Thérapie ciblée dans l'Histiocytose à cellules de langerhans chez l'enfant

Jean Donadieu
Registre national des histiocytoses
Centre de référence
www.eurohistio.net
Hopital Trousseau 75012 Paris

L’histiocytose langerhansienne en 4 dia..

Terminologie/ historique

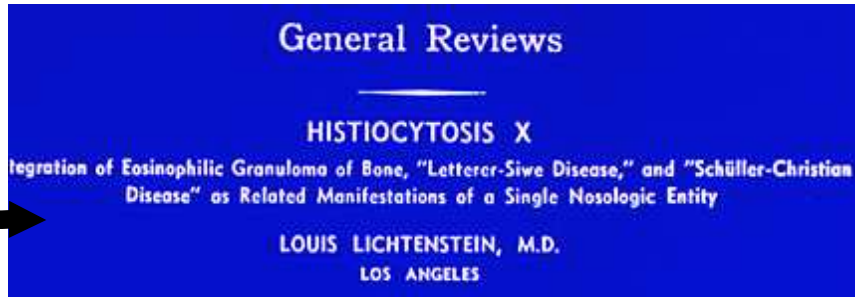
Hand Schuller Christian

Letterer Siwe - Abt

Granulome à éosinophile

Hashimoto Prizker

Forme cutanéo pulmonaire de Julien Marie



General Reviews

HISTIOCYTOSIS X

tegration of Eosinophilic Granuloma of Bone, "Letterer-Siwe Disease," and "Schüller-Christian Disease" as Related Manifestations of a Single Nosologic Entity

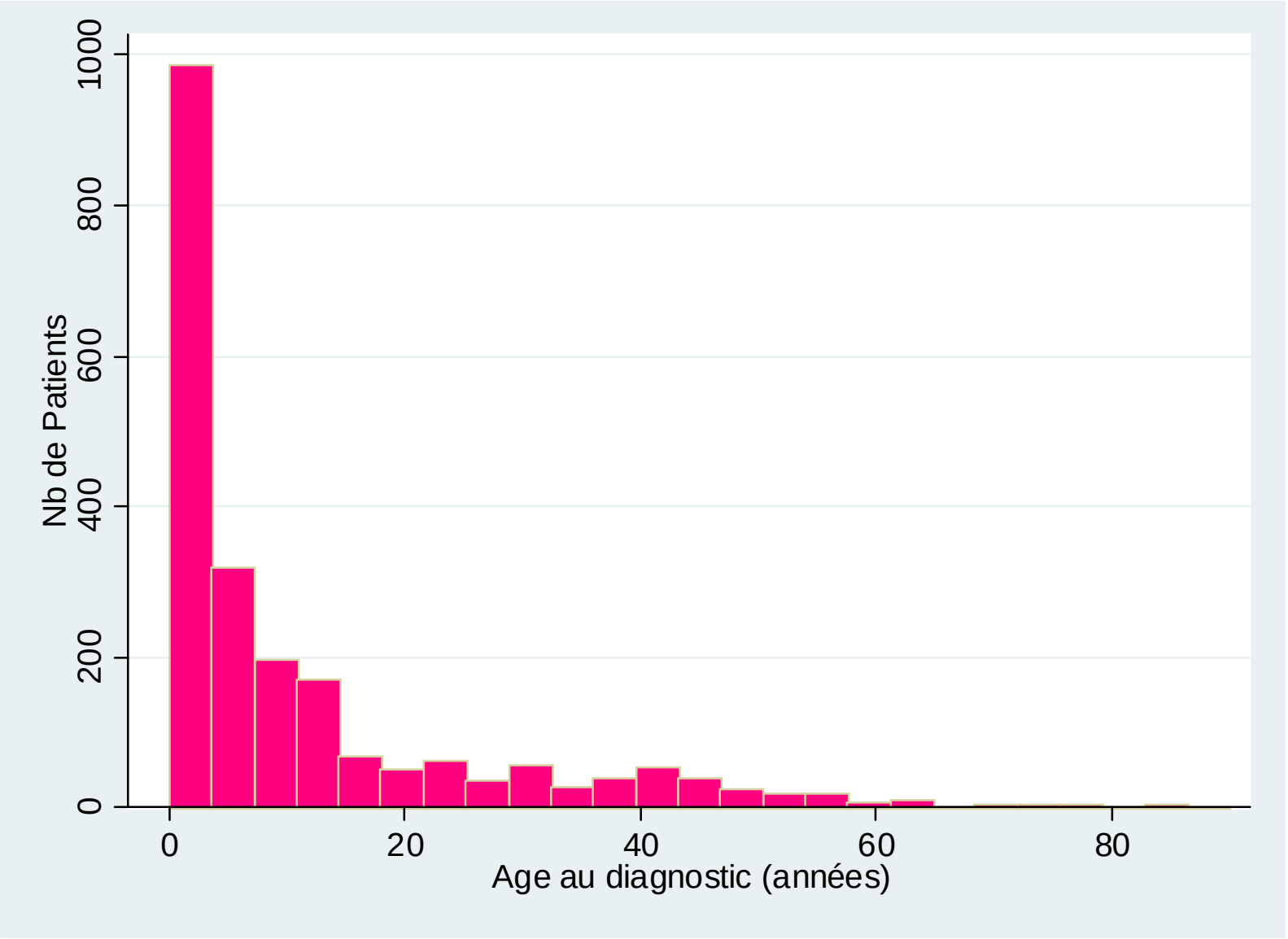
LOUIS LICHTENSTEIN, M.D.

LOS ANGELES

Histiocytose à Cellules de Langerhans

Epidémiologie Incidence $5/10^6$ par an.

