Thérapies ciblées dans les histiocytoses réfractaires: Une étude EU

European Consortium for HistiOcytosis

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Groupe d'Etude des Histiocytoses

Association Histiocytose France

original report

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

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abstract

PURPOSE Off-label use of vemurafenib (VMF) to treat *BRAF*^{V600E} 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*^{V600E} 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*^{V600E} clone.

CONCLUSION VMF seemed safe and effective in children with refractory *BRAF*^{V600E}-positive LCH. Additional studies are needed to find effective maintenance therapy approaches.

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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 sensiilité et adolescent

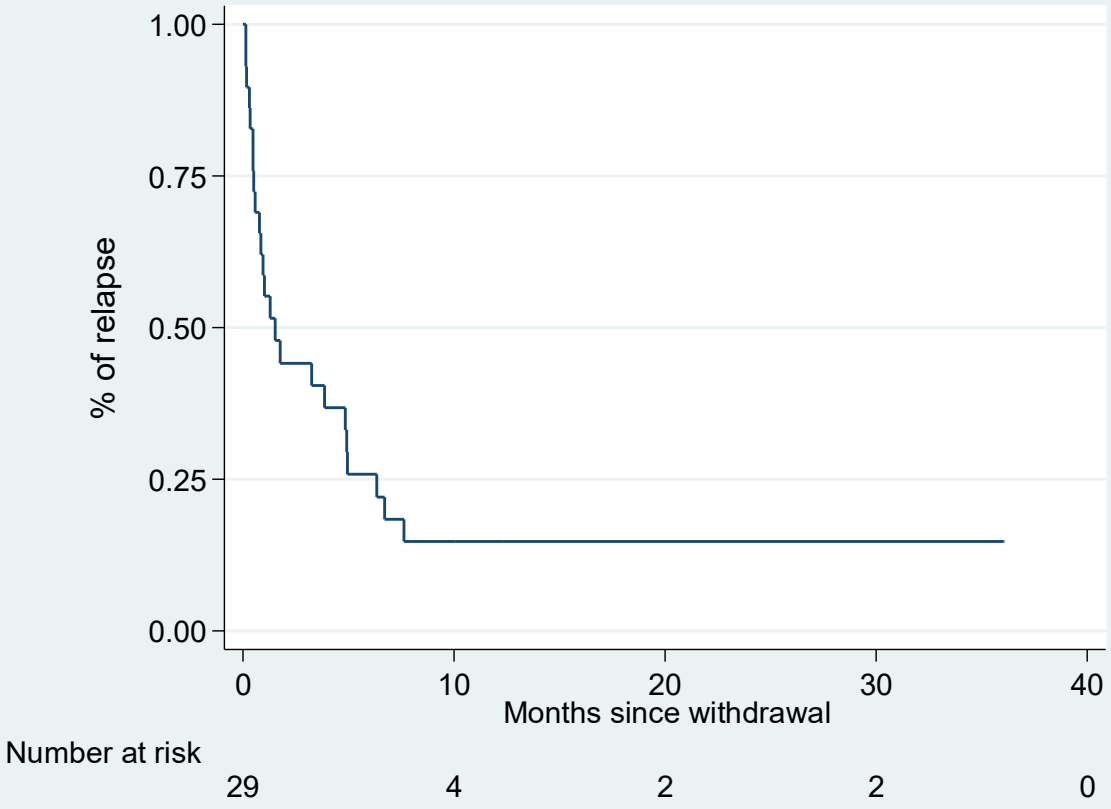
N'éradique pas la maladie

Les limites

- **Reactivation à l'arrêt**
- **Pas d'éradiction 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

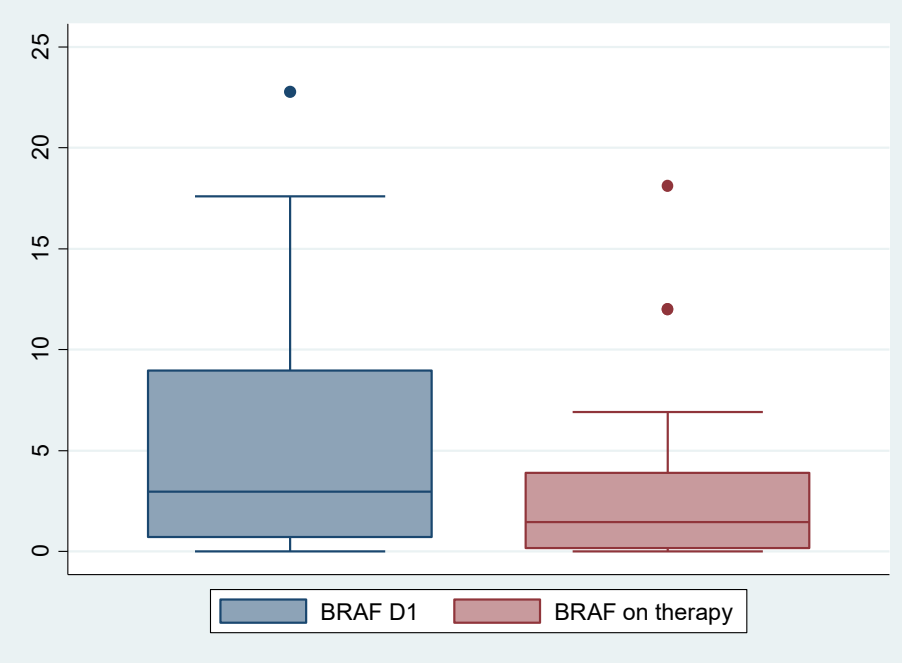
bjh research paper

Circulating cell-free *BRAF*^{V600E} as a biomarker in children with Langerhans cell histiocytosis

