NEOPLASIA A CELLUE DENDRITICHE PLASMOCITOIDI BLASTICHE

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HIGHLIGHTS IN EMATOLOGIA
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Disclosures of Name Surname

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Jazz pharmaceutical							X
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NEOPLASIA A CELLUE DENDRITICHE PLASMOCITOIDI BLASTICHE

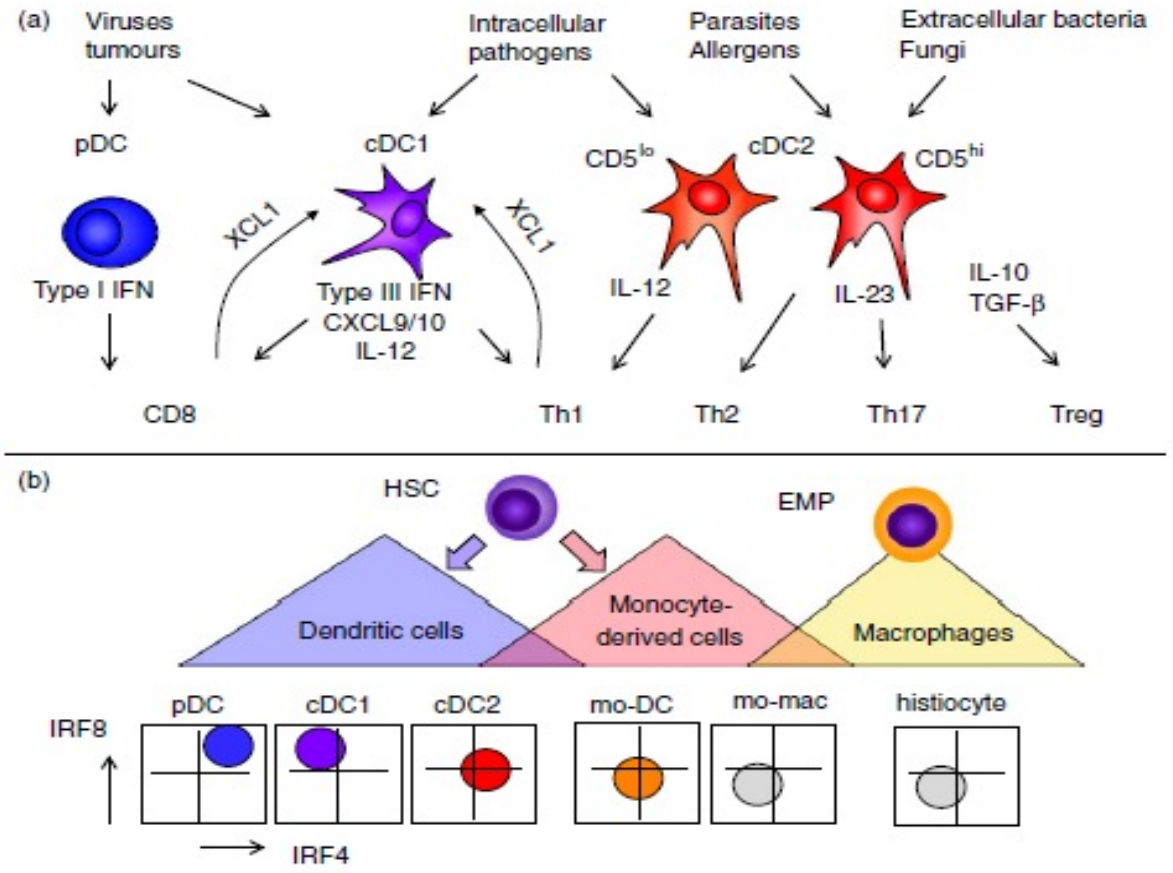
Definizione
Nomenclatura
Epidemiologia
Aspetti clinici
Anatomia patologica e morfologia
Citoflorimetria
Terapia e prospettive future

DEFINIZIONE ED EPIDEMIOLOGIA

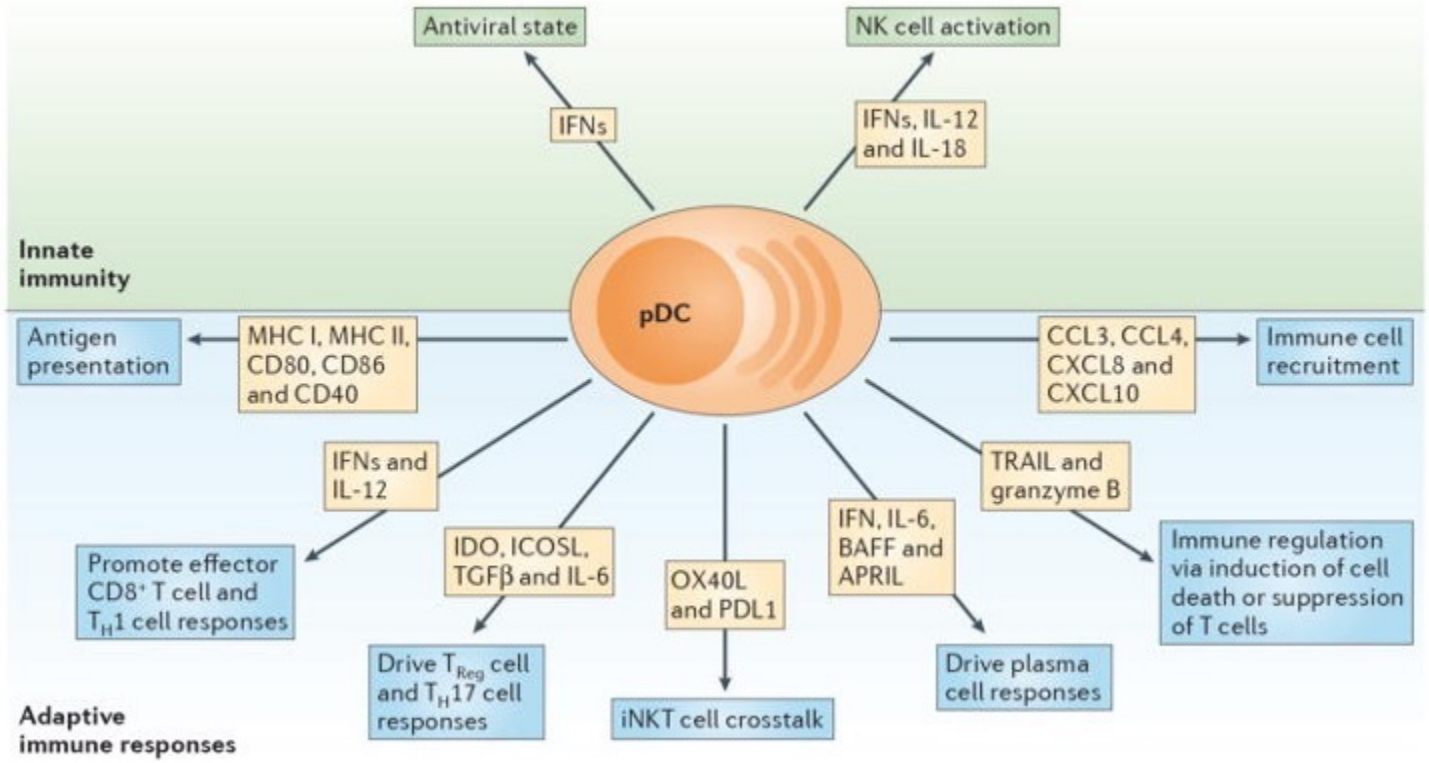
La neoplasia cellule dentritiche plasmocitoidi blastiche (BPDCN) è una malattia ematologica rara ad andamento aggressivo. Frequente è la localizzazione cutanea. Può presentarsi anche un coinvolgimento di

1. Midollo osseo e sangue periferico (citopenia periferica)
2. Sistema Nervoso Centrale (9-38%)
3. Linfonodi (50%)
4. Organi ipocondriaci (fegato e milza 9%).

A causa dei cambiamenti nella nomenclatura non è nota l'esatta incidenza della BPDCN. Tuttavia è riportata essere di 0,04 casi ogni 100,000 abitanti con una maggior prevalenza nel maschio con M:F 5:1.
Età mediana di 60-70 anni.



Collin M et al 2018



Swiecki M et al 2015

NOMENCLATURA

1995 Descritta per la prima volta come leucemia acuta agranulare CD4+ a cellule NK (Bordy JP et al 1995).

1997 Definizione di cellule dendritiche plasmocitoidi blastiche (Grouard et al 1997).

2008 La WHO la inserisce nel gruppo delle leucemie acute mieloidi (Vardiman et al 2008).

Blastic plasmacytic dendritic cell neoplasm
This is a new category that includes most cases previously classified as blastic NK-cell lymphoma/leukemia or agranular CD4+ CD56+ hematodermic neoplasm; it is derived from a precursor of plasmacytoid dendritic cells.

2022 La nuova WHO la differenzia dalle leucemie acute mieloidi collocandola nel gruppo dei disordini delle neoplasie istiocitarie (Khoury et al 2022

REVIEW ARTICLE OPEN

Check for updates

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

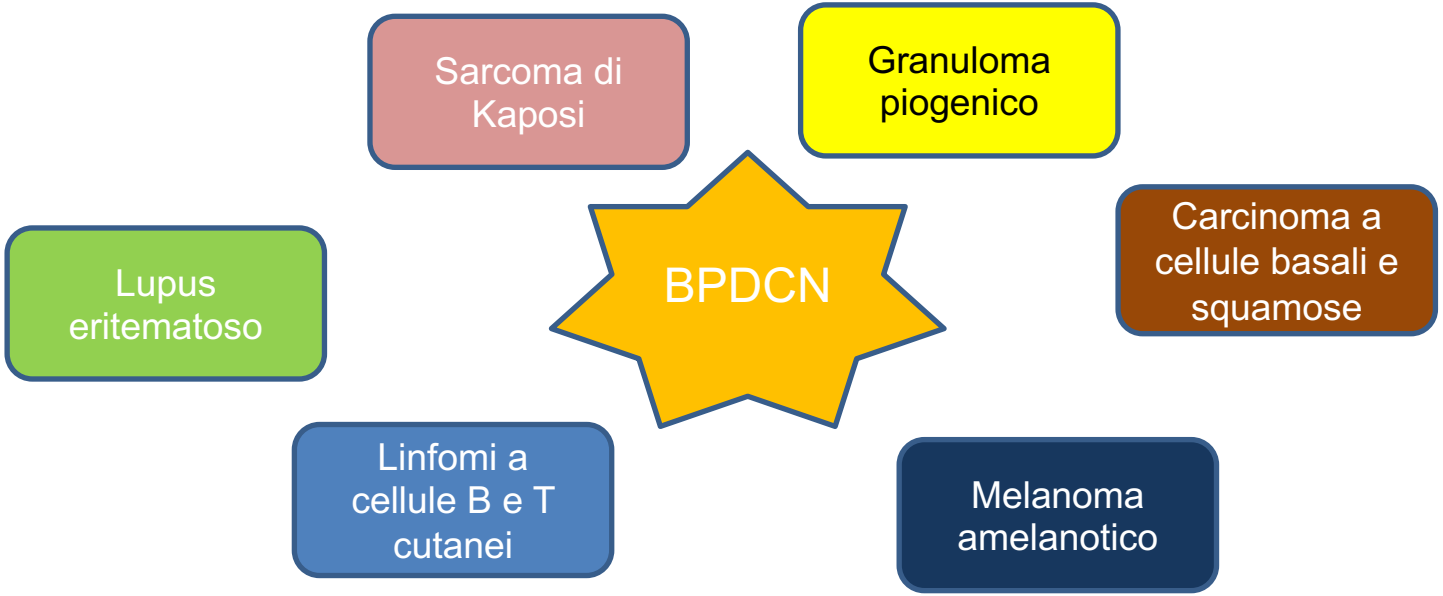
2022

Joseph D. Khoury[1✉], Eric Solary[2✉], Oussama Abla[3], Yassmine Akkari[4], Rita Alaggio[5], Jane F. Apperley[6], Rafael Bejar[7],

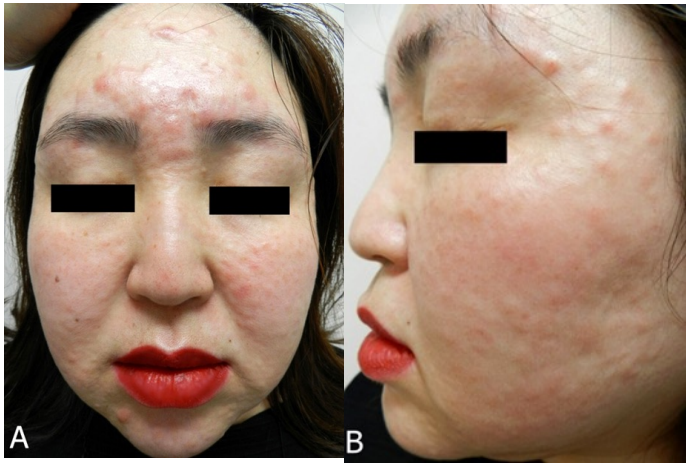
NEOPLASIE DELLE CELLULE DENDRITICHE PLASMACITOIDI
• Proliferazione di cellule dendritiche plasmacitoidi mature associata a neoplasia mieloide
• Neoplasia delle cellule dendritiche plasmacitoidi blastiche
NEOPLASIE A CELLULE DI LANGERHANS E ALTRE NEOPLASIE DELLE CELLULE DENDRITICHE
➢ *Neoplasie a cellule di Langerhans*
• Istiocitosi a cellule di Langerhans
• Sarcoma a cellule di Langerhans
➢ *Altre neoplasie delle cellule dendritiche*
• Tumore a cellule dendritiche indeterminate
• Sarcoma a cellule dendritiche interdigitanti
NEOPLASIE ISTIOCITICHE
• Xantogranuloma giovanile
• Malattia di Erdheim-Chester
• Malattia di Rosai-Dorfman
• Istiocitosi ALK-positiva
• Sarcoma istiocitico

