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S.C. ANATOMIA PATOLOGICA
CITOFUOFIMETRIA ONCOEMATOLOGICA
SAVONA

**Morfologia e immunofenotipo
nella LAM NPM1 mutata**



Dichiariamo che negli ultimi due anni
NON abbiamo avuto rapporti,
anche di finanziamento, con soggetti
portatori di interessi commerciali
in campo sanitario.



LAM NPM1 mutata



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

Daniel A. Arber,¹ Attilio Orazi,² Robert P. Hasserjian,³ Michael J. Borowitz,⁴ Katherine R. Calvo,⁵ Hans-Michael Kvasnicka,⁶ Sa A. Wang,⁷ Adam Bagg,⁸ Tiziano Barbui,⁹ Susan Branford,¹⁰ Carlos E. Bueso-Ramos,⁷ Jorge E. Cortes,¹¹ Paola Dal Cin,¹² Courtney D. DiNardo,⁷ Hervé Dombret,¹³ Eric J. Duncavage,¹⁴ Benjamin L. Ebert,¹⁵ Elihu H. Estey,¹⁶ Fabio Facchetti,¹⁷ Kathryn Foucar,¹⁸ Naseema Gangat,¹⁹ Umberto Gianelli,²⁰ Lucy A. Godley,¹ Nicola Gökkübuget,²¹ Jason Gotlib,²² Eva Hellström-Lindberg,²³ Gabriela S. Hobbs,³ Ronald Hoffman,²⁴ Elias J. Jabbour,⁷ Jean-Jacques Kiladjan,¹³ Richard A. Larson,¹ Michelle M. Le Beau,¹ Mignon L.-C. Loh,²⁵ Bob Löwenberg,²⁶ Elizabeth Macintyre,²⁷ Luca Malcovati,²⁸ Charles G. Mullighan,²⁹ Charlotte Niemeyer,³⁰ Olatoyosi M. Odenike,¹ Seishi Ogawa,³¹ Alberto Orfao,³² Elli Papaemmanuil,³³ Francesco Passamonti,²⁸ Kimmo Porkka,³⁴ Ching-Hon Pui,²⁹ Jerald P. Radich,³⁵ Andreas Reiter,³⁶ Maria Rozman,³⁷ Martina Rudelius,³⁸ Michael R. Savona,³⁹ Charles A. Schiffer,⁴⁰ Annette Schmitt-Graeff,⁴¹ Akiko Shimamura,^{15,42} Jorge Sierra,⁴³ Wendy A. Stock,¹ Richard M. Stone,¹⁵ Martin S. Tallman,⁴⁴ Jürgen Thiele,⁴⁵ Hwei-Fang Tien,⁴⁶ Alexandar Tzankov,⁴⁷ Alessandro M. Vannucchi,⁴⁸ Paresh Vyas,⁴⁹ Andrew H. Wei,⁵⁰ Olga K. Weinberg,⁵¹ Agnieszka Wierzbowska,⁵² Mario Cazzola,²⁸ Hartmut Döhner,⁵³ and Ayalew Tefferi¹⁹

