Maladie de Rosai-Dorfman
Maladie d'Erdheim-Chester

Julien Haroche
Fleur Cohen-Aubart
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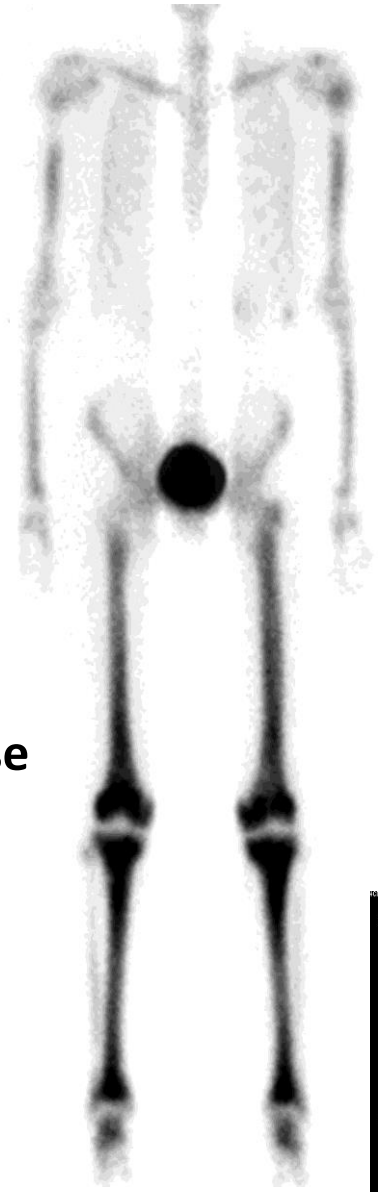
Service de Médecine Interne 2
Centre de Référence des Histiocytoses
Groupe Hospitalier Pitié-Salpêtrière

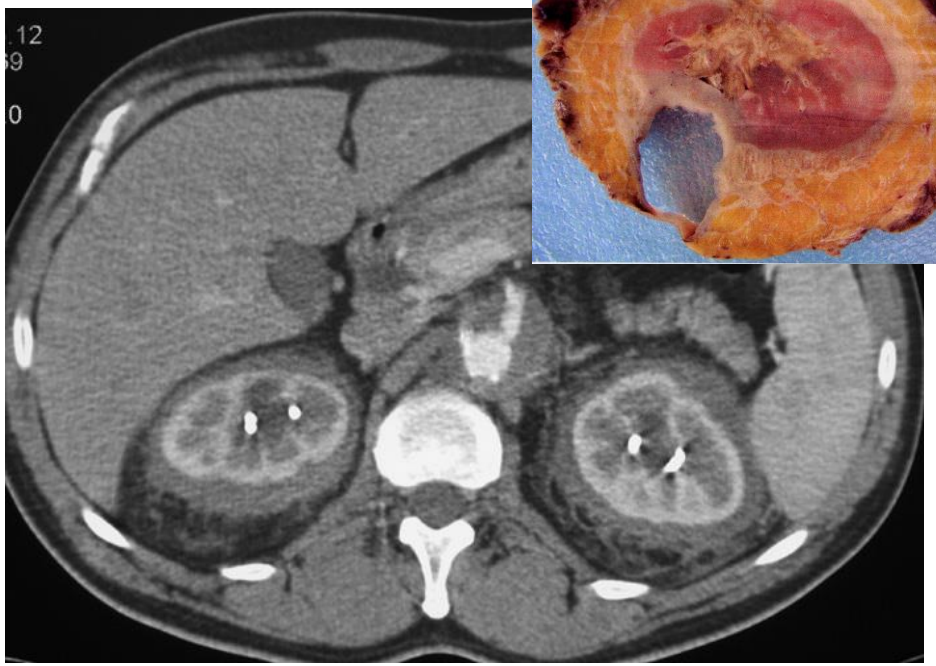
GEH, 20 Novembre 2020

Entre 1000 & 1500 cas depuis 1930



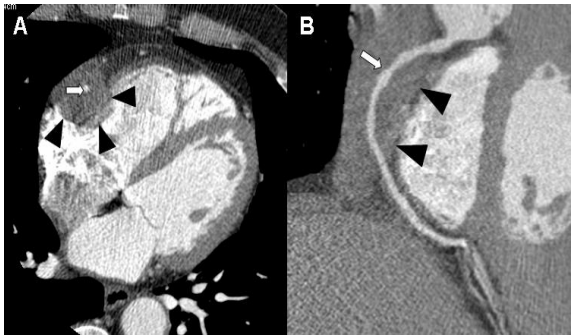
Scintigraphie osseuse
(^{99} Tc)

96%



« rein chevelu »
et infiltration péri-rénale

≈ 60%



37%

Cohorte suivie à la Pitié-Salpêtrière (Novembre 2020)