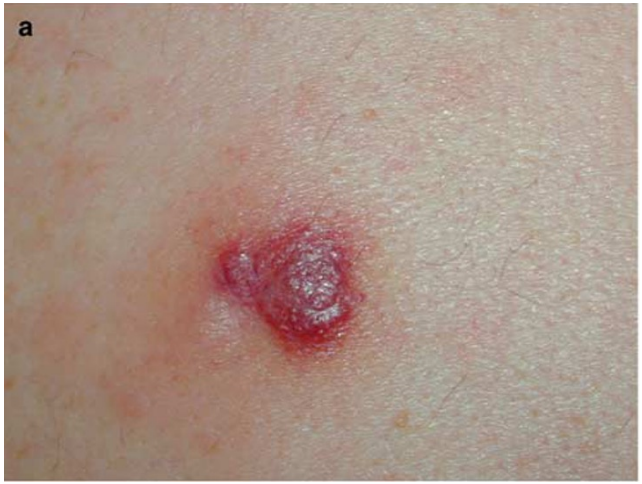
ASPETTI CLINICI

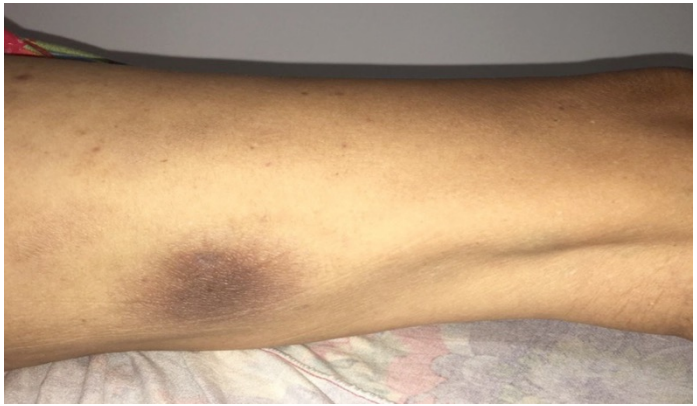
Nel 90% dei casi si ha un coinvolgimento cutaneo entrando quindi in diagnosi differenziale con patologie cutanee autoimuni e/o neoplastiche. **Ruolo chiave del dermatologo**



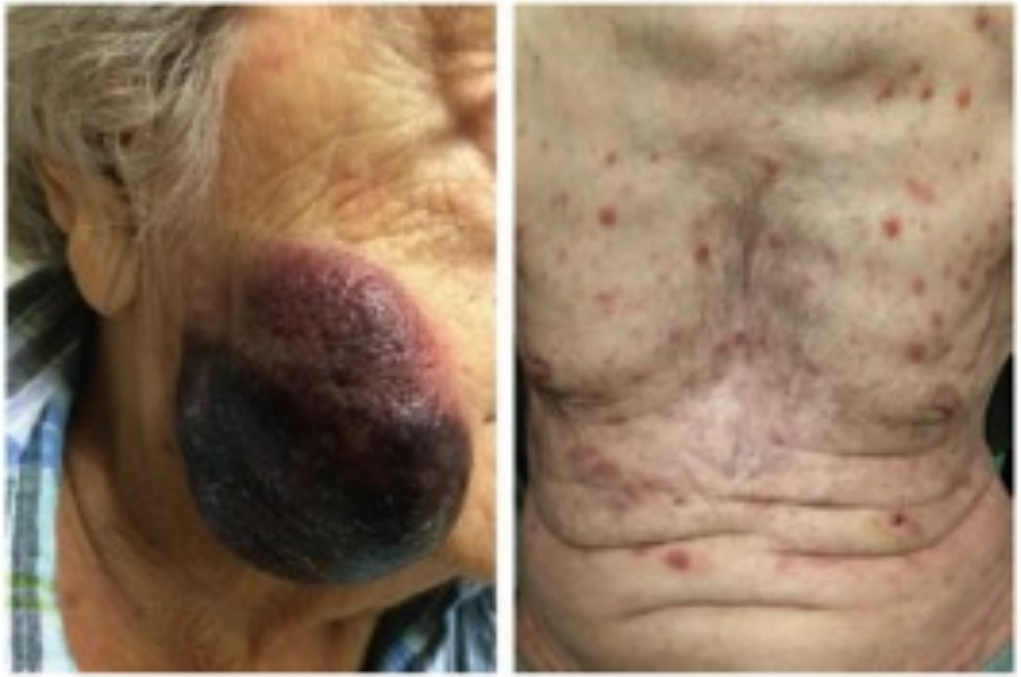
ASPETTI CLINICI







ASPETTI CLINICI



ANATOMIA PATOLOGICA

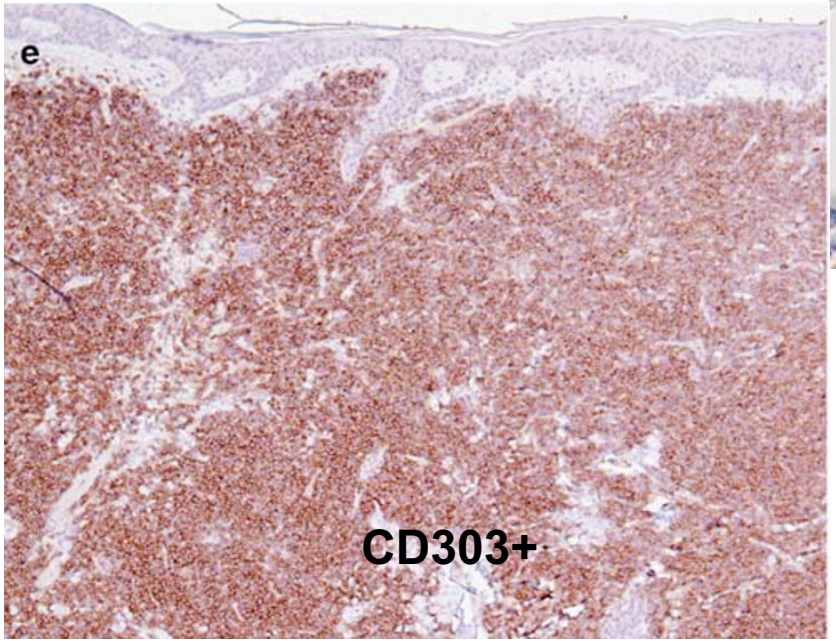
Ruolo chiave del patologo
Diagnosi Differenzale

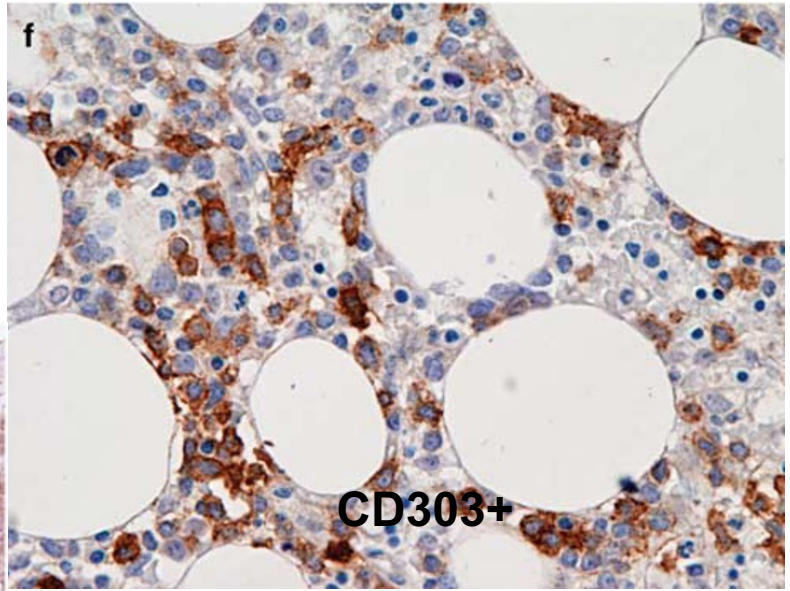
Leucemia mieloide acuta
con espressione aberrante di
CD4/CD56/CD123

Linfoma/leucemia linfoblastica T e B (TdT+)

Linfoma T periferico, linfoma extranodale
Nk tipo nasale a localizzazione cutanea

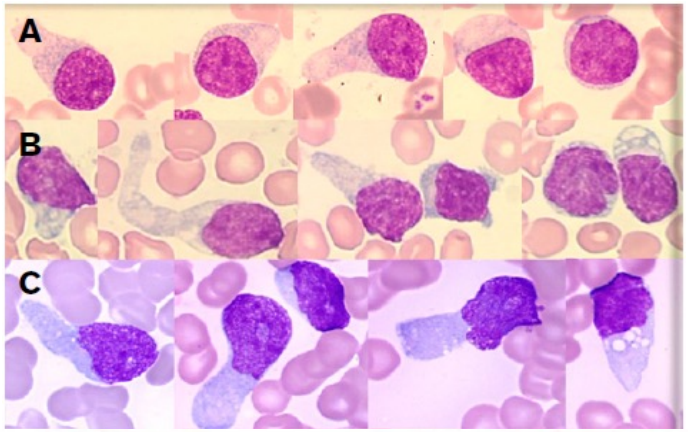
Linfoma B della cute.

