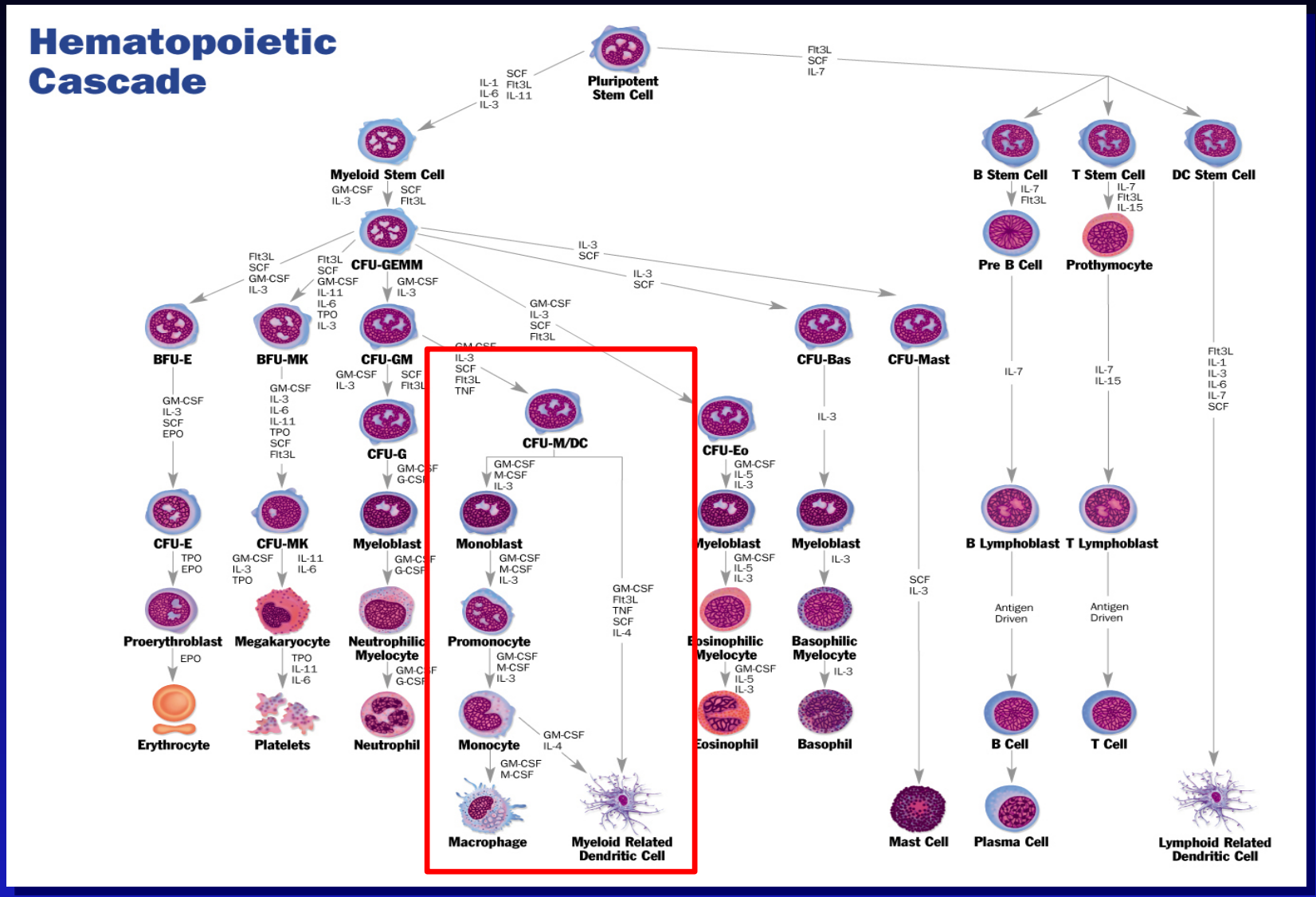
ECD Clinical Challenges

- ECD can affect one system or many
  - Patients may go to a specialist who does not recognize that symptoms outside their interest are part of the ECD constellation
- By the time symptoms arise, the disease is often advanced
- There is no simple diagnostic test
- Since it is a rare disease, it is not an early diagnostic consideration

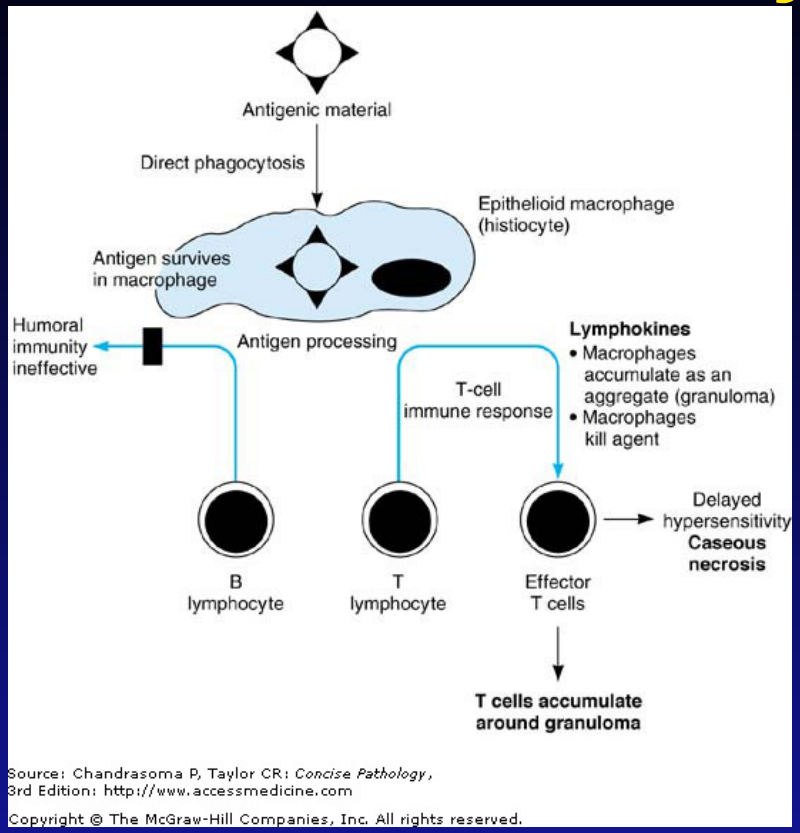
What is ECD?

- Previously considered an inflammatory or possibly autoimmune disease
- Now known that ECD is caused by acquired mutations in cells that become “histiocytes.”
  - Blood cell cancers
    - Myeloproliferative neoplasm

What is a “histiocyte?”