Registre français depuis 93 : 2100 cas

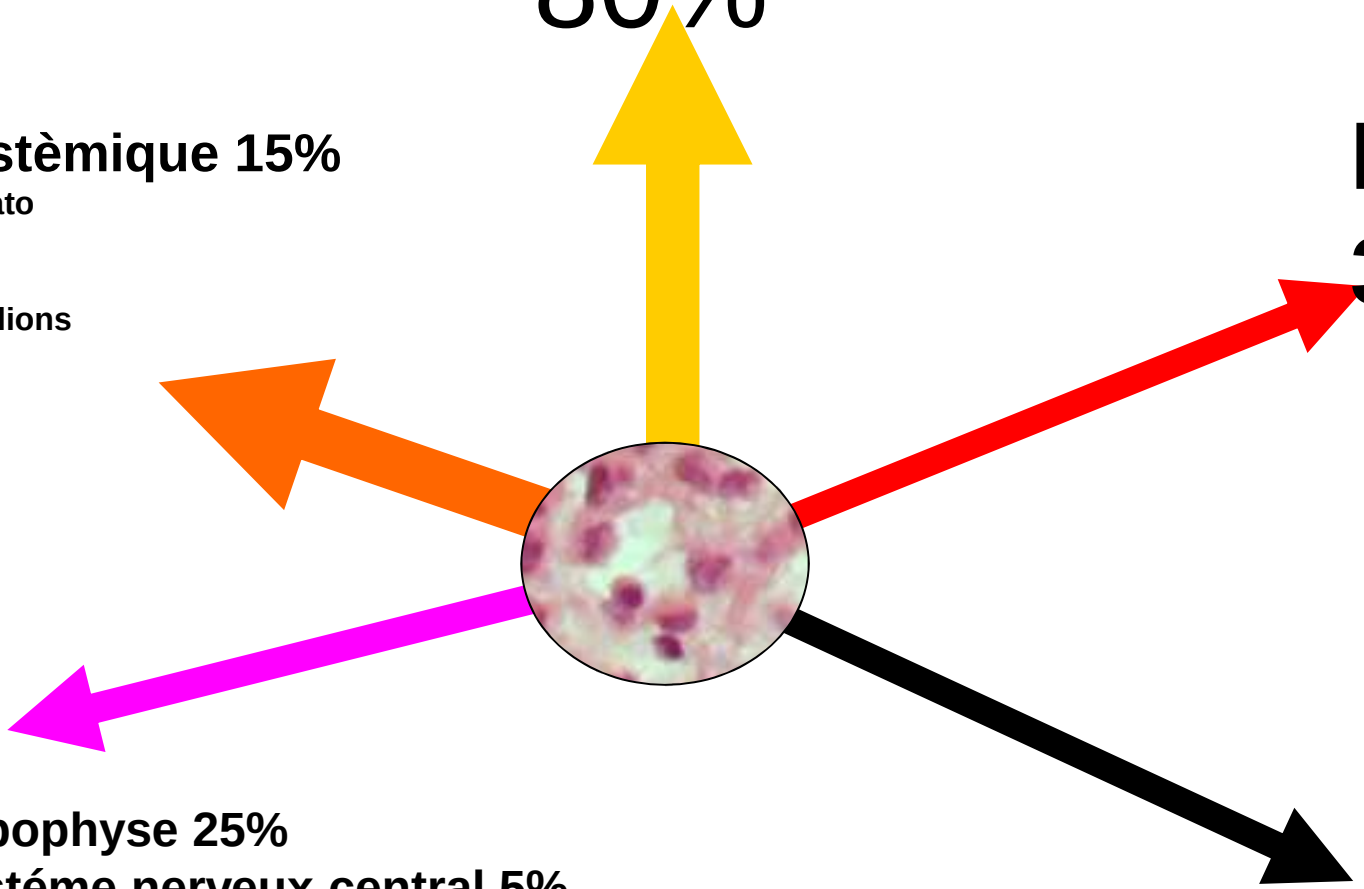


UNE maladie
Nombreuses facettes

Os
80%

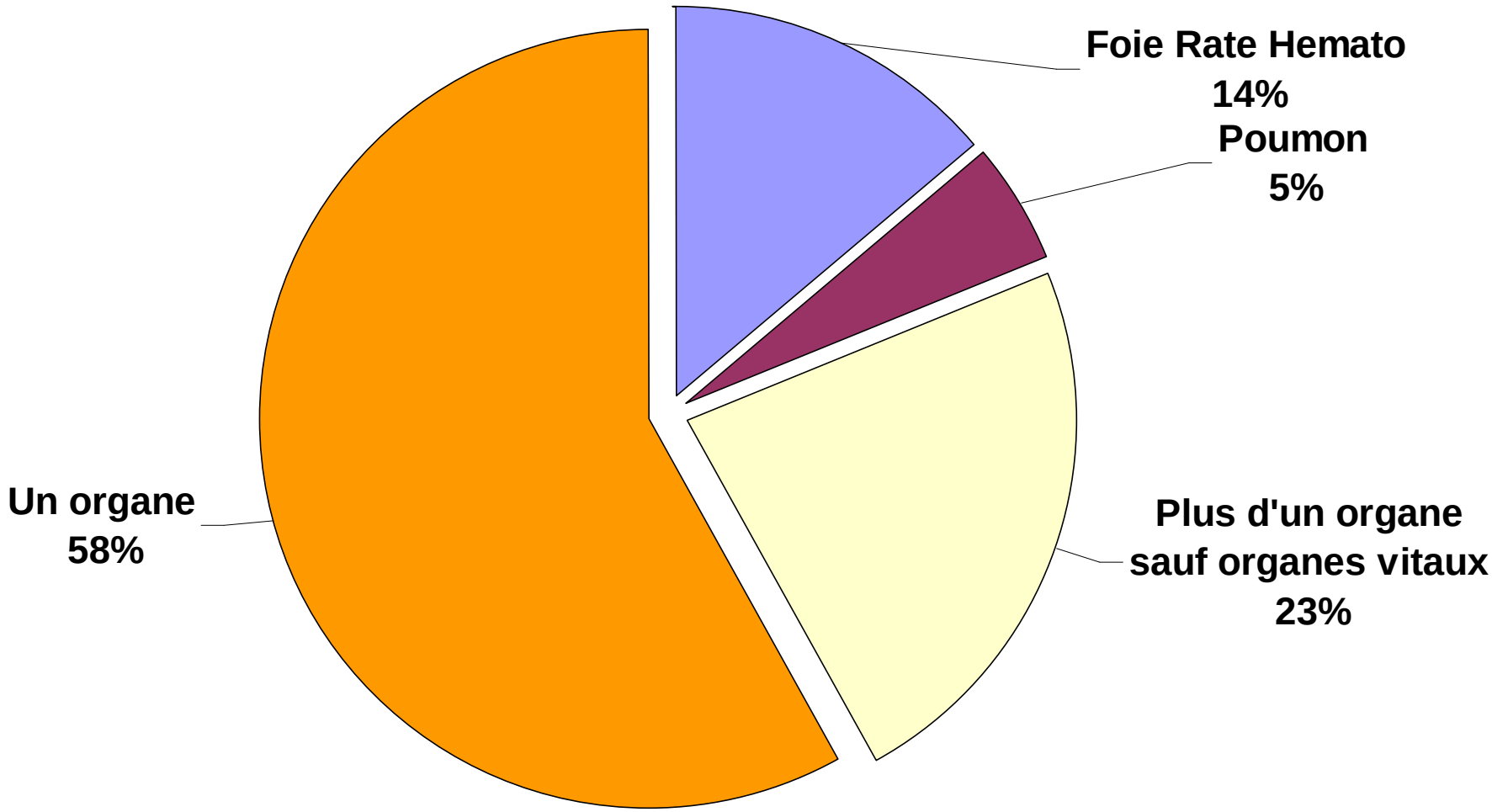
Systèmique 15%
hémato
Foie
Rate
ganglions

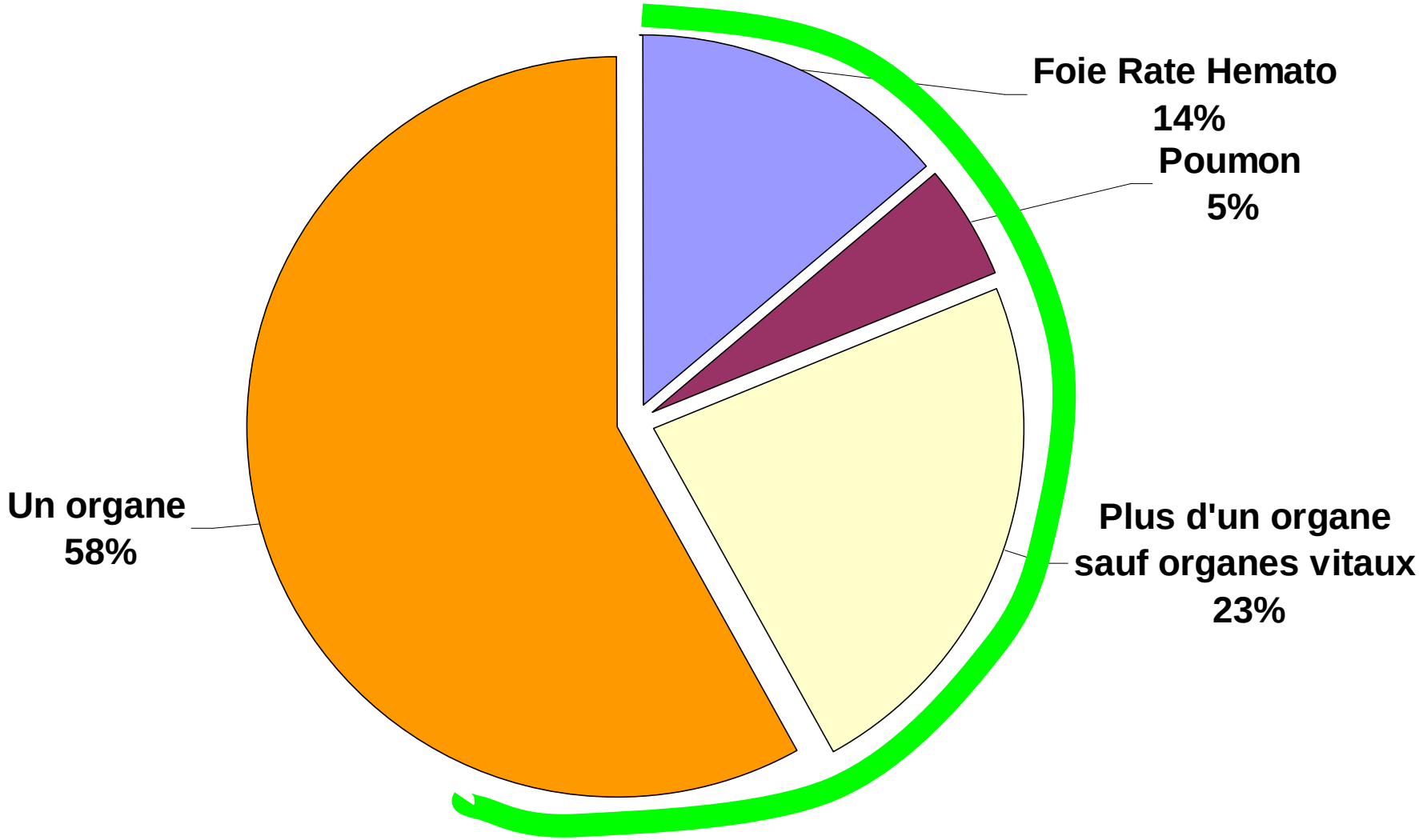
Peau
35%



Hypophyse 25%
Systéme nerveux central 5%

Poumon
12%


Foie Rate Hemato
14%
Poumon
5%
Plus d'un organe
sauf organes vitaux
23%
Un organe
58%