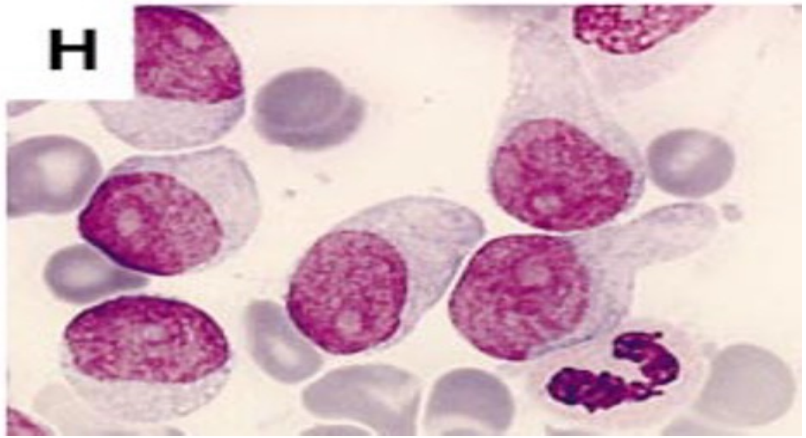


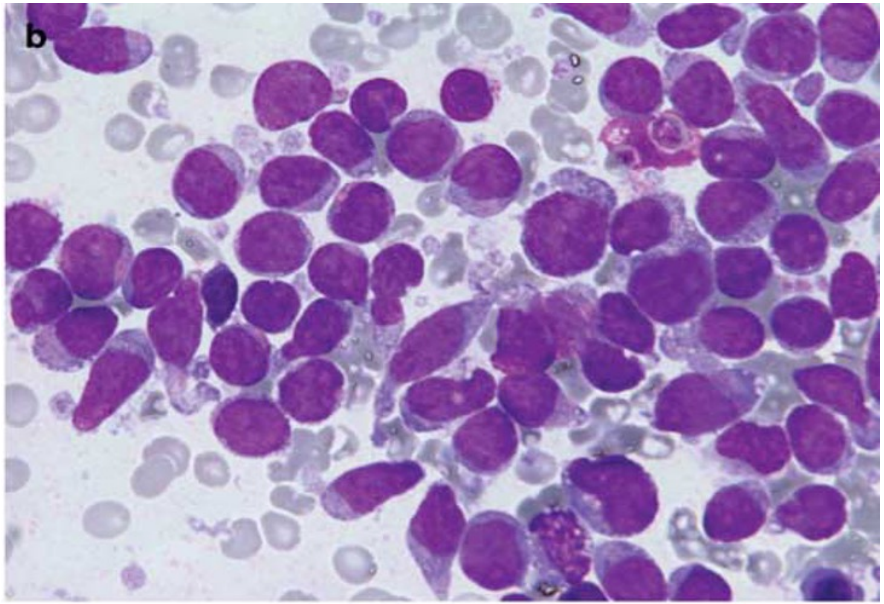


BPDCN

MORFOLOGIA

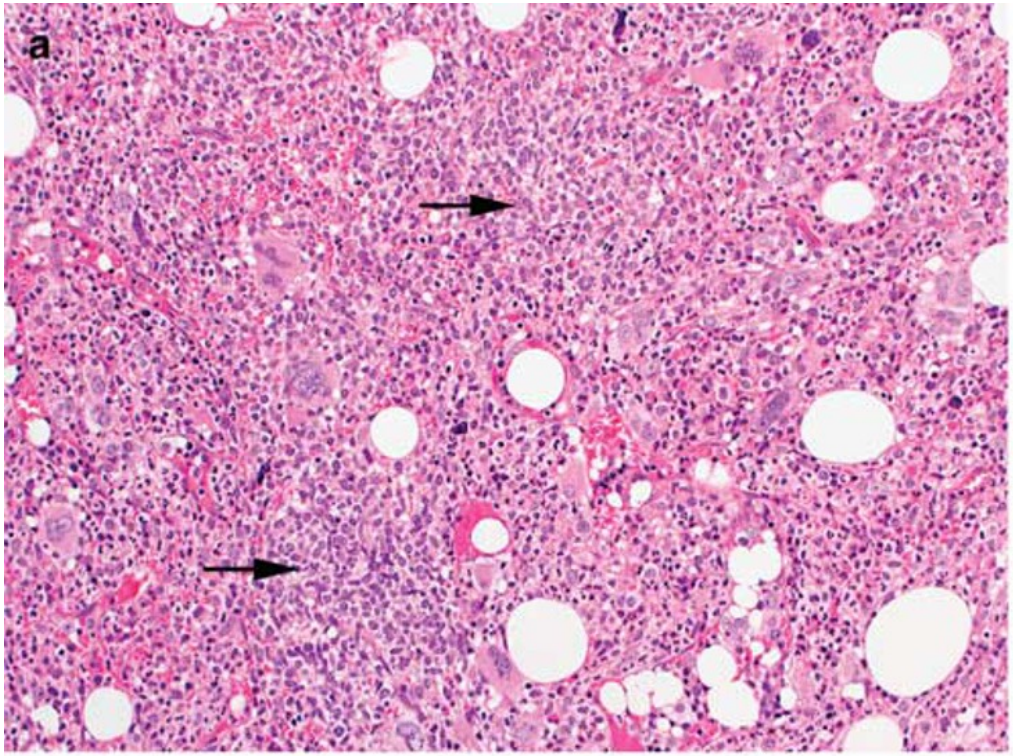






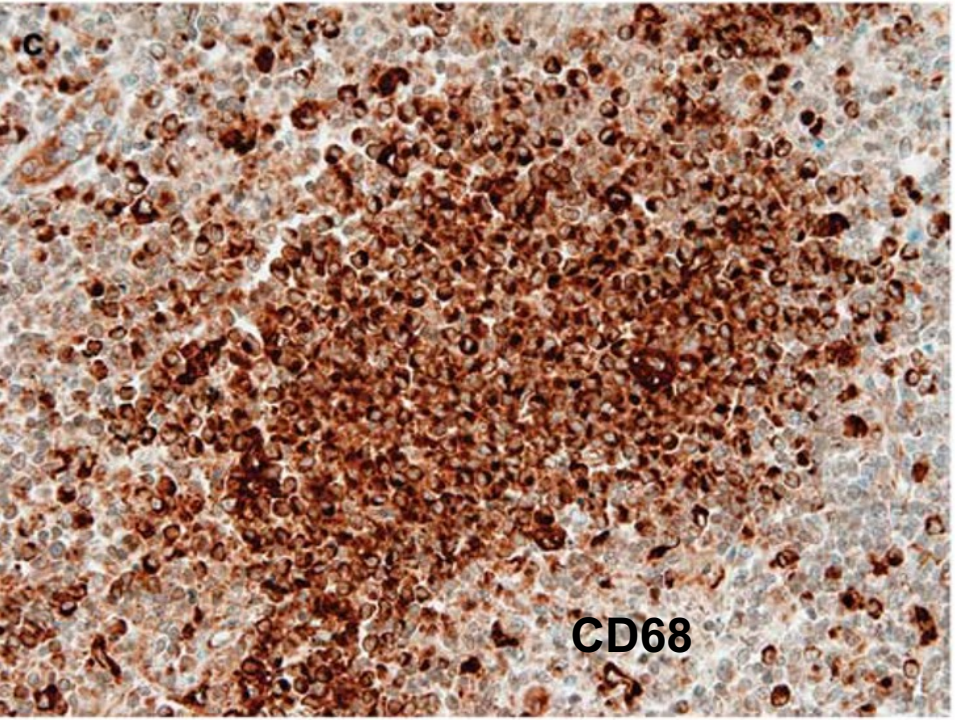
Garnache-Ottou F 2019

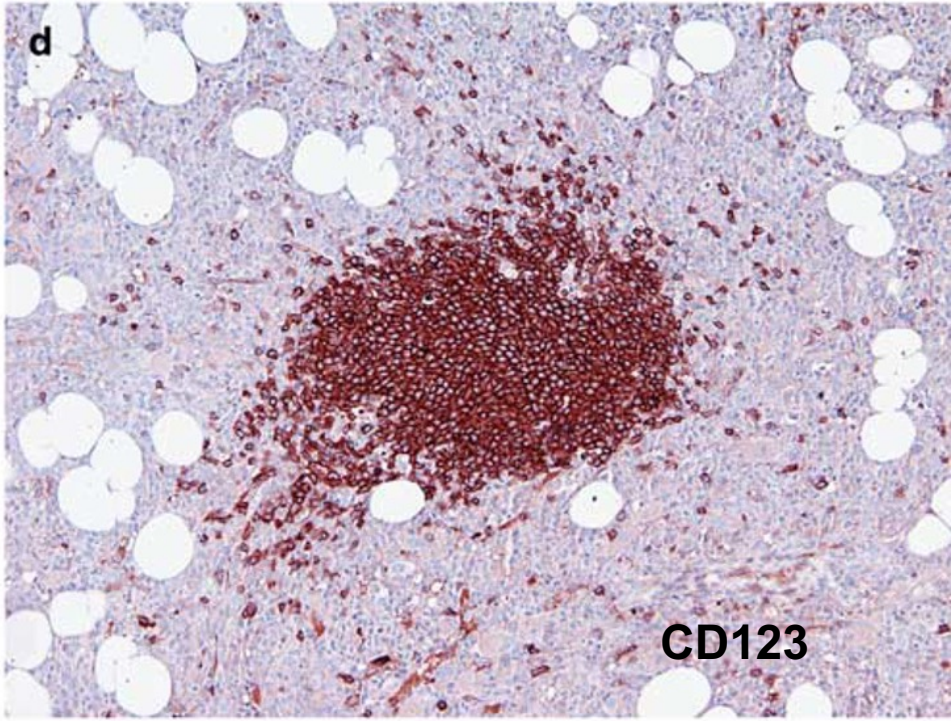
ANATOMIA PATOLOGICA



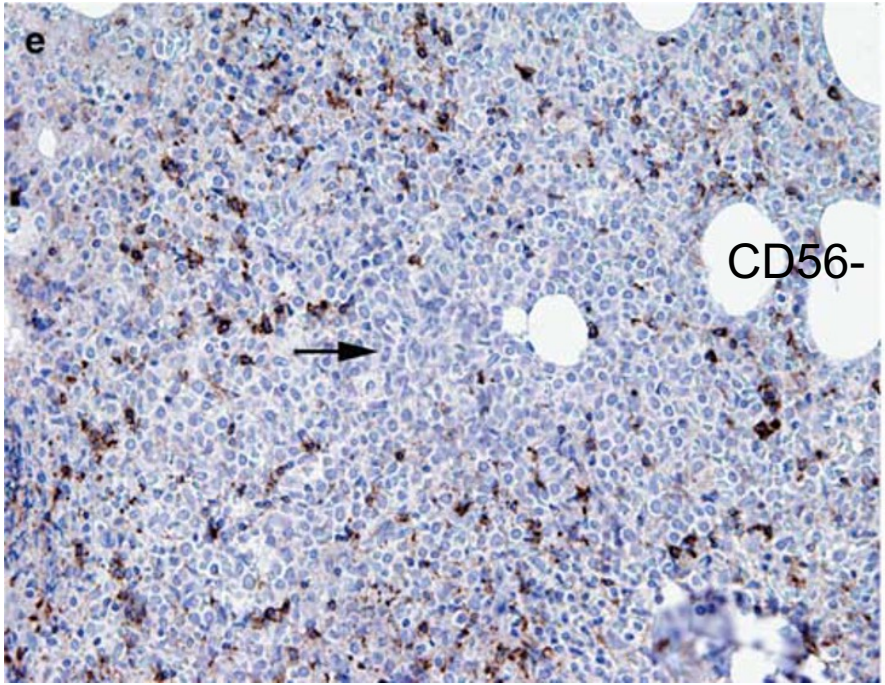
MPDCP

ANATOMIA PATOLOGICA





ANATOMIA PATOLOGICA



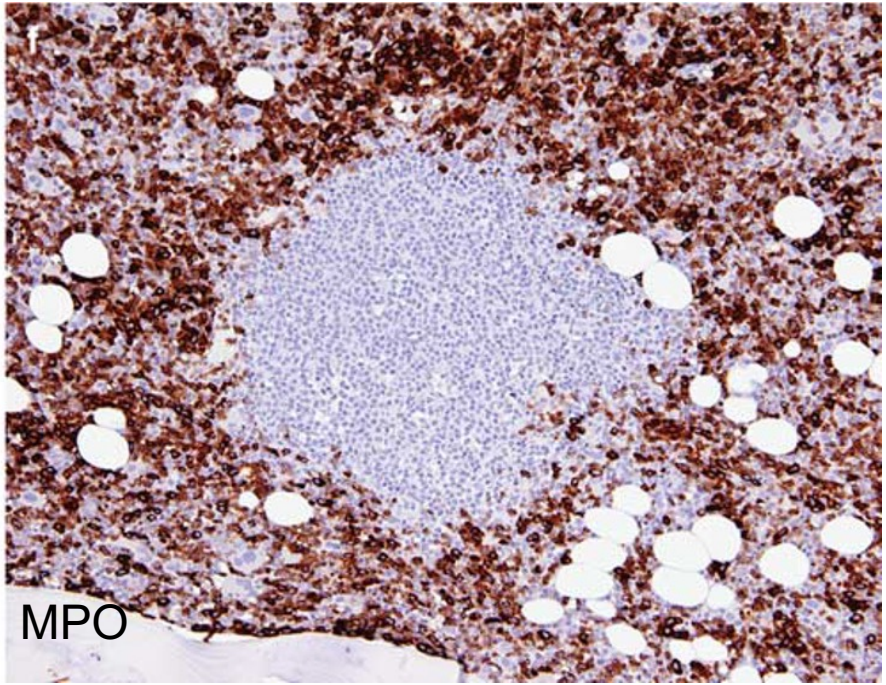


Table 3. Differential diagnosis of hematopoietic malignancies based on skin biopsy.

	CD123	CD4	CD56	MPO	EBER	CD3
BPDCN	+	+	+	-	-	-
MPDCP with associated myeloid neoplasms	+	+	-	+	-	-
Leukemia cutis/myeloid sarcoma	+/-	+/-	+	+	-	-
Extranodal NK/T cell lymphoma	-	-	+	-	+	+
Classic primary cutaneous T cell lymphoma	-	-	+	-	-	+

Abbreviations: EBER, Epstein-Barr virus-encoded small RNA; MPO, myeloperoxidase.

RUOLO DELLA CITOFLUORIMETRIA

- Diagnosi e sua conferma.
- Conferma e quantificazione della contaminazione del liquor SNC.
- Quantificare la presenza di un infiltrato midollare o su sangue periferico.
- Monitoraggio della malattia minima residua.

RUOLO DELLA CITOFLUORIMETRIA

Phenotype	pDC/IPC
Myeloid marker	
CD11b	—
CD11c	—
CD13	—
CD14	—
CD33	—
Lymphoid marker	
Pre-Tα	+
Ig1-like 14.1	+
Spi-B	+
Pattern recognition receptors	
TLR1	+
TLR2	—
TLR3	—
TLR4	—
TLR5	—
TLR6	+
TLR7	+ +
TLR8	—
TLR9	+ +
TLR10	+
Mannose R	—
BDCA2	+
CD1a, b, c, d	—
Other differentially expressed antigens	
CD4	+ +
CD45RA	+
CD45RO	—
IL-3R	+ + +
GM-CSFR	+
Function	
IFN-α/β production	+ + + + +
IL-12 production	—
Phagocytosis	—

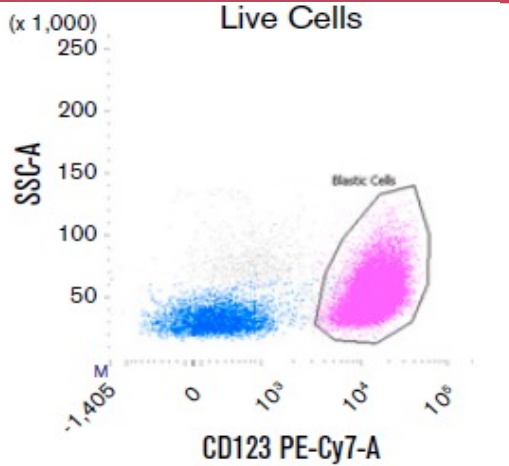
Expected positive expression:
CD123*
TCF4*
TCL1*
CD303 *
CD304*
CD4
CD56
Expected negative markers:
CD3
CD14
CD19
CD34
Lysozyme
Myeloperoxidase

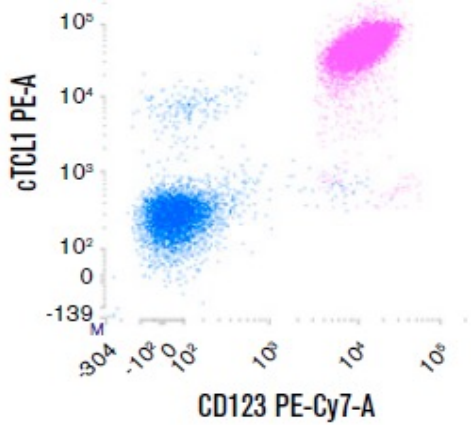
Liu YJ et al 2005, Khoury JD et al 2022

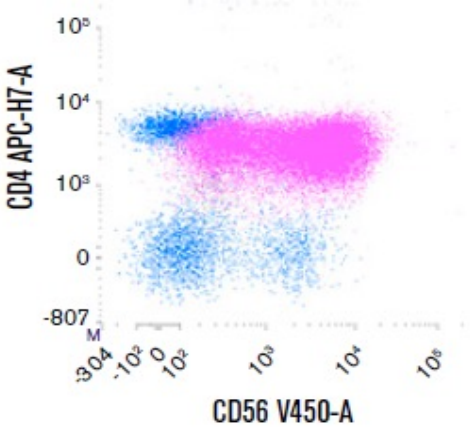
RUOLO DELLA CITOFLUORIMETRIA

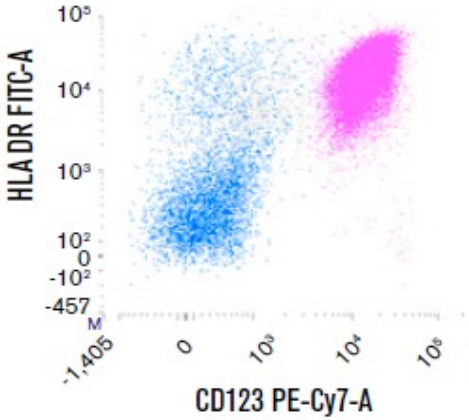
Table 2. Immunophenotypic diagnostic criteria of blastic plasmacytoid dendritic cell neoplasms according to 5th WHO classification.

