ECD treatment options: current (and on the horizon)

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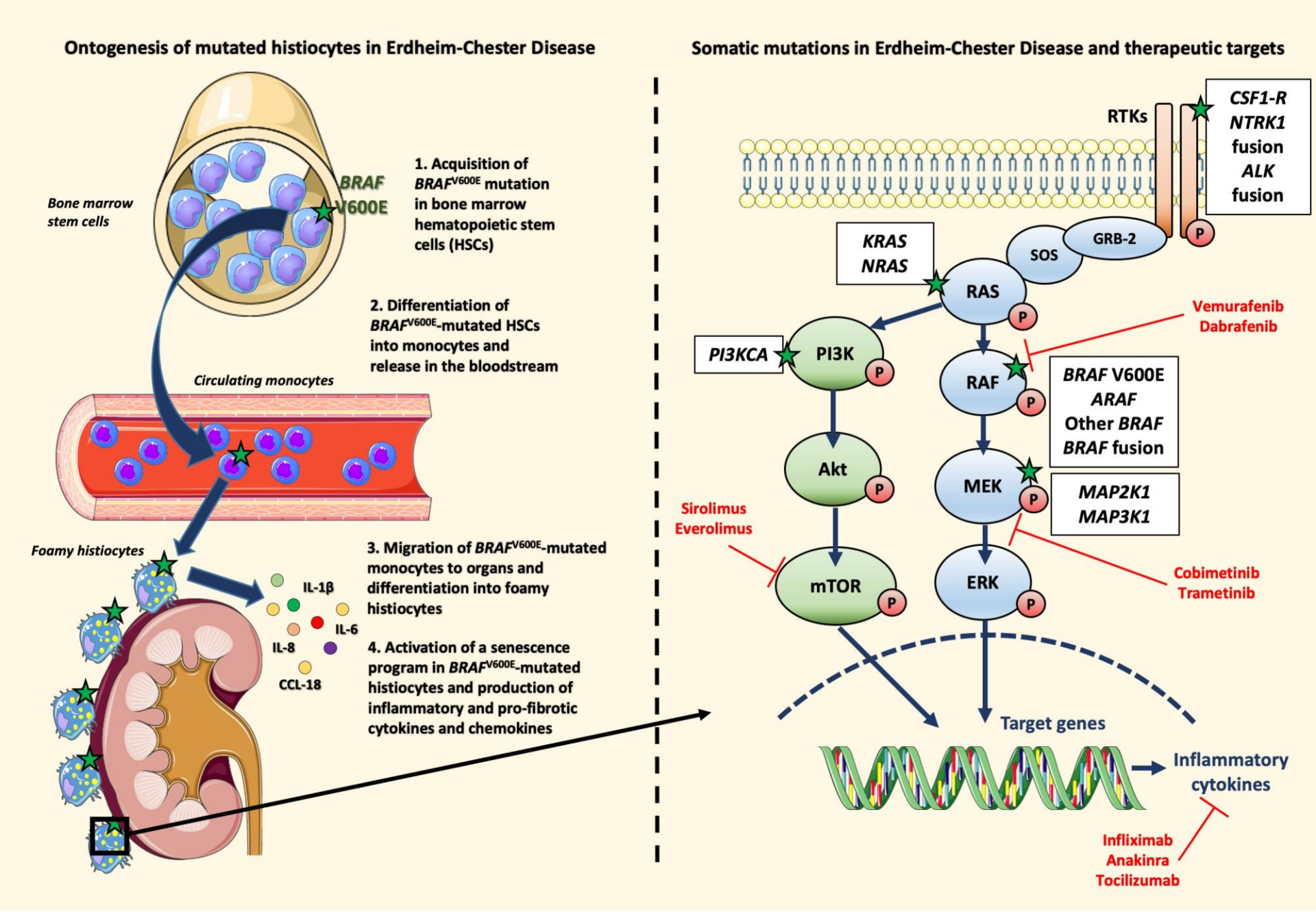
May 26nd 2025
ECD GA, 10th Annual Meeting
Bareclona