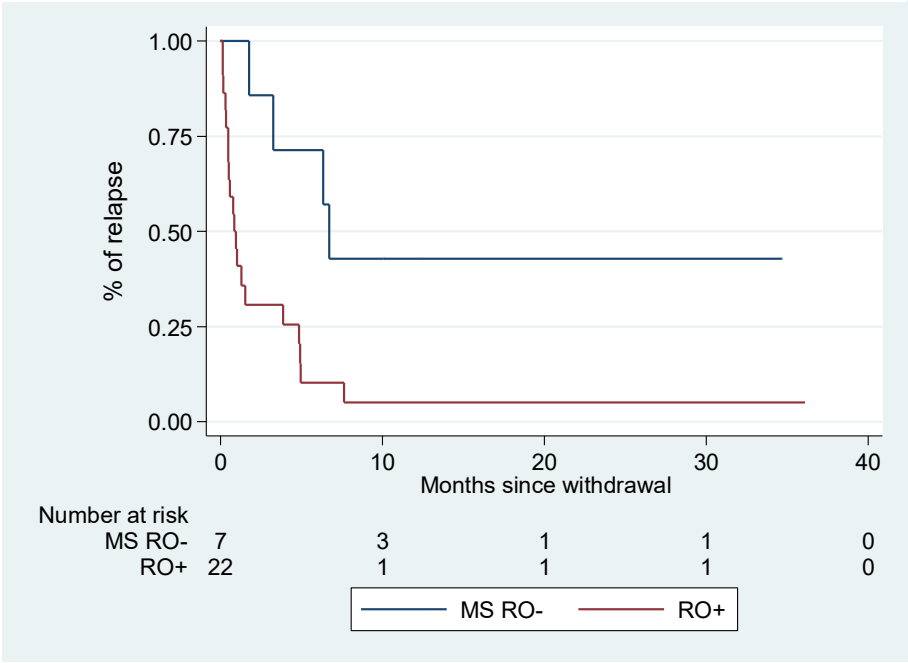
33 pts evaluated

Decreased but No eradication

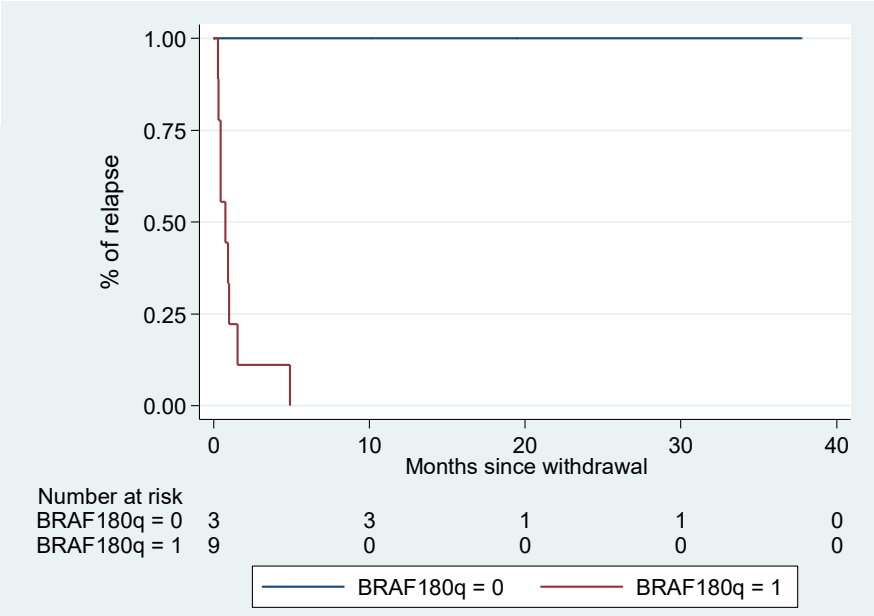
3.1 % vs 0.7 %

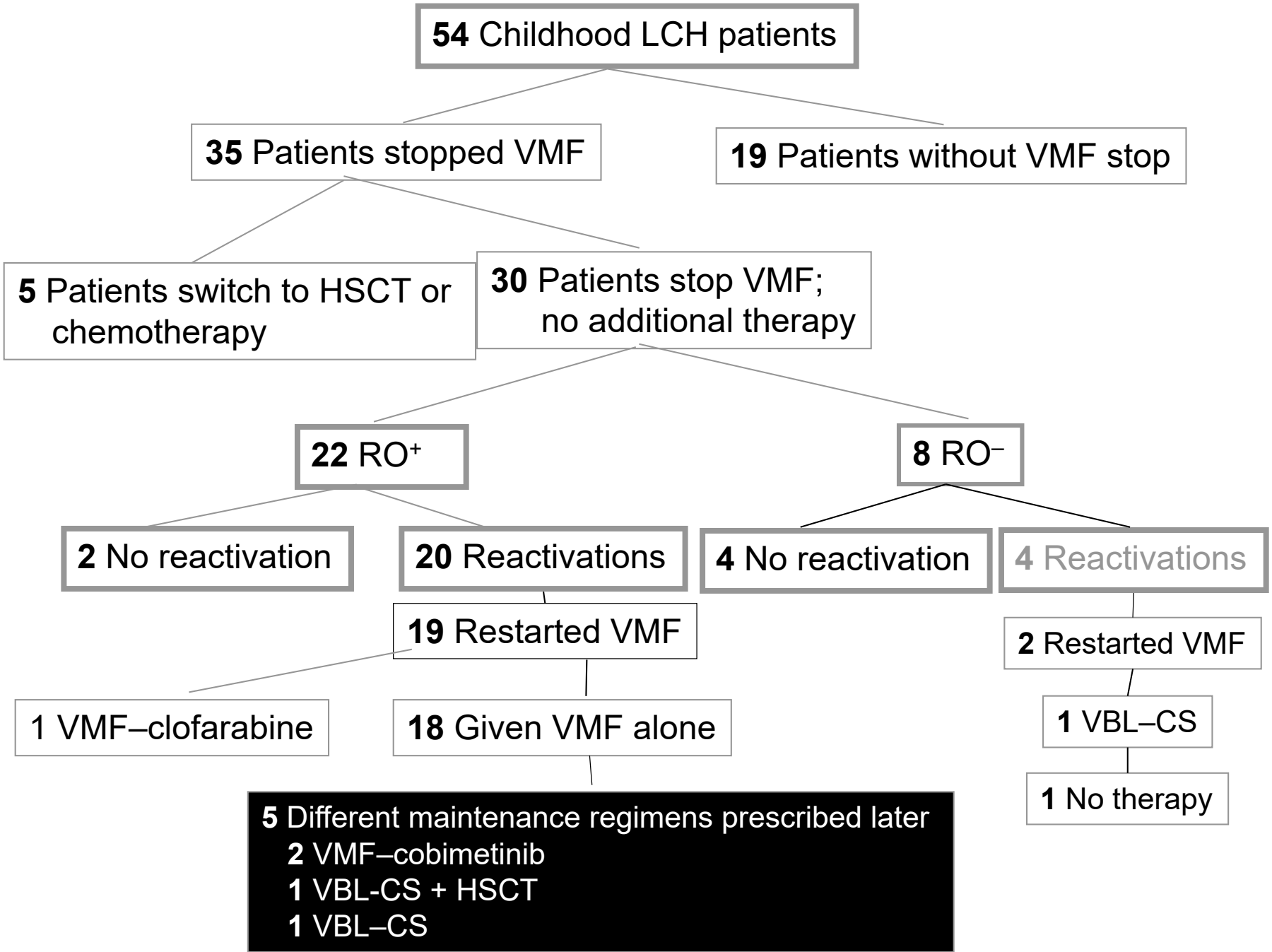


RO + vs RO-

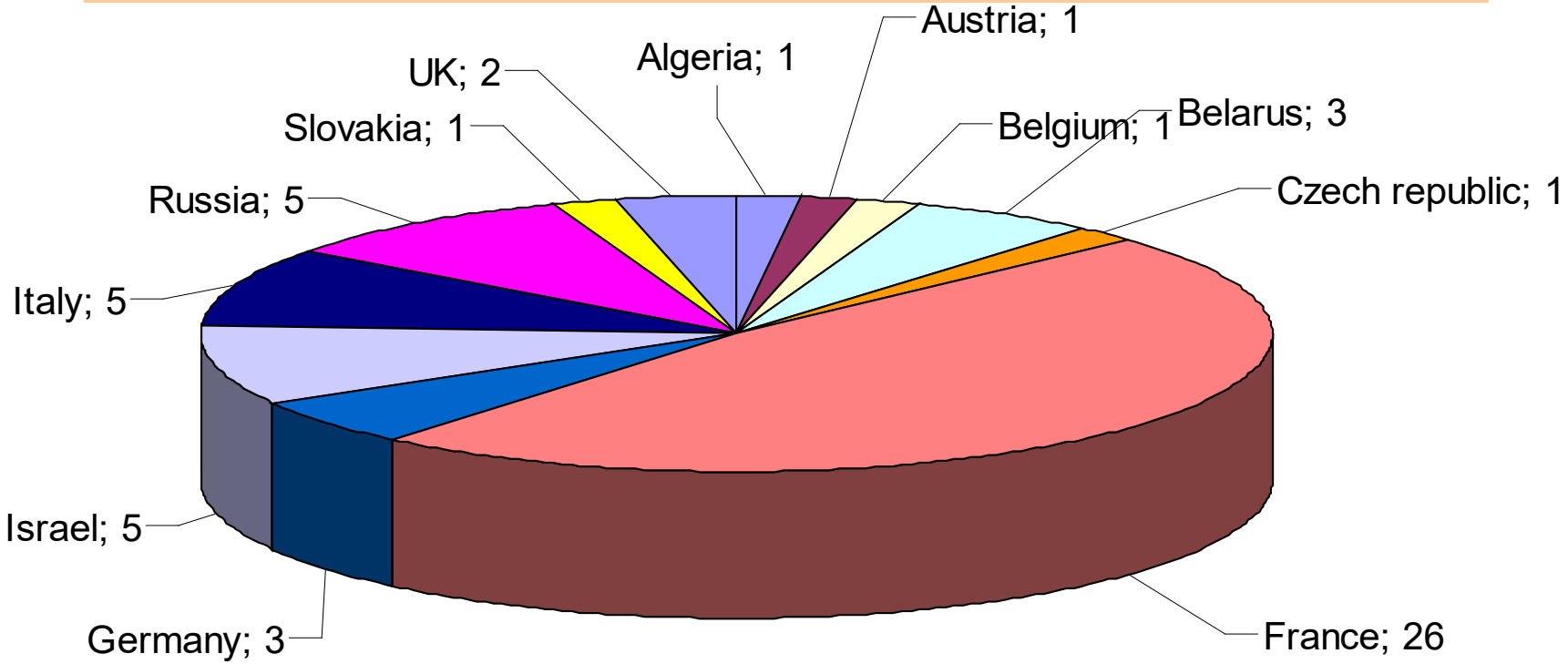


Braf Load + vs -




54 Childhood LCH patients
35 Patients stopped VMF
19 Patients without VMF stop
5 Patients switch to HSCT or chemotherapy
30 Patients stop VMF; no additional therapy
22 RO+
8 RO–
2 No reactivation
20 Reactivations
4 No reactivation
4 Reactivations
19 Restarted VMF
2 Restarted VMF
1 VMF–clofarabine
18 Given VMF alone
1 VBL–CS
1 No therapy
5 Different maintenance regimens prescribed later
2 VMF–cobimetinib
1 VBL-CS + HSCT
1 VBL–CS

Geographic origin



Median follow up since D1 : 22 months

Constat

- Toujours Hors AMM : pas de soutien d'industriel
- Une pratique qui s'est répandu
- 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 withVemu and 3 no