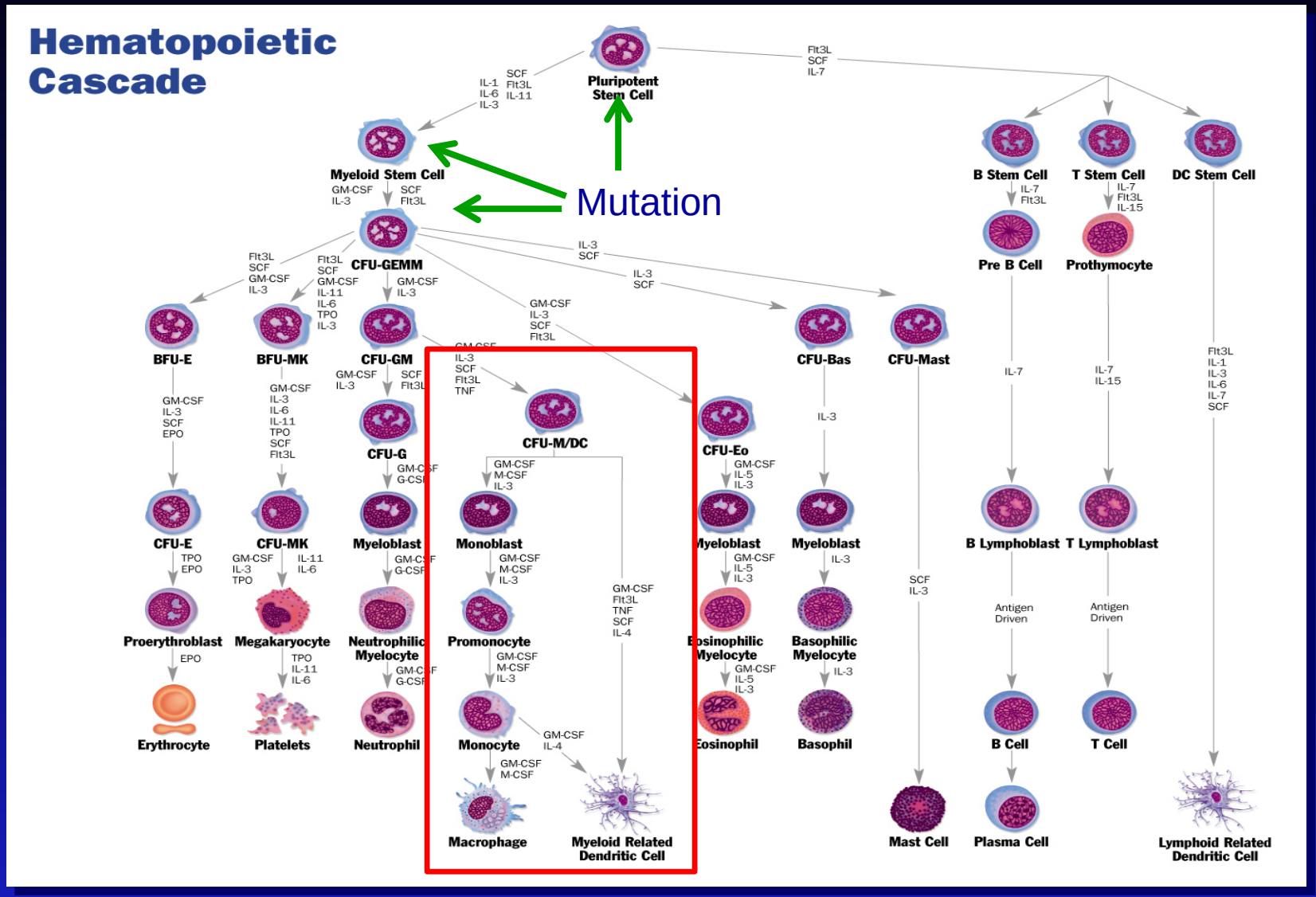


What is a “histiocyte?”



- Normal histiocytes help people to develop an immune response to infection

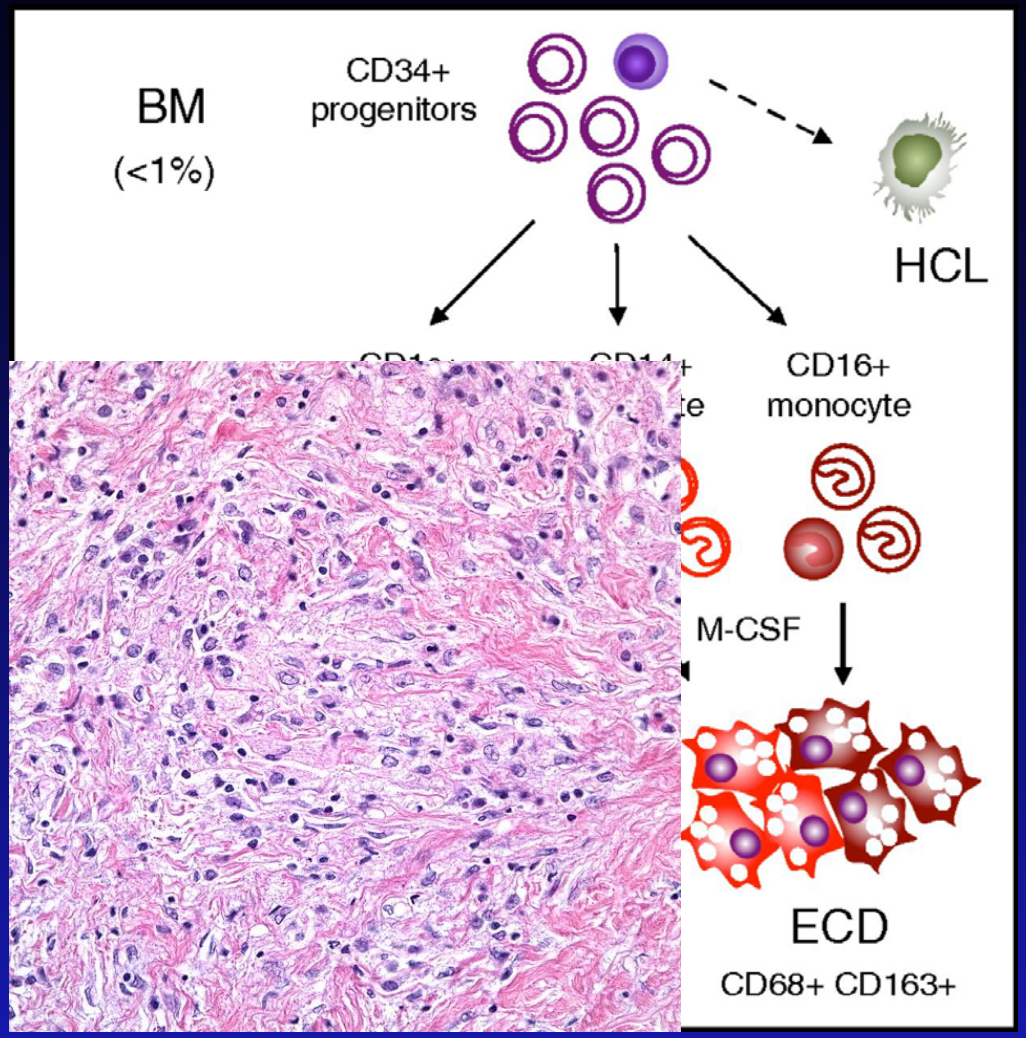
What goes wrong in ECD?



