

# UNA NUOVA STORIA: il **TAGRAXOFUSP** e la **BPDCN**



**BOLOGNA - 2 MAGGIO 2023**  
STARHOTELS EXCELSIOR

## **SESSIONE I**

**Ottimizzazione del percorso diagnostico e terapeutico**

Moderatore: P.L. Zinzani, Bologna

10.50-11.20

Ottimizzazione Diagnostica *S.A. Pileri, Bologna*



Istituto  
Europeo  
di Oncologia



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Roche					+		
Takeda					+		
Diatech						+	
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Guideline Article - Expert opinion

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## **Unmet Clinical Needs and Management Recommendations for Blastic Plasmacytoid Dendritic Cell Neoplasm: A Consensus-based Position Paper From an Ad Hoc International Expert Panel**

Livio Pagano<sup>1,2</sup>, Pier Luigi Zinzani<sup>3,4</sup>, Stefano Pileri<sup>5</sup>, Pietro Quaglino<sup>6</sup>, Branko Cuglievan<sup>7</sup>, Emilio Berti<sup>8,9</sup>, Naveen Pemmaraju<sup>10</sup>, Francesco Onida<sup>11,12</sup>, Rein Willemze<sup>13</sup>, Alberto Orfao<sup>14,15</sup>, Giovanni Barosi<sup>16</sup>

## List of UCNs Proposed by the Panel

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1. Optimization of subclassification: pediatric vs adult
2. Optimization of the prognostic stratification
3. Indication to allotransplant
4. Indication to autotransplant
5. Optimization of the staging pathway
6. Optimization of the diagnostic pathway
7. CNS prophylaxis
8. Multidisciplinary management coordination
9. Making the pediatric groups more aware of the disease
10. Optimization of subclassification: plasmacytoid vs AXL+ dendritic cell neoplasms.
11. Therapeutic recommendations for young (and fit) patients
12. Mechanism of drug resistance
13. Therapeutic recommendations for elderly or unfit patients

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CNS = central nervous system; UCN = unmet clinical need.

# International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Daniel A. Arber,<sup>1</sup> Attilio Orazi,<sup>2</sup> Robert P. Hasserjian,<sup>3</sup> Michael J. Borowitz,<sup>4</sup> Katherine R. Calvo,<sup>5</sup> Hans-Michael Kvasnicka,<sup>6</sup> Sa A. Wang,<sup>7</sup> Adam Bagg,<sup>8</sup> Tiziano Barbui,<sup>9</sup> Susan Branford,<sup>10</sup> Carlos E. Bueso-Ramos,<sup>7</sup> Jorge E. Cortes,<sup>11</sup> Paola Dal Cin,<sup>12</sup> Courtney D. DiNardo,<sup>7</sup> Hervé Dombret,<sup>13</sup> Eric J. Duncavage,<sup>14</sup> Benjamin L. Ebert,<sup>15</sup> Elihu H. Estey,<sup>16</sup> Fabio Facchetti,<sup>17</sup> Kathryn Foucar,<sup>18</sup> Naseema Gangat,<sup>19</sup> Umberto Gianelli,<sup>20</sup> Lucy A. Godley,<sup>1</sup> Nicola Gökbuget,<sup>21</sup> Jason Gotlib,<sup>22</sup> Eva Hellström-Lindberg,<sup>23</sup> Gabriela S. Hobbs,<sup>3</sup> Ronald Hoffman,<sup>24</sup> Elias J. Jabbour,<sup>7</sup> Jean-Jacques Kiladjian,<sup>13</sup> Richard A. Larson,<sup>1</sup> Michelle M. Le Beau,<sup>1</sup> Mignon L.-C. Loh,<sup>25</sup> Bob Löwenberg,<sup>26</sup> Elizabeth Macintyre,<sup>27</sup> Luca Malcovati,<sup>28</sup> Charles G. Mullighan,<sup>29</sup> Charlotte Niemeyer,<sup>30</sup> Olatoyosi M. Odenike,<sup>1</sup> Seishi Ogawa,<sup>31</sup> Alberto Orfao,<sup>32</sup> Elli Papaemmanuil,<sup>33</sup> Francesco Passamonti,<sup>28</sup> Kimmo Porkka,<sup>34</sup> Ching-Hon Pui,<sup>29</sup> Jerald P. Radich,<sup>35</sup> Andreas Reiter,<sup>36</sup> Maria Rozman,<sup>37</sup> Martina Rudelius,<sup>38</sup> Michael R. Savona,<sup>39</sup> Charles A. Schiffer,<sup>40</sup> Annette Schmitt-Graeff,<sup>41</sup> Akiko Shimamura,<sup>15,42</sup> Jorge Sierra,<sup>43</sup> Wendy A. Stock,<sup>1</sup> Richard M. Stone,<sup>15</sup> Martin S. Tallman,<sup>44</sup> Jürgen Thiele,<sup>45</sup> Hwei-Fang Tien,<sup>46</sup> Alexandar Tzankov,<sup>47</sup> Alessandro M. Vannucchi,<sup>48</sup> Paresh Vyas,<sup>49</sup> Andrew H. Wei,<sup>50</sup> Olga K. Weinberg,<sup>51</sup> Agnieszka Wierzbowska,<sup>52</sup> Mario Cazzola,<sup>28</sup> Hartmut Döhner,<sup>53</sup> and Ayalew Tefferi<sup>19</sup>

REVIEW ARTICLE

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

Joseph D. Khoury <sup>1</sup>✉, Eric Solary <sup>2</sup>✉, Oussama Abla<sup>3</sup>, Yasmine Akkari <sup>4</sup>, Rita Alaggio<sup>5</sup>, Jane F. Apperley <sup>6</sup>, Rafael Bejar <sup>7</sup>, Emilio Berti<sup>8</sup>, Lambert Busque <sup>9</sup>, John K. C. Chan<sup>10</sup>, Weina Chen <sup>11</sup>, Xueyan Chen<sup>12</sup>, Wee-Joo Chng<sup>13</sup>, John K. Choi <sup>14</sup>, Isabel Colmenero <sup>15</sup>, Sarah E. Coupland<sup>16</sup>, Nicholas C. P. Cross <sup>17</sup>, Daphne De Jong<sup>18</sup>, M. Tarek Elghetany<sup>19</sup>, Emiko Takahashi <sup>20</sup>, Jean-Francois Emile <sup>21</sup>, Judith Ferry<sup>22</sup>, Linda Fogelstrand<sup>23</sup>, Michaela Fontenay<sup>24</sup>, Ulrich Germing<sup>25</sup>, Sumeet Gujral<sup>26</sup>, Torsten Haferlach <sup>27</sup>, Claire Harrison<sup>28</sup>, Jennelle C. Hodge<sup>29</sup>, Shimin Hu <sup>1</sup>, Joop H. Jansen<sup>30</sup>, Rashmi Kanagal-Shamanna <sup>1</sup>, Hagop M. Kantarjian <sup>31</sup>, Christian P. Kratz <sup>32</sup>, Xiao-Qiu Li<sup>33</sup>, Megan S. Lim<sup>34</sup>, Keith Loeb<sup>35</sup>, Sanam Loghavi <sup>1</sup>, Andrea Marcogliese<sup>19</sup>, Soheil Meshinchi<sup>36</sup>, Phillip Michaels<sup>37</sup>, Kikkeri N. Naresh <sup>35</sup>, Yasodha Natkunam <sup>38</sup>, Reza Nejati<sup>39</sup>, German Ott<sup>40</sup>, Eric Padron <sup>41</sup>, Keyur P. Patel<sup>1</sup>, Nikhil Patkar <sup>42</sup>, Jennifer Picarsic<sup>43</sup>, Uwe Platzbecker <sup>44</sup>, Irene Roberts<sup>45</sup>, Anna Schuh <sup>46</sup>, William Sewell<sup>47</sup>, Reiner Siebert<sup>48</sup>, Prashant Tembhare <sup>42</sup>, Jeffrey Tyner <sup>49</sup>, Srdan Verstovsek <sup>31</sup>, Wei Wang <sup>1</sup>, Brent Wood<sup>50</sup>, Wenbin Xiao <sup>51</sup>, Cecilia Yeung <sup>35</sup> and Andreas Hochhaus <sup>52</sup>✉

## Plasmacytoid dendritic cell neoplasms: recognition of clonal proliferations detected in association with myeloid neoplasms and refinement/update of the diagnostic criteria for blastic plasmacytoid dendritic cell neoplasm

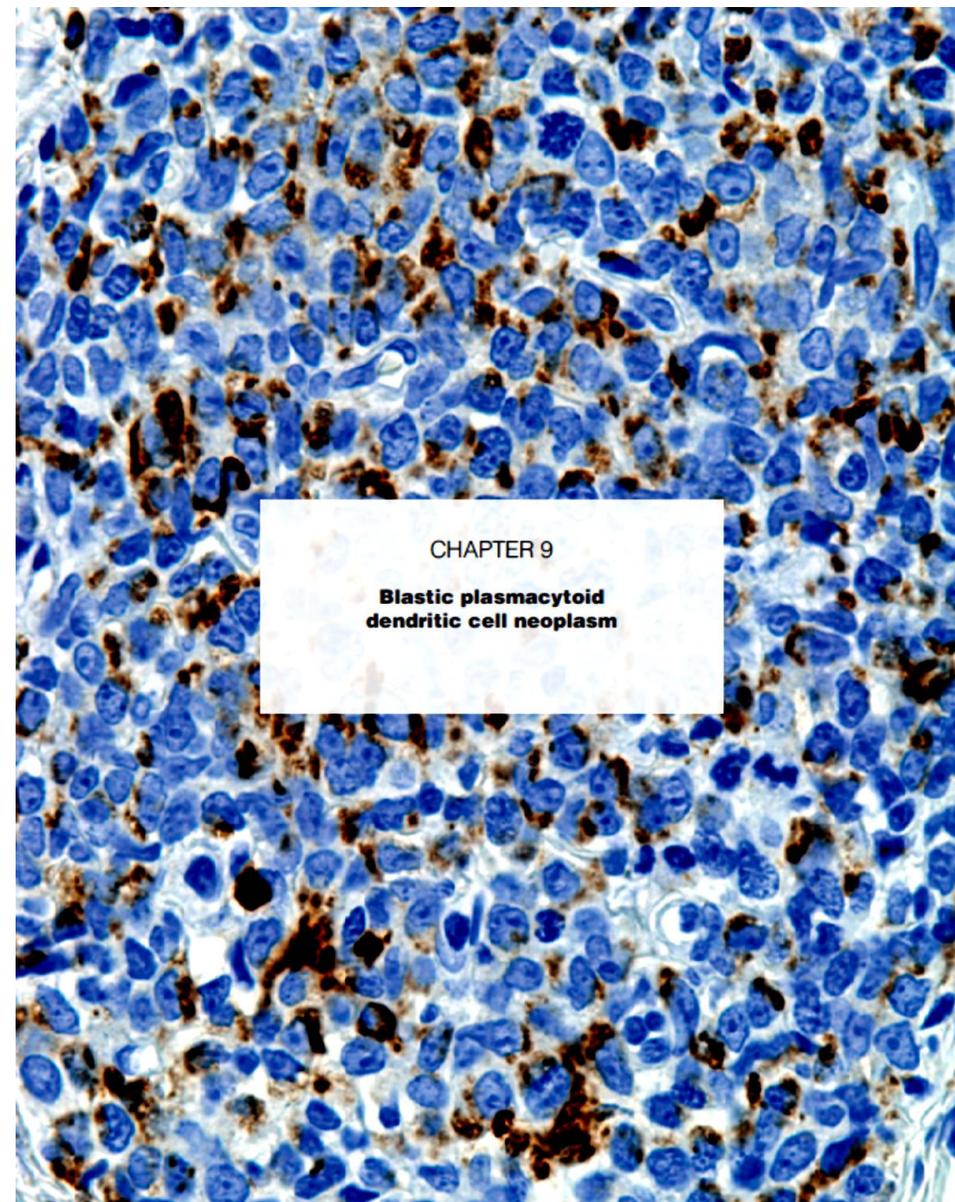
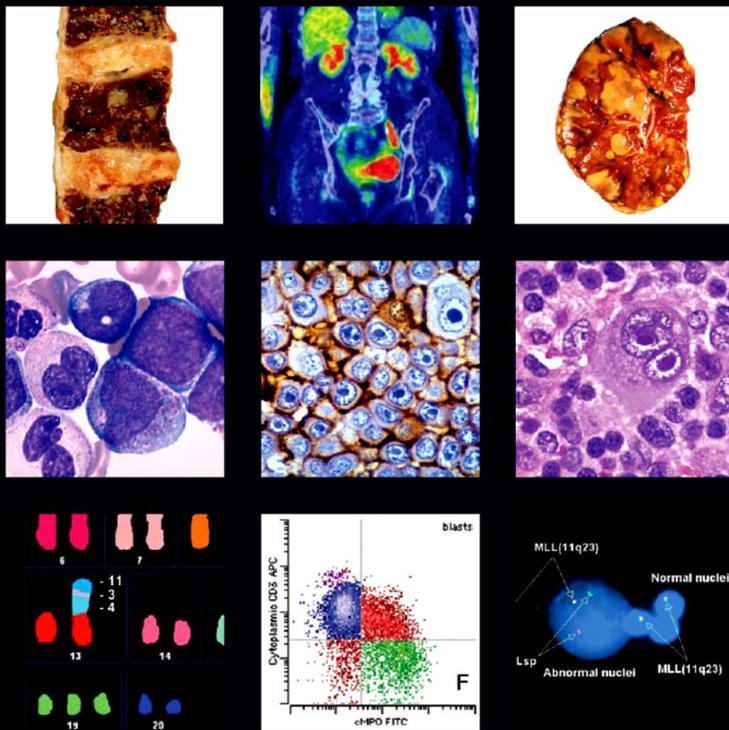
Mature plasmacytoid dendritic cell proliferation (MPDCP) associated with myeloid neoplasm reflects recent data showing that these represent clonal proliferation of pDCs with low grade morphology identified in the context of a defined myeloid neoplasm. Clonal MPDCP cells accumulate in the bone marrow of patients with myeloproliferative CMML harbouring activating RAS pathway mutations [84]. Patients with AML can have clonally expanded pDCs (pDC-AML), which share the same mutational landscape as CD34<sup>+</sup> blasts, and frequently arise in association with *RUNX1* mutations [85, 86]. It is unknown whether the pathogenetic mechanisms leading to MPDCP in association with MDS or MDS/MPN and with AML are the same. The framework for diagnosing blastic plasmacytoid dendritic cell neoplasm remains largely the same, with emphasis on immunophenotypic diagnostic criteria. (Table 15)

**Table 15.** Immunophenotypic diagnostic criteria of blastic plasmacytoid dendritic cell neoplasm.

<b>Expected positive expression:</b>
CD123*
TCF4*
TCL1*
CD303 *
CD304*
CD4
CD56
<b>Expected negative markers:</b>
CD3
CD14
CD19
CD34
Lysozyme
Myeloperoxidase
<b>Immunophenotypic diagnostic criteria:</b>
-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.

# WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Steven H. Swerdlow, Elias Campo, Nancy L. Harris, Elaine S. Jaffe, Stefano A. Pileri, Harald Stein, Jürgen Thiele, Daniel A. Arber, Robert P. Hasserjian, Michelle M. Le Beau, Attilio Orazi, Reiner Siebert