Cohorte actuelle > 320 pts

263 patients (*fin 2019*) parfaitement caractérisée

15%

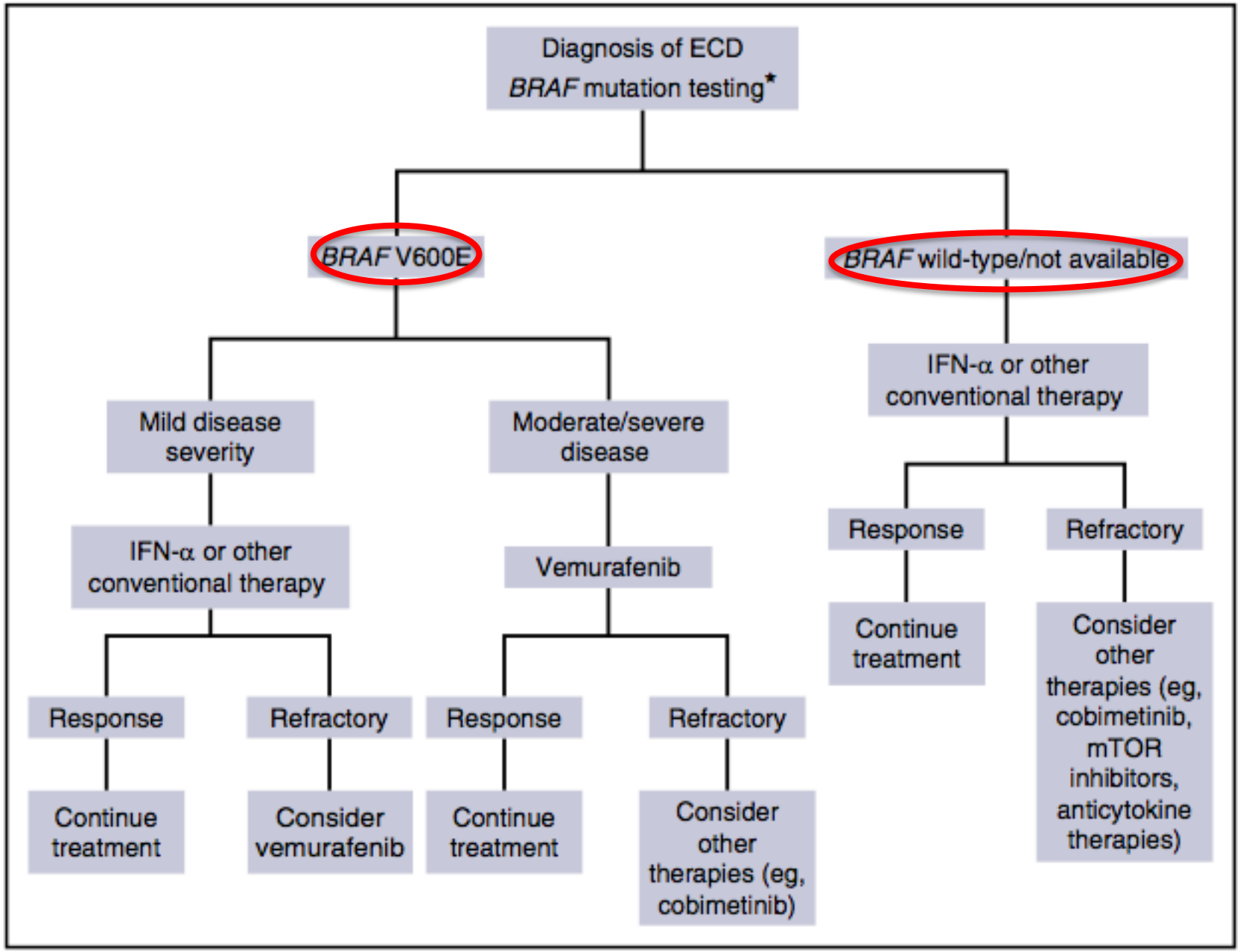
38 patients avec HL + MEC
1 patient avec HL + MEC + Rosai-Dorfman
1 patient avec MEC + Rosai-Dorfman

96 décès (11/2020)

Cohen-Aubart, Am J Hematol 2018

	All (n=217)	V600E (n=119)	WT (n=63)	p
Sex (M/F)	152/65	81/38	48/15	0.30
Age at first symptoms (mean, SD)	52.87 (15.54)	53.18 (14.95)	51.32 (16.23)	0.44
Age at diagnosis (mean, SD)	57.09 (14.33)	57.85 (13.70)	55.03 (15.55)	0.22
Mixed histiocytosis	30 (14%)	21 (18%)	8 (13%)	0.52
Long bone involvement	175 (81%)	102 (86%)	42 (66%)	0.003*
Cardiac involvement	107 (49%)	80 (67%)	15 (24%)	<0.0001*
Right auricular mass	84 (39%)	66 (55%)	7 (11%)	<0.0001*
Vascular involvement	129 (59%)	82 (69%)	30 (48%)	0.006*
Xanthelasma	52 (24%)	35 (29%)	12 (19%)	0.16
Diabetes insipidus	57 (26%)	40 (34%)	8 (13%)	0.003*
CNS involvement	80 (37%)	51 (43%)	15 (24%)	0.02*
Retro-orbital involvement	43 (20%)	22 (18%)	6 (10%)	0.13
Retroperitoneal involvement	131 (60%)	81 (68%)	31 (49%)	0.02*
Deaths	57 (26%)	27 (23%)	13 (21%)	-

Demographic and clinical characteristics of 217 patients with ECD, including 182 patients with BRAF genotyping



Vaglio & Diamond, *Blood* 2017

	Cox survival analysis		
Variable	Univariate HR (95% CI)	Multivariate HR (95% CI)	p-value
Sex M*	1.15 (0.58; 2.31)	1.96 (0.89; 4.28)	0.0932
Age at diagnosis (per year increase)*	1.05 (1.02; 1.08)	**1.06 (1.03; 1.09)**	**0.0001**
BRAF^{V600E}	1.27 (0.54; 2.94)	1.73 (0.68; 4.41)	0.2495
BRAF missing	2.02 (0.85-4.79)	2.02 (0.83; 4.94)	0.1220
CNS involvement	1.37 (0.73; 2.55)	**2.62 (1.28;5.37)**	**0.0084**
Cardiac involvement	1.36 (0.72; 2.57)		
Lung involvement	3.01 (1.58; 5.75)	**2.74 (1.38; 5.43)**	**0.0038**
Vascular involvement	1.27 (0.64; 2.50)		
Xanthelasma	0.74 (0.35; 1.56)		
Diabetes insipidus	0.43 (0.18; 1.04)		
Retroperitoneal involvement	2.10 (1.05; 4.22)	**3.85 (1.68; 8.83)**	**0.0014**
IFN-alpha treatment	0.56 (0.26; 1.19)	**0.38 (0.16; 0.89)**	**0.0257**
Targeted therapy	0.41 (0.16; 1.06)	**0.33 (0.11; 0.93)**	**0.0364**

Predictors of poor survival in ECD (multivariate survival analysis using the Cox proportional hazard ratio). CNS, central nervous system; IFN, interferon

* Adjustment variables

Cohen-Aubart, Am J Hematol 2018

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

En Nov 2020: 130 pts ont reçu une thérapie ciblée dans le service; 110 encore sous TT

Cohen-Aubart, *Blood* 2017

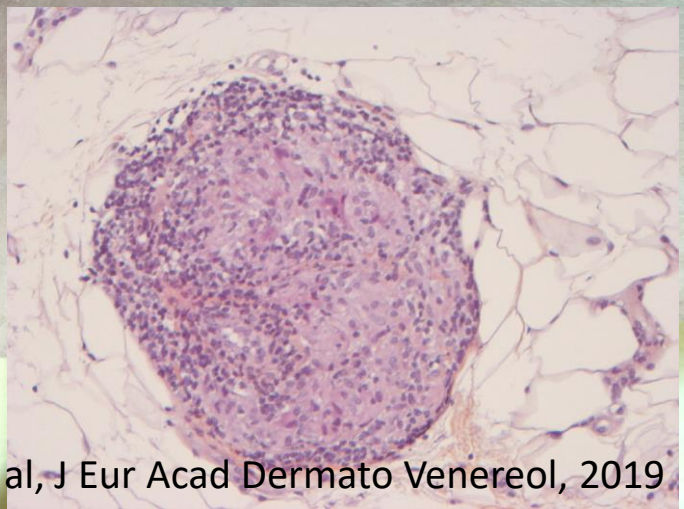
Table 2. Side effects of BRAF and MEK inhibitors