ECD Biology

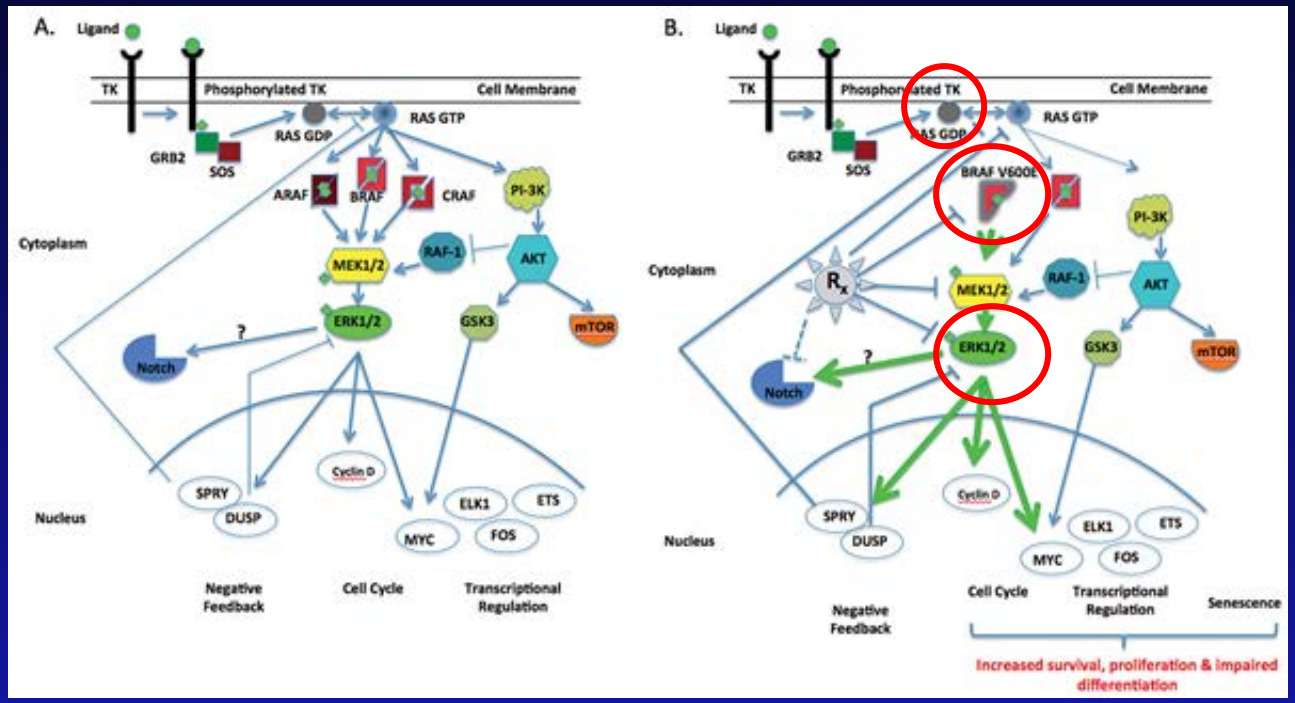
The mutation causes the histiocytes to grow without the normal controls.

The mutated histiocytes retain some normal characteristics and attract other immune cells



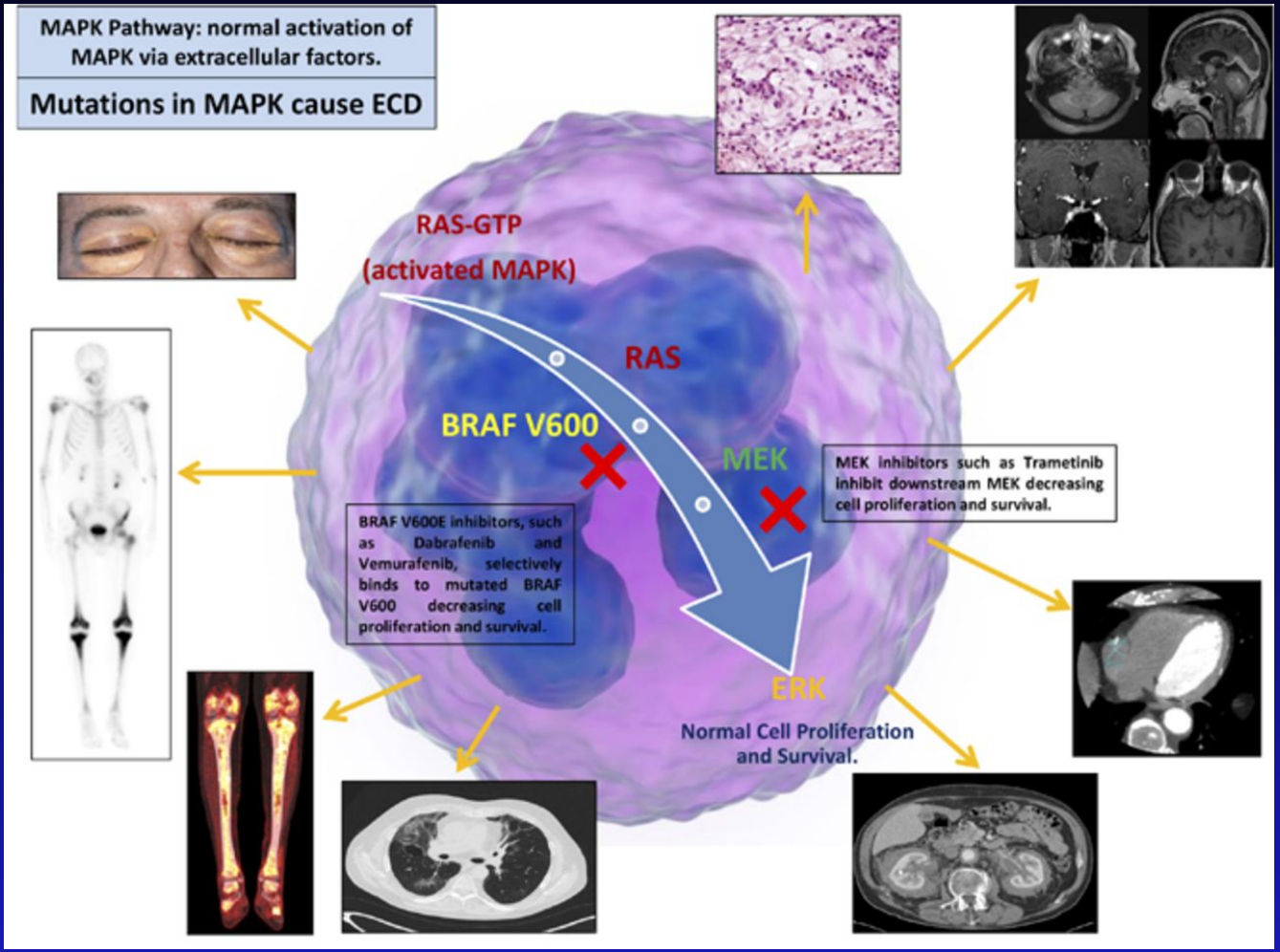
Paul Milne et al. Blood 2017;130:167-175