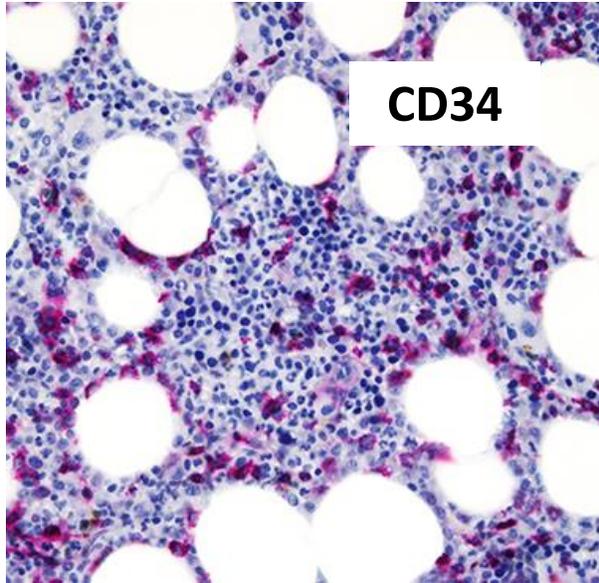
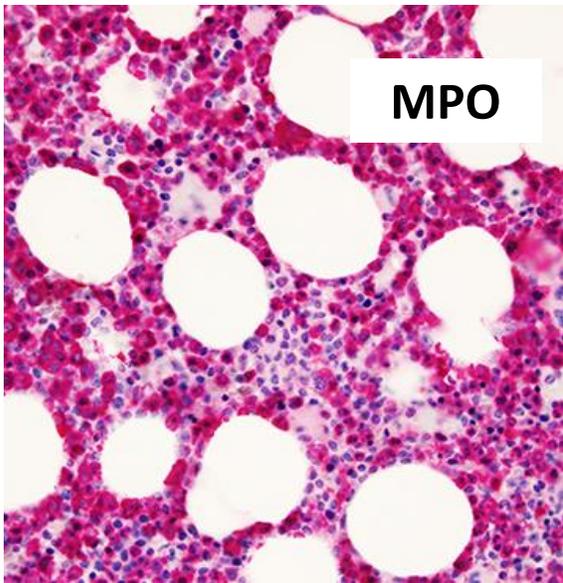
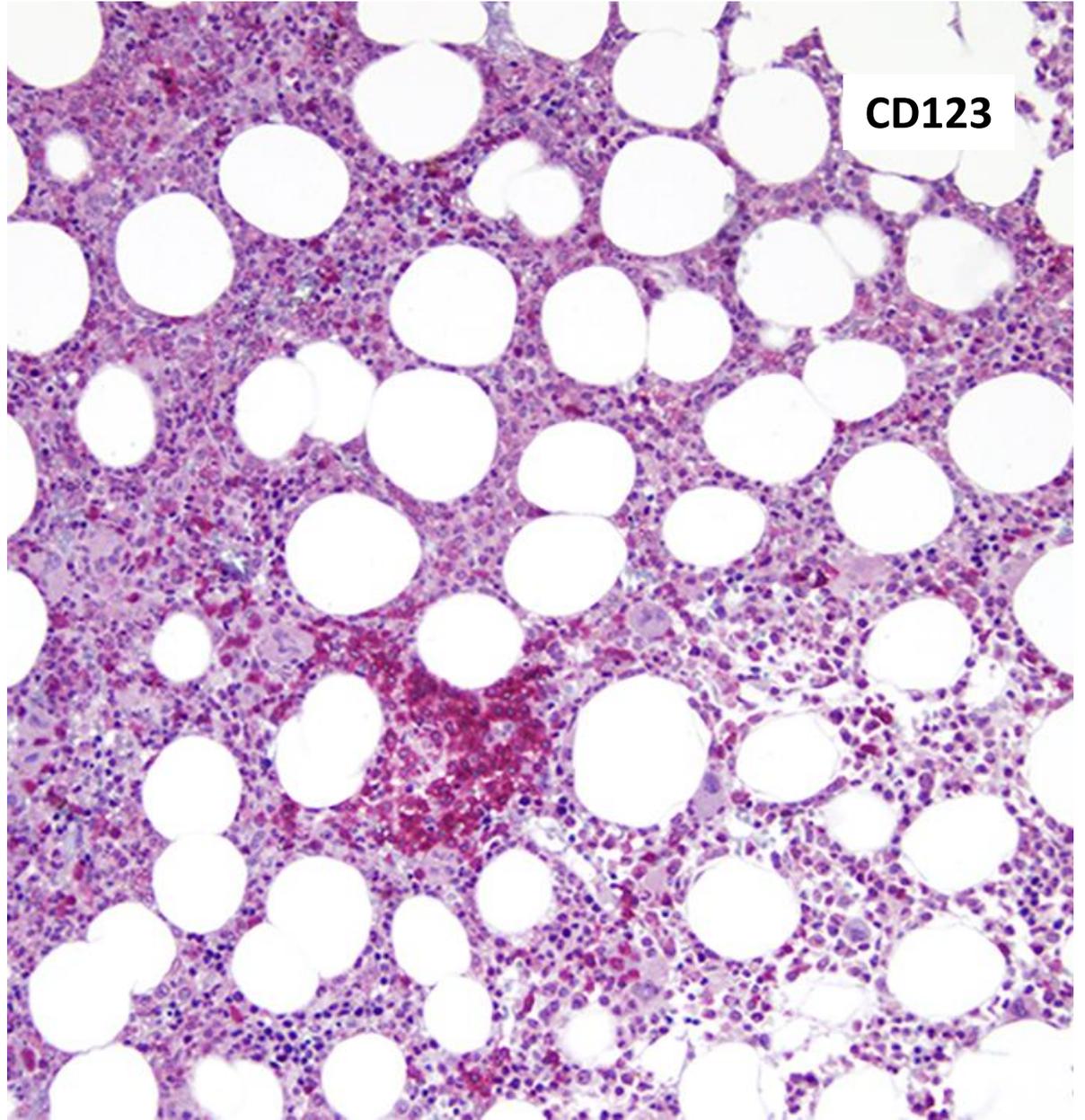
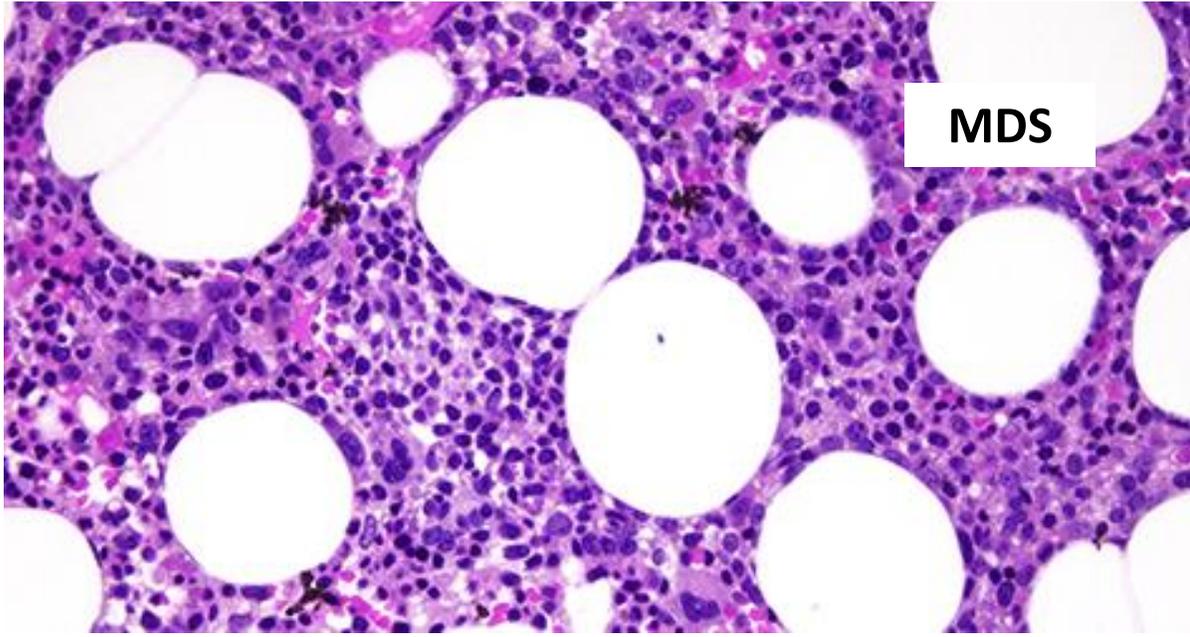
## 5<sup>th</sup> Edition of the WHO Classification

### **Plasmacytoid dendritic cell neoplasms: recognition of clonal proliferations detected in association with myeloid neoplasms and refinement/update of the diagnostic criteria for blastic plasmacytoid dendritic cell neoplasm**

Mature plasmacytoid dendritic cell proliferation (MPDCP) associated with myeloid neoplasm reflects recent data showing that these represent clonal proliferation of pDCs with low grade morphology identified in the context of a defined myeloid neoplasm. Clonal MPDCP cells accumulate in the bone marrow of patients with myeloproliferative CMML harbouring activating RAS pathway mutations [84]. Patients with AML can have clonally expanded pDCs (pDC-AML), which share the same mutational landscape as CD34<sup>+</sup> blasts, and frequently arise in association with *RUNX1* mutations [85, 86]. It is unknown whether the pathogenetic mechanisms leading to MPDCP in association with MDS or MDS/MPN and with AML are the same. The framework for diagnosing blastic plasmacytoid dendritic cell neoplasm remains largely the same, with emphasis on immunophenotypic diagnostic criteria. (Table 15)

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Myeloid  
Sarcoma

*RUNX1* mutations

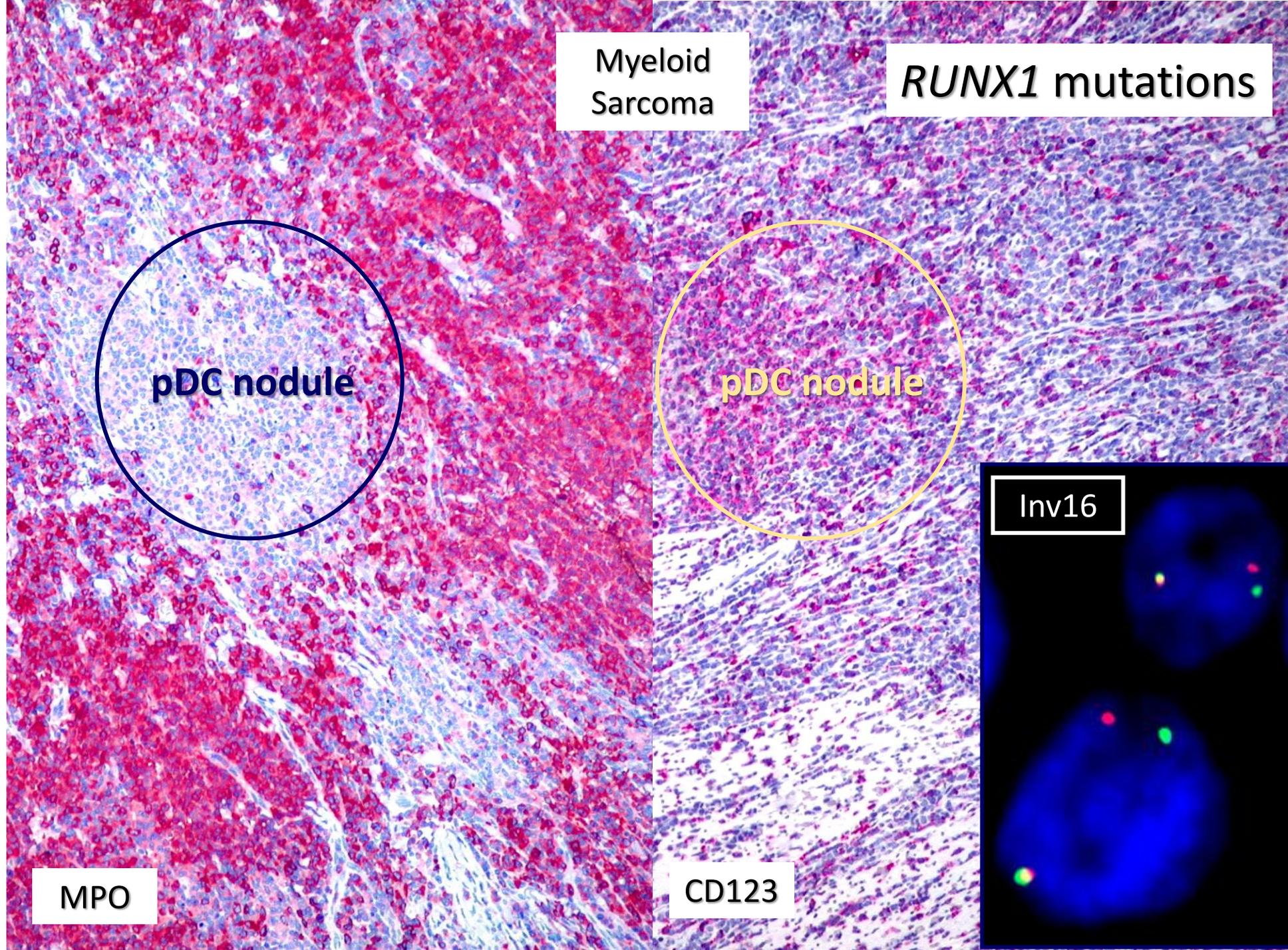
pDC nodule

pDC nodule

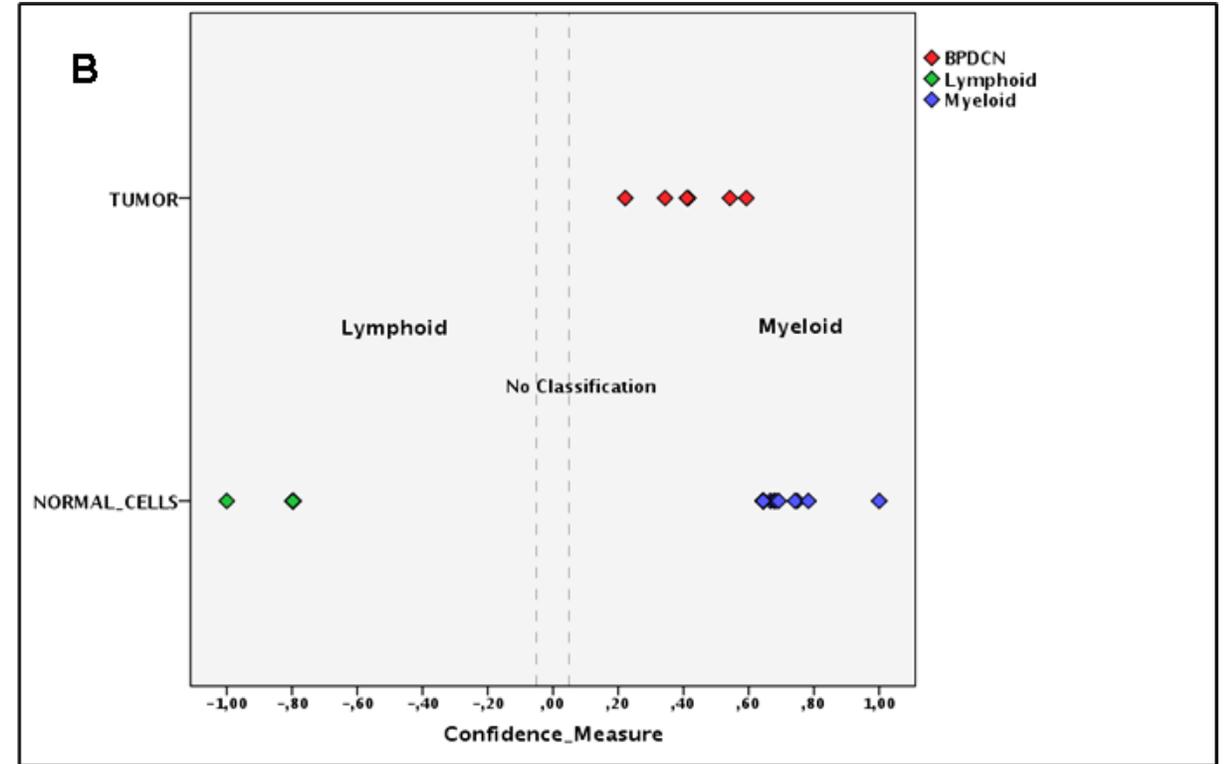
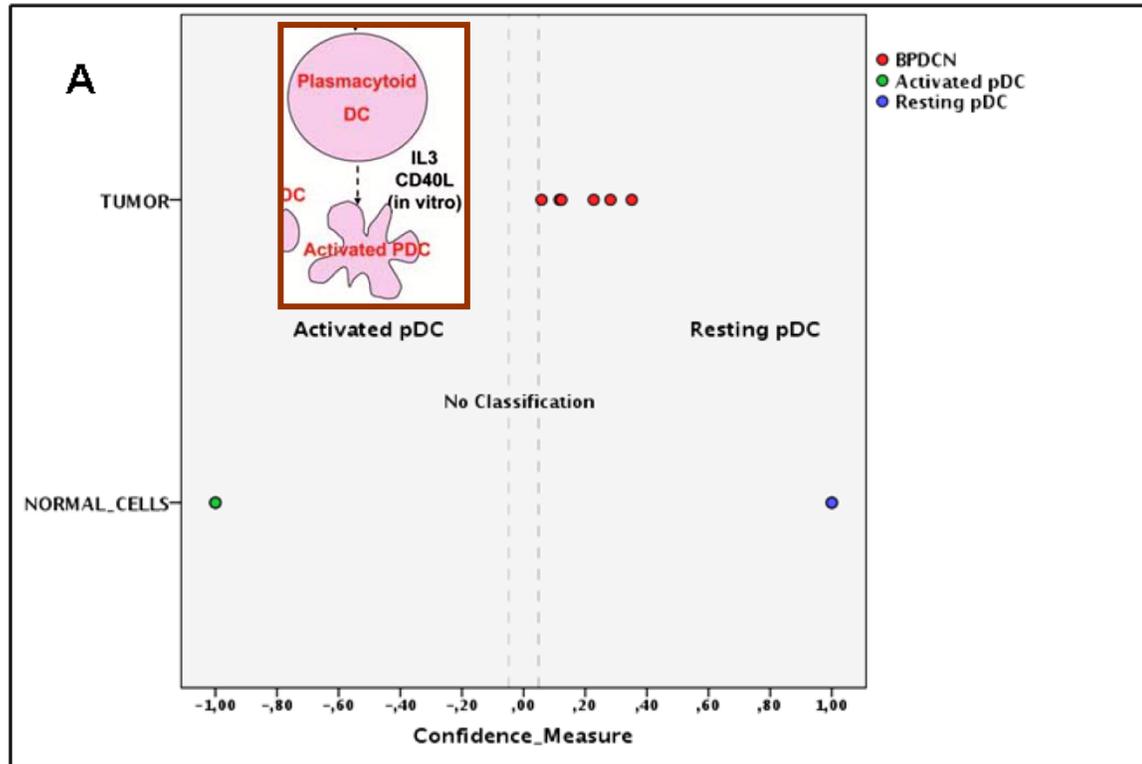
MPO

CD123

Inv16



# Sapienza MR, ....., Pileri SA, Leukemia 2014; 28; 1606-1616



# Blastic Plasmacytoid Dendritic Cell Neoplasm: State of the Art and Prospects

*Cancers* 2019, 11, 595;

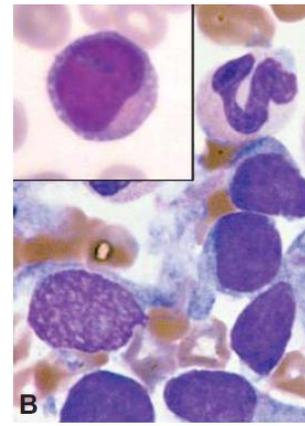
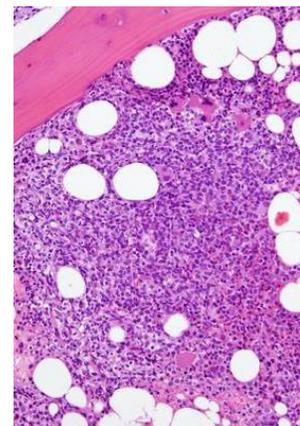
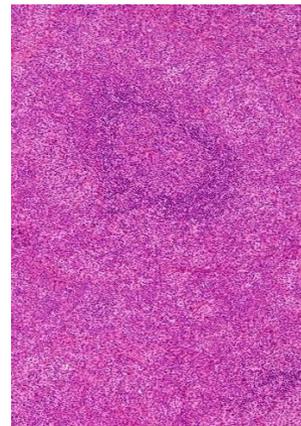
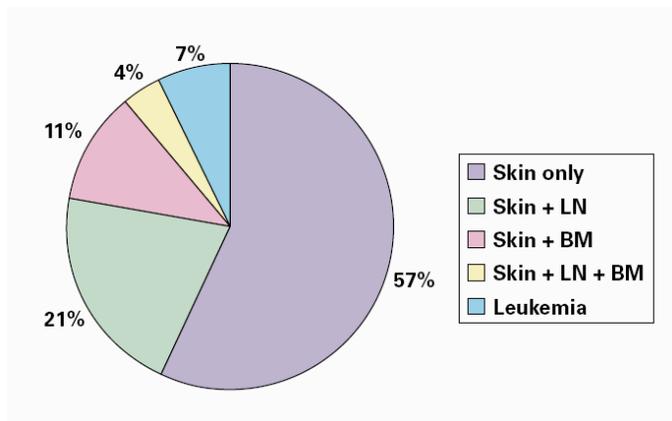
Maria Rosaria Sapienza <sup>1,†</sup> , Alessandro Pileri <sup>2,†</sup>, Enrico Derenzini <sup>3,†</sup>, Federica Melle <sup>1</sup>,  
Giovanna Motta <sup>1</sup>, Stefano Fiori <sup>1</sup>, Angelica Calleri <sup>1</sup>, Nicola Pimpinelli <sup>4</sup>, Valentina Tabanelli <sup>1</sup>   
and Stefano Pileri <sup>1,\*</sup> 

Blastic plasmacytoid dendritic cell neoplasms: results of an international  
survey on 398 adult patients