	Vemurafenib, n (%)	Cobimetinib, n (%)
Photosensibility, pilar keratosis	16 (32)	—
Acne rash	—	8 (53)
DRESS	2 (4)	
DRESS-like*	1 (2)	—
Cutaneous allergy	1 (2)	1 (7)
Spinocellular carcinoma	4 (8)	—
Basocellular carcinoma	3 (6)	—
Melanoma	1 (5)	—
Actinic keratosis	2 (4)	—
Bowen disease	1 (2)	—
Multiple nevi	3 (6)	—
Eyelid keratoacanthoma	1 (2)	—
Nausea, vomiting	1 (2)	4 (27)
Arthralgia	7 (14)	
Renal vasculitis	1 (2)	—
Tuberculosis	1 (2)	—
Deep vein thrombosis	1 (2)	—
Neutropenia	1 (2)	—
Scotoma and syncope	1 (2), combination therapy; ophthalmic examination was normal, and electrocardiogram and electrophysiological studies were also normal	
QT prolongation, torsade de pointes and cardiac arrest	1, treatment was resumed after ICD implantation (2)	—
Gastric cancer	1 (no RAF or RAS mutation) (2)	—
Cardiac failure	1 case, reversible when the dose was tapered (2)	—
Hypertriglyceridemia	1 (2)	—
Depressive episode	1 (2)	—
Rhabdomyolysis	—	4 (27)
Sarcoidosis-like disease	3 (6)	—

Since 2016: + 3 melanomas; 1 adeno K pancreas KRAS mutated; 2 pancreatitis; 2 MDS

Cohen-Aubart, *Blood* 2017

Sarcoidosis under vemurafenib



Amoura A et al, J Eur Acad Dermato Venereol, 2019

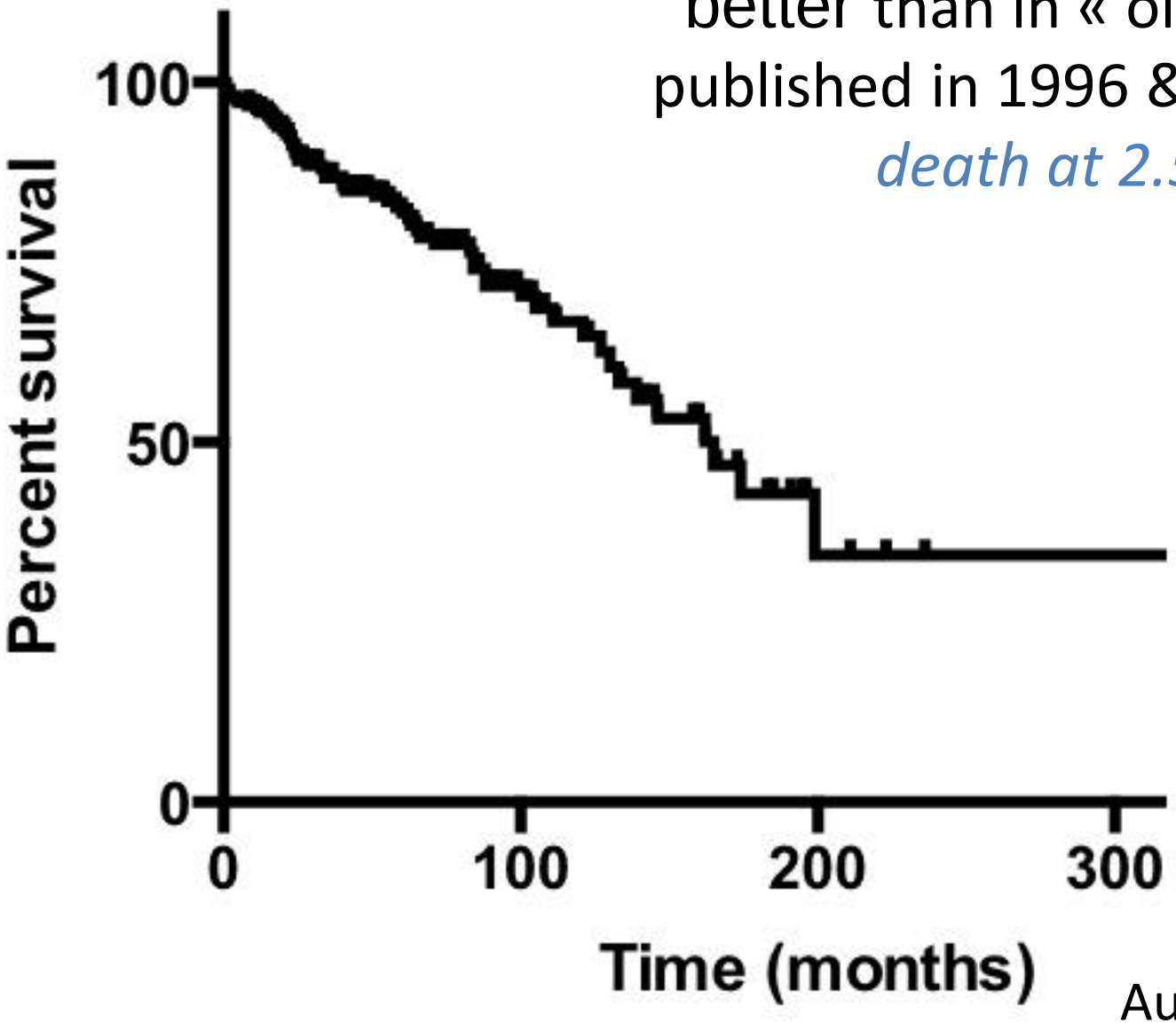
Effets indésirables des ITK

	ITK anti-BRAF	ITK anti-MEK
Cutanés	Carcinome basocellulaire, mélanome, DRESS syndrome	Acné
	KPE, Hyperkératose, kératose pilaire, actinique, séborrhéique Photosensibilité, rash, xérose, éruption	
Cardiologiques	Allongement du QTc (ECG)	Baisse de la FEVG (ETT)
Digestifs	Nausées, vomissement, diarrhées, constipation,	
Hépatiques	Elévation des enzymes hépatiques et de la bilirubine	
Oculaires	Uvéite (rare)	Rétinopathie séreuse (examen oph complet)