ECD Mutations



BRAF
NRAS
MAP2K

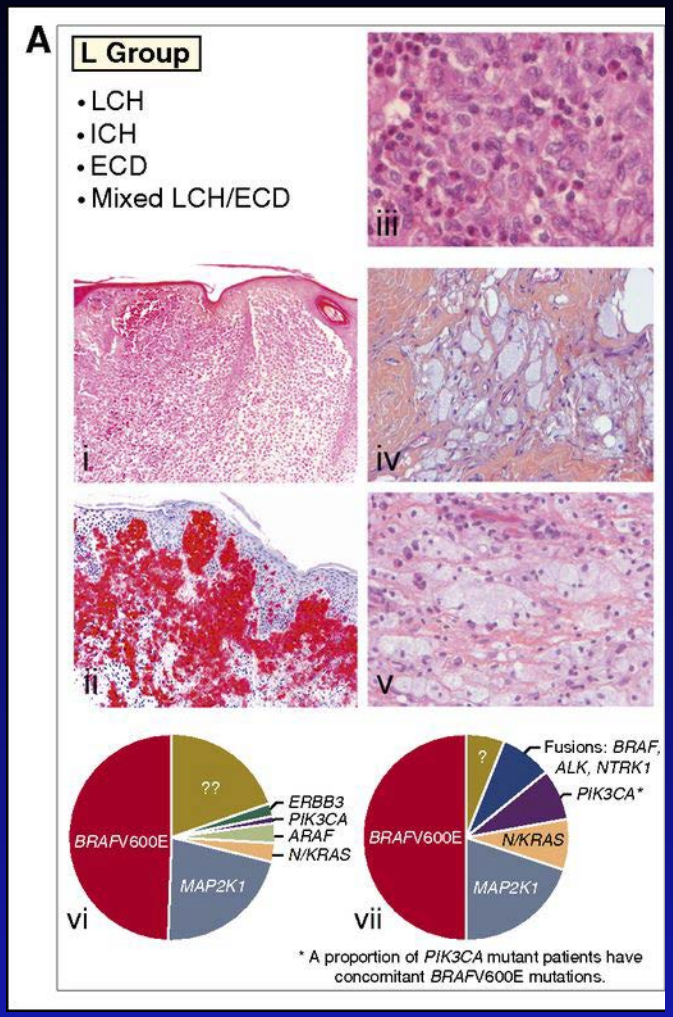
ECD Mutations



Significance of ECD Mutations

- BRAF mutations had been previously seen in other cancers (e.g. melanoma, thyroid, lung, Langerhans cell histiocytosis etc.)
  - BRAF inhibitory drugs had been previously tested
- Confirmed that ECD belonged in the “cancer family
- Allowed the biology of the disease to be better understood.

ECD Classification

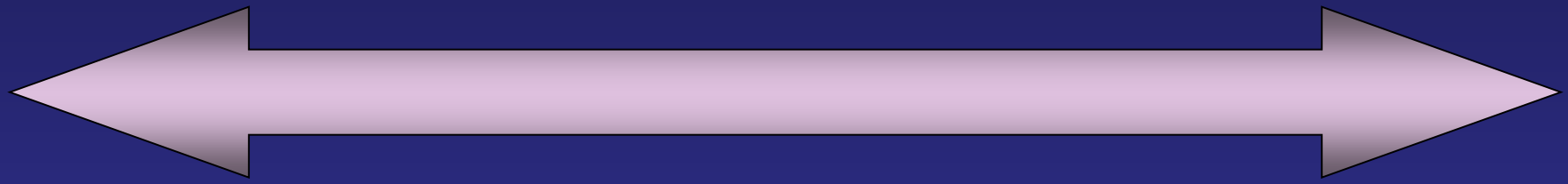


Jean-François Emile et al. Blood 2016;127:2672-2681

- Association between ECD and Langerhans cell histiocytosis
  - Patients with both rare histiocytoses
  - LCH usually preceded ECD
- ECD also seen in patients with other “monocytic” cancers