Foie Rate Hemato
14%
Poumon
5%
Plus d'un organe
sauf organes vitaux
23%
Un organe
58%

Une petite histoire des traitements de l'histiocytose L..

- Avant les années 1960

- 1963 → 1990 Emergence de traitement régulièrement efficace

Une petite histoire des traitements de l'histiocytose..

- Avant les années 1960
- 1963 → 1990 Emergence de traitement régulièrement efficace
- 1990→ 2000 Structuration de protocole / définition de groupes de patients/ tentatives de traitement de 2 ème ligne
- 2000→ … Intérêt de cures intensives 2 Cda Arac

Treatment of reticuloendotheliosis with vinblastine sulfate

Preliminary report

Three patients with proved reticuloendotheliosis (Letterer-Siwe syndrome) were treated with vinblastine sulfate in doses of 0.2 to 0.3 mg. per kilogram weekly for 8 to 15 weeks. The response in all three patients was so gratifying as to encourage further trials with this agent.

Frances R. Beier, M.D.,* L. Gilbert Thatcher, M.D., and M. Eugene Lahey, M.D.**

SALT LAKE CITY, UTAH

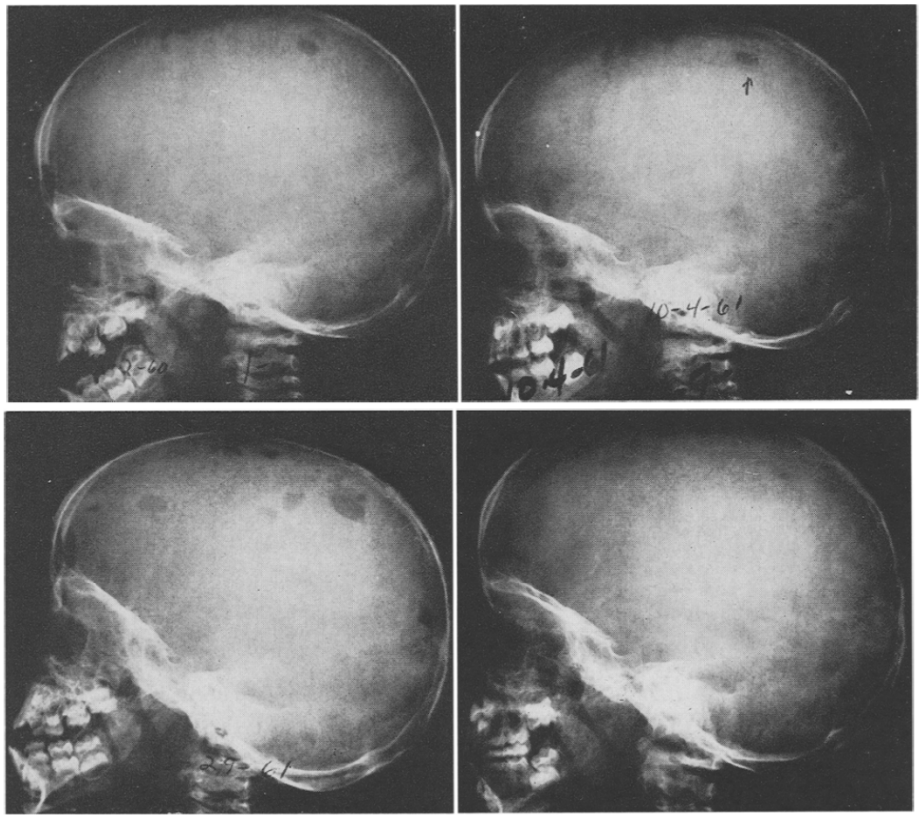


Fig. 1. Case 1. *A*, Multiple osteolytic lesions in the calvarium, at 18 months of age. *B*, Increase in size and number of lesions while treated with prednisone at 21 months of age. *C*, Beginning healing of lesions three months after initiation of vinblastine sulfate therapy at 28 months of age. *D*, Resolution of lesions at 3 years of age.

I N D U C T I O N | **EVALUATION** | **M A I N T E N A N C E**

Corticosteroid (CS)

CS : 40 mg /m² x28 days, then decrease

VBL | **VBL** | **VBL** | **VBL** | **VBL** | **VBL**

Vinblastine (VBL) 6 mg/m², always <10 mg

NAD >

CS D1 to D5 | **CS** D1 to D5 | **CS** D1 to D5

6MP 50 mg/m² if RO+

VBL | **VBL** | **15 Courses** | **VBL**

01 02 03 04 05 06 07 WEEK 08 09 10 11 12 . // . 51 52 53

AD Better > **2nd Induction** **then evaluation**

SECOND LINE THERAPY

AD Worse RO- > **2-CdA Monotherapy**

AD Worse RO+ > **2-CdA and Cytarabine**

Cladribine and cytarabine in refractory multisystem Langerhans cell histiocytosis: results of an international phase 2 study

Jean Donadieu,[1] Frederic Bernard,[2] Max van Noesel,[3] Mohamed Barkaoui,[1] Odile Bardet,[4] Rosella Mura,[5] Maurizio Arico,[6] Christophe Piguet,[7] Virginie Gandemer,[8] Corinne Armari Alla,[9] Niels Clausen,[10] Eric Jeziorski,[2] Anne Lambilliote,[11] Sheila Weitzman,[12] Jan Inge Henter,[13] Cor Van Den Bos,[14] and the Salvage Group of the Histiocyte Society

[1]Service d'Hémato-Oncologie Pédiatrique, Hopital Trousseau, Paris Registre des Histiocytoses Centre de Référence des Histiocytoses, Assistance Publique-Hôpitaux de Paris (APHP), Paris, France; [2]Hémato Oncologie Pédiatrique, Centre Hospitalier Universitaire (CHU) de Montpellier, Montpellier, France; [3]Department of Pediatric Hematology Oncology, Erasmus MC–Sophia's Children's Hospital, Rotterdam, The Netherlands; [4]Direction Recherche et Innovation, Centre Hospitalier Régional Universitaire (CHRU) Montpellier–Centre Administratif André Benech, Montpellier, France; [5]Pediatric Hematology Oncology, Ospedale microcetemico, Cagliari, Italy; [6]Pediatric Hematology Oncology, Azienda Sanitaria Provinciale, Ragusa, Italy; [7]Pediatric Hémato Oncology, CHU, Limoges, France; [8]Pediatric Hémato Oncology, CHU, Rennes, France; [9]Pediatric Hémato Oncology, CHU, Grenoble, France; [10]Pediatric Hematology Oncology, Universitets Hospital of Aarhus at Skejby, Aarhus, Denmark; [11]Pediatric Hémato Oncology, Hopital Jean De Flandre, CHU, Lille, France; [12]Pediatric Hematology Oncology, The Hospital for Sick Children, Toronto, ON, Canada; [13]Department of Women's and Children's Health, Karolinska Institute, Karolinska Univeristy Hospital, Stockholm Sweden; and [14]Department of Pediatric Oncology, Emma Children's Hospital/Academic Medical Center, Amsterdam, The Netherlands

Key Points

- Patients with LCH, risk organs, refractory to standard VBL-steroid regimen have a poor survival, ~30%.
- In a phase 2 study, with 5 years' median follow-up, cladribine and Ara-C was shown to improve the survival up to 85% for this group.