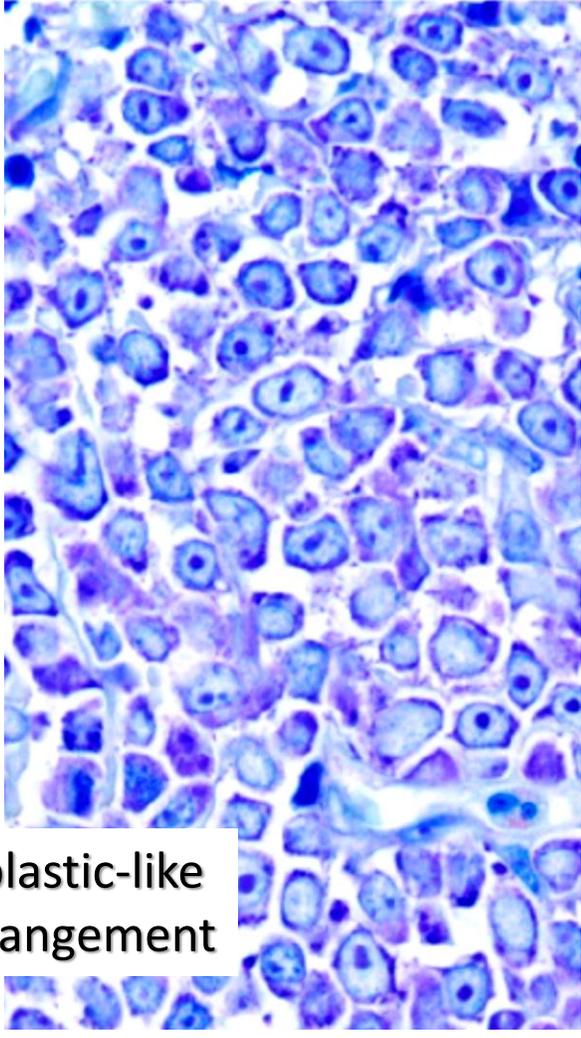
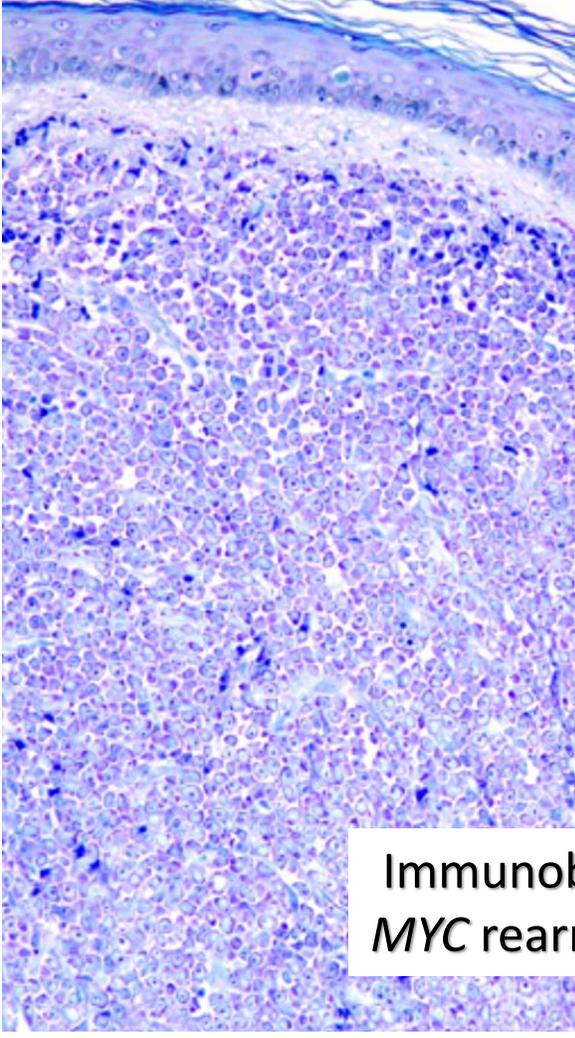
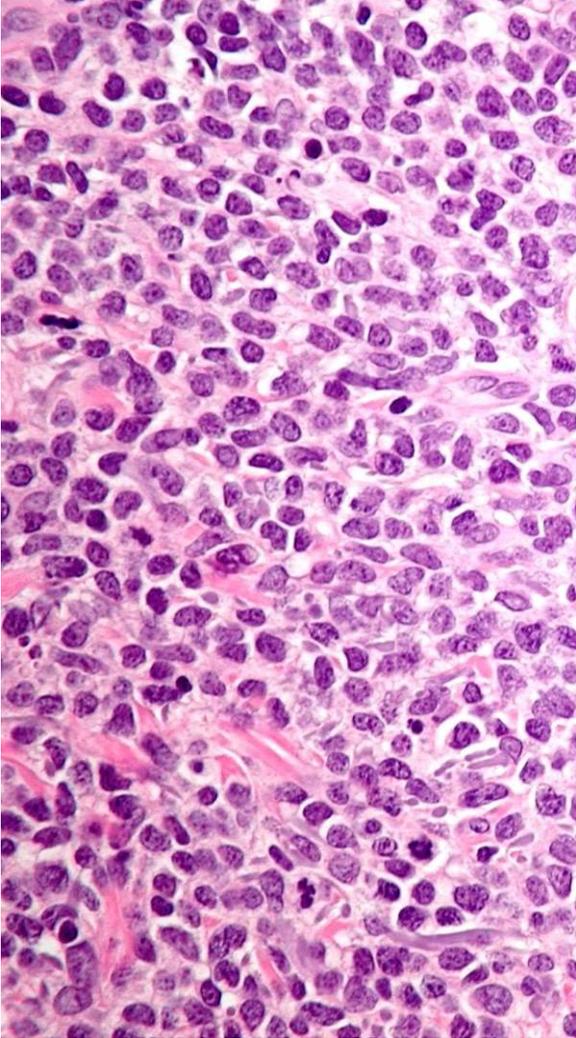
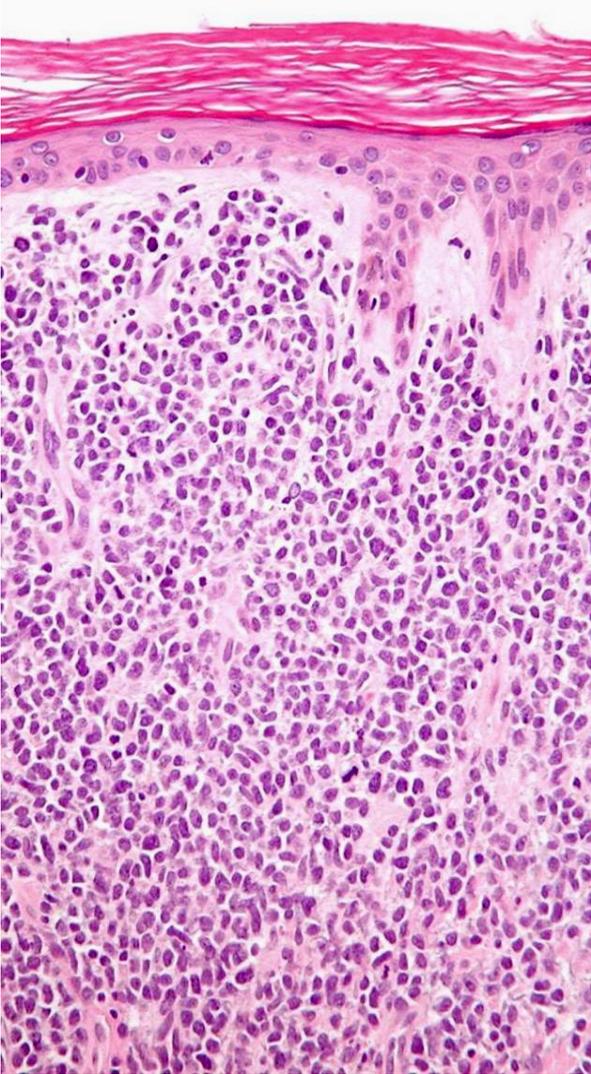
**blood** advances 13 OCTOBER 2020 • VOLUME 4, NUMBER 19

Kamel Laribi,<sup>1</sup> Alix Baugier de Materre,<sup>2</sup> Mohamad Sobh,<sup>3</sup> Lorenzo Cerroni,<sup>4</sup> Caterina Giovanna Valentini,<sup>5</sup> Tomohiro Aoki,<sup>6</sup> Ritsuro Suzuki,<sup>7</sup>  
Kengo Takeuchi,<sup>8</sup> Arthur E. Frankel,<sup>9</sup> Carlo Cota,<sup>10</sup> David Ghez,<sup>11</sup> Ronan Le Calloch,<sup>12</sup> Livio Pagano,<sup>5</sup> and Tony Petrella<sup>13</sup>

- Orphan tumour [prevalence (0.44% of all hematological malignancies) and therapeutic problems].
- Mean/median age: 57.5 – 66 yrs.
- Rare in childhood (better response to ALL therapies?).
- M/F: 3.5/1.
- Presentation: skin (57%); skin and lymph nodes (21%); skin and BM (11%); skin, lymph nodes and BM (4%); leukaemic (7%).
- CNS involvement: 30 – 60%.



Morphology: ambiguous (leukaemia/lymphoma)



Immunoblastic-like  
*MYC* rearrangement

# Phenotype: distinctive profile by marker combination on routine sections

TCF4+ (\*)

CD123+ (\*)

CD303+/-

CD56+

TCL1A+

CD4+

CD43+

CD45RA+

MYC+ (IB-like cases)

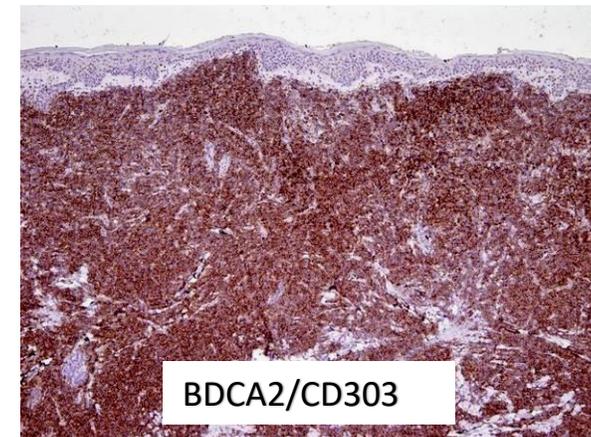
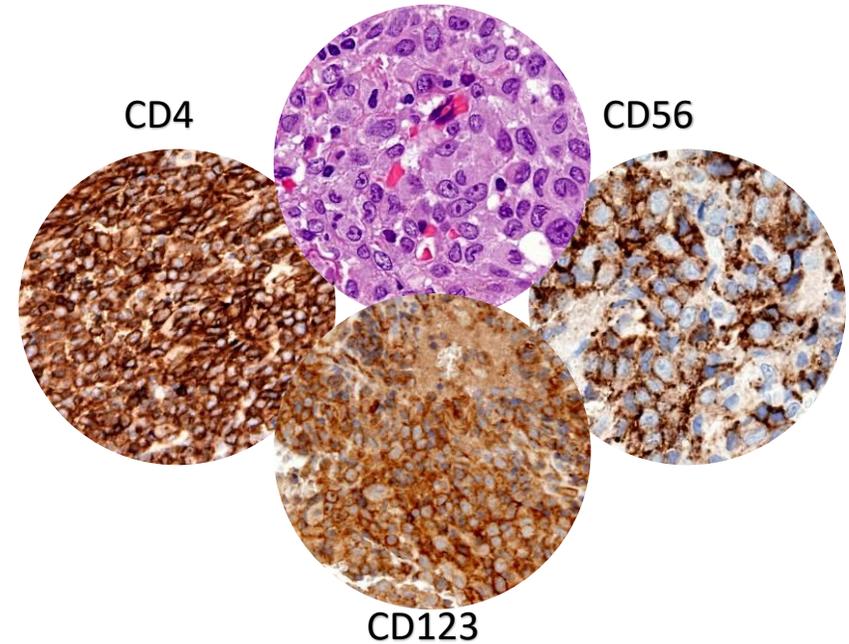
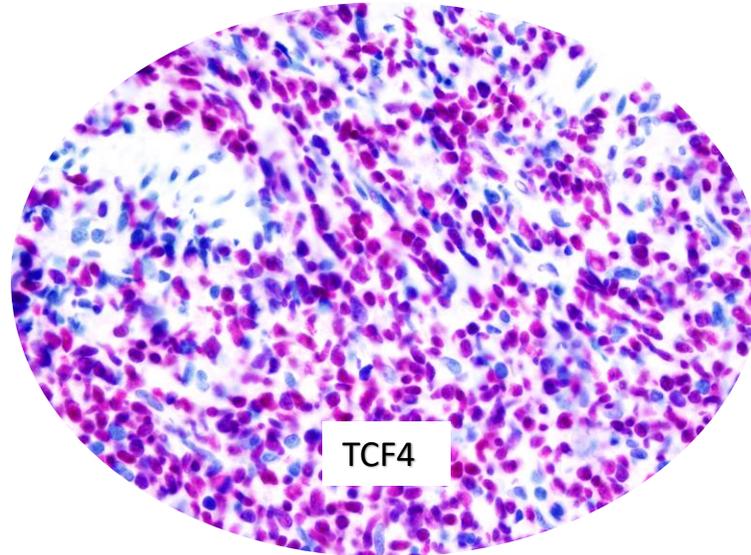
CD68+/- (dot-like)

BCL2 (\*)

Regular negativity for CD3, CD13, CD16, CD19,  
CD20, LAT, Lysozyme, MPO, and NPM1

Possible aberrant expression of some B or T cell  
markers

(\*Druggable)



# Cytoplasmic nucleophosmin is not detected in blastic plasmacytoid dendritic cell neoplasm

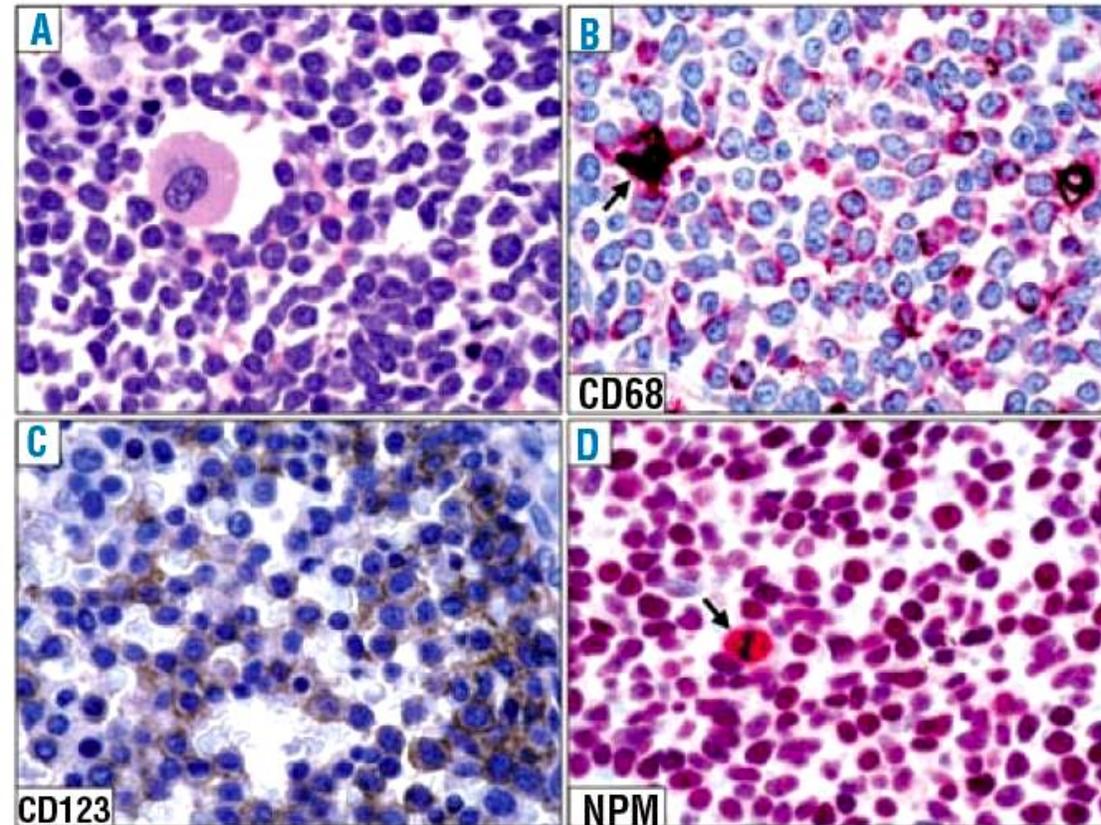
Fabio Facchetti,<sup>1</sup> Stefano A. Pileri,<sup>2</sup> Claudio Agostinelli,<sup>2</sup> Maria Paola Martelli,<sup>3</sup> Marco Paulli,<sup>4</sup> Adriano Venditti,<sup>5</sup> Massimo F Martelli,<sup>3</sup> and Brunangelo Falini<sup>3</sup>

\*FF and SAP contributed equally to this work.

haematologica | 2008; 94(2)

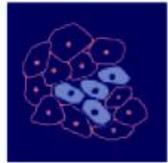
| 285 |

Case	Age/Sex	Sites	CD4	CD56	CD123	TCL1	CLA	CD34	NPM
1	73/F*	Skin, Ln, Bm	+	+	+	+	+	-	Nuclear
2	63/M*	Skin, Bm	+	+	+	+	+	-	Nuclear
3	60/M*	Skin	+	+	+	+	+	-	Nuclear
4	60/M*	Skin	+	+	+	+	+	-	Nuclear
5	63/M	Skin, Bm, Ln	-	+	+	na	+	-	Nuclear
6	71/M	Skin, Bm	+	+	+	na	ad	-	Nuclear
7	67/M	Skin	+	+	+	na	+	-	Nuclear
8	61/M	Bm	-	±	na	+	+	-	Nuclear
9	70/F	Skin	±	+	+	-	±	na	Nuclear
10	81/M	Skin	-	+	+	+	±	na	Nuclear
11	60/M	Bm	-	+	ad	+	±	-	Nuclear
12	39/M	Bm	na	+	ad	±	+	-	Nuclear
13	48/M	Skin	+	+	+	na	na	na	Nuclear



# A Druggable TCF4- and BRD4-Dependent Transcriptional Network Sustains Malignancy in Blastic Plasmacytoid Dendritic Cell Neoplasm

Michele Ceribelli,<sup>1,7</sup> Zhiying Esther Hou,<sup>2</sup> Priscilla N. Kelly,<sup>1</sup> Da Wei Huang,<sup>1</sup> George Wright,<sup>3</sup> Karthik Ganapathi,<sup>4,11</sup> Moses O. Egbuomwan,<sup>4</sup> Stefania Pittaluga,<sup>4</sup> Arthur L. Shaffer,<sup>1</sup> Guido Marcucci,<sup>5</sup> Stephen J. Forman,<sup>5</sup> Wenming Xiao,<sup>6</sup> Rajarshi Guha,<sup>7</sup> Xiaohu Zhang,<sup>7</sup> Marc Ferrer,<sup>7</sup> Laurence Chaperot,<sup>8,9</sup> Joel Plumas,<sup>8,9</sup> Elaine S. Jaffe,<sup>4</sup> Craig J. Thomas,<sup>7</sup> Boris Reizis,<sup>2,10,\*</sup> and Louis M. Staudt<sup>1,12,\*</sup>