Histiocytic Diseases

Less aggressive **More aggressive**



Langerhans' cell histiocytosis

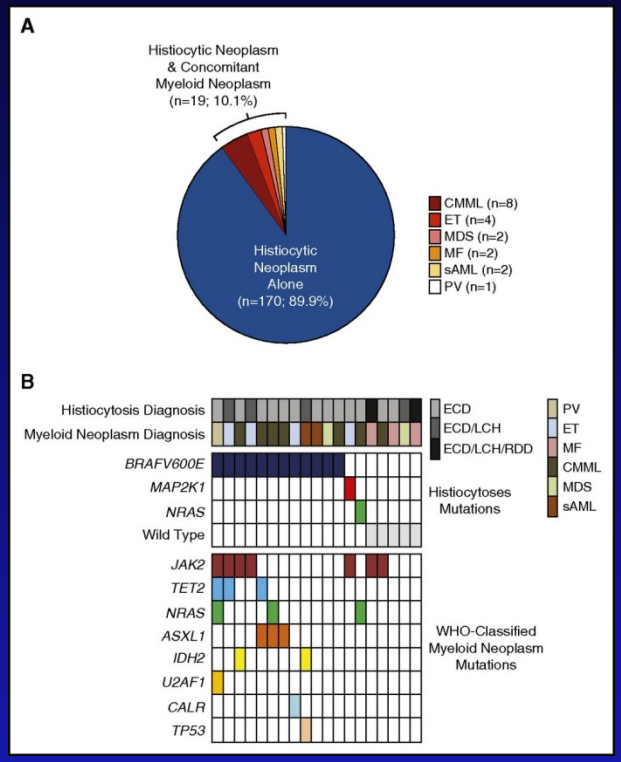
Erdheim-Chester Disease

Chronic Myelomonocytic Leukemia

Histiocytic sarcoma

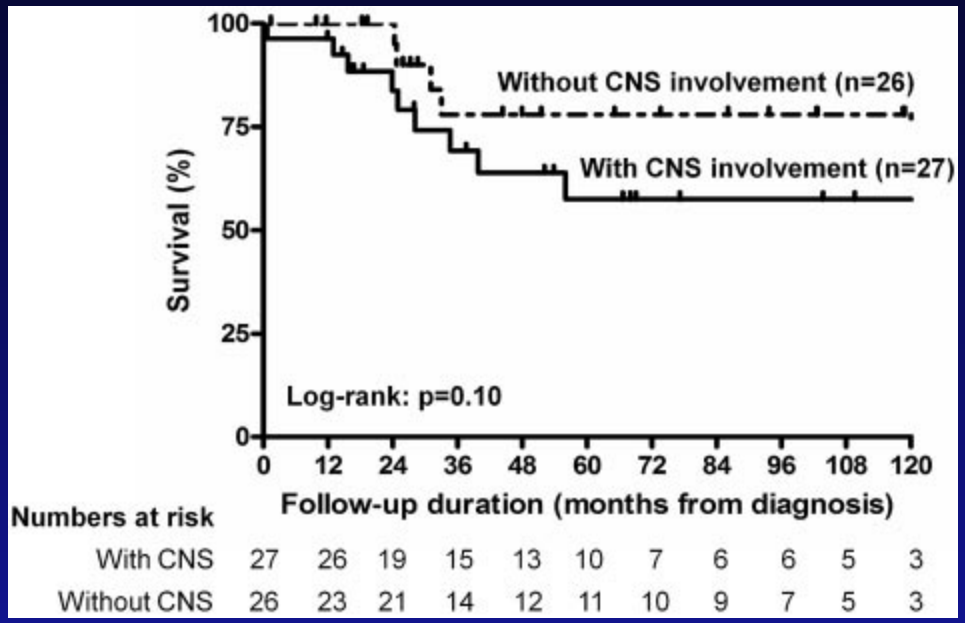
Acute monoblastic leukemia

Histiocytic diseases are more commonly associated with other blood cancers



Matthias Papo et al. Blood 2017;130:1007-1013

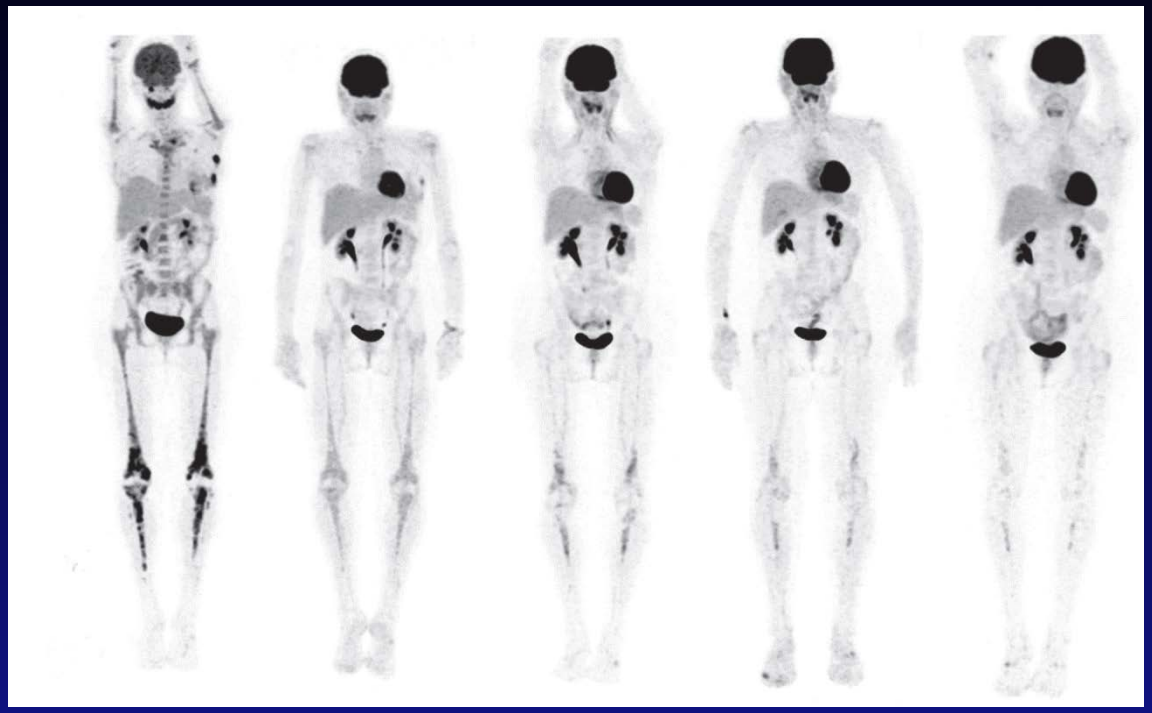
ECD Treatment-Interferon



- CNS involvement is associated with worse prognosis

Arnaud et al Blood 117:2778, 2011

ECD-Vemurafenib



8 patients with interferon-refractory ECD

- 100% response by 6 months
- Durable up to 16 months

Haroche et al J Clin Oncol 33:411, 2015

Response of ECD and LCH to Vemurafenib

Table 2. Preliminary Best Response According to Cohort.*

Variable	NSCLC (N=20)	Colorectal Cancer		Cholangio-carcinoma (N=8)	ECD or LCH (N=18)	Anaplastic Thyroid Cancer (N=7)
		Vemurafenib (N=10)	Vemurafenib + Cetuximab (N=27)			
Patients with ≥1 postbaseline assessment — no.	19	10	26	8	14	7
Complete response — no. (%)	0	0	0	0	1 (7)	1 (14)
Partial response — no. (%)	8 (42)	0	1 (4)	1 (12)	5 (36)	1 (14)
Stable disease — no. (%)	8 (42)	5 (50)	18 (69)	4 (50)	8 (57)	0
Progressive disease — no. (%)	2 (11)	5 (50)	7 (27)	3 (38)	0	4 (57)
Missing data — no. (%)†	1 (5)	0	0	0	0	1 (14)
Overall response — no. (%) [95% CI]	8 (42) [20–67]	0	1 (4) [<1–20]	1 (12) [<1–53]	6 (43) [18–71]	2 (29) [4–71]

Hyman et al N Engl J Med 373: 726-36, 2015

Other Therapies in ECD

"Conventional" Chemotherapies

- Cladribine (Goyal et al. JAMA Oncol.3:1253, 2017)
- Cytarabine (Cao et al. Ann Hematol epub ahead of print)
- Zoledronate (Poiroux et al. Joint Bone Spine 83: 573, 2016)

