Disturbance of monocytes homeostasis in histiocytosis is close to chronic myelomonocytic leukemia and correlated with phenotype and disease activity

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Disclosures

Julien Haroche and Fleur-Cohen Aubart are investigators in an academic study on the efficacy of Cobimetinib for treating histiocytosis.

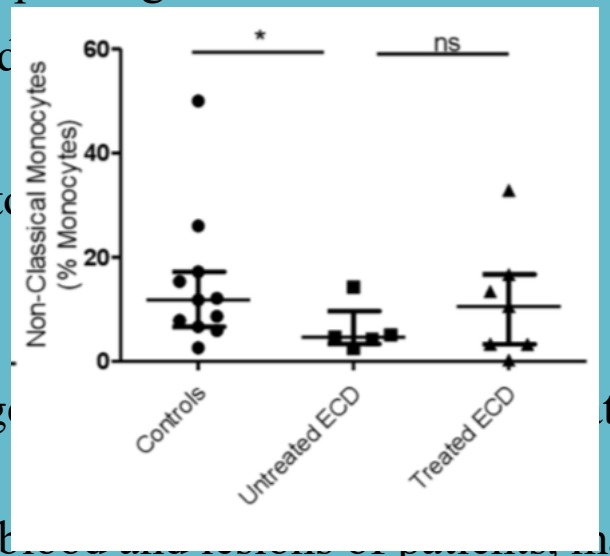
The other authors declare no competing interest related to this study.

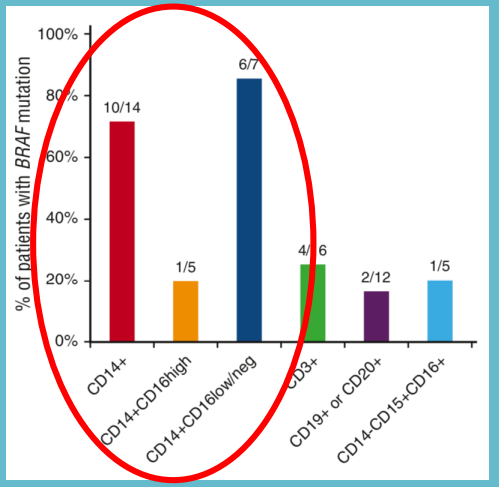
Presentation Plan

- Background
- Purpose
- Materials and Methods
- Results
- Discussion
- Conclusion

Background

- Histiocytosis are an heterogenous group of organ diseases[1].
- Proliferation and accumulation of dend
- Cells origins[2]:
  - Hematopoietic stem cell progenit
  - Fetal liver
  - Yolk sac
- Occurrence of MAP-kinase pathway g topoietic stem cell progenitors and CD14+ monocytes[3]
- Cytokine and chemokine networks in b ainly ECD[4]
- Dual connection between inflammatory/clonal component in monocyte/macrophage lineage: inflammatory myeloid neoplasm
- Phenotyping in ECD patients: decrease of $CD14^{+}CD16^{++}$ "non-classical" monocytes resembling CMML[5]





1: Emile JF: *Lancet* 2021
2: Durham BH: *Semin Cell Dev Biol*. 2019
3: Durham BH: *Blood* 2017
4: Cohen-Aubart F: *Haematologica* 2021
5: Papo M: *Annals of Rheumatic Diseases* 2020

Background

- Little is known about monocytes homeostasis in histiocytic disorders

- And the difference with myeloid neoplasms and inflammatory disorders

Primary Outcome

Compare monocytes homeostasis between:

- Histiocytosis
- CMML (heterogenous myelodysplastic/myeloproliferative overlapping disease with MAP-kinase involvment)[1]
- Essential thrombocytopenia (homogenous restricted myeloproliferative neoplasm)
- Giant cell arteritis (T-cell mediated vasculitis)
- Healthy donors

1: Sevin M: *Blood* 2021

Secondary Outcomes

- **Intrinsic factors:**
  - Type of histiocytosis
  - Mutational status
  - Association with CHIP
  - Association with myeloid neoplasm
  - Targeted therapies exposure
- **Environmental factors**
  - Systemic inflammation
  - VEGF-A production
  - Lipid abnormalities

Modulate monocyte homeostasis?

Materials and Methods

- **Histiocytosis**

From 2020-2021

Histology reviewed by Jean-Francois Emile

Full NGS in tissue biopsy for $BRAF^{WT}$ patients

Bone marrow analysis for CHIP

Complete biological test

- **Control group**

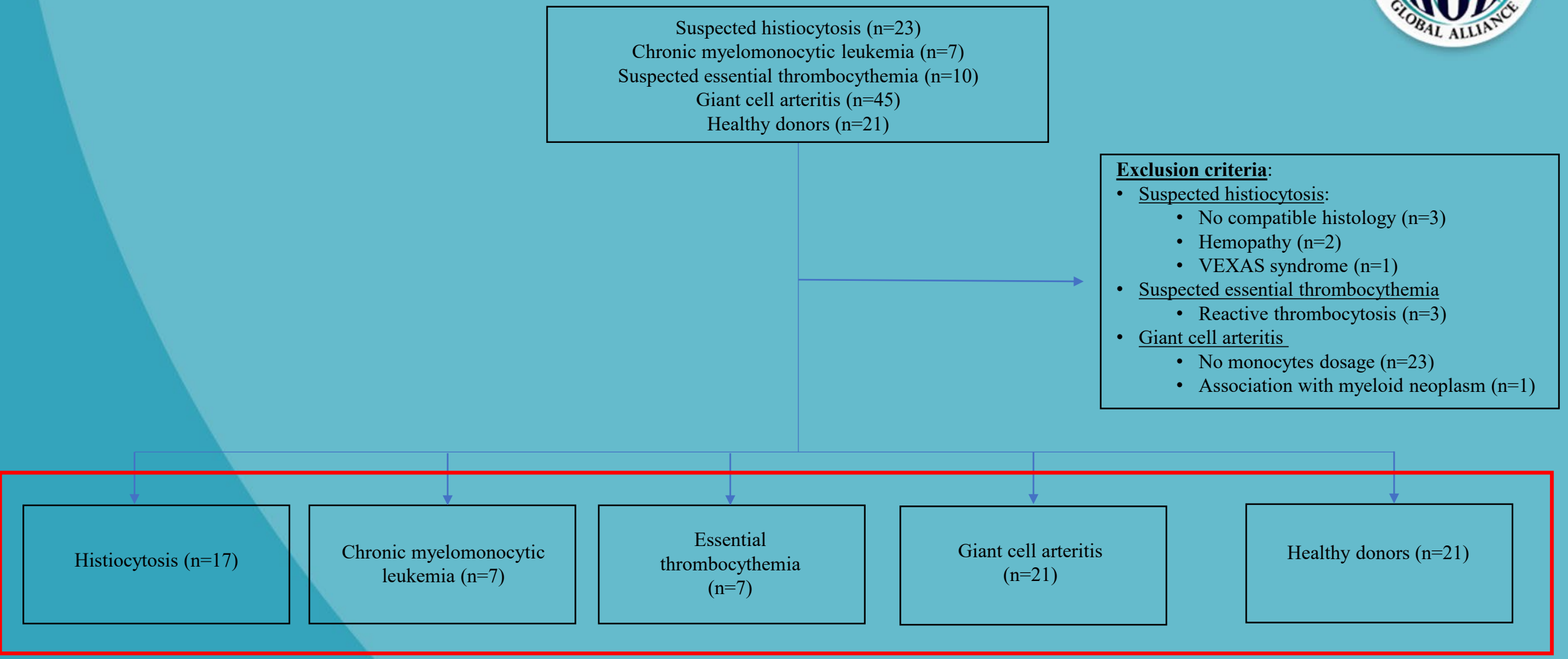
Historical cohort of CMML

Prospective cohort of ET

Center cohort of GCA with monocytes phenotyping

Volunteers healthy donors.

Flow chart of study design



Results

- 17 histiocytosis:
  - 8 Erdheim-Chester Disease (5/8 *BRAF*^{V600E})
  - 5 Langerhans Cell Histiocytosis (2/5 *BRAF*^{V600E})
  - 4 Rosai-Dorfman Disease (2/4 *MAP2K1* mutation)
  - 3 concomitant myeloid neoplasm (1 CMML, 2 ET in ECD patients)
  - 6 concomitant CHIP (4 ECD, 1 RDD, 1 LCH)
- 7 CMML
- 7 ET
- 21 Giant cell arteritis from whom 7 had aortitis
- 21 Healthy donors

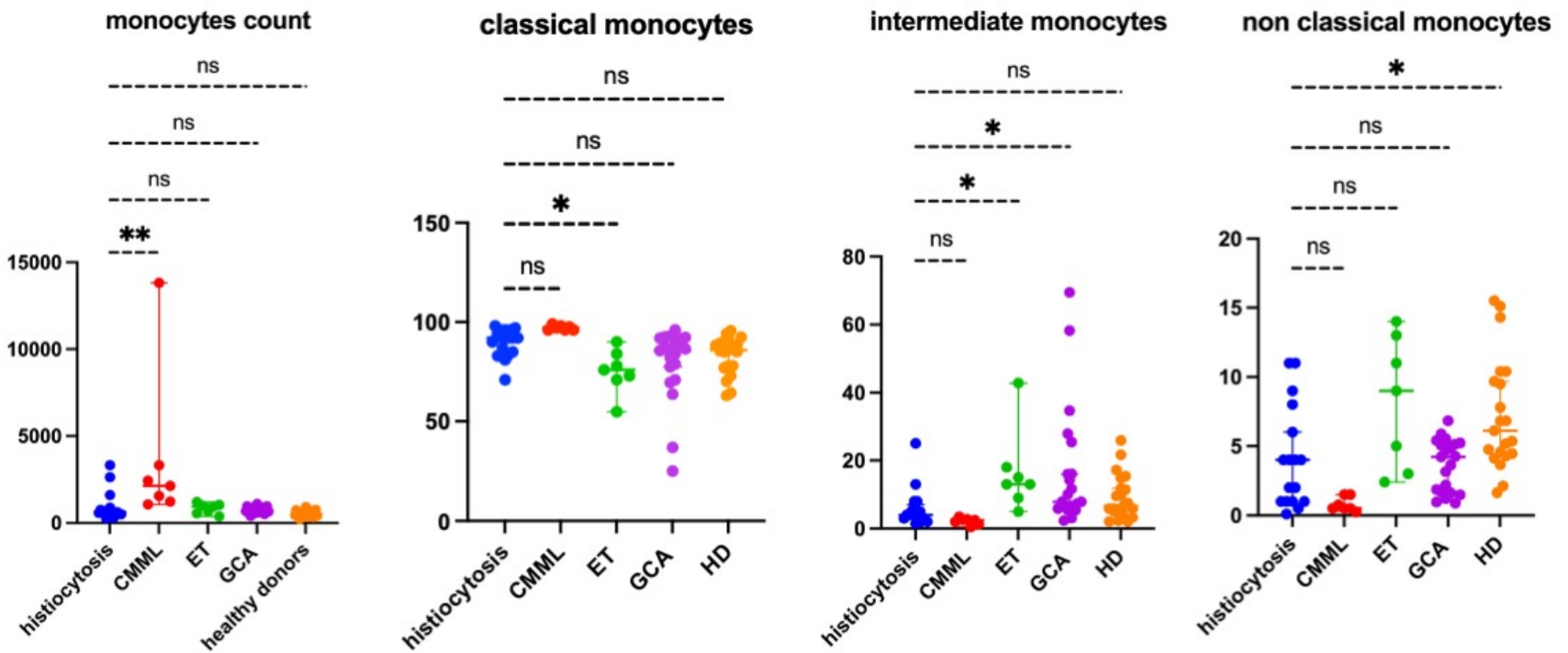
Patient Characteristics

Case	Age at diagnosis	Age at dosage	Type of histiocytosis	Localization of histiocytosis	Tissue disclosing histiocytic infiltration	Mutational status	Myeloid neoplasm	CHIP	Bone marrow mutation	Prior therapy	Therapy at dosage time	% of PBMC	Classical monocytes	Transitional monocytes	Non-classical monocytes	Disease activity
#1	71	71	ECD	mesentery, bone, CNS, peri-renal, heart	mesentery, perinephric fat	BRAF, KRAS, TET2	CMML	0	TET2,ZRS2,KRAS NRA,/BRAF	BRAF-inhibitor	IL-1 blockers	26%	96%	3%	1%	Partial metabolic response
#2	68	72	ECD	mesentery, bone, CNS, peri-renal, heart, bone marrow	mesentery, perinephric fat	BRAF	CMML	0	TET2,SRSF2 CLB,NRAS	BRAF-inhibitor	None	25%	96%	2%	2%	Partial metabolic response
#3	71	73	ECD	heart, bones, vessels, mesentery, peri-renal	mesentery, perinephric fat	BRAF	ET	0	JAK2,TET2 NF1	None	MEK-inhibitor	3%	96%	3%	1%	Partial metabolic response
#4	24	25	ECD	vessels, bone, sinus	vessels	No mutation	0	0	none		IL-1 blockers	7%	92%	7%	1%	Progressive metabolic disease
#5	72	77	ECD	bone, lung , skin, vessels	skin/bone	BRAF	0	1	KRAS,SH2B3 SRSF2,TET2	BRAF-inhibitor	BRAF inhibitor	33%	94%	5%	1%	Partial metabolic response
#6	64	66	ECD	bone, peri-renal, mesentery	mesentery	No mutation	0	1	TET2	MEK-inhibitor	MEK-inhibitor	3.8%	81%	8%	11%	stable metabolic disease
#7	81	81	ECD	bone, heart, vessel, CNS, peri-renal	perinephric fat	BRAF	0	1	ASXL1,NF1 TET2,U2AF1	Interferon	Interferon	4.9%	92%	4%	4%	Progressive metabolic disease
#8	58	63	ECD	bone, mesentery, peri-renal	mesentery	No mutation	0	1	DNMT3A	Interferon, IL-1 blockers, TNF-alpha inhibitor, MEK-inhibitor	MEK-inhibitor	8%	71%	24%	4%	stable metabolic disease
#9	69	71	RDD	perirenal	perinephric fat	MAP2K1	0	1	TET2,ASXL1 DNMT3A,JAK2	Rituximab	steroids	7%	83%	5%	11%	Complete metabolic response
#10	39	41	RDD	skin, bone, eyes,	skin	MAP2K1	0	0	none	steroids	None	6.3%	97%	2%	1%	Complete metabolic response
#11	67	67	RDD	bone	bone	No mutation	0	0	none	steroids	None	12%	92%	4%	4%	Partial metabolic response
#12	62	65	RDD	skin, lymph node	lymph node	No mutation	0	0	none	None	None	7.4%	87%	5%	8%	Complete metabolic response
#13	61	64	LCH	liver, endocrine, bone, skin	liver, skin	BRAF, DNMT3A	0	0	none	Vinblastine/steroids	Vinblastine	9%	85%	13%	2%	Progressive metabolic disease
#14	12	22	LCH	bone, skin, endocrine, lung	bone, skin	No mutation	0	0	none	Vinblastine/steroids	None	9%	98%	1.5%	0.5%	Partial metabolic response
#15		68	LCH	Lung, bones	lung	No mutation	0	1	ASXL1	None	None	5.5%	92%	4%	4%	Progressive metabolic disease
#16	18	44	LCH	lung, hypophysis, bones	bone	No mutation	0	0	none	None	None	8.4%	83%	8%	9%	Complete metabolic response
#17	59	63	LCH	Lung, bones, pituitary gland	bone	BRAF	0	0	none	none	None	8.3%	90%	4%	6%	Progressive metabolic disease

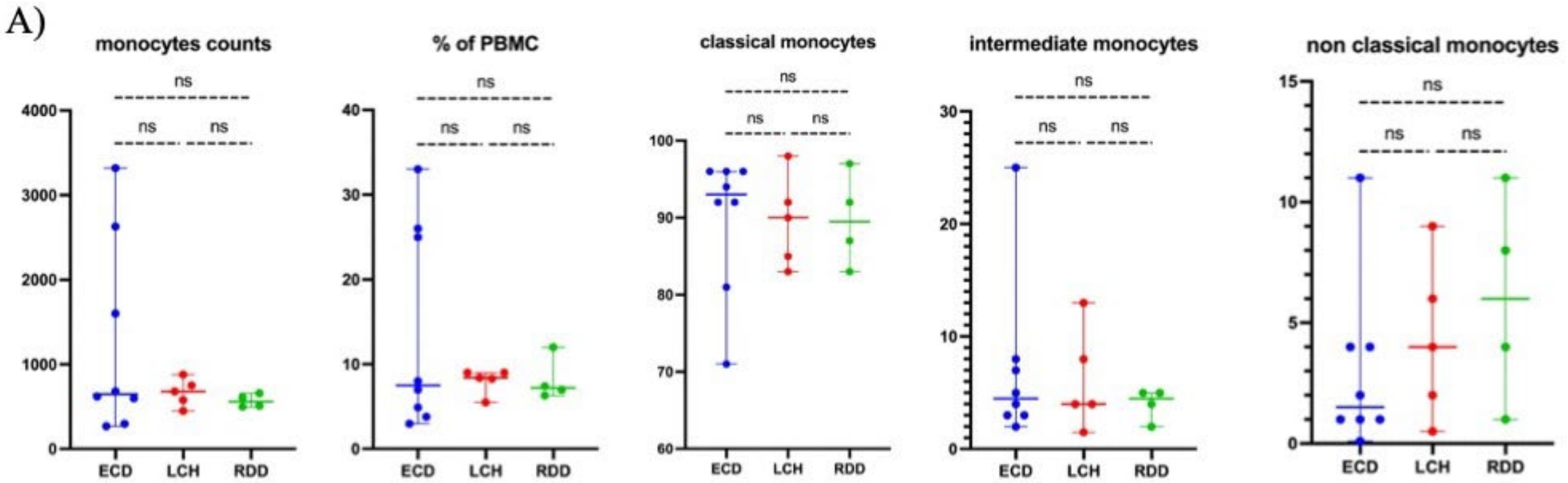
Patient Characteristics

	Histiocytosis (n=17)	Chronic myelomonocytic leukemia (n=7)	Essential thrombocytopenia (n=7)	Giant cell arteritis (n=21)	Healthy donors (n=21)	P value
Age at blood sampling (years), median [IQR]	66 [53-71]*'	80 [76-84]	82 [77-87]	76 [66-81]	73[57-82]	**0.0032**
Sex M/F	10/7	4/3	2/5	7/14	9/12	0.4605
Type of histiocytosis, n (%)						
ECD	8 (47)					
LCH	5 (30)					
RDD	4 (23)					
Hb (g/dL), median [range]	13.0 [11.5-14.70] '+	10.4 [9.0-12.1]	9.2 [9.0-14.30]	11.0 [10.2-12.05]	13.6 [12.65-14.45]	<0.0001
White count cell (/mm³)	8100 [5800-9020]	6800 [5000-9900]	9500 [7700-14400]	9600 [6600-11050]	5600 [4700-6800]	0.0010
Neutrophils (/mm³)	4720 [3700-6305]	2990 [2100-4030]	7040 [5240-9900]	6780 [4665-8255]	3240 [2735-4180]	<0.0001
Lymphocytes (/mm³)	1610 [1150-2230]	1800 [850-2270]	1780 [1060-2860]	1570 [1225-1710]	1620 [1090-2175]	0.8910
Total monocytes (/mm³)	615 [345.5] '	2130 [2090]	940 [490]	707 [260]	490 [255]	<0.0001
Platelet count (G/L)	224 [175-362] *	88 [37-150]	478 [423-1206]	NA	NA	0.0003
CRP (mg/L)	4.0 [2.150-13.10] *+	NA	49.1 [12.7-130]	75.70 [46-99.5]	2.9 [2.9-2.9]	<0.0001
Triglycerides (g/L)	1.505 [0.76-2.14]*	NA	0.51[0.365-0.995]	NA	NA	0.0147

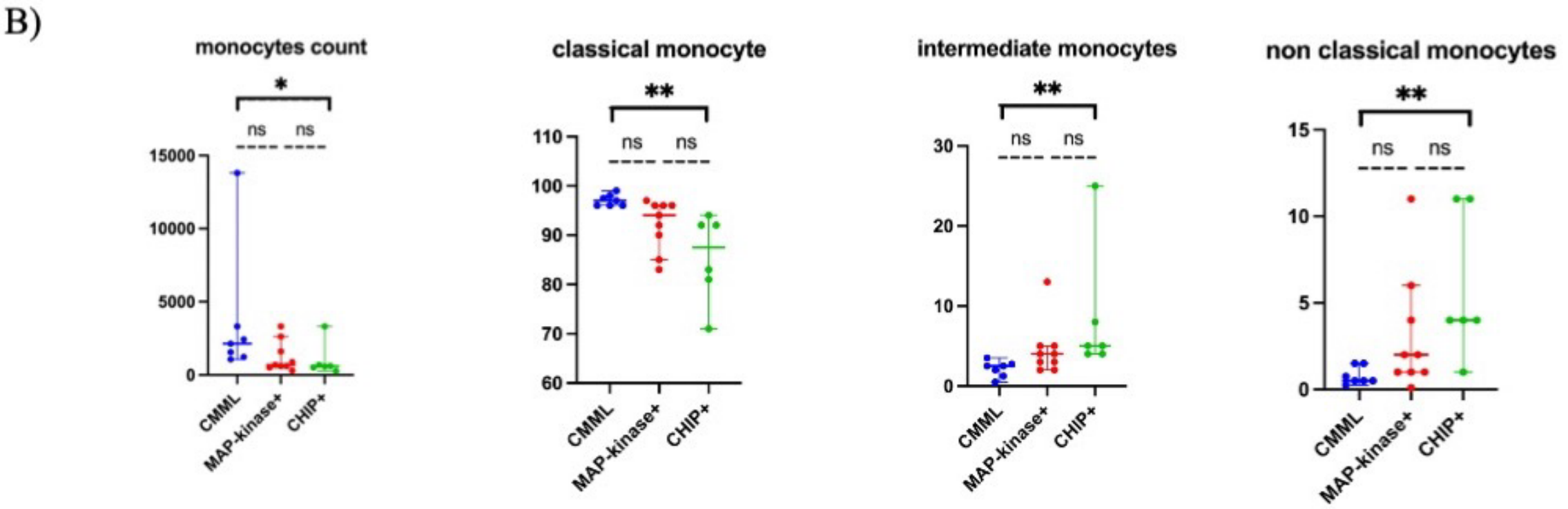
Monocyte distribution in histiocytosis is close to CMML



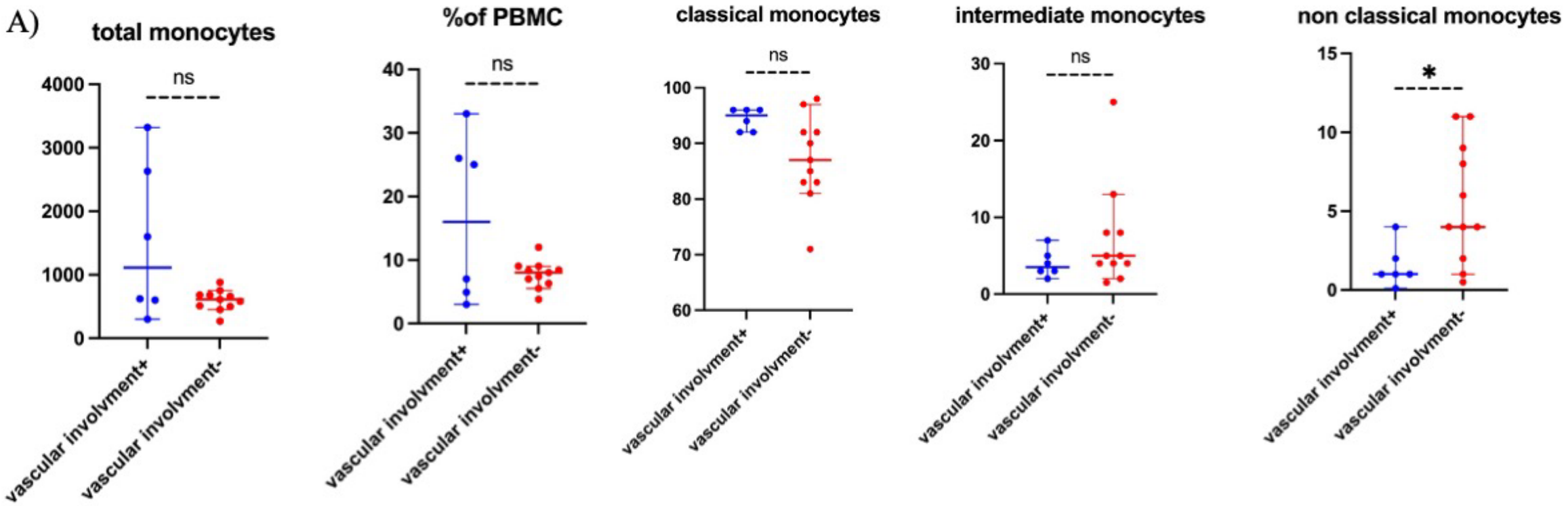
Monocyte distribution is similar in the different histiocytosis



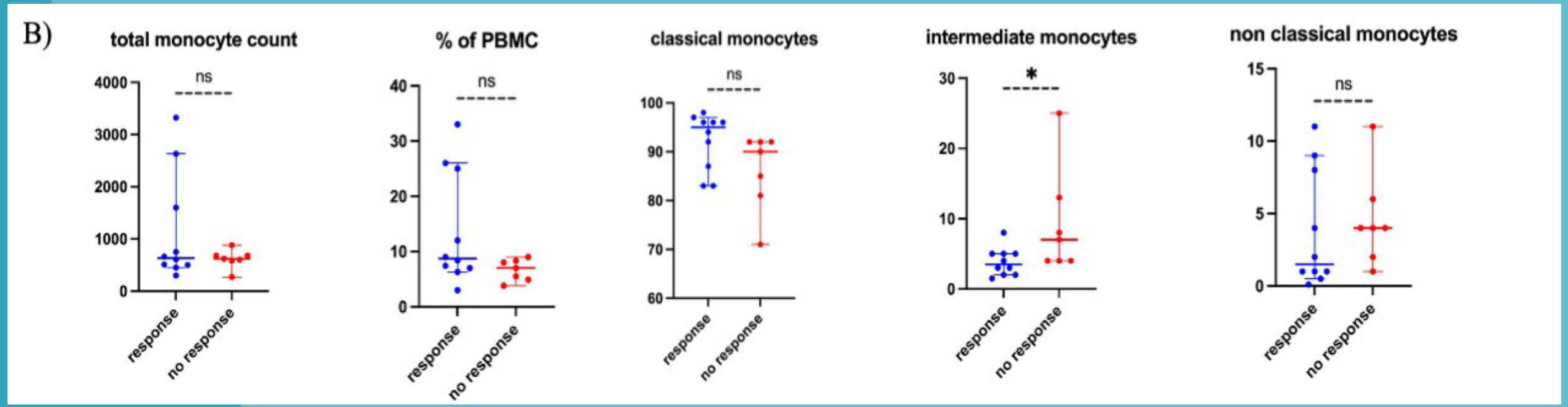
MAP-kinase mutated histiocytosis are close to CMML



Decrease of “non-classical” monocytes correlates with vascular involvment



Decrease of “intermediate” monocyte is correlated with metabolic response



Results

- Logistic linear regression model:
  - Type of histiocytosis
  - Hemoglobin
  - White count cell
  - Neutrophile count
  - Lymphocyte count
  - C reactive protein level
  - VEGF-A
  - Cholesterol/ LDL/HDL/ triglyceride

NO INFLUENCE ON MONOCYTE HOMEOSTASIS

Discussion

- Limits of the study:

- Small cohort for LCH and RDD patients
- Analysis on circulating cells without correlation with bone marrow niche
- No transcriptomic analysis
- No group of naïve vs treated patients

Discussion

Majors strengths

- Comparison of monocyte homeostasis between histiocytic disorders with both homogenous and heterogenous myeloproliferative neoplasm
- Comparison with T-cell mediated vasculitis

- Bone marrow analysis for NGS

- Review of biopsy specimen for reported MAP-kinase pathway mutations

Unanswered questions and furthers directions

- Evaluation of monocyte subset distribution as a marker of disease activity?
- Modulation of monocytes homeostasis with BRAF/MEK inhibitors?
- Deep functional analysis of monocytes in histiocytic disorders
- The absence of influence of “intrinsic” or ”extrinsic” factors question the role of trained immunity not only in ECD but all histiocytic disorders?

Conclusion

- Monocyte subset distribution is homogenous in histiocytosis
- It's close to CMML
- Different from ET and GCA
- Useful to assess vascular phenotype
- It can be a surrogate marker of disease activity

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