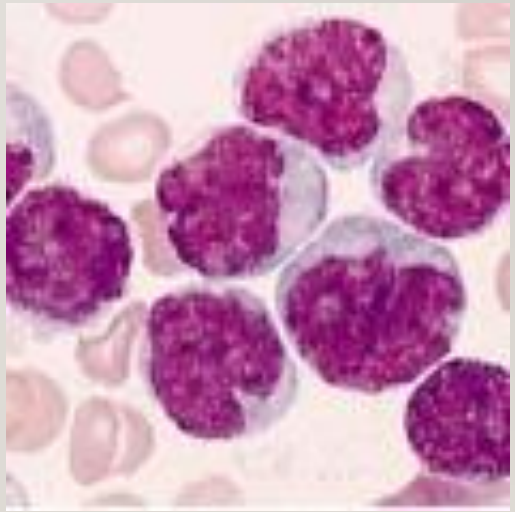
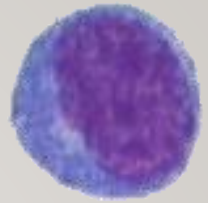
BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASMS: BPDCN

KEYNOTE
ACS2024 – HOBART
October 21, 2024



Pr. Marie Christine Béné - Nantes University, Paris

PLASMACYTOID CELLS



- A few words of history
  - Lennert and Remmele, 1958 (Acta Haematologica, Basel)
    - Tissue sections ➔ plasma cell-like morphology
    - Abundant in T-cell zones of lymphoid tissues

      « T associated plasma cells » or

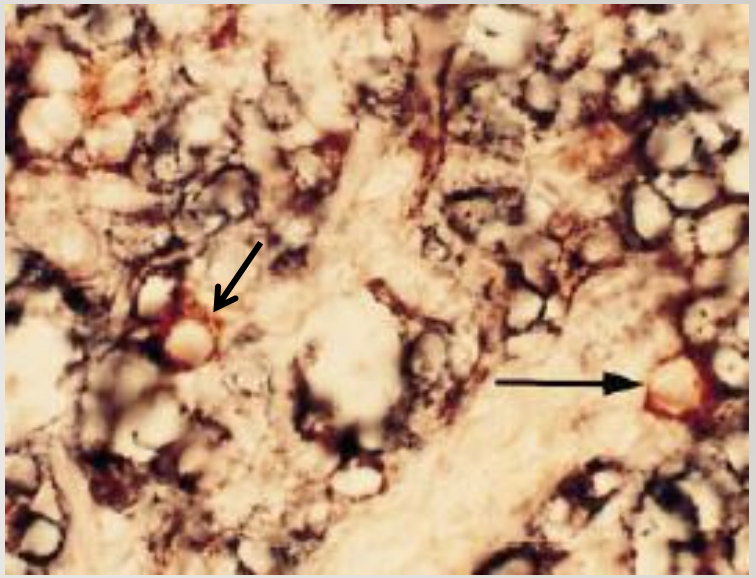
      « Plasmacytoid T cells »

  - Facchetti et al., 1988 (Am J Pathol): immunophenotypic characterization

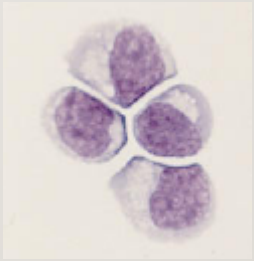
    CD4+, CD31+, CD36+, CD68+

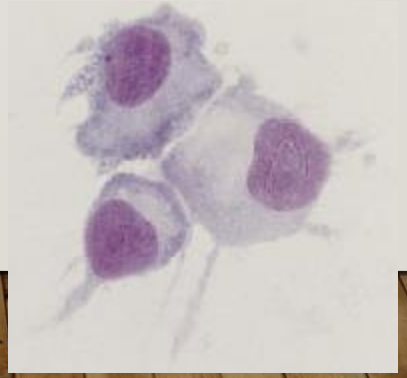
    lin-

PLASMACYTOID CELLS
CD3-CD11C-CD4+

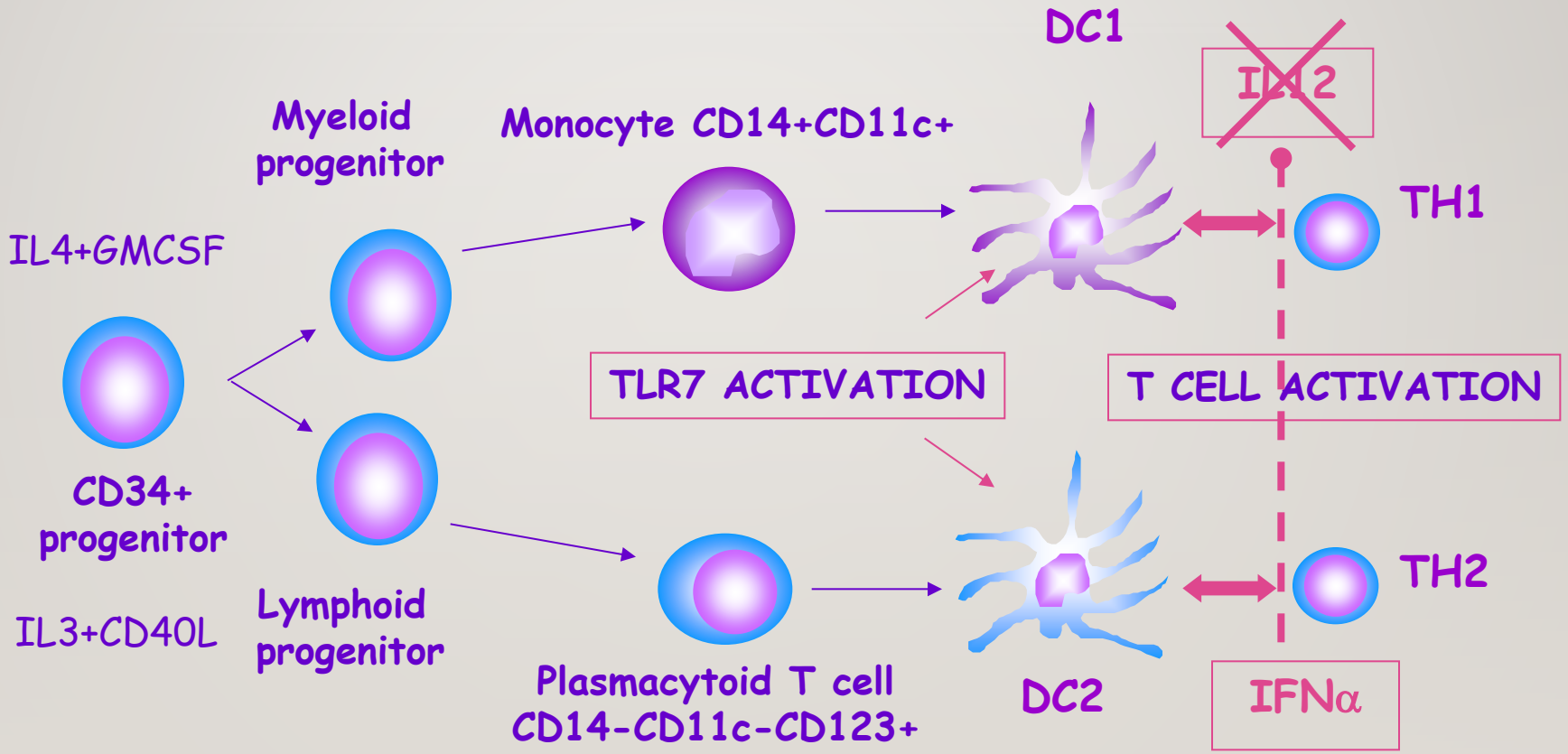


- Grouard et al. 1997
  (J exp Med)
  - Immunohistological localization in tonsils near HEV
  - Isolation
  - Demonstration of IL-3 dependency and differenciation in DC