2022

AML with mutated NPM1 $\geq 10\%$



Leukemia

www.nature.com/leu

REVIEW ARTICLE OPEN

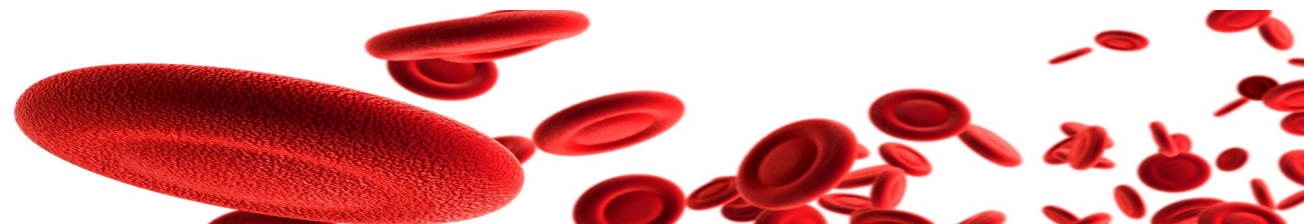
Check for updates

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

Joseph D. Khoury,^{1,65} Eric Solary,^{2,53} Oussama Ablal,³ Yasmine Akkari,⁴ Rita Alaggio,⁵ Jane F. Apperley,⁶ Rafael Bejar,⁷ Emilio Berti,⁸ Lambert Busque,⁹ John K. C. Chan,¹⁰ Weina Chen,¹¹ Xueyan Chen,¹² Wee-Joo Chng,¹³ John K. Choi,¹⁴ Isabel Colmenero,¹⁵ Sarah E. Coupland,¹⁶ Nicholas C. P. Cross,¹⁷ Daphne De Jong,¹⁸ M. Tarek Elghetany,¹⁹ Emiko Takahashi,²⁰ Jean-Francois Emile,²¹ Judith Ferry,²² Linda Fogelstrand,²³ Michaela Fontenay,²⁴ Ulrich Germing,²⁵ Sumeet Gujral,²⁶ Torsten Haferlach,²⁷ Claire Harrison,²⁸ Jennelle C. Hodge,²⁹ Shimin Hu,¹ Joop H. Jansen,³⁰ Rashmi Kanagal-Shamanna,³¹ Hagop M. Kantarjian,³¹ Christian P. Kratz,³² Xiao-Qiu Li,³³ Megan S. Lim,³⁴ Keith Loeb,³⁵ Sanam Loghavi,¹ Andrea Marcocci,¹⁹ Soheil Meshinchi,³⁶ Phillip Michalek,³⁷ Kikkeri N. Naresh,³⁵ Yasodha Natkunam,³⁸ Reza Nejati,³⁹ German Ott,⁴⁰ Eric Padron,⁴¹ Keyur P. Patel,¹ Nikhil Patkar,⁴² Jennifer Picarsic,⁴³ Uwe Platzbecker,⁴⁴ Irene Roberts,⁴⁵ Anna Schuh,⁴⁶ William Sewell,⁴⁷ Reiner Siebert,⁴⁸ Prashant Tembhare,⁴² Jeffrey Tyner,⁴⁹ Srdan Verstovsek,³¹ Wei Wang,¹ Brent Wood,⁵⁰ Wenbin Xiao,⁵¹ Cecilia Yeung,³⁵ and Andreas Hochhaus.^{52,53}

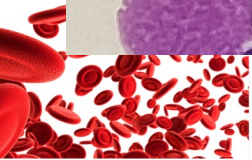
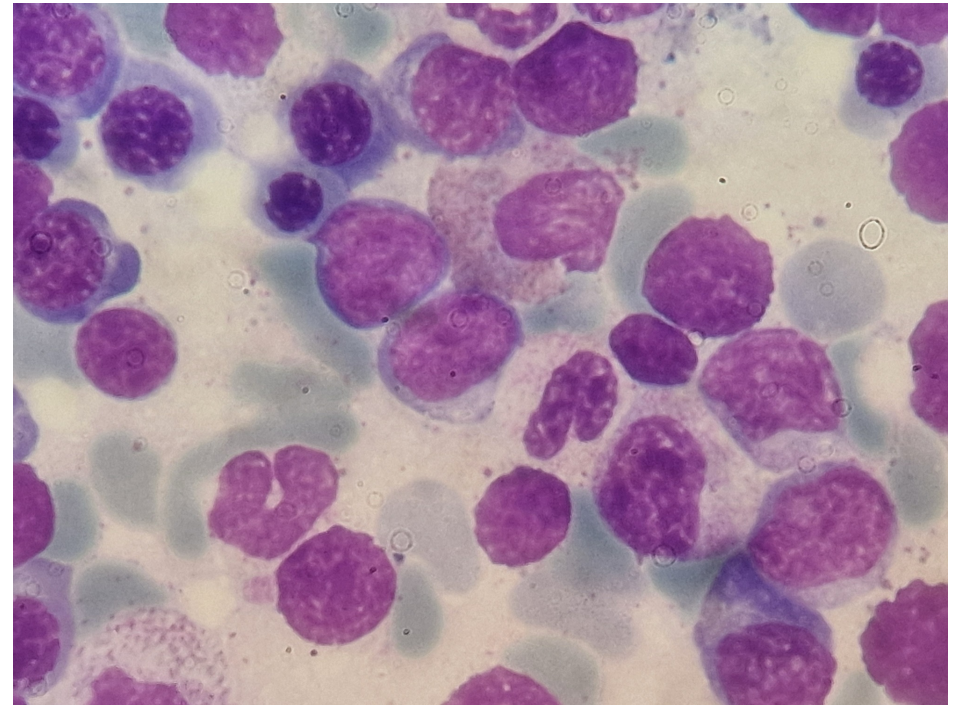
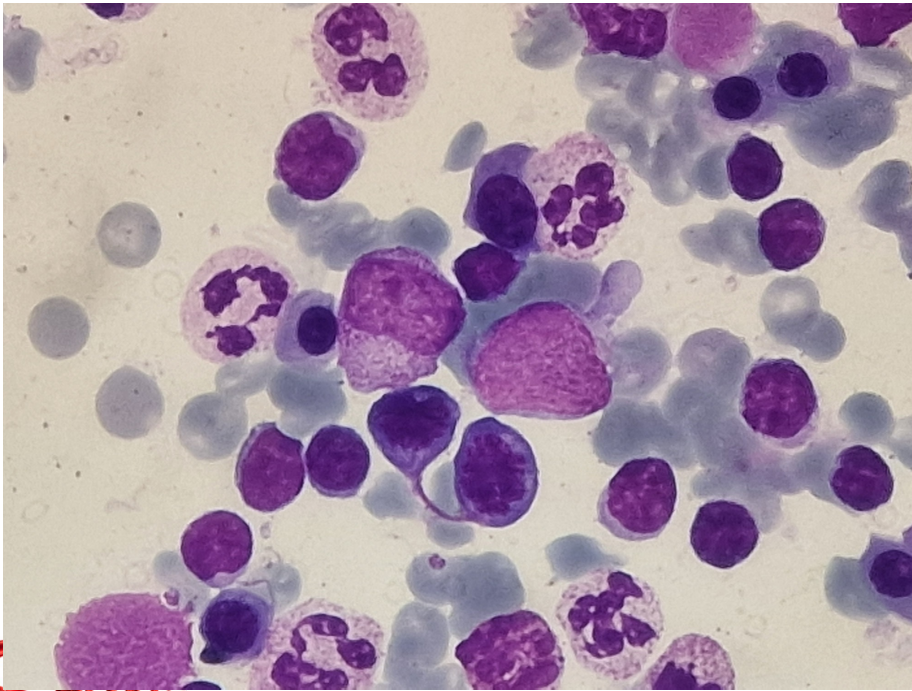
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AML with NPM1 mutation can be diagnosed irrespective of the blast count, albeit again with emphasis on judicious clinicopathologic correlation.