*cancers*



*Review*

# CD123 as a Therapeutic Target in the Treatment of Hematological Malignancies

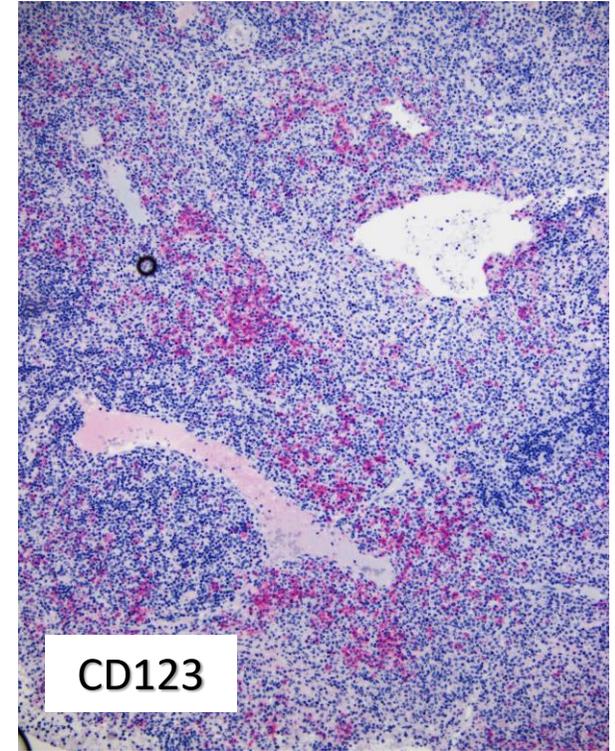
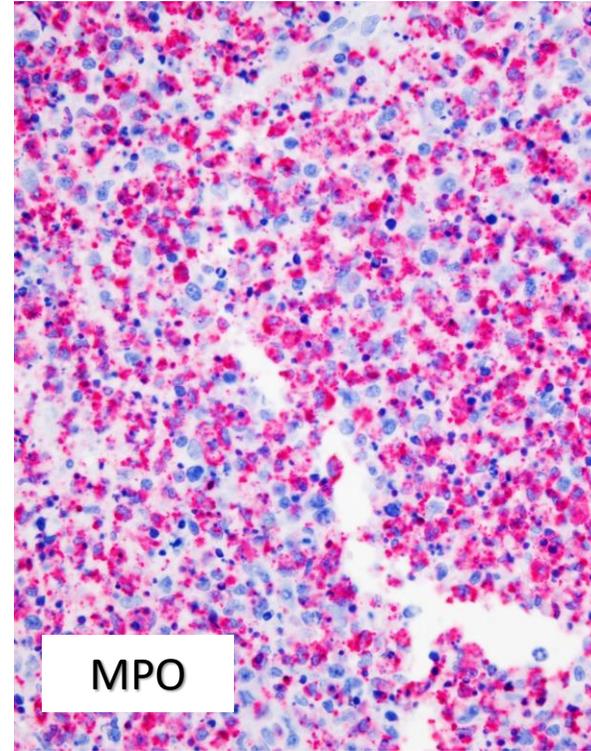
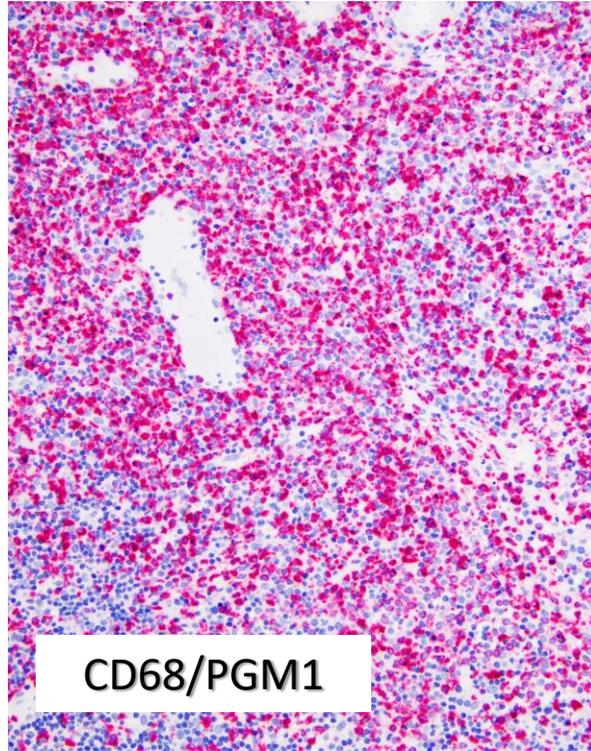
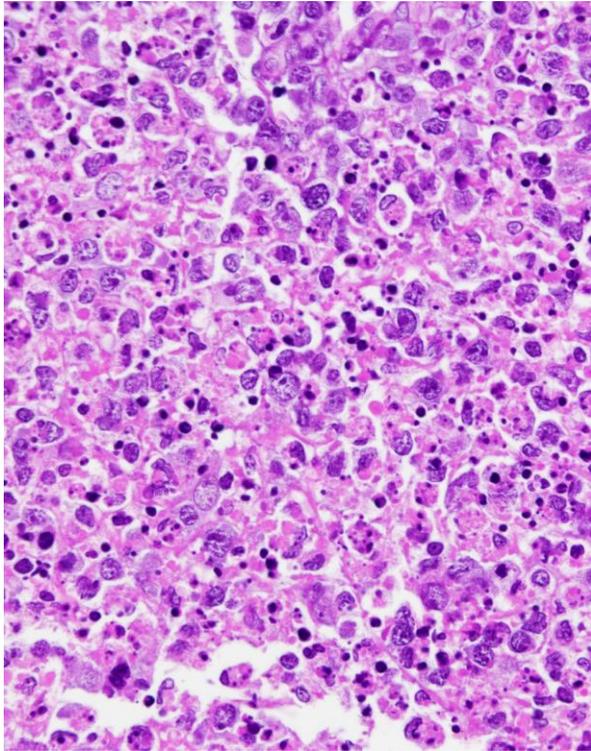
Ugo Testa \* , Elvira Pelosi and Germana Castelli

*Cancers* 2019, 11, 1358

# CD123

- Interleukin 3 receptor  $\alpha$ -chain (IL3R $\alpha$ ).
- Membrane receptor that heterodimerizes with the  $\beta$  common ( $\beta$ c) subunit to constitute the functional IL3 receptor (IL3R).
- IL3R is the IL3 specific member of the beta  $\beta$ c family of receptors, which also includes IL5R and granulocyte monocyte colony stimulating factor (GM CSF) receptor.
- It functions in regulating growth, proliferation, survival and differentiation of hematopoietic cells, along with immunity and inflammatory response.

Strongest level of CD123 staining is on plasmacytoid dendritic cells

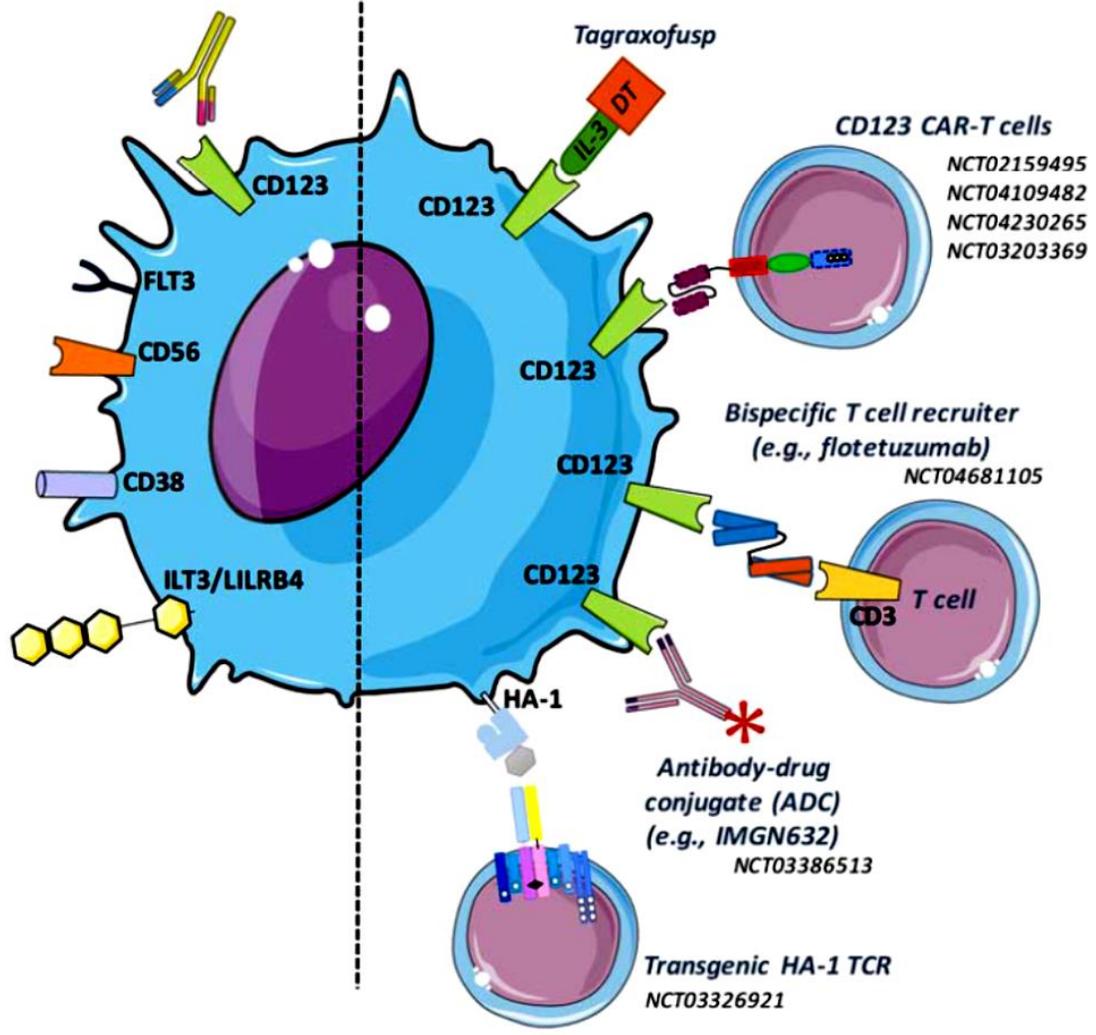


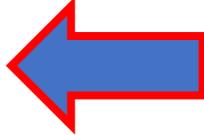
Kikuchi's lymphadenitis

From the bench... 

... to bedside... 

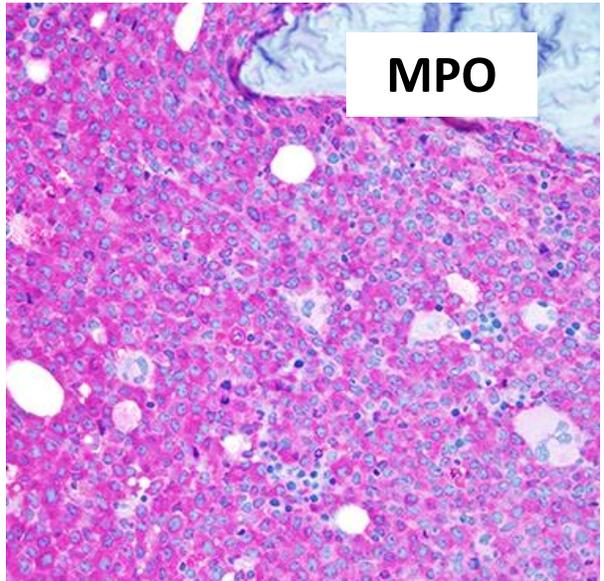
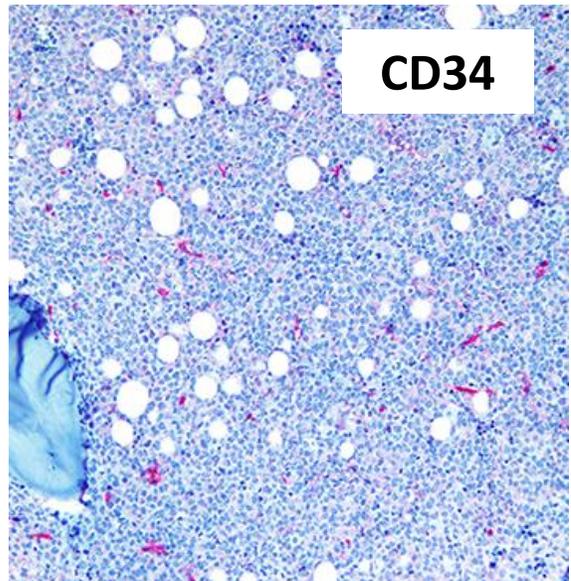
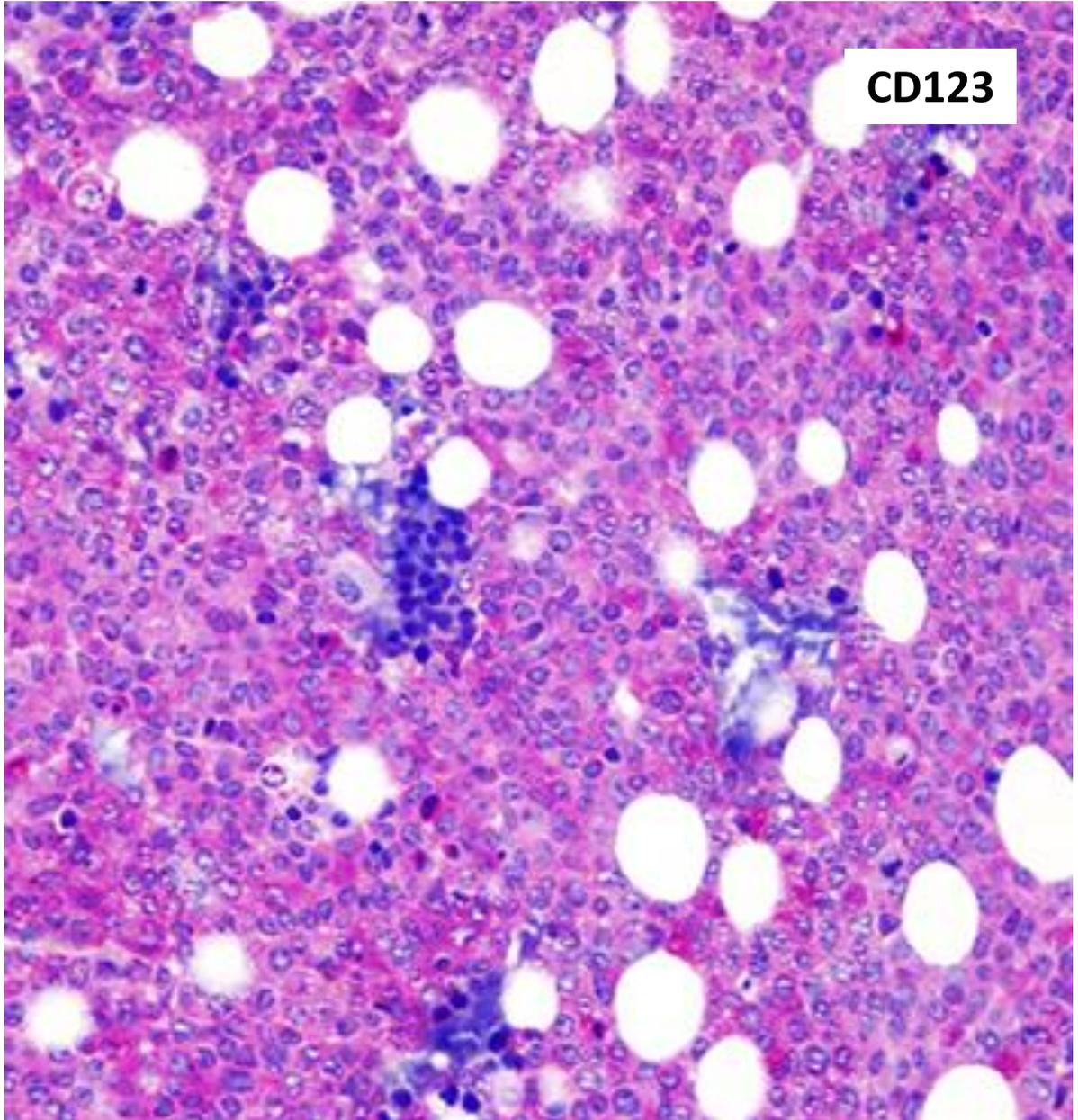
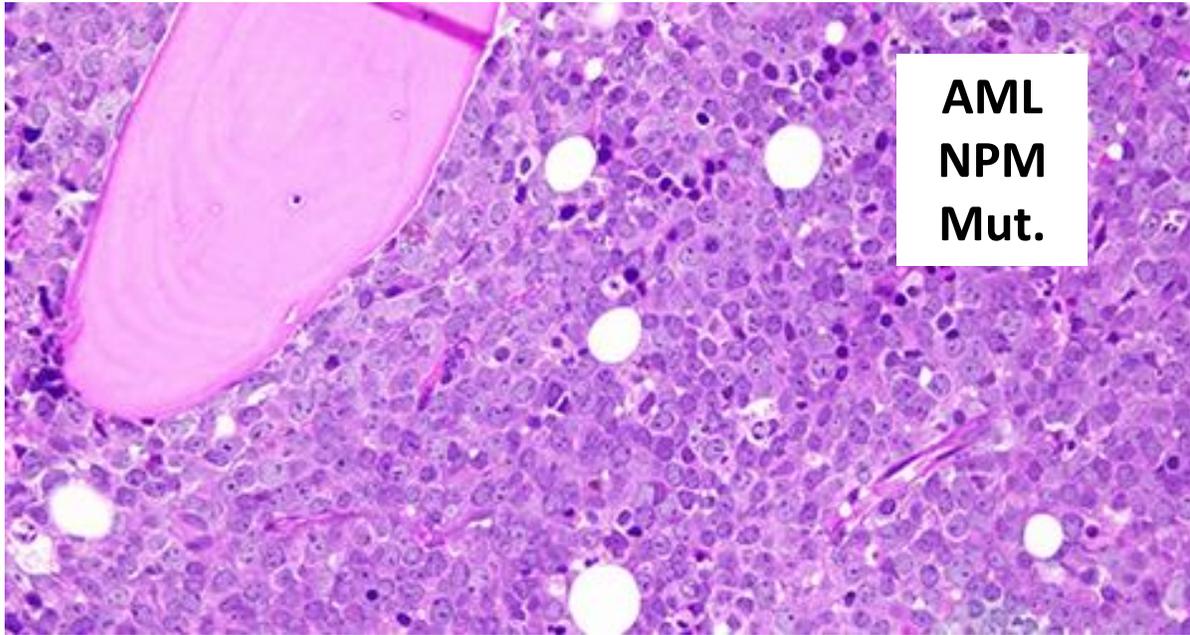
... and approval 