Other Therapies in ECD

"Anti-Inflammatory" Agents

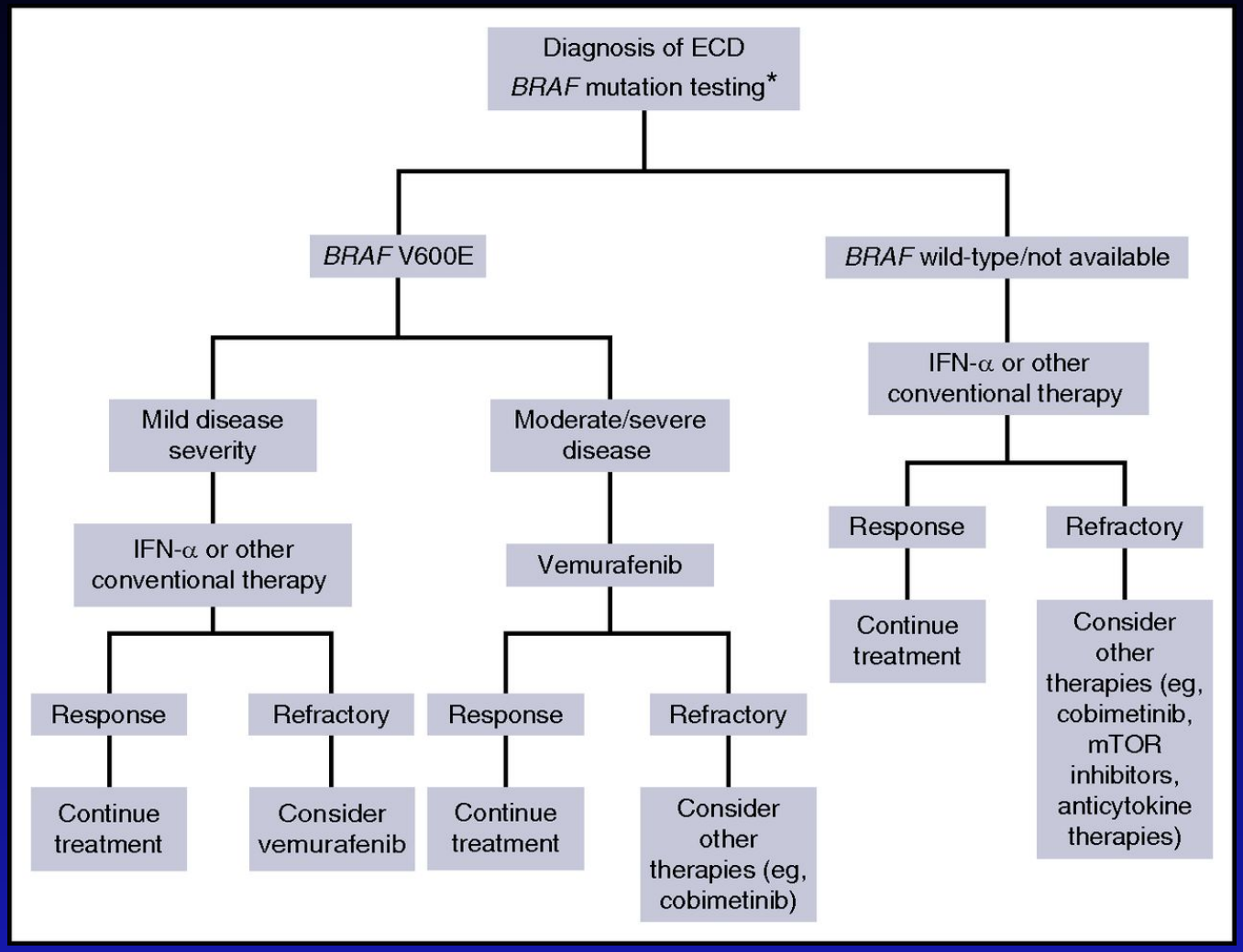
- Anakinra (Franconieri et al. Acta Oncol 55:930, 2016, Cohen-Aubart et al. Blood 127:1509, 2016, Diamond et al. Blood 128:1896, 2016)
- Infliximab (Dagna et al. J Clin Oncol 30:e286, 2012)
- Sirolimus (Gianfreda et al. Blood 126:1163, 2015)

Other Therapies in ECD

"Targeted" Agents (beyond BRAF inhibitors)

- Imatinib (Haroche et al. Blood 111:5413, 2008)
- Cobimetinib (Diamond et al. Cancer Discov 6:154, 2016, Cohen-Aubart et al. Epub ahead of print)
- Trametinib (Nordmann et al. Blood 129:879, 2017)

Proposed Therapeutic Approach to ECD



Augusto Vaglio, and Eli L. Diamond Blood 2017;130:1282-1284

Proposed Therapeutic Approach to ECD

	Treatment	Recommendations
First-line therapy	Interferon alfa or pegylated interferon alfa	Best choice as front-line treatment of Erdheim-Chester disease; tolerance issues observed (fatigue, depression); pegylated form is better tolerated; this treatment is a major independent predictor of survival in Erdheim-Chester disease;[63] higher doses (9 million units given three times per week) recommended in cases with meningeal infiltration, subsellar and retrosellar masses, and pericardial and pseudo-atrial infiltration
Second-line therapy (or first-line therapy for life-threatening manifestations)	Vemurafenib and other BRAF inhibitors	Most impressive treatment responses seen if *BRAF*^{V600E} mutation is present (in 57–70% of patients) in multisystemic and refractory Erdheim-Chester disease despite interferon alfa therapy (eg, CNS and cardiovascular complications of Erdheim-Chester disease); safety issues (in particular, development of squamous-cell carcinoma); informed and signed consent mandatory; optimal length of treatment to be determined in future studies and in particular with the LOVE trial (NCT02089724); less effective in neurodegenerative Erdheim-Chester disease; vemurafenib accessible through the basket trial (NCT01524978) in the USA and the AcSé trial in France (NCT02304809)
Second-line therapy (or first-line therapy for life-threatening manifestations)	Cobimetinib and other MEK inhibitors alone or in combination	MEK inhibitors seem promising (perhaps even more so than BRAF inhibitors) in patients with wild-type BRAF; combination therapy (anti-BRAF plus anti-MEK) seems efficacious; a trial of combination therapy with trametinib plus dabrafenib (NCT02281760) is ongoing in the USA; the cobimetinib trial (NCT02649972) initiated for patients with wild-type *BRAF* or *BRAF*^{V600E} who are unable to take a BRAF inhibitor or have previously received treatment with a BRAF inhibitor that was discontinued because of intolerable side-effects or toxicity before disease progression is ongoing
Second-line therapy	Steroids	Usually not effective in Erdheim-Chester disease, except in severe exophthalmos or macrophage activation syndrome
Second-line therapy	Anakinra	Effective in mild Erdheim-Chester disease (bone pain, high concentrations of C-reactive protein); disappointing responses in severe cases with CNS and heart complications (eg, cardiac tamponade occurring with therapy)
Second-line therapy	Double autologous stem cell transplantation	Anecdotal efficacy was reported in 3 of 3 patients with Erdheim-Chester disease, but no improvement was seen in 2 of 3 patients[77]
Second-line therapy	Cladribine	Potential benefit observed in treatment of Erdheim-Chester disease with CNS involvement refractory to interferon alfa,[78] but unfavourable outcomes observed in unpublished small-scale studies at Pitié-Salpêtrière Hospital
Second-line therapy	Infliximab	Beneficial after 12–18 months in 2 of 2 patients with Erdheim-Chester disease with cardiac involvement; efficacy needs to be studied further[79]
Second-line therapy	Imatinib	Effective in three histiocytosis cases, but discouraging results seen in 6 of 6 patients with Erdheim-Chester disease in another study[80]
Second-line therapy	Sirolimus	Objective responses or disease stabilisation seen when combined with prednisone[25]