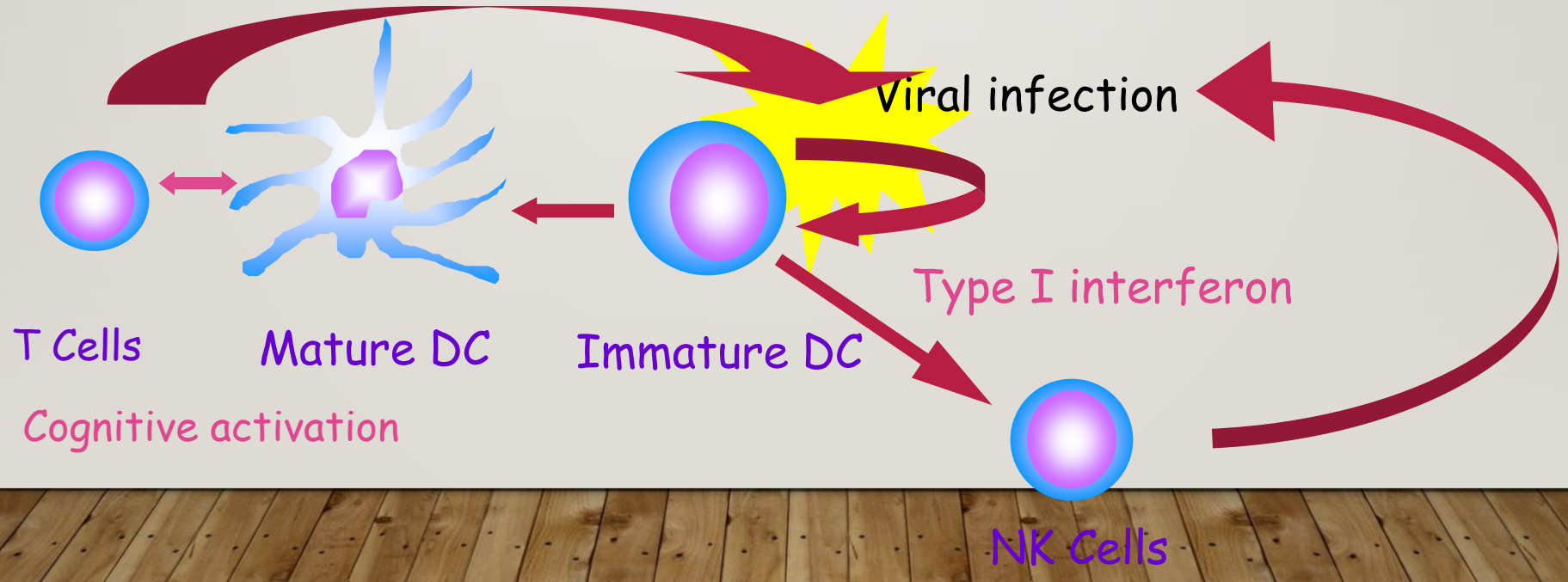


DENDRITIC CELLS



OTHER CHARACTERISTICS OF DC2 LYMPHOPLASMACYTOID DENDRITIC CELLS

- Sensitive to HIV
- Expand upon Flt3 injection or culture
- Could link innate and cognate immunity



PLASMACYTOID DENDRITIC CELLS

+

subsets

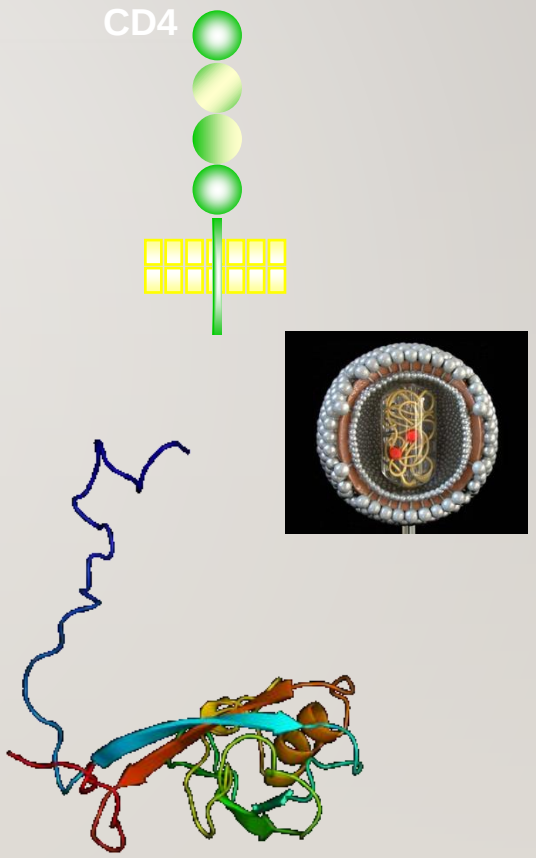
- Immunophenotypic features : not just CD4/CD56

(from Galibert et al., 2001, Sem Immunol)

CD1	CD11a	CD68	CD23	CD40	CD123
CD2	CD11b	CD71	CD28	CD80	CD125
CD3	CD11c	CD32	CD30	CD83	
CD4	CD13	CD36	CD16	CD86	
CD5	CD33	CD38	CD56		
CD7	CD14	CD44	CD57	DR	
CD8	CD15	CD49e	CD94	CD45RA	
CD10	CD65	FceRI			

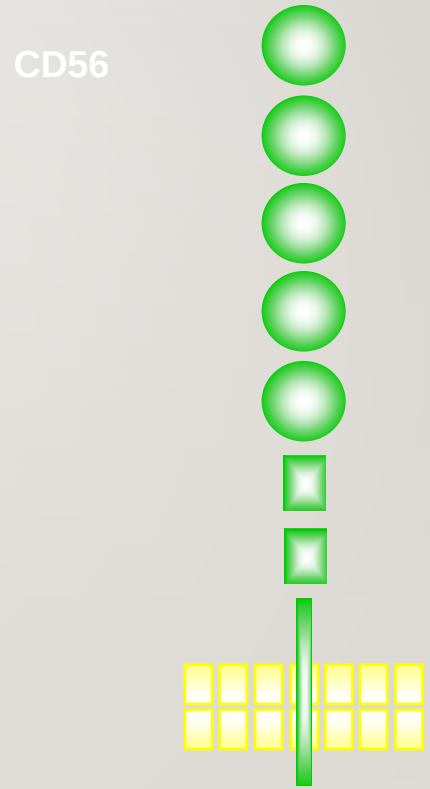
WHY CD4?

