

**5ème JOURNÉE NATIONALE MARIH
APPORTS ET LIMITES DE LA GÉNÉTIQUE
Paris, 20 Juin 2019**

**Apport du séquençage haut débit
dans le diagnostic et traitement des histiocytoses**

Jean-François Emile

Service de pathologie & EA4340-BCOH
Ambroise Paré hospital, APHP & Versailles University

France



Révolution moléculaire dans les histiocytoses

Recurrent *BRAF* mutations in Langerhans cell histiocytosis

Gayane Badalian-Very,¹⁻³ Jo-Anne Vergilio,^{4,5} Barbara A. Degar,⁶⁻⁸ Laura E. MacConaill,⁹ Barbara Brandner,¹⁻³ Monica L. Calicchio,⁴ Frank C. Kuo,^{5,10} Azra H. Ligon,^{5,10,11} Kristen E. Stevenson,¹² Sarah M. Kehoe,⁹ Levi A. Garraway,^{1-3,9,13} William C. Hahn,^{1-3,9,13} Matthew Meyerson,^{1,2,9,13} Mark D. Fleming,^{4,5} and Barrett J. Rollins¹⁻³

BLOOD, 16 SEPTEMBER 2010 • VOLUME 116,

- Confirms that LCH is a clonal disease
- Demonstrates that LCH is a neoplasia
- Gate is open for targeted therapies

Avant BRAF

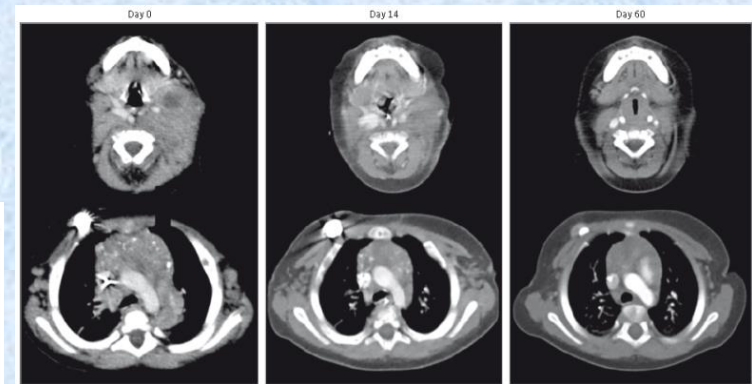
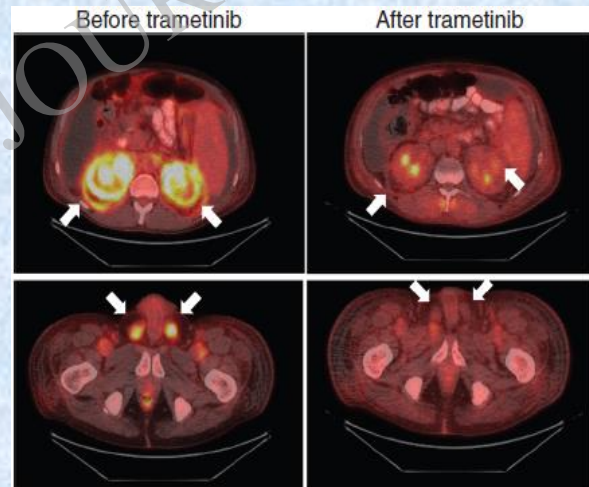
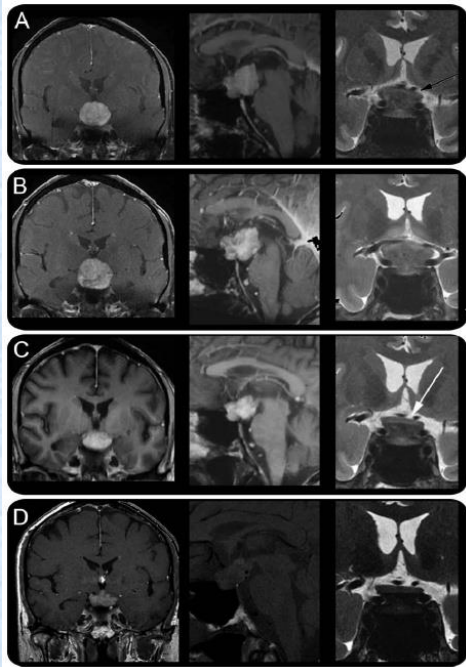
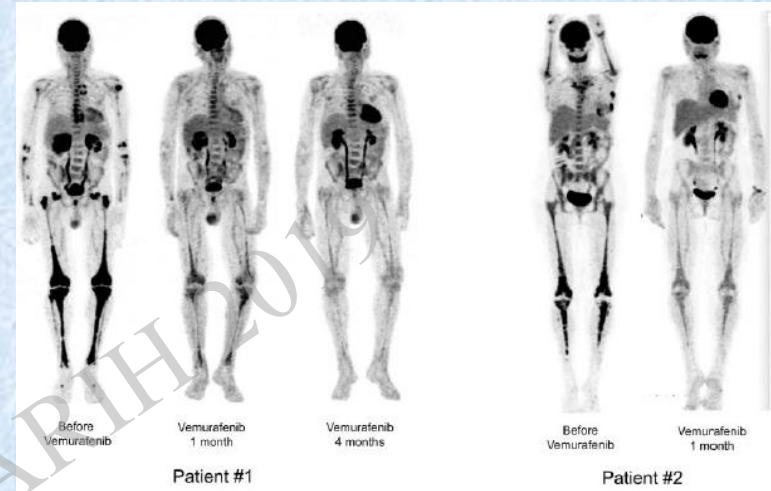
Clonality

- LCH: Willman CL et al. N Engl J Med. 1994
- ECD: Chettrit J et al. Hum Pathol 1999

Targeted therapy

- GM-CSF = autocrine growth factor of LCH: Emile JF et al. Histopathology 1993, Virchows Arch 1995
- Anti-GM-CSF treatment in JMML: Bernard F et al. Blood 2002

Today: Vemurafenib is active in patients with BRAF V600E mutations



Pictures from
Haroche Blood 2012
Haroche J Clin Oncol 2014
Héritier JAMA Oncol 2015
Diamond Cancer Discov 2015
Cohen-Aubart Neurology 2014

