BRAF ^{V600E} mutation is associated with a cardiac and neurological phenotype in Erdheim-Chester disease: results from a 165-patient cohort

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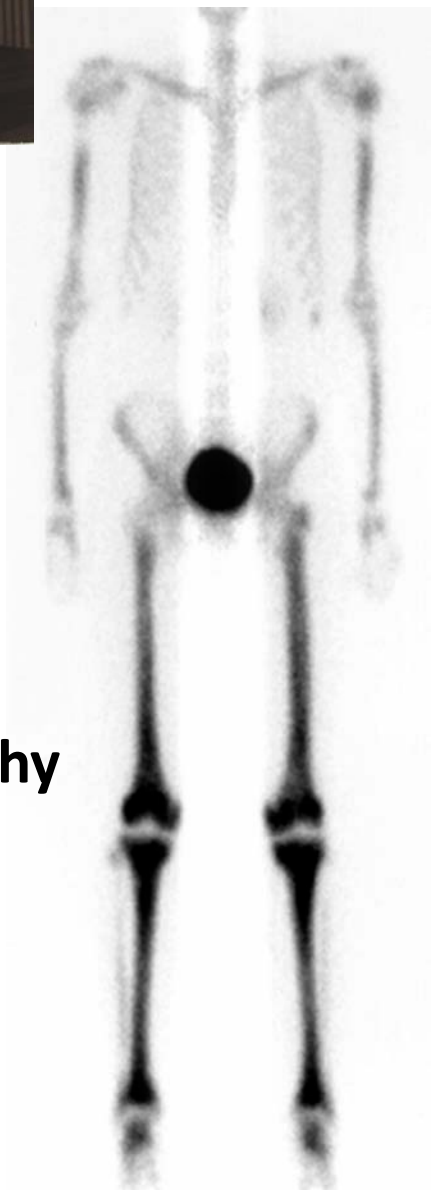
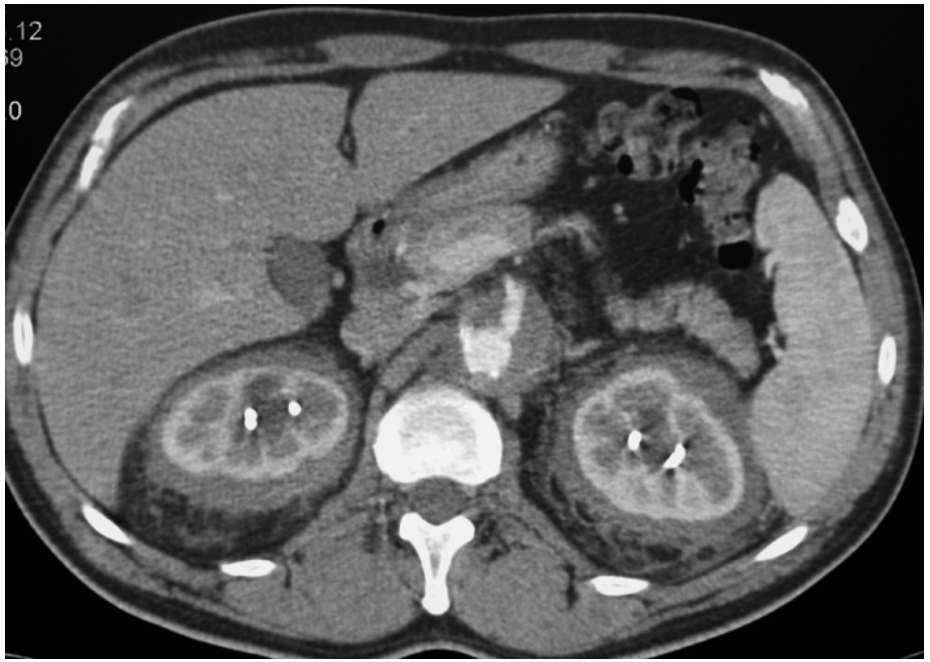




Bone scintigraphy
(^{99} Tc)

