

# Thérapies ciblées dans les histiocytoses réfractaires: Une étude EU

European Consortium for  
HistiOcytosis



# Vemurafenib for Refractory Multisystem Langerhans Cell Histiocytosis in Children: An International Observational Study

Jean Donadieu, MD, PhD<sup>1</sup>; Islam Amine Larabi, MD<sup>2</sup>; Mathilde Tardieu, MD<sup>3</sup>; Johannes Visser, MD<sup>4</sup>; Caroline Hutter, MD<sup>5</sup>; Elena Sieni, MD<sup>6</sup>; Nabil Kabbara, MD<sup>7,8</sup>; Mohamed Barkaoui, MSc<sup>1</sup>; Jean Miron, MSc<sup>1</sup>; François Chalard, MD<sup>1</sup>; Paul Milne, MD, PhD<sup>9</sup>; Julien Haroche, MD, PhD<sup>10</sup>; Fleur Cohen, MD<sup>10</sup>; Zofia Hélias-Rodzewicz, MD<sup>11</sup>; Nicolas Simon, MD<sup>12</sup>; Mathilde Jehanne, MD<sup>13</sup>; Alexandra Kolenova, MD<sup>14</sup>; Anne Pagnier, MD<sup>3</sup>; Nathalie Aladjidi, MD<sup>15</sup>; Pascale Schneider, MD<sup>16</sup>; Geneviève Plat, MD<sup>17</sup>; Anne Lutun, MD<sup>18</sup>; Anne Sonntagbauer, MD<sup>19</sup>; Thomas Lehmbecher, MD<sup>19</sup>; Alina Ferster, MD<sup>20</sup>; Viktoria Efreanova, MD<sup>21</sup>; Martina Ahlmann, MD<sup>22</sup>; Laurence Blanc, MD<sup>23</sup>; James Nicholson, MD<sup>4</sup>; Anne Lambilliotte, MD<sup>24</sup>; Houda Boudiaf, MD<sup>25</sup>; Andrej Lissat, MD<sup>26</sup>; Karel Svojr, MD<sup>27</sup>; Fanette Bernard, MD<sup>28</sup>; Sarah Elitzur, MD<sup>29</sup>; Michal Golan, MD<sup>30</sup>; Dmitriy Evseev, MD<sup>31</sup>; Michael Maschan, MD<sup>31</sup>; Ahmed Idbaih, MD, PhD<sup>32</sup>; Olga Slater, MD<sup>33</sup>; Milen Minkov, MD<sup>5</sup>; Valerie Taly, MD, PhD<sup>34</sup>; Matthew Collin, MD, PhD<sup>9</sup>; Jean-Claude Alvarez, MD, PhD<sup>9</sup>; Jean-François Emile, MD, PhD<sup>11</sup>; and Sébastien Héritier, MD, PhD<sup>11,11</sup>


**PURPOSE** Off-label use of vemurafenib (VMF) to treat *BRAF*<sup>V600E</sup> mutation–positive, refractory, childhood Langerhans cell histiocytosis (LCH) was evaluated.

**PATIENTS AND METHODS** Fifty-four patients from 12 countries took VMF 20 mg/kg/d. They were classified according to risk organ involvement: liver, spleen, and/or blood cytopenia. The main evaluation criteria were adverse events (Common Terminology Criteria for Adverse Events [version 4.3]) and therapeutic responses according to Disease Activity Score.

**RESULTS** LCH extent was distributed as follows: 44 with positive and 10 with negative risk organ involvement. Median age at diagnosis was 0.9 years (range, 0.1 to 6.5 years). Median age at VMF initiation was 1.8 years (range, 0.18 to 14 years), with a median follow-up of 22 months (range, 4.3 to 57 months), whereas median treatment duration was 13.9 months (for 855 patient-months). At 8 weeks, 38 complete responses and 16 partial responses had been achieved, with the median Disease Activity Score decreasing from 7 at diagnosis to 0 ( $P < .001$ ). Skin rash, the most frequent adverse event, affected 74% of patients. No secondary skin cancer was observed. Therapeutic plasma VMF concentrations (range, 10 to 20 mg/L) seemed to be safe and effective. VMF discontinuation for 30 patients led to 24 LCH reactivations. The blood *BRAF*<sup>V600E</sup> allele load, assessed as circulating cell-free DNA, decreased after starting VMF but remained positive (median, 3.6% at diagnosis, and 1.6% during VMF treatment;  $P < .001$ ) and was associated with a higher risk of reactivation at VMF discontinuation. None of the various empirical therapies (hematopoietic stem-cell transplantation, cladribine and cytarabine, anti-MEK agent, vinblastine, etc) used for maintenance could eradicate the *BRAF*<sup>V600E</sup> clone.

**CONCLUSION** VMF seemed safe and effective in children with refractory *BRAF*<sup>V600E</sup>-positive LCH. Additional studies are needed to find effective maintenance therapy approaches.

J Clin Oncol 37. © 2019 by American Society of Clinical Oncology

Creative Commons Attribution Non-Commercial No Derivatives 4.0 License 

Thérapie ciblée : autres indications  
Neuro Deg:  
Foie / cholangite sclérosante  
JXG  
Rosai

# Vemurafenib

## Pour les patients réfractaires

## Efficace +++ rapidité

## Dosage sanguin 10 - 30 mg/l

## Tolérance OK sauf photo sensibilité et adolescent

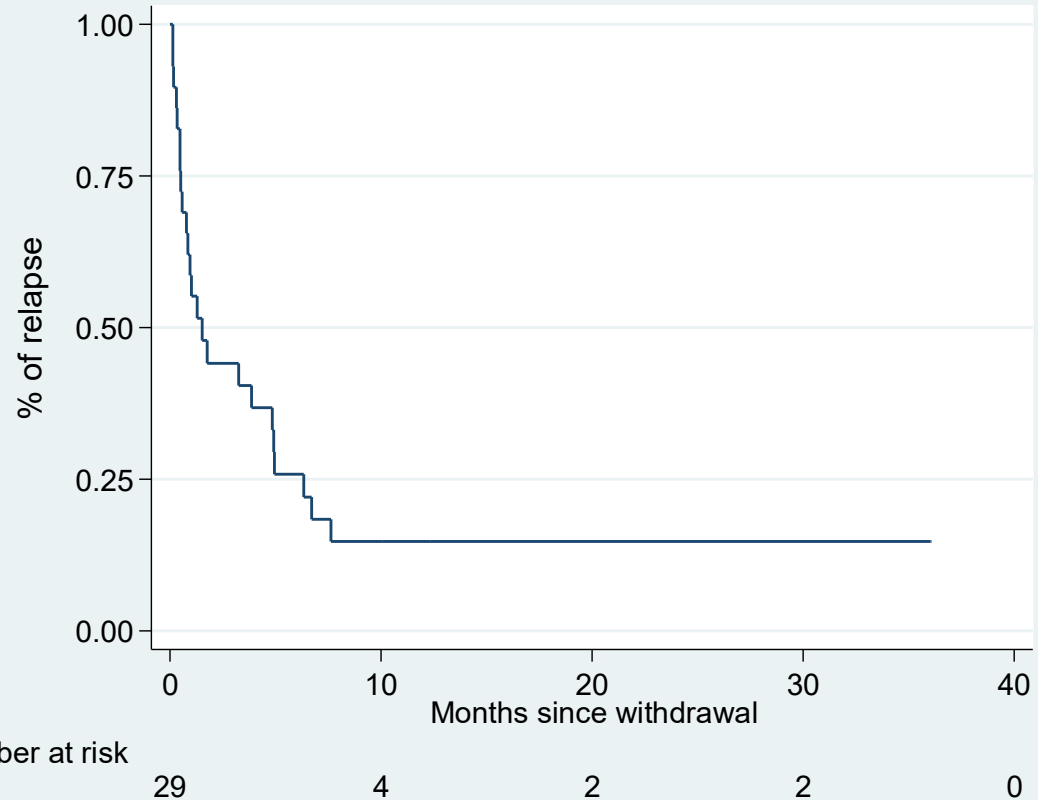
## N'éradique pas la maladie

# Les limites

- **Reactivation à l'arrêt**
- **Pas d'éradication du Clone histi**
- **Suivi assez court 22 mois**