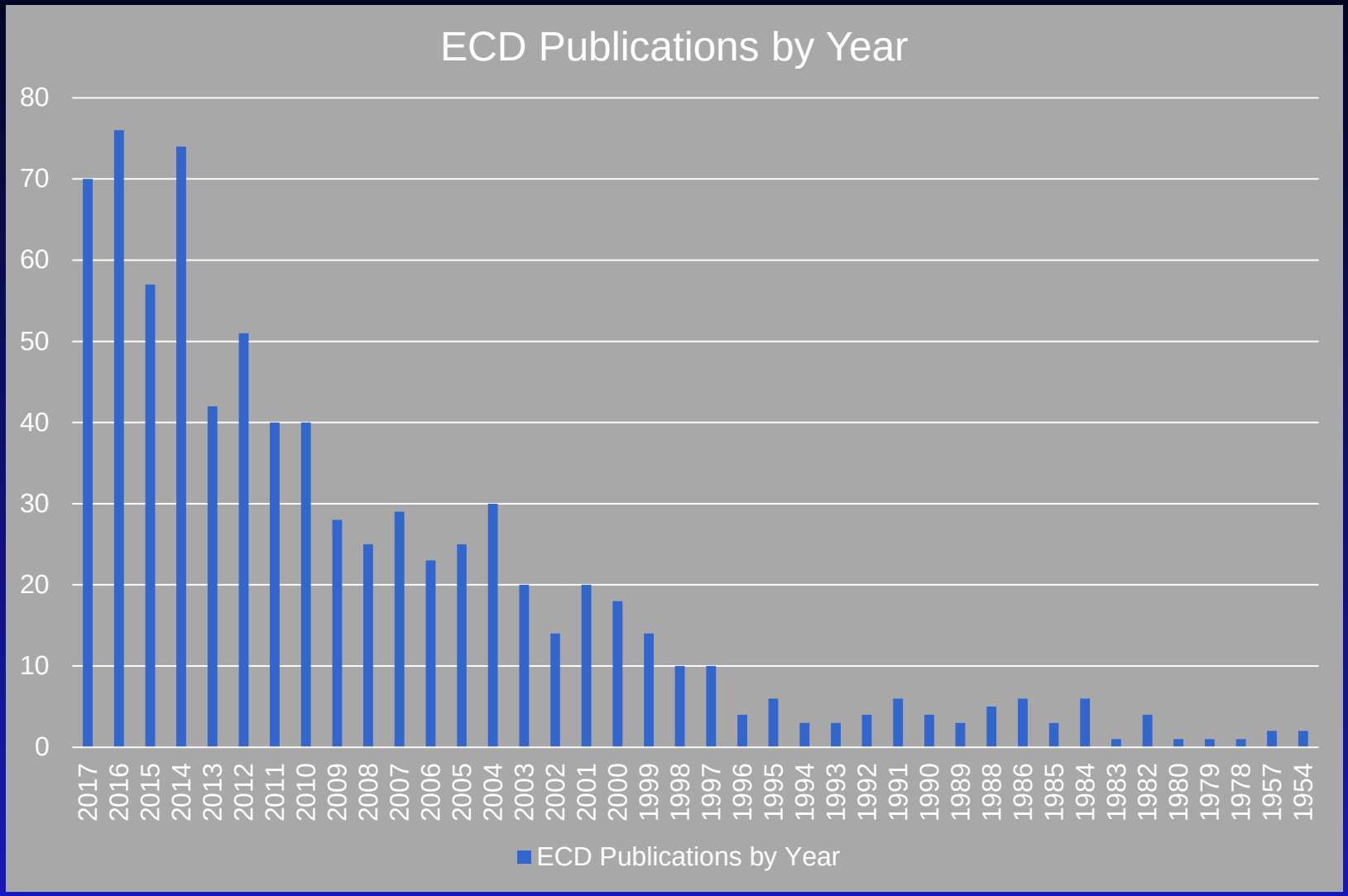
Table 2: Treatment recommendations for patients with Erdheim-Chester disease

Haroche et al. Lancet Oncol 2017;18:e113-e125

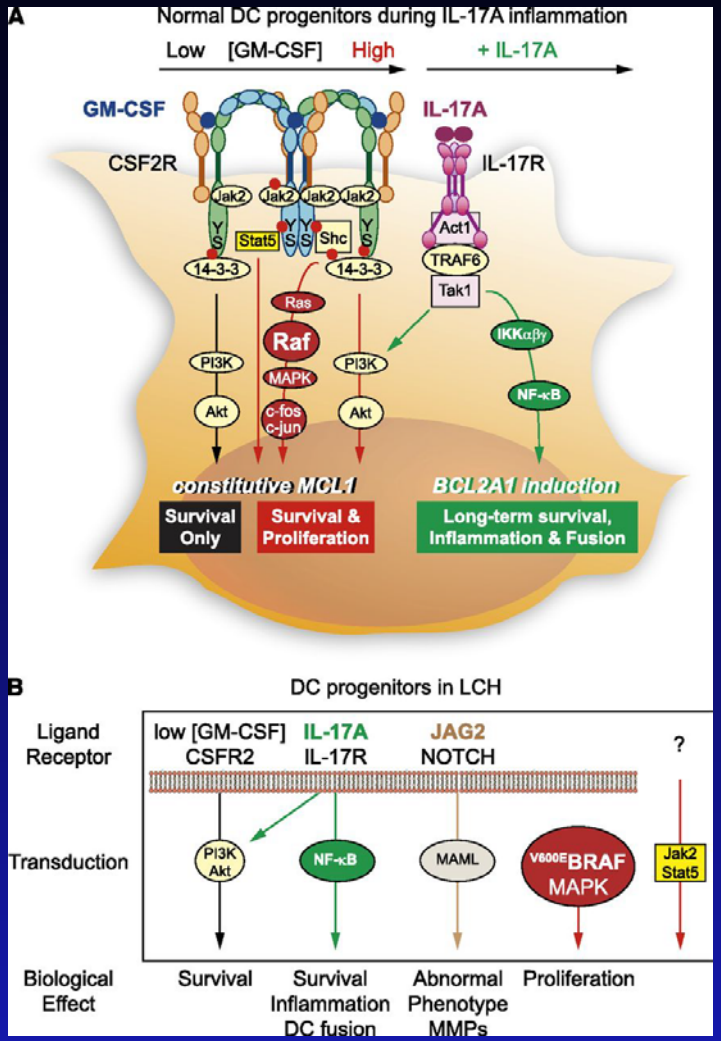
Challenges in ECD for 2018

- Nomenclature and classification
  - Underlying biology
- Treatment
  - Paucity of patients prevents the establishment of standard treatments
    - **Need for participation in the registry!!!**
  - Heterogeneity of diseases hinders the development and recognition of effective therapy