Quelques résultats

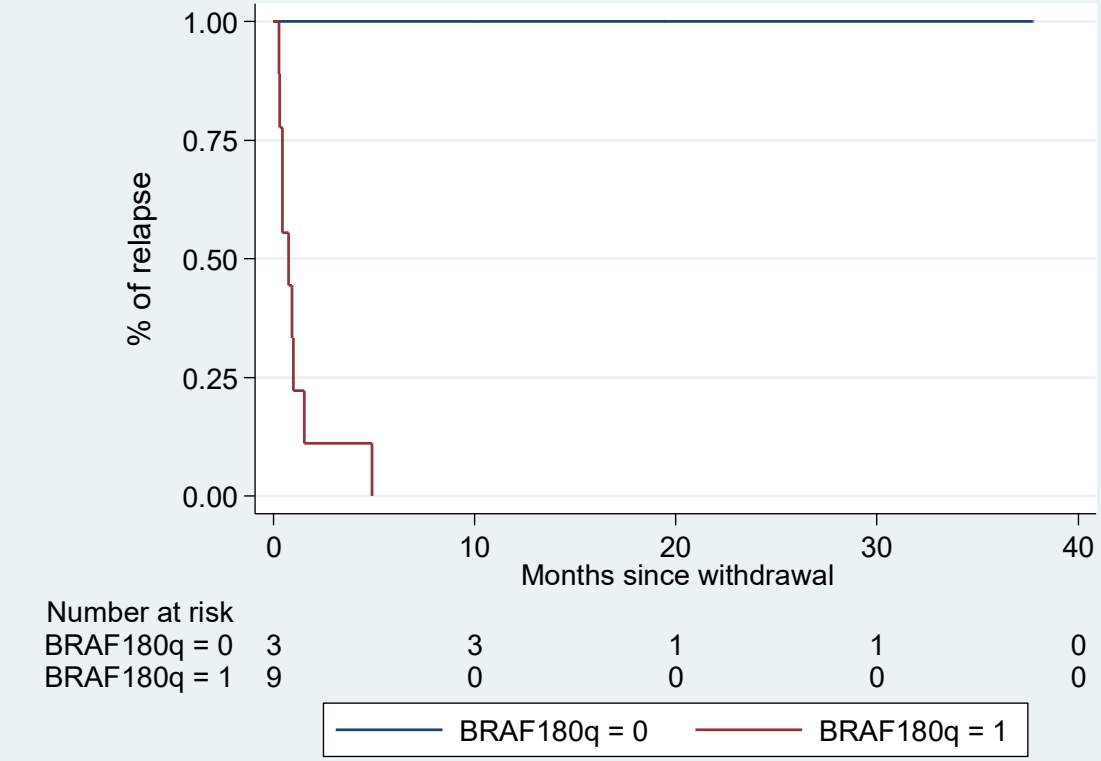
- 2 Décés chez des RO + traités : les 2 liés à des arrets trop précoces ou dosage insuffisants
- Safety: Chez les enfants < 5 ans : 0 EIG graves
- Efficacité de faible dose au long cours de vemu (5 mg/kg/jour)
- 6 patients : atteintes ND sous Vemu

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

B raf Load and targeted therapy

Persistent Braf Load is associated with reactivation



~ 50% des HL présentent une mutation somatique *BRAF* ^{V600E}

~ 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

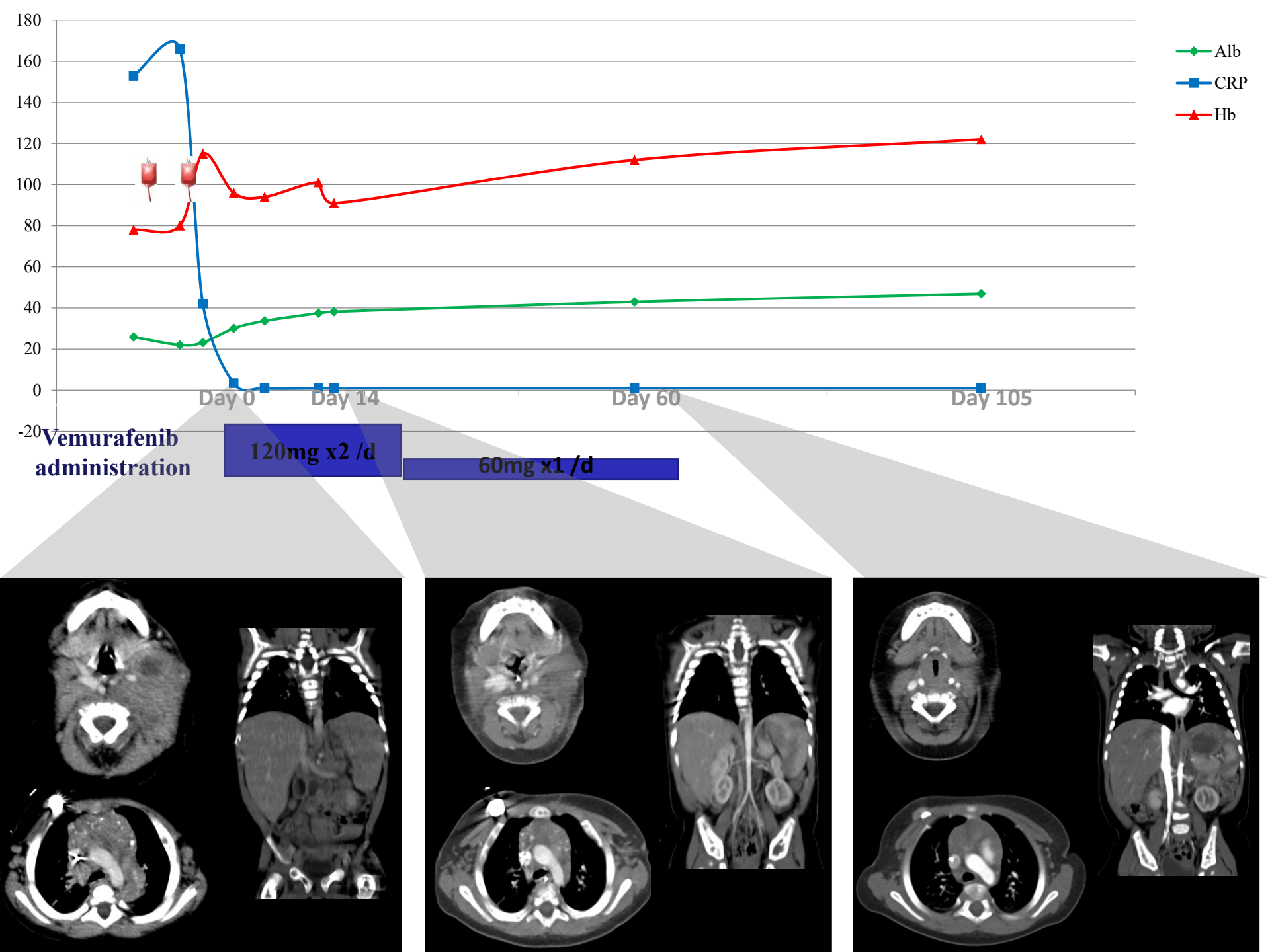
Traitement ciblé dans l'HL de l'enfant : premiére publication avec du Vemurafenib

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 $CD207^+$ 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.


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

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

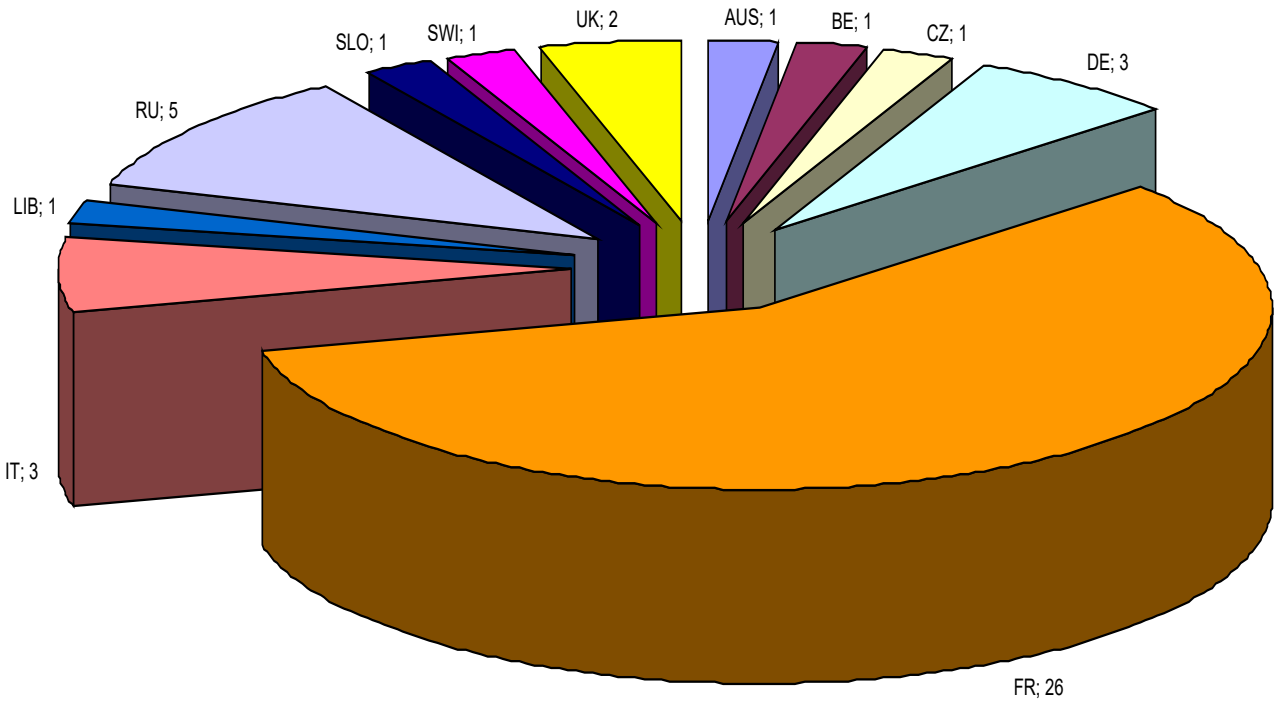
Guidelines

- 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 : critéres 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)