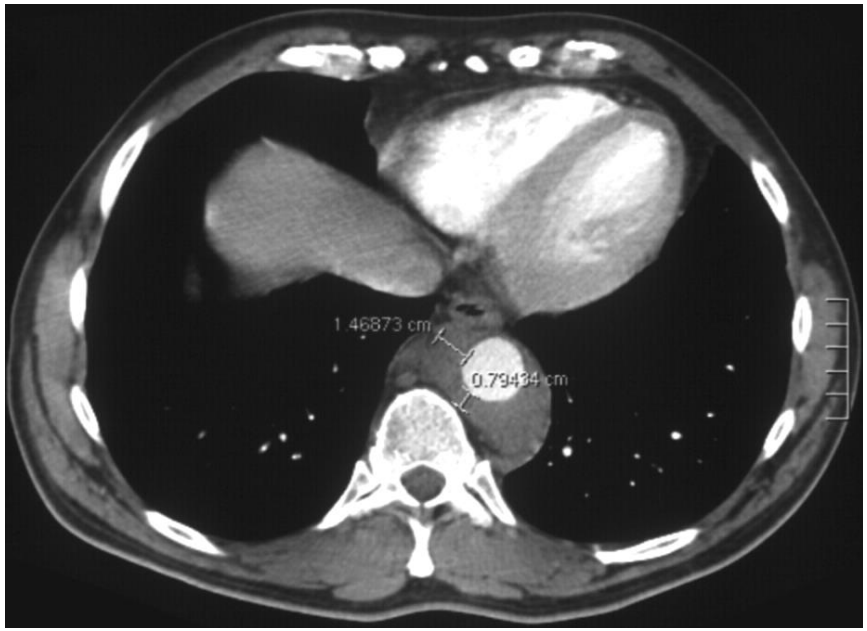
Plan

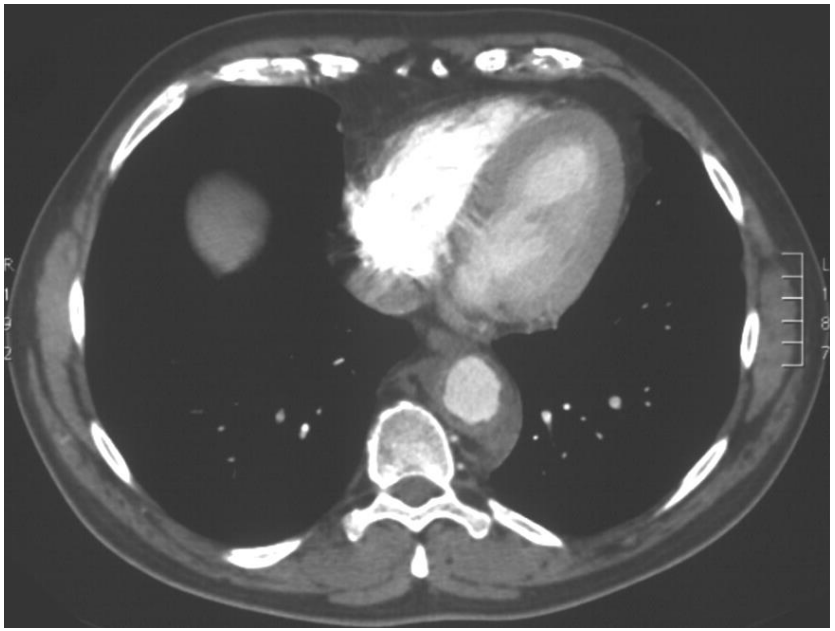
- Hear about the current treatment options available to help someone living with ECD
- Which treatments are considered under different circumstances?
- How are treatments administered and for what length of time? How is dosage determined? What is the lowest level of treatment possible?