- Ig superfamily molecule
- T-cell marker defining T-helper cells
- Also present on monocytes and dendritic cells
- Binds to the constant part of MHC Class II in the immunological synapse
- Signal transduction through $p56^{lck}$
- HIV-receptor together with CXCR4 or CCR5
- Co-receptor of the chemokine IL-16
- IL-16 produced by epithelial cells

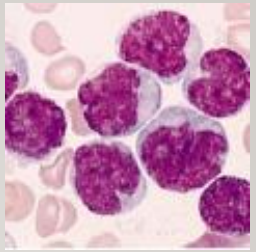


WHY CD56?

- Ig superfamily molecule
- Allso known as N-CAM « neural cell adhesion molecule »
- Homophilic and heterophilic bonds
- Neurite extension and guidance
- Modulated by polysialylation
- Cerebellum, muscle-nerve junctions
- Small cell lung carcinoma
- NK cells
- pDC
- Adhesion?
- Interaction with NK cells?

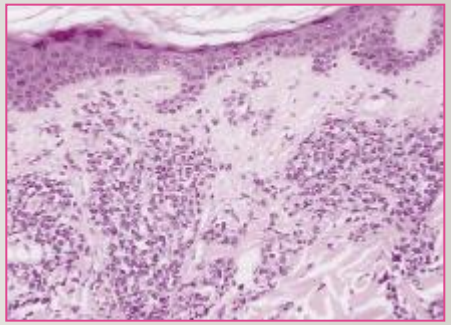


PLASMACYTOID MALIGNANCIES



- Facchetti et al. 1988 (J Pathol): *Plasmacytoid T cells in a case of lymphocytic infiltration of the skin.*
- Plasmacytoid T cell leukemia or lymphoma in 1990
  - Rare disease
  - Elderly men
  - Generalized lymphadenopathy
  - Accumulation of PC like cells in the bone marrow, spleen or lymph nodes
  - Later develop acute or chronic myelomonoctytic leukemia that may carry the same chromosomal abnormality as the initial clone
  - Exctinct entity

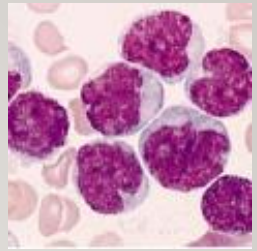
THE CD4+CD56+ ENTITY



1994	Hayashi	1 pt	gastrointestinal involvement	
1996	Dummer	1 pt	skin lesions	
1997	Drenou	1 pt	inguinal mass	BM++
1998	Bagot	1 pt	skin nodules	BM later
1998	Uchiyama	1 pt	angiocentric infiltrates	
1999	Kameoka	2 pts	skin nodules	BM++
1999	Petrella	7pts	skin nodules	BM 1 then 6 pts
2000	Ginarte	1 pt	skin lesions	
2000	Nagatani	4 pts	skin lesions	BM later
2001	Hofbauer	1 pt	skin nodules	BM
2001	Kato	1 pt	skin nodules	BM, nasopharynx, LN
2001	Kimura	1 pt	skin lesions	BM, LN
2002	Feuillard	23 pts	skin lesions	BM++

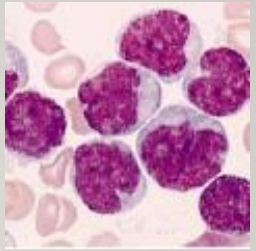
2002	Bayerl	5 pts	skin lesions		BM
2002	Chang	15 pts	skin lesions		
2002	Petrella	7 pts	skin tumors		
2004	Hallerman	1 pt	skin tumor		
2004	Machet	2 pts	skin tumors		
2005	Kim	4 pts	skin lesions		
2006	Ng	5 pts	skin lesions		BM
2006	Martin	2 pts	skin lesions		BM
2007	Pilichowka	3 pts	skin lesions		
2008	Shiman	1 pt	skin lesion		
2009	Mulijono	1 child	skin lesion		
2009	An	2 pts	skin		BM
2009	Kaune	1 pt	skin lesion		BM
2009	Löffler	1 pt	skin lesions		BM
2010	Lopez	1 pt	skin tumor		
2010	Dalle	47 pts	skin lesions		BM, LN Allo SCT
2010	Tsagarakis	22 pts	skin involvement		BM
2010	Cota	33 pts	variability of skin lesions		
2010	Prystupa	1 pt	skin lesions		BM
2010	Hwuang	1 pt	skin lesion		BM, LN
2010	Chang	1 pt	skin lesions (lupus)		BM, LN
2010	Xue	1 pt	skin tumors		BM
2010	Su	1 pt	skin lesions		BM
2011	Matsuo	1 pt	conjunctiva		
2011	Inoue	1 pt	orbital cavity		BM
2011	Hashikawa	26 pts	skin lesions	←	BM
2011	Rauh	3 pts	no skin involvement	←	BM
……. And more					

FROM PLASMACYTOID TO DC MALIGNANCIES



- Chaperot et al., 2001 (Blood)
  - Hypothesis :
    - CD4+CD56+ are the malignant counterpart of plasmacytoid dendritic cells
    - They are of lymphoid origin
  - Methods
    - 7 patients with bone marrow infiltration
    - Cytokine dependence for viability
    - Differentiation into DC
    - IL-3Rα, FasL, pre-Tα, perforin, CD56 mRNA
    - Functional capacities

CHARACTERISTICS OF CD4+CD56+ PDC LEUKEMIA



- Feuillard et al, 2002 (Blood)
- Multicentric collection of cases ➔ 23 patients
- Immunophenotypic definition criteria
  - coexpression of CD4 and CD56
  - absence of CD13, CD33, CD3, CD5, pan-B markers
- Clinical features, extensive immunophenotyping, treatment, outcome

BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM

- WHO 2008 included in acute leukemia section
- WHO 2016 quoted after acute myeloid leukemia
- WHO 2022:
  - ” Plasmacytoid dendritic cell neoplasms: recognition of clonal proliferations detected in association with myeloid neoplasms”
  - Refinement/update of the diagnostic criteria for blastic plasmacytoid dendritic cell neoplasm »: norion of MDCP
  - BPDCN unchanged

5TH WHO 2022 CRITERIA FOR BPDCN IMMUNOPHENOTYPE. IN MYELOID TUMORS

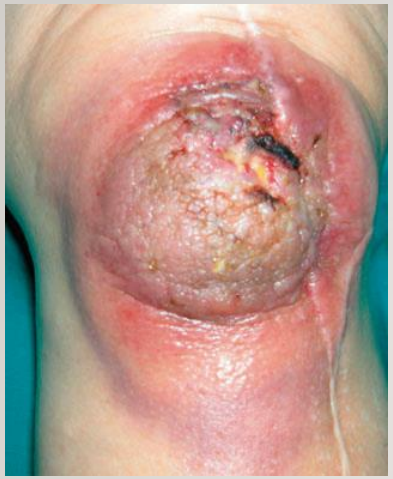
- Expected positive expression:
- CD123*
- TCF4*
- TCL1*
- CD303 *
- CD304*
- CD4
- CD56