# Reactivation at therapy withdrawn

**Therapy was  
withdrawn in 29  
patients after 4.9  
months of  
duration**



# Braf Load and targeted therapy

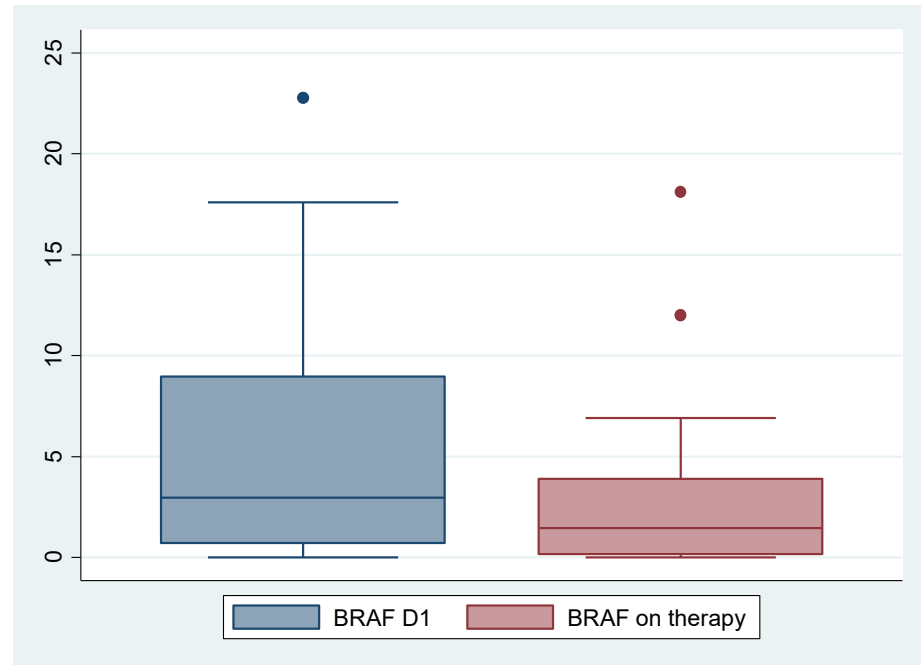
**bjh** research paper

Circulating cell-free *BRAF*<sup>V600E</sup> as a biomarker in children with Langerhans cell histiocytosis