Effets spécifiques des ITK

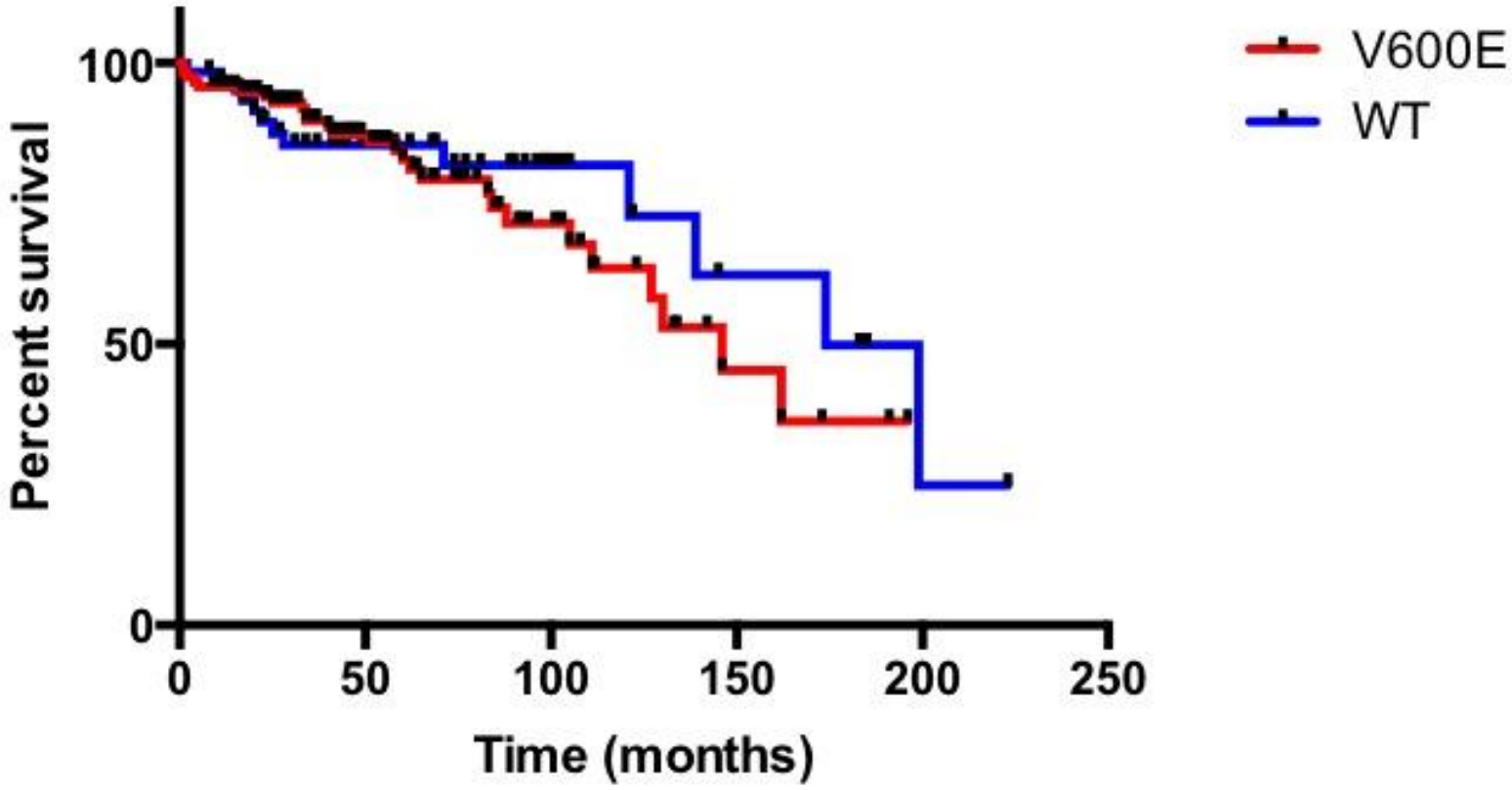
ITK anti-BRAF	ITK anti-MEK
Arthralgies	Musculaire - **élévation CPK et troubles musculaires, rhabdomyolyse**
SMD, Progression d'ADK pancréatique préexistant avec mutations KRAS	hémorragies
Pancréatite (effet de classe souvent)	Œdèmes, OMI Déshydratation, Hyponatrémie
Autres : AEG, Alopécie, Céphalées, dysgueusie, toux, granulomatose, augmentation de la créatinine?	Autres : pyrexie

In 2018 prognosis of ECD is better than in « older series » published in 1996 & 2004 ≈ *60% death at 2.5 yrs*



August 2018
217 ECD patients

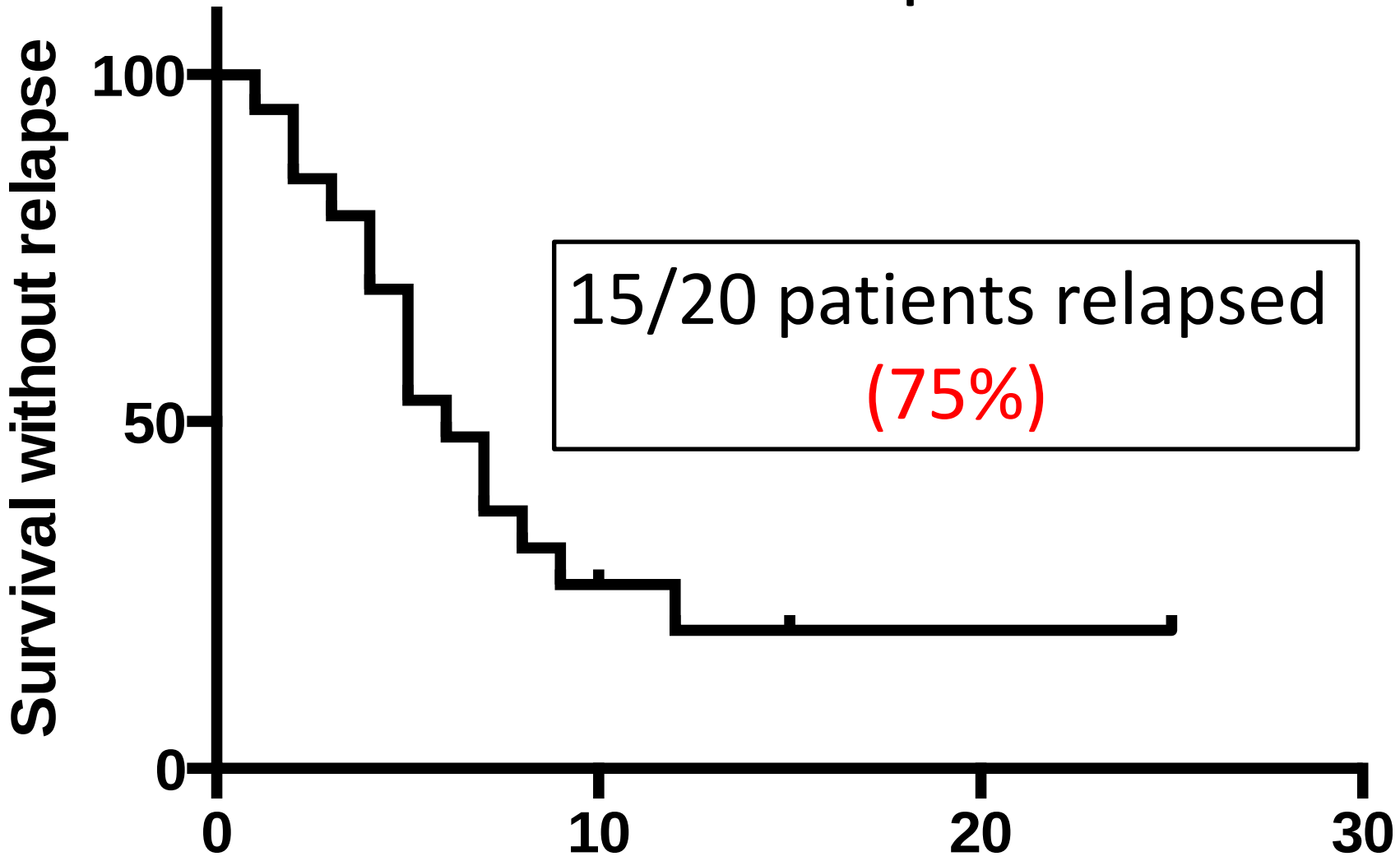
No difference in survival V600E / WT (p = 0.4)