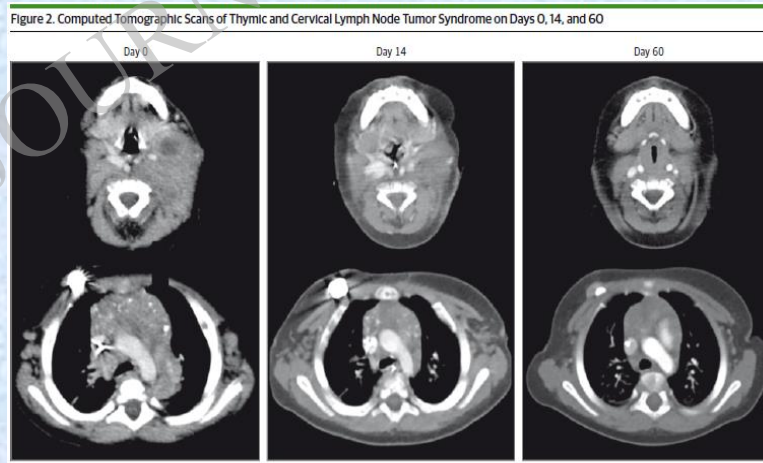


Argentine
Juin 2019

vemurafenib
→

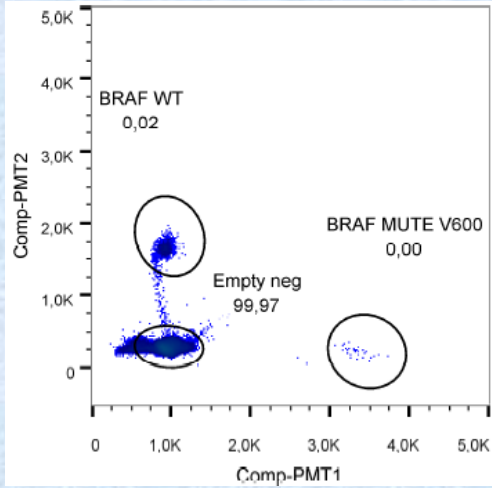


Courtoisie de J Braier



8-month-old girl

Somatic mutations in histiocytoses: How?

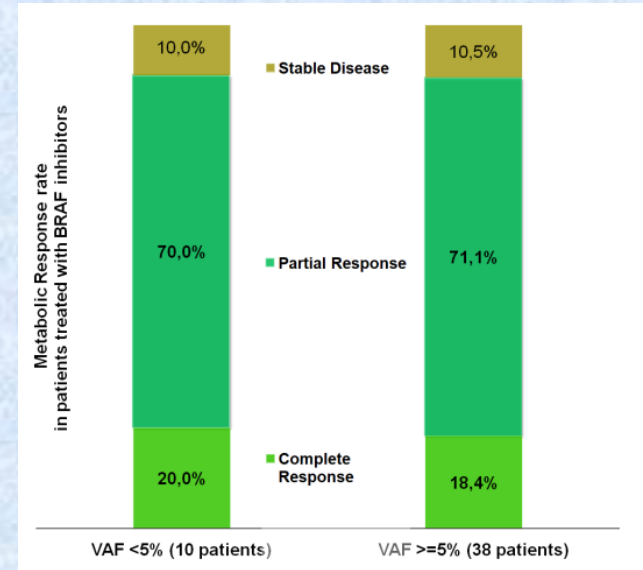
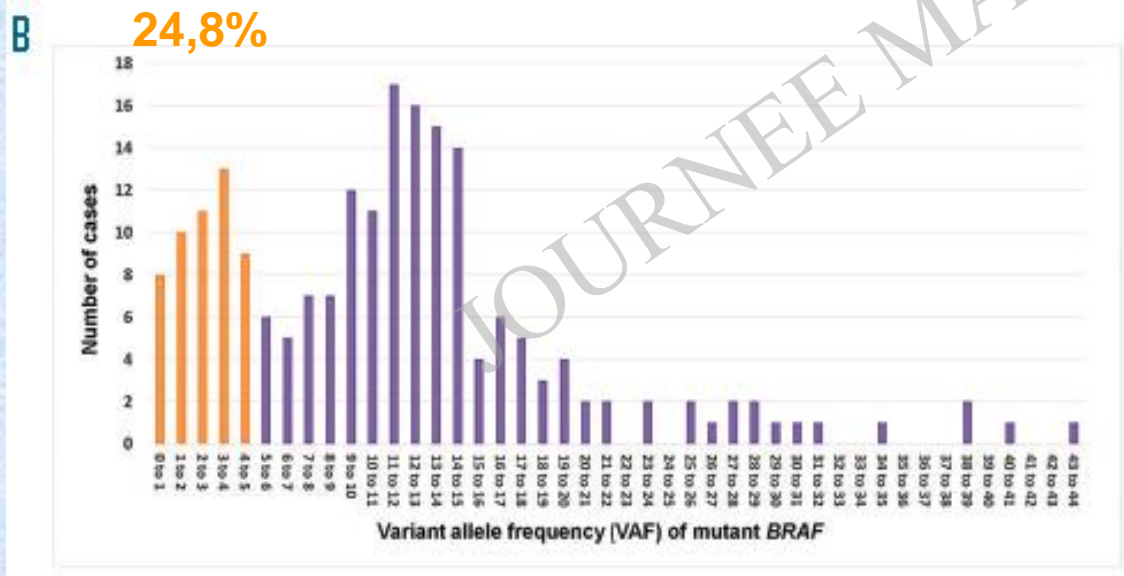


Digital droplet PCR

Highly sensitive methods are required to detect mutations in histiocytoses

haematologica 2019; 104:e98

Sarah Melloul,^{1*} Zofia Hélias-Rodzewicz,^{1,2*} Fleur Cohen-Aubart,^{3,4*} Frédéric Charlotte,^{3,5} Sylvie Fraïtag,⁶ Nathalie Terrones,^{1,2} Quentin Riley,⁶ Thibaud Chazal,⁴ Sébastien Hérvier,^{1,7} Anne Moreau,⁶ Marianne Kambouchner,⁹ Marie Christine Copin,¹⁰ Jean Donadieu,^{1,7} Valérie Taly,¹¹ Zahir Amoura,^{3,4} Julien Haroche^{2,4} and Jean François Emile^{1,2}



→ To be performed in platforms experienced in analysing histiocytosis samples

Somatic mutations in histiocytoses: why?

Understanding of the disease
Better classification

Diagnosis

- . Microbiopsies,
- . difficult diagnoses

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

Jean-François Emile,^{1,2} Oussama Abla,³ Sylvie Fraitag,⁴ Annacarin Horne,⁵ Julien Haroche,^{6,7} Jean Donadieu,^{1,8} Luis Requena-Caballero,⁹ Michael B. Jordan,¹⁰ Omar Abdel-Wahab,¹¹ Carl E. Allen,¹² Frédéric Charlotte,^{7,13} Eli L. Diamond,¹⁴ R. Maarten Egeler,³ Alain Fischer,^{15,16} Juana Gil Herrera,¹⁷ Jan-Inge Henter,¹⁸ Filip Janku,¹⁹ Miriam Merad,²⁰ Jennifer Picarsic,²¹ Carlos Rodriguez-Galindo,²² Barret J. Rollins,^{23,24} Abdellatif Tazi,²⁵ Robert Vassallo,²⁶ and Lawrence M. Weiss,²⁷ for the Histiocyte Society

BLOOD, 2 JUNE 2016

Prognostic

BRAF Mutation Correlates With High-Risk Langerhans Cell Histiocytosis and Increased Resistance to First-Line Therapy