LAM NPM1 mutata e displasia

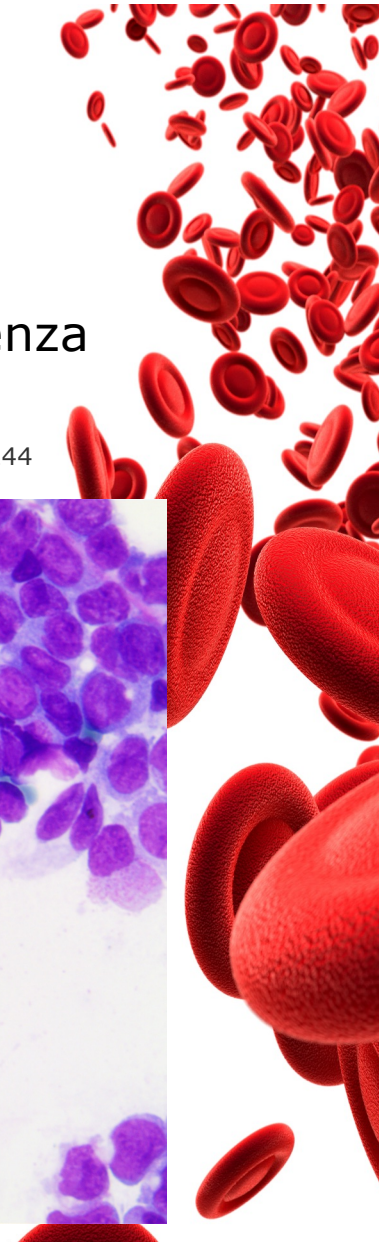
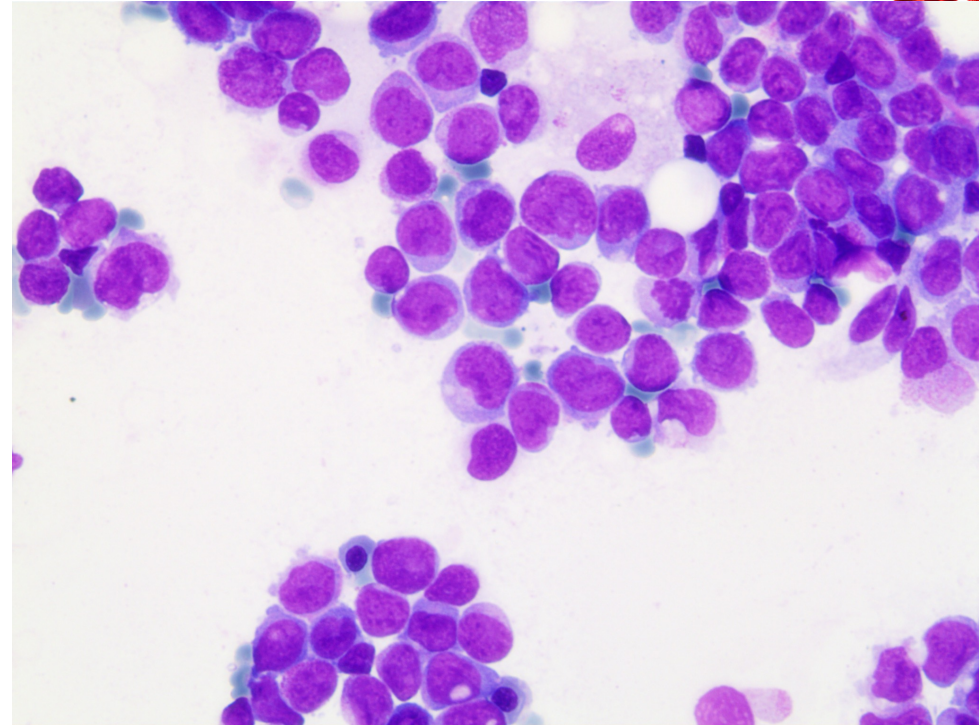
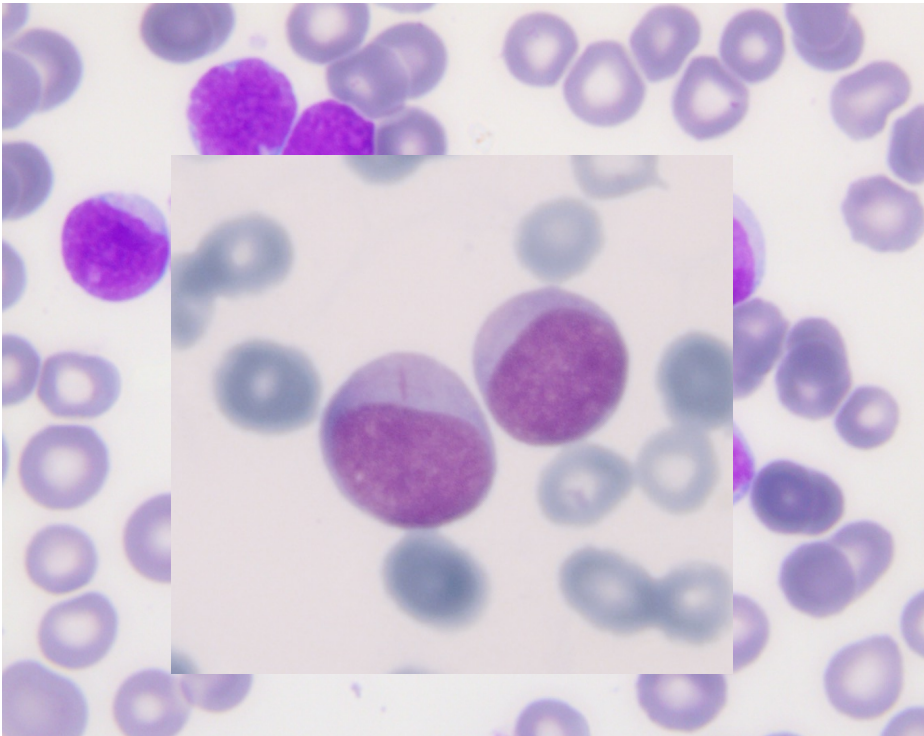
Le AML NPM1mut hanno displasia multilineare nel 23% dei casi ma non sono considerate AML-mielodisplasia correlate