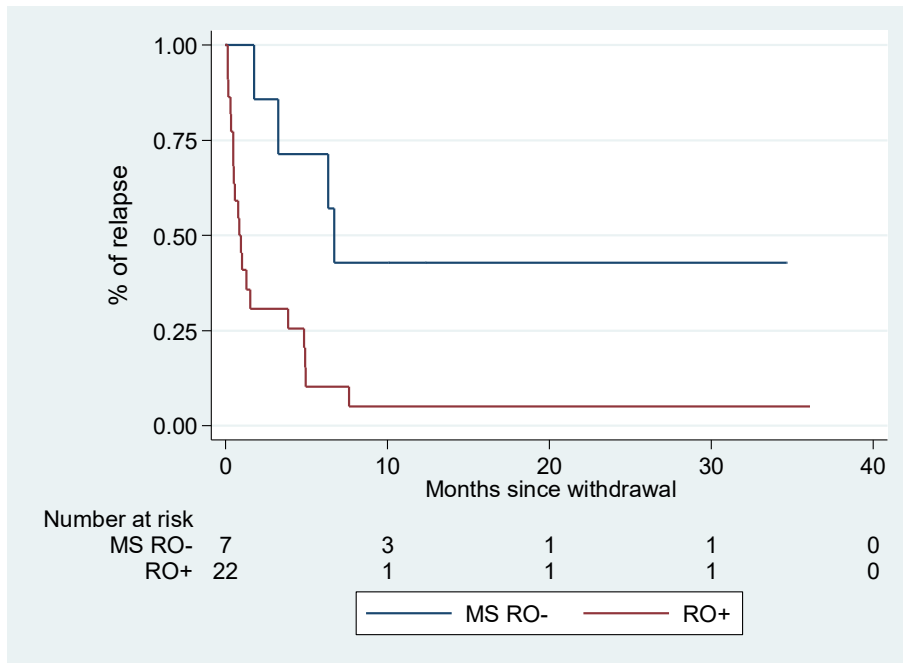
**33 pts evaluated**

**Decreased but No eradication**

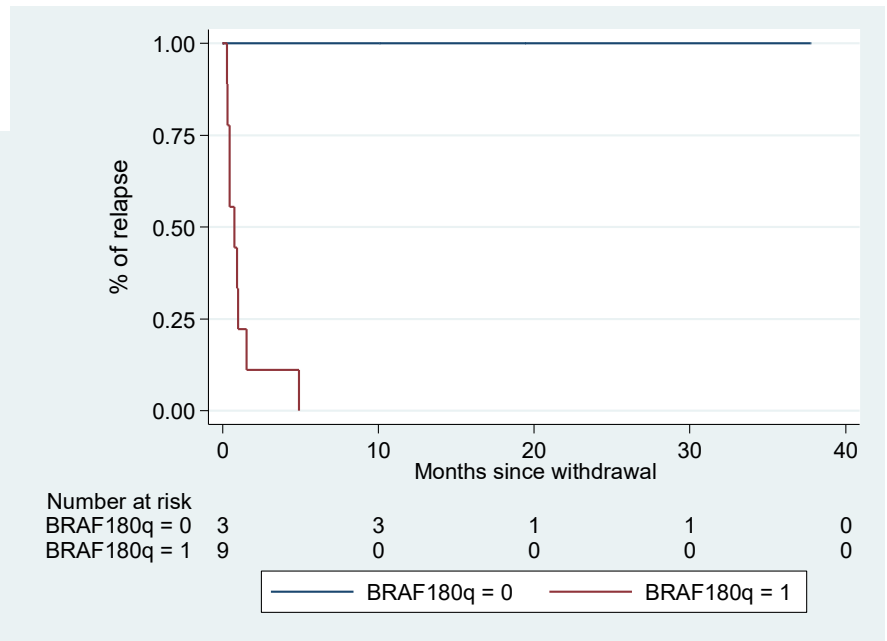
**3.1 % vs 0.7 %**

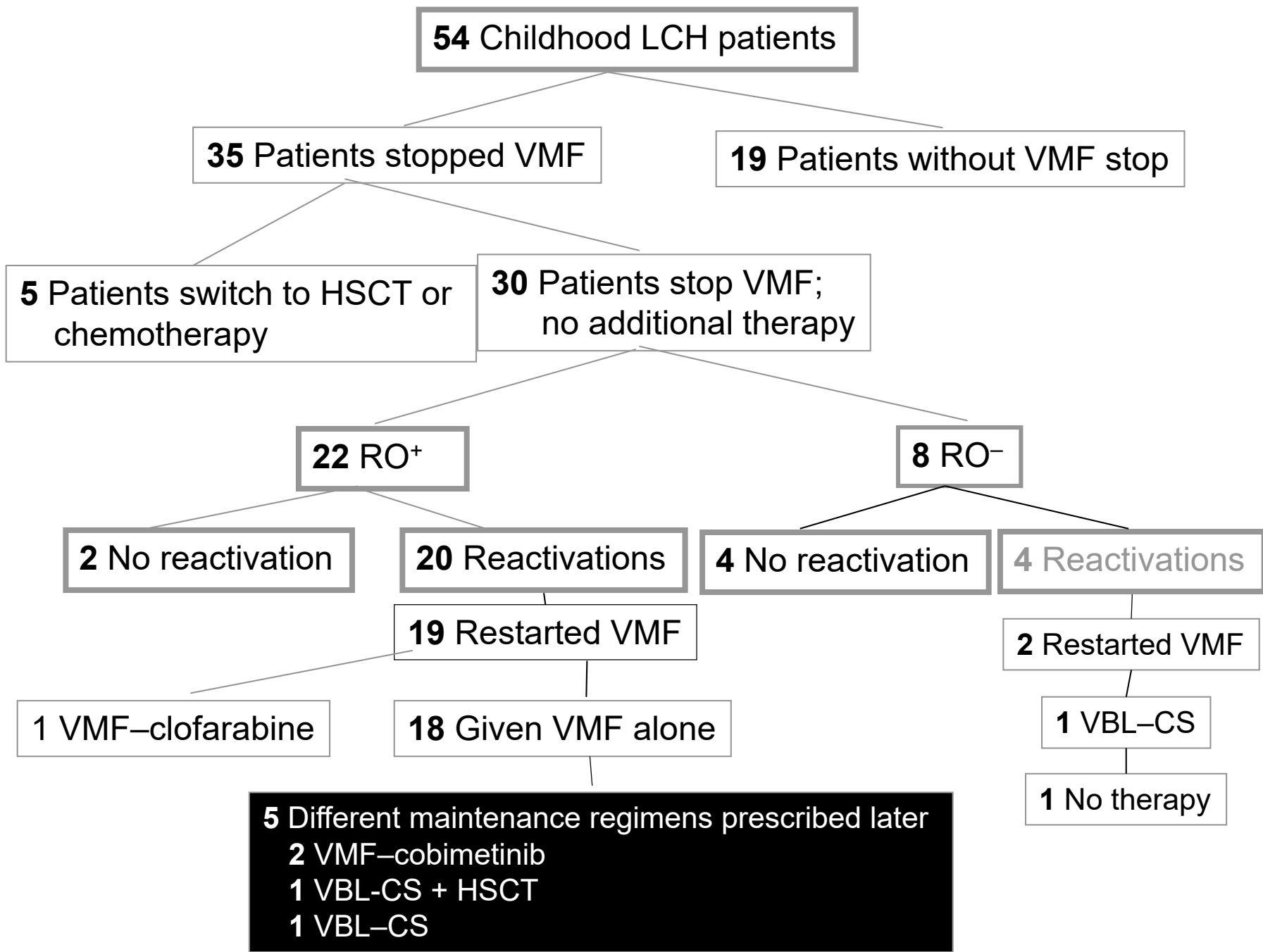


# RO + vs RO-

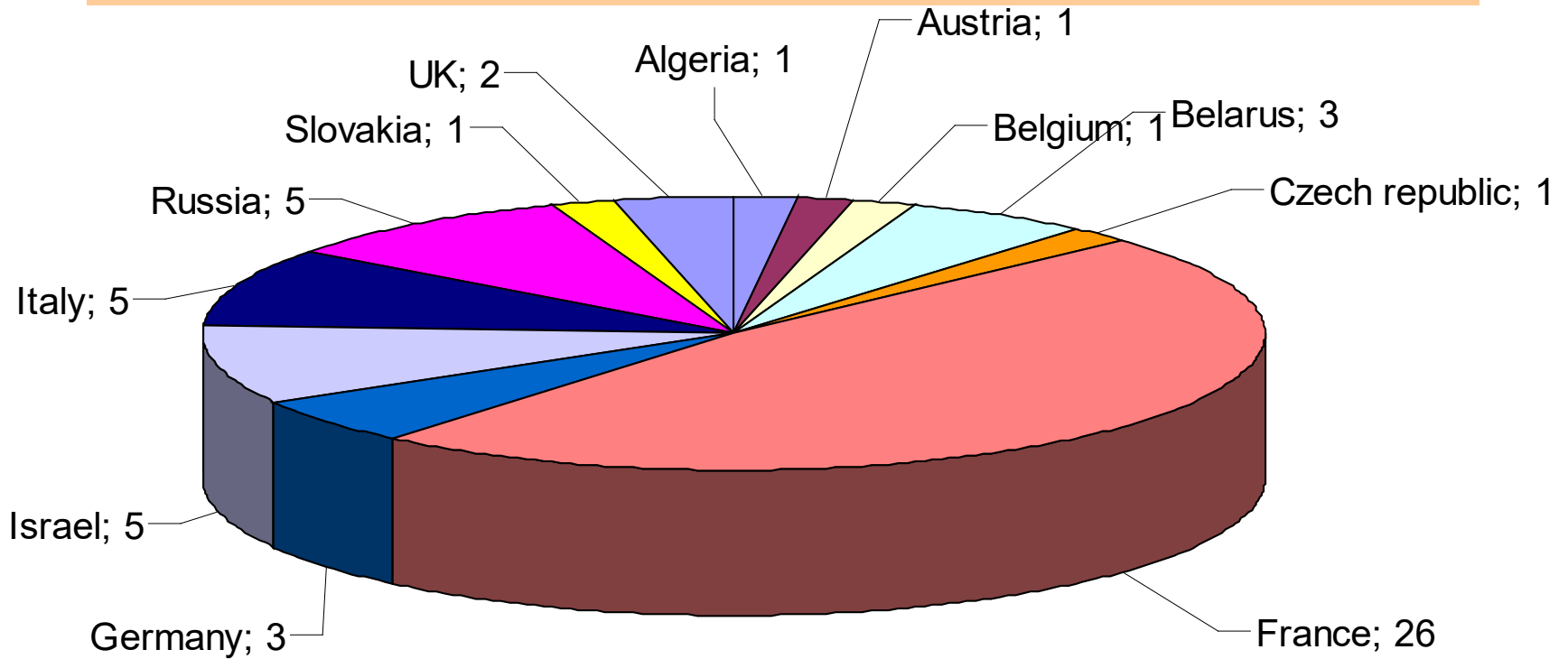


# Braf Load + vs -





# Geographic origin



Median follow up since D1 : 22 months



# Constat

- Toujours Hors AMM : pas de soutien d'industriel
- Une pratique qui s'est répandue
- Un réseau fonctionnel

# Projet

- Collecter tous les cas EU
- Analyser au long la pratique
- Etendre le recrutement des suivis biologiques

# Etats sept 2021

- Accord de toutes les équipes
  - Donc en plus: NL / SW / Spain
- 130 patients inclus et environ 50 patients attendus
- Des Suivis  $> 5$  ans



# Type of reactivation and outcome

- In RO+ all reactivations were ‘systemic’
  - Management: *Vemurafenib resumed and always efficient again*
    - Maintenance with chemo or HSCT: no proven efficacy in a
      - 3 HSCT
      - 3 2 Cda Arac
      - 3 VLB steroid
      - 2 anti MEK + Vemu
- In RO- all reactivations were RO-
  - 2 treated with Vemu and 3 no

# Quelques résultats

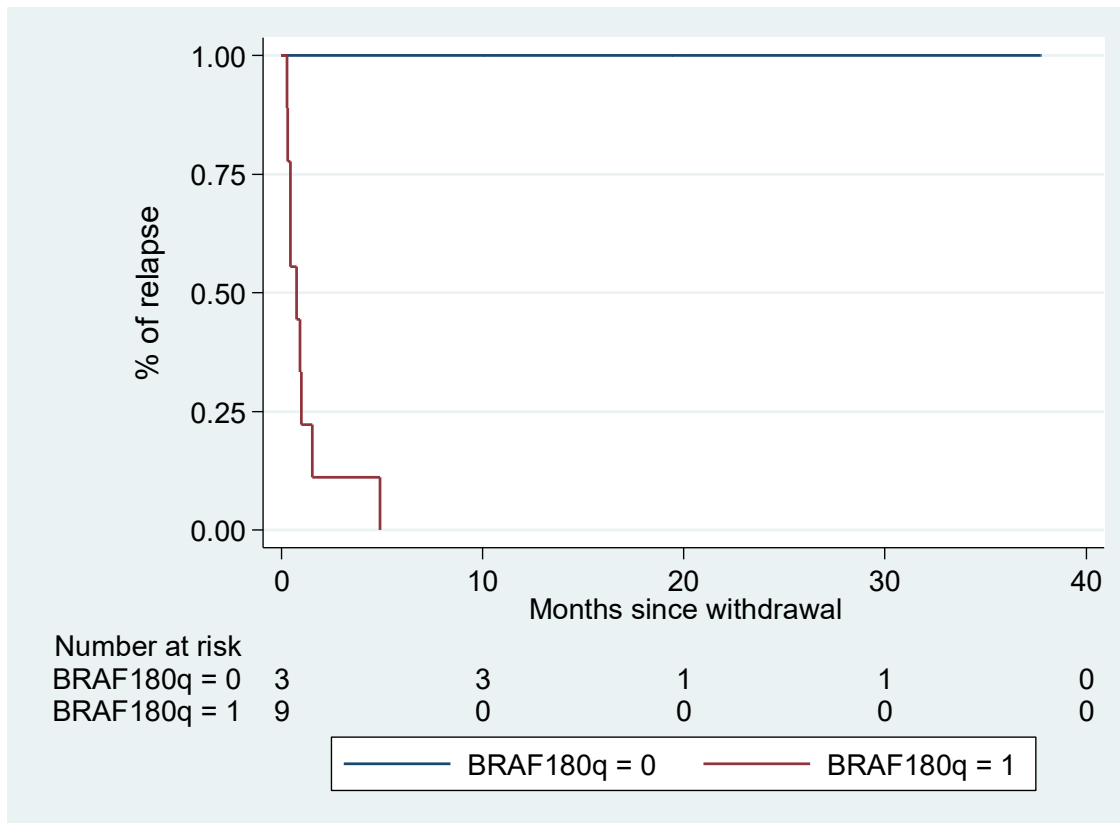
- 2 Décès chez des RO + traités : les 2 liés à des arrêts trop précoces ou dosage insuffisants
- Safety: Chez les enfants < 5 ans : 0 EIG graves
- Efficacité de faible dose au long cours de vemu ( 5 mg/kg/jour)
- 6 patients : atteintes ND sous Vemu

# Type of reactivation and outcome

- In RO+ all reactivations were ‘systemic’
  - Management: *Vemurafenib resumed and always efficient again*
- In RO- all reactivations were RO-
  - 2 treated with Vemu and 3 no