Sébastien Héritier, Jean-François Emile, Mohamed-Aziz Barkaoui, Caroline Thomas, Sylvie Fraitag, Sabah Boudjemaa, Florence Renaud, Anne Moreau, Michel Peuchmaur, Catherine Chassagne-Clément, Frédérique Dijoud, Valérie Rigau, Despina Moshous, Anne Lambilliotte, Françoise Mazingue, Kamila Kebaili, Jean Miron, Eric Jeziorski, Geneviève Plat, Nathalie Aladjidi, Aïna Ferster, Hélène Pacquement, Claire Galambrun, Laurence Brugières, Guy Leverger, Ludovic Mansuy, Catherine Paillard, Anne Deville, Corinne Armari-Alla, Anne Lutun, Marion Gillibert-Yvert, Jean-Louis Stephan, Fleur Cohen-Aubart, Julien Haroche, Isabelle Pellier, Frédéric Millot, Brigitte Lescoeur, Virginie Gandemer, Christine Bodemer, Roger Lacave, Zofia Hélias-Rodzewicz, Valérie Taly, Frédéric Geissmann, and Jean Donadieu

J Clin Oncol 34. © 2016

Recurrent *BRAF* mutations in Langerhans cell histiocytosis

Gayane Badalian-Very,^{1,3} Jo-Anne Vergilio,^{4,5} Barbara A. Degar,^{6,8} Laura E. MacConaill,⁹ Barbara Brandner,^{1,3} Monica L. Calicchio,⁴ Frank C. Kuo,^{5,10} Azra H. Ligon,^{5,10,11} Kristen E. Stevenson,¹² Sarah M. Kehoe,⁹ Levi A. Garraway,^{1,3,9,13} William C. Hahn,^{1,3,9,13} Matthew Meyerson,^{1,2,9,13} Mark D. Fleming,^{4,5} and Barret J. Rollins¹⁻³

BLOOD, 16 SEPTEMBER 2010

Follow up of patients during treatment

Targeted therapies

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

*Julien Haroche,^{1,2} *Fleur Cohen-Aubart,^{1,2} *Jean-François Emile,³ *Laurent Arnaud,^{1,2} Philippe Maksud,⁴ Frédéric Charlotte,⁵ Philippe Cluzel,⁶ Aurélie Drier,⁷ Baptiste Hervier,^{1,2} Neïla Benameur,⁸ Sophie Besnard,⁹ Jean Donadieu,¹⁰ and Zahir Amoura^{1,2}

(Blood. 2013;121(9):1495-1500)

La révolution moléculaire des histiocytoses

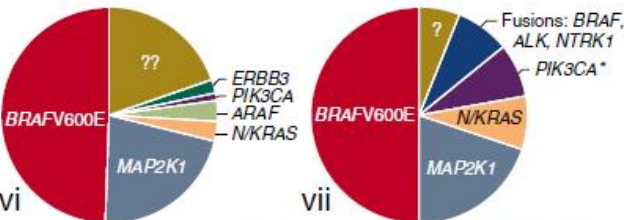
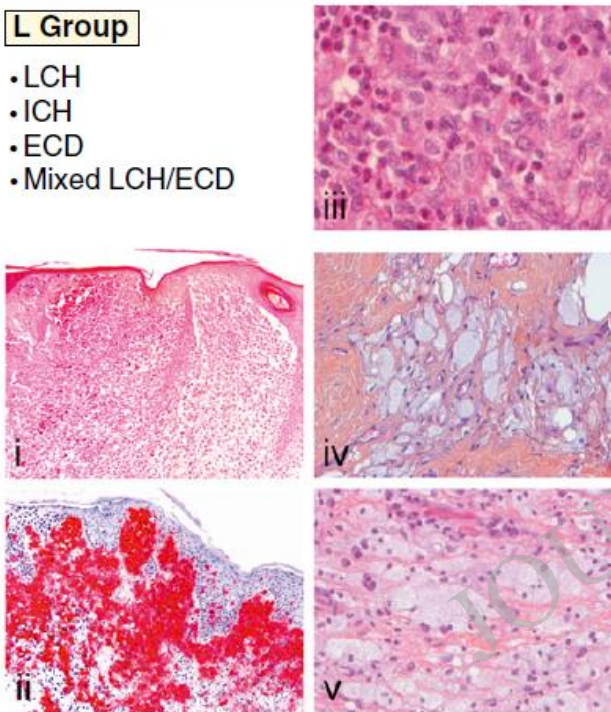
Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

Jean-François Emile,^{1,2} Oussama Abla,³ Sylvie Fraitag,⁴ Annacarin Horne,⁵ Julien Haroche,^{6,7} Jean Donadieu,^{1,8} Luis Requena-Caballero,⁹ Michael B. Jordan,¹⁰ Omar Abdel-Wahab,¹¹ Carl E. Allen,¹² Frédéric Charlotte,^{7,13} Eli L. Diamond,¹⁴ R. Maarten Egeler,³ Alain Fischer,^{15,16} Juana Gil Herrera,¹⁷ Jan-Inge Henter,¹⁸ Filip Janku,¹⁹ Miriam Merad,²⁰ Jennifer Picarsic,²¹ Carlos Rodriguez-Galindo,²² Barret J. Rollins,^{23,24} Abdellatif Tazi,²⁵ Robert Vassallo,²⁶ and Lawrence M. Weiss,²⁷ for the Histiocyte Society

BLOOD, 2 JUNE 2016

L Group

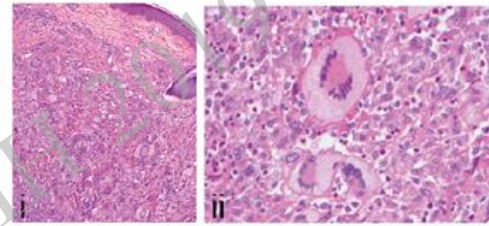
- LCH
- ICH
- ECD
- Mixed LCH/ECD



* A proportion of *PIK3CA* mutant patients have concomitant *BRAFV600E* mutations.

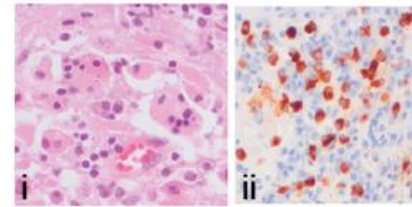
C Group

- Cutaneous non-LCH
 - XG family: JXG, AXG, SRH, BCH, GEH, PNH
 - Non-XG family: cutaneous RDD, NXG, othjer NOS
- Cutaneous non-LCH with a major systemic component



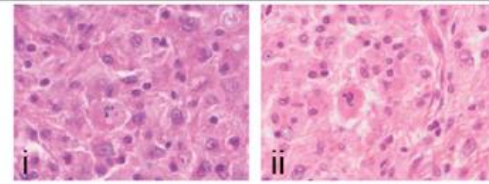
R Group

- Familial Rosai-Dorfman Disease (RDD)
- Sporadic RDD
 - Classical RDD
 - Extra-nodal RDD
 - RDD with neoplasia or immune disease
 - Unclassified