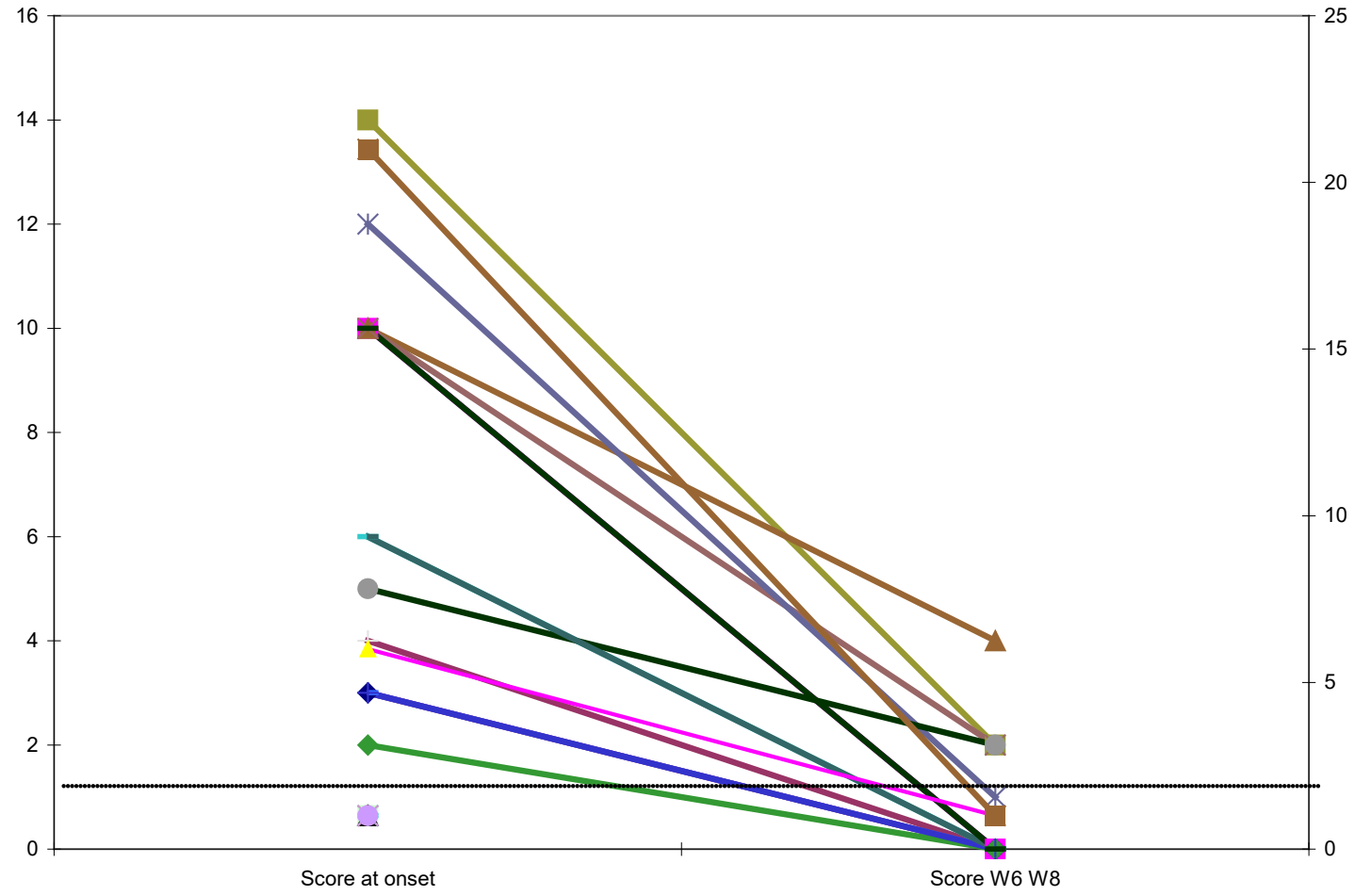
ARD group n=38

- 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

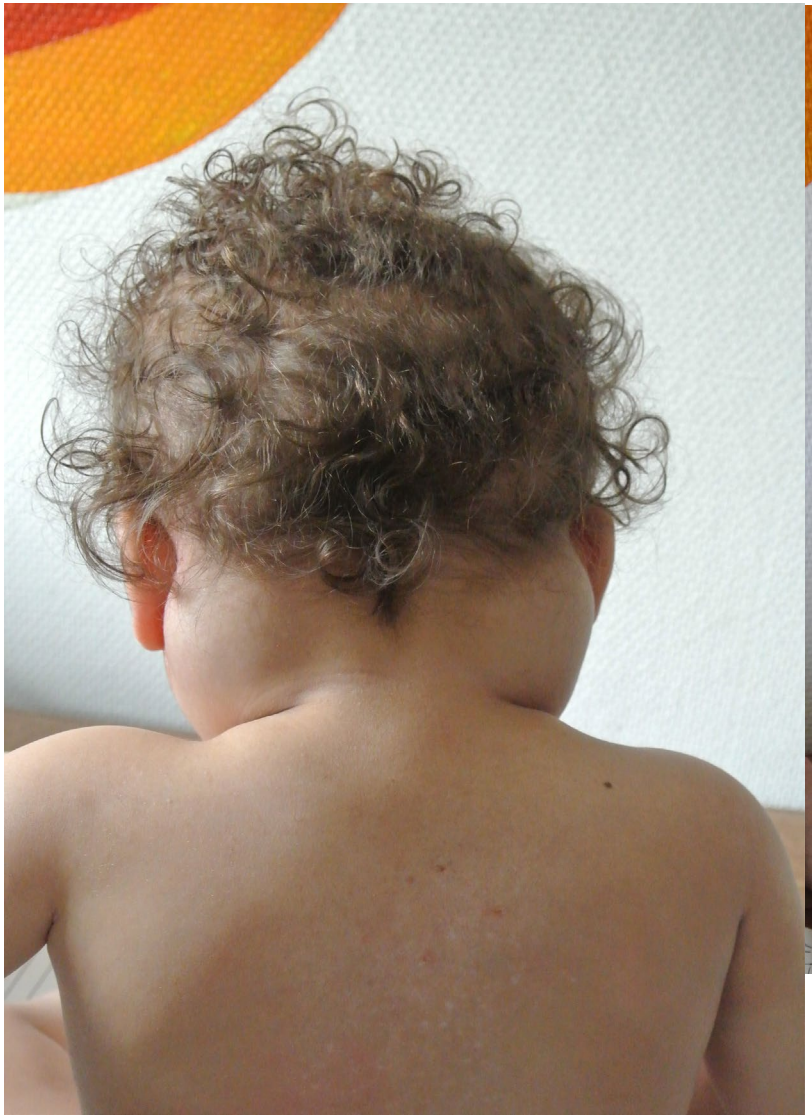
- Therapy before VEMU:
  - All VLB steroid
  - 2 Cda mono: 7
  - 2 Cda Arac 9
- Medium Score D1: 6