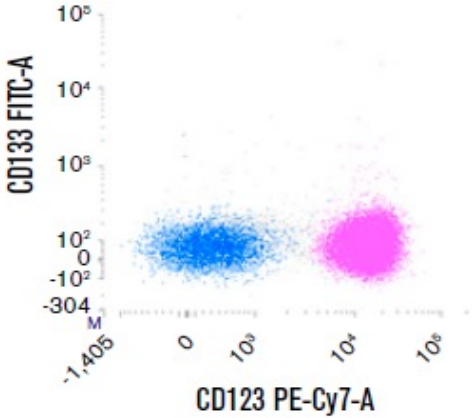
Expected positive expression: CD123*, TCF4*, TCL1*, CD303*, CD304*, CD4, CD56
Expected negative markers: CD3, CD14, CD19, CD34, lysozyme, myeloperoxidase
Immunophenotypic diagnostic criteria
- Expression of CD123 and one other pDC marker(*) in addition to CD4 and/or CD56
- Expression of any three pDC markers and the absent expression of all expected negative markers

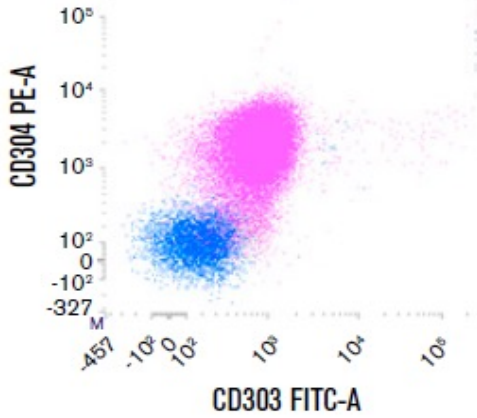

Live Cells
(x 1,000)
SSC-A
Blastic Cells
CD123 PE-Cy7-A

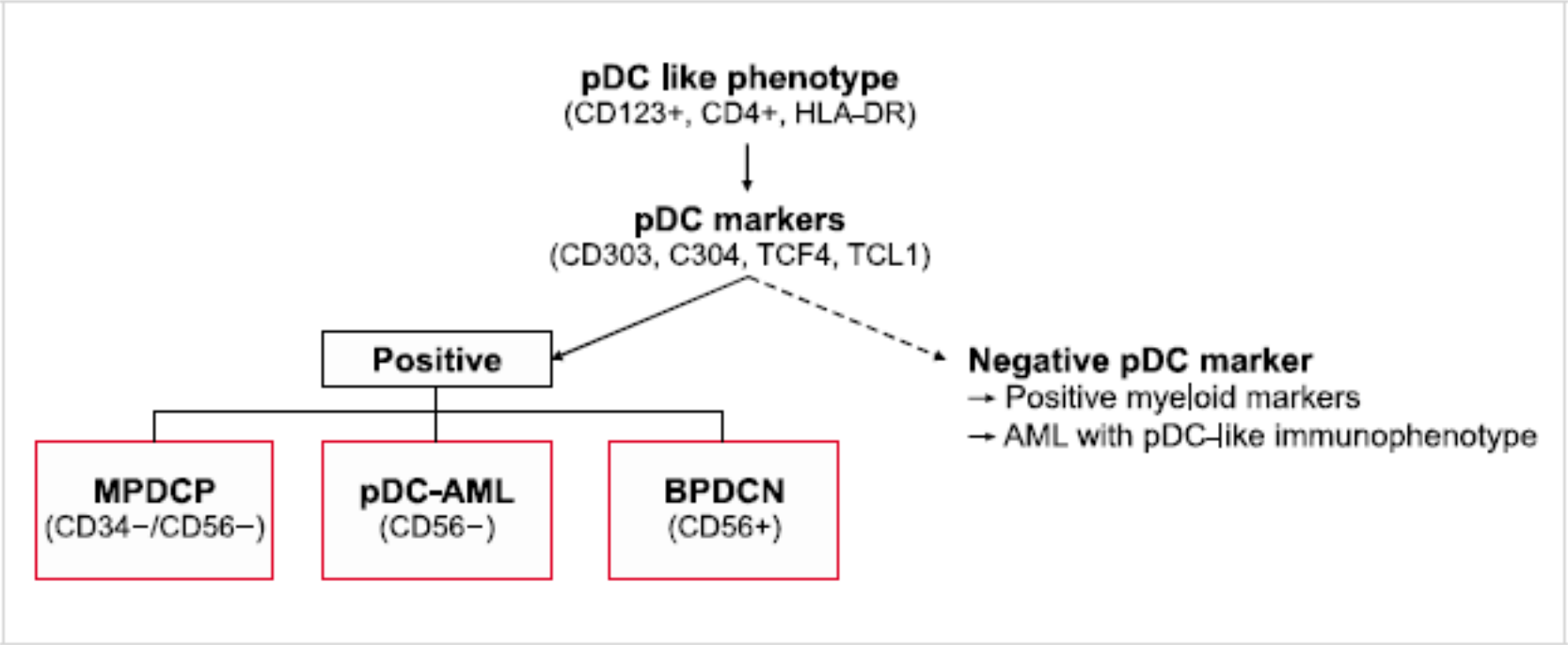

cTCL1 PE-A
CD123 PE-Cy7-A

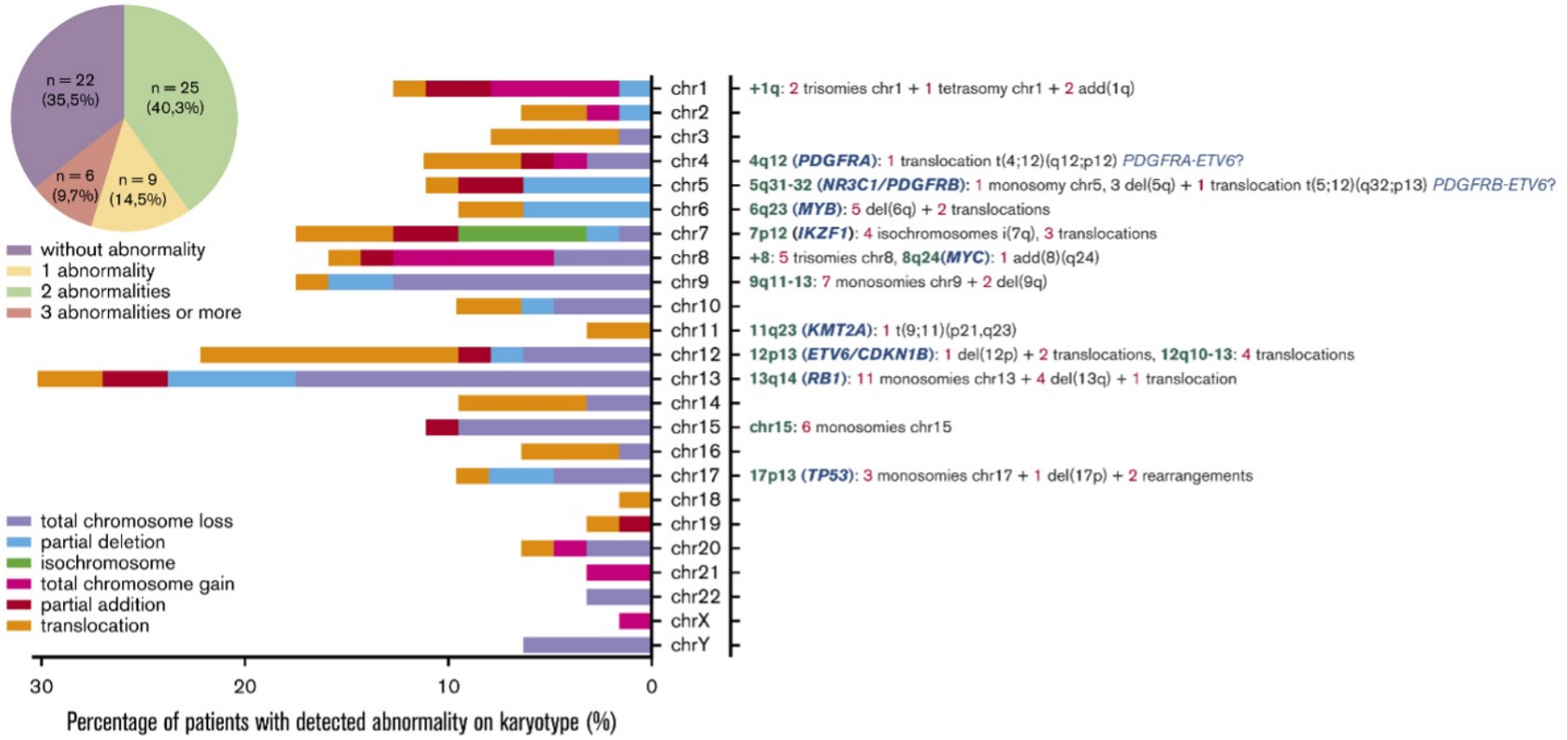

CD4 APC-H7-A
CD56 V450-A


HLA DR FITC-A
CD123 PE-Cy7-A


CD133 FITC-A
CD123 PE-Cy7-A


CD304 PE-A
CD303 FITC-A


pDC like phenotype
(CD123+, CD4+, HLA-DR)
pDC markers
(CD303, C304, TCF4, TCL1)
Positive
Negative pDC marker
→ Positive myeloid markers
→ AML with pDC-like immunophenotype
MPDCP
(CD34−/CD56−)
pDC-AML
(CD56−)
BPDCN
(CD56+)



Garnache-Ottou F et al 2019

Articoli	Tecnica	Geni mutati
Jardin et al, 2011	aCGH/SNP	*TET2, TP53*
Alayed K et al, 2013	PCR assay/TS	*TET2*
Taylor et al, 2013	TS	*TET2, TP53, ASXL1, IDH2, KRAS, ABL1, ARID1A, GNA13, U2AF1, SRSF2, IRF8, ZRSR2*
Menezes J et al, 2014	WES/TS	*DNMT3A, IDH1, IDH2, TET1, TE2, ASXL1, ATRX, EZH2, KRAS, NRAS, ETV6, HOXB9, IKZF1, IKZF2, IKZF3, RUNX1, ZEB2, SF3B1, SRSF2, U2AF1, ZRSR2, NPM1, FLT3, FLT3-ID, JAK2, KIT, TP53, CBLB, CBLC, UBE2G2*
Stenzinger et al, 2014	TS	*NRAS, ATM, MET, KRAS, IDH2, KIT, APC, RB1, VHL, BRAF, MLH1,TP53, RET*
Emadali et al, 2016	TS	*ASXL1, EZH2*
Togami et al, 2016	WES/TS	*ZRSR2, SRSF2, SF3B1, U2AF1, SF3A2, SF3B4, TET2, ASXL1, TP53, GNB1, NRAS, IDH2, ETV6, DNMT3A, RUNX1, CRIPAK, NEFH, HNF1A, PAX3, SSC5D*
Sapienza et al, 2019	WES/TS	*ARID1A, CHD8, SMARCA5, SMARCAD1,SMARCD1, TET2, IDH2, ASH1L, ASXL1, ASXL3, MLL2, MLL3, MLL4, SETMAR, SUZ12, KDM4D, PHF2, EP300, EP400, MYST3, MYST4, PHC1, PHC2, EYA2, SRCAP, NRAS, KRAS, BRCA1, ATM, ATR, RAD52, ZRSR2, RET, MAPK1, BRAF, RUNX2, SYK, WNT10, WNT7B, BCL9L, WNT3*
Ladikou et al, 2018	TS	*TET2, RHOA*
Szczepaniak et al, 2019	TS	*ASXL1, TET2, NF1*

aCGH: Array Comparative Genetic Hybriditation; SNP: Single Nucleotide Polymorphisms; PCR: Polymerase Chain Reaction; TS: Targeted Sequencing, WES: Whole Exone Sequencing.

Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study

Livio Pagano,[1] Caterina Giovanna Valentini,[1] Alessandro Pulsoni,[2] Simona Fisogni,[3] Paola Carluccio,[4]

Studio retrospettivo 2013
43 pz

Age	68 yr
M/F	31/12
hemoglobin	10 g/dl (6-14)
WBC	5,8x10e3/L (0,55-300)
Platelets	68x10e8/L (1-290)
Lactate dehydrogenase	476 U/L (177-2724)
Skin lesions Lymphoadenopaties Splenomegaly Hepatomegaly Extramedullari localizations (other than skin) SNC	33 (77%) 24 (56%) 19 (44%) 18(42%) 9 (21%) 16%
AML like-ALL like	**60%-35% (26 vs 15)**

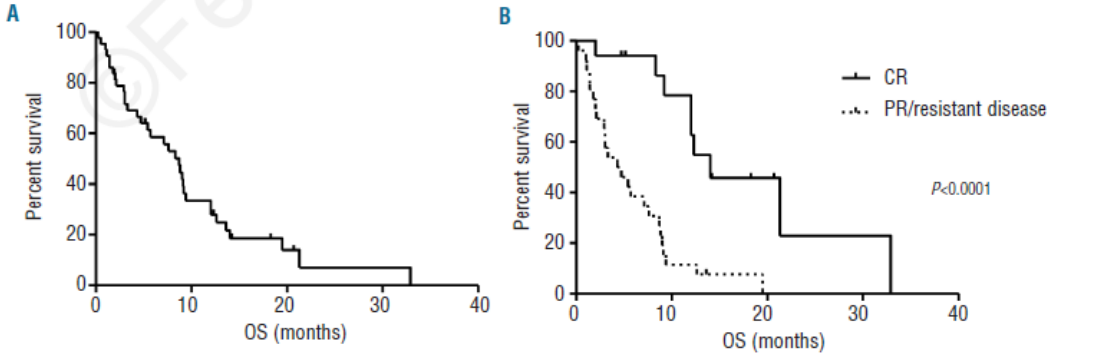


Figure 1. (A) Overall survival (OS) of the whole population (43 patients). The median survival was 8.7 months (range, 0.2-32.9). (B) OS in the 17 patients who reached complete remission (CR) after induction compared to patients in partial remission (PR) or with resistant disease. The median OS was 14 months (range, 2-32.9) and 4.5 months (range, 0.2-19.5), respectively (*P*<0.0001).

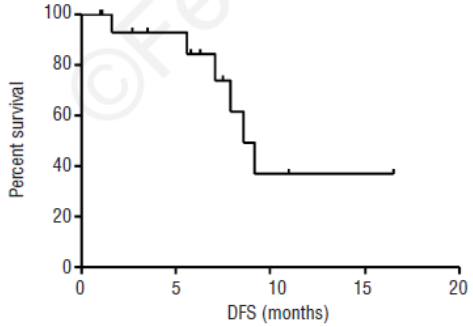


Figure 2. Disease-free survival (DFS) in the 17 patients achieving complete remission. The median DFS was 8.6 months (range, 1-16.5).

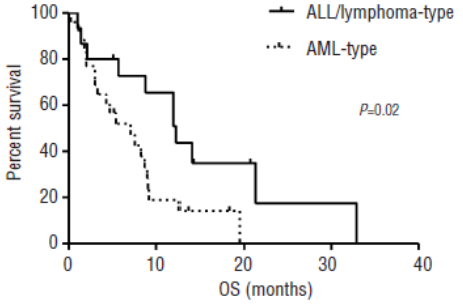


Figure 3. Overall survival (OS) according to types of induction therapy. The median OS was 12.3 months (range 1-32.9) in patients who received an ALL/lymphoma-type regimen and 7.1 months (range, 0.2-19.5) in those treated with an AML-type regimen (*P*=0.02).

CONCLUSIONI

CR 41%.

Pz trattati con regime ALL like

Presentavano una migliore Sopravvivenza.

I pz sottoposti a trapianto allogenico In prima remissione presentano un vantaggio significativo di OS.

31,3 mesi vs 12 mesi (in Dalle et al 2010).

How should we diagnose and treat blastic plasmacytoid dendritic cell neoplasm patients?

Studio retrospettivo 2019

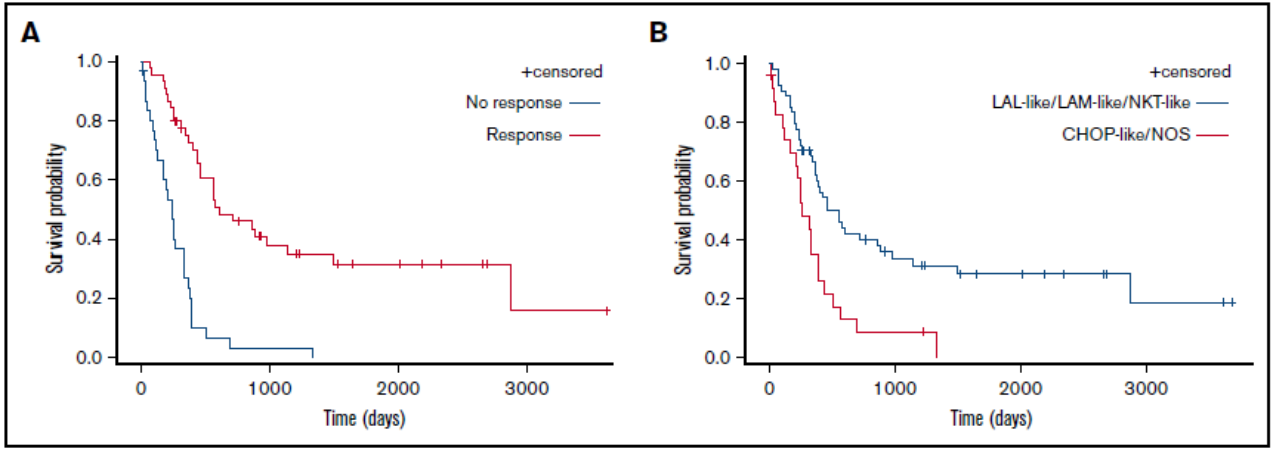
Francine Garnache-Ottou,[1] Chrystelle Vidal,[2] Sabeha Biichlé,[1] Florian Renosi,[1] Eve Poret,[1] Maïder Pagadoy,[2] Maxime Desmarets,[2]

	n (%) or mean [range]
Tumoral involvement (N = 86)	
Skin	73* (84.9)
Lymph nodes	48 (55.8)
Spleen	19 (22)
Liver	15 (17.4)
Cerebrospinal fluid	4 (4.5)
Eye	3 (3.5)

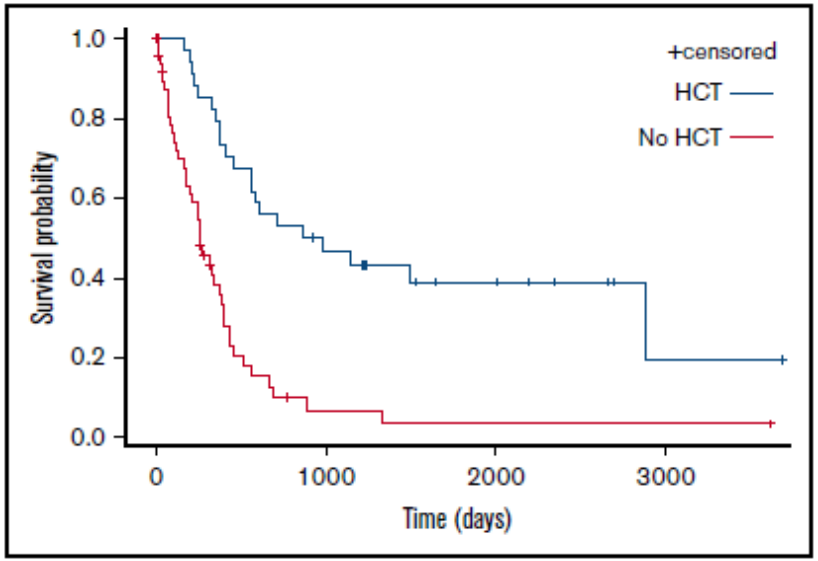
PZ 86

Garnache-Ottou F et al 2019

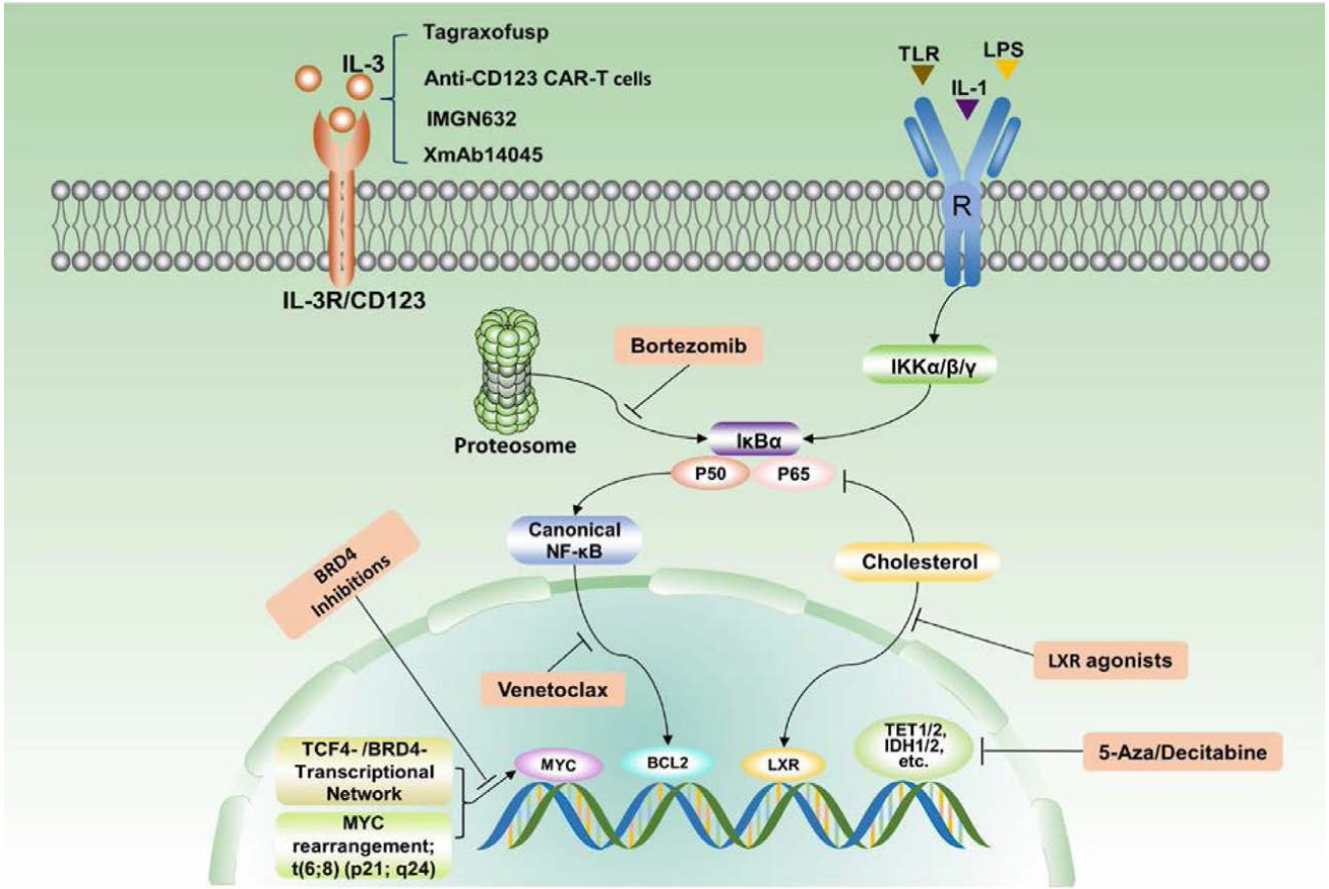
Treatment group	Complete remission, n (%)	Remission duration, median (range), mo	Relapse rate, n (%) of CR patients	HCT, n (%) of CR patients
AML-like (n = 19)	13 (68.4)	68 (4-399)*	4 (28.5)	7 (2 auto) (36.8-53.8)
ALL-like (n = 19)	15 (78.9)	47 (6-224)	5 (33.3)	7 (46.7)
Aspa-MTX (n = 16)	12 (75)	26 (5-166)	4 (33.3)	6 (37.5-50)
CHOP-like (n = 16)	6 (37.5)	17 (4-22)*	4 (66.7)	2 (12.5-33.3)
NOS (n = 10)	1	35	0	0

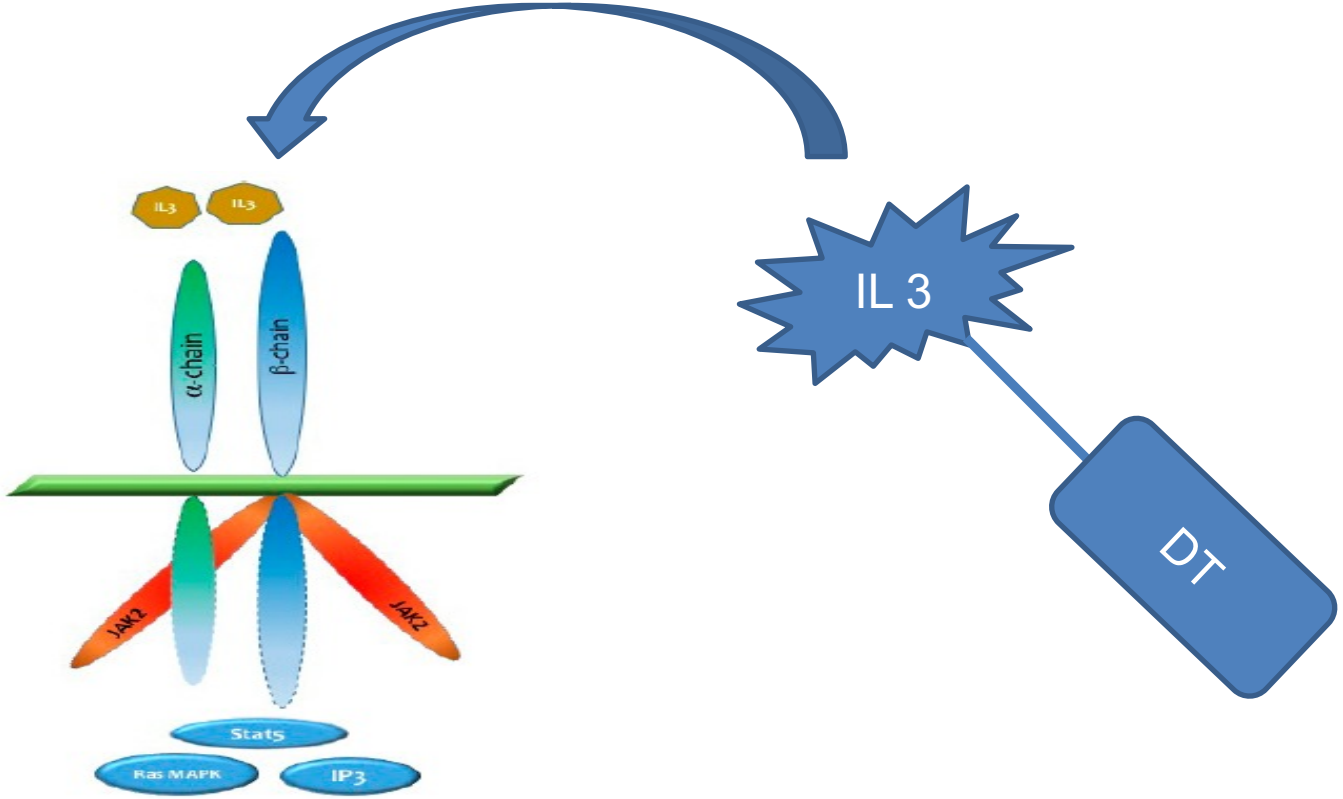


Garnache-Ottou F et al 2019



We believe that this approach offers the vast majority of BPDCN patients their best chance at gaining access to HCT as a consolidation