# Braf Load and targeted therapy

**Persistent Braf Load is associated with reactivation**





**~ 50% des HL présentent une mutation  
somatique *BRAF*<sup>V600E</sup>**

**~ 95 % de HL réfractaires “Risk organs” sont B Raf  
mutés**

**Vemurafenib est disponible  
HORS AMM  
1 cp = 240 mg**



# Les questions résiduelles

- Toxicité au long cours
- Biomonitoring / Charge Braf
- Schéma au long cours

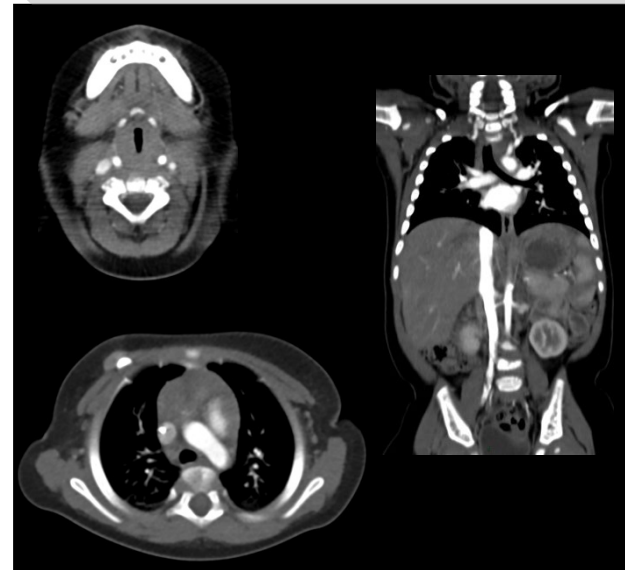
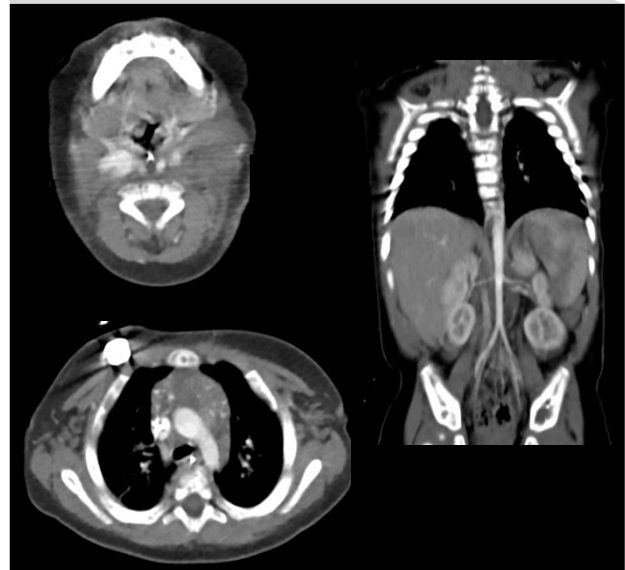
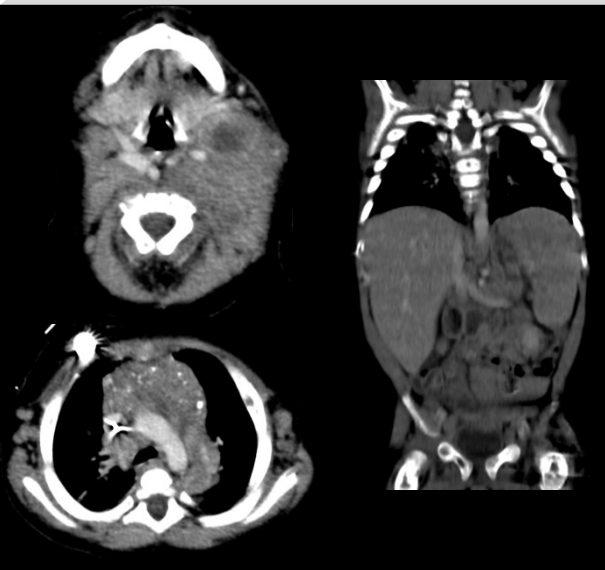
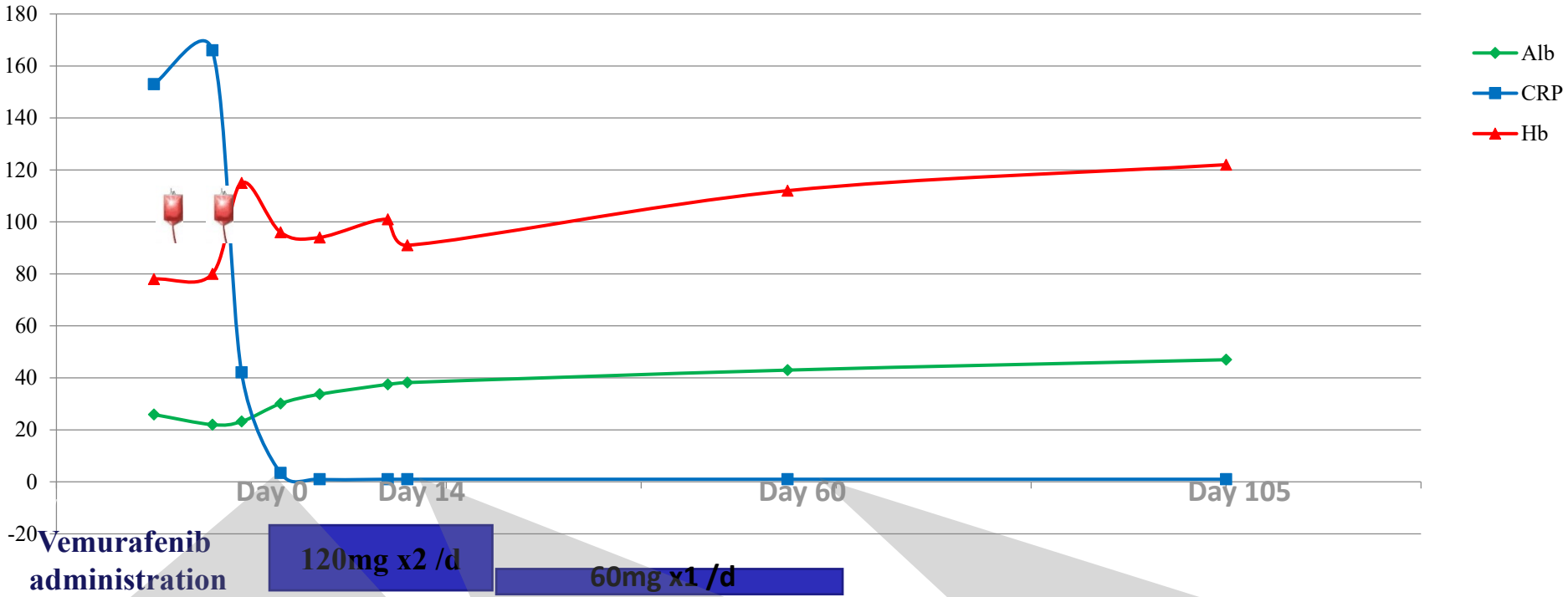
# Traitement ciblé dans l'HL de l'enfant : première publication avec du Vemurafenib

## 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<sup>+</sup> 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.<sup>1</sup> Because somatic *BRAF* V600E mutation plays an important role in LCH pathophysiology,<sup>2</sup> BRAF inhibitors could offer a new therapeutic approach<sup>3</sup> but, to our knowledge, have never been proposed as a treatment in infants.



# Hors AMM mais organisé

- 2 groupes cibles
  - HL réfractaire
  - HL Neuro degenerative
- PK recommandé mais pas obligatoire
- Une drogue à évaluer ( une seule à la fois...)
- Objectifs principaux :
  - Efficacité
  - Sécurité
- Aspects réglementaires
  - HORS AMM mais on a écrit des guidelines et – outre l'inclusion dans un registre – lettre d'information aux parents
  - Le recueil des données doit être acceptées / signature

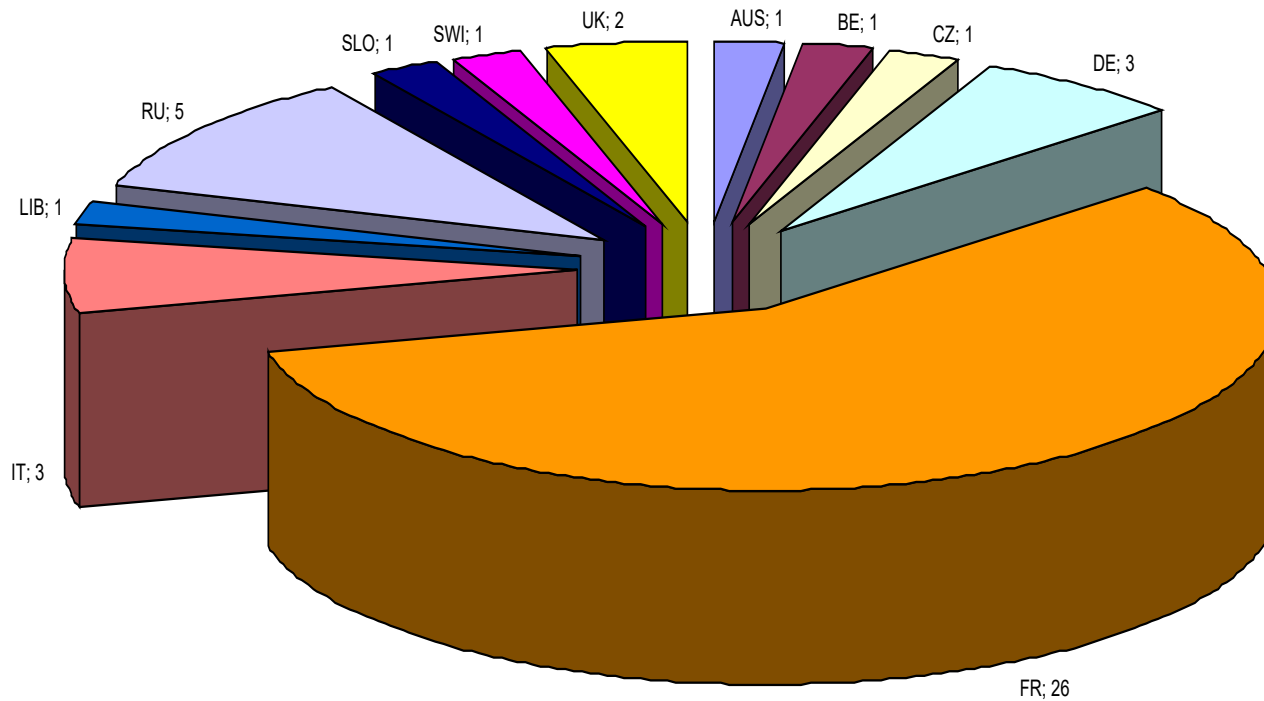
# Guidelines

- Patients B Raf V600E
- Dose 20 mg/kg - pour au moins 2 mois puis selon avis cliniciens
- Pas d'autres médicaments associés mais on recueille les données dans tous les cas