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

DAS J1 vs semaine 6

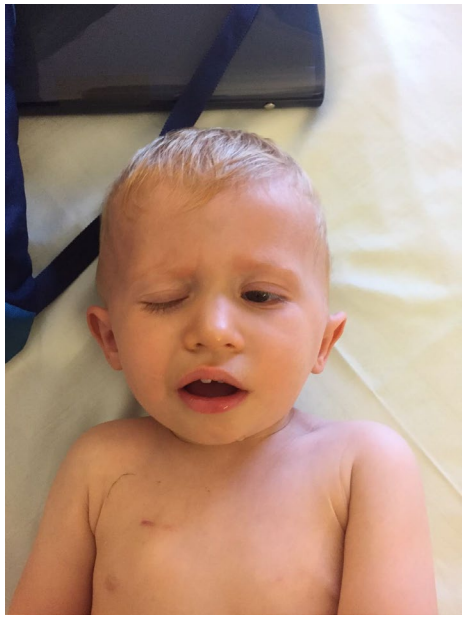


Day -1

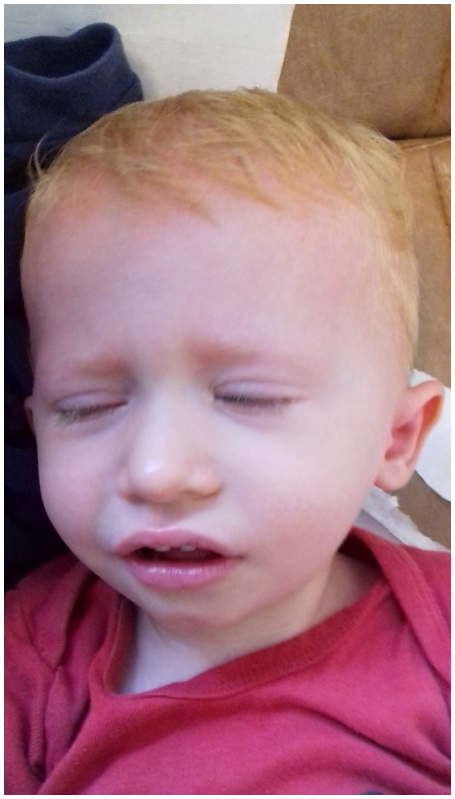


D14 after Vemu

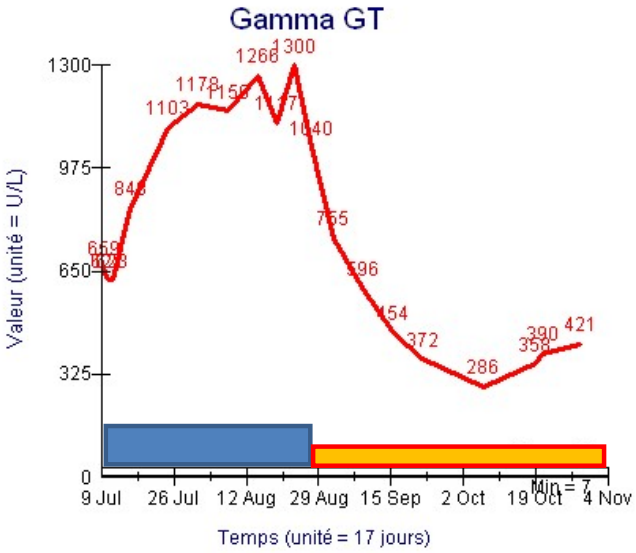
30 aout

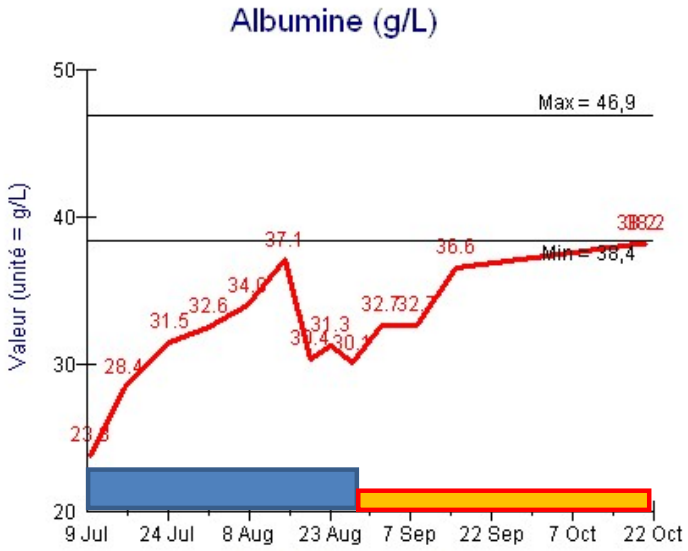


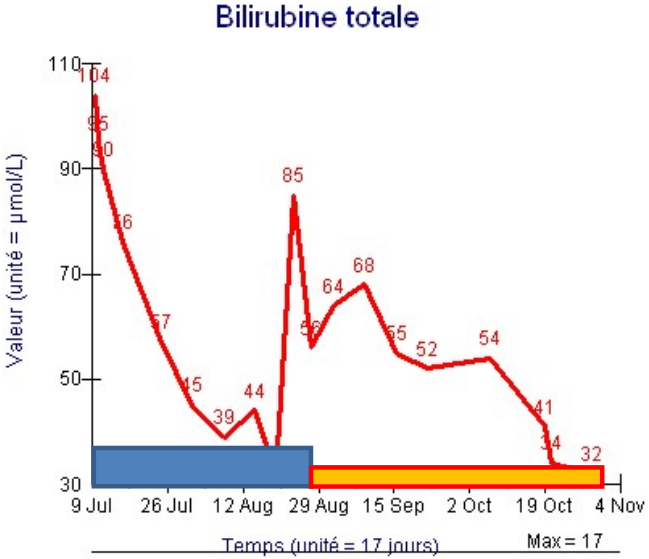
8/9/17 J7 Vemu

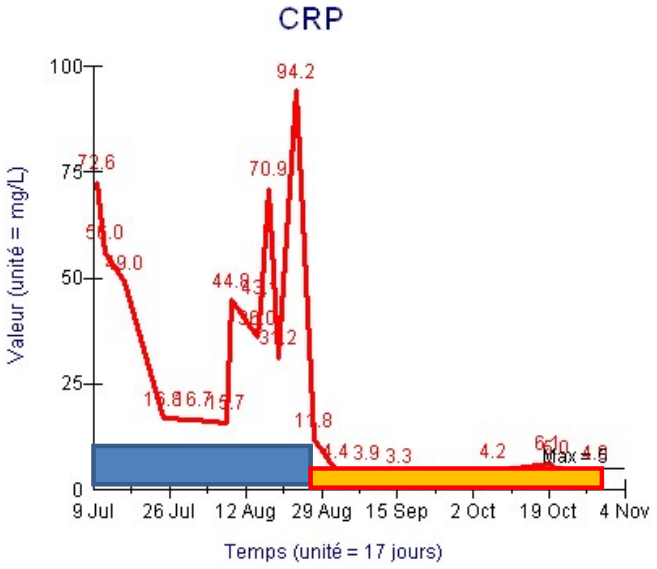


29/9/17

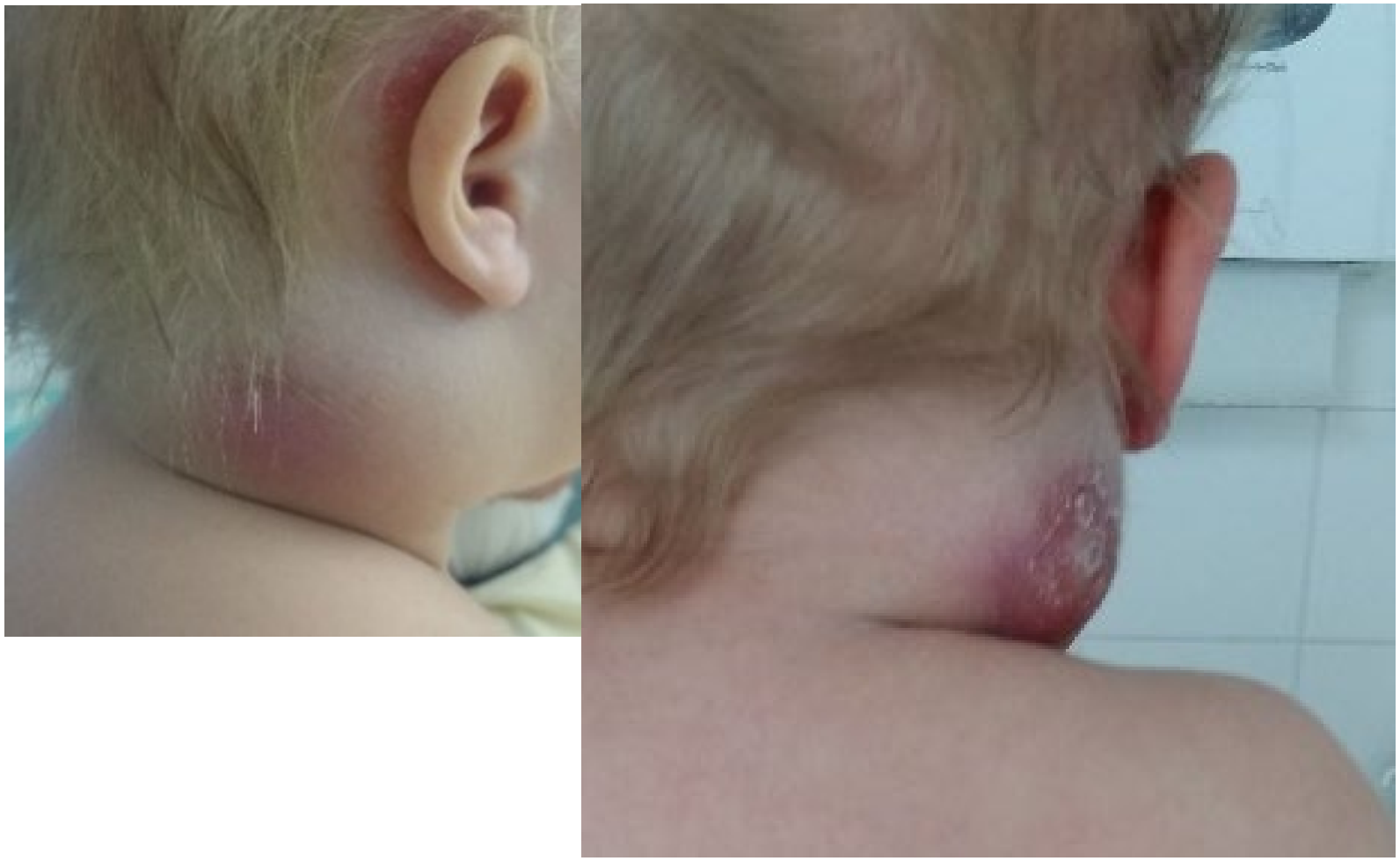

Gamma GT
Valeur (unité = U/L)
1300
975
650
325
0
1268
1300
1178
1103
1040
848
755
596
454
372
286
390
421
9 Jul
26 Jul
12 Aug
29 Aug
15 Sep
2 Oct
19 Oct
4 Nov
Temps (unité = 17 jours)