(96%)

"Hairy kidney aspect"
and peri-renal infiltration

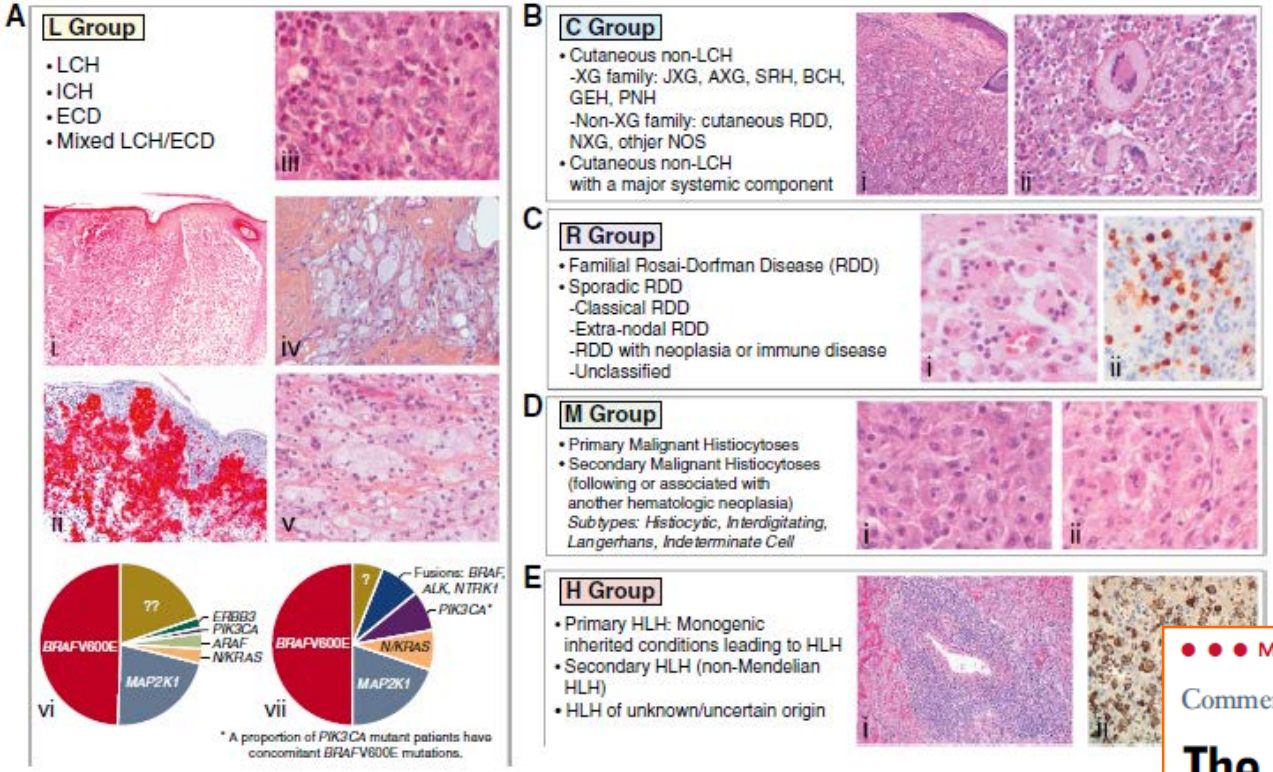
(≈ 50%)

Classification taking into account molecular alterations

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 • VOLUME 127



MYELOID NEOPLASIA

Comment on Emile et al, page 2672

The histiocytoses: as easy as ABC (or LCMRH)