Median survival
BRAF 146 months
WT 174 months

August 2018
217 ECD patients

The *LOVE* study : relapses after treatment interruption



Cohen-Aubart, *Blood* 2017

LETTER

https://doi.org/10.1038/s41586-019-1012-y

Efficacy of MEK inhibition in patients with histiocytic neoplasms

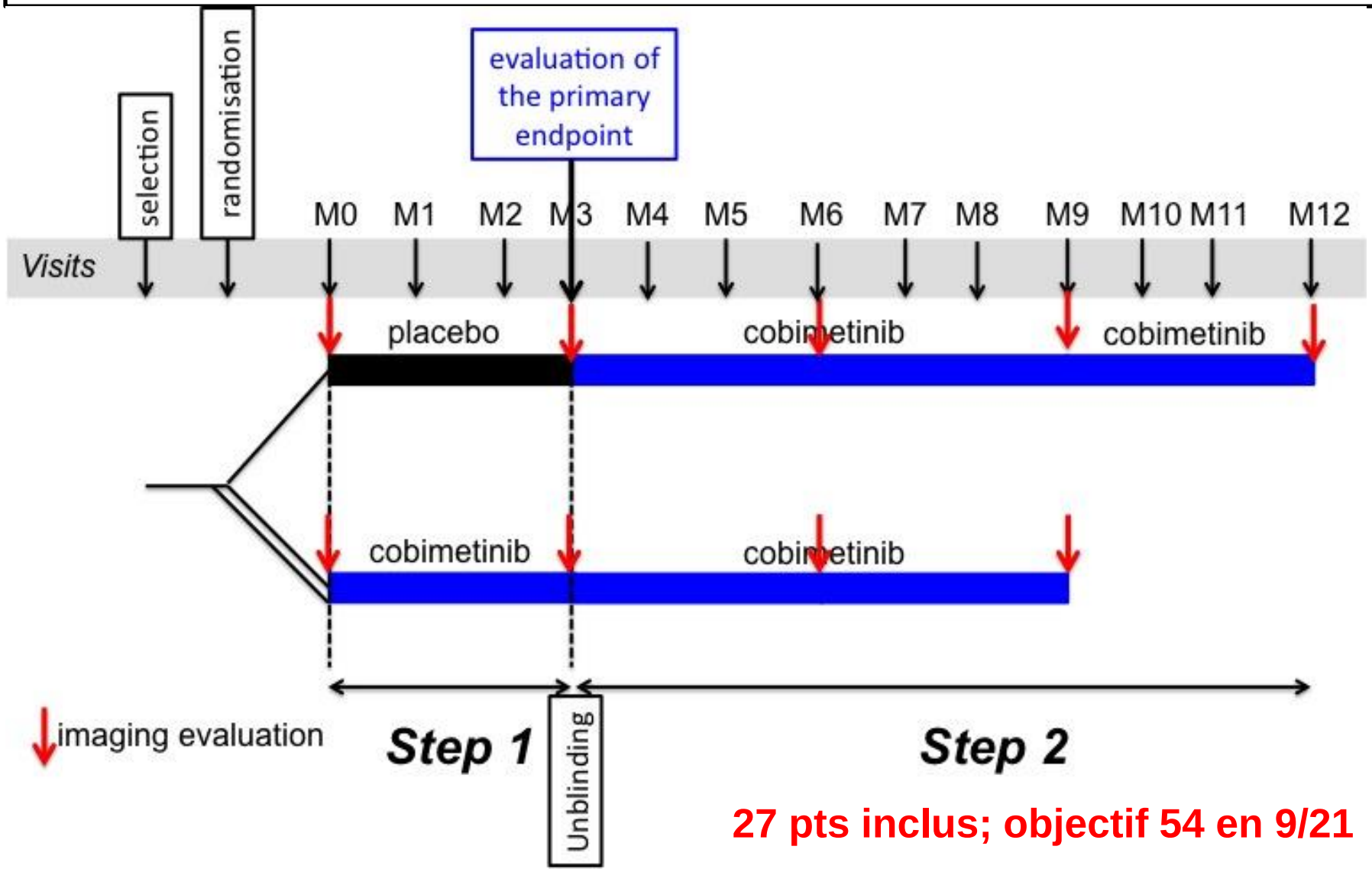
Eli L. Diamond[1,2,12], Benjamin H. Durham[3,4,12], Gary A. Ulaner[2,5], Esther Drill[6], Justin Buthorn[1], Michelle Ki[4], Lillian Bitner[4], Hana Cho[4], Robert J. Young[2,5], Jasmine H. Francis[7], Raajit Rampal[2,8], Mario Lacouture[2,9], Lynn A. Brody[5], Neval Ozkaya[3,10], Ahmet Dogan[3], Neal Rosen[2,8,11], Alexia Iasonos[2,6], Omar Abdel-Wahab[2,4,8]* & David M. Hyman[2,8]*