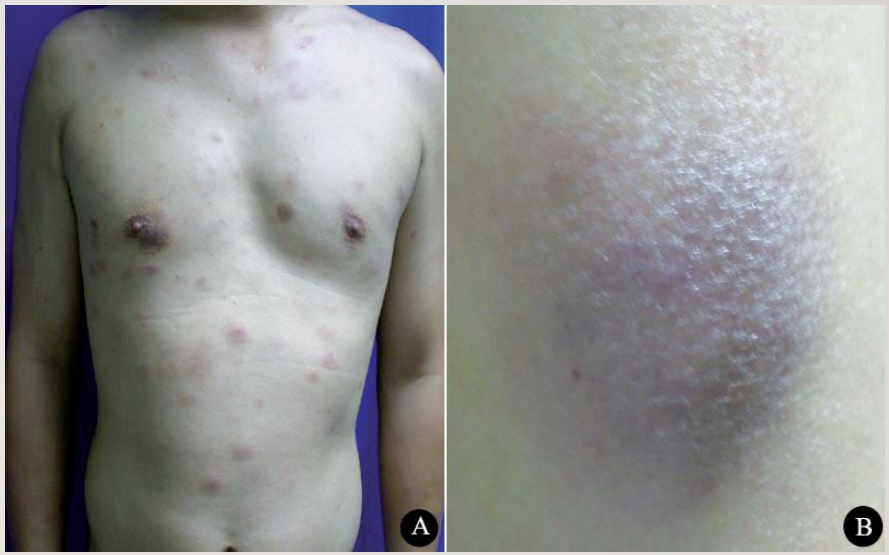
- Expected negative expression:
- CD3
- CD14
- CD19
- CD34
- Lysozyme
- Myeloperoxidase

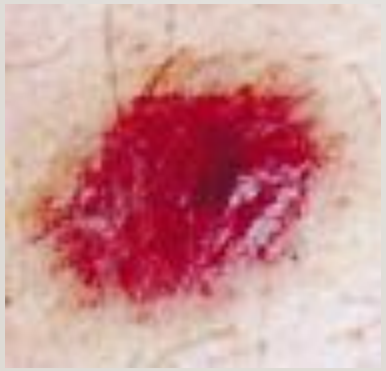
Immunophenotypic diagnostic criteria:
-Expression of CD123 and one other pDC marker (*) in addition to CD4 and/or CD56.
or,
-Expression of any three pDC markers (*) and absent expression of all expected negative markers.