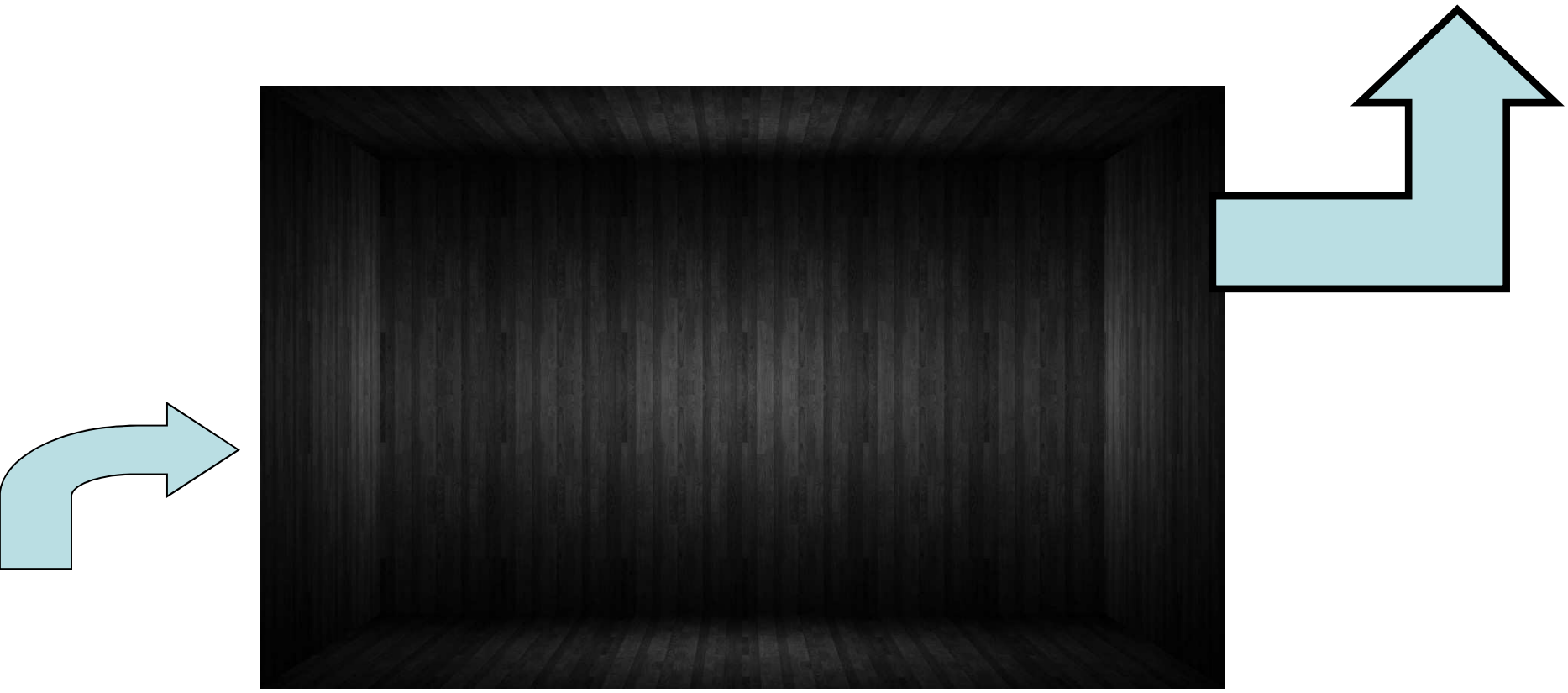
An international phase 2 study combining cladribine and cytarabine (Ara-C) was initiated for patients with refractory, risk-organ–positive Langerhans cell histiocytosis (LCH) in 2005. The protocol, comprising at least two 5-day courses of Ara-C (1 g/m^2 per day) plus cladribine (9 mg/m^2 per day) followed by maintenance therapy, was administered to 27 patients (median age at diagnosis, 0.7 years; median follow-up, 5.3 years). At inclusion, all patients were refractory after at least 1 course of vinblastine (VBL) plus corticosteroid, all had liver and spleen involvement, and 25 patients had hematologic cytopenia. After 2 courses, disease status was nonactive (n = 2), better (n = 23), or stable (n = 2), with an overall response rate of 92%. Median disease activity scores decreased from 12 at the start of therapy to 3 after 2 courses ($P < .0001$). During maintenance therapy, 4 patients experienced reactivation in risk organs. There were 4 deaths; 2 were related to therapy toxicity and 2 were related to reactivation. All patients experienced severe toxicity, with World Health Organization grade 4 hematologic toxicity and 6 documented severe infections. The overall 5-year survival rate was 85% (95% confidence interval, 65.2%-94.2%). Thus, the combination of cladribine/Ara-C is effective therapy for refractory multisystem LCH but is associated with high toxicity. (*Blood*. 2015;126(12):1415-1423)

Sous presse ..

bjh british journal of haematology

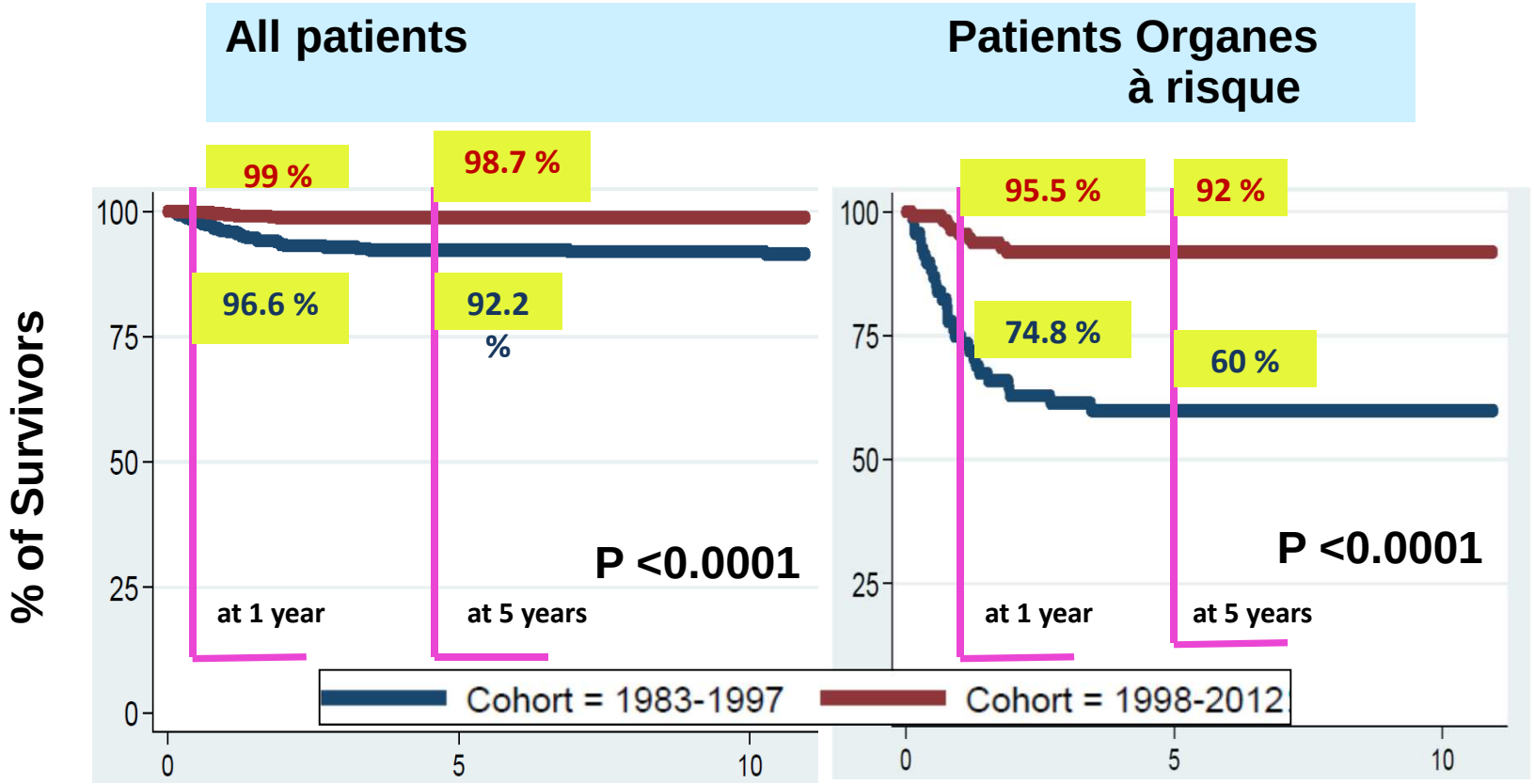
Langerhans cell histiocytosis: therapeutic strategy and outcome in a 30-year nationwide cohort of 1478 patients under 18 years of age

Effet Boite Noire



On ne comprend pas ce que l’on fait mais cela marche souvent….