Tagraxofusp  



<b>Drugs</b>	<b>Indication</b>	<b>Phase</b>	<b>Status</b>	<b>Identifiers</b>
Tagraxofusp (human IL-3 conjugated to a truncated diphtheria toxin)	AML or MDS	I/II	Completed	NCT00397579
Tagraxofusp	BPDCN, AMLK	I/II	Active, not recruiting	NCT02113982
Tagraxofusp	Relapsed/Refractory Multiple Myeloma	I/II	Ongoing	NCT02661022
Tagraxofusp	MDR-positive AML in remission	I/II	Ongoing	NCT02270463
Tagraxofusp	High-risk myeloproliferative neoplasms	I/II	Ongoing	NCT02268253
Tagraxofusp	AML or high-risk MDS	I/II	Ongoing	NCT03113643



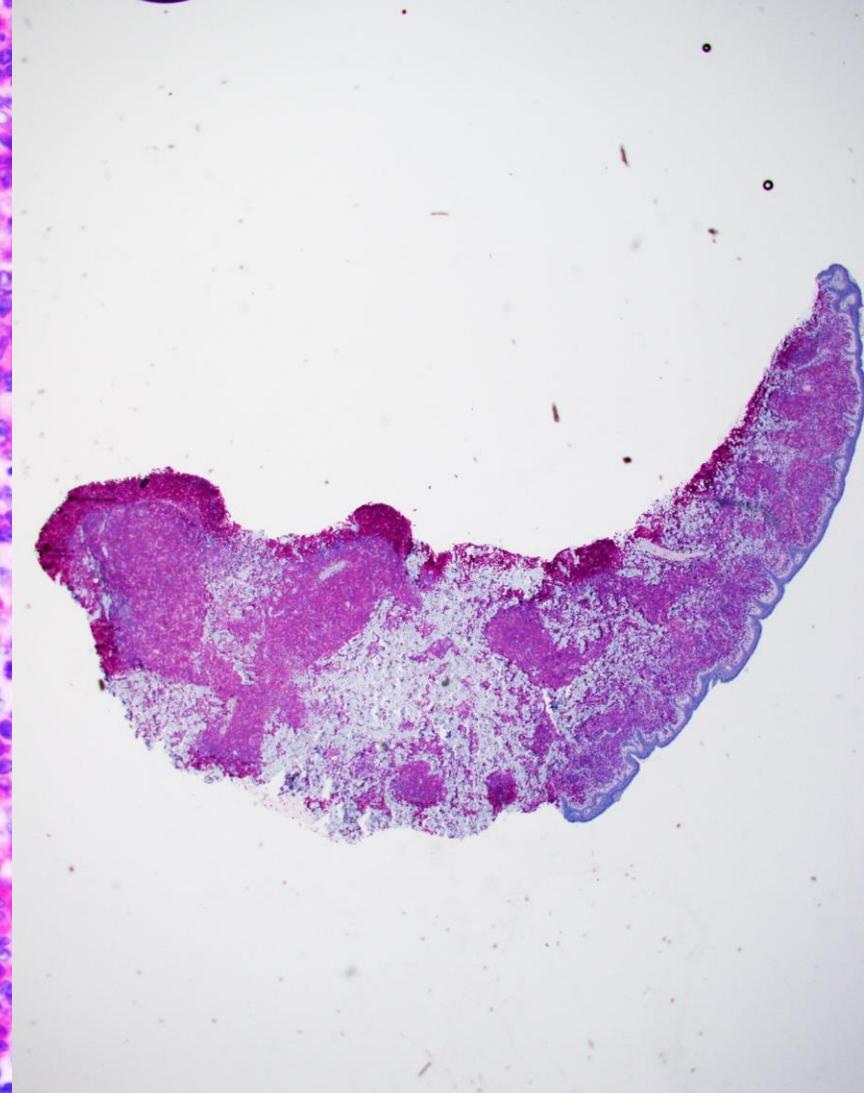
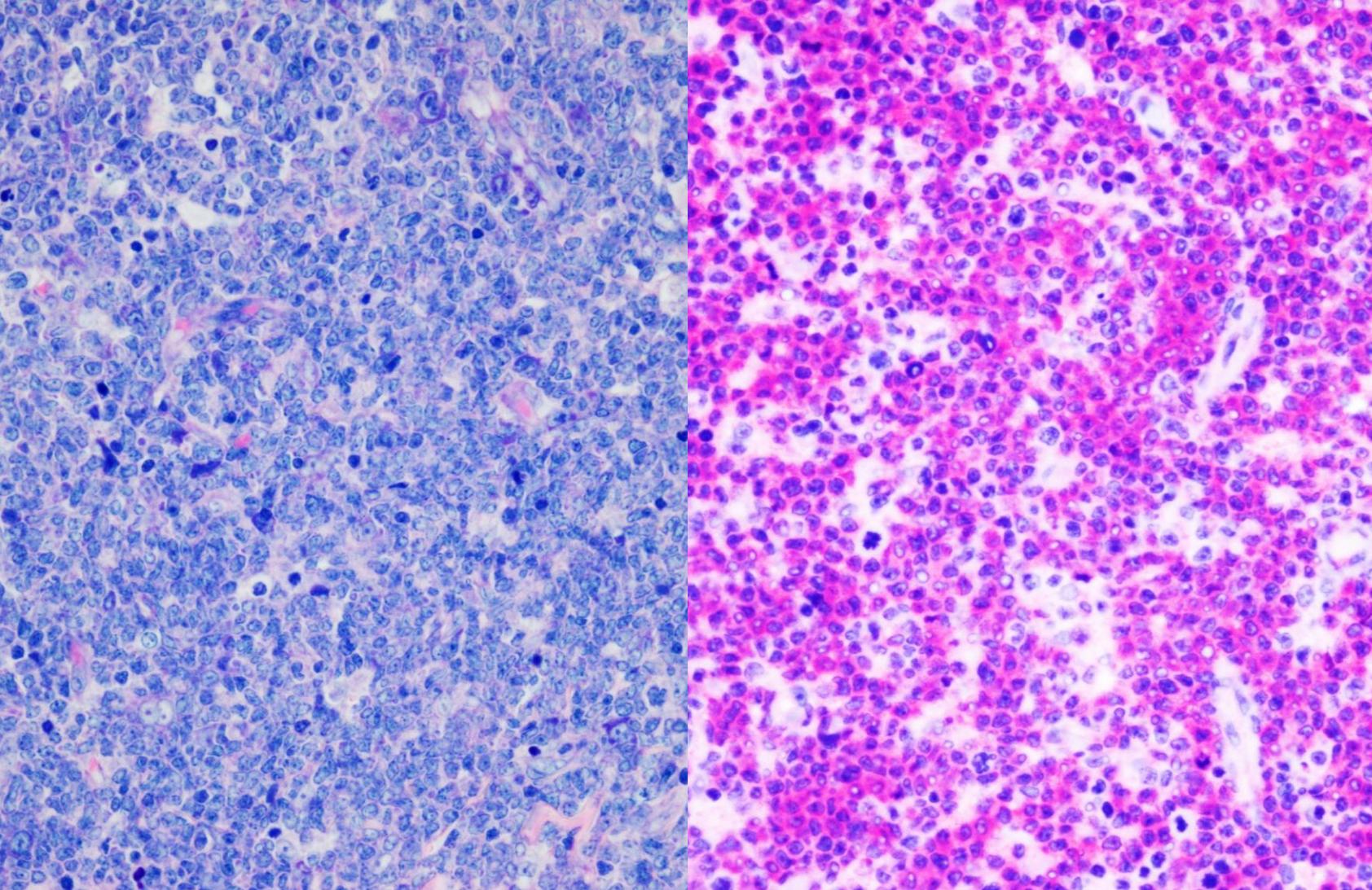
The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2019;380:1628-37.

ORIGINAL ARTICLE

# Tagraxofusp in Blastic Plasmacytoid Dendritic-Cell Neoplasm

Naveen Pemmaraju, M.D., Andrew A. Lane, M.D., Ph.D., Kendra L. Sweet, M.D.,  
Anthony S. Stein, M.D., Sumithira Vasu, M.D., William Blum, M.D.,  
David A. Rizzieri, M.D., Eunice S. Wang, M.D., Madeleine Duvic, M.D.,  
J. Mark Sloan, M.D., Sharon Spence, M.S., Shay Shemesh, M.S.,  
Christopher L. Brooks, Ph.D., John Balser, Ph.D., Ivan Bergstein, M.D.,  
Jeffrey E. Lancet, M.D., Hagop M. Kantarjian, M.D.,  
and Marina Konopleva, M.D., Ph.D.

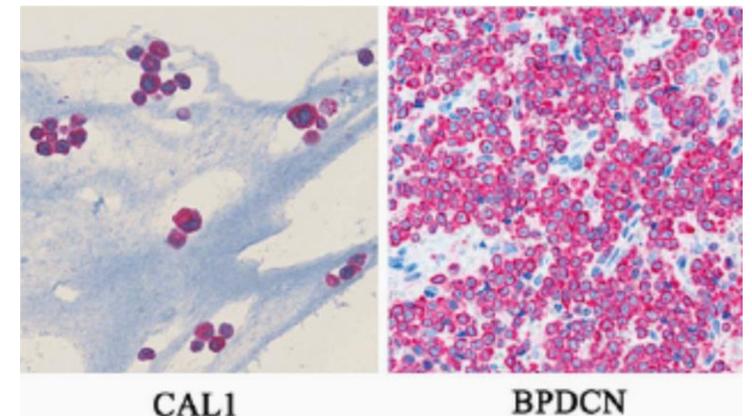
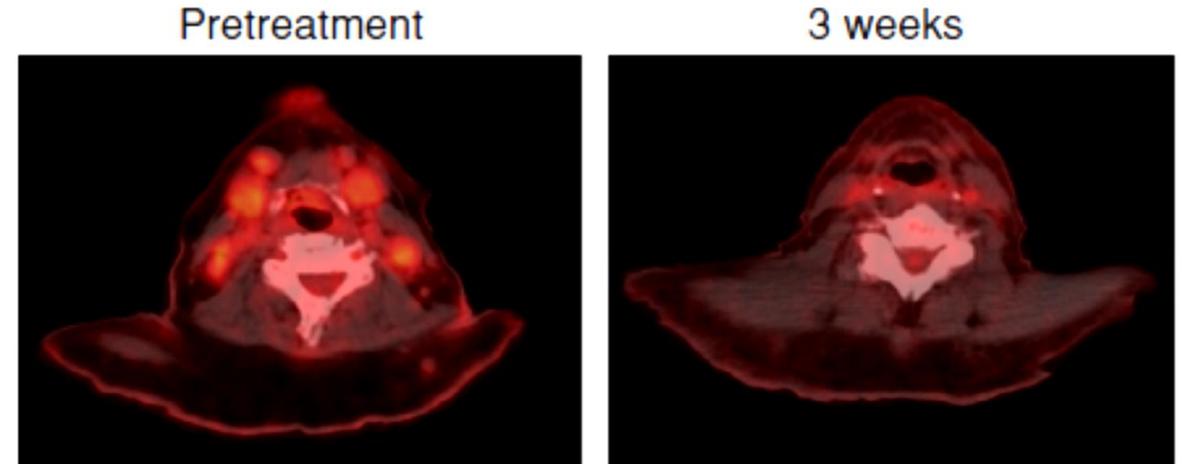


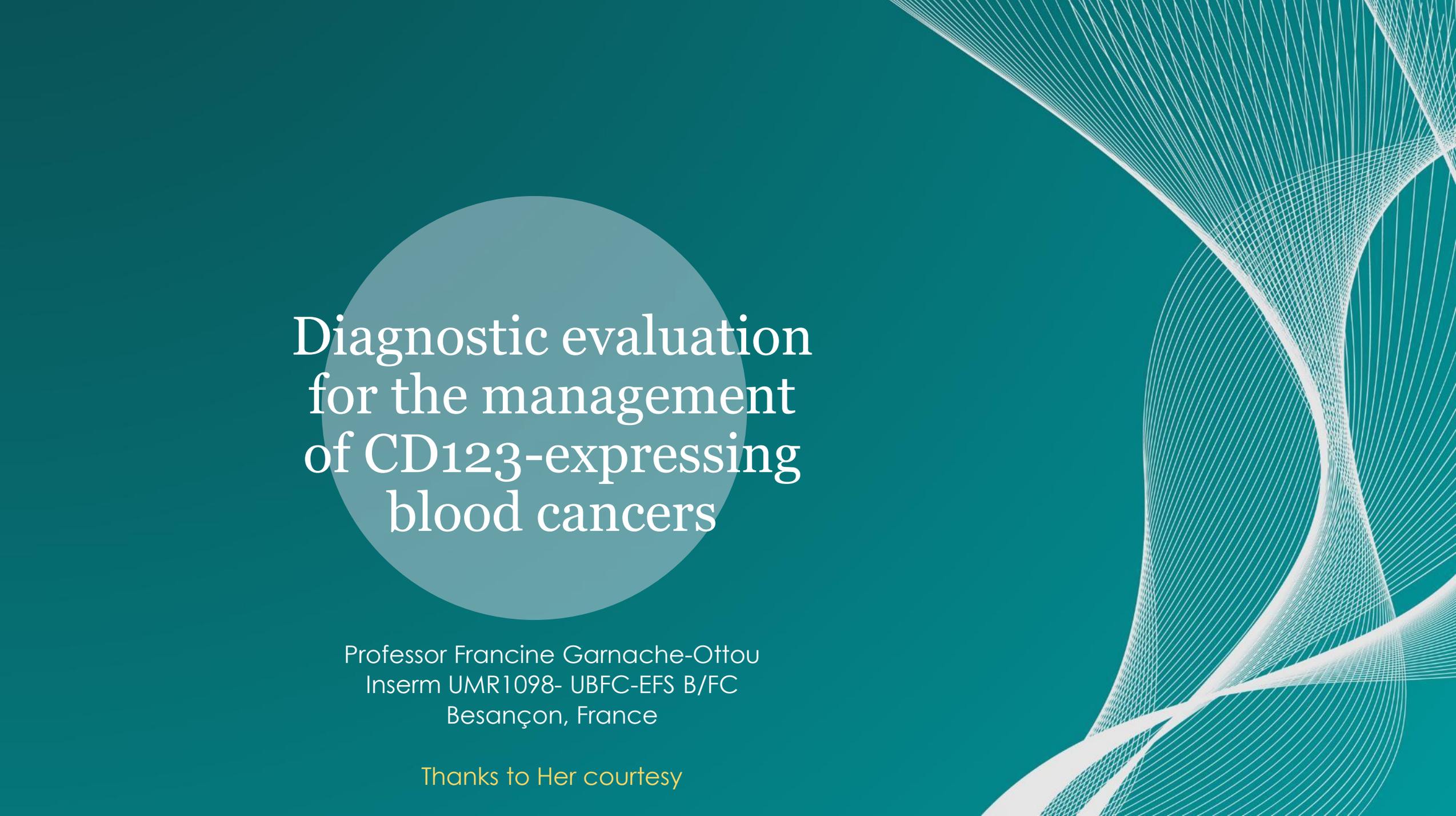
CD123 - BPDCN

# Blastic Plasmacytoid Dendritic Cell Neoplasm Is Dependent on BCL2 and Sensitive to Venetoclax

Joan Montero <sup>1</sup>, Jason Stephansky <sup>1</sup>, Tianyu Cai <sup>2</sup>, Gabriel K. Griffin <sup>3</sup>,  
Lucia Cabal-Hierro <sup>1</sup>, Katsuhiko Togami <sup>1</sup>, Leah J. Hogdal <sup>1</sup>, Ilene Galinsky <sup>1</sup>,  
Elizabeth A. Morgan <sup>3</sup>, Jon C. Aster <sup>3</sup>, Matthew S. Davids <sup>1</sup>, Nicole R. LeBoeuf <sup>4</sup>,  
Richard M. Stone <sup>1</sup>, Marina Konopleva <sup>2</sup>, Naveen Pemmaraju <sup>2</sup>, Anthony Letai <sup>1</sup>,  
and Andrew A. Lane

*Cancer Discov*; 7(2); 156–64, 2017.