M Group

- Primary Malignant Histiocytoses
- Secondary Malignant Histiocytoses (following or associated with another hematologic neoplasia)
 - Subtypes: *Histiocytic, Interdigitating, Langerhans, Indeterminate Cell*



H Group

- Primary HLH: Monogenic inherited conditions leading to HLH
- Secondary HLH (non-Mendelian HLH)
- HLH of unknown/uncertain origin



● ● ● MYELOID NEOPLASIA

Comment on Emile et al, page 2672

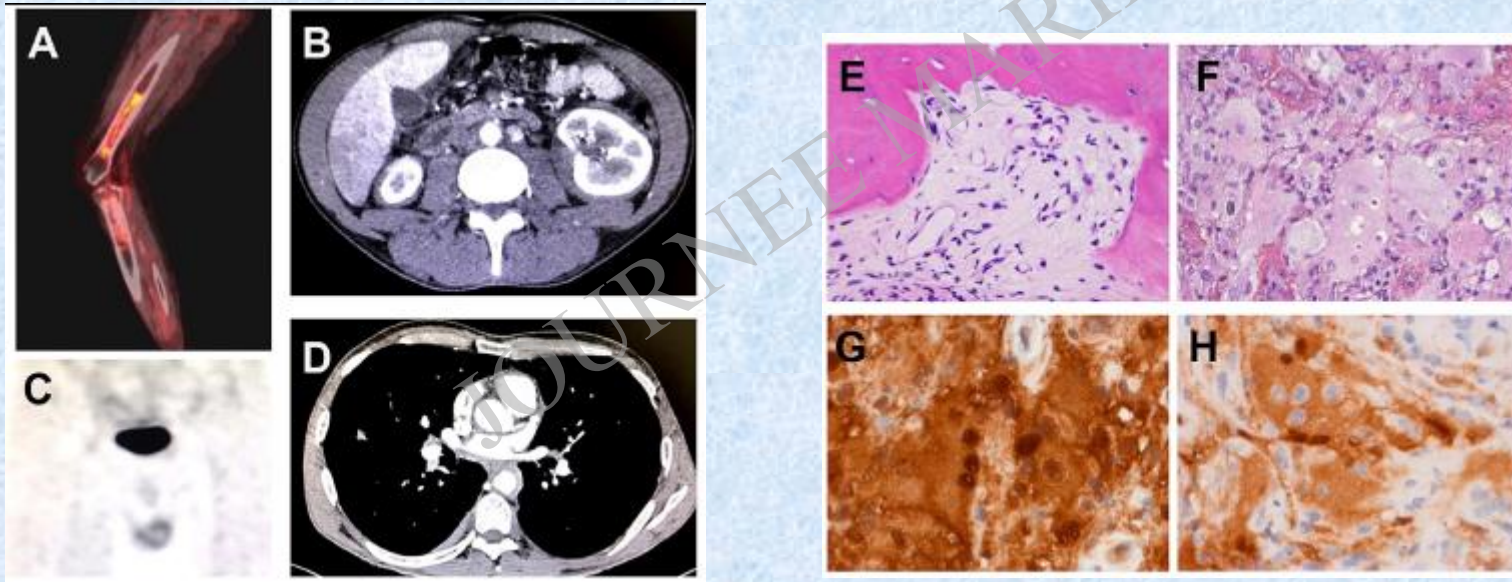
The histiocytoses: as easy as ABC (or LCMRH)

La classification va évoluer

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

by Jérôme Razanamahery, Eli L. Diamond, Fleur Cohen-Aubart, Karl-Heinz Plate, Giota Lourida, Frederic Charlotte, Zofia Hélias-Rodzewicz, Gaurav Goyal, Ronald S. Go, Ahmet Dogan, Omar Abdel-Wahab, Benjamin Durham, Neval Ozkaya, Zahir Amoura, Jean-Francois Emile, and Julien Haroche

Haematologica 2019 [Epub ahead of print]



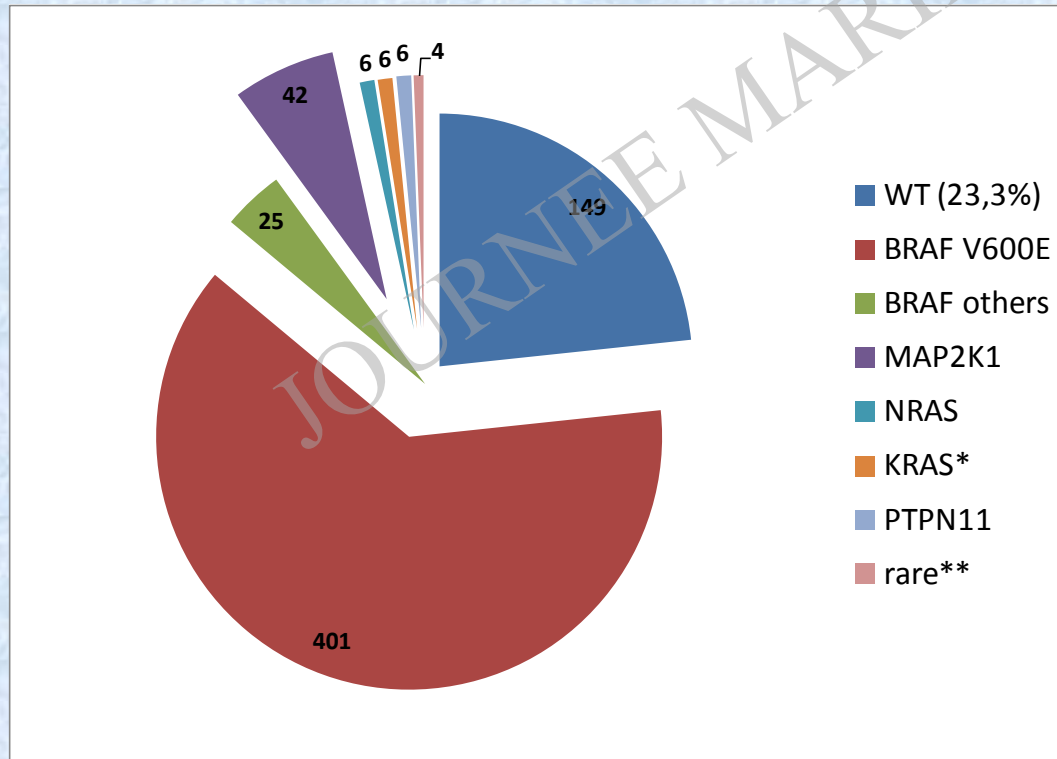
→ To be performed in platforms experienced in analysing histiocytosis samples

Mutations of the MAPkinase pathway: Data of French network

639 samples all types of histiocytoses

Analyzed for

- *BRAF*^{V600E} with high sensitivity (at least 1000 amplified droplets)
- and/or NGS targeted on genes of the MAP kinase pathway



mutations somatiques histiocytoses : Intérêt du NGS

Variété des mutations (Avril 2019)