LAM NPM1 mutata: caratteristiche morfologiche

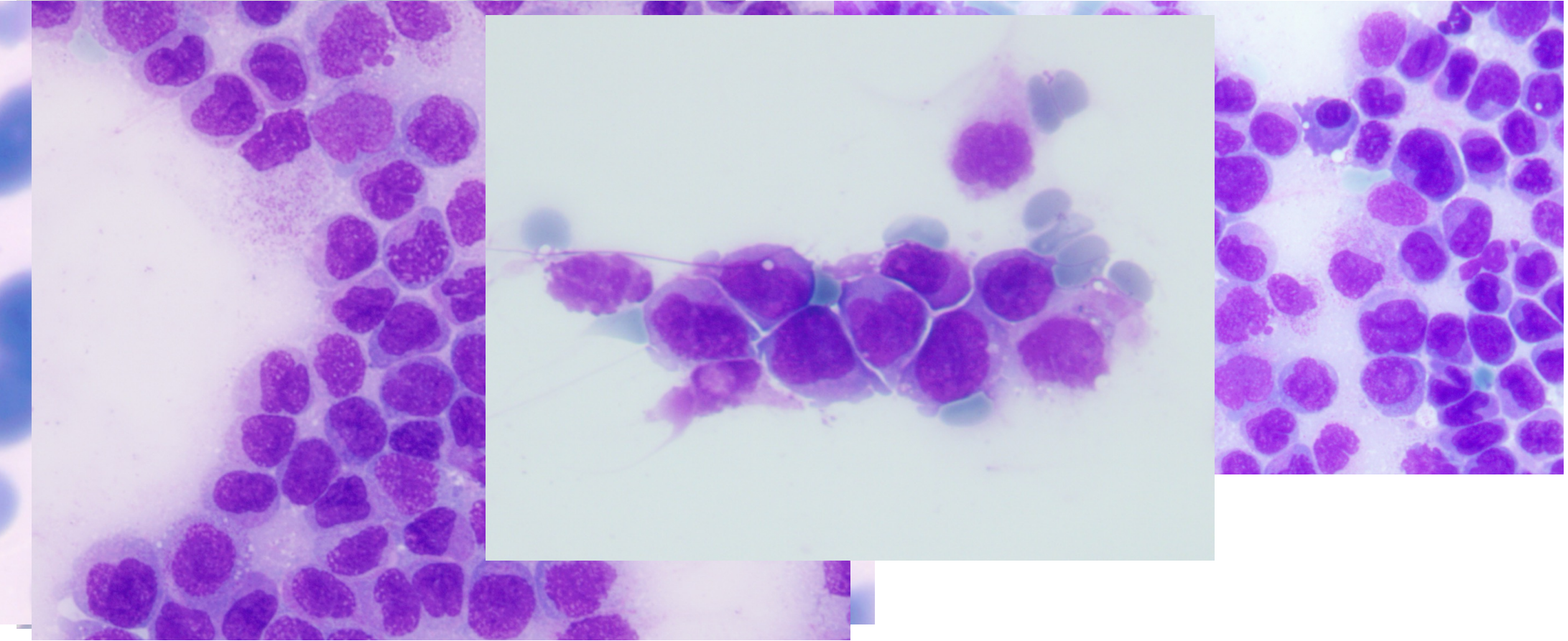
1. caratteristiche citologiche della leucemia mieloblastica acuta con o senza maturazione (con talvolta la presenza di bastoncelli di Auer) 2/3

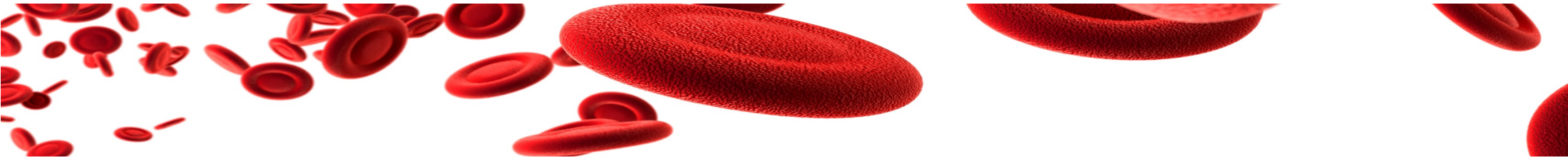
Vedi Barbara J. Bain; Marie C. Béné *Acta Haematol* (2019) 141 (4): 232-244





2. caratteristiche citologiche della leucemia mielomonocitica acuta o monocitica/monoblastica 1/3





La caratteristica distintiva è la presenza di blasti leucemici con nuclei cup-like. Ciò si osserva in particolare nei casi con duplicazione tandem interna *FLT3* coesistente



Park BG, Chi HS, Jang S, Park CJ, Kim DY, Lee JH, et al. Association of cup-like nuclei in blasts with *FLT3* and *NPM1*. *Blood*. 2015 Jun;90(6):560.1 mutations in acute myeloid leukemia. *Ann Hematol*. 2013 Apr;92(4):451-7.