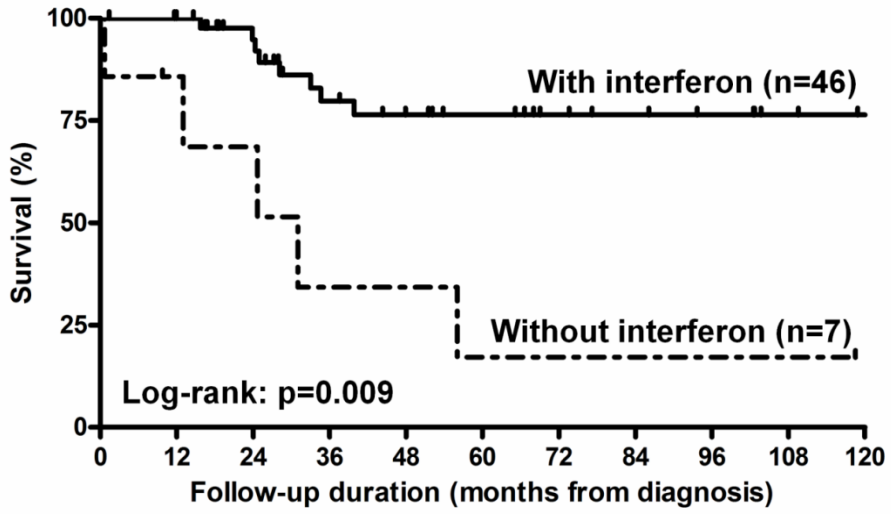
Brief report

BLOOD, 1 NOVEMBER 2005 • VOLUME 106, NUMBER 9

Successful treatment of Erdheim-Chester disease, a non–Langerhans-cell histiocytosis, with interferon-α

Fadi Braiteh, Cynthia Boxrud, Bita Esmaeli, and Razelle Kurzrock

CNS involvement and treatment with interferon-alpha are independant prognostic factors in Erdheim-Chester disease: a multicenter survival analysis of 53 patients



Numbers at risk

Interferon-alpha	46	43	35	26	22	19	15	13	11	8	6
No interferon-alpha	7	6	5	3	3	2	2	2	2	2	1

Arnaud, Hervier, Haroche, et al. Blood 2011

Clinical and therapeutic predictors of survival in Erdheim-Chester disease (multivariate survival analysis using Cox proportional hazard model).

	Univariate Analysis	Cox multivariate survival analysis†	
	P-value	**HR (95% CI)**	**P-value**
Gender	0.55	-	-
Cardiovascular involvement	0.57	-	-
CNS involvement	**0.10**	**2.51 (1.28-5.52)**	**0.006**
Hypophyseal involvement	0.93	-	-
Paranasal sinus involvement	0.54	-	-
Maxillary involvement	0.23	-	-
Xanthelasma	0.98	-	-
Orbital involvement	0.57	-	-
Pulmonary involvement	0.21	-	-
Retroperitoneal involvement	0.31	-	-
Adrenal involvement	0.53	-	-
Treatment with interferons*	**0.03**	**0.32 (0.14-0.70)**	**0.006**

*Interferons: treatment with interferon-alpha and/or PEGylated-interferon alpha. P-values <0.20 in univariate analysis were entered in the multivariate model. HR: hazard ratio, 95% CI: 95% Confidence Interval. †Adjusted for the age at compilation (quartiles of the distribution), the use of corticosteroids or of any other immunosuppressive drugs.

Arnaud, Hervier, Haroche, et al. Blood 2011

Background

57 to 70 % of ECD patients carry the *BRAF*^{V600E} mutation, ECD re-classified as an inflammatory myeloid neoplasm.

Phenotype and clinical course of ECD are heterogeneous, ranging from asymptomatic to life-threatening multi-organ involvement.

Previous studies report that CNS involvement and interferon-alpha treatment are independent predictors of survival of ECD.

Even though **IFN α**, anakinra, infliximab and cladribine are largely used to treat ECD, BRAF targeting treatments are increasingly prescribed.

We aimed to determine a genetic-phenotype correlation in a large cohort of ECD patients and analyze the factors associated with survival in the era of *BRAF* genotyping.