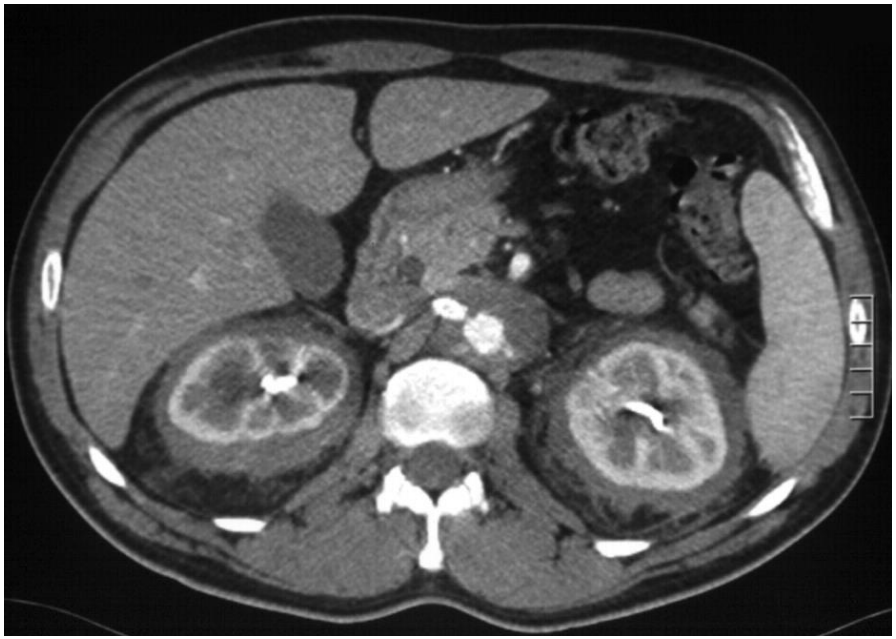


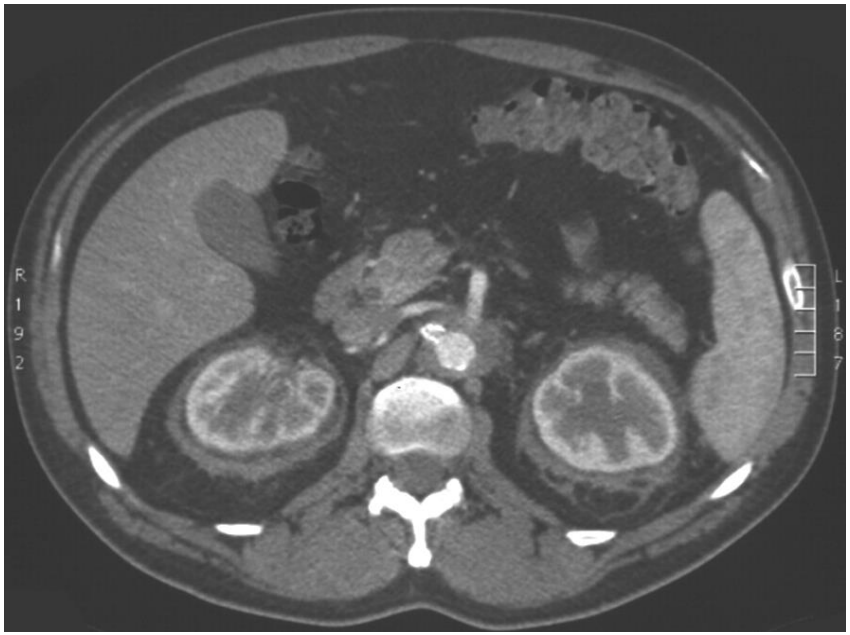
Pegoraro, *Leukemia* 2020

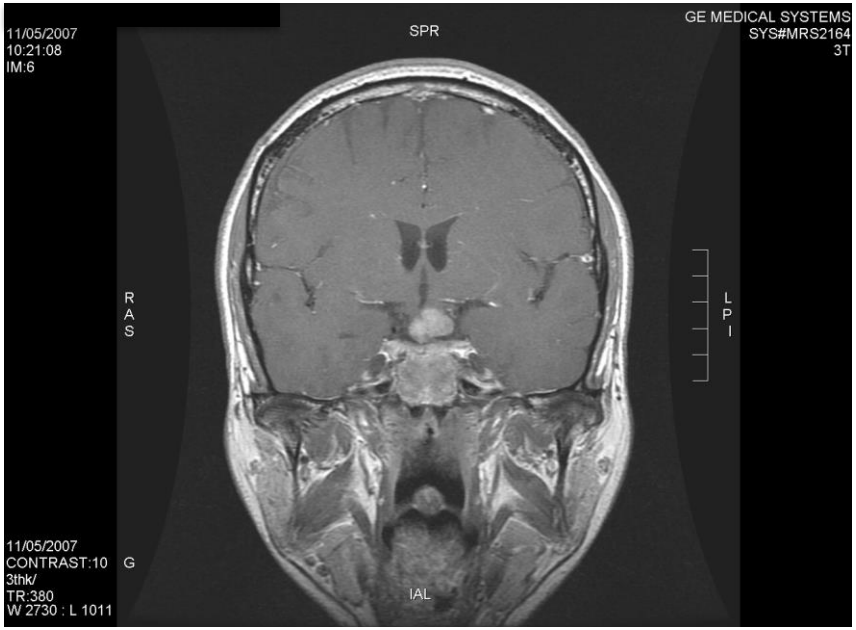
Interferon alpha 3M X 3



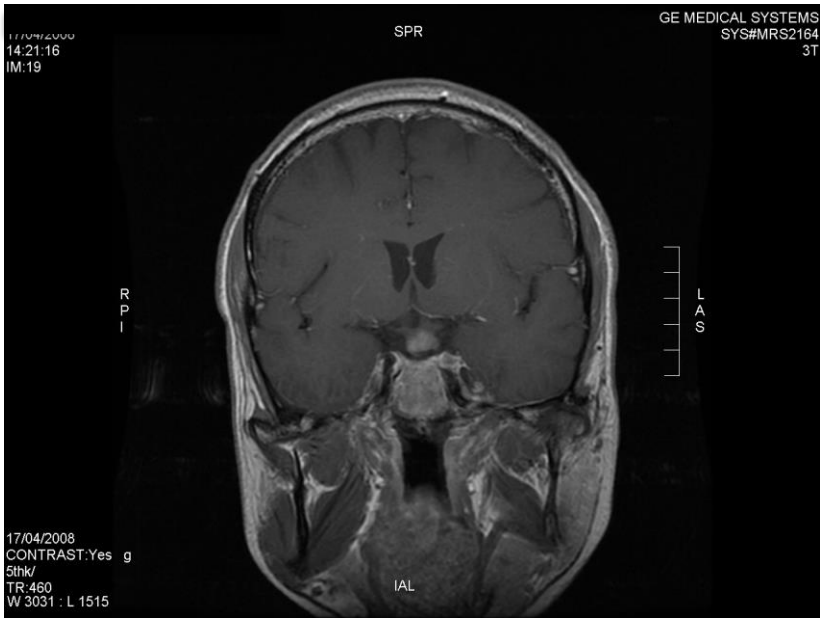








05/2007



04/2008

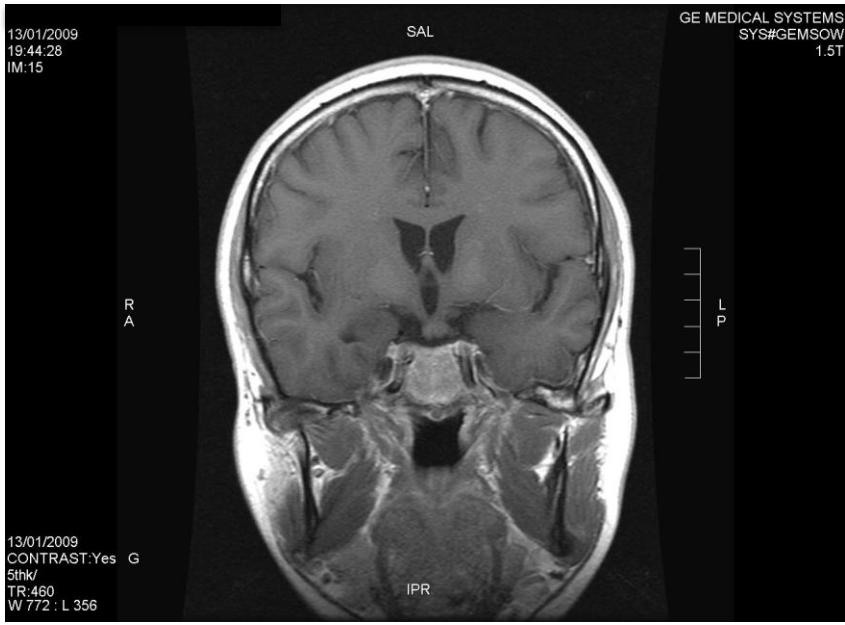
Man, 30-year-old, referred to our institution in October 2006

ECD diagnosed on bone biopsy in September 2002

CNS involvement only with sus and retro-sellar infiltration with diabetes insipidus, hypogonadism and complex partial seizures