We enrolled and treated a total of 18 patients (Extended Data Table 1), who had a variety of histiocytic neoplasms that included Erdheim–Chester disease ($n = 12$ patients), Langerhans cell histiocytosis ($n = 2$), Rosai–Dorfman disease ($n = 2$) and mixed histiocytosis ($n = 2$). Eighty-nine per cent (16 out of 18) of patients had received at least 1 previous therapy and 56% (10 out of 18) had received 2 or more previous therapies. Five patients (28%) had an Eastern Cooperative Oncology Group performance status of ≥ 2.

activate ERK. In the 18 patients that we treated, the overall response rate was 89% (90% confidence interval of 73–100). Responses were durable, with no acquired resistance to date. At one year, 100% of

Mars 2019

" Cobimetinib for *BRAF*-wild-type histiocytoses : a randomized, placebo-controlled, double blind study"
PHRC National 2017 Etude COBRAH



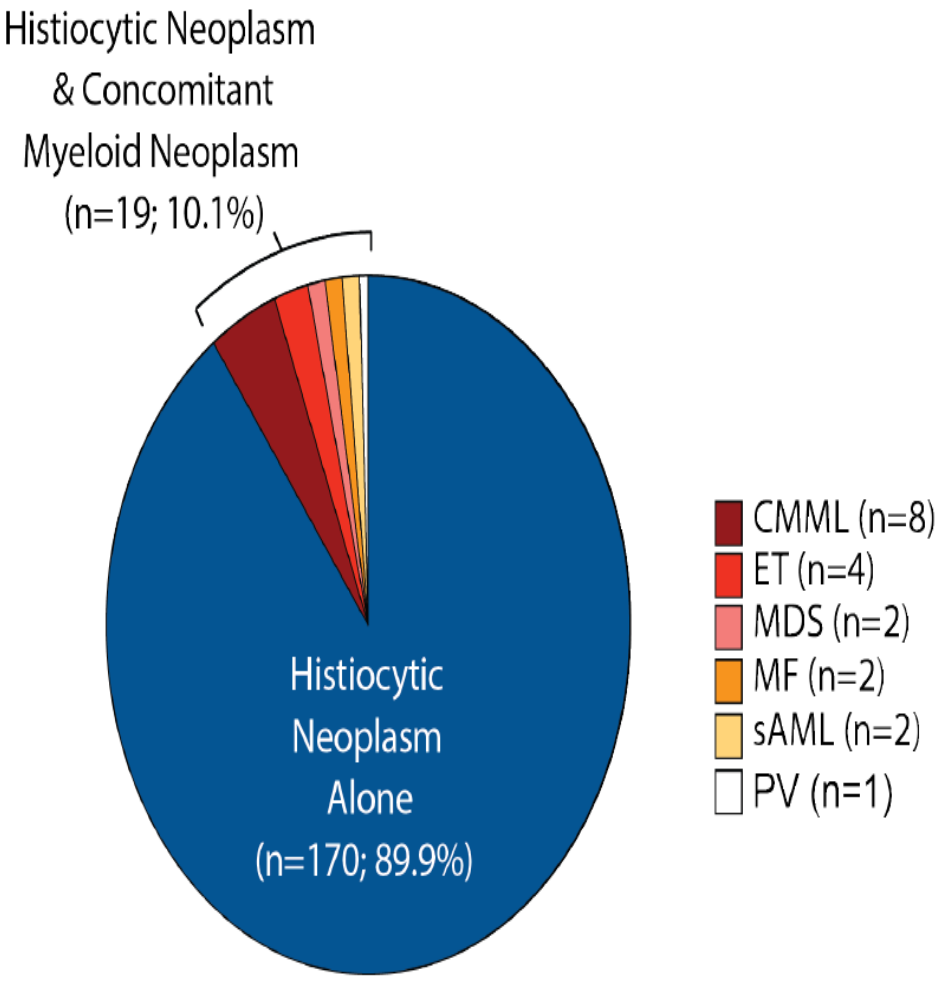
27 pts inclus; objectif 54 en 9/21

Association of both Langerhans cell histiocytosis and Erdheim-Chester disease linked to the *BRAF*^{V600E} mutation

Baptiste Hervier,[1-3] Julien Haroche,[1-3] Laurent Arnaud,[1-3] Frédéric Charlotte,[2,4] Jean Donadieu,[5] Antoine Néel,[6] François Lifermann,[7] Carles Villabona,[8] Bruno Graffin,[9] Olivier Hermine,[10] Aude Rigolet,[1,2] Camille Roubille,[11] Eric Hachulla,[12] Thierry Carmoi,[13] Maud Bézier,[14] Véronique Meignin,[14] Marie Conrad,[15] Laurence Marie,[16] Elise Kostrzewa,[17] Jean-Marie Michot,[18] Stéphane Barete,[19] Valerie Taly,[20] Karine Cury,[19] Jean-François Emile,[21,22] and Zahir Amoura,[1-3] on behalf of the French Histiocytoses Study Group

BLOOD, 14 AUGUST 2014 • VOLUME 124, NUMBER 7

23 LCH + ECD



Papo, *Blood* 2017

High frequency of clonal hematopoiesis in Erdheim-Chester disease

Fleur Cohen Aubart,[1,2] Damien Roos-Weil,[3,4,*] Marine Armand,[4,*] Alice Marceau-Renaut,[5,6,*] Jean-François Emile,[7,8] Nicolas Duployez,[5,6] Frédéric Charlotte,[9] Stéphanie Poulain,[5,6] Raphael Lhote,[1,2] Zofia Helias-Rodzewicz,[7,8] Véronique Della-Valle,[4] Olivier Bernard,[4] Karim Maloum,[10] Florence Nguyen-Khac,[10] Jean Donadieu,[11] Zahir Amoura,[1,2] Omar Abdel-Wahab,[12,13] and Julien Haroche[1,2]