# Data collections

- Tous les médecins qui ont traités des patients en EU ont été contactés
- En France: patients incluent dans le registre
- CRF standard – type 2 cda Arac
- Critère d'évaluation
  - Effets secondaire : CTC AE v4
  - Efficacité:
    - ARD: Disease activity score
    - RECIST criteria
    - Neuro deg : critères SARA

# Origine géographique



**Suivi médian depuis J1: 14 mois**



# La population : 44 patients

## Neuro Degenerative n=6

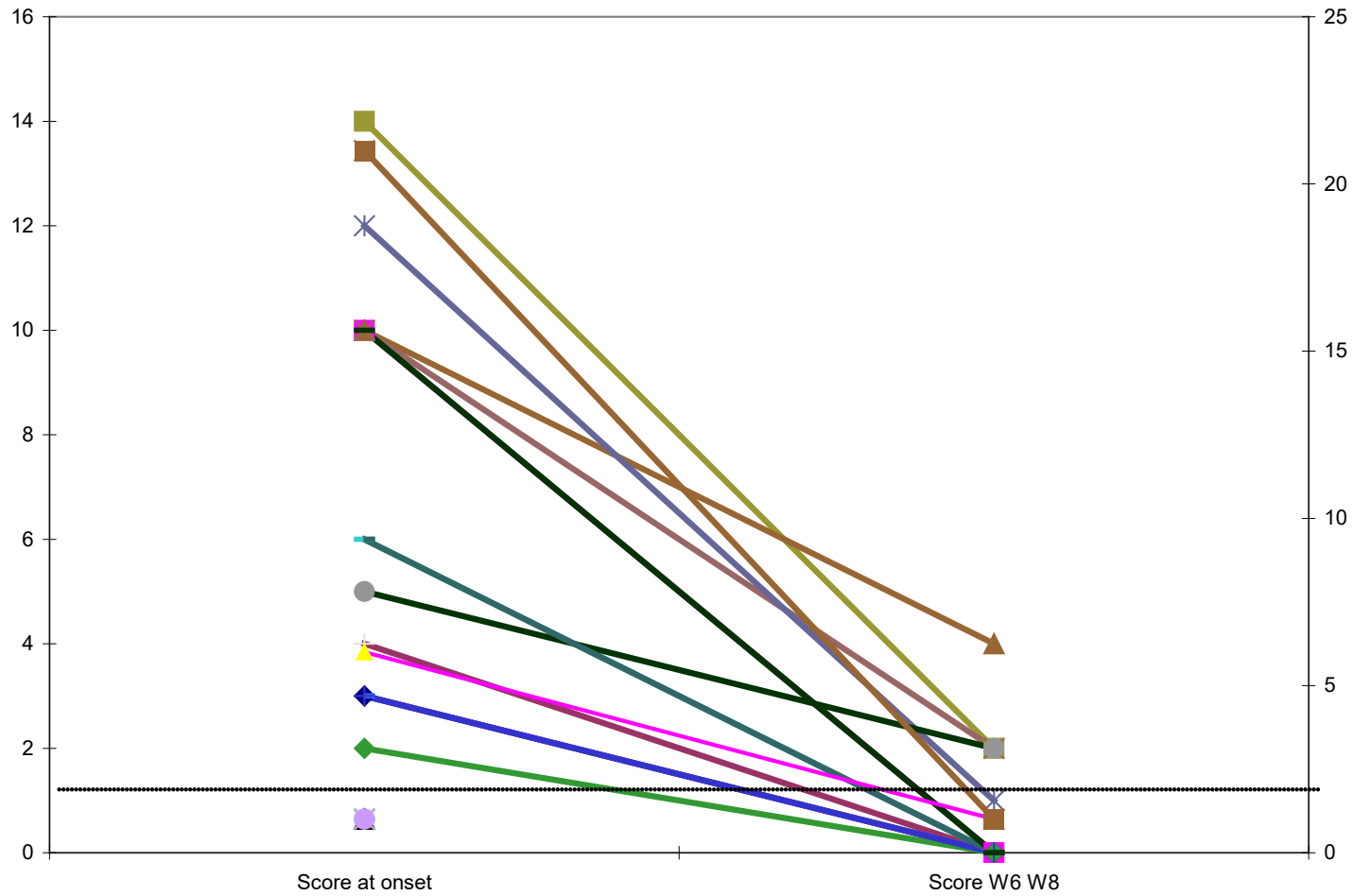
- **Age at diagnosis**  
1.7 y [0.6-2.7y]
- **Time Diagnostic to start: 11.3 years**
- **MS LCH : 5**
- **Therapy before VEMU:**
  - All VLB steroid
  - Ig Iv 1
  - 13 cis ret. Acid 5
- **4 wheel chairs**
- **Median SARA : 26 (1 with mild ND SARA 2)**

## ARD group n=38

- **Age at diagnosis**  
0.9 y [0.1 – 3.5 y]
- **Time Diagnostic to start: 0.8 years**
- **RO +30**
- **with sclerosing cholangitis 3**
- **RO- 8**
- **Therapy before VEMU:**
  - All VLB steroid
  - 2 Cda mono: 7
  - 2 Cda Arac 9
- **Medium Score D1: 6**

	<b>Neuro Degenerative</b>	<b>RO-</b>	<b>Sclerosing cholangitis</b>	<b>RO+ refractory</b>
	<b>Neuro n=6</b>	<b>ARD 'Active refractory disease' n=38</b>		
<b>N</b>	<b>6</b>	<b>8</b>	<b>3</b>	<b>27</b>
<b>Target organ</b>	<b>CNS Marche Fonction Cognitive</b>	<b>OS après 2 lignes de trt</b>	<b>Foie</b>	<b>Hematologie Ganglion Foie Rate Os</b>
<b>Age diagn.</b>	<b>1.7 ans (0.5-2.8 ans)</b>	<b>0.8 (0.2-3.4 ans)</b>		
<b>Age D1</b>	<b>13 ans (6.6 ans → 20 ans)</b>	<b>1.8 ans (0 → 14 ans)</b>		
<b>Evaluable mois 3</b>	<b>6</b>	<b>34</b>		
<b>Duration of therapy</b>	<b>Durée médiane 4.1 mois. Durée cumulative de trt par vemurafenib therapy 246 mois / patient.</b>			
<b>Réponse</b>	<b>1 Réponse / le patient vu très tot</b>	<b>Complète réponse 7/8 1 réponse partielle</b>	<b>Pas de réponse sur sur la CS mais réponse sur signes associées</b>	<b>100% response NAD ADB</b>