Tagraxofusp
IL-3
Anti-CD123 CAR-T cells
IMGN632
XmAb14045
TLR
LPS
IL-1
R
IL-3R/CD123
Bortezomib
Proteosome
IKKα/β/γ
IκBα
P50
P65
Canonical NF-κB
BRD4 Inhibitions
Cholesterol
LXR agonists
Venetoclax
TCF4- /BRD4- Transcriptional Network
MYC rearrangement; t(6;8) (p21; q24)
MYC
BCL2
LXR
TET1/2, IDH1/2, etc.
5-Aza/Decitabine


IL3
IL3
α-chain
β-chain
JAK2
JAK2
Stat5
Ras MAPK
IP3
IL 3
DT

Tagraxofusp in Blastic Plasmacytoid Dendritic-Cell Neoplasm

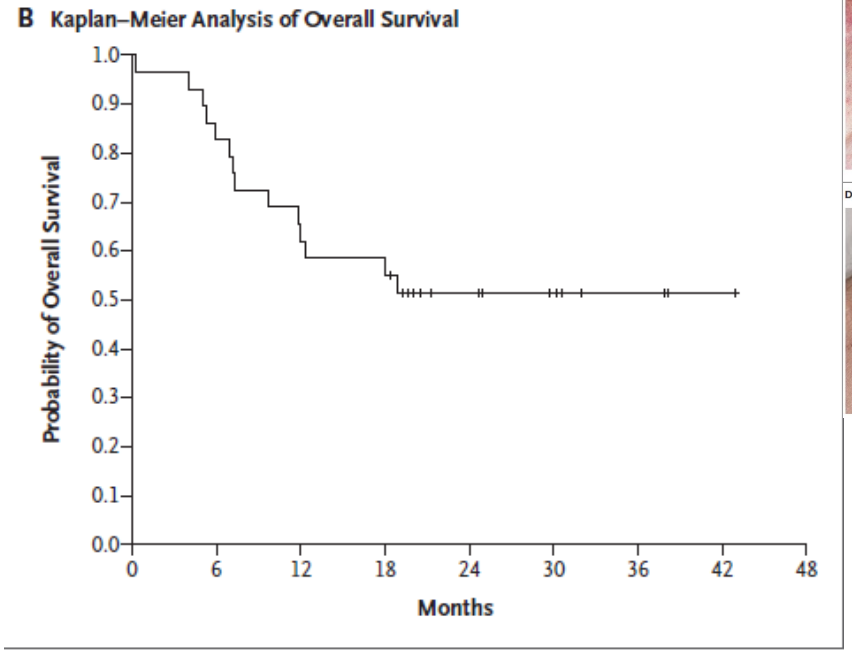
Naveen Pemmaraju, M.D., Andrew A. Lane, M.D., Ph.D., Kendra L. Sweet, M.D.,

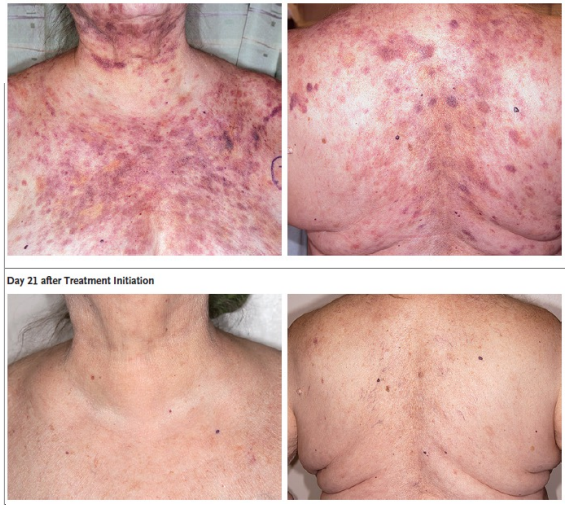
Studio prospettico in I linea e R/R 47 pz. 2019

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	No Previous Treatment (N=32)	Previous Treatment (N=15)	All Patients (N=47)
Median age (range) — yr	68 (22–84)	72 (44–80)	70 (22–84)
Male sex — no. (%)	26 (81)	13 (87)	39 (83)
White race — no. (%)†	30 (94)	13 (87)	43 (91)
ECOG performance-status score — no. (%)‡			
0	17 (53)	5 (33)	22 (47)
1	15 (47)	10 (67)	25 (53)
BPDCN manifestation — no. (%)			
Bone marrow	15 (47)	9 (60)	24 (51)
Peripheral blood	7 (22)	1 (7)	8 (17)
Skin	31 (97)	13 (87)	44 (94)
Lymph nodes	13 (41)	8 (53)	21 (45)
Previous lines of therapy — no. (%)			
1	NA	9 (60)	NA
2–4	NA	4 (27)	NA
>4	NA	2 (13)	NA

12 mcg/kg giorni 1-5 ogni 21 giorni





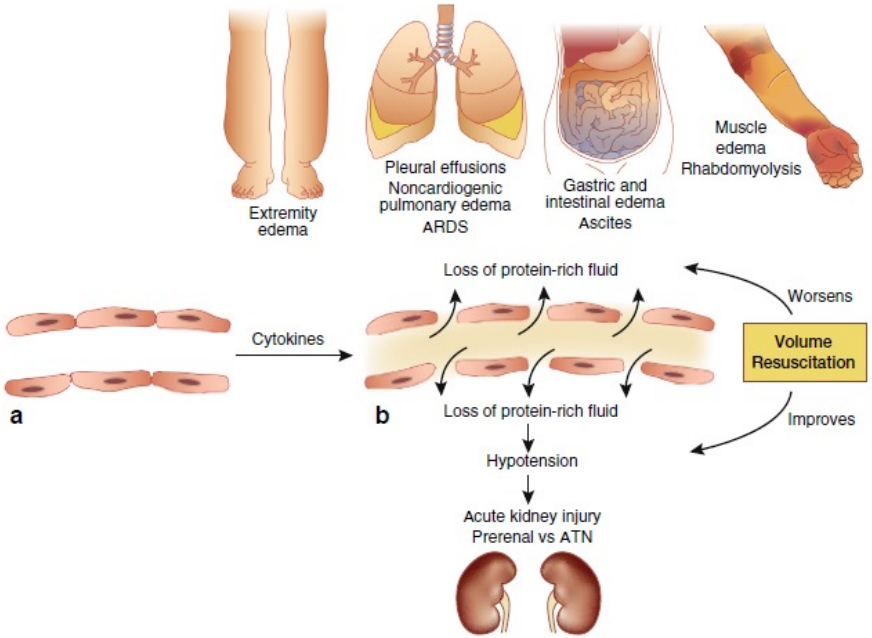
ORR 72% in I linea di cui il 45% a HSCT.
ORR 67% nei R/R.

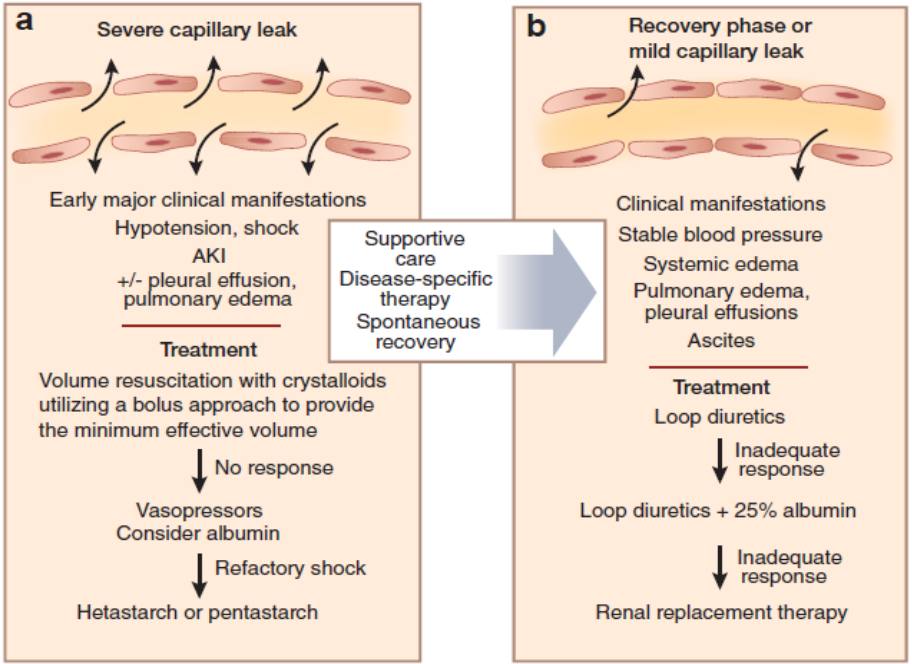
Long-Term Benefits of Tagraxofusp for Patients With Blastic Plasmacytoid Dendritic Cell Neoplasm

2022

Naveen Pemmaraju, MD[1]; Kendra L. Sweet, MD[2]; Anthony S. Stein, MD[3]; Eunice S. Wang, MD[4]; David A. Rizzieri, MD[5];

EVENTI AVVERSI: 19% dei casi Capillary Leak Syndrome





Characteristics and outcomes of patients with blastic plasmacytoid dendritic cell neoplasm treated with frontline HCVAD

Retrospettivo
In prima linea di trattamento 2022

Variable	Frontline HCVAD based, n = 35	Frontline SL-401, n = 37	Frontline other treatment, n = 28	P
Sex				
Male	33 (94)	27 (73)	21 (75)	**.045**
Female	2 (6)	10 (27)	7 (25)	
Age at Dx, median (range), y	61 (20-86)	68 (21-84)	65 (14-86)	**.035**
WBCs at Dx, median, (range), $\times 10^9$/L	6.4 (1.7-76.5)	5.8 (1.9-56.8)	6.0 (1.5-179)	.85
Hgb at Dx, median (range), g/dL	13.3 (6.8-17.0)	13.1 (8.3-17)	13.0 (7.7-17.1)	.088
Plt at Dx, median (range), $\times 10^9$/L	141 (11-365)	146 (39-407)	136 (22-260)	.779
LDH, U/L at Dx, median (range), (n = 30)	508 (121-4108)	505 (164-1800)	523 (266-505)	.841
BM Bl at Dx, median (range), %	5 (0-95)	14 (0-94	11 (0-86)	.788
Involvement of BPDCN disease				
Bone marrow	25 (71)	26 (70)	21 (75)	.911
Skin	27 (77)	34 (92)	18 (64)	**.024**
Lymph node	14 (40)	6 (16)	4 (14)	**.022**
CNS	7 (20)	1 (3)	4 (14)	**.07**
CR	28 (80)	22 (59)	12 (43)	**.01**

Characteristics and outcomes of patients with blastic plasmacytoid dendritic cell neoplasm treated with frontline HCVAD

2022

Naveen Pemmaraju,[1] Nathaniel R. Wilson,[2] Guillermo Garcia-Manero,[1] Koji Sasaki,[1] Joseph D. Khoury,[3] Nitin Jain,[1]

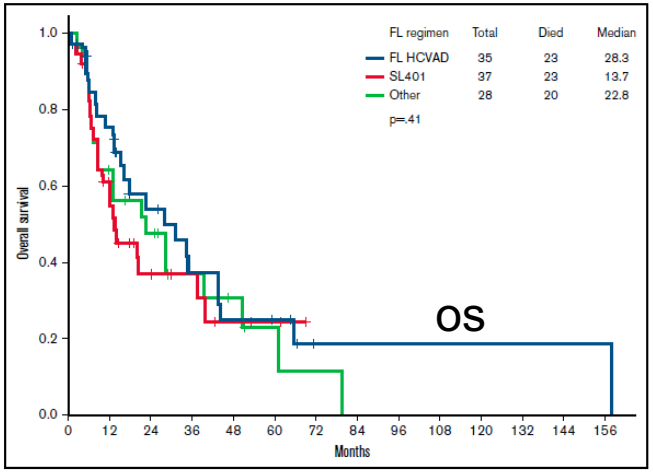


Figure 1. OS. There was no difference in median OS between those who received frontline (FL) HCVAD and those who did not (28.3 months with FL HCVAD vs 13 months with SL-401 vs 22.8 months with other treatment regimens; $P = .41$).