BRAF non p.V600E

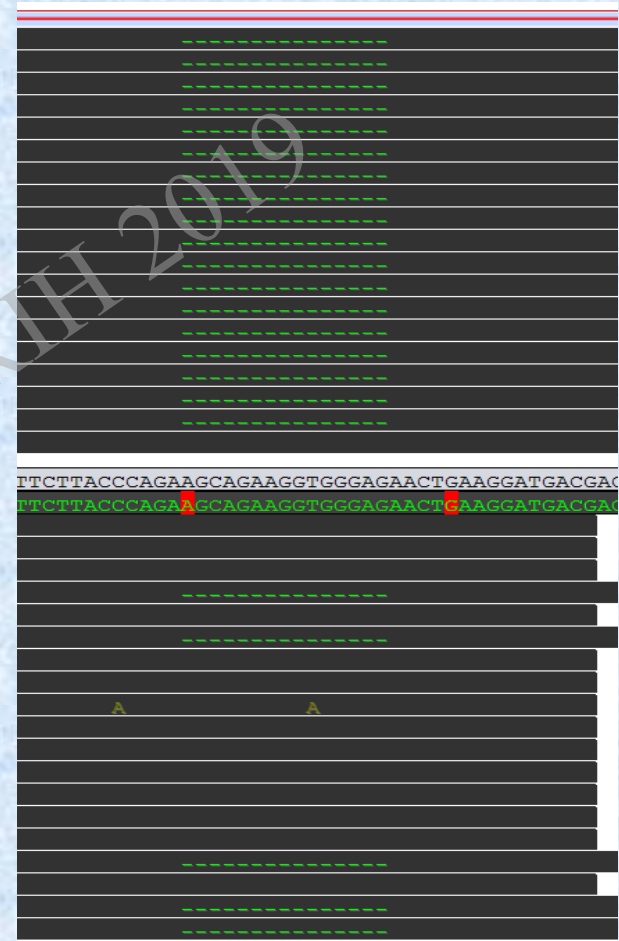
36 patients mutés

19 mutations différentes

MAP2K1

63 patients mutés

27 mutations différentes

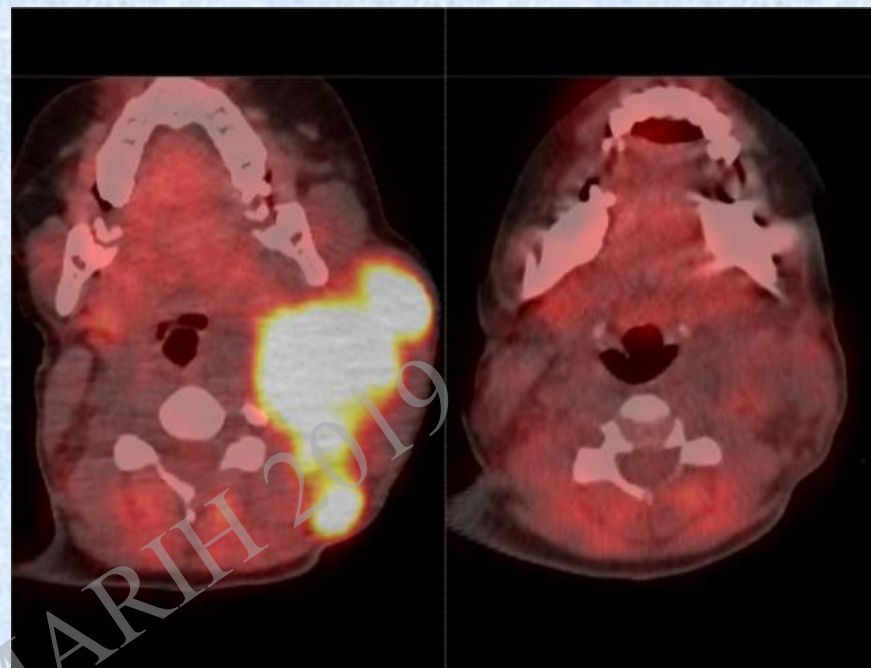


Targeted NGS
on tumor DNA

11 year old female with massive cervical lymph node infiltrated by Rosai Dorman disease

Detection of a *MAP2K1* mutation with VAF<1%

Treated with trametinib



Courtoisie de J Donadieu

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

Fleur Cohen Aubart,^{1,2} Jean-François Emile,^{3,4} Fabrice Carrat,^{2,5,6} Frédéric Charlotte,^{2,7} Neila Benameur,⁸ Jean Donadieu,⁹ Philippe Maksud,¹⁰ Ahmed Idbaih,¹¹ Stéphane Barete,¹² Khê Hoang-Xuan,¹¹ Zahir Amoura,^{1,2} and Julien Haroche^{1,2}

BLOOD, 14 SEPTEMBER 2017

15 pts/20 (75%) récidivent après interruption du ttt
mais bonne réponse après reprise

Other mutations

64 year old female with disseminated malignant histiocytosis progressing after 3 lines of chemotherapy

Detection of a *PTPN11* mutation

Treated with trametinib

Courtesy of Dr L Farnault (submitted)