# DAS J1 vs semaine 6



**Day -1**



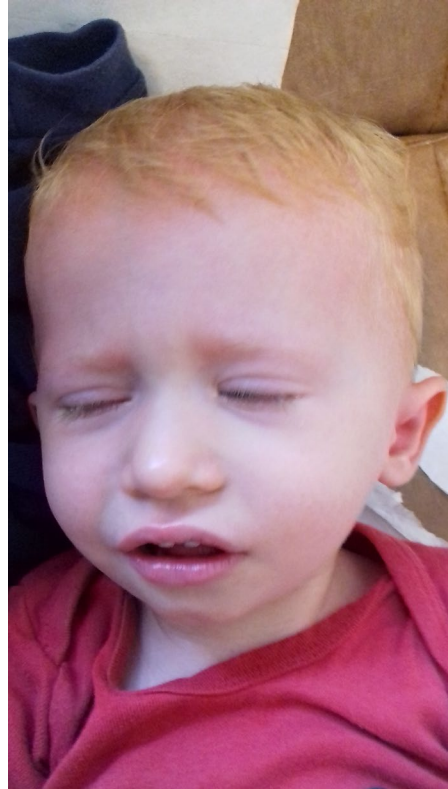
**D14 after Vemu**



**30 aout**

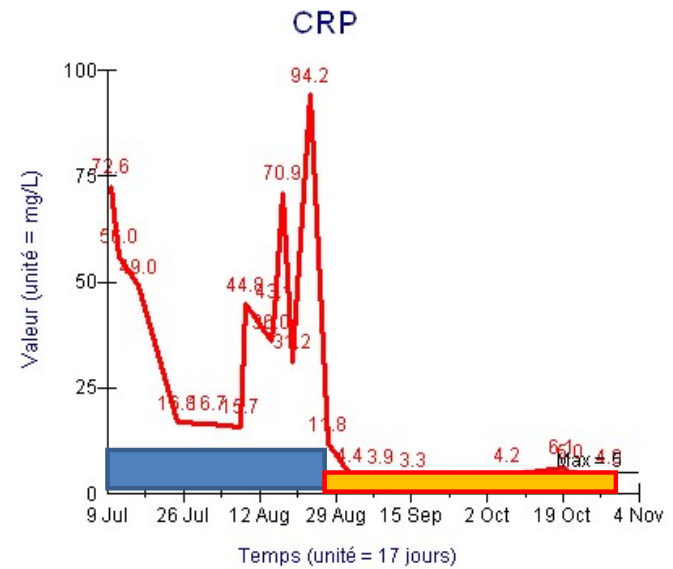
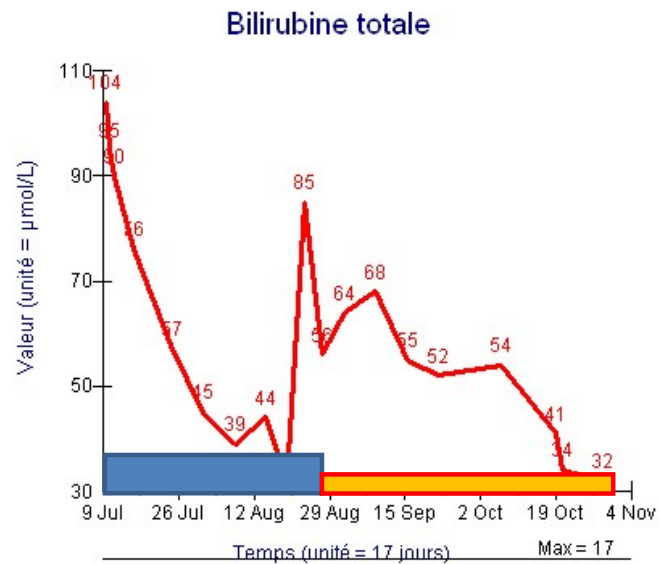
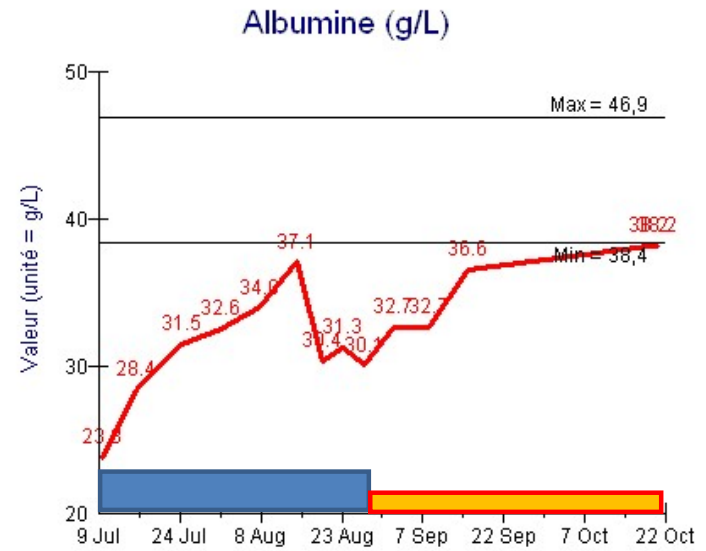
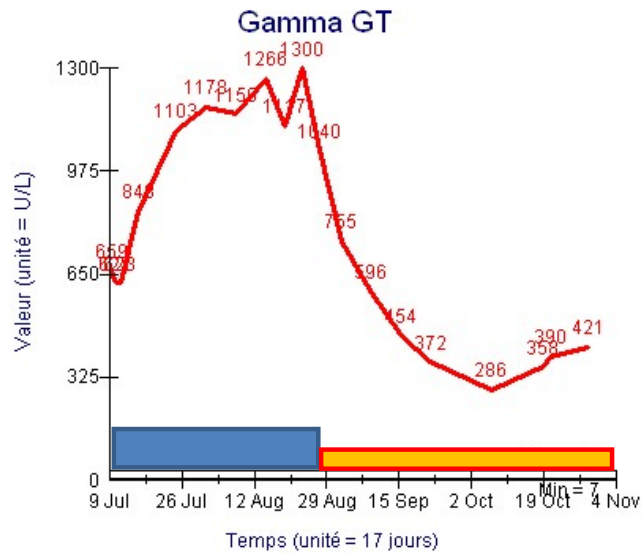


**8/9/17 J7 Vemu**



**29/9/17**





# Nécrose ganglionnaire J19



# Toxicité



	<b>Neuro Degenerative</b>	<b>RO-</b>	<b>Sclerosing cholangitis</b>	<b>RO+ refractory</b>
<b>N</b>	<b>6</b>	<b>8</b>	<b>3</b>	<b>27</b>
<b>Severe toxicity or therapeutic withdrawn</b>	2 : malaise n=1 Rash cutanée n=1 Panniculitis =2	Skin rash 12 Panniculitis 2 1 décès (not related)		
<b>Survie</b>	<b>1 décès</b>	<b>97%</b> <b>1 Décès</b>		

**Pas de tumeur cutanée secondaire**

# Décès NDD

- **Garçon**
- **Diagnostic 8 mois: Peau Os 2 reactivations**
- **Environ 48 months VLB steroid 6 MP**
- **DI at 9 ans**
- **ND : 1 er symptome à 10 ans**
- **Trt par ATRA (> 3 ans) sans effet**
- **A J1 de vemu: 20 ans SARA score 38, chaise roulante progressif**
- **Dans les premiers 10 jours, dose of 20 mg/kg:**
  - **Fièvre**
  - **Asthénie**
  - **Bilan negatif**
  - **Récupération en 3 jours**
  - **Dose de vemu 10 mg/l**
  - **2 eme tentative Mois 3 : 10 mg/kg : idem**
- **Par la suite atteinte neurologique progressive. DC 2 ans plus tard Autopsie atteinte neuro dégénérative extensive.**

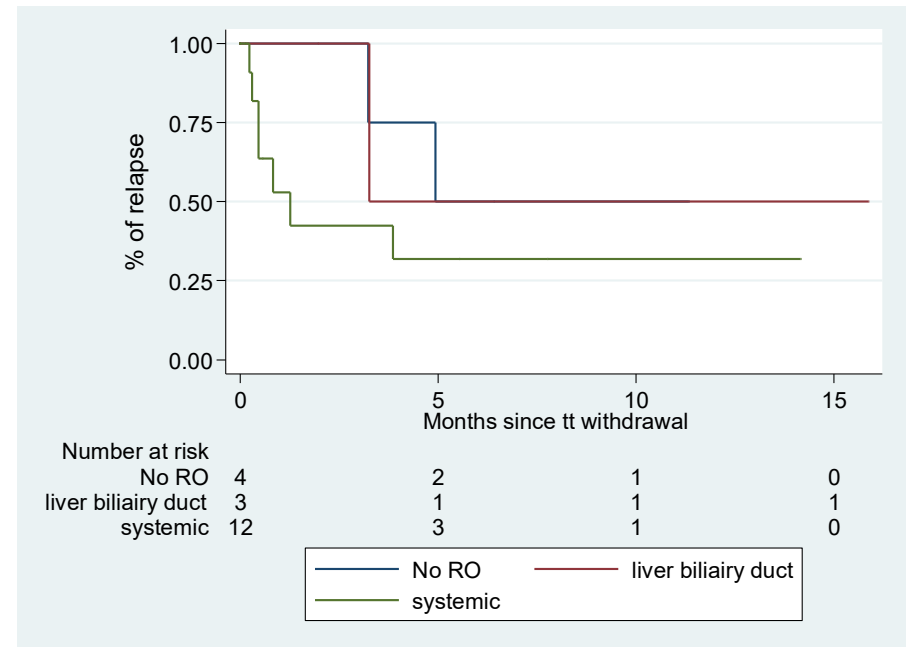
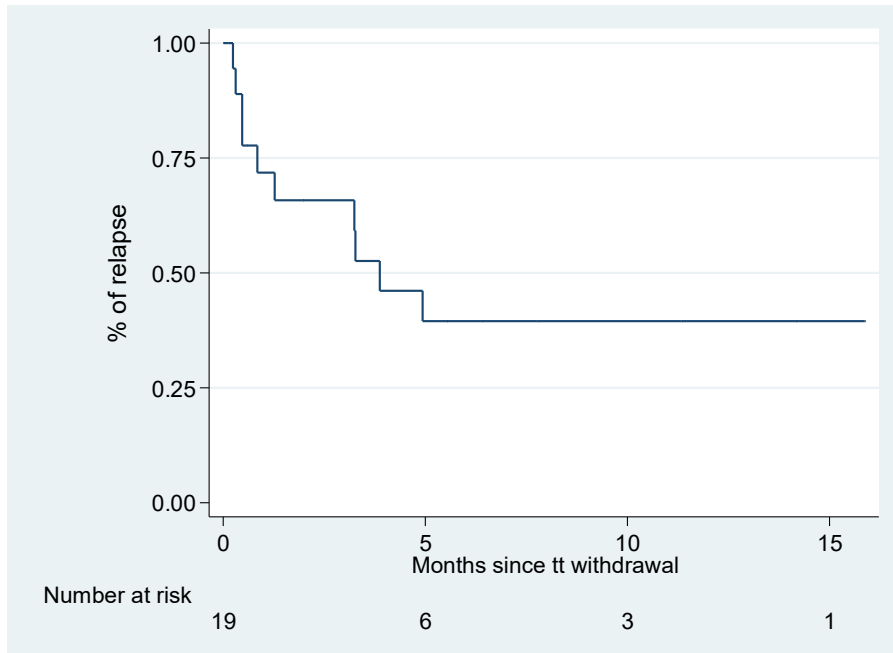
# Décès ARD

- Diagnostic à 6 mois: Peau, foie, Rate, Poumon, Hématologie.
- DAS au diagnostic 18.
- VBL et steroid 2 inductions: Puis 2 cures de 2 Cda Arac puis 3 cures de 2 Cda,
- A 18 mois : maladie active.
- Vemurafenib J1 DAS 22 (peau, foie rate, poumon hemato).
- vemurafenib (34 mg/kg/day)
- A 2 mois DAS 5.
- Dose augmentée à 51 mg/kg puis 68mg/kg.
  - Après 2 mois: nausée, vomissement: traitement stop Aggravation DAS 14.
- Décision alors de traiter par Vemurafenid et Clofarabine (20 mg/m<sup>2</sup>/day x 5 days)
- Décès à J19 :septicémie.
- Pas de PK.