SURVIE cohorte nationale française 1983-2012



Number at risk						
Cohort 1983-1997	*483*	*283*	*209*	68	37	33
Cohort 1998-2012	*995*	*462*	*148*	112	71	32

Des progrés trés significatifs pour la survie des patients ont été accompliés dans les 15 derniéres années et la mortalité par histiocytose est maintenant inférieure à 2%. C'est encore trop, mais quand même..

Problémes résiduels…

- Formes graves
  - Toxicité ++++
  - Durée hospitalisation 50 jours sous flux
- Séquelles à long terme
  - Atteinte neuro dégénérative
  - Cholangite sclérosante
  - Insuffisance respiratoire
- Formes récidivantes

B RAF et l’histiocytose

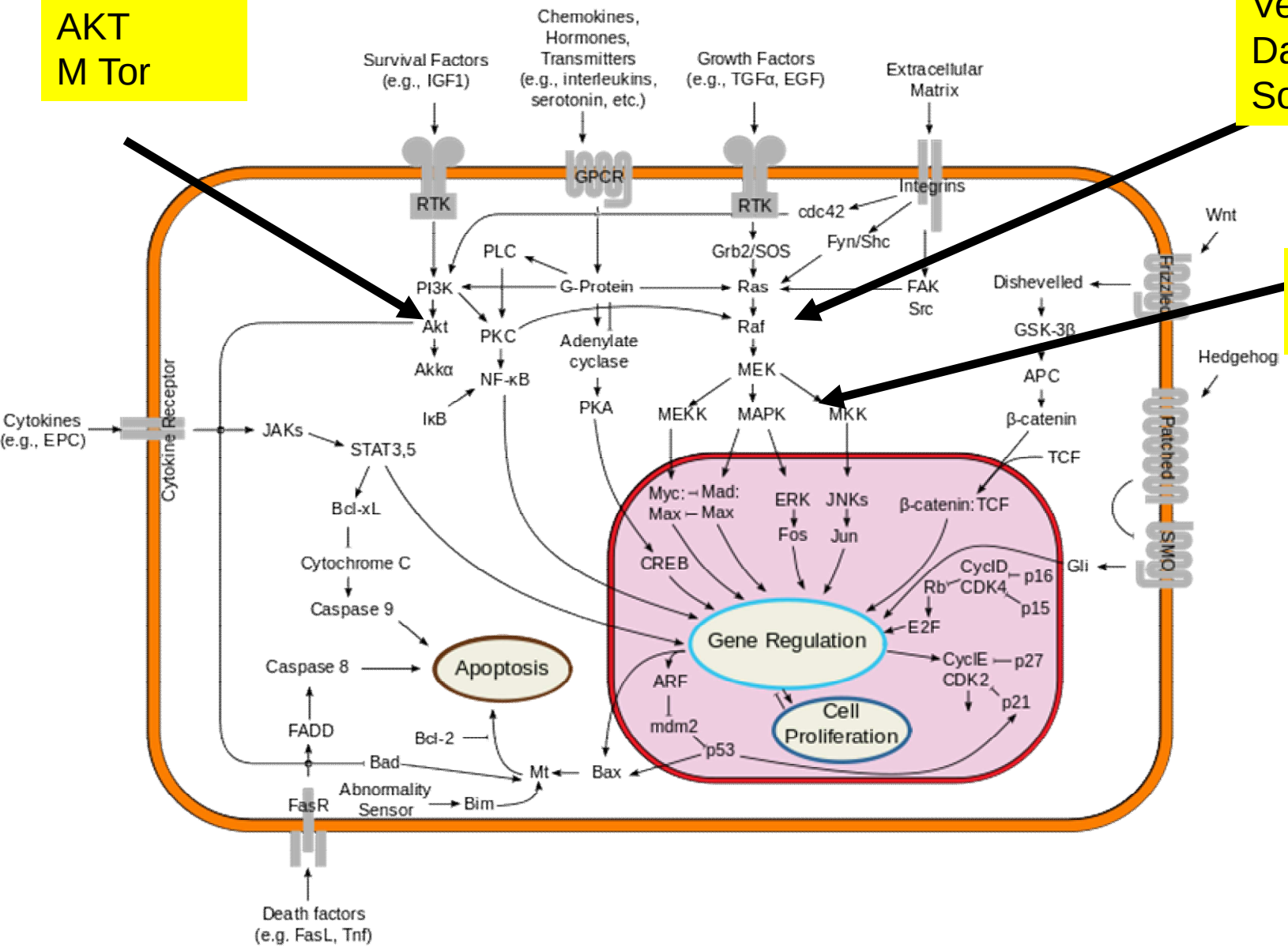
- Un changement de concept...
- B RAF V600E= formes graves
- Autres mutations: Voie Mapkinase ou voies paralléles

Conséquences fonctionnelles de B raf….