Major side effects to vinblastine in 2002

IFN alpha 9 M x 3 per week initiated in October 2006

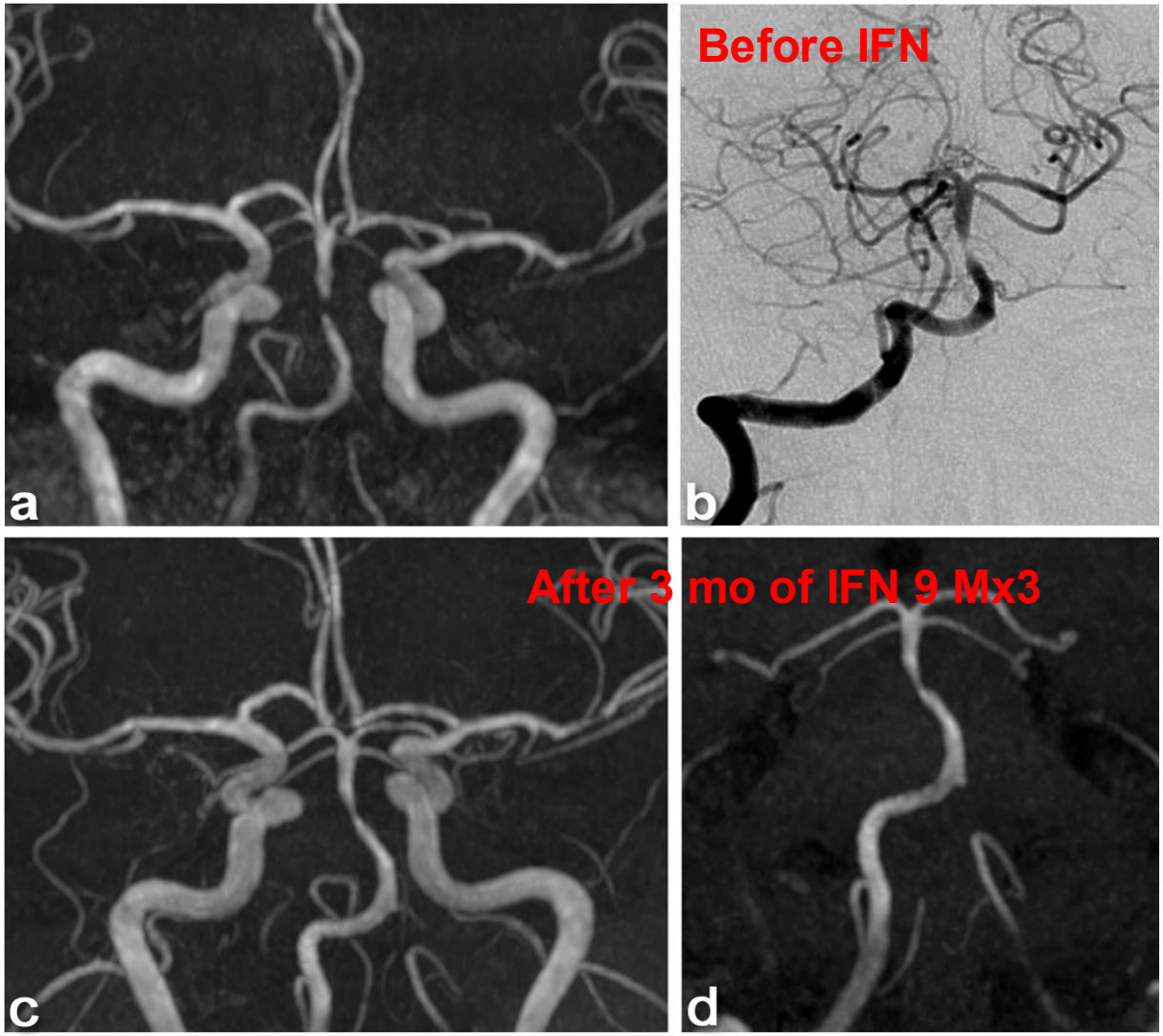


01/2009

60-year-old woman, elevated CRP, recurrent sinusitis, bilateral stenosis of the renal arteries, periaortic infiltration, pericardial effusion and a right atrial tumour

In August 2007, sudden cortical blindness associated with memory impairment.

Cerebral MRI revealed multiple vertebro-basilar ischemic infarcts, due to a severe narrowing of the basilar artery



IFN alpha treatment was initiated and at 3 mo, clinical and biological outcome were favourable. Cardiovascular investigations showed partial regression of atrial infiltration and complete regression of pericardial effusion. Cerebral MRI showed important regression of basilar stenosis (50% versus prethrombotic).

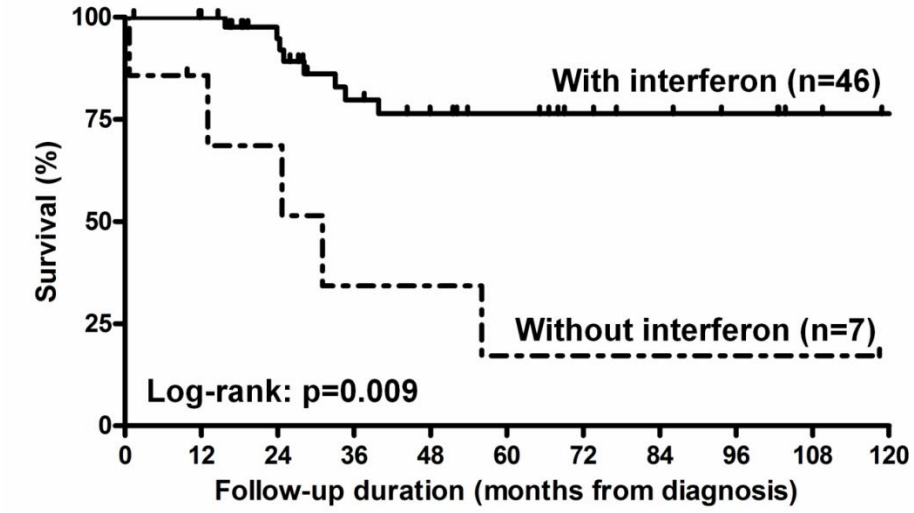
Brief report

BLOOD, 1 NOVEMBER 2005 • VOLUME 106, NUMBER 9

Successful treatment of Erdheim-Chester disease, a non–Langerhans-cell histiocytosis, with interferon-α

Fadi Braiteh, Cynthia Boxrud, Bita Esmaeli, and Razelle Kurzrock

CNS involvement and treatment with interferon-alpha are independant prognostic factors in Erdheim-Chester disease: a multicenter survival analysis of 53 patients



Numbers at risk											
Interferon-alpha	46	43	35	26	22	19	15	13	11	8	6
No interferon-alpha	7	6	5	3	3	2	2	2	2	2	1

Arnaud, Hervier, Haroche, et al. Blood 2011

2nd line

Anakinra

Aouba *Blood* 2010
Cohen-Aubart *Blood* 2016

Remicade

Cohen-Aubart *ARD* 2018

Sirolimus

Gianfreda *Blood* 2015
Pegoraro *Blood* 2020

BRAFi & MEKi

My thoughts about PEG-INF

- I believe most patients should be treated (***unless*** no pain, CRP negative, no heart / CNS, very limited disease; in these rare situations « wait and see » possible)
- PEG-INFa remains a good first-line TT in pts not « too old », with no psychiatric contraindication; interesting in pts with overt MPN. Worth giving a try for 6 mo to 1 - 2 yr and see if efficacious and tolerable. If not consider other therapy, in particular TT if indicated.
- I do not consider PEG-INFa anymore front-line in 2025 if CNS or heart (*i.e.* pericardium) involvements (unless if no access to TT).