# Outcome & relapse

**No reactivation in NDD patients**

**Among 29 ARD patients 19 patients had stopped therapy**



# Type de reactivations et devenir

- 19 patients ARD, 10 reactivations were observed.
- 3 were considered as mild (skin rash or Diabetes insipidus) : not treated
- 2 were in RO -organ 1 VLB 1 vemu
- 6 was observed in RO+. 6 Treated by vemu

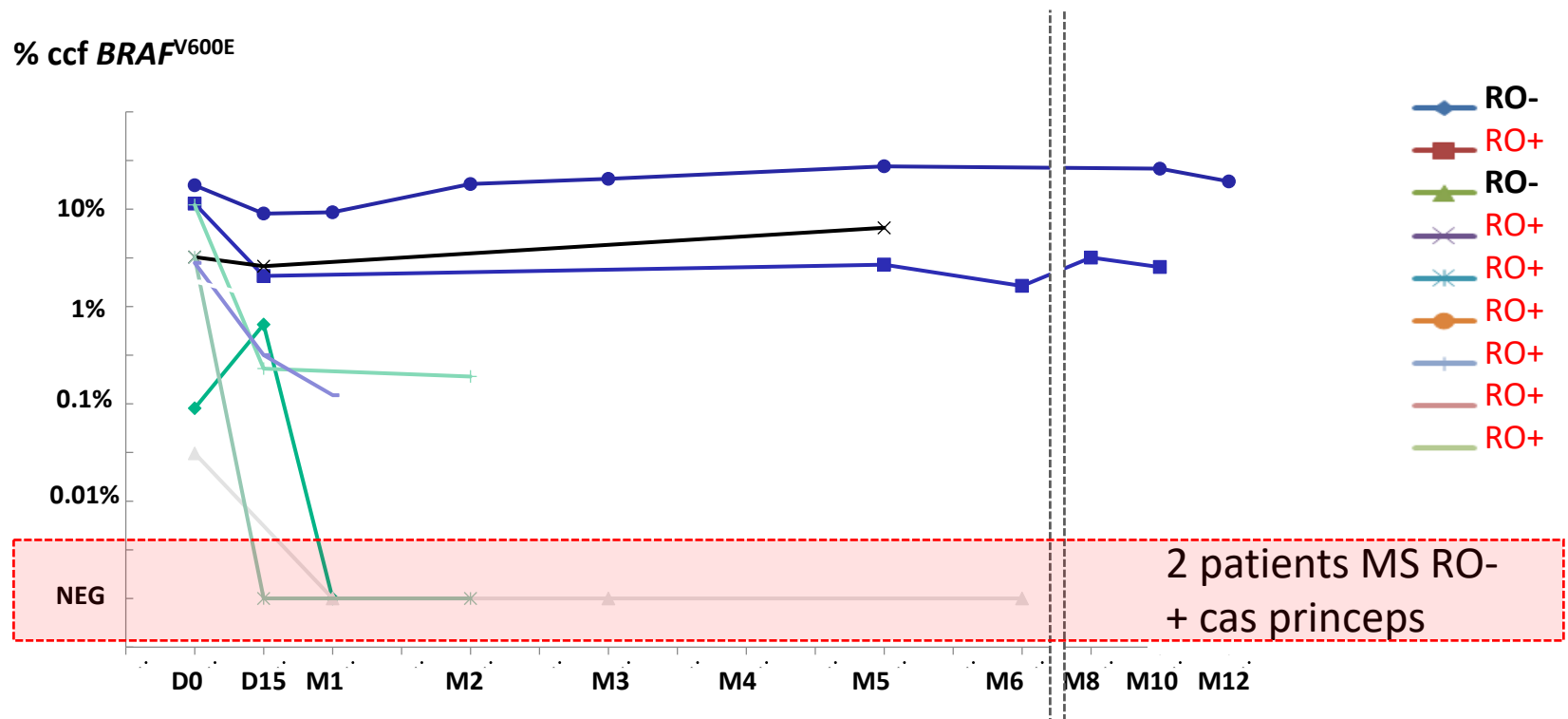
# Cf DNA response



## Step 2 : to study a prospective cohort focused on:

- RO+ LCH at diagnosis
- RO- resistant to 1st line chemotherapy

### Results: Patients under BRAF inhibitors

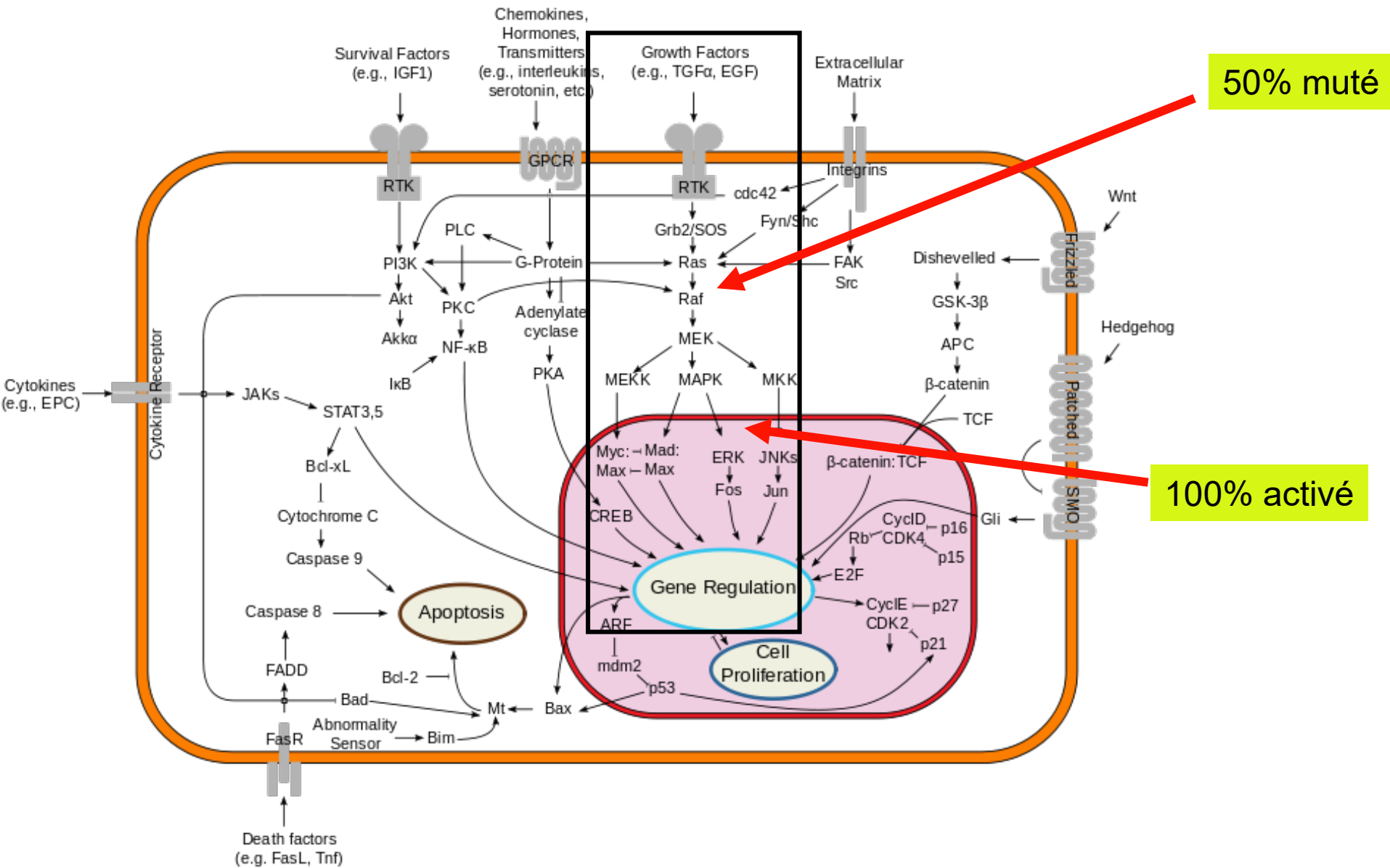




# Vemurafenib

- Monotherapie VEMURAFENIB actif dans les formes réfractaires BRAF V600E
  - Proche de 100% de response
  - Response dans un très court délai
- Tolérance : acceptable (>>> que HSCT ou 2 Cda Arac ou clofarabine ou haute dose steroïde)
  - Pas de kerato acanthoma
  - Patient en externe
- Neuro degenerative : Non si forme symptomatique
- La periode initial (3 months) Trop court
- Cf DNA très utile pour suivre les patients