Series of Pitié-Salpêtrière (December 2016)

165 patients (119 M, 46 F)

(40 abroad mainly EU)

14%

21 patients with LCH + ECD
1 patient with LCH + ECD + Rosai-Dorfman
1 patient with ECD + Rosai-Dorfman

38 deaths (23%)

Mean age at diagnosis 56.4

BRAF^{V600E} and 165 ECD (no data for 32 pts)

133 patients ECD « exploitable tissue »

88 patients (65%) mutated

45 patients (35%) WT

2017

	All (n=165)	*BRAF*^{V600E} (n=88)	*BRAF* WT (n=45)	p*
Sex (M/W)	119/46	62/26	35/10	NS
Age at first symptoms (mean, SD)	51.7 (15.7)	51.2 (15.4)	51.8 (16.7)	NS
Age at diagnosis (mean, SD)	56.4 (14.4)	56.1 (14.1)	56.0 (15.6)	NS
Mixed histiocytosis	25 (15%)	18 (20%)	6 (13%)	0.34
Other hematologic disease**	13 (8%)	8 (9%)	3 (7%)	NS
Long bone involvement	132 (80%)	75 (85%)	30 (67%)	NS
Cardiac involvement	88 (53%)	64 (73%)	12 (27%)	**<0.0001**
Right atrium pseudotumor	67 (41%)	50 (57%)	4 (9%)	**<0.0001**
Coronary infiltration	44 (27%)	30 (34%)	7 (16%)	**0.03**
Pericardial involvement	51 (31%)	31 (35%)	11 (24%)	0.24
Vascular involvement	105 (64%)	65 (74%)	24 (53%)	0.14
Coated aorta	76 (46%)	49 (56%)	17 (38%)	NS
Skin involvement	54 (33%)	34 (39%)	13 (29%)	0.33
Xanthelasma	44 (27%)	29 (33%)	9 (20%)	0.16
Diabetes insipidus	47 (28%)	31 (35%)	7 (16%)	**0.03**
CNS involvement	61 (37%)	36 (41%)	11 (24%)	0.08
Cerebellar involvement	28 (17%)	20 (23%)	2 (4%)	**0.007**
Retro-orbital involvement	36 (22%)	27 (31%)	5 (11%)	**0.02**
Lung involvement	58 (35%)	29 (33%)	17 (38%)	NS
Retroperitoneal involvement	95 (58%)	56 (64%)	23 (51%)	NS

165 ECD and MH patients seen at Pitié-Salpêtrière in 2017 (*submitted*)

	All (n=165)	*BRAF*^{V600E} (n=88)	*BRAF* WT (n=45)	p*
Deaths (n, %)	41 (24.8%)	17 (19.3%)	8 (17.8%)	
Survival, months (median)	162	130	174	0.51
Corticosteroids	53 (32%)	29 (33%)	13 (29%)	
IFN-α or PEG-IFN-α	124 (75%)	65 (74%)	33 (73%)	
Anakinra	19 (12%)	9 (10%)	3 (7%)	
Infliximab	16 (10%)	8 (9%)	4 (9%)	
Tocilizumab	1	0	1	
Targeted therapy**	56 (34%)	49 (56%)	5 (11%)	**< 0.0001**
Others***	8/6/3	2/2/1	1/1/1	

Treatments and survival of ECD patients (ECD, Erdheim-Chester disease) * Comparison between *BRAF* V600E and WT ** vemurafenib, dabrafenib, cobimetinib ***glivec, sutent, stem cell transplantation