Anakinra (kineret)

- Anti-IL1 receptor
- Good indication when bone pain and high CRP, in particular when CI to- or side-effects with PEG INF
- But heart and CNS can develop while on the drug
- In my opinion good option for mild-ECD

- Italian study (*Rheumatology*, 2025): interesting to associate with targeted therapies to improve drug retention

mTORi (sirolimus, everolimus)

- mTORi's, even if used as monotherapy, represent a valid alternative to conventional ECD treatments, as they induce high response rates and are generally well tolerated.
- In nonsevere disease or those who have no access or contraindications to targeted therapies or IFN-α.
- mTORi's induced responses in both *BRAF*^{V600E} and wild-type patients, they could be used irrespective of the *BRAF* status.

Inhibiteur de BRAF

Vemurafenib **Avril 2012 (France)**

Approved for unresectable or metastatic melanoma with the BRAF *V600E* mutation

Advised posology **960 mg twice /d** (**4 tablets x 2**)

Duration of treatment: untill progression of disease or unacceptable toxicity occurs

Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the *BRAF* V600E mutation

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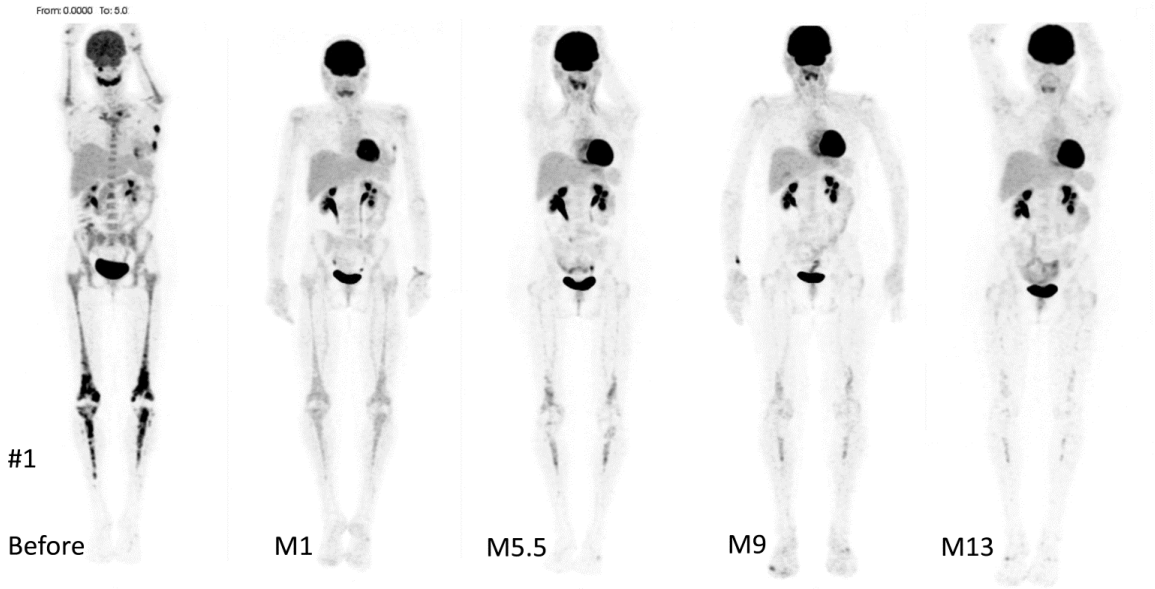
Key Points

- Treatment with vemurafenib induced a dramatic response in 3 patients with histiocytosis harboring *BRAF* V600E mutations.
- Tumor response was observed in both Erdheim-Chester disease and Langerhans cell histiocytosis.

Histiocytoses are rare disorders of unknown origin with highly heterogeneous prognosis. *BRAF*^{V600E} gain-of-function mutations have been observed in 57% of cases of Langerhans cell histiocytosis (LCH) and 54% of cases of Erdheim-Chester disease (ECD), but not in other types of histiocytoses. Targeted therapy with an inhibitor of mutated BRAF (vemurafenib) improves survival of patients with melanoma. Here, we report vemurafenib treatment of 3 patients with multisystemic and refractory ECD carrying the *BRAF*^{V600E} mutation; 2 also had skin or lymph node LCH involvement. The patients were assessed clinically, biologically (CRP values), histologically (skin biopsy), and morphologically (positron emission tomography [PET], computed tomography and magnetic resonance imaging). For all patients, vemurafenib treatment led to substantial and rapid clinical and biologic improvement, and the tumor response was confirmed by PET, computed tomography, and/or magnetic resonance imaging 1 month after treatment initiation. For the first patient treated, the PET response increased between months 1 and 4 of treatment. The treatment remained effective after 4 months of follow-up although persistent disease activity was still observed. Treatment with vemurafenib, a newly approved BRAF inhibitor, should be considered for patients with severe and refractory *BRAF*^{V600E} histiocytoses, particularly when the disease is life-threatening. (*Blood*. 2013;121(9):1495-1500)

Reproducible and sustained efficacy of targeted therapy with Vemurafenib in Eight patients with BRAFV600E mutated Erdheim-Chester disease

A



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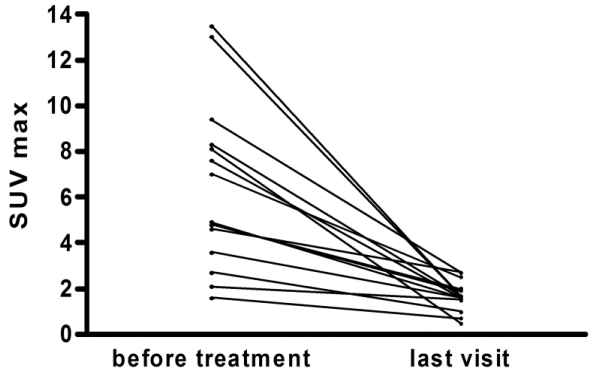


All patients were in PMR at M6

Haroche *J Clin Oncol* 2015

Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study)