# Diagnostic evaluation for the management of CD123-expressing blood cancers

Professor Francine Garnache-Ottou  
Inserm UMR1098- UBFC-EFS B/FC  
Besançon, France

Thanks to Her courtesy

# BPDCN immunophenotype

**CD123<sup>++</sup> HLA-DR<sup>+strong</sup> CD4<sup>+/-</sup> CD56<sup>+/-</sup>**

**cCD3<sup>-</sup> CD19<sup>-</sup> MPO<sup>-</sup> CD64<sup>-</sup> CD14<sup>-</sup>**

⊗ cCD3+Low

**CD303<sup>+</sup> (77%)**

**CD304<sup>+</sup> (93%)**

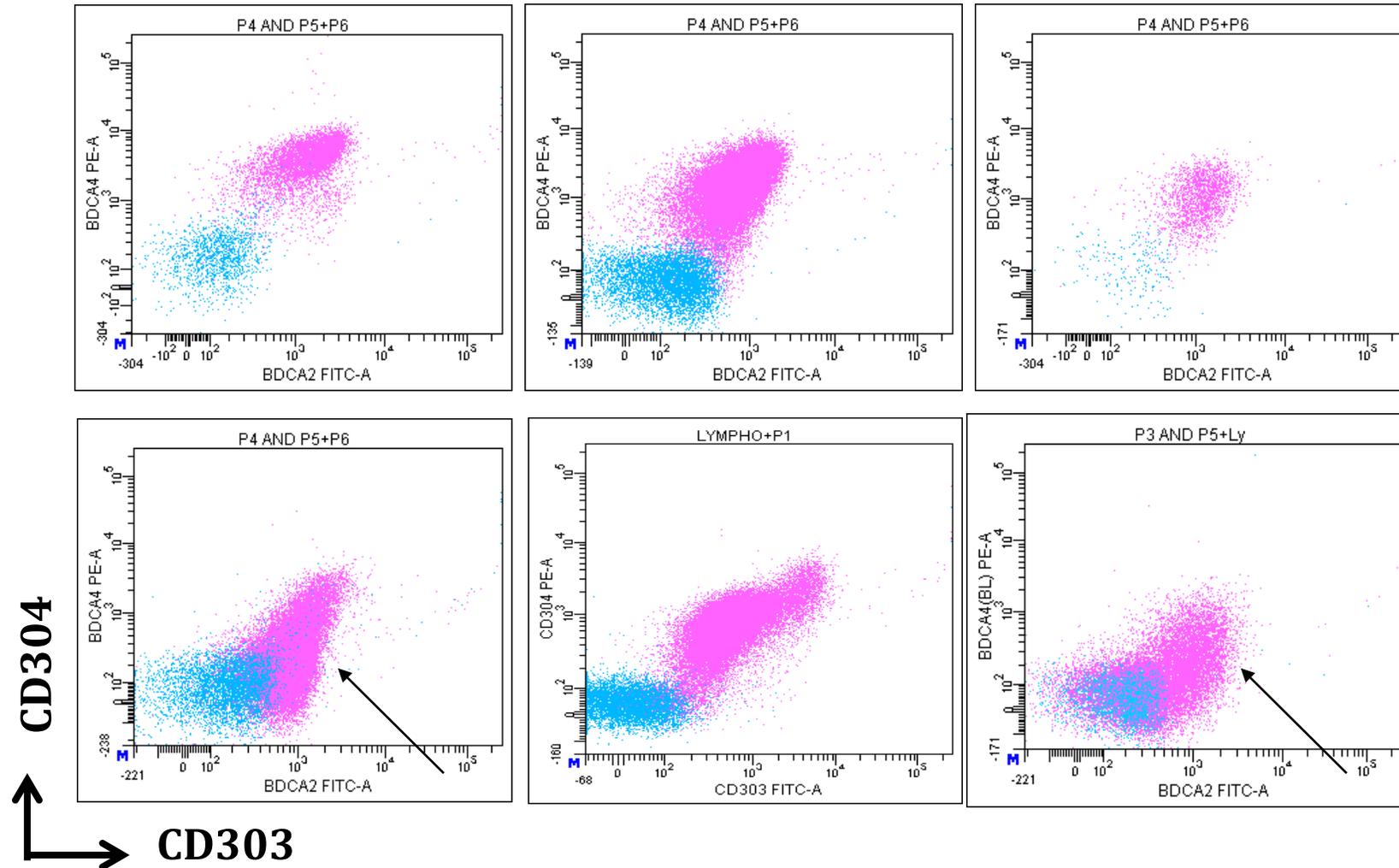
**TCL1<sup>++</sup> (93%)**

**cBadLamp<sup>+</sup> (100%)**

**nTCF4<sup>+</sup> (100%)**

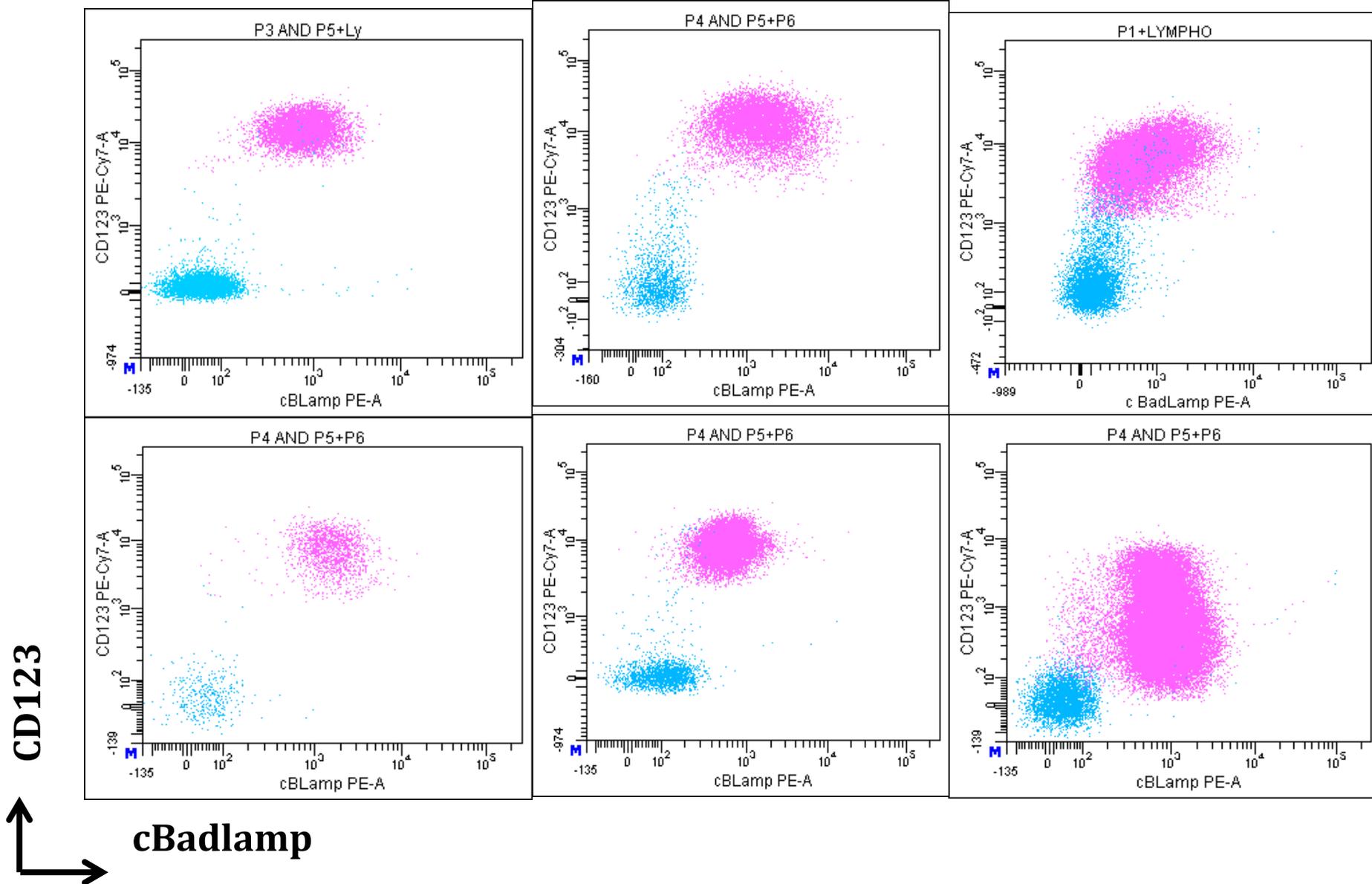
CD303+: 77% (46/60 cases)

CD304+: 93% (56/60 cases)



# cBadLamp<sup>+</sup>: 100% (56/56)

*brain and dendritic cell-associated lysosome-associated membrane protein*



Garnache-Ottou et al developed a scoring system for the diagnosis of BPDCN by applying a large series of markers to 20 BPDCN cases and 113 acute lymphoid leukemia (ALL) and AML cases. They identified that the expression of CD4 (CD56±) and lack of CD11c, cCD3, cCD79a, and MPO scored 1 point; CD123 high and BDCA4/CD303+ scored 1 point each, and the expression of BDCA2/CD303 scored 2 points.<sup>12</sup> Accordingly, the diagnosis of BPDCN was trustworthy when the total score was >2 points, which is applicable for typical or atypical BPDCN immunophenotype.

Garnache-Ottou F, Vidal C, Biichlé S, et al. How should we diagnose and treat blastic plasmacytoid dendritic cell neoplasm patients? *Blood Adv.* 2019;3:4238–4251.

### *Recommendations and proposals*

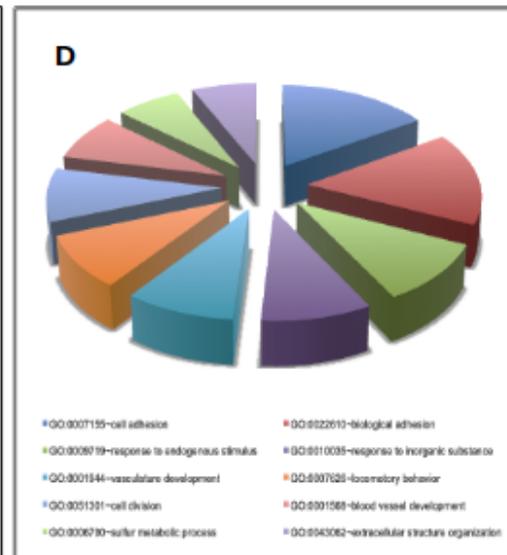
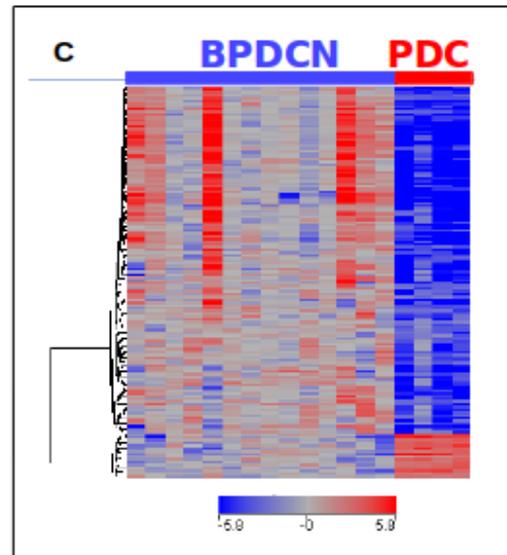
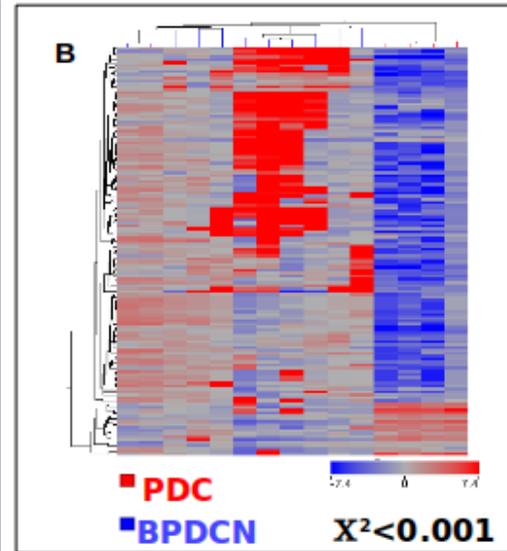
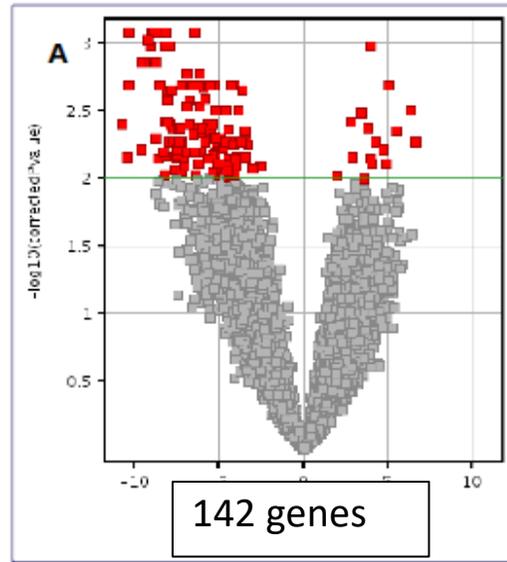
- ★ The final diagnosis of BPDCN should be made either by tumor skin biopsy immunohistochemistry or by BM cell flow cytometry.
- ★ The close collaboration of the clinician with the pathologist is essential in the diagnostic process. A description of the macroscopic characteristics of cutaneous lesions should always be followed by a detailed description of the morphologic and molecular features of the tumor.
- ★ Whenever possible, the immunohistochemical description should be integrated with the FACS analysis data, since there is not always total equivalence between the phenotypic profile on tissue sections and peripheral blood.
- ★ The results of the case series do not allow to trace of a diagnostic immune-histochemical algorithm based on the presence/absence of key markers.

The panel of biomarkers listed by WHO diagnostic criteria should be initially used with additional biomarkers that are useful for excluding differential diagnosis in the case of non-standard results including peripheral T/NK-cell lymphomas, myeloid sarcoma, and cutaneous involvement by AML.
- ★ For this endeavor, the search for CD303 and TCF4 is worthy because of their high specificity.
- ★ Molecular analysis of the malignant cells is not necessary for the diagnosis.

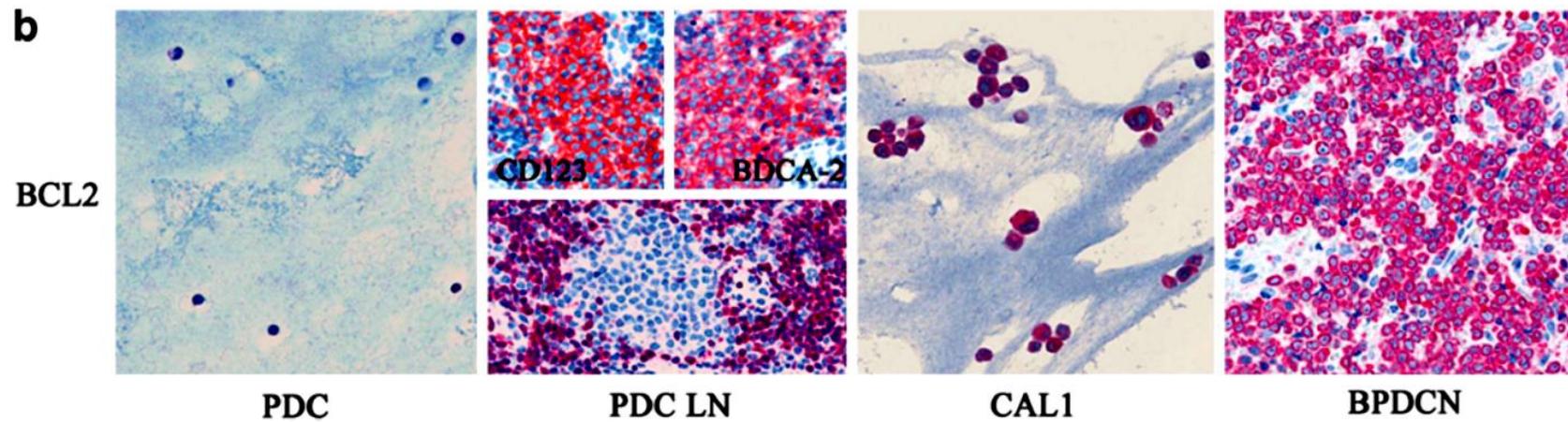
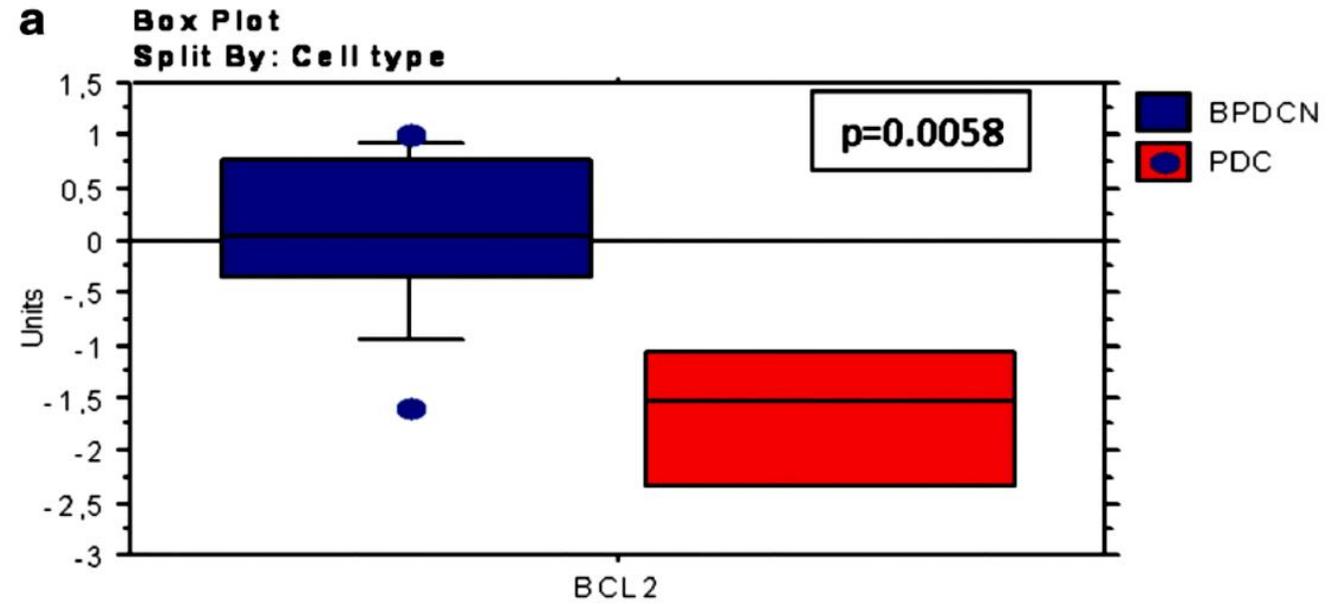
*Leukemia*. 2014 August ; 28(8): 1606–1616. doi:10.1038/leu.2014.64.