Albumine (g/L)
Valeur (unité = g/L)
50
40
30
20
Max = 46,9
Min = 38,4
37.1
36.6
34.0
32.6
31.5
28.4
9 Jul
24 Jul
8 Aug
23 Aug
7 Sep
22 Sep
7 Oct
22 Oct


Bilirubine totale
Valeur (unité = µmol/L)
110
90
70
50
30
104
85
68
64
57
55
54
52
45
44
41
39
34
32
9 Jul
26 Jul
12 Aug
29 Aug
15 Sep
2 Oct
19 Oct
4 Nov
Temps (unité = 17 jours)
Max = 17


CRP
Valeur (unité = mg/L)
100
75
50
25
0
94.2
72.6
70.9
44.8
16.8
16.7
15.7
11.8
4.2
9 Jul
26 Jul
12 Aug
29 Aug
15 Sep
2 Oct
19 Oct
4 Nov
Temps (unité = 17 jours)

Nécrose ganglionnaire J19



Toxicité

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

Pas de tumeur cutanée secondaire

Décés 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:**
  - **Fiévre**
  - **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.**

Décés ARD

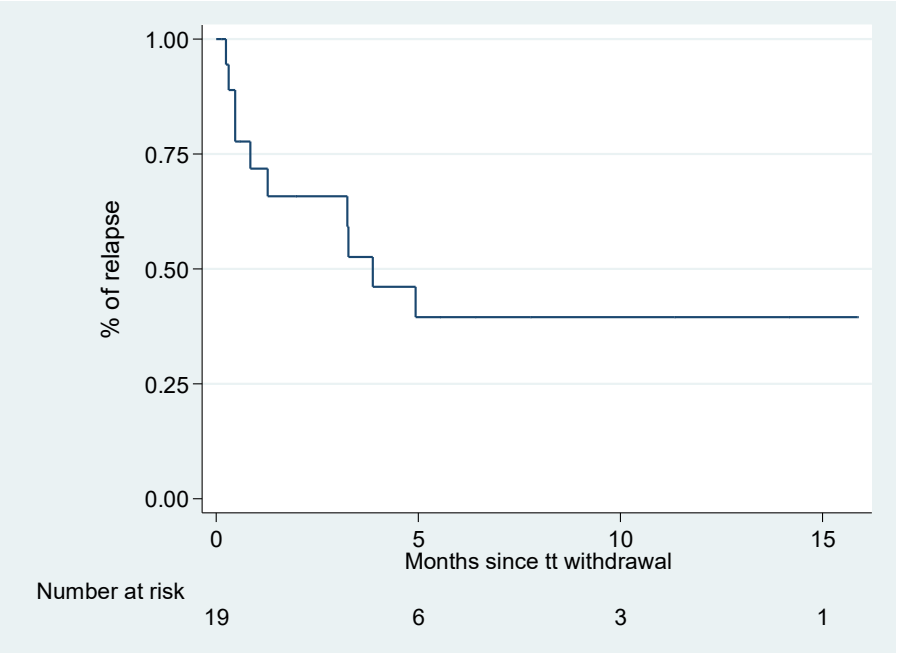
- Diagnostic à 6 mois: Peau, foie, Rate, Poumon, Hematologie.
- DAS au diagnostic 18.
- VBL et steroid 2 inductions: Puis 2 cures de 2 Cda Arac puis 3 cures de 2 Cda,
- A 18 mois : maladie active.
- Vemurafenib J1 DAS 22 (peau, foie rate, poumon hemato).
- vemurafenib (34 mg/kg/day)
- A 2 mois DAS 5.
- Dose augmentée à 51 mg/kg puis 68mg/kg.
  - Aprés 2 mois: nausée, vomissement: traitement stop Aggravation DAS 14.

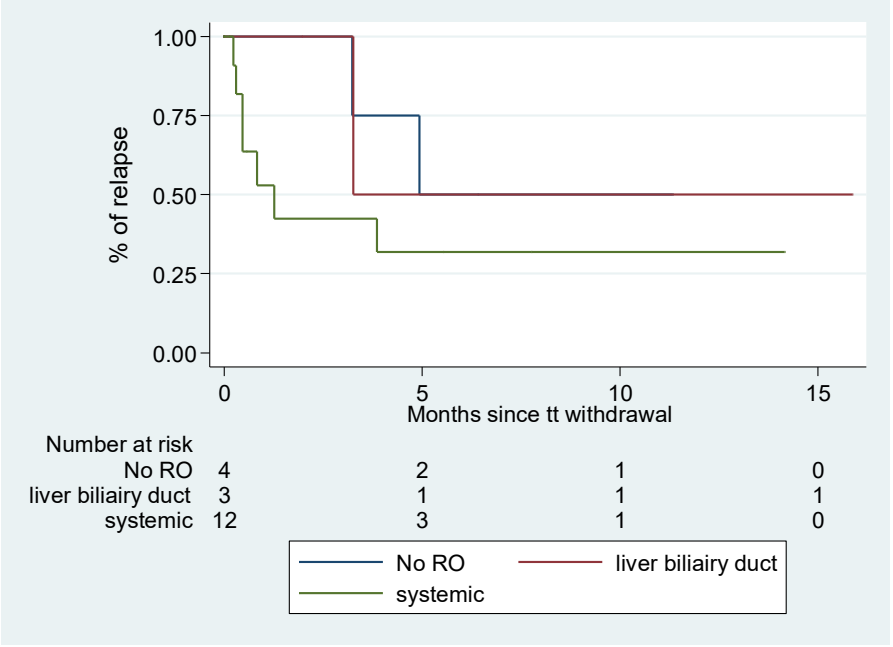
- Décision alors de traiter par Vemurafenid et Clofarabine (20 mg/m2/day x 5 days)
- Décés à J19 :septicémie.
- Pas de PK.

Outcome & relapse

No reactivation in NDD patients

Among 29 ARD patients 19 patients had stopped therapy





Type de reactivations et devenir

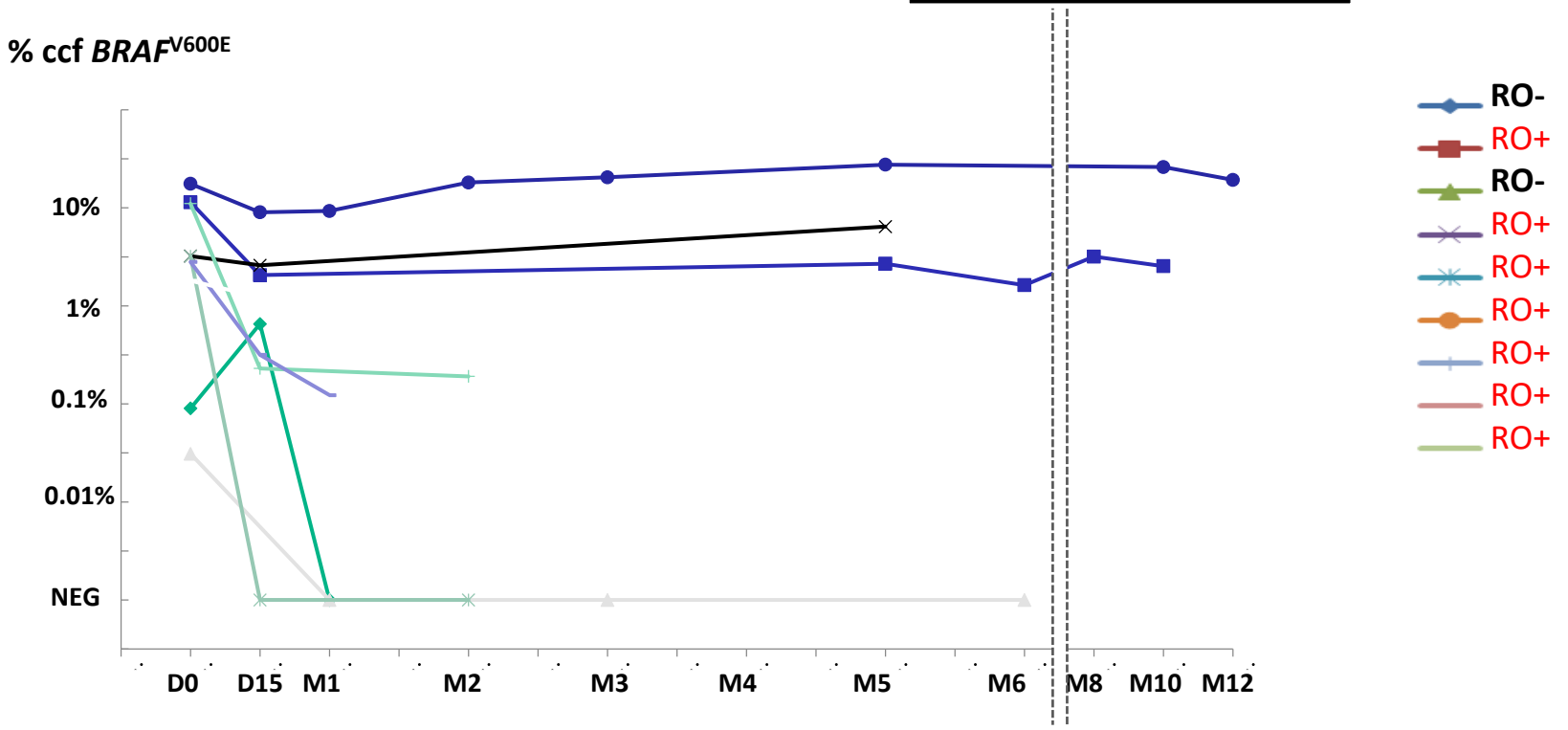
- 19 patients ARD, 10 reactivations were observed.
- 3 were considered as mild (skin rash or Diabetes insipidus) : not treated
- 2 were in RO -organ 1 VLB 1 vemu
- 6 was observed in RO+. 6 Treated by vemu