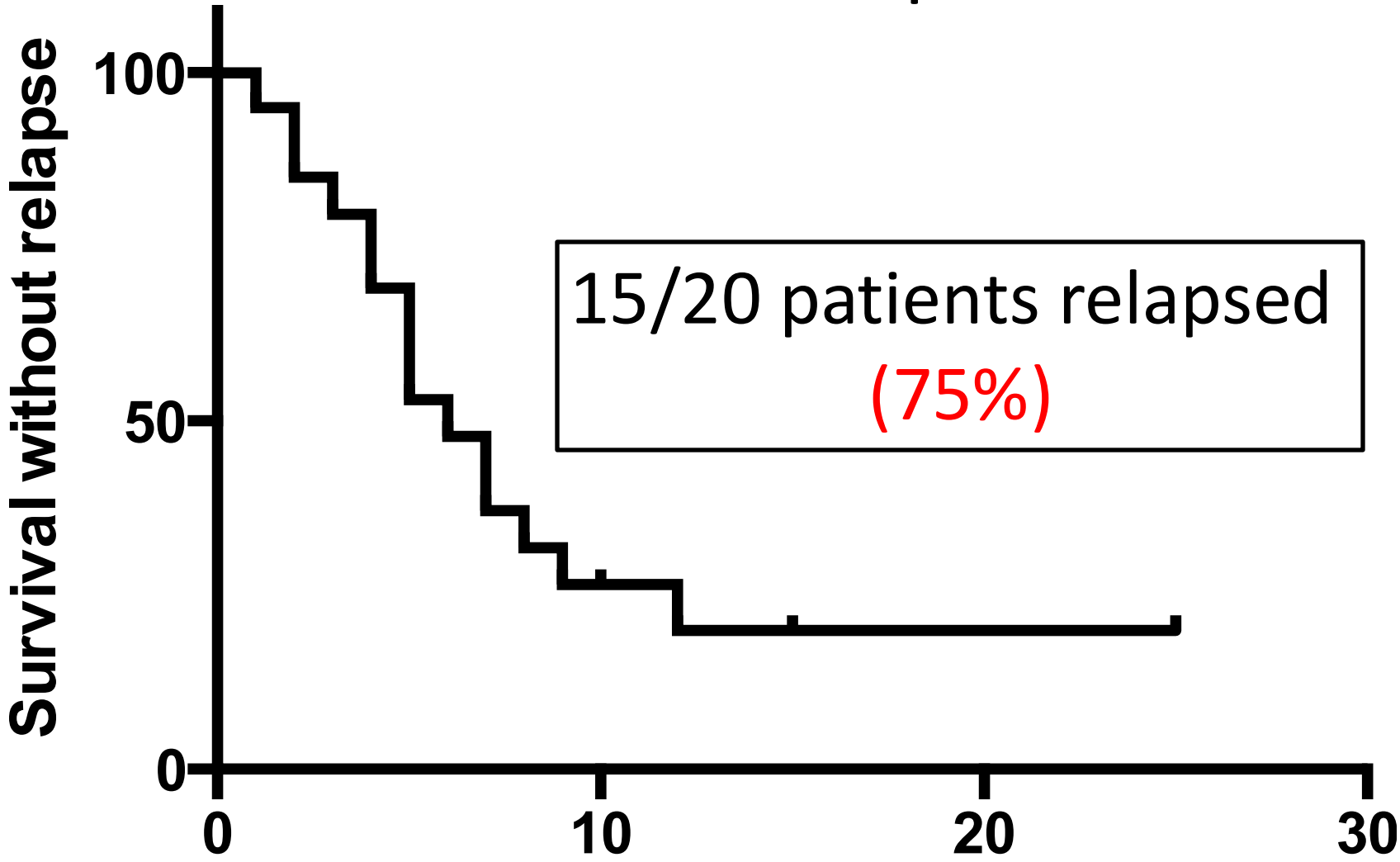
Table 1. Clinical characteristics of treated patients

	Vemurafenib* (n = 50) or dabrafenib (n = 1)	Cobimetinib (n = 15)
Sex	15 females and 36 males	3 females and 12 males
Age at diagnosis, median (range), y	57 (17-72)	56 (34-71)
BRAF^{V600E}	49 (96)	10† (67)
BRAF WT	2† (4)	5 (33)
Mixed histiocytosis (ECD + LCH)	15 (29)	5 (33)
CNS	26 (51)	9 (60)
Cerebellar	15 (29)	7 (47)
Lung	18 (35)	6 (40)
Vascular	39 (76)	12 (80)
Heart	38 (75)	10 (67)
Xanthelasma	19 (37)	3 (20)
Diabetes insipidus	23 (45)	5 (33)
Retroperitoneal fibrosis	33 (65)	11 (73)
Bones	44 (86)	13 (87)
Previous treatments		
Anakinra	6 (12)	2 (13)
Interferon-α	36 (71)	11 (73)
Deaths	5 (10)	0
Targeted treatments‡		
Vemurafenib/dabrafenib, n	51	12
Cobimetinib, n	12	15

In 2025, 250 pts have received targeted therapies in our center

Cohen-Aubart, *Blood* 2017

The *LOVE* study : relapses after treatment interruption



Cohen-Aubart, *Blood* 2017

BRAF inhibitors

- Full dose (8 VEM as for melanoma): NOT tolerable (since first studies in 2012)
- Full dose = 4 VEM a day
- Usually start at 4 VEM and generally taper to 3 VEM at 6 mo, 2 VEM at 12-18 mo, and 1 at 2 yr depending on tolerance and efficacy (really a case-by-case decision)
- Intermittent dosing: tolerable to nearly everyone (needs further study with blood dosage & PK)

- No CNS disease: low-mid dosing to best response and then as low/frequent dosing to maintain
- If CNS disease: mid-high dosing to best response and then intermittent mid-high dosing (interval determined by side effects; as little as one week on, three weeks off) (Eli Diamond strategy)

- Skin surveillance twice per year for SCC / BCC / melanoma / keratoacanthoma. Photoprotection +++

MEK inhibitors

- Full dose for cancer (60 mg COBIMETINIB): Very rarely tolerable in ECD (gut, skin) ; full dose = 40 mg
- Usually start at 40 mg COBI and generally taper to 20 mg at 1 or 2 years depending on tolerance and efficacy (really a case-by-case decision, sorry to insist on this point)