## **Molecular profiling of blastic plasmacytoid dendritic cell neoplasm reveals a unique pattern and suggests selective sensitivity to NF- $\kappa$ B pathway inhibition**

**MR Sapienza<sup>1</sup>, F Fuligni<sup>1</sup>, C Agostinelli<sup>1</sup>, C Tripodo<sup>2</sup>, S Righi<sup>1</sup>, MA Laginestra<sup>1</sup>, A Pileri Jr<sup>3</sup>, M Mancini<sup>1</sup>, M Rossi<sup>1</sup>, F Ricci<sup>4</sup>, A Gazzola<sup>1</sup>, F Melle<sup>1</sup>, C Mannu<sup>1</sup>, F Ulbar<sup>1</sup>, M Arpinati<sup>1</sup>, M Paulli<sup>5</sup>, T Maeda<sup>6</sup>, D Gibellini<sup>7</sup>, L Pagano<sup>8</sup>, N Pimpinelli<sup>3</sup>, M Santucci<sup>9</sup>, L Cerroni<sup>10</sup>, CM Croce<sup>11</sup>, F Facchetti<sup>12</sup>, PP Piccaluga<sup>1,13</sup>, SA Pileri<sup>1,13</sup>, and for the AIRC 5xMille consortium ‘Genetics-driven targeted management of lymphoid malignancies’ and the Italian Registry on Blastic Plasmacytoid Dendritic Cell Neoplasm<sup>14</sup>**

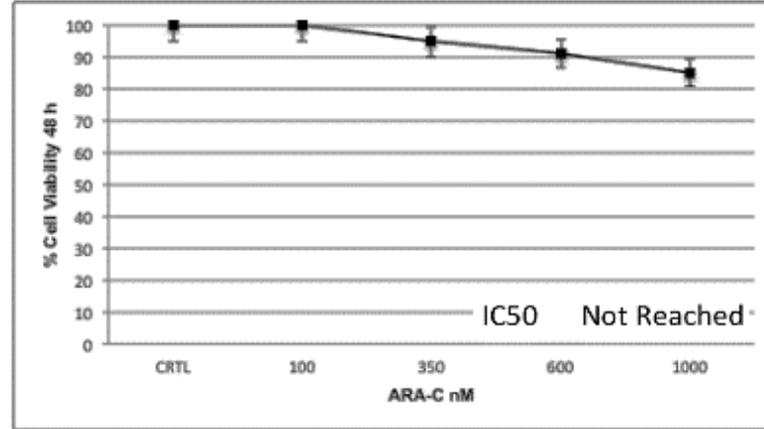
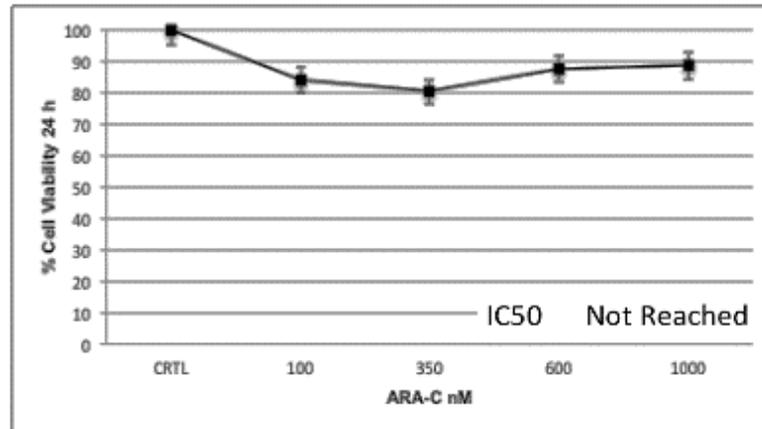
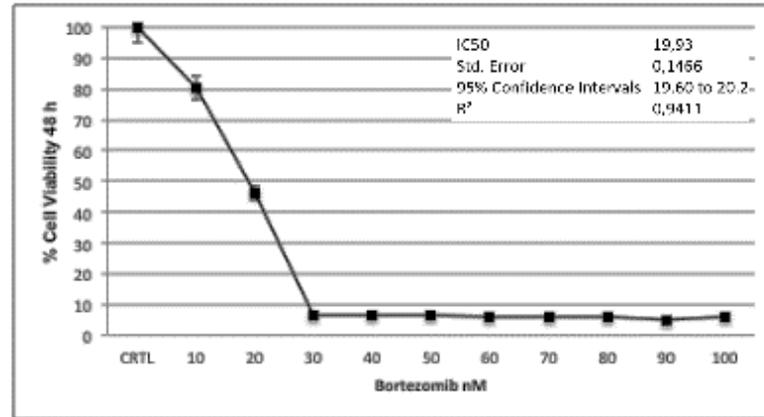
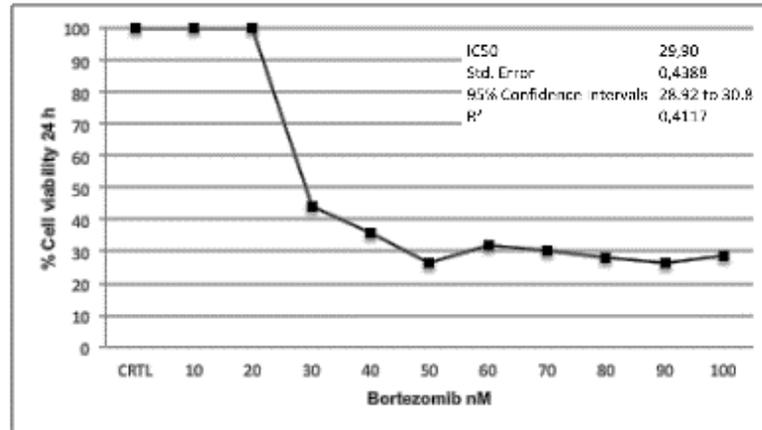


# Constitutive expression of BCL2





# Bortezomib and CAL-1 cell line



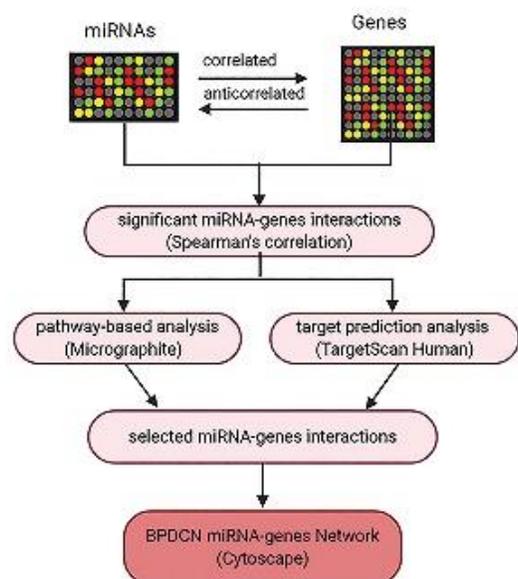
*tResearch Article*

# Newly-discovered neural features expand the pathobiological knowledge of blastic plasmacytoid dendritic cell neoplasm

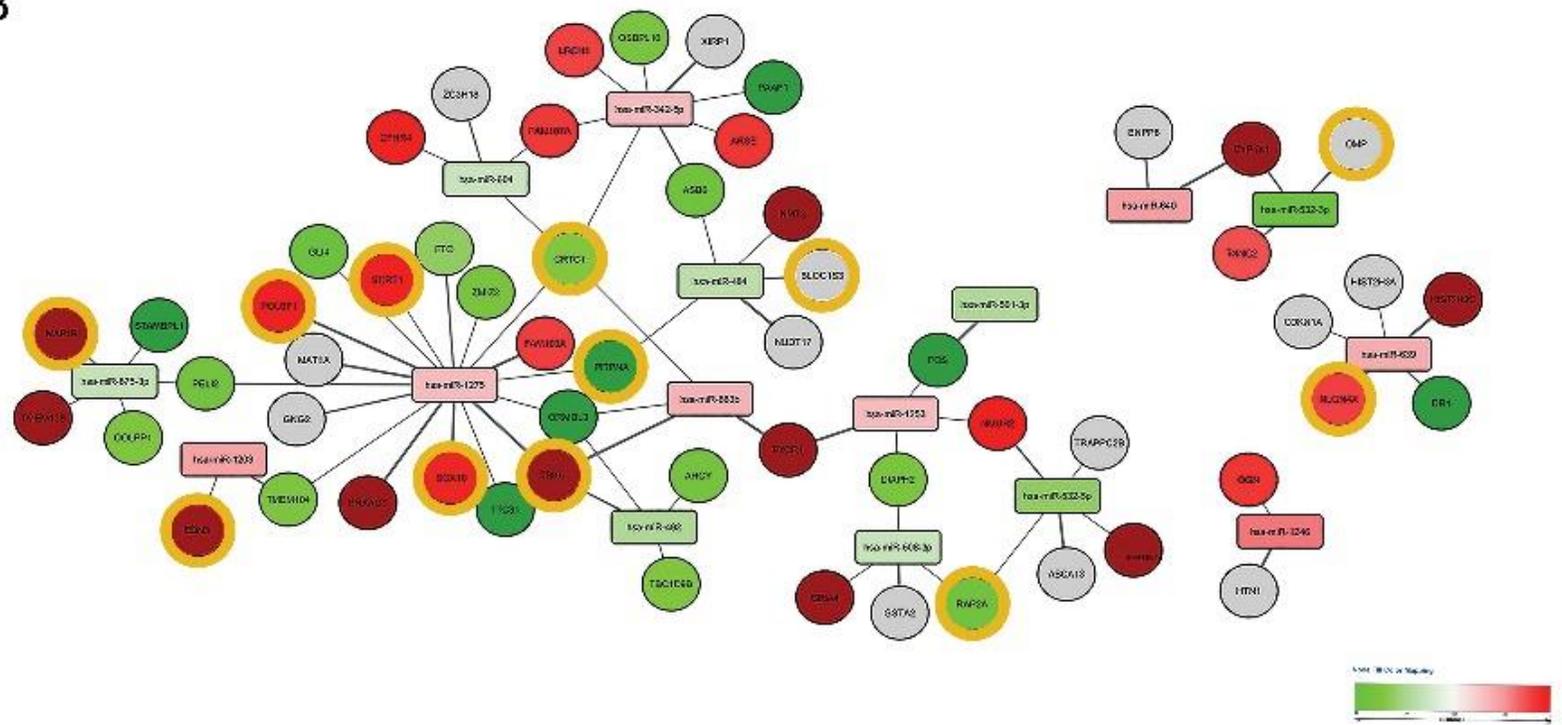
**Maria Rosaria Sapienza <sup>1\*</sup>, Giuseppe Benvenuto <sup>2\*</sup>, Manuela Ferracin <sup>3</sup>, Fabio Fuligni<sup>4</sup>, Claudio Tripodo<sup>5</sup>, Beatrice Belmonte<sup>5</sup>, Daniele Fanoni<sup>6</sup>, Saveria Mazzara<sup>1</sup>, Federica Melle<sup>1</sup>, Giovanna Motta<sup>1</sup>, Valentina Tabanelli<sup>1</sup>, Jessica Consiglio<sup>7</sup>, Vincenzo Mazzara<sup>1</sup>, Marcello Del Corvo<sup>1</sup>, Stefano Fiori<sup>1</sup>, Alessandro Pileri<sup>3</sup>, Gaetano Ivan Dellino<sup>8</sup>, Lorenzo Cerroni<sup>9</sup>, Fabio Facchetti<sup>10</sup>, Emilio Berti <sup>6,11</sup>, Elena Sabattini<sup>12</sup>, Marco Paulli<sup>13</sup>, Carlo Maria Croce<sup>7</sup> and Stefano A. Pileri<sup>1</sup>.**



A



B



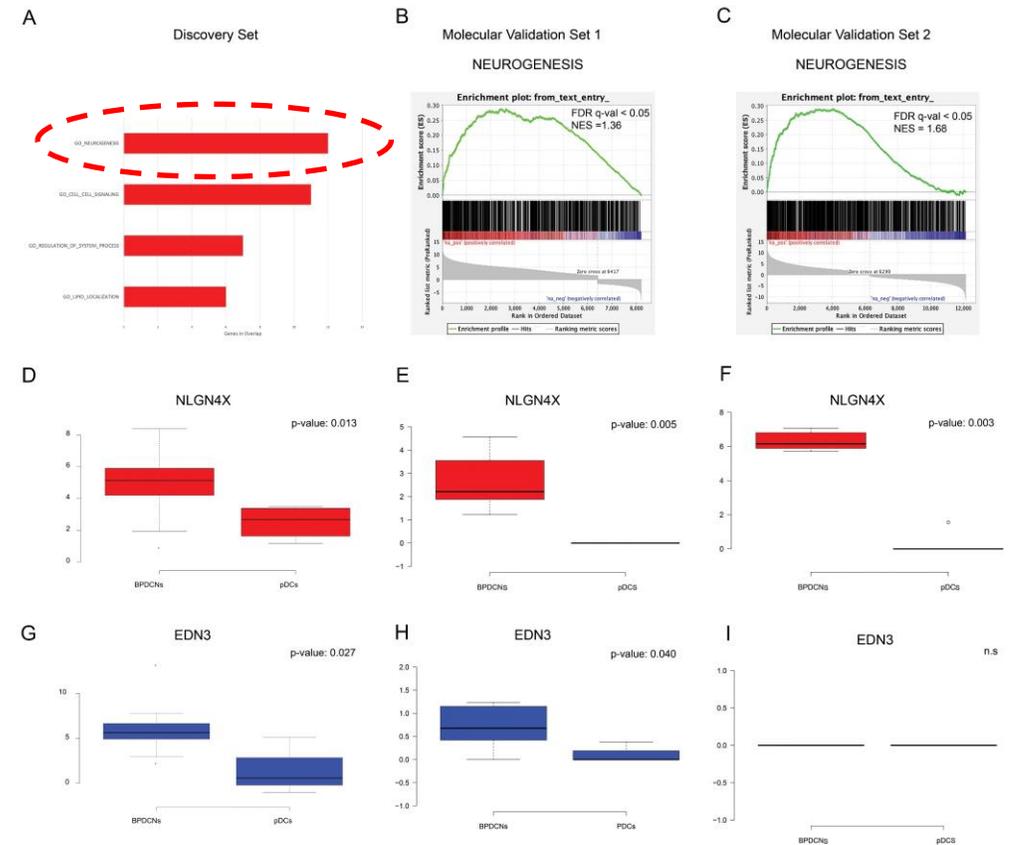
16 miRNAs and 57 genes

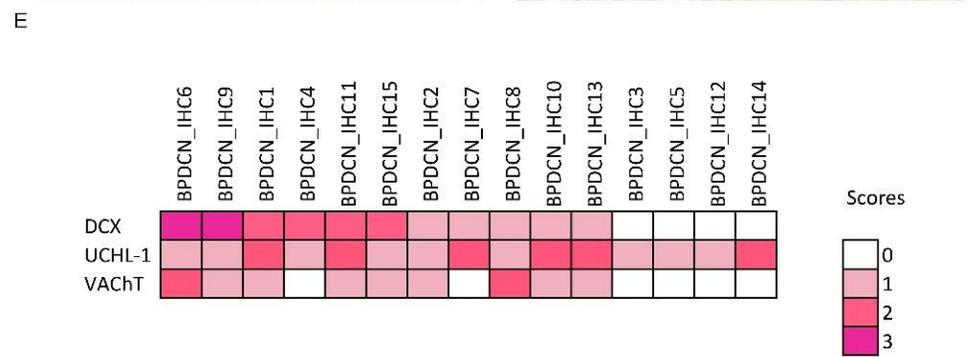
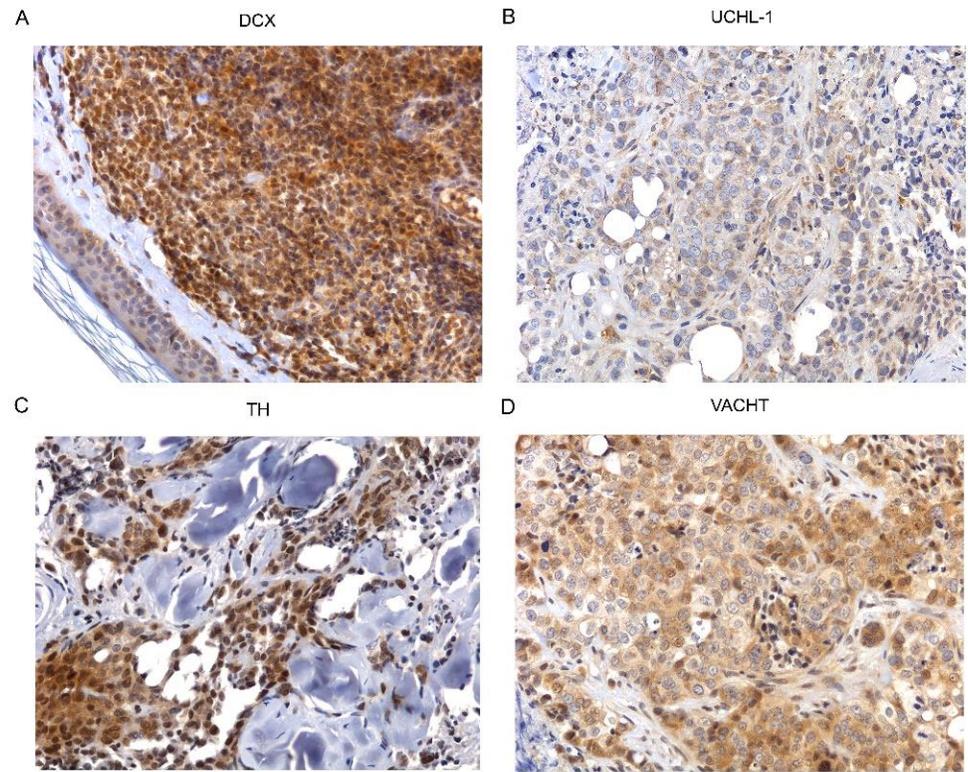
GSEA of the network genes revealed that the **neurogenesis** was the biological process most significantly influenced by miRNA dysregulation (A). Data confirmed in two RNA sequencing validation sets *in silico* (B,C).

Among the network genes neural-related we focused on **EDN3** and **NLGN4X**, possibly involved in tumor dissemination.

These genes are known to play a relevant role as therapeutic targets and prognostic factors in cancer patients.

Neurogenesis





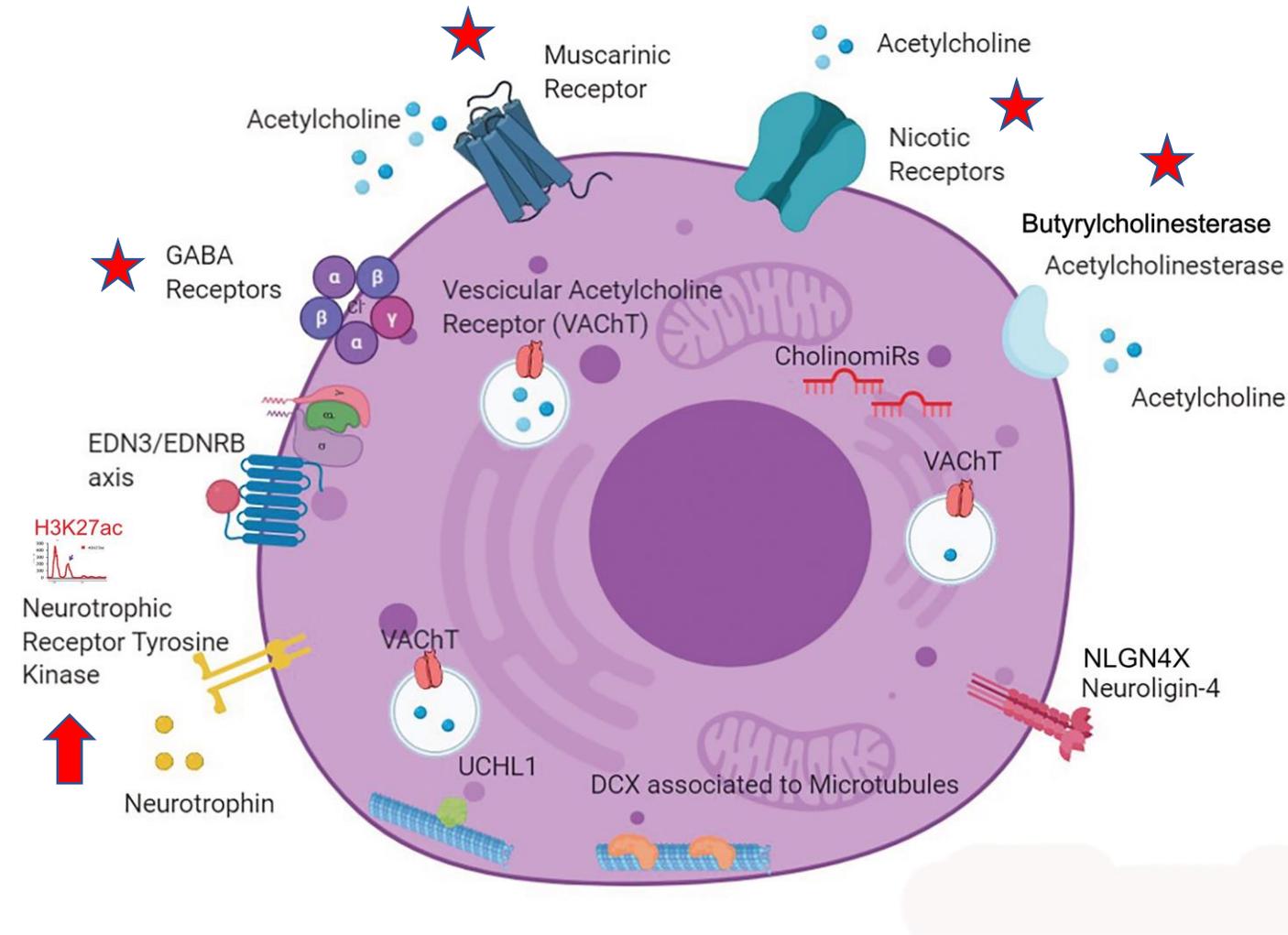
Based on our molecular results we interrogated tumor samples for the presence of two progenitor neural markers:  
 DCX (Doublecortin) and UCHL-1 (Ubiquitin C-terminal hydrolase 1 )

We next asked whether tumor cells could transmit neural signals

The most relevant neurotransmitters of the peripheral nervous system are acetylcholine and catecholamines.