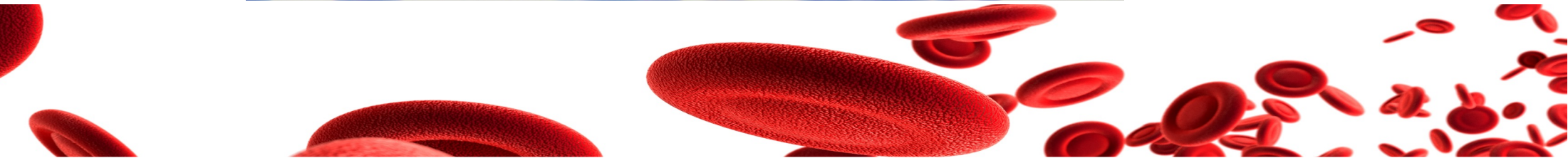
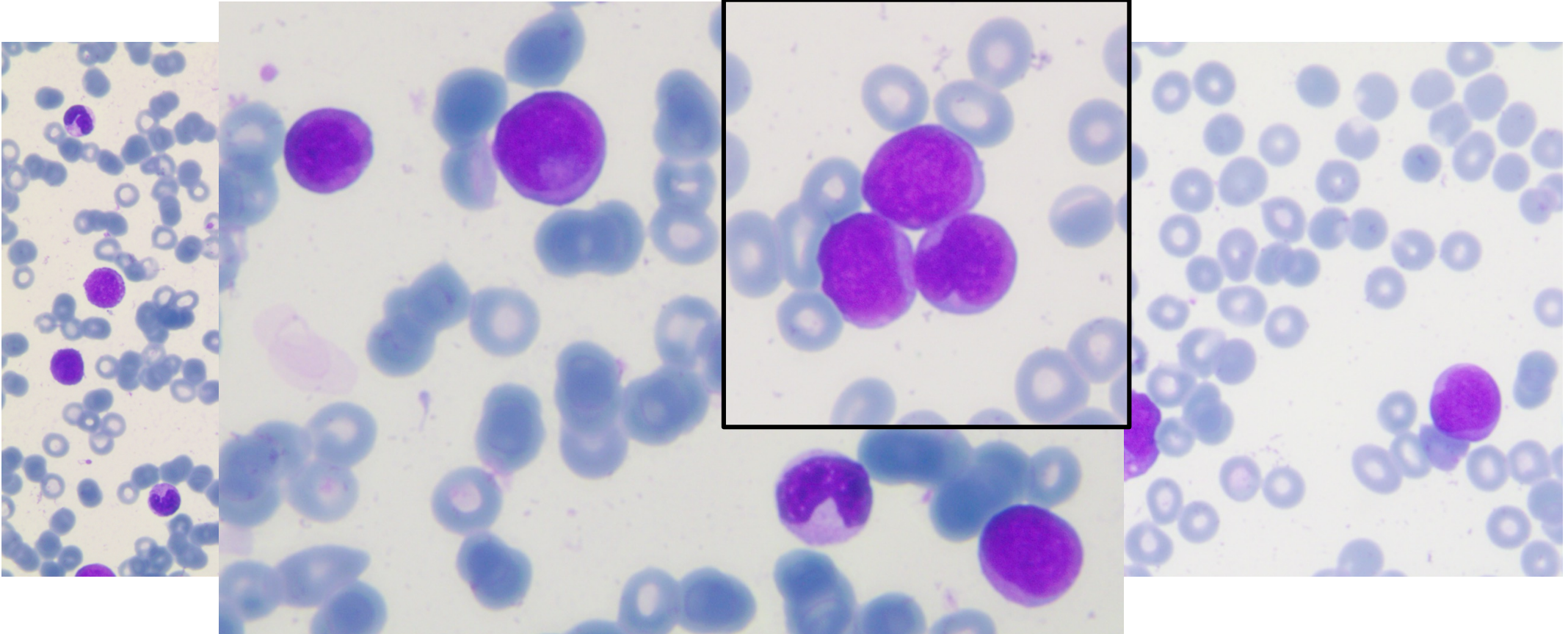
Am J Hematol. 2015 Jun;90(6):560.1 mutations in acute myeloid leukemia. *Ann Hematol*. 2013 Apr;92(4):451-7.