Remission duration probably

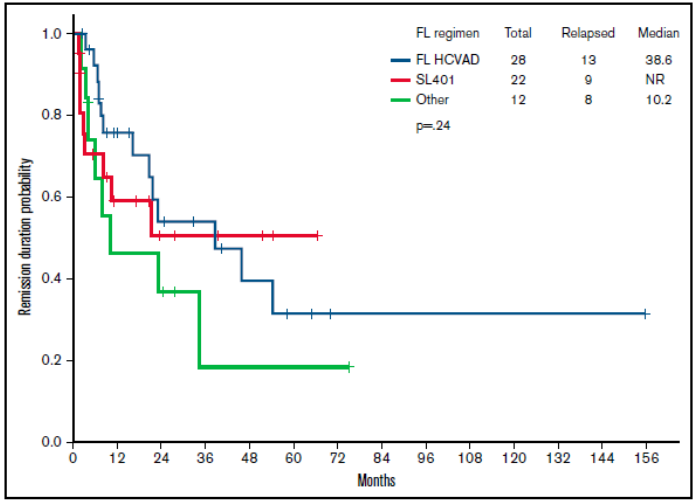


Figure 2. Remission duration probability. There was no difference in median remission duration probability between those who received frontline (FL) HCVAD and those who did not (38.6 months with FL HCVAD vs NR with SL-401 vs 10.2 months with other treatment regimens; $P = .24$).

especially for younger/fit patients.[9] Despite no improvement in median OS compared with other treatment regimens, the ability to yield a higher CR rate with low rates of adverse events suggests that HCVAD retains an important role in the frontline treatment of BPDCN. As above, HCVAD represents the optimal combination of vinca alkaloid, glucocorticoid, anthracycline, and combination chemotherapy, in addition to intrathecal chemotherapy, as an intensive and efficacious frontline regimen for BPDCN.

These results establish high rates of CR for patients treated with frontline HCVAD and confirm a baseline role, even in the modern targeted-therapy era, for cytotoxic chemotherapy regimens in the treatment of BPDCN; in particular, confirming a role for HCVAD-based chemotherapy in BPDCN. Further studies are ongoing to

North American Blastic Plasmacytoid Dendritic Cell Neoplasm Consortium: position on standards of care and areas of need

2023

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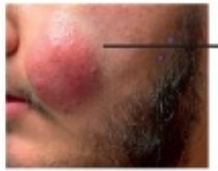
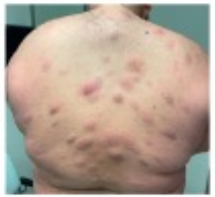
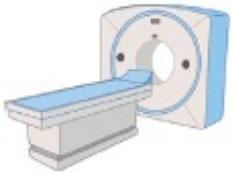
Outline of diagnostic evaluation for BPDCN

Cutaneous and systemic evaluation



- Violaceous skin lesions on inspection
- Skin biopsy and baseline photography

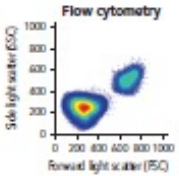




- PET-CT or CT scan for assessment of lymph nodes and/or other extra-medullary disease

Cytomorphological evaluation

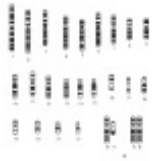
- Bone marrow aspirate and biopsy



- Flow cytometry evaluation
  1. **CD123, CD4, D56**
  2. **CD303**
  3. **TCL1**
  4. **TCF4**

- CSF evaluation for assessment of CNS disease

Adjunct tests



- Cytogenetics

- NGS for myeloid mutation assessment

Author and study period	Type of study	Therapy details*	Response rates [(N)/%]†	OS dynamics	SCT-specific outcomes
Roos-Weil et al[33] (EBMT analysis; 2000-2009)	Retrospective (only patients receiving transplant included)	**Nontargeted** AML/ALL-type = 27 NHL-type = 7	N/A		Allo-SCT in CR1 = 19 Allo-SCT ≥ CR1 = 15 3 y OS = 43%
Laribi et al[121] 2001-2017	Retrospective	**Nontargeted** AML-type = 53 ALL-type = 96 NHL-type = 150	AML-type Rx f/b SCT = 14/16 (88%) ALL-type Rx f/b SCT = 31/33 (94%) NHL-type Rx f/b SCT = 12/12 (100%)	Median OS = 18 mo	**5 years OS** AML-type therapy f/b allo-SCT = 59.5% ALL-type therapy f/b allo-SCT = 47.3% NHL-type therapy f/b allo-SCT = 71.1% No allo-SCT = 9.6% for leukemia-type therapy, 8.3% for lymphoma-type therapy
Yun et al[72] 2001-2019	Retrospective	**Mixed** AML-like = 1 ALL-type = 11 NHL-like = 10 SL-401 = 12	N/A 11 (100) 9 (90) 9 (75)		mOS with SCT = NR mOS without SCT ≈ 3 y
Pagano et al[10] 2005-2011	Retrospective	**Nontargeted** AML-type = 26 ALL-type = 15	7/16 (44) 10/15 (67)	Median OS = 8.7 mo After AML-type Rx = 7.1 mo After ALL-type Rx = 12.3 mo	**SCT = 6** mOS with SCT = 22.7 mo mOS without SCT= 7.1 mo
Aoki et al[31] (JSHCT analysis; 2002-2015)	Retrospective (only patients receiving transplant included)	**Nontargeted** AML-type =4 ALL-type = 10 NHL-type = 11	N/A	4 y OS = 65% After AML-type Rx = 67% After ALL-type Rx = 70% After NHL-type Rx = 62%	**4 y OS** After auto-SCT = 82% After allo-SCT = 69%
Taylor et al[24] 2000-2017	Retrospective	**Nontargeted** AML-type = 9 ALL-type = 35 Others = 10	N/A	2 y OS = 49%	**SCT = 25; (allo = 20, auto = 5)** 2 y OS after SCT = 60%
Pemmaraju et al[30] 1999-2020	Retrospective	**Mixed** ALL-type = 35 SL-401 = 37 Others = 28	80% 59% 43%	**Median OS** After ALL-type Rx= 28.3 mo After SL-401 = 13.7 mo After other Rx = 22.8 mo	**% responders proceeding to allo-SCT in CR1** 15/28 (54%) 13/22 (59%) 4/12 (33%) SCT specific survival data N/A
Pemmaraju et al[71] 2014-2019	Prospective clinical trial (long-term follow-up, 34 mo)	**Targeted** SL-401 (F/L) = 65§	75%	2 y OS = 40%	**SCT = 19‡** 2 y OS after SCT = 66% 2 y OS without SCT ≈ 30%

North American Blastic Plasmacytoid Dendritic Cell Neoplasm Consortium: position on standards of care and areas of need

Naveen Pemmaraju,[1] Hagop Kantarjian,[1] Kendra Sweet,[2] Eunice Wang,[3] Jayastu Senapati,[1] Nathaniel R. Wilson,[4] Marina Konopleva,[1]

- Anche nell'era della target therapy non vi è consenso pieno sulla scelta del trattamento e quindi i pazienti dovrebbero essere arruolati in trials clinici.
- Nella pratica clinica, fuori dai trials , la scelta risulta difficile tuttavia per i pazienti giovani fit può risultare utile o regimi chemioterapici ALL like o tagraxofusp in monoterapia in vista di trapianto allogenico.
- Negli anziani unfit tagraxofusp o HMA+ Venetoclax.
- Il panel consiglia inoltre la profilassi SNC
- Tuttavia…

The final therapy decision is thus dependent on multiple factors, including the toxicity profile of these drugs, patient and physician preference, and drug availability and affordability. As

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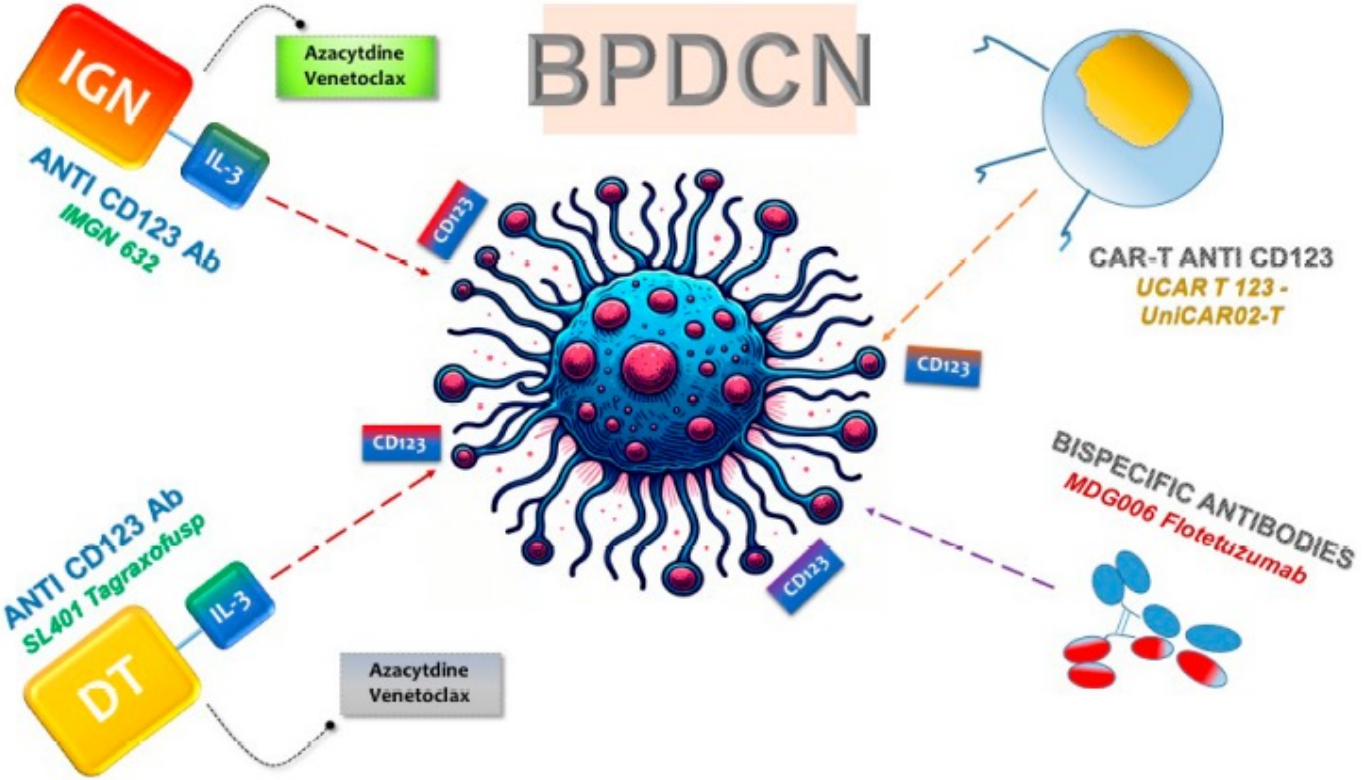
PROSPETTIVE FUTURE

- Standardizzazione e definizione di MRD (attraverso la MCF vs NGS).
- MRD che valuti i diversi compartimenti della malattia (cute, SL, BM e sangue).
- Una MRD standardizzata permetterebbe anche di stabilire l'utilità o meno di HSCT in certi setting di pazienti come ad esempio pazienti anziani o unfit con multiple co-morbidità.
- Una MRD standardizzata potrebbe inoltre fungere da guida per un approccio terapeutico ottimale sia in prima linea che nelle forme R/R.



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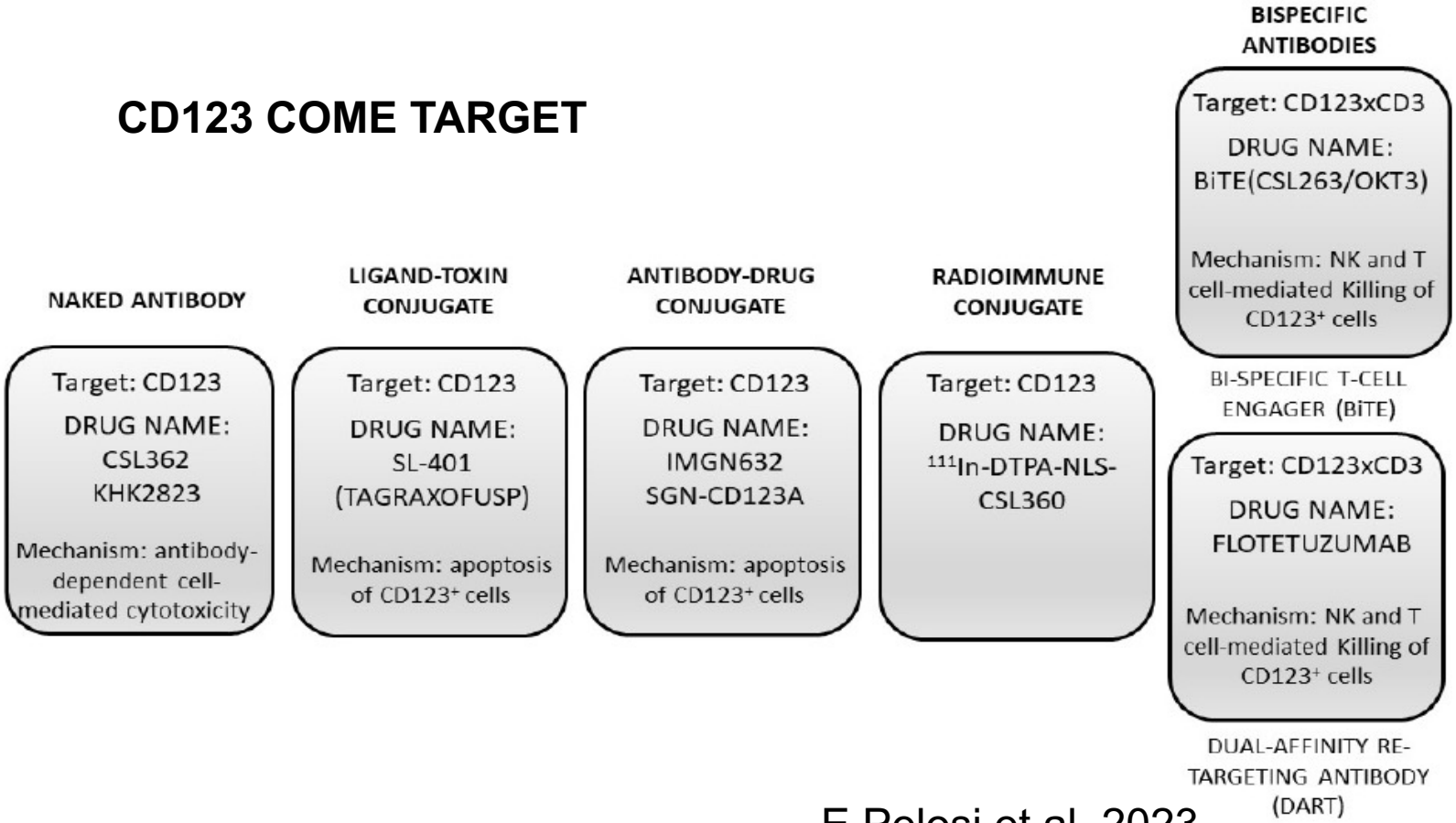
CD123 COME TARGET