BPDCNs were positive for the vesicular acetylcholine transporter, VACHT, the rate limiting factor for acetylcholine storage and release and negative for the tyrosine hydroxylase enzyme, TH, essential for the catecholamine biosynthesis

# The final output: a new BPDCN cell model neural-oriented



RNA and CHIP sequencing data were further investigated (RNAseq > overexpression of 35 neural-related genes; CHIP seq > role of acetylation in the neural signal induction)

The final output we gained was the picture of a BPDCN cell, neural-oriented and dense of neural factors, potentially allowing them to interact with nervous elements and acquire more mobility and aggressiveness

**30-60% of BPDCNs show CNS involvement at the time of diagnosis or relapse**

# TET2 and TP53 mutations are frequently observed in blastic plasmacytoid dendritic cell neoplasm



Fabrice Jardin<sup>1</sup>  
Philippe Ruminy<sup>1</sup>  
Francoise Parmentier<sup>1</sup>

Exome sequencing reveals novel and recurrent mutations with clinical impact in blastic plasmacytoid dendritic cell neoplasm

J Menezes, F Acquadro, M Wiseman, G Gómez-López, R N Salgado, J G Talavera-Casañas, I Buño, J V Cervera, S Montes-Moreno, J M Hernández-Rivas, R Ayala, M J Calasanz, M J Larrayoz, L F Brichs, M Gonzalez-Vicent, D G Pisano, M A Piris, S Álvarez and J C Cigudosa

Leukemia. 2014; 28:823-9

## Targeted ultra-deep sequencing reveals recurrent and mutually exclusive mutations of cancer genes in blastic plasmacytoid dendritic cell neoplasm

Albrecht Stenzinger<sup>1,\*</sup>, Volker Endris<sup>1,\*</sup>, Nicole Pfarr<sup>1</sup>, Mindaugas Andrulys<sup>1</sup>, Korinna Jöhrens<sup>2</sup>, Frederick Klauschen<sup>2</sup>, Udo Siebolts<sup>3</sup>, Thomas Wolf<sup>1</sup>, Philipp-Sebastian Koch<sup>4</sup>, Miriam Schulz<sup>5</sup>, Wolfgang Hartschuh<sup>6</sup>, Sergij Goerdts<sup>4</sup>, Jochen K. Lennerz<sup>7,10</sup>, Claudia Wickenhauser<sup>3</sup>, Wolfram Klapper<sup>8</sup>, Ioannis Anagnostopoulos<sup>2,\*\*</sup> and Wilko Weichert<sup>1,9,\*\*</sup>

## Targeted sequencing

### RESEARCH ARTICLE

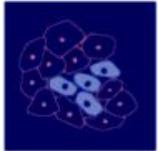
WILEY

## Whole-genome analysis uncovers recurrent *IKZF1* inactivation and aberrant cell adhesion in blastic plasmacytoid dendritic cell neoplasm

Armando N. Bastidas Torres<sup>1</sup> | Davy Cats<sup>2</sup> | Hailiang Mei<sup>2</sup> | Daniele Fanoni<sup>3</sup> |  
Jessica Gliozzo<sup>4</sup> | Laura Corti<sup>4</sup> | Marco Paulli<sup>5</sup> | Maarten H. Vermeer<sup>1</sup> |  
Rein Willemze<sup>1</sup> | Emilio Berti<sup>4</sup> | Cornelis P. Tensen<sup>1</sup>

## Transcriptomic and genomic heterogeneity in blastic plasmacytoid dendritic cell neoplasms: from ontogeny to oncogenesis

Florian Renosi,<sup>1,2</sup> Anne Roggy,<sup>2</sup> Ambre Giguélay,<sup>3,4</sup> Lou Soret,<sup>1</sup> Pierre-Julien Vially,<sup>5</sup> Meyling Cheok,<sup>6</sup> Sabeha Biichle,<sup>1</sup> Fanny Angelot-Delette,<sup>1</sup> Vahid Asnafi,<sup>7</sup> Elizabeth Macintyre,<sup>7</sup> Sandrine Geffroy,<sup>6,8</sup> Mary Callanan,<sup>9</sup> Tony Petrella,<sup>10</sup> Eric Deconinck,<sup>1,11</sup> Etienne Daguindau,<sup>1,11</sup> Véronique Harrivel,<sup>12</sup> Sabrina Bouyer,<sup>13</sup> Véronique Salaun,<sup>14</sup> Pascale Saussoy,<sup>15</sup> Jean Feuillard,<sup>16</sup> Pascal Fuseau,<sup>17</sup> Philippe Saas,<sup>1</sup> Olivier Adotévi,<sup>1</sup> Fabrice Jardin,<sup>4</sup> Christophe Ferrand,<sup>1,2</sup> Claude Preudhomme,<sup>6,8</sup> Jacques Colinge,<sup>3</sup> Christophe Roumier,<sup>6,8</sup> and Francine Garnache-Ottou<sup>1,2</sup>



*Article*

# Integrated Clinical Genotype-Phenotype Characteristics of Blastic Plasmacytoid Dendritic Cell Neoplasm

C. Cameron Yin <sup>1,\*</sup>, Naveen Pemmaraju <sup>2</sup> , M. James You <sup>1</sup>, Shaoying Li <sup>1</sup>, Jie Xu <sup>1</sup>, Wei Wang <sup>1</sup>, Zhenya Tang <sup>1</sup> , Omar Alswailmi <sup>1</sup>, Kapil N. Bhalla <sup>2</sup>, Muzaffar H. Qazilbash <sup>3</sup>, Marina Konopleva <sup>2</sup> and Joseph D. Khoury <sup>1,\*</sup> 



# **Blastic plasmacytoid dendritic cell neoplasm: genomics mark epigenetic dysregulation as a primary therapeutic target**



Ferrata Storti Foundation

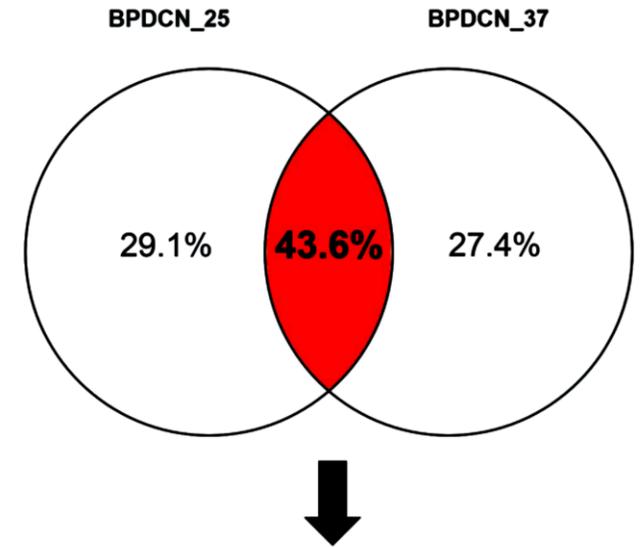
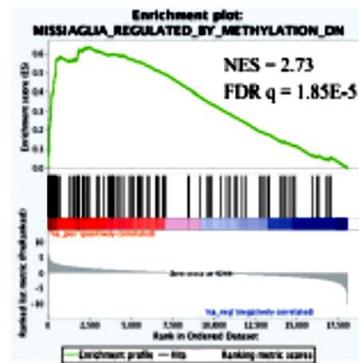
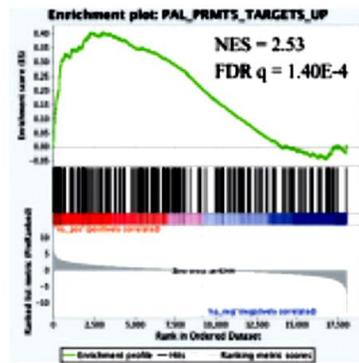
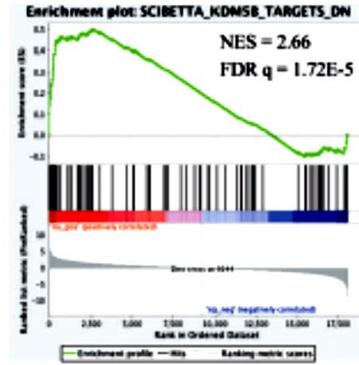
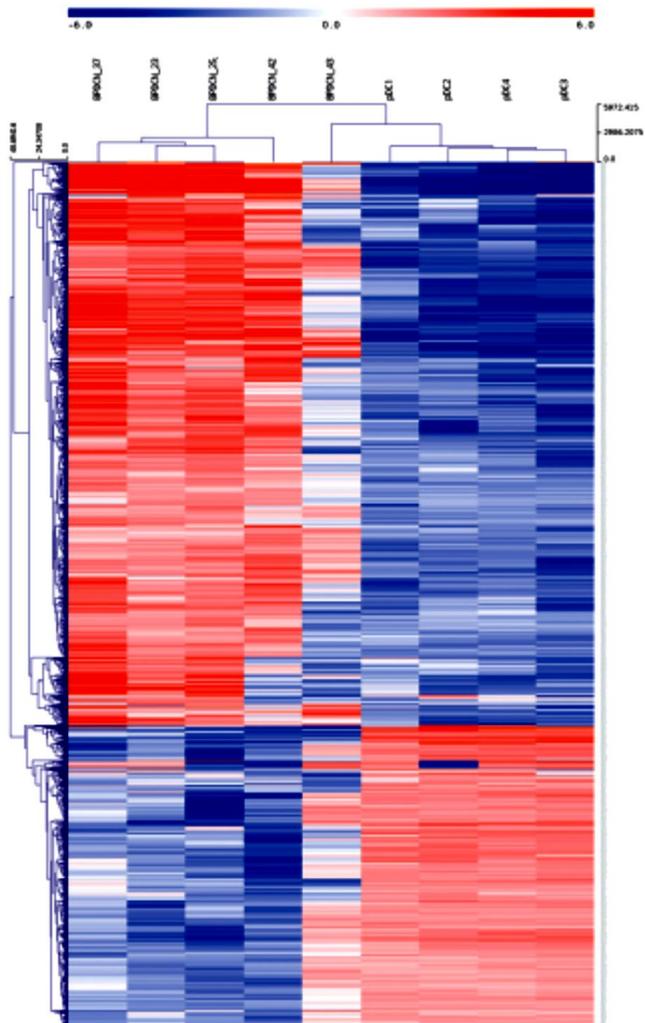
Maria Rosaria Sapienza,<sup>1\*</sup> Francesco Abate,<sup>2,3\*</sup> Federica Melle,<sup>4</sup>  
Stefania Orecchioni,<sup>5</sup> Fabio Fuligni,<sup>6</sup> Maryam Etebari,<sup>1</sup> Valentina Tabanelli,<sup>4</sup>  
Maria Antonella Laginestra,<sup>1</sup> Alessandro Pileri,<sup>7,8</sup> Giovanna Motta,<sup>4</sup>  
Maura Rossi,<sup>1</sup> Claudio Agostinelli,<sup>1</sup> Elena Sabattini,<sup>1</sup> Nicola Pimpinelli,<sup>8</sup>  
Mauro Truni,<sup>9</sup> Brunangelo Falini,<sup>10</sup> Lorenzo Cerroni,<sup>11</sup> Giovanna Talarico,<sup>5</sup>  
Rossana Piccioni,<sup>12</sup> Stefano Amente,<sup>13</sup> Valentina Indio,<sup>14</sup>  
Giuseppe Tarantino,<sup>14</sup> Francesco Brundu,<sup>2</sup> Marco Paulli,<sup>15</sup> Emilio Berti,<sup>16</sup>  
Fabio Facchetti,<sup>17</sup> Gaetano Ivan Dellino,<sup>12,18</sup> Francesco Bertolini,<sup>5</sup>  
Claudio Tripodo,<sup>19\*</sup> Raul Rabadan<sup>2,3\*</sup> and Stefano A. Pileri<sup>4†\*</sup>

**Haematologica** 2019

Volume 104(4):729-737

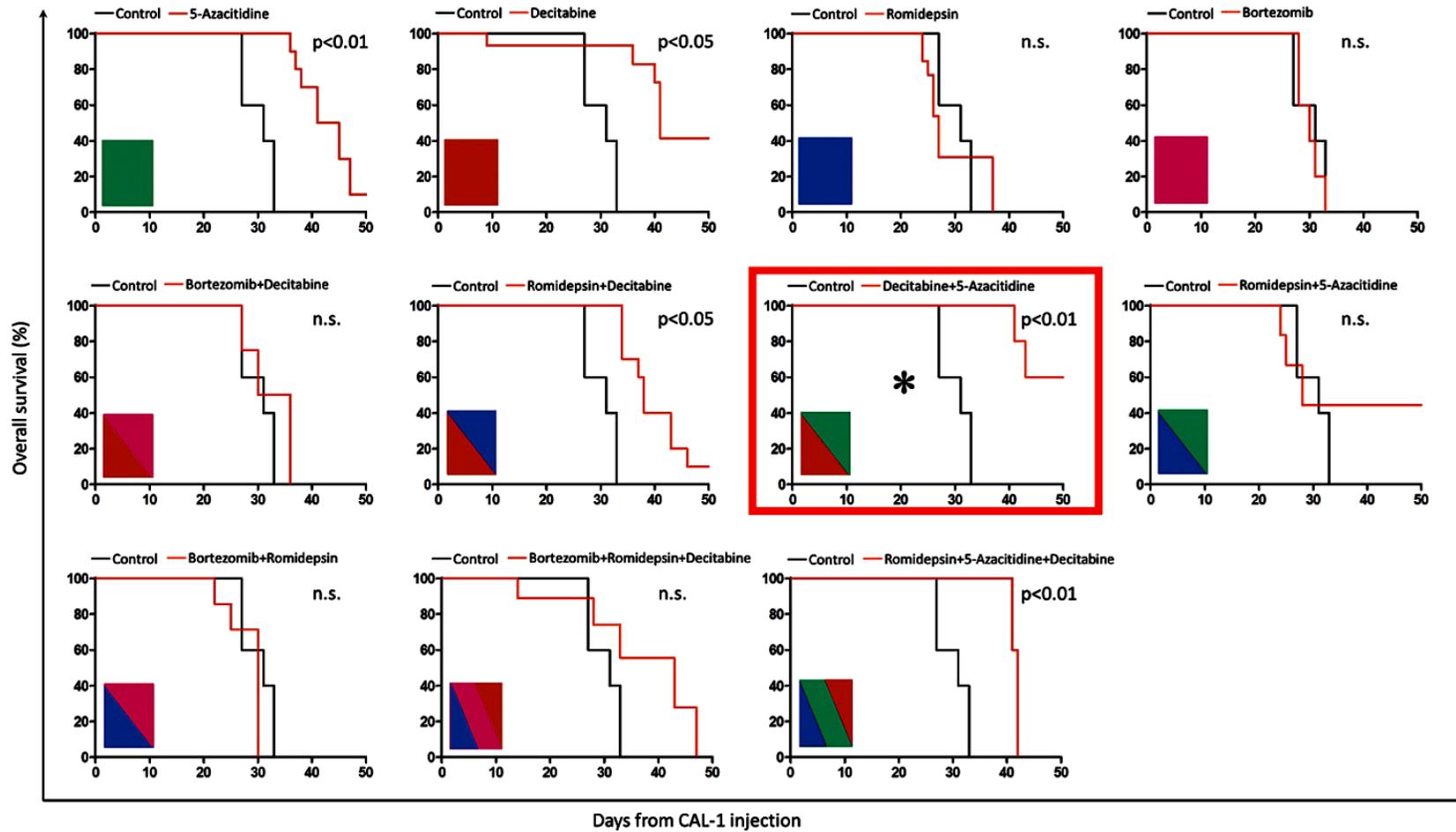
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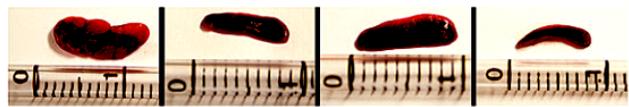


Common H3K27Ac promoters





Days 39



Control

Deci

Aza

Deci + Aza

# **Tagraxofusp followed by combined azacitidine and venetoclax in blastic plasmacytoid dendritic cell neoplasm: A case report and literature review**

**Yazan Samhouri<sup>1</sup> , Sorana Ursu<sup>1</sup>, Nina Dutton<sup>1</sup>, Verma Tanvi<sup>2</sup> and Salman Fazal<sup>1</sup>**

*J Oncol Pharm Practice*

2021, Vol. 27(4) 990–995

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DOI: 10.1177/1078155220951850

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Thank you

danke 謝謝 ngiyabonga  
спасибо таафетай lava mersi kua ora barka welain tack teşekkür ederim mahalo  
Баярлалаа  
nami nandri kiitos dankie mauruuru koszonom  
spasibo taafetai lava yinaka спасиби blagodarom kua ora barka welain tack misaotra matondo paldies grazzi  
enkosi bedankt bayarlalaa gracie hvala mauruuru koszonom  
dank je  
akun dankon aciú  
gracias tapadh leat  
xвала asante manana obigada murakoze tenki  
dziękuje sagolun chnorakaloutioun gracias ago gracias sulpay djere dieuf tau mochchakkeram mamnun  
obrigado sobodi dekuji mesi didi madloba kam sah hamnida najis tuke rahmat sukriya kop khun krap taiku go raibh maith agat  
arigatō takk dakujem trugarez  
merci ありがとう tanemirt rahmet grazie arigatō takk dakujem trugarez shukriya merce мерси  
ευχαριστώ diolch dhanyavadagalu shukriya merce мерси  
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