Inhibiteurs
AKT
M Tor

Vemurafenib
Dabratenib
Sorafenib

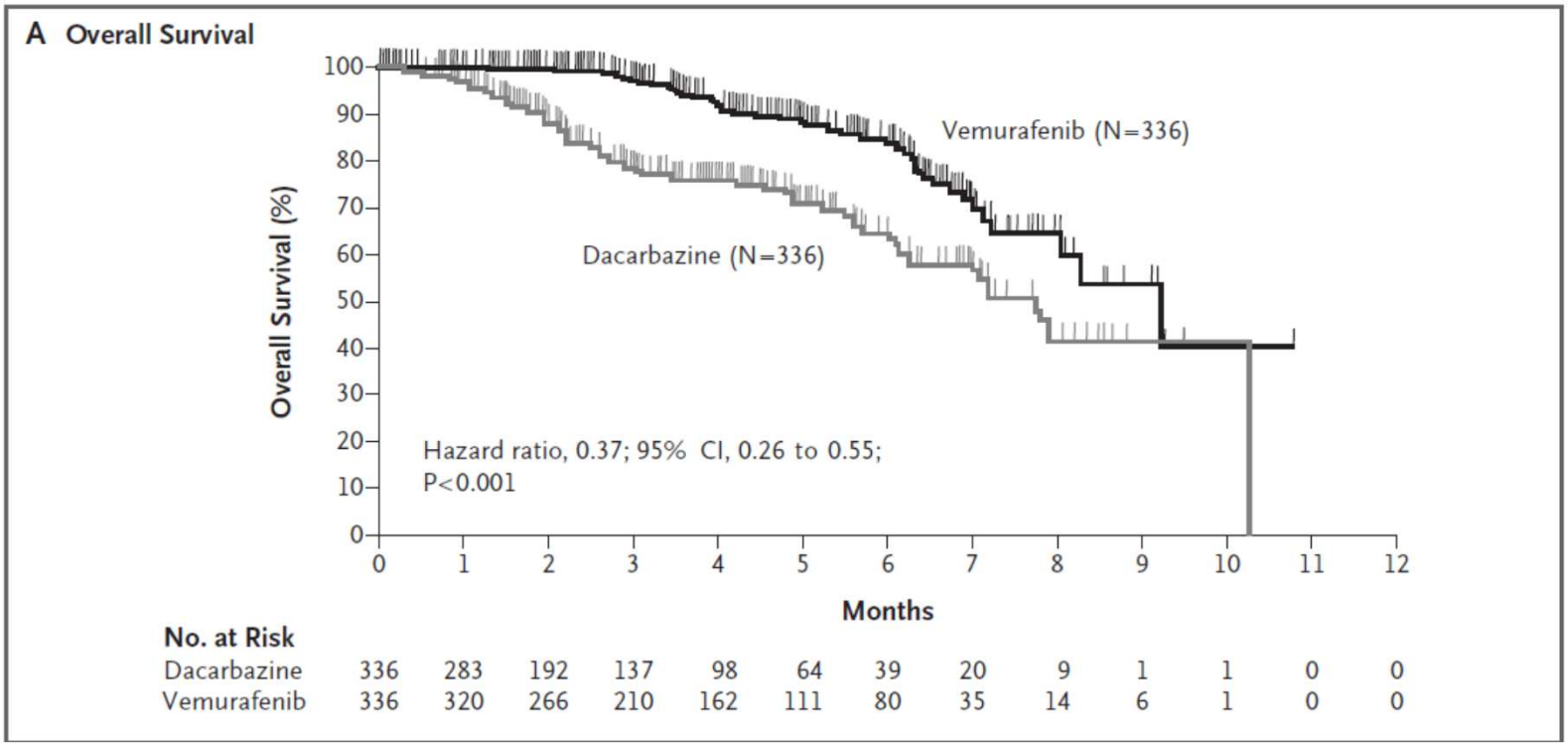
Cobimetinib
Trametinib



B raf et thérapeutique

- L’expérience majeure vient du MELANOME

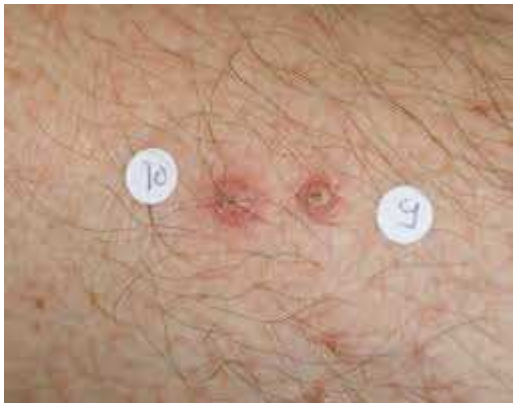
Mais…

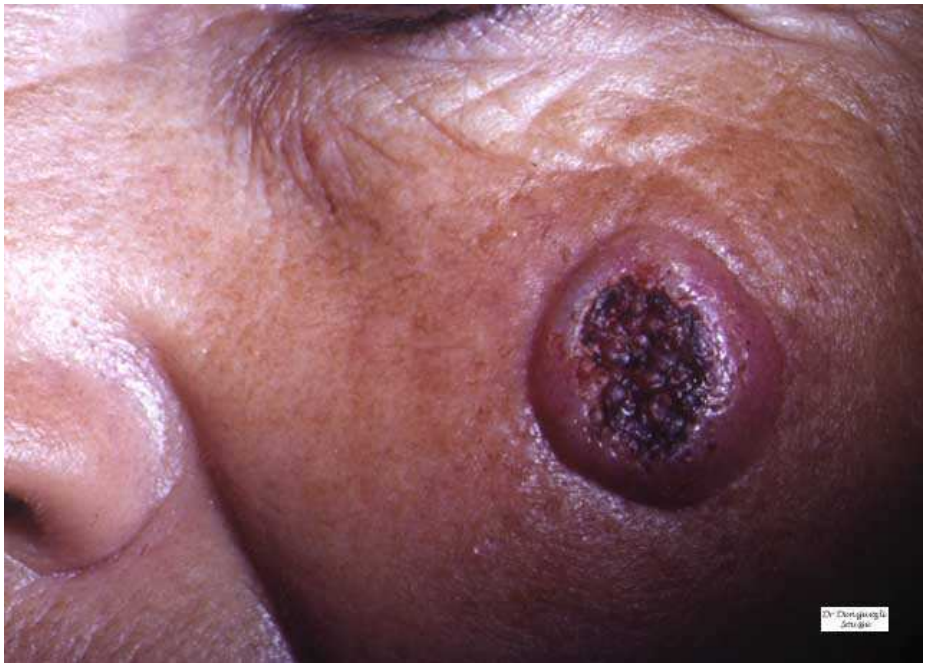


- Un seul B raf inhibitor .. Tt continu… rechute / échappement par acquisition mutations NRAS

Complications 20 à 30% de complications

- Kerato ancanthomes

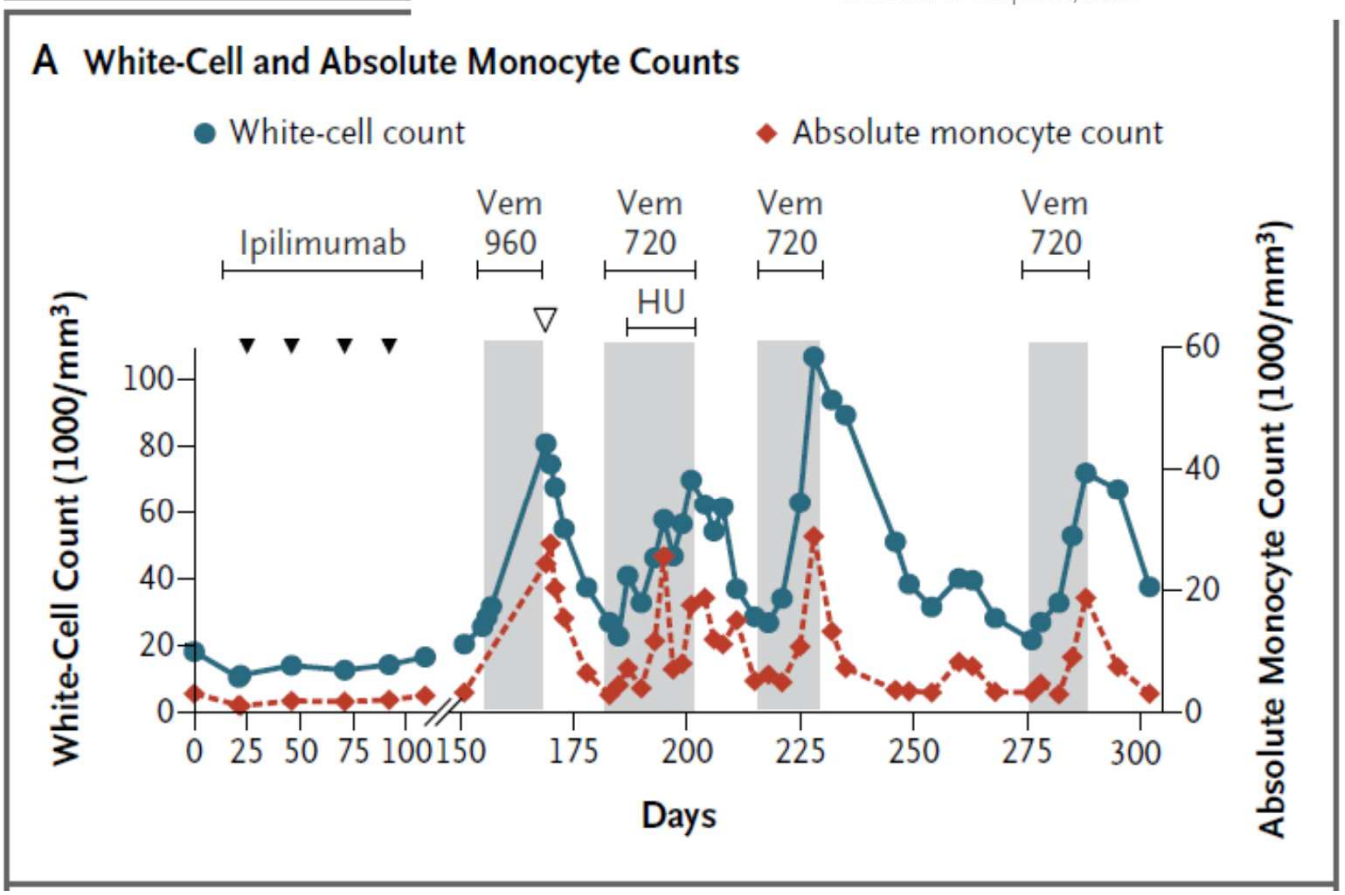




Autre complication: une forme
D'anomalie hématologique :
syndrome
Myélo monocytaire

Progression of RAS-Mutant Leukemia during RAF Inhibitor Treatment

Margaret K. Callahan, M.D., Ph.D., Raajit Rampal, M.D., Ph.D., James J. Harding, M.D., Virginia M. Klimek, M.D., Young Rock Chung, M.Sc., Taha Merghoub, Ph.D., Jedd D. Wolchok, M.D., Ph.D., David B. Solit, M.D., Neal Rosen, M.D., Ph.D., Omar Abdel-Wahab, M.D., Ross L. Levine, M.D., and Paul B. Chapman, M.D.