The Promise of the Future

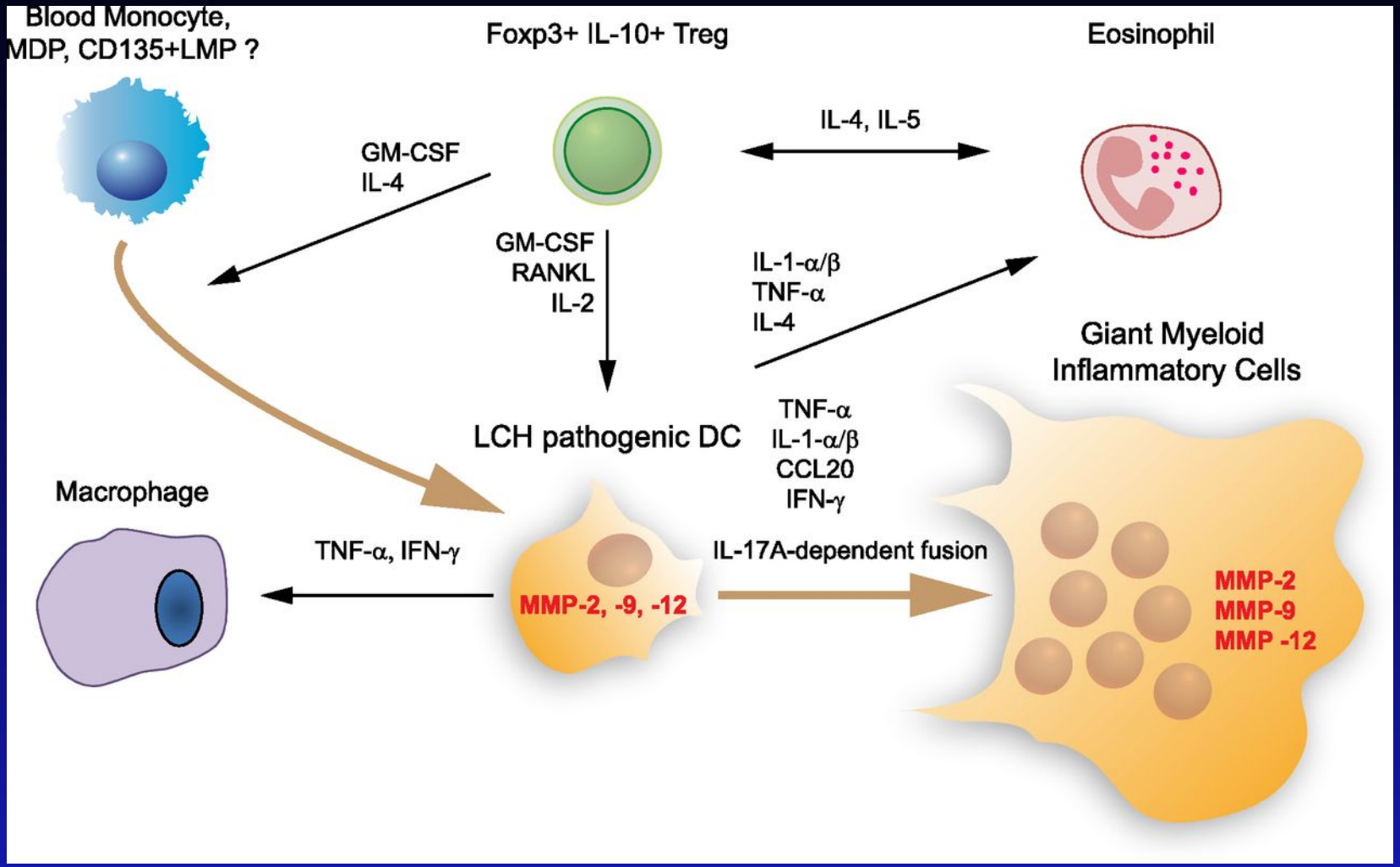


Mechanisms of accumulation of LCH pathogenic DCs through proliferation and prolonged survival.



Christine Delprat, and Maurizio Aricò Blood 2014;124:867-872

Major cell, cytokine, and protease players in LCH lesion.



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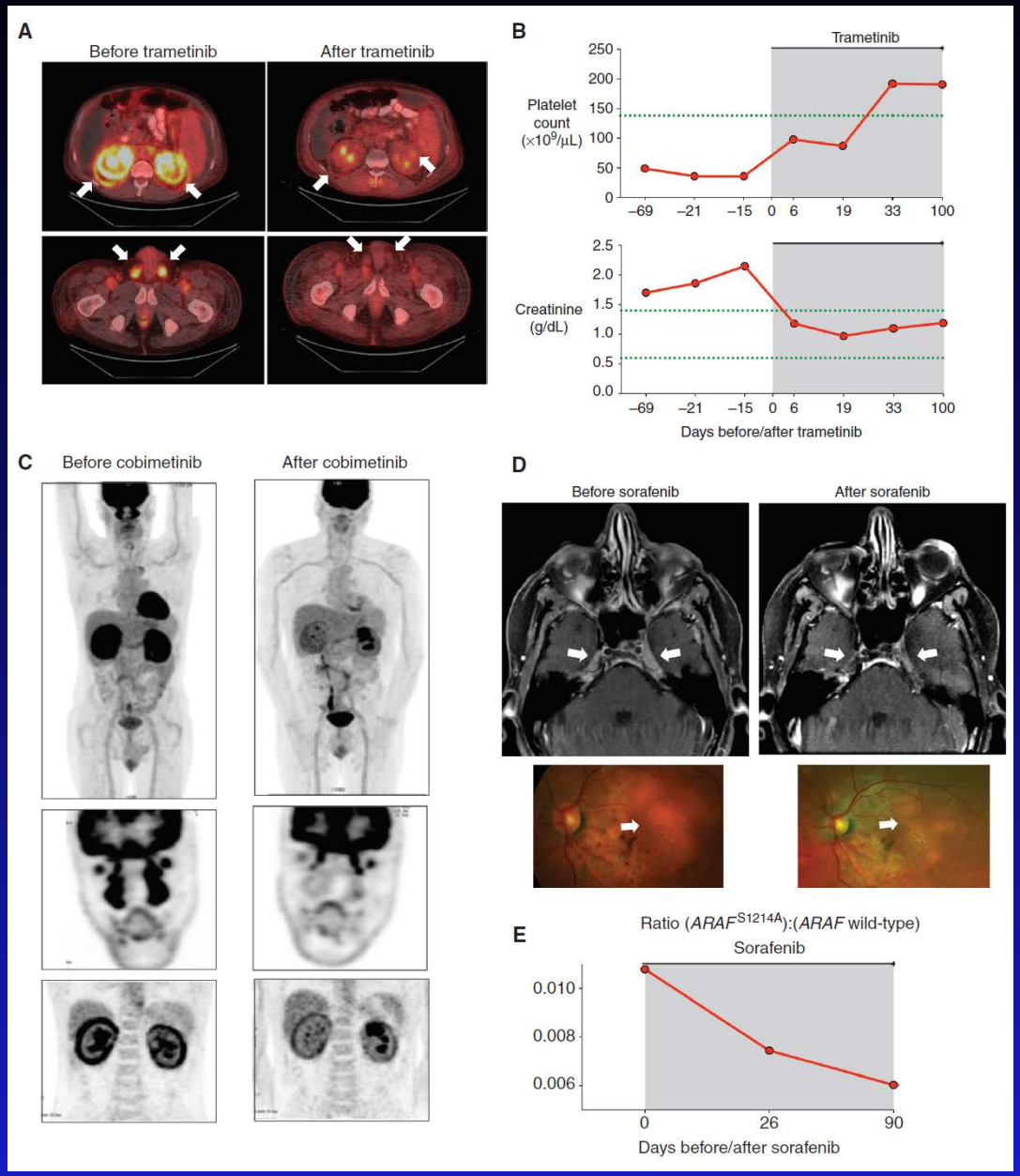
Histiocytosis response to other targeted agents



Diamond et al Cancer Discov 6:154, 2015