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CD123 COME TARGET

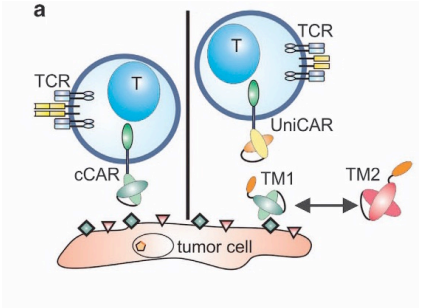
First generation CART
These CART are based on a CD3ζ intracellular domain, in the absence of costimulatory domains.
Limitations: limited proliferation and short life-span in vivo.

Second-third generation CART
Improvements: increased proliferation, cytotoxicity and longer in vivo life span.

Fourth-fift generation CART
Improvements: enhanced cytotoxicity against tumor cells and controlled cytokine production in response to interaction with tumor cells.

UCART123
Allogeneic TCRαβ-deficient CART cells targeting CD123.
TALEN gene editing technology is used to generate TCRαβ-negative allogeneic CD123 CART cells.
A CD20 safety switch is introduced in CAR vector to allow CAR elimination with rituximab.

UNICART
Inert CAR T platform for specific manipulation
Targeting module (TM) consisting of a highly flexible CD123-binding moiety, linked to a small peptide recognized by the UNICART effector T cells
Given the short pharmacokinetic half-life and fast internalization of TM, the system allows a rapid on/off switchability.



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Study ID	Therapeutic Strategy	Condition/Disease	Phase	Status
NCT03113643	***Tagraxofusp*** plus azacitidine ± venetoclax	AML, MDS, BPDCN	I	Recruiting
NCT04216524	***Tagraxofusp*** plus azacitidine and chemotherapy	BPDCN	II	Recruiting
NCT03386513	***IMGN632***	AML, ALL, BPDCN, MPN	I/II	Active, not recruiting
NCT04086264	***IMGN632*** alone or plus azacitidine ± venetoclax	CD123-Positive AML	I/II	Recruiting
NCT03203369	Chimeric Antigen Receptor T cells ***UCART 123***	BPDCN	I	Terminated
NCT04109482	Chimeric Antigen Receptor T cells ***MB-102***	BPDCN	I/II	Terminated
NCT02159495	Chimeric Antigen Receptor T cells ***CD123^{+} CAR T cells***	AML, BPDCN	I	Active, not recruiting
NCT04230265	Chimeric Antigen Receptor T cells ***UniCAR02-T + TM123***	AML, BPDCN	I	Recruiting
NCT04681105	Bispecific antibodies ***Flotetuzumab***	AML, BPDCN	I	Active, not recruiting

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Target	Drugs	Phase	Disease	Outcome	Adverse Events
CD123	Tagraxofusp	III	BPDCN 32 untreated 13 prev. treated	CR+CRi 54%; in untreated patients 72%; 52% OS at 24 months	Capillary Leak Syndrome 21%
CD123	Tagraxofusp	I	40 R/R AML 5 R/R MDS	AMLs: CR 2.5%; PR 2.5% MDS: PR 2.5%	Capillary Leak Syndrome 31%
CD123 BCL2	TAG+AZA TAG+AZA+VEN	I	14 AML (FL) 12 R/R AML 3 R/R BPDCN 4 MDS	TAG-AZA: AML (FL) CRi 20%; R/R AML CR 0% TAG-AZA-VEN: AML (FL) CR+CRi 89%; R/R AML CR 0%; R/R BPDCN CR+CRi 66%	Capillary Leak Syndrome 33%
CD123	IMGN632 (Pivekimab Sunirine)	I	67 R/R AML	CR+CRi 20%	Cytokine Release Syndrome 16%
CD123 BCL2	IMGN632 AZA VEN	Ib/II	35 R/R AML	CR+CRi 31%	Cytokine Release Syndrome 37%
CD123	IMGN632	I	23 R/R BPDCN	CR+CRi 22% PR 8%	Cytokine Release Syndrome 22%
CD123 CD3	APV0436 (BiTE)	I	22 R/R AML, either pAML or sAML	CR+CRi 32%	Cytokine Release Syndrome 18%
CD123 CD3	XmAb 14045 (Vibecotamab) (BiTE)	I	104 R/R AML	CR+CRi 14% (evaluated in 51 patients at optimal dose)	Cytokine Release syndrome 59%
CD123 CD3	Flotetuzumab (DART)	I/II	88 R/R AML	CR+CRi 30% (evaluated in 46 patients at optimal dose)	Cytokine Release Syndrome 13%
CD123 CD3	Flotetuzumab (DART)	I	17 R/R pediatric AML	CR+CRi 12% PR 6%	Cytokine Release Syndrome 9%
CD123	UniCAR-T	I	14 R/R AML	Blast cell count reduction (10 patients), CRi (2 patients), CR with MRD negativity (1 patient)	Cytokine Release Syndrome (12/14)
CD123	Anti-CD123 allogeneic CAR-T	I	16 R/R AML	SD (2/16), blast cell count reduction (1 patients), CR with MRD negativity (1 patient)	Cytokine Release Syndrome (15/16)
CD123	CAR-T	I	12 R/R pediatric AML	Blast cell count reduc (1 patient), CR (1 pati	

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CONCLUSIONI

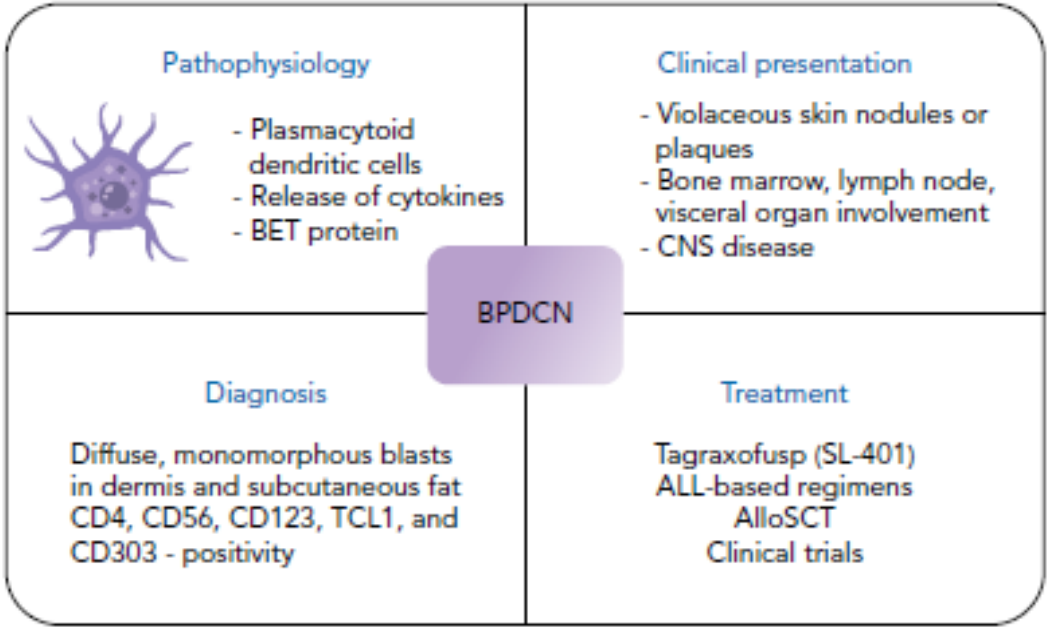
1. La BPDCN è una malattia rara a prognosi infausta che richiede una attenta valutazione multidisciplinare per una corretto approccio clinico-diagnostico e terapeutico.

2. Negli ultimi anni si è assistito al passaggio da un trattamento chemo-based a una target therapy aprendo la possibilità per trattamento chemo-free con buone ORR.

Prospettive future

1. Possibili combinazioni dei nuovi anti CD123 con ipometilanti e inibitori di BCL2 non solo per BPDCN ma anche per AML CD123+.

2. Necessaria la standardizzazione e la definizione di MRD utile non solo nel follow-up ma anche nel decision making ivi compreso il ruolo del HSCT.



GRAZIE PER L'ATTENZIONE

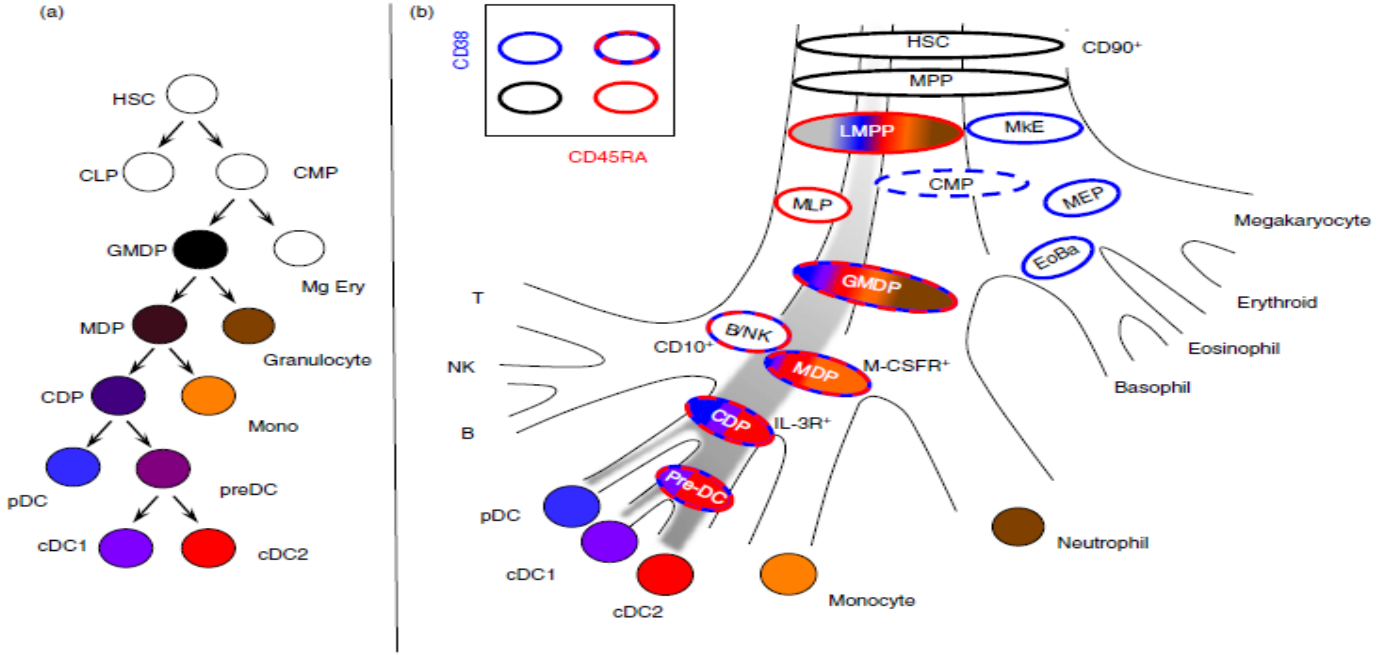


Figure 2. Classical and revised models of human haematopoiesis. (a) In classical models of haematopoiesis, cell potential partitions by successive bifurcations descending from the apex where common lymphoid and common myeloid progenitors (CLP; CMP) arise from the haematopietic stem cell (HSC). Each progenitor population has homogeneous differentiation potential such that every cell has an equal probability of two mutually exclusive fates. Hence, dendritic cells (DC) were proposed to arise in the sequence: CMPs, granulocyte–macrophage DC progenitor (GMDP), macrophage DC progenitor (MDP), common DC progenitor (CDP) with a final pre-DC stage leading to conventional DC1 (cDC1) and cDC2. Each population is given a uniform colour to indicate homogeneous potential. (b) Experimental data support several revisions to the classical model. First lineage is primed in early progenitors so that most populations contain only cells with a single potential. Second, lymphoid and myeloid potential run together originating as the lymphoid primed multi-potent progenitor (LMPP) that separates from megakaryocyte and erythroid potential (MkE) at the apex. Hence the gates defined by CD38 (blue borders) and CD45RA (red borders) contain phenotypically related cells but with restricted potentials, indicated by bands of colour each corresponding to a discrete lineage.

Collin M et al 2018