[1]Service de Médecine Interne 2, [2]Centre National de Référence Histiocytoses, and [3]Service d'Hématologie, Hôpital de la Pitié-Salpêtrière, Assistance Publique Hôpitaux de Paris (AP-HP), Sorbonne Université, Paris, France; [4]Gustave Roussy, Unité 1170, INSERM, Villejuif, France; [5]Institut de Recherche Contre le Cancer de Lille, Unité Mixte de Recherche (UMR) 9020 and [6]Cancer Heterogeneity, Plasticity and Resistance to Therapies (CANTHER), UMR-S 1277, Centre Hospitalier Universitaire (CHU) Lille, INSERM, Centre National de la Recherche Scientifique (CNRS), Université de Lille, Lille, France; [7]EA4340, Université Versailles-Saint Quentin, Versailles, France; [8]Département de Pathologie, Hôpital Ambroise Paré, AP-HP, Boulogne, France; [9]Service d'Anatomopathologie and [10]Service d'Hématologie Biologique, Hôpital de la Pitié-Salpêtrière, AP-HP, Sorbonne Université, Paris, France; [11]Service d'Hématologie Pédiatrique, Hôpital Trousseau, AP-HP, Paris, France; and [12]Human Oncology and Pathogenesis Program and [13]Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

KEY POINTS

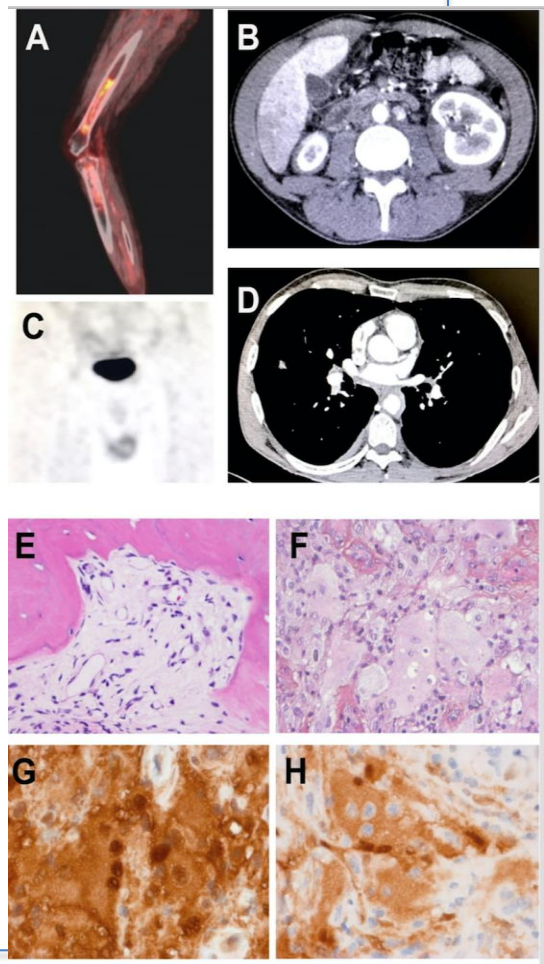
- **ECD patients have a very high frequency of clonal hematopoiesis and concomitant overt myeloid malignancies.**
- **ECD patients with clonal hematopoiesis are older and have more frequent retroperitoneal involvement and *BRAF*V600E mutations.**

Erdheim-Chester disease (ECD) is a clonal hematopoietic disorder characterized by the accumulation of foamy histiocytes within organs (in particular, frequent retroperitoneal involvement) and a high frequency of *BRAF*^{V600E} mutations. Although ECD is not commonly recognized to have overt peripheral blood (PB) or bone marrow (BM) disease, we recently identified that ECD patients have a high frequency of a concomitant myeloid malignancy. Given this finding and the fact that clonal hematopoiesis frequency precedes development of myeloid malignancies, we conducted a systematic clinical and molecular analysis of the BM from 120 ECD patients. Surprisingly, 42.5% of ECD patients (51 of 120) had clonal hematopoiesis whereas 15.8% of patients (19 of 120) developed an overt hematologic malignancy (nearly all of which were a myeloid neoplasm). The most frequently mutated genes in BM were *TET2*, *ASXL1*, *DNMT3A*, and *NRAS*. ECD patients with clonal hematopoiesis were more likely to be older ($P < .0001$), have retroperitoneal involvement ($P = .02$), and harbor a *BRAF*^{V600E} mutation ($P = .049$) than those without clonal hematopoiesis. The presence of the *TET2* mutation was associated with a *BRAF*^{V600E} mutation in tissue ECD lesions ($P = .0006$) and *TET2*-mutant ECD patients were more likely to have vascular involvement than *TET2* wild-type ECD patients. Clonal hematopoiesis mutations in ECD were detected in cells derived from CD34^{+}CD38^{-} BM progenitors and PB monocytes but less frequently present in PB B and T lymphocytes. These data identify a heretofore unrecognized high frequency of clonal hematopoiesis in ECD patients, reaffirm the development of additional high risk of myeloid neoplasms in ECD, and provide evidence of a BM-based precursor cell of origin for many patients with ECD.
(*Blood*. 2020;00(00):1-9)

Cohen-Aubart, *Blood* 2020

Erdheim-Chester Disease with concomitant Rosai-Dorfman like lesions: a distinct entity mainly driven by *MAP2K1*

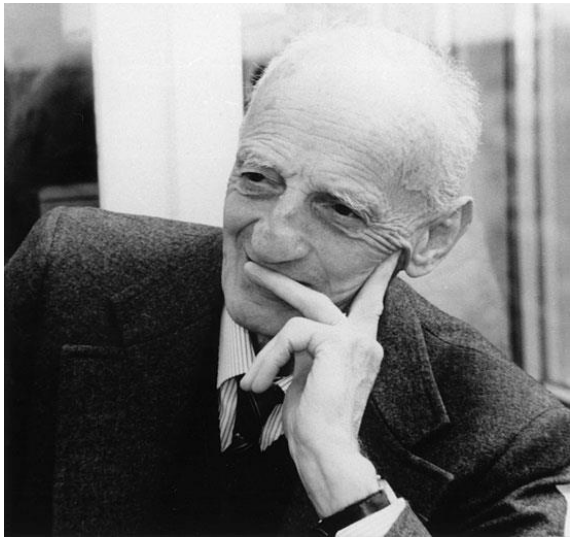
- Patients with ECD with classical imaging and compatible histology
- Tissue biopsy disclosing RDD lesion (mostly) during follow-up
- <u>Three referral center for Histiocytosis:</u>
  - Pitié-Salpêtrière Hospital (n=168)
  - Memorial Sloan Kettering Cancer Center (n= 96)
  - Mayo Clinic (n=89)
- Thirteen patients (12 men, 1 woman)
- <u>RDD location:</u>
  - 7 testis
  - No lymph node
  - No *BRAF* mutation on both ECD or RDD samples
  - 9 *MAP2K1* mutation
  - 1 *PIK3CA* mutation



Razanamahery, *Haematologica* 2019 (in press)