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



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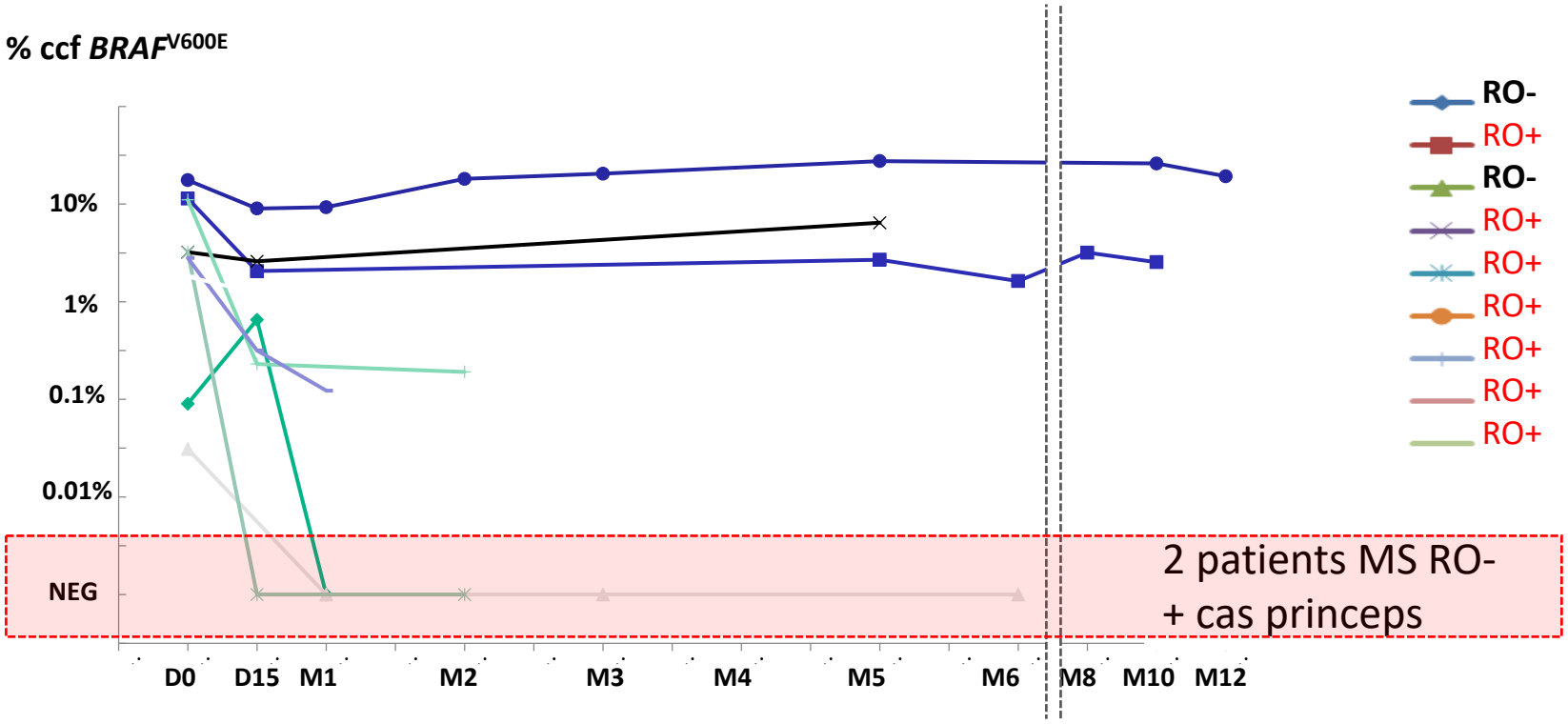
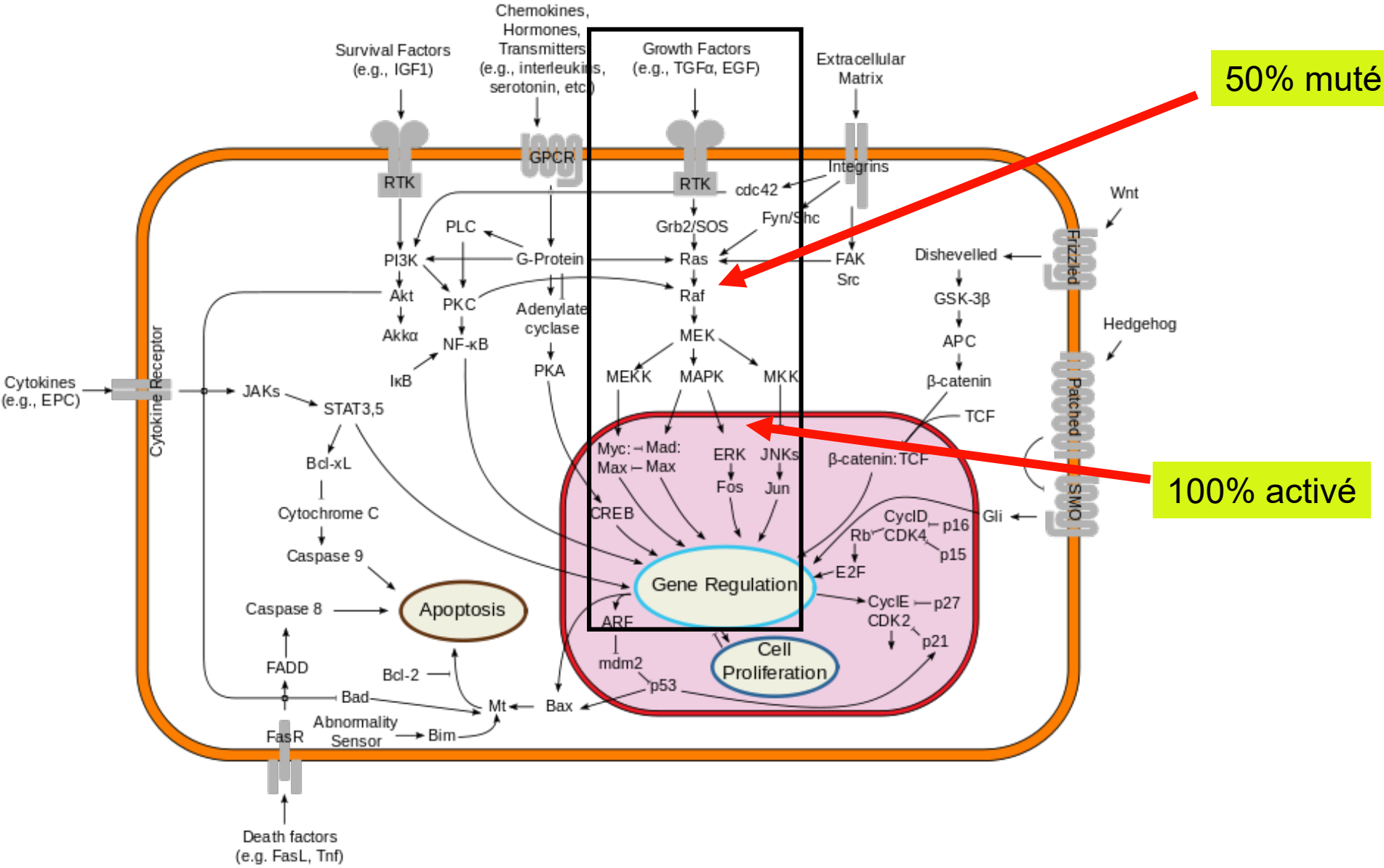