submitted

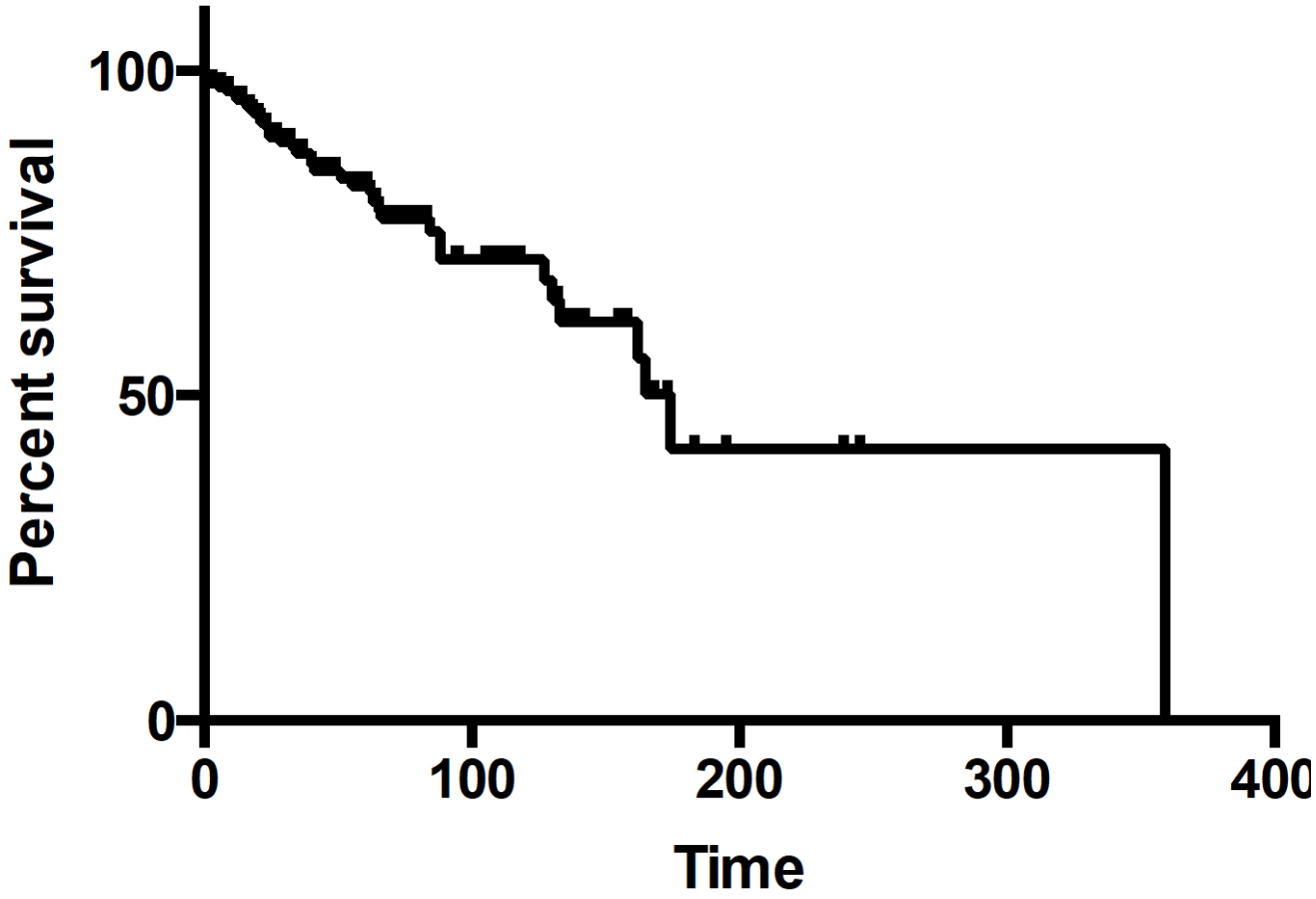
	Cox survival analysis		
Variable	Univariate HR (95% CI)	Multivariate HR (95% CI)	p-value
Sex M*	1.15 (0.58; 2.31)	1.96 (0.89; 4.28)	0.0932
Age at diagnosis (per year increase) *	1.05 (1.02; 1.08)	**1.06 (1.03; 1.09)**	**0.0001**
$BRAF^{V600E}$	1.27 (0.54; 2.94)	1.73 (0.68; 4.41)	0.2495
BRAF missing	2.02 (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