~~Maladie de~~ Destombes-Rosai-Dorfman

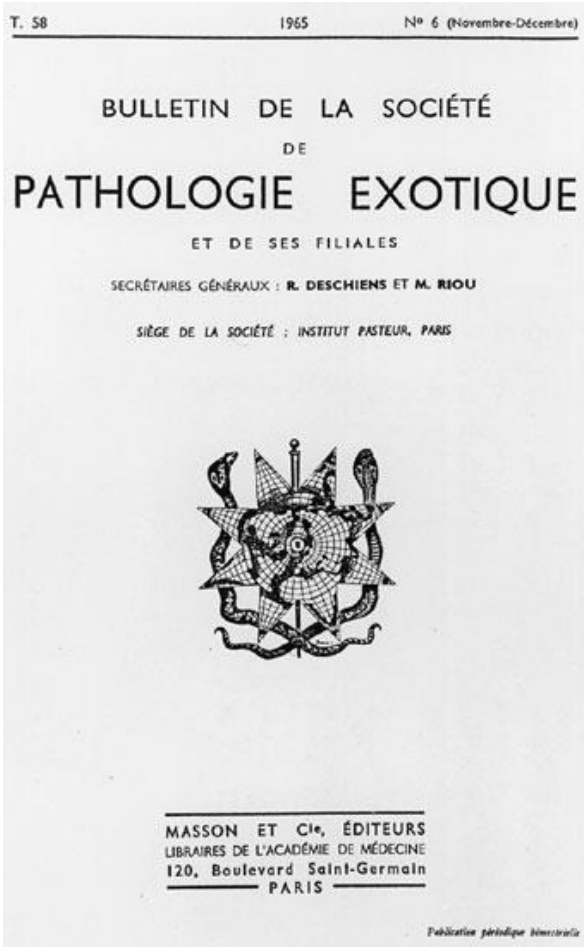
Histiocytose polymorphe décrite pour la première fois en 1965 par le Français Pierre Paul Louis Lucien Destombes



1912-2002

Puis en 1969 par les américains

Rosai et Dorfman



T. 58 1965 N° 6 (Novembre-Décembre)

BULLETIN DE LA SOCIÉTÉ

DE

PATHOLOGIE EXOTIQUE

ET DE SES FILIALES

SECRÉTAIRES GÉNÉRAUX : R. DESCHIENS ET M. RIOU

SIÈGE DE LA SOCIÉTÉ : INSTITUT PASTEUR, PARIS

MASSON ET Cie, ÉDITEURS
LIBRAIRES DE L'ACADÉMIE DE MÉDECINE
120, Boulevard Saint-Germain
PARIS

Publication périodique bimestrielle

Etude multicentrique sous l'égide du Registre National des Histiocytoses

Cas rétrospectifs : 2004 - 2014

Critère d'inclusion : diagnostic anatomo-pathologique de MRD

Critère d'exclusion: absence de données suffisantes exploitables

47 patients inclus : 29 hommes, 18 femmes

Age moyen au diagnostic 20,3 ans (de 1 à 60 ans)

- Ganglions n=32 (68 %)
- Os n=9 (19%)
- Peau n=7 (15%)
- SNC n=7 (15%)
- ORL n=5 (11%)
- Œil n=3

Depuis plus de 100 patients inclus
Analyse en cours

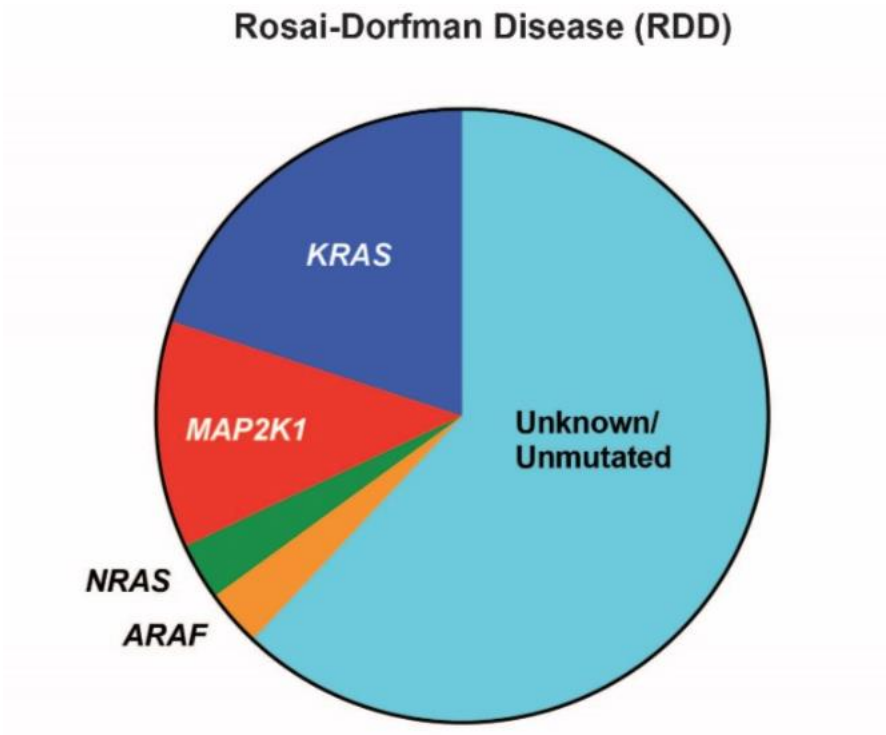
Cohen-Aubart, SNFMI Juin 2015

Registre Français
Classification en 3 groupes

- Forme typique (avec adénopathies) : n=26 (55%)
- Forme histologique typique mais absence d'atteinte ganglionnaire: n=14 (30%)

  SNC isolé n=6; os isolé n=5
- Signes histologiques évocateurs mais coexistence avec une autre histiocytose ou une maladie hématologique n= 7 (syndrome myéloprolifératif, Erdheim-Chester, lymphome de Hodgkin)

Cohen-Aubart, SNFMI Juin 2015



blood®

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Consensus recommendations for the diagnosis and clinical management of Rosai-Dorfman-Destombes disease

Oussama Abla Dr., Eric Jacobsen, Jennifer Picarsic, Zdenka Krenova, Ronald Jaffe, Jean-Francois Emile, Benjamin H. Durham, Jorge Braier, Frédéric Charlotte, Jean Donadieu, Fleur Cohen Aubart, Carlos Rodriguez-Galindo, Carl Allen, James A. Whitlock, Sheila Weitzman, Kenneth L. McClain, Julien Haroche and Eli L. Diamond