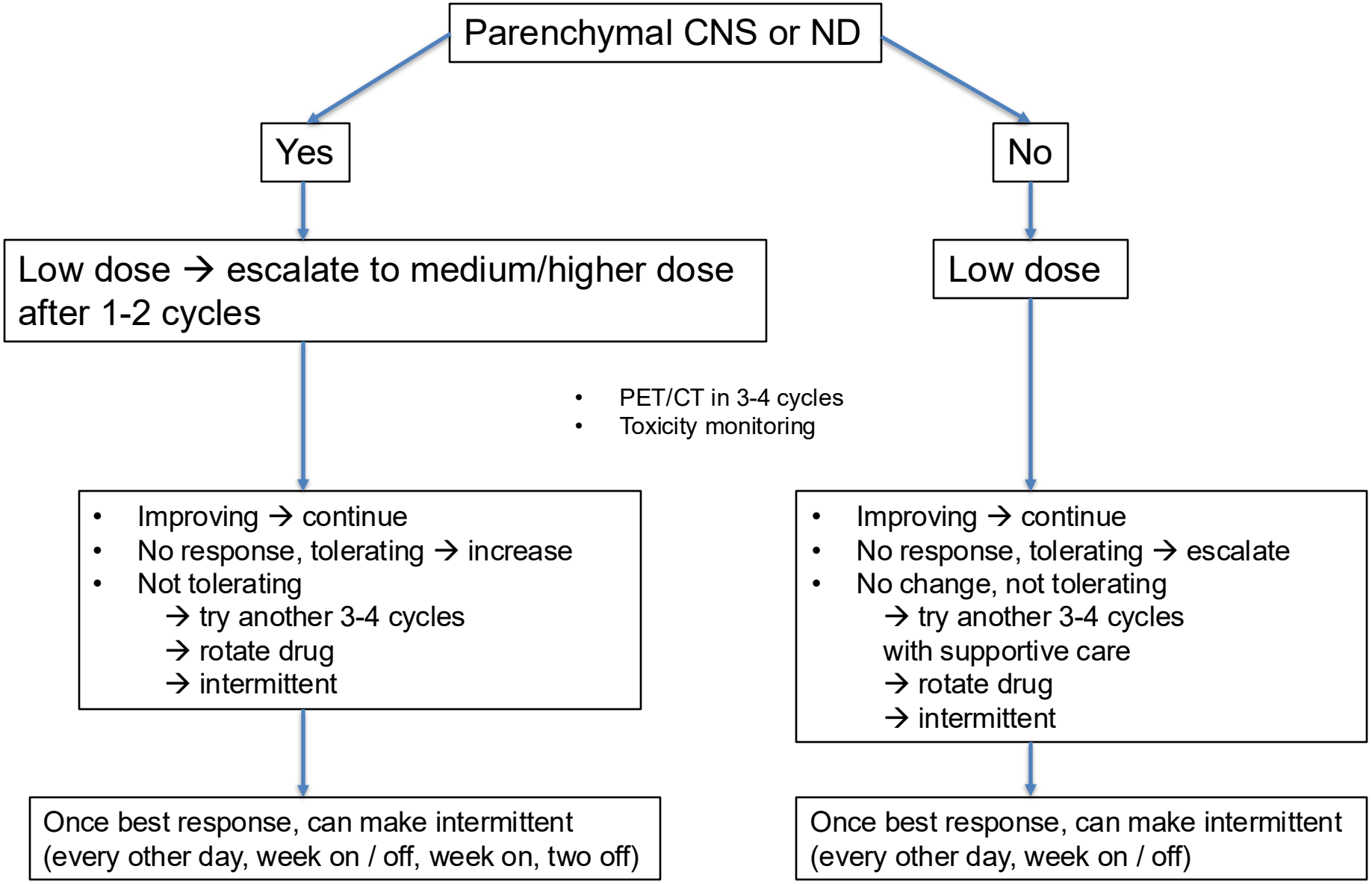
- Intermittent dosing: probably an option after reaching a plateau or best response; needs further study with blood dosage & PK

- No CNS disease: low-mid dosing to best response and then as low/frequent dosing to maintain
- CNS-disease: mid-high dosing to best response and then intermittent mid-high dosing (interval determined by side effects)

- Eye examination and echocardiography prior to and on treatment

Courtesy of
Eli DIAMOND

Specific Dosing Strategy



Rotate drugs in the same class to try manage side effects

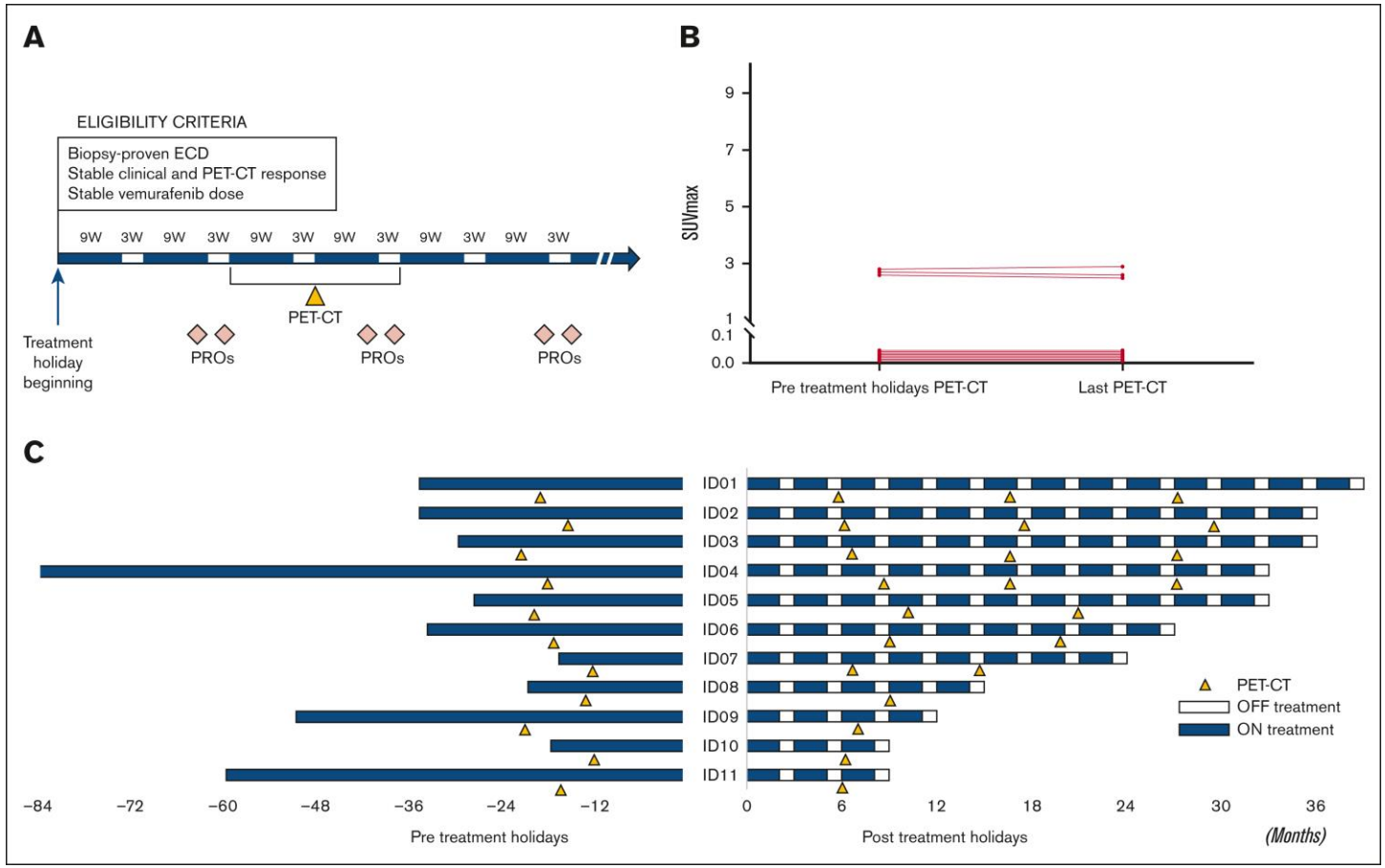
- VEMURAFENIB / DABRAFENIB / ENCORAFENIB
- COBIMETINIB / TRAMETINIB / BINIMETINIB