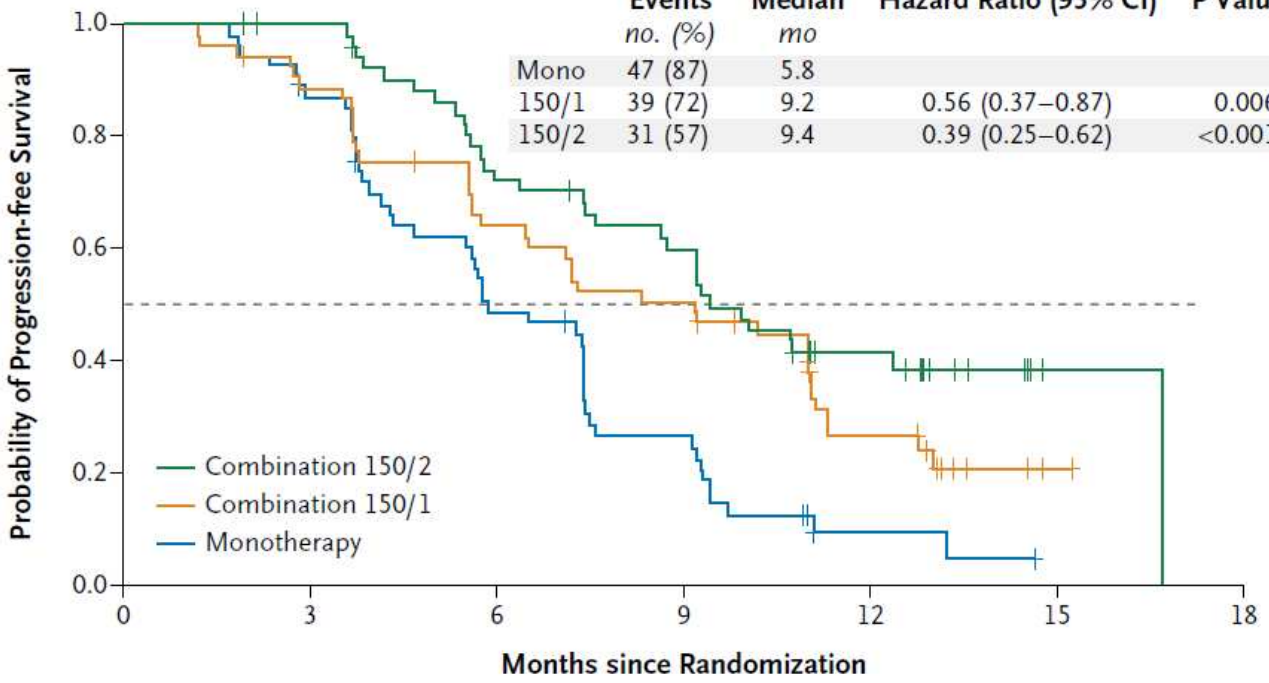
Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

Keith T. Flaherty, M.D., Jeffery R. Infante, M.D., Adil Daud, M.D., Rene Gonzalez, M.D., Richard F. Kefford, M.D., Ph.D., Jeffrey Sosman, M.D., Omid Hamid, M.D., Lynn Schuchter, M.D., Jonathan Cebon, M.D., Ph.D., Nageatte Ibrahim, M.D., Ragini Kudchadkar, M.D., Howard A. Burris III, M.D., Gerald Falchook, M.D., Alain Algazi, M.D., Karl Lewis, M.D., Georgina V. Long, M.D., Ph.D., Igor Puzanov, M.D., M.S.C.I., Peter Lebowitz, M.D., Ph.D., Ajay Singh, M.D., Shonda Little, M.P.H., Peng Sun, Ph.D., Alicia Allred, Ph.D., Daniele Ouellet, Ph.D., Kevin B. Kim, M.D., Kiran Patel, M.D., M.B.A., and Jeffrey Weber, M.D., Ph.D.

Dafratenib + Trametinib

A Progression-free Survival

	Events *no. (%)*	Median *mo*	Hazard Ratio (95% CI)	P Value
Mono	47 (87)	5.8		
150/1	39 (72)	9.2	0.56 (0.37–0.87)	0.006
150/2	31 (57)	9.4	0.39 (0.25–0.62)	<0.001



No. at Risk

Monotherapy	54	46	25	13	2	0
Combination 150/1	54	47	33	26	11	1
Combination 150/2	54	52	36	29	15	1

Et les histiocytoses…

Histio non langerhansienne

Reproducible and Sustained Efficacy of Targeted Therapy With Vemurafenib in Patients With *BRAF*^{V600E}-Mutated Erdheim-Chester Disease

Julien Haroche, Fleur Cohen-Aubart, Jean-François Emile, Philippe Maksud, Aurélie Drier, Dan Tolédano, Stéphane Barete, Frédéric Charlotte, Philippe Cluzel, Jean Donadieu, Neïla Benameur, Philippe A. Grenier, Sophie Besnard, Jean-Paul Ory, François Lifermann, Ahmed Idbaih, Brigitte Granel, Bruno Graffin, Baptiste Hervier, Laurent Arnaud, and Zahir Amoura

J Clin Oncol 32.

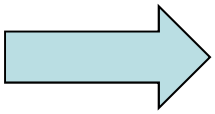
Histio. Langerhansienne
Dans l'équation…

- Age pédiatrique
- 3 à 4 formes hématologiques réfractaires par an
- 2 atteintes neuro dégénératives
- 4 atteintes multi récidivantes

en France

EU

Idem X 5



Le domaine des histiocytoses n'atteindra jamais un nombre suffisant pour organiser des essais randomisés

Approche pédiatrique

- Pas à Pas
  - 3 groupes ‘cibles’
    - Formes systémiques résistantes
    - Cholangite sclérosante
    - Atteinte neuro dégénérative
  - Obtenir des données de PK
  - Commencer par une molécule
  - Travailler un cadre réglementaire
    - Orphan designation
    - ACsé