# Voie des mapkinases dans l'histio

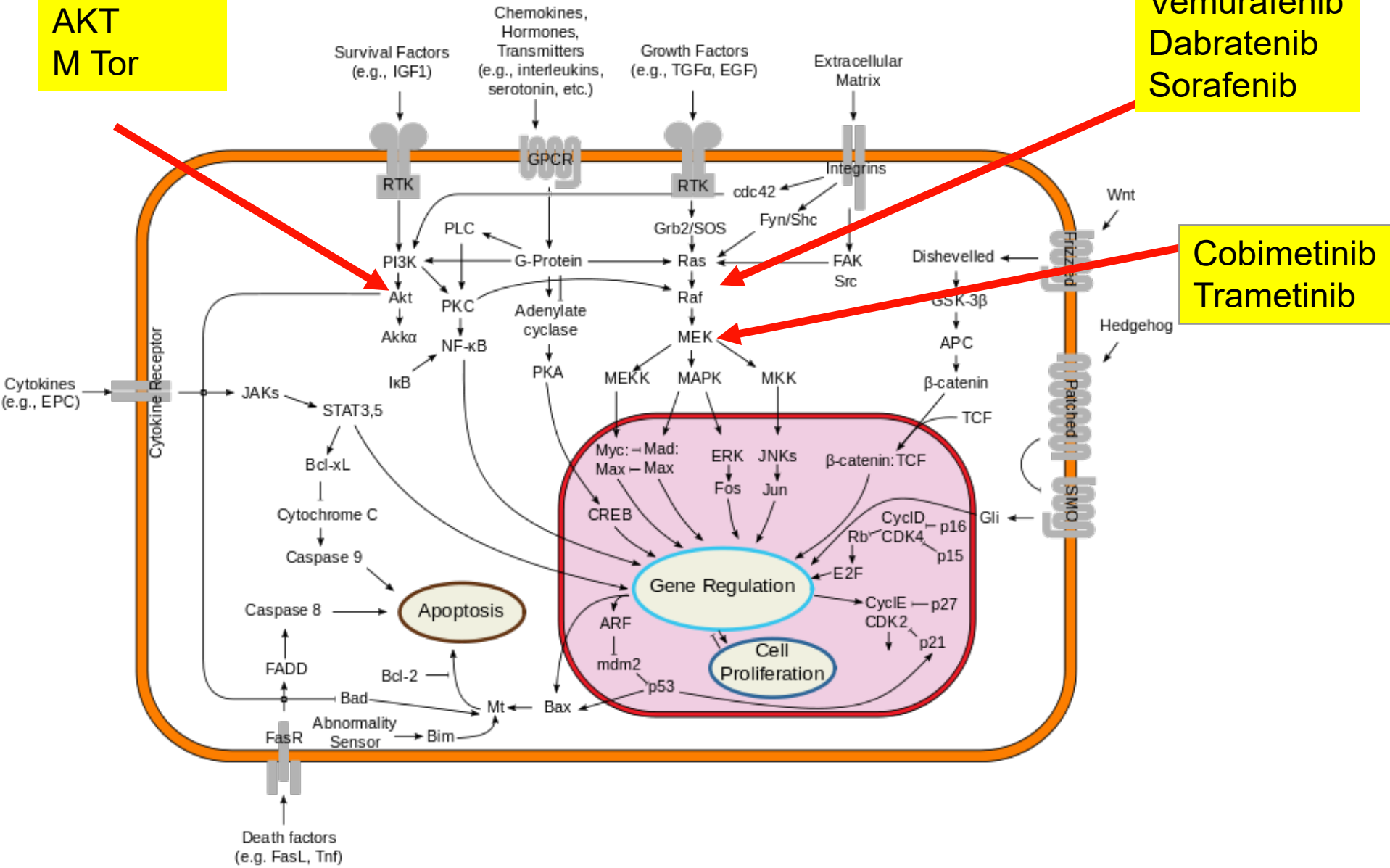


# Thérapies ciblées dans les histiocytoses

Inhibiteurs  
AKT  
M Tor

Vemurafenib  
Dabrafenib  
Sorafenib

Cobimetinib  
Trametinib



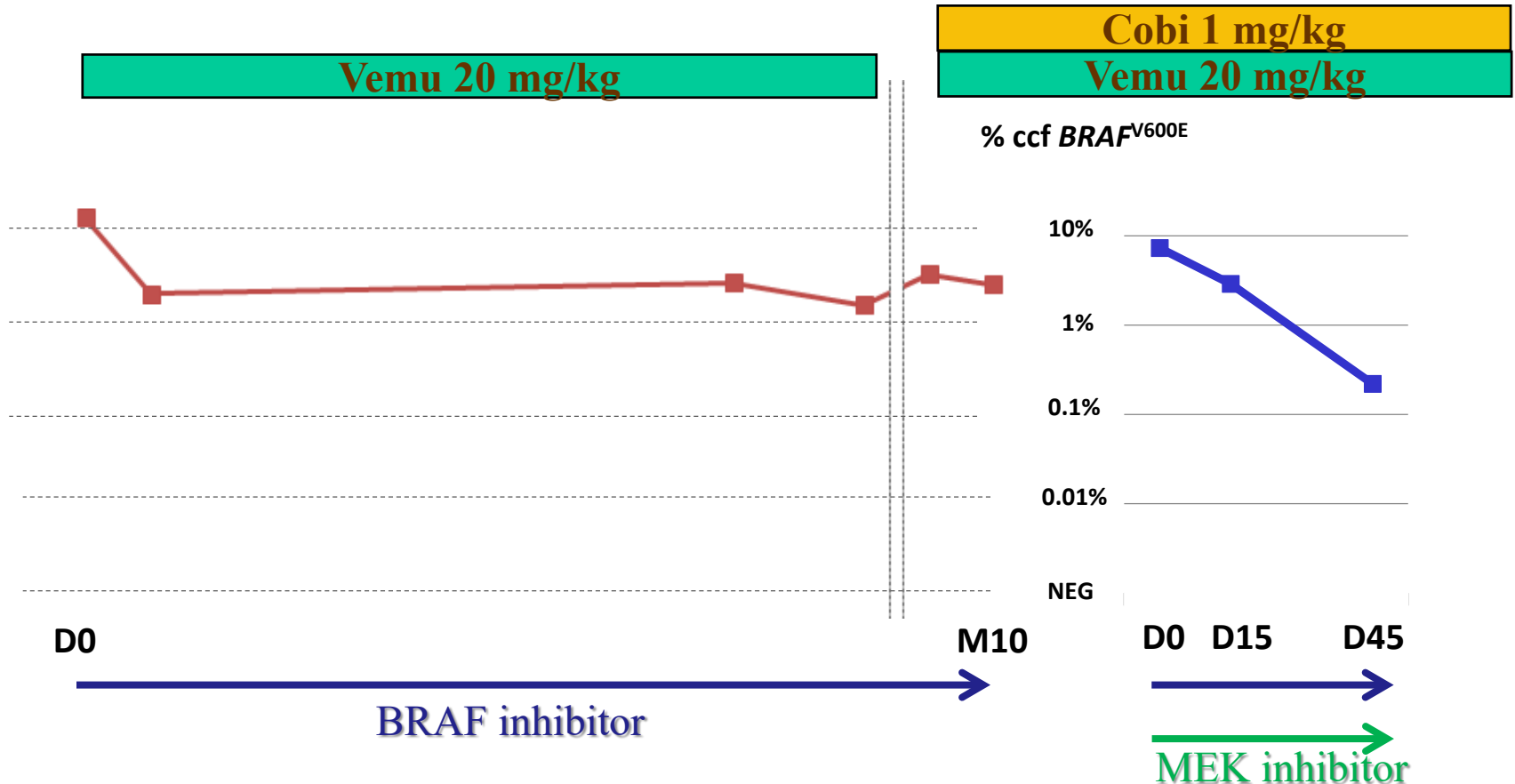
# Gabriel

- Diagnostic à 8 mois
- Tt par VLB steroide pendant 10 mois
- Réactivation sous ttrt
  - Inflammation Anemie Os Peau foie rate
- Décision d'un tt par Vemurafenib
  - Efficacité rapide / EIG 0
  - 6 mois de tt
  - Rechute à J15 de trt
  - Reprise du Vemurafenib 10 mois
  - Après 9 mois, cf DNA ~ 10%
  - Ajout du cobimetinib 1 mg /kg/jour depuis 3 mois
  - Tolérance parfaite

**Step 2 :** to study a prospective cohort focused on:

- RO+ LCH at diagnosis
- RO- resistant to 1st line chemotherapy

**Results: Patient under BRAF inhibitors + MEK inhibitor**



# Conclusion

- Changement de la prise en charge des formes réfractaires
- Tolérance acceptable
- Non curatif
- Cf DNA très utile
  
- Association avec anti MEK ? Autre approches ?