Sometimes usefull but class effect (for incense pancreatitis with BRAFi, cardiac toxicity with MEKi)

BRAFi and MEKi inhibition

- BRAFi monotherapy for BRAF mutated ECD, MEK otherwise (unless mutant outside the MAP pathway)
- The risk of paradoxical activation of the MAPK pathway occurs when a BRAF inhibitor is used while there is also a RAS mutation (KRAS, NRAS or HRAS).
- This paradoxical activation of the MAPK pathway can lead to an acceleration of an underlying hematological disease (MDS, CMML or MPN which can all have RAS mutations).
- Worsening of hematological diseases/AML have been described in some patients with RAS-mutated myeloid hematological diseases who have received a BRAF inhibitor, although the incidence is completely unknown.

Treatment holidays in patients with Erdheim-Chester disease receiving vemurafenib: a prospective pilot study



Dual therapy ?

- Consider dual BRAF/MEK or single-agent MEK for BRAF-mutated
  - Concurrent MPN (JAK2 ?, Cal-R?, RAS mutant)
  - Other cancers plausibly with these mutations, TP53
  - Massive/bulky → dual
  - Parenchymal symptomatic CNS → dual
- Probably also when ND with recent onset
- Further studies needed
- Problem managing toxities with this strategy

RESEARCH ARTICLE

Sustained, complete response to pexidartinib in a patient with *CSF1R*-mutated Erdheim–Chester disease

Jithma P. Abeykoon, Terra L. Lasho, Surendra Dasari, Karen L. Rech, Wasantha K. Ranatunga, Michelle K. Manske, Alexander Tischer, Aishwarya Ravindran, Jason R. Young **... See all authors**

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Abstract

Erdheim–Chester disease (ECD) is a histiocytic neoplasm that predominantly harbors mitogen-activated protein kinase (MAPK) pathway variants. MAPK inhibitors typically are effective treatments, but mutations outside the MAPK pathway, such as *CSF1R* variants, may cause refractory ECD. We describe a patient with a novel somatic mutation in *CSF1R* (*CSF1R*$^{R549\_E554delinsQ}$) that resulted in refractory ECD affecting the central nervous system. Cell model studies, RNA sequencing analysis, and *in silico* protein modeling suggested that she had a gain-of-function mutation occurring in a region critical for autoinhibition. The patient was treated with pexidartinib, a CSF1R inhibitor, and has had a complete clinical and metabolic response lasting more than 1.5 years to date. To our knowledge, this is the first report to describe successful treatment of a patient with ECD by using an agent that specifically targets CSF1R. This case also highlights the critical role of individualized molecular profiling to identify novel therapeutic targets in ECD.

Other treatments and prevention

- DDAVP, thyroid and all endocrinopathies
- Pain killers (NSAID, opïoids, steroids with BRAFi)
- Antidepressive drugs
- Doxicycline (with MEKi)
- Vaccines (especially if non targeted with pneumococcus, zoster, flu, COVID)
- Kinesitherapy

Take home messages (I)

- ECD = myeloid inflammatory neoplam; 10% pts have overt hematologic malignancy (MPN, MDS): therapeutic implications
- BRAF mutation is associated with cardiac & neurologic phenotype in ECD.
- ND only with BRAF
- Interferon-alpha & targeted therapies (BRAF and/or MEK inhibitors) improve survival of ECD patients.
- LOVE Study : 75% ECD & mixed histiocytosis relapse; rechallenge always works
- No resistance to BRAFi in ECD (or mixed histiocytosis) after > 13 years, no resistance to MEKi with follow-up period of 10 years; ≈ 240 adults treated at Pitié-Salpêtrière
- Current strategy never stop TT: taper and…?

Take home messages (II)

- New approaches : TT holydays +++; or stop TT and go back to conventionnal therapy (PEG-INF, Sirolimus); case-by-case discussion (always)
- Future : Pan-ERK / pan-RAF agents, CSF1r inh ?
- Off label or BRAF & MEKi use in France and Europe (ODD); no EMA approval
- Only treat severe patients: heart and/or CNS (frequent SAE)
- BRAF & MEKi effective, but safety issues, acsessibility, cost
- Future: monitoring / dosage of drugs, blood *BRAF* & *MAP2K1* VAF (liquid biopsy)
- Ongoing international clustering project with > 1100 ECD patients will probably help refine treatment strategy

Thank you

The patients / family / care givers

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