Thérapeutique ciblée

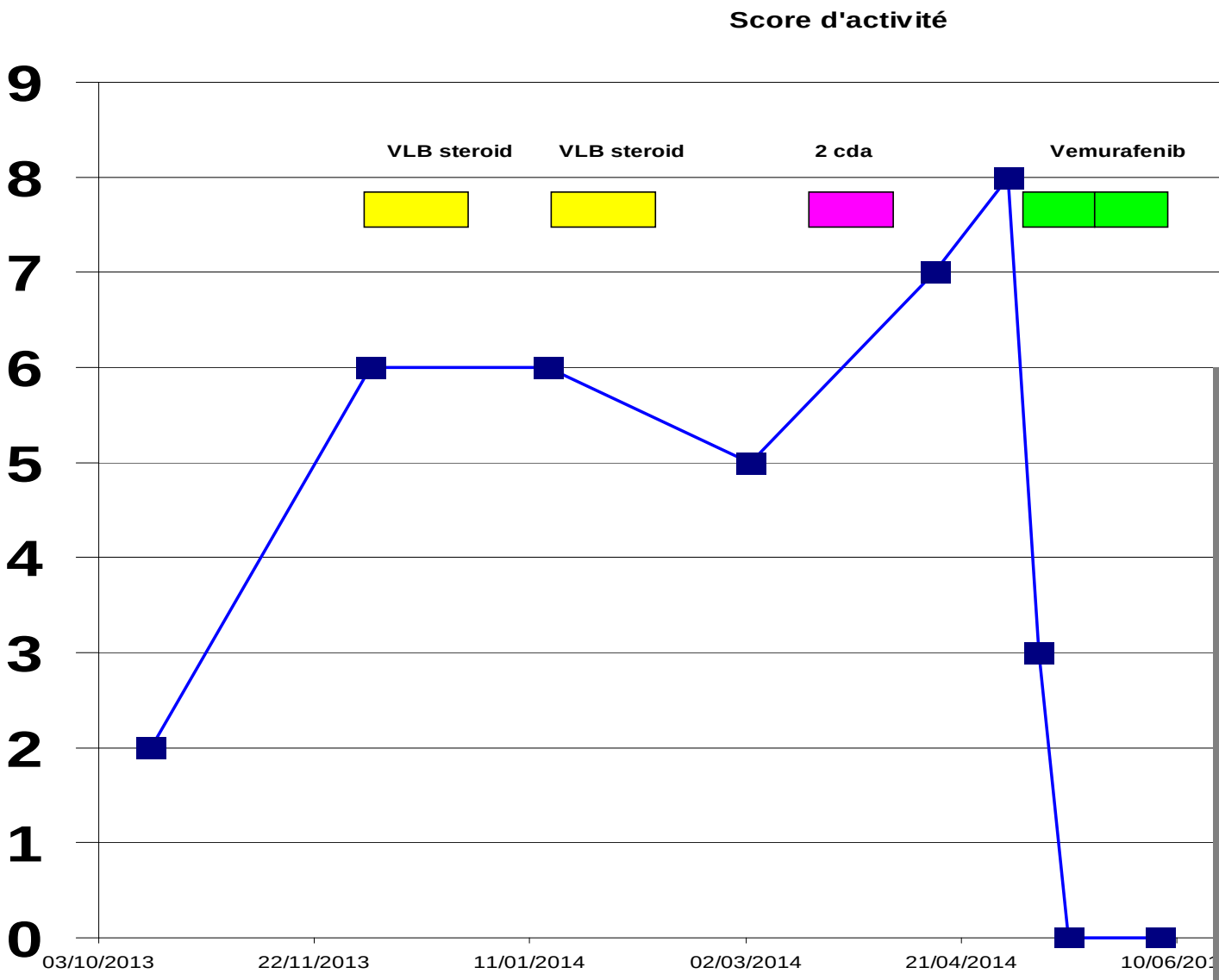
- Un Cas pilote: Vemurafenib,

Letters

RESEARCH LETTER

Vemurafenib Use in an Infant for High-Risk Langerhans Cell Histiocytosis

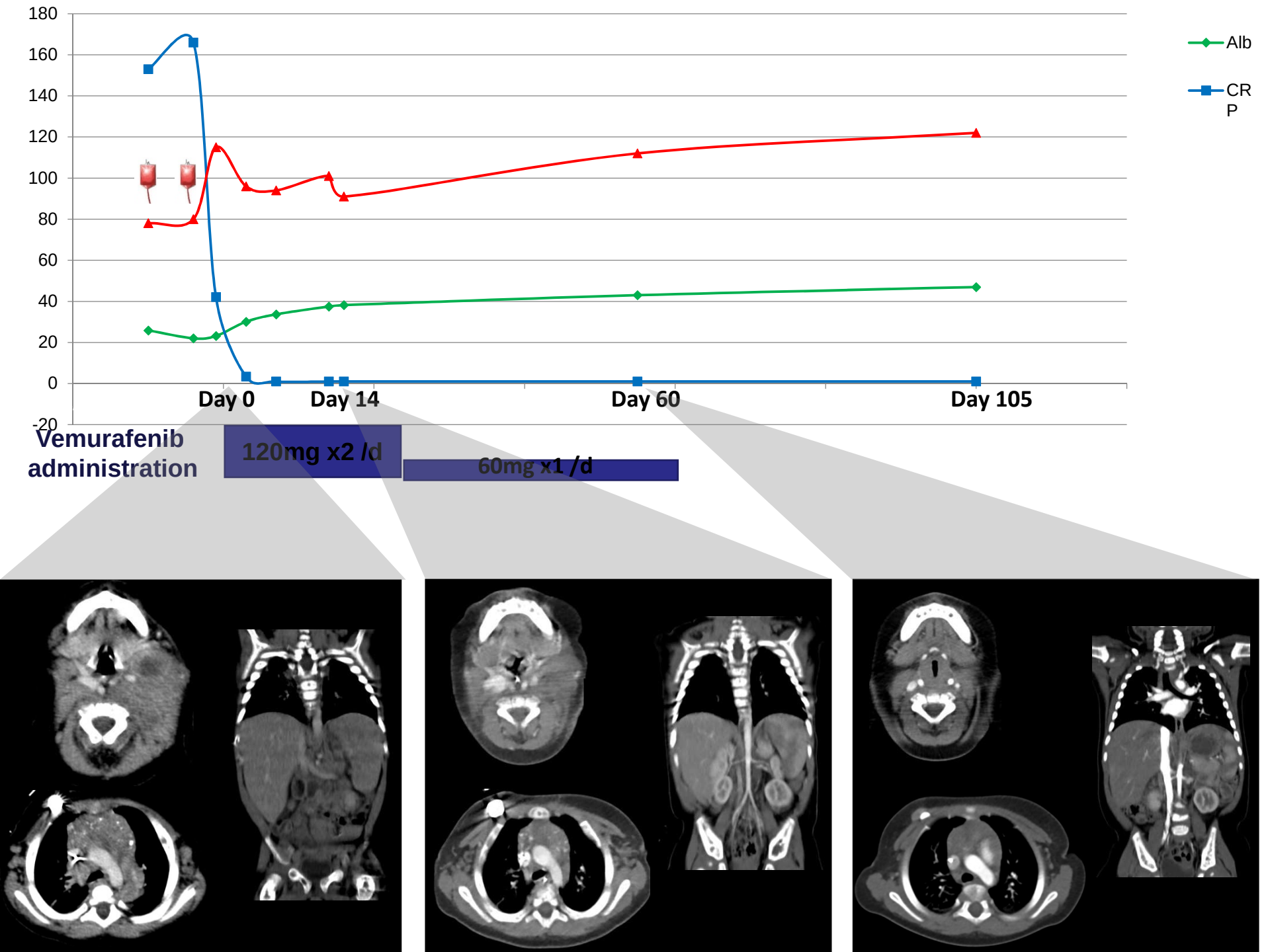
Langerhans cell histiocytosis (LCH) is a clonal disorder characterized by lesions containing pathological CD207$^+$ dendritic cells. Refractory high-risk LCH is a life-threatening disease that affects mostly infants. Patients with a Disease Activity Score (DAS) higher than 6, in whom vinblastine sulfate-steroid treatment had failed, have a greater than 50% risk of death, which mostly concerns children younger than 2 years.[1] Because somatic *BRAF* V600E mutation plays an important role in LCH pathophysiology,[2] BRAF inhibitors could offer a new therapeutic approach[3] but, to our knowledge, have never been proposed as a treatment in infants.



Semaine 1

Arret Morphine
Stop fiévre
Diminution HSM et GG
Stop transfusion

Sortie D21


180
160
140
120
100
80
60
40
20
0
-20
Alb
CRP
Day 0
Day 14
Day 60
Day 105
Vemurafenib administration
120mg x2 /d
60mg x1 /d

Phase Pilote

- Dose 20 mg/kg - Maxi 3 mois
- Patients B Raf V600E

	Neuro Dégénératif	cholangite sclérosante	Systémique réfractaire
N	5	2	10
Organes cibles	Encéphale Syndr Cérébelleux Fonct Sup Marche	Foie	Hémato GG Foie Rate Os
Toxicité sévère ou arrêt de tt	2 : arrêt du tt malaise n=1 et Eruption n=1	0	0
Age inclusion	12 ans	1,5 ans	1,5 ans
Évaluable à 3 mois	3	2	10
Réponse	1 réponse partielle	Pas de réponse	100% de réponse
Dose PK			adaptation de dose 2
Suivi aprés stop	2 Médiane 1 ans	2 Médiane 3 mois	10 Médiane 4 mois *Rechute peau et os et systémique dans 40%*

Conclusions

- Avec B raf, on peut commencer à penser l'histiocytose à travers des événements moléculaires
  - Nouveaux gènes impliquées et tests fonctionnels
  - Thérapeutiques ciblées
- Il faut cibler les indications
- Utilité de rester connecter à la problématique mélanome..
- Phase pilote:
  - Le vemurafenib est possible.
  - Toxicité acceptable
  - Efficacité dans formes systémiques mais récidive après 3 mois