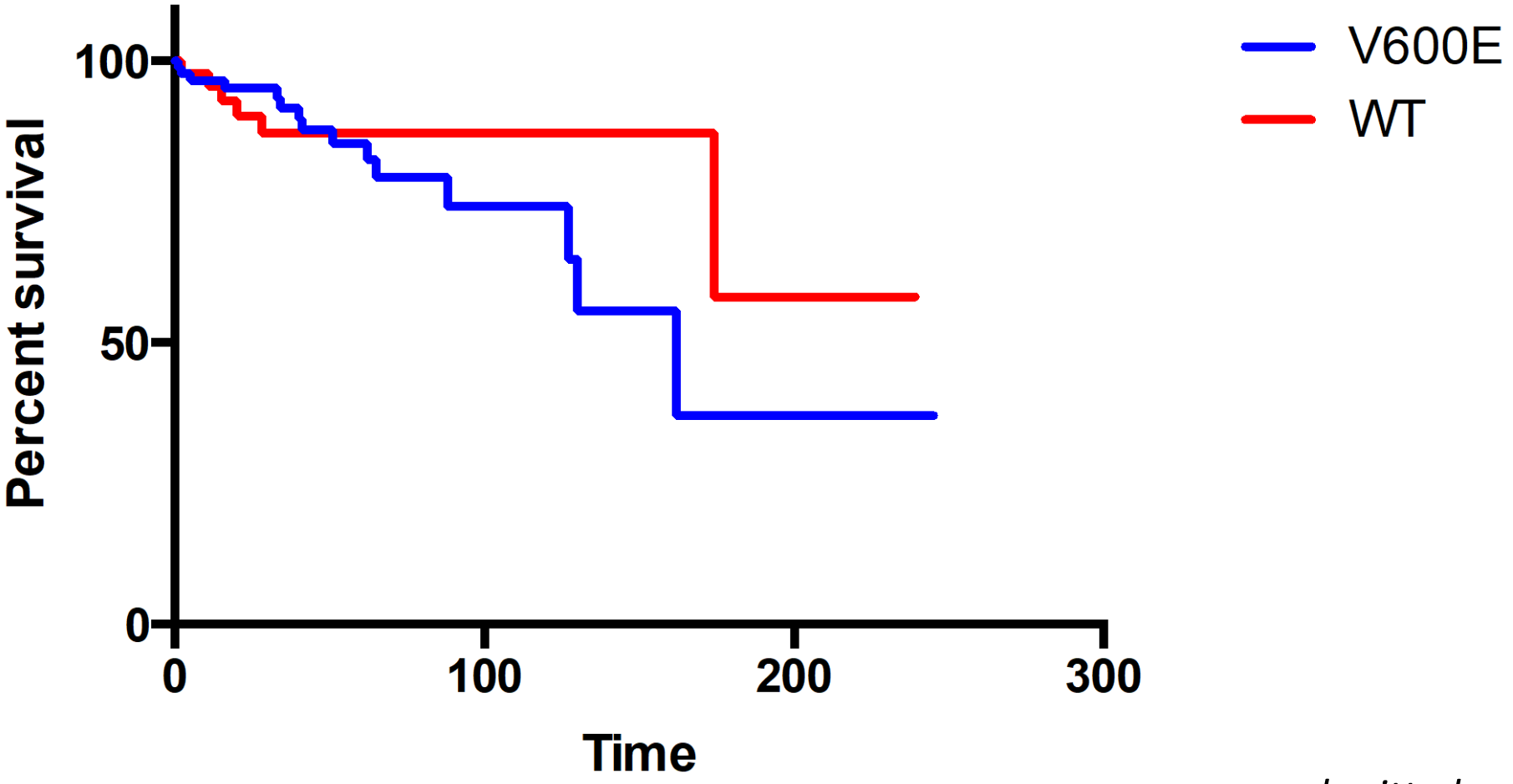
submitted

Global survival (median : 162 months)



In 2016 prognosis of ECD is better than in « older series »
published in 1996 & 2004 ≈ 60% death at 3 yrs

No difference of survival V600E / WT (p = 0.51)