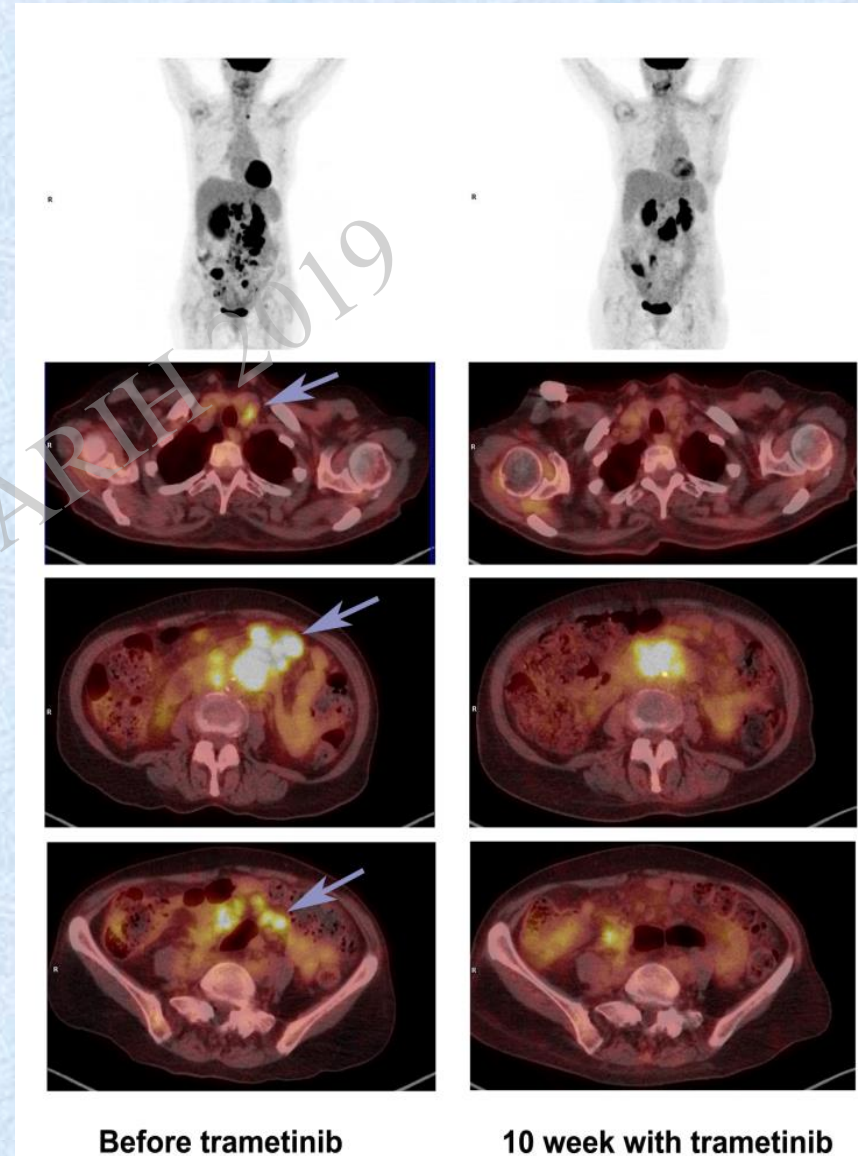
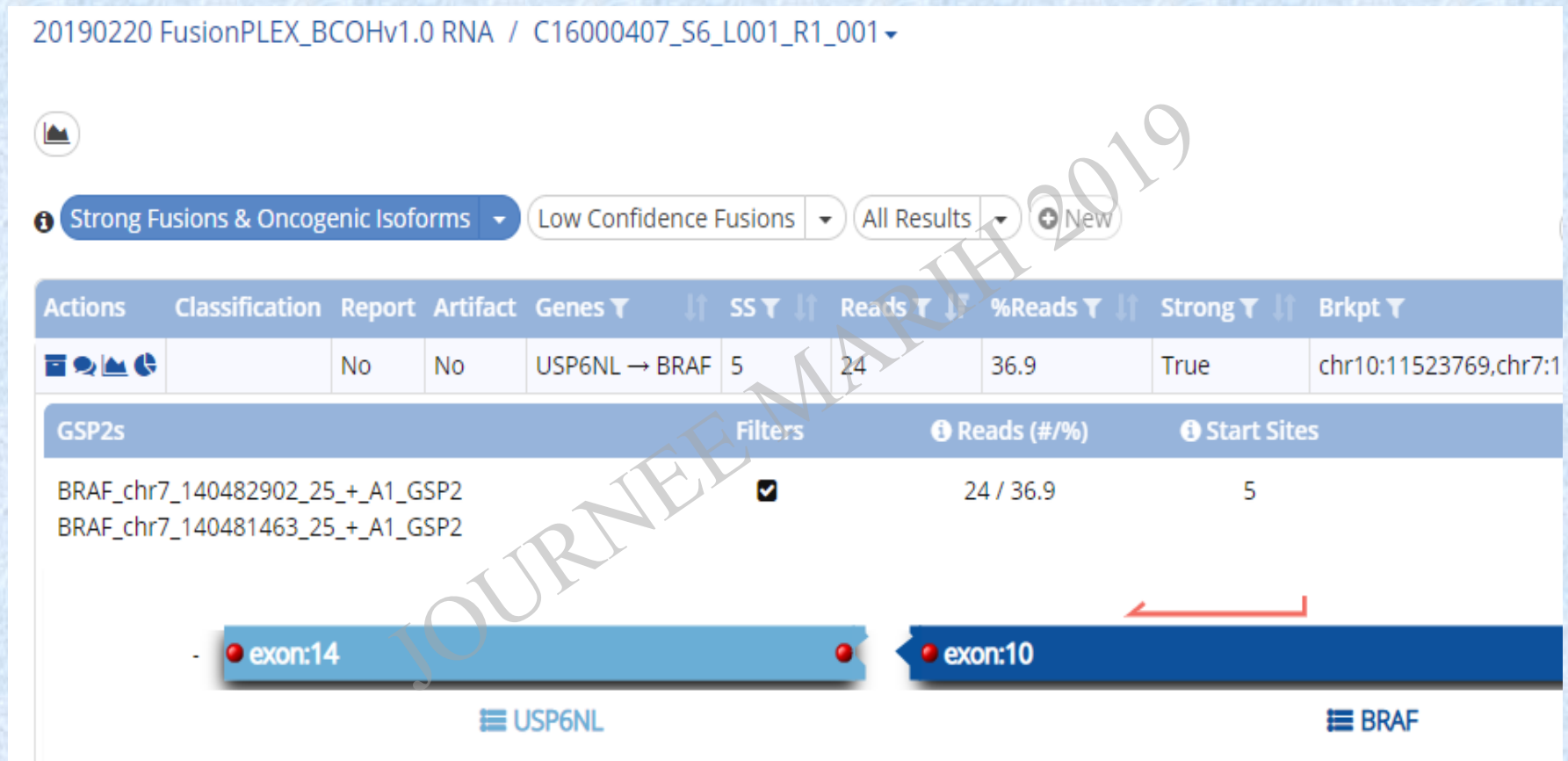
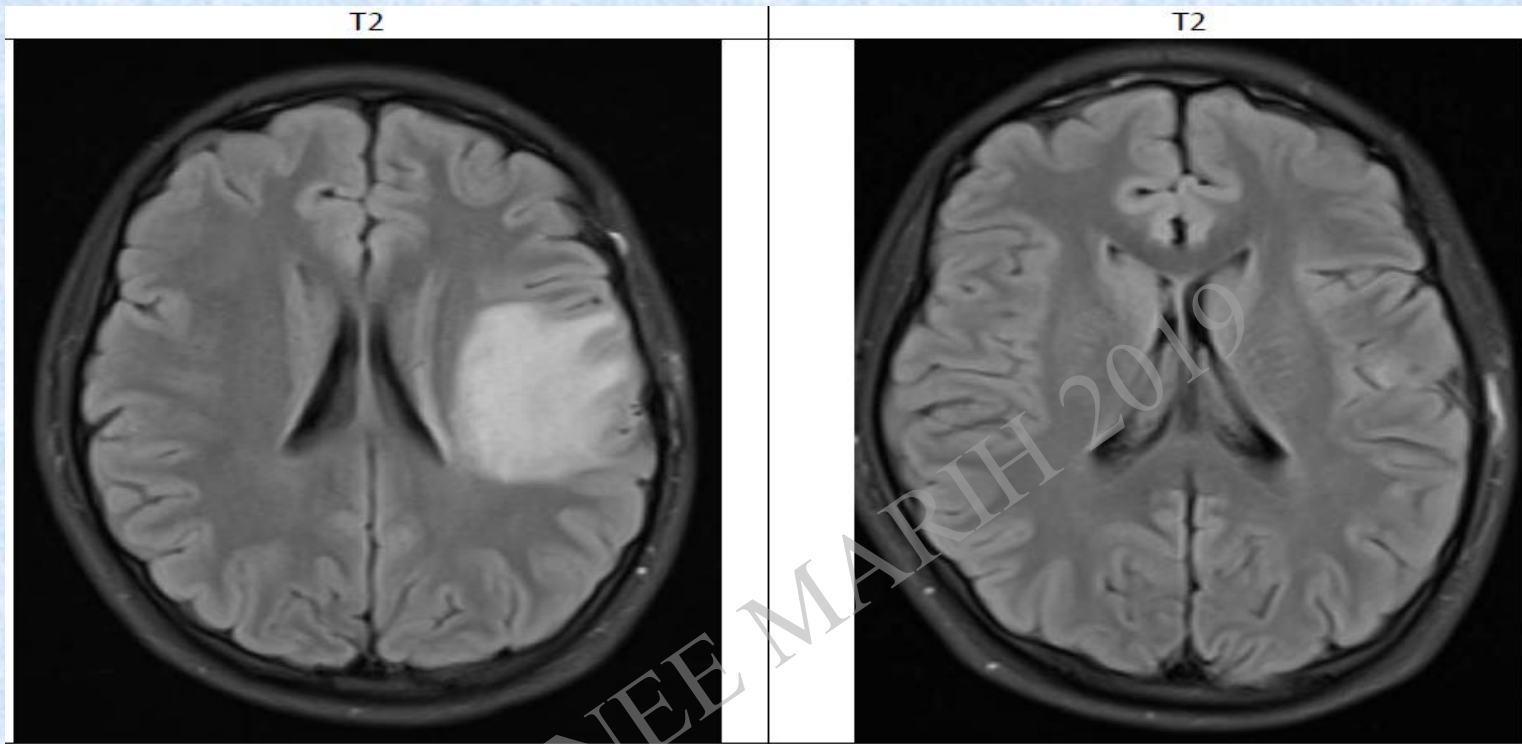