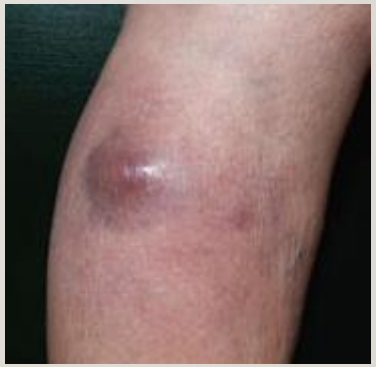
SKIN

PLEIOMORPHIC SKIN LESIONS

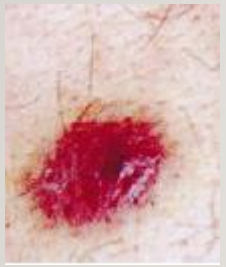


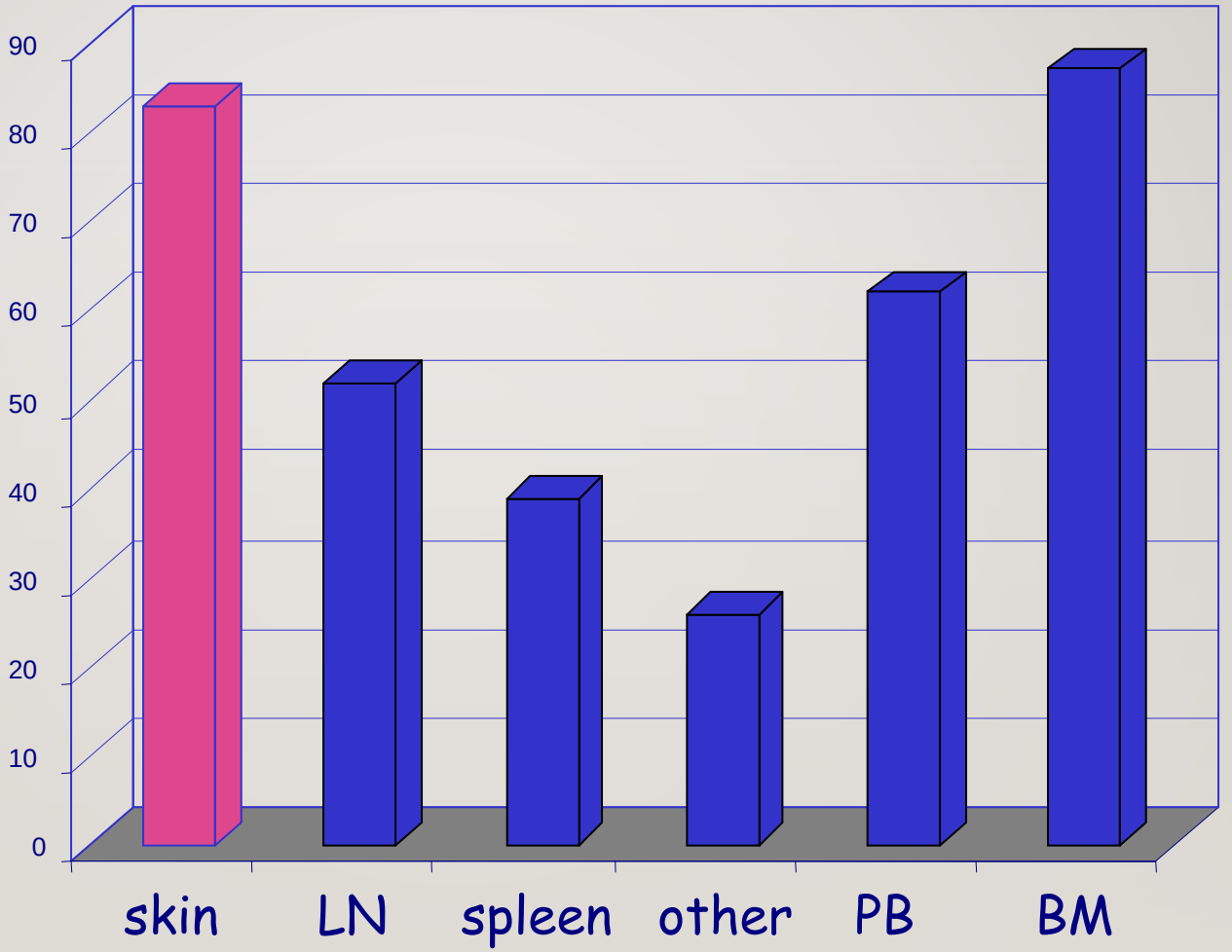




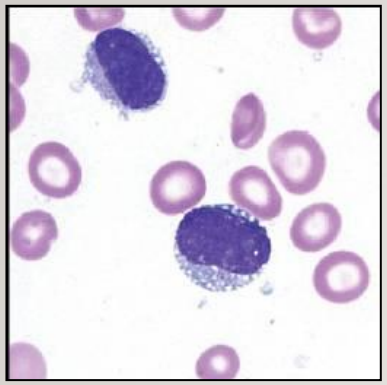


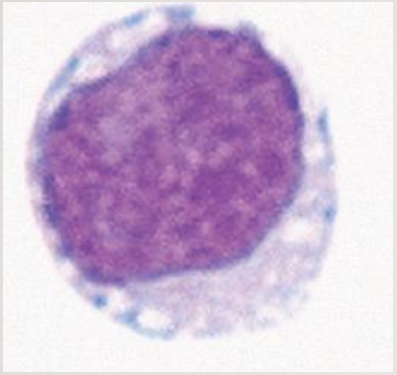
PDC LEUKEMIA :TUMORAL SYNDROME

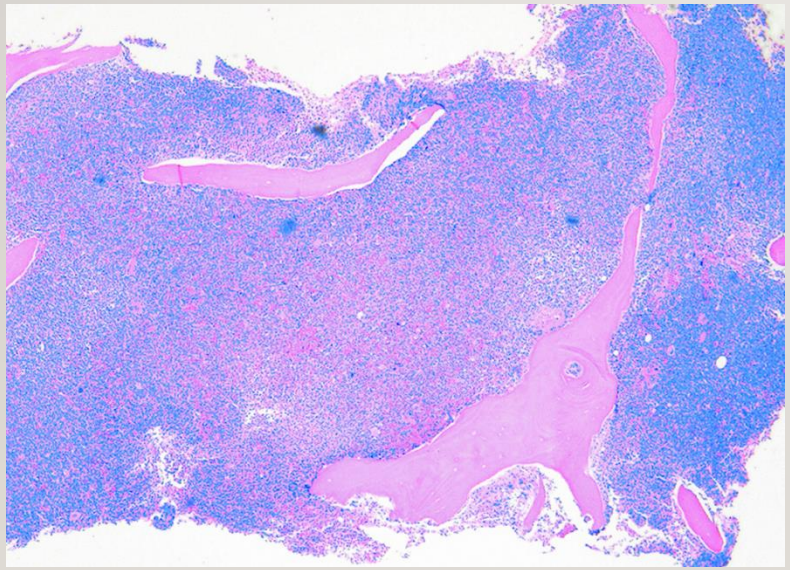


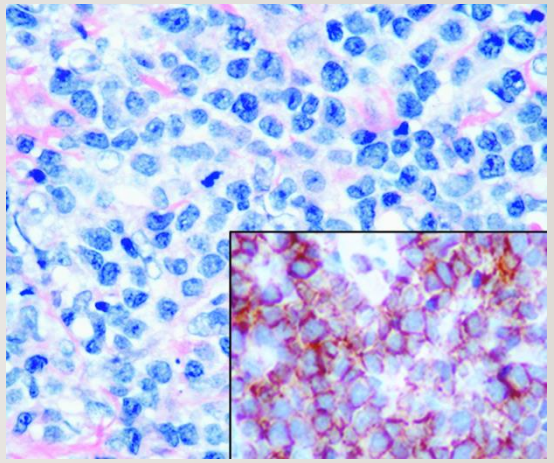


CELL CHARACTERISTICS

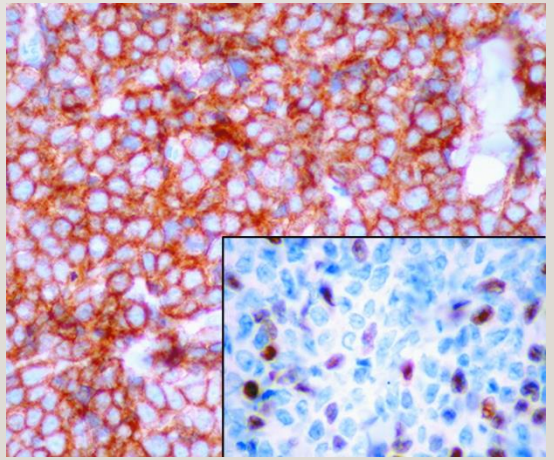








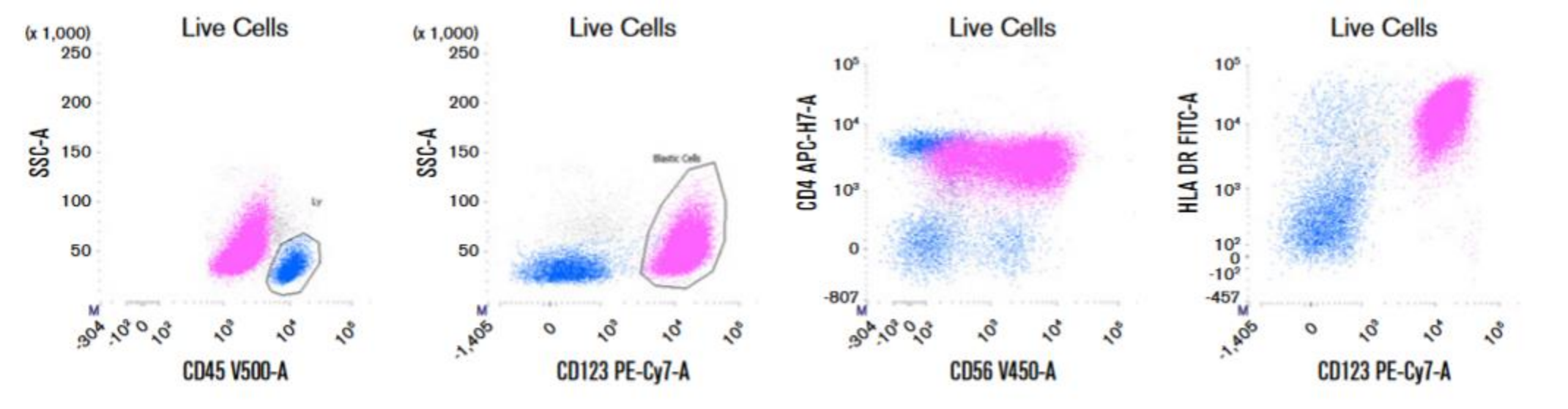
CD56



CD4

TdT

IMMUNOPHENOTYPE



Garnache Ottou, Blood Advances 2019

SYSTEMATIC REVIEW OF CASES PRESENTED IN PUBLICATIONS (PUBMED 1965-2016 AND OTHER DATABASES)