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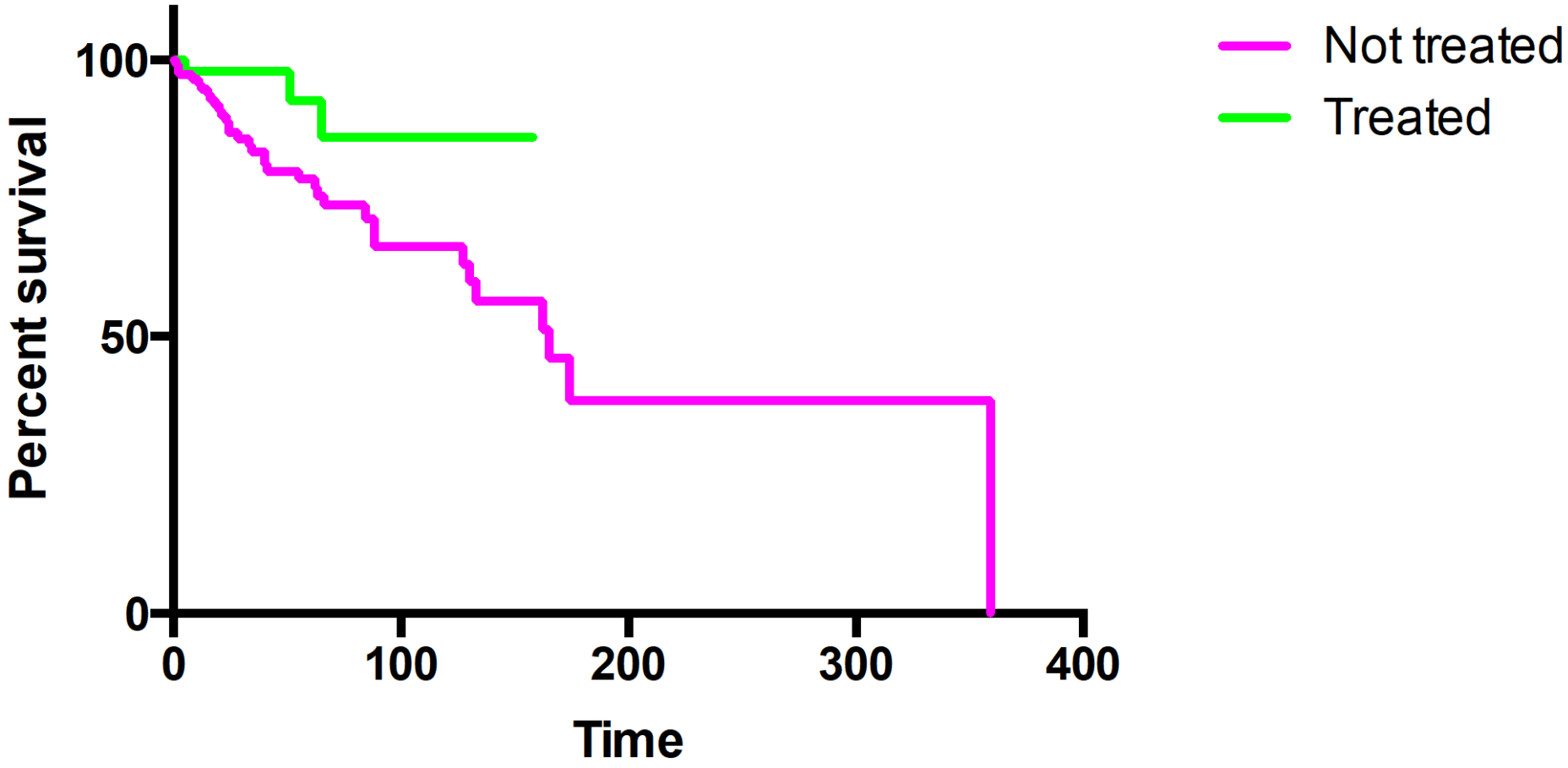
Treatment with BRAF inhibitors improves survival ($p < 0.0001$)



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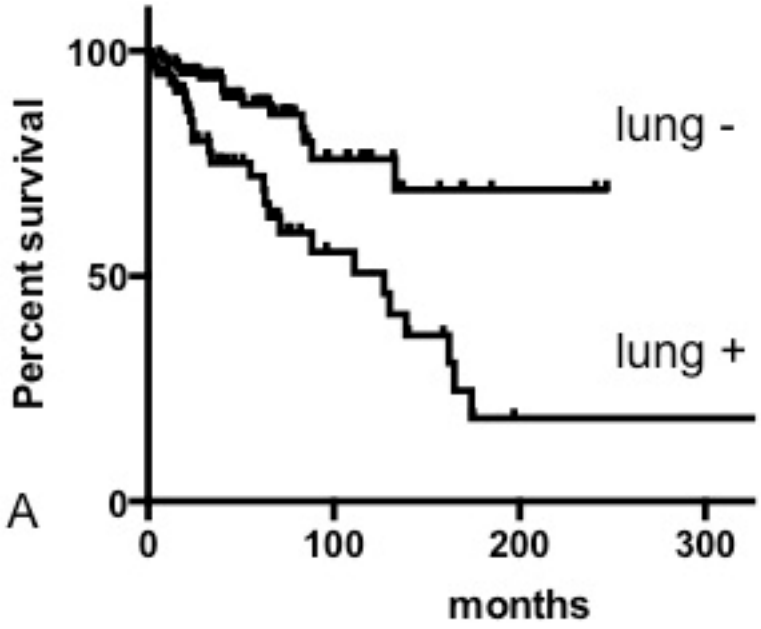
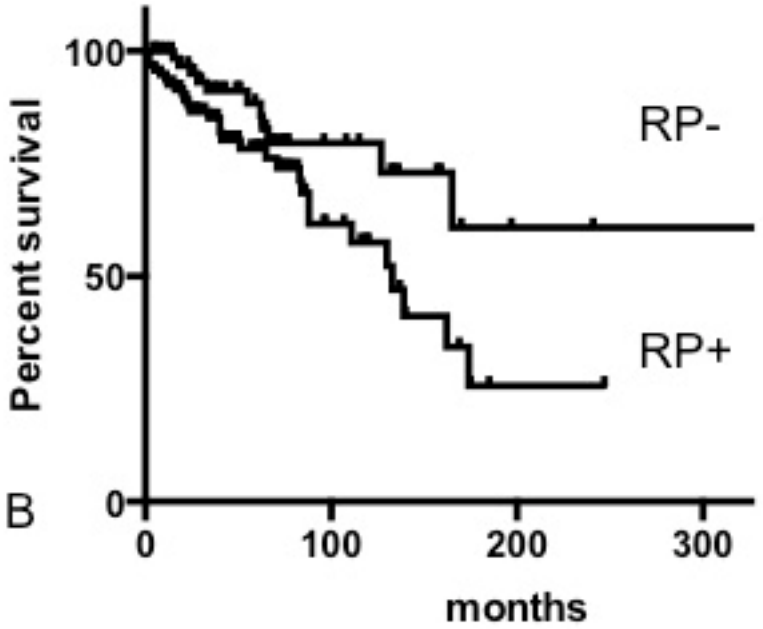

Percent survival
100
50
0
lung -
lung +
A
0
100
200
300
months


Percent survival
100
50
0
RP-
RP+
B
0
100
200
300
months

submitted

Conclusions (I)

- *BRAF*^{V600E} mutation is associated with a cardiac and neurological phenotype in ECD

- Retroperitoneal involvement, central nervous system and lung involvements are associated with a worse survival in ECD

- Interferon-alpha and targeted therapies (BRAF and/or MEKi) improve survival in ECD.

Conclusions (II)

- BRAF has no influence so far on the survival of ECD patients (≠ pediatric LCH)

- LOVE Study : 75% relapse Cohen-Aubart, *Blood* 2017

- No resistance to BRAF inhibition so far in ECD or MH after more than 5 y, no resistance to MEK inhibition even if follow-up only of 2 y

Thank you

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Jean Donadieu

Kathy Brewer and the ECD global alliance
The patients

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