Vemurafenib

- Monotherapie VEMURAFENIB actif dans les formes réfractaires BRAF V600E
  - Proche de 100% de response
  - Response dans un trés court délai
- Tolérance : acceptable (>>> que HSCT ou 2 Cda Arac ou clofarabine ou haute dose steroide)
  - Pas de kerato acanthoma
  - Patient en externe
- Neuro degenerative : Non si forme symptomatique

- La periode initial (3 months) Trop court
- Cf DNA trés utile pour suivre les patients

Voie des mapkinases dans l'histio



50% muté

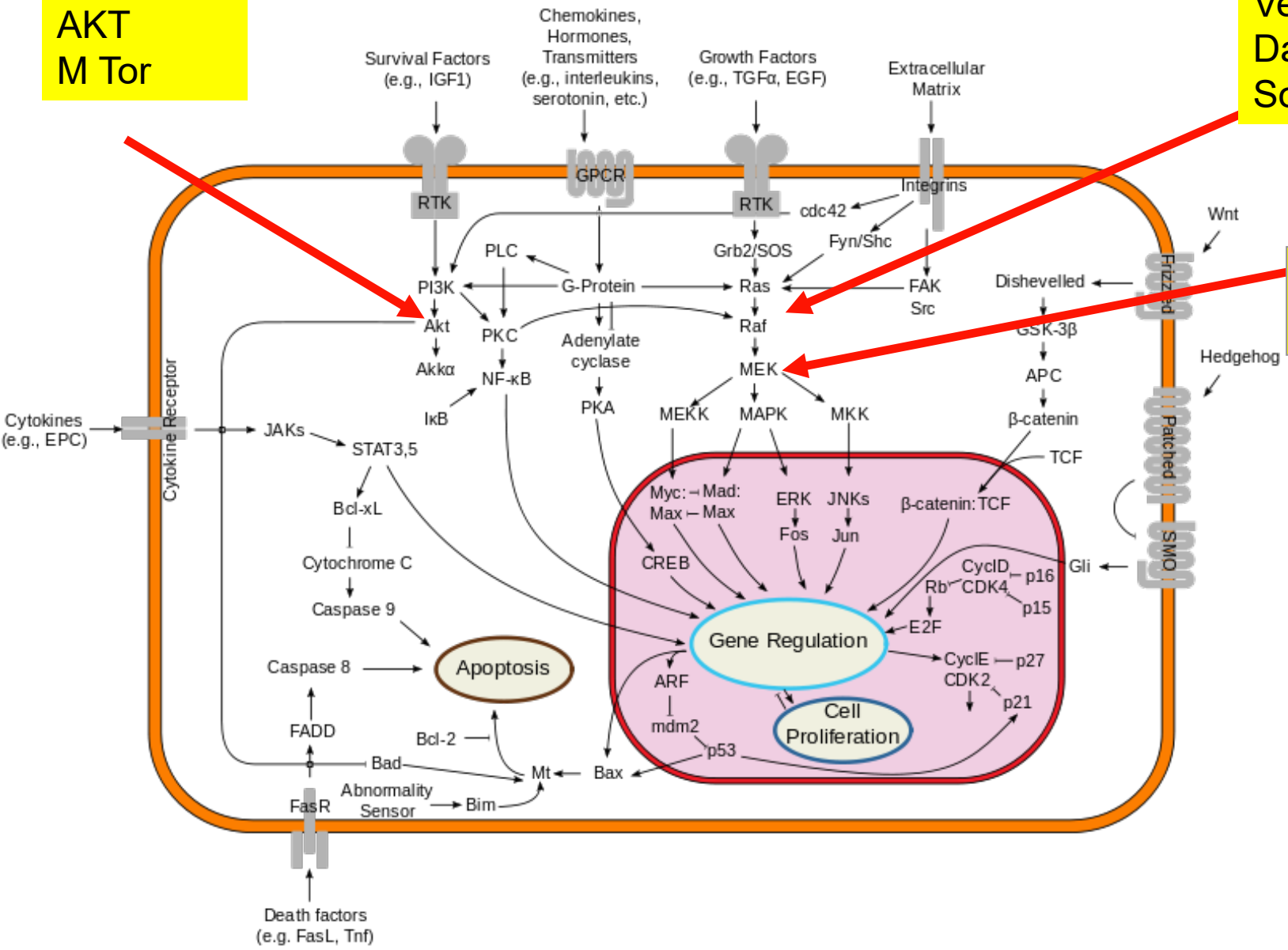
100% activé

Thérapies ciblées dans les histiocytoses

Inhibiteurs
AKT
M Tor

Vemurafenib
Dabratenib
Sorafenib

Cobimetinib
Trametinib



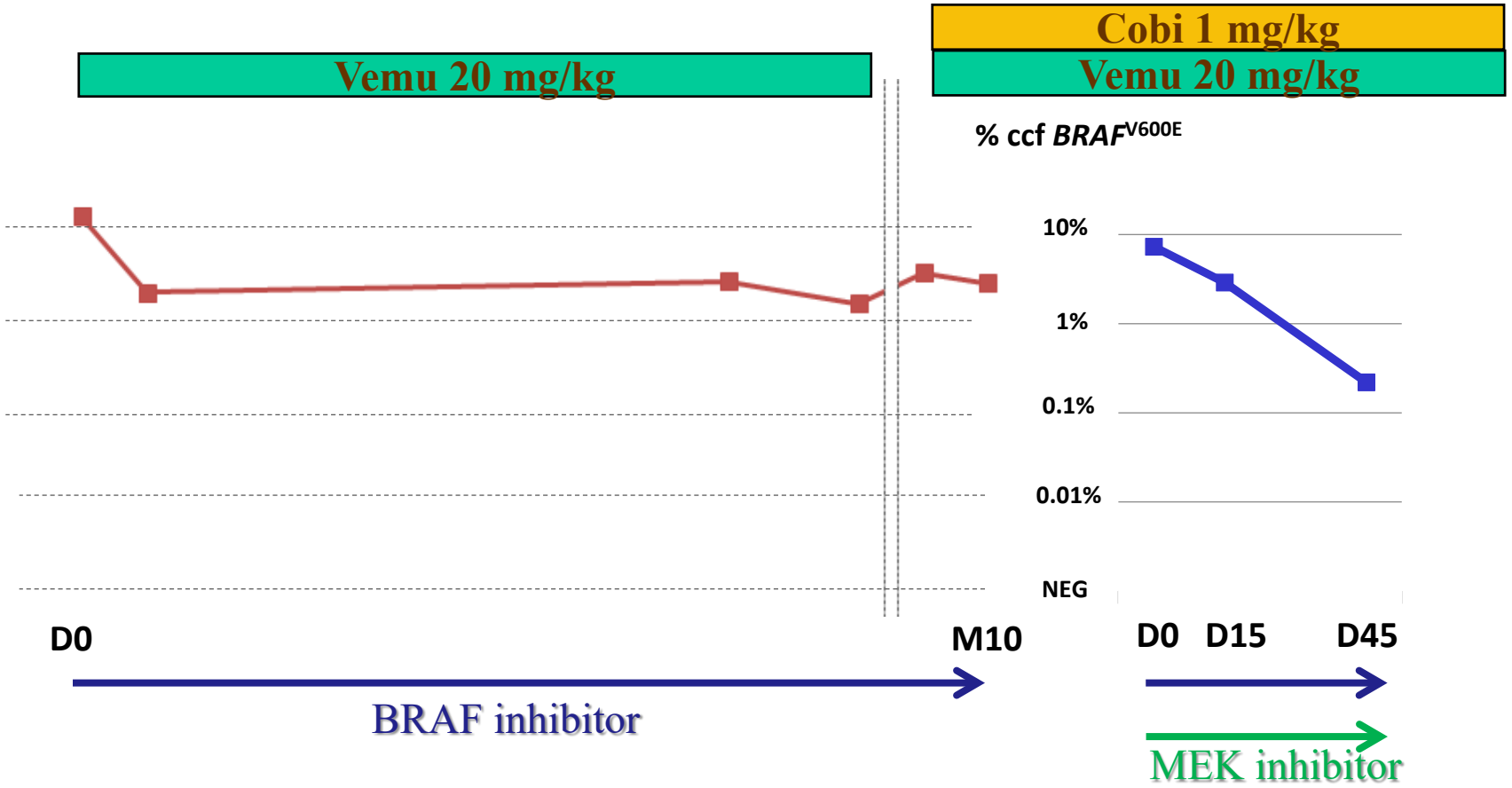
Gabriel

- 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 ?