Figure 2

Altérations somatiques histiocytoses : Intérêt du RNA seq



Détection of gene fusion sur ARN extraits de tissus fixés et inclus en paraffine



Alectinib (2 mois)

Courtoisie de A Beilken

Allemagne
Mars 2019

Jean-François Emile

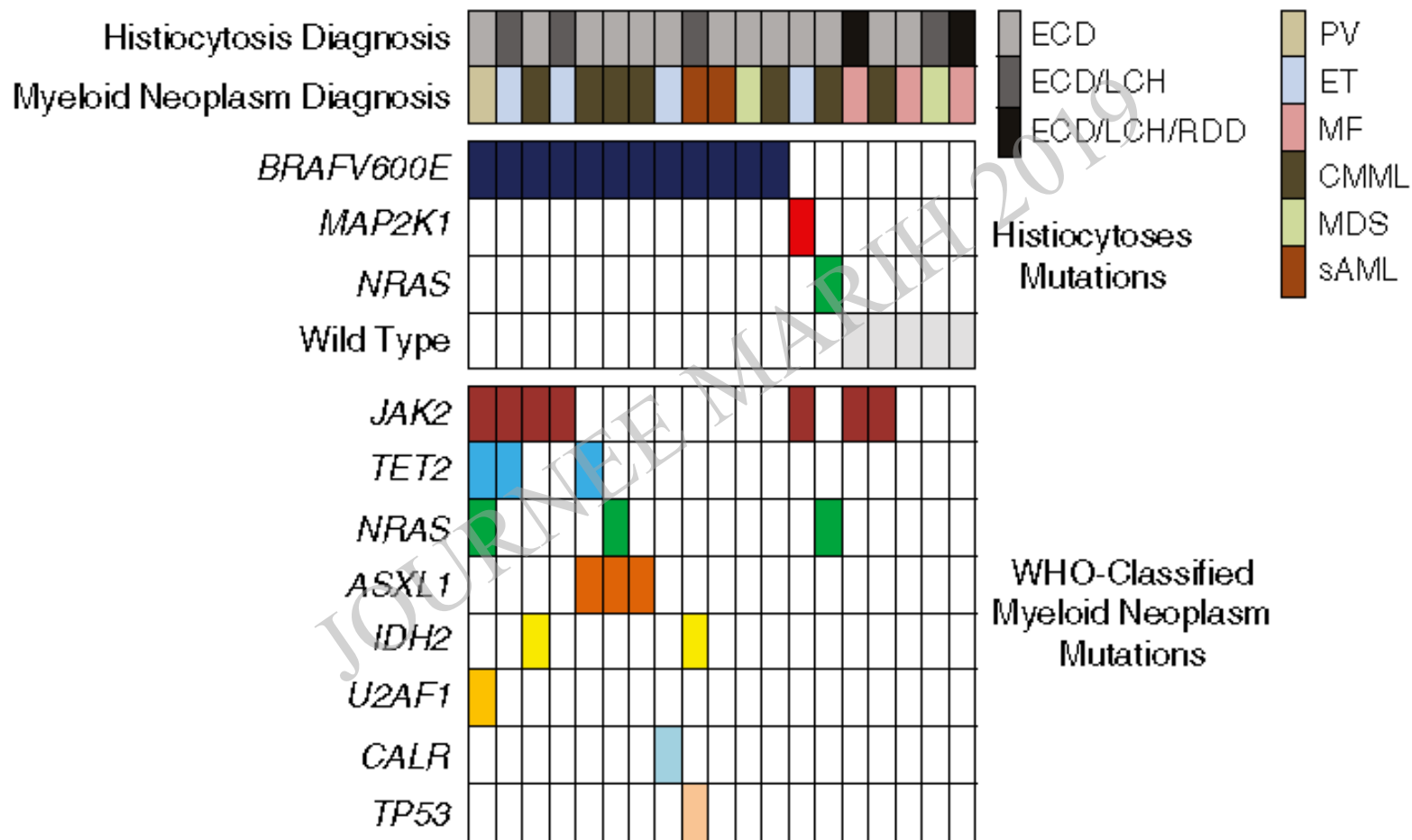
Service de pathologie & EA4340-BCOH

Ambroise Paré hospital, APHP & Versailles University

France

Genes altered in myeloproliferative neoplasia or myelodysplastic syndrome (MPN/MDS)

B



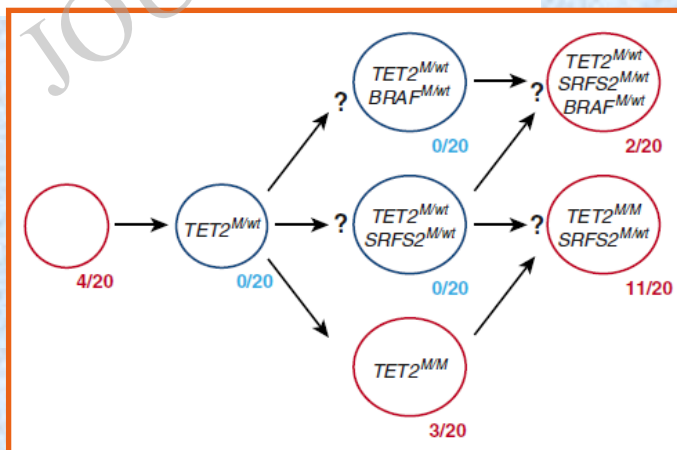
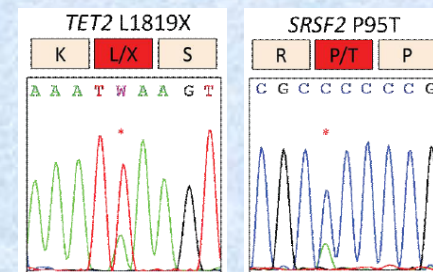
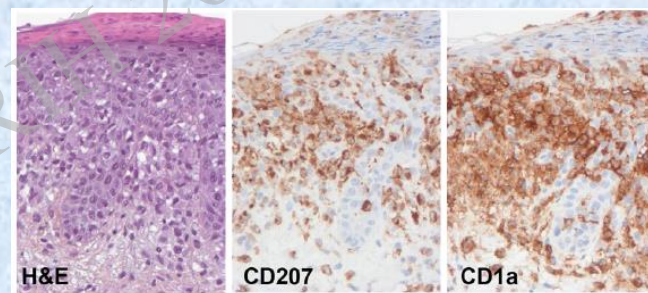
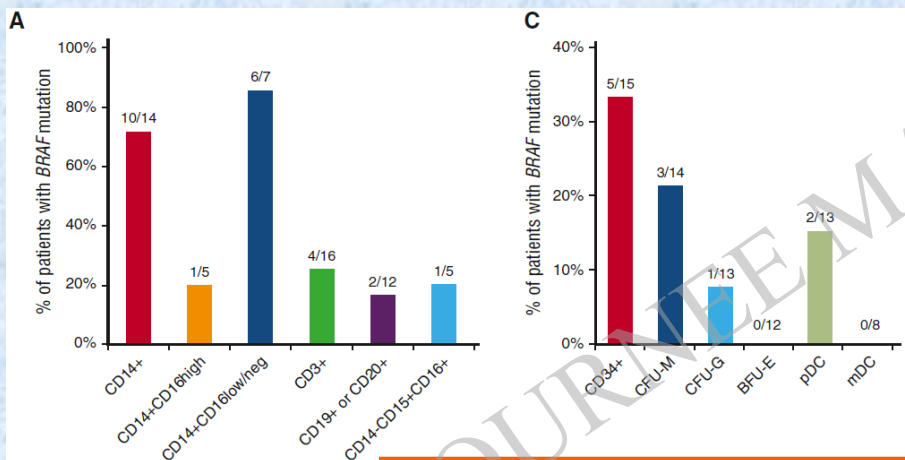
10% of patients with ECD also MPN/MDS

Néoplasies myéloïdes inflammatoires ?

Functional evidence for derivation of systemic histiocytic neoplasms from hematopoietic stem/progenitor cells

Benjamin H. Durham,^{1,2,*} Damien Roos-Weil,^{3,*} Claude Baillou,^{4,*} Fleur Cohen-Aubart,⁵ Akihide Yoshimi,² Makoto Miyara,^{4,6} Matthias Papo,⁵ Zofia Hélias-Rodzewicz,^{7,8} Nathalie Terrones,⁸ Neval Ozkaya,¹ Ahmet Dogan,¹ Raajit Rampal,⁹ Fanny Urbain,⁵ Lucie Le Fèvre,⁵ Eli L. Diamond,¹⁰ Christopher Y. Park,¹¹ Thomas Papo,¹² Frédéric Charlotte,¹³ Guy Gorochov,^{4,6} Valérie Taly,¹⁴ Olivier A. Bernard,³ Zahir Amoura,⁵ Omar Abdel-Wahab,^{2,9,†} François M. Lemoine,^{4,†} Julien Haroche,^{5,†} and Jean-François Emile^{7,8,†}

BLOOD, 13 JULY 2017

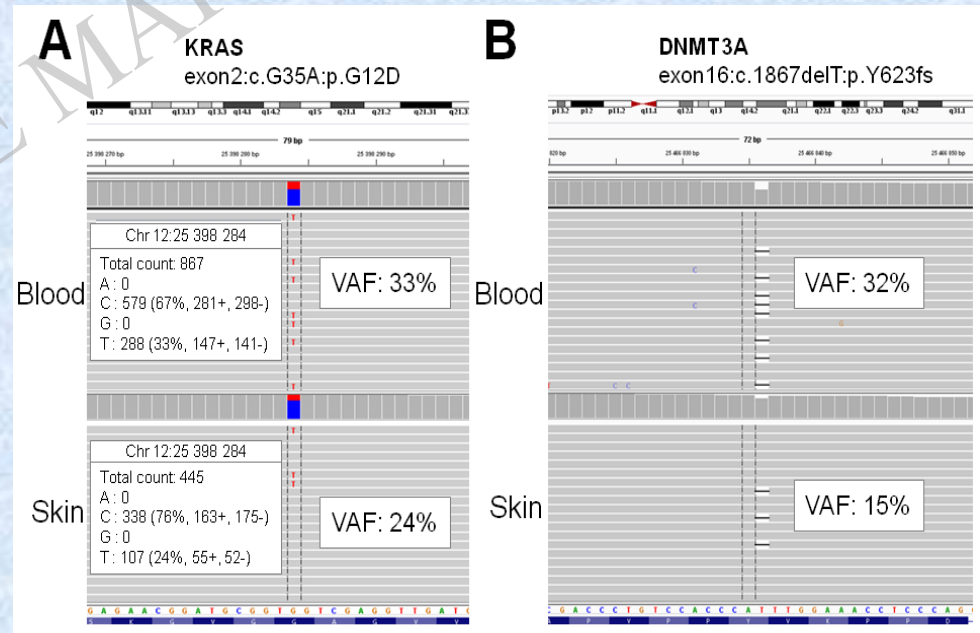


Néoplasies myéloïdes inflammatoires ?



Erdheim-Chester disease associated with chronic myelomonocytic leukemia harboring the same clonal mutation

Bonnet et al. Haematologica (sous presse)



Remerciements

- **Pathologistes**, Members of the French panel : S Boudjemaa, F Charlotte, C Chassagne, F Dijoud, S Fraitag, V Meignin, K Mokhtari, A Moreau
- Z Hélias-Rodzewicz, S Melloul, and techniciens du Laboratoire d'Ambroise Paré
- Scientifiques: R Chakraborty (Houston), R Saffroy (Villejuif), V Taly (Paris)
- Collègues du MSKCC: O Abdel-Wahab, EL Diamond
- **Réseau français des histiocytoses, et notamment**
J Donadieu, J Haroche, F Cohen-Aubart, S Héritier, A Idbaih, A Tazi, MA Barkaoui