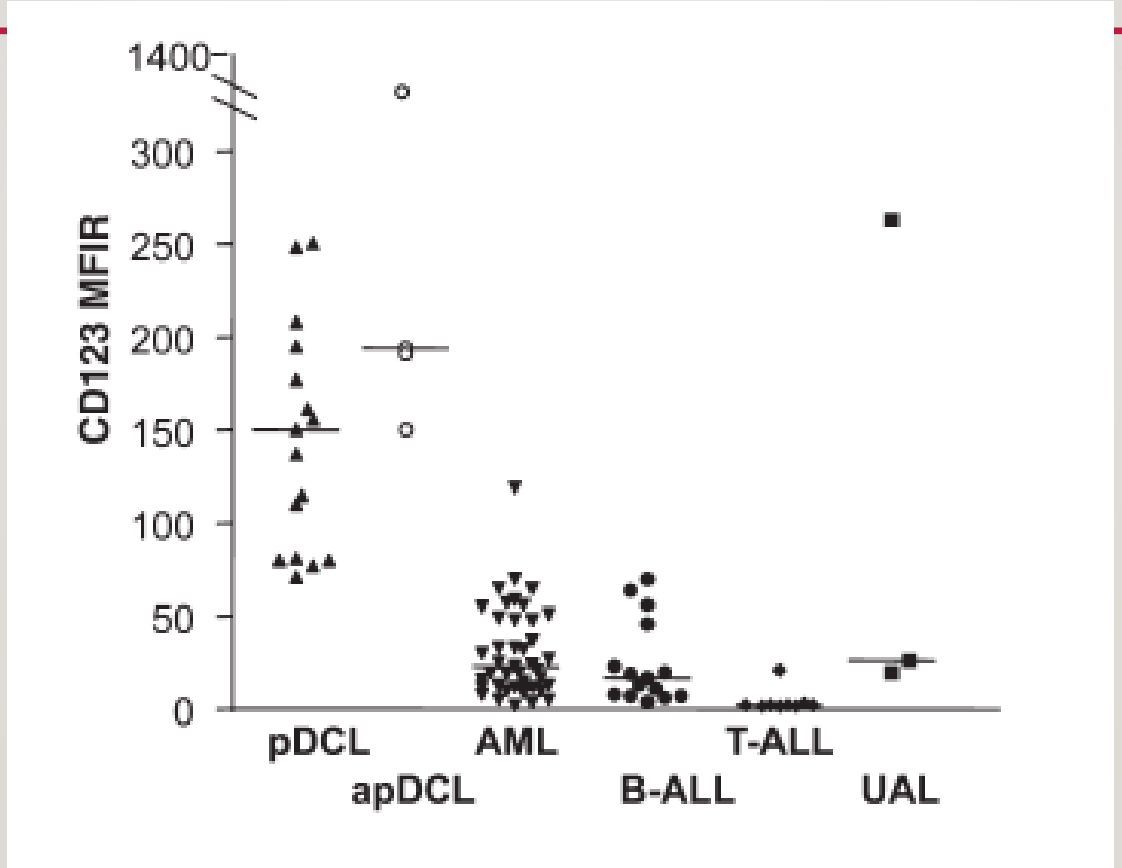
- 357 cases
- 74 pediatric, 283 adults
- M:F 41:33 (1.3) for children, 209:74 (2.8) for adults ($p<0.01$)
- Bone marrow affected in 66% of cases, blood 40%
- CNS in 17 of 38 children, for adults usually not reported
- Lymph nodes 47%, spleen 27%

Kim et al. 2017 J Pediatr Hematol oncol

REVISED IMMUNOPHENOTYPIC CRITERIA GARNACHE OTTOU *ET AL.*, 2010, BJH

- 16 typical BPDCN, 4 atypical
- 113 acute leukemias
  - 79 AML, 12 T-ALL, 19 BCP-ALL
  - 5 cases with CD4+/CD56+ expression
    - Associated to cCD79, cCD22 and CD19 in a BCP-ALL
    - Associated to myeloid antigens (MPO, CD11c, CD13, CD33) in 4 AML

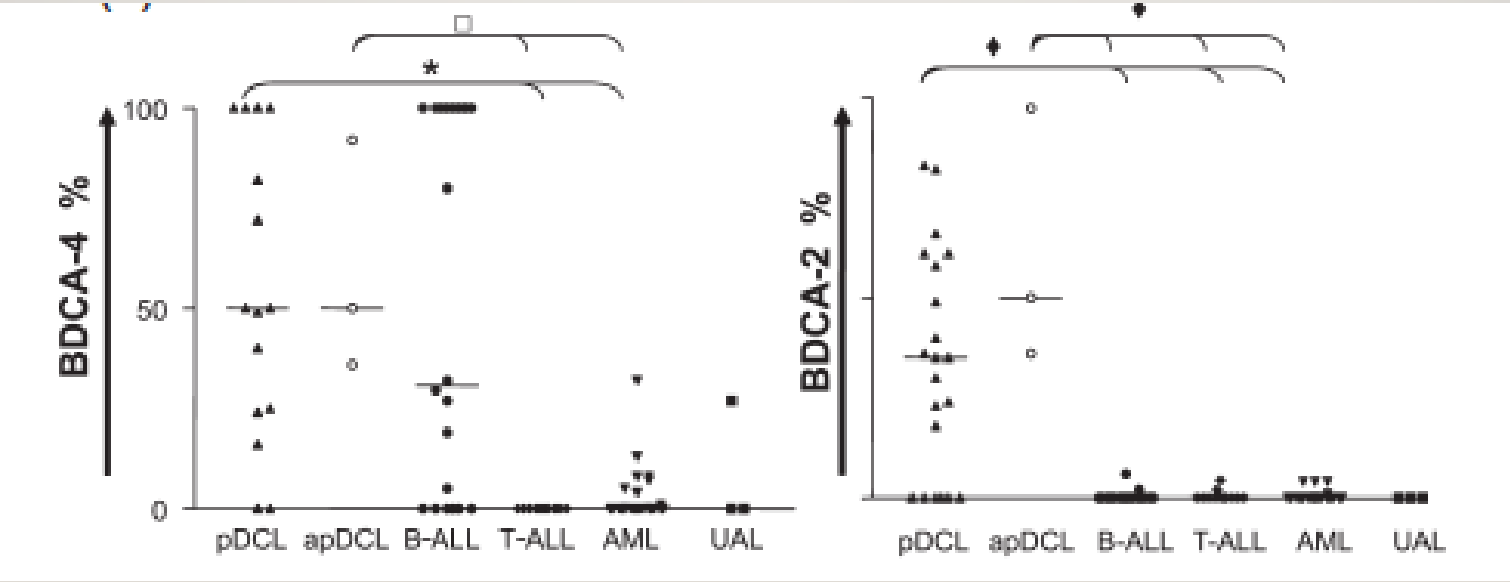
SPECIFICITY OF CD123



Garnache Ottou *et al.*, 2010, BJH

BDCA-2 BDCA- 4
BLOOD DENDRITIC CELL ANTIGENS

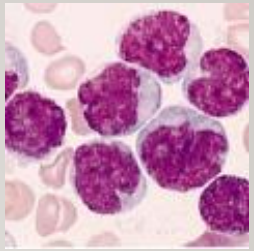
- BDCA-2, CD303, type C lectin
- BDCA-4, neuropilin



Garnache Ottou *et al.*, 2010, BJH

TREATMENT

BPDCN
TREATMENT AND OUTCOME
FEUILLARD *ET AL*, 2002

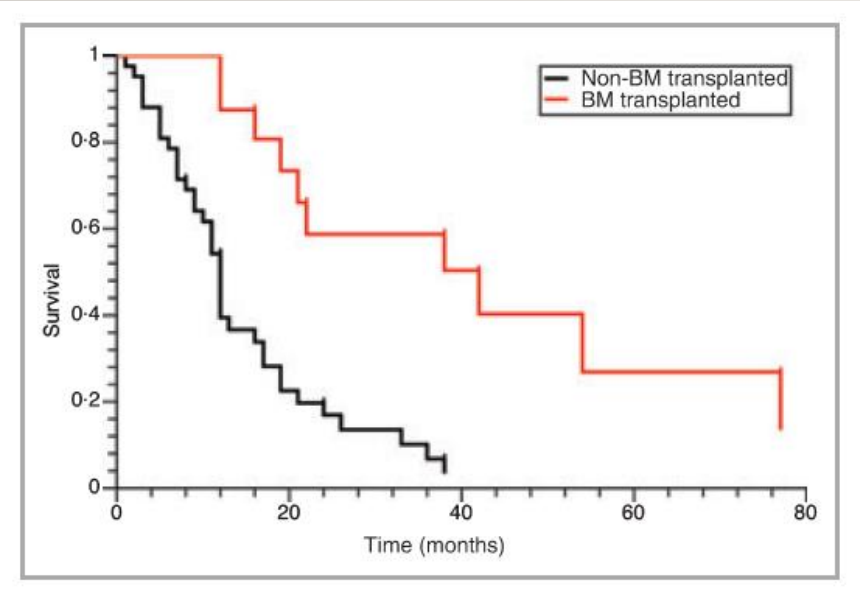


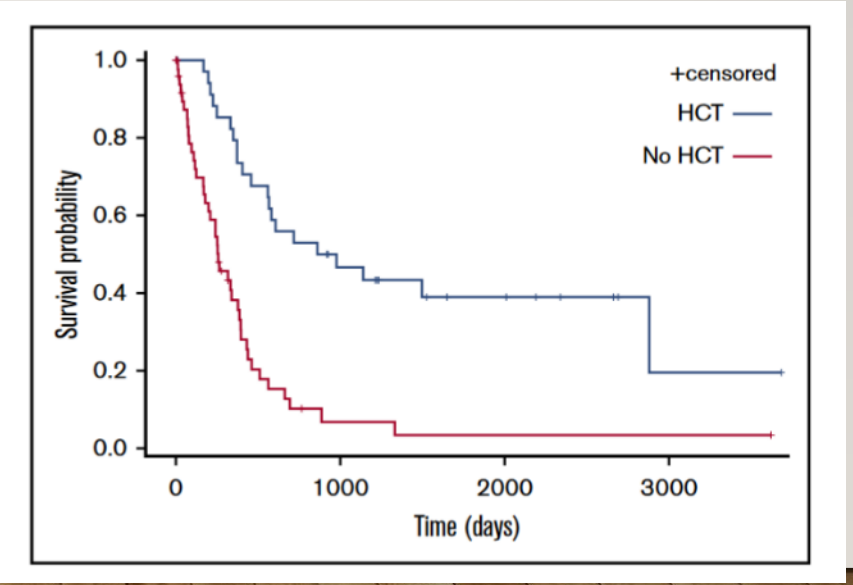
- CR rate : 86%
- Skin lesions reappear at relapse
- 83% of patients who achieved complete remission have had a relapse
- The median time of relapse was 9 months (range, 3-18 months).
- Five patients had a relapse in the CNS.
- Among patients treated by polychemotherapy, overall survival was 52% (10 of 19) after 1-year of follow-up and 25% (4of 16) after 24 months of follow-up.
- Among the 3 patients who benefited from allogeneic bone marrow transplantation, 2 were still in complete remission after 60 months of follow-up.

TREATMENT

DALLE ET AL, 2010 B J DERMATOL

- CR obtained in about 55% of cases
- Rapid relapse
- Allo SCT to be seriously considered





LEUKEMIC PRESENTATION OF BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM

Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: 10-Color flow cytometry diagnosis and HyperCVAD therapy

Uday Deotare,[1] Karen W.L. Yee,[1]* Lisa W. Le,[2] Anna Porwit,[3] Anne Tierens,[3] Rumina Musani,[3] David Barth,[3] Emina Torlakovic,[3] Aaron Schimmer,[1] Andre C. Schuh,[1] Matthew Seftel,[1,4] Mark D. Minden,[1] Vikas Gupta,[1] and Elizabeth Hyjek[3]*

American Journal of Hematology, Vol. 91, No. 3, March 2016

Of 9 pts 7 responded to HyperCVAD and 4 were alive in CR after HSCT

TABLE I. Patient Characteristics

Characteristic	All (n = 9)
Median age, y (range)	66 (25–91)
Age ≥ 70 y	4 (44%)
Gender	4 F: 5 M
Antecedent hematologic disorder	0 (0%)
Presence of B symptoms	4 (44%)
Duration of symptoms prior to diagnosis, mos, median (range)	5 (1–6)
Clinical features	
Skin lesions	8 (89%)
Lymphadenopathy	7 (78%)
Hepatomegaly	0 (0%)
Splenomegaly	2 (22%)
Central nervous system[a]	0 (0%)
Cytogenetic risk group (MRC 2010 AML stratification)	
Intermediate risk	3 (33%)
Adverse risk	2 (22%)
Unknown	4 (44%)
Baseline hemoglobin (g/L), median (range)	117 (86–147)
Baseline white blood cell count ($\times 10^9$/L), median (range)	3.5 (1–35.1)
Baseline platelet count ($\times 10^9$/L), median (range)	99 (11–238)
Baseline peripheral blast count ($\times 10^9$/L), median (range)	0 (0–14)
Bone marrow blasts infiltration (%), median (range)[b]	66 (27–94)

2020 INTERNATIONAL SURVEY 398 ADULTS

Table 3. Patient characteristics according to treatment

	Chemotherapy+ allo-HSCT (n = 61)	Chemotherapy+ auto-HSCT (n = 16)	Chemotherapy without consolidation (n = 222)
Age, median (range), y	50 (18-70)	63 (19-68)	68 (18-87)
Disseminated with cutaneous involvement	37 (60)	12 (75)	133 (60)
Disseminated noncutaneous	12 (20)	1 (6)	20 (9)
Cutaneous isolated	12 (20)	3 (19)	69 (31)
ALL-type	33 (53)	6 (38)	57 (26)
AML-type	16 (27)	1 (6)	36 (16)
NHL-type	12 (20)	9 (56)	129 (58)
Response to treatment			
CR	57 (94)	16 (100)	153 (69)
PR	2 (3)	0	31 (14)
PD	2 (3)	0	38 (17)
Relapse	16/60 (27)	5/16 (31)	131/168 (78)

Unless otherwise noted, data are n (%). Patients treated with new drugs (n = 6), radiotherapy (n = 27), or palliative approaches (n = 62) were excluded.

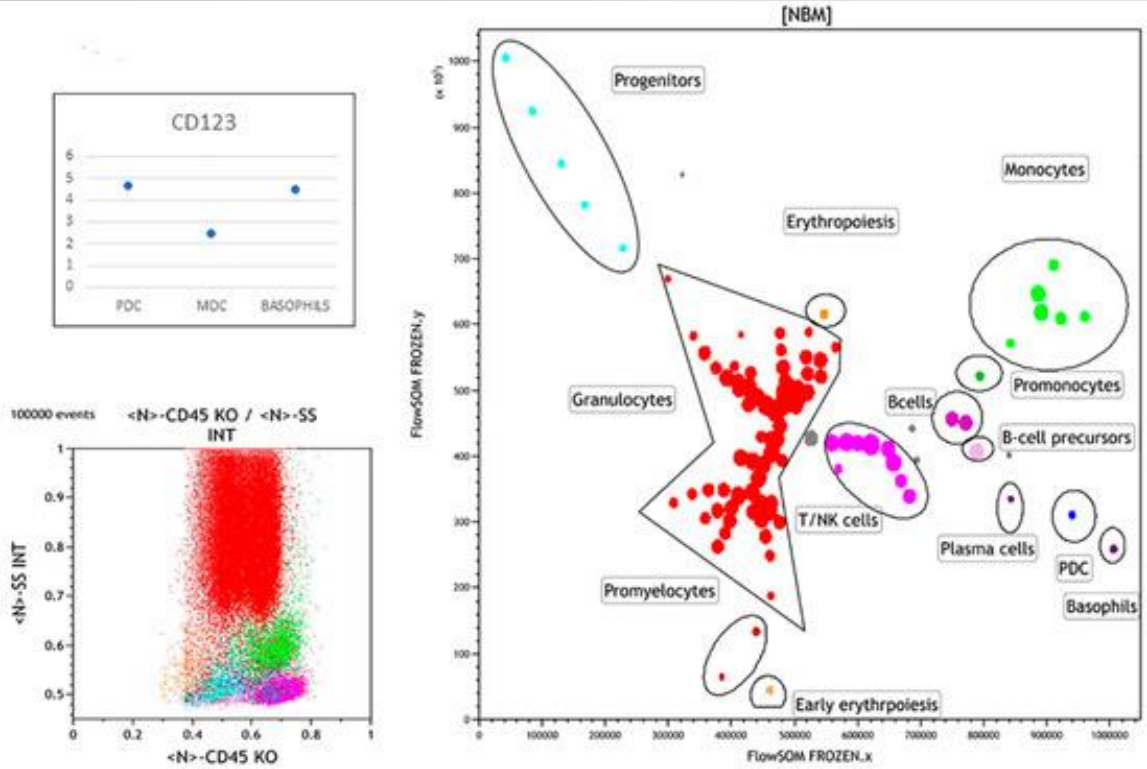
Laribi *et al*, Blood Advances 2019

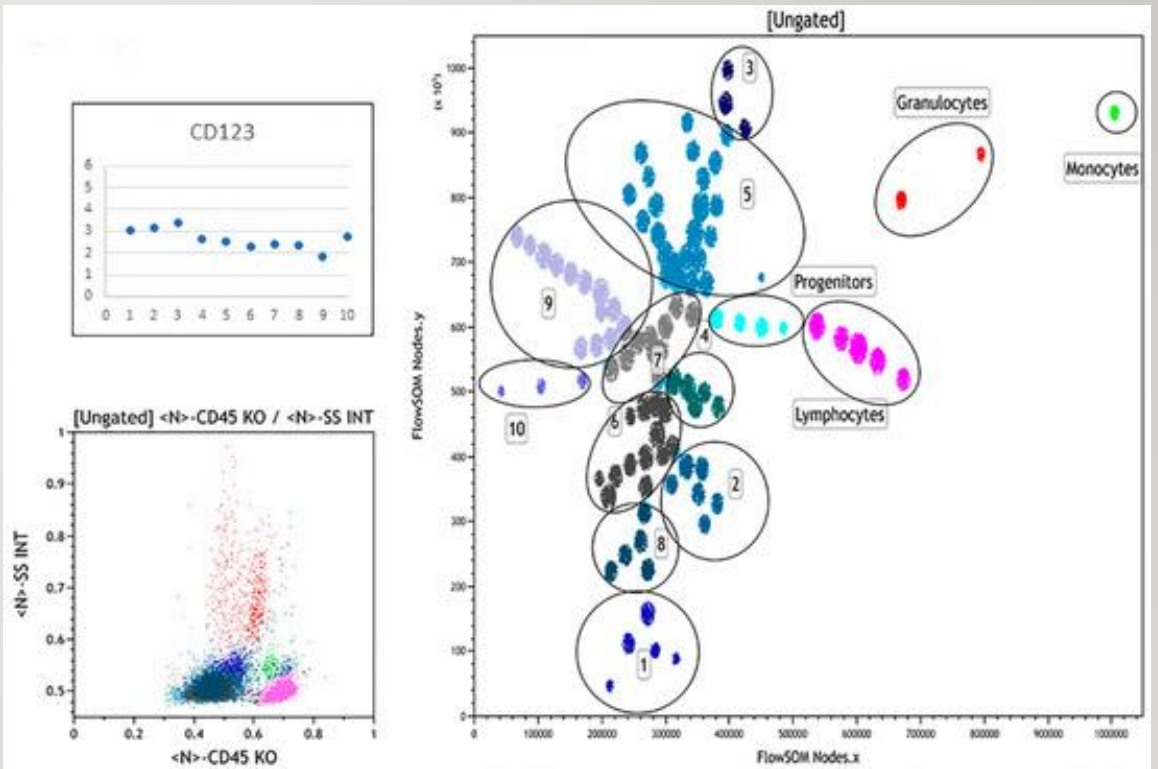
RECENT FINDINGS

- Gene expression profiling
  - Confirmed resting/precursor pDC counterpart
  - Upregulation of Cylcin D1 and BCL2 ➔ venetoclax?
  - Aberrant activation of NFkB ➔ bortezomib?
- Efficacy of allo-SCT
- SL-401/Tagraxofusp
  - diphtheria toxin fused to IL-3) targeting CD123
  - encouraging results at ASH 2017
- CD123 targeting with bispecifics, CAR T-cells

STILL A MYSTERIOUS DISEASE…

HETEROGENEITY DEMONSRATED BY AI: FLOWSOM





Porwit A, Béné MC, Hemato 2021

IN CONCLUSION

- Rare disease
- Cutaneous/mucosal involvement
- Leukemic forms
- Specific immunophenotype
- Probable counterpart of Pdc2 but disputed
- Poor prognosis: look for donor
- Perhaps new therapeutic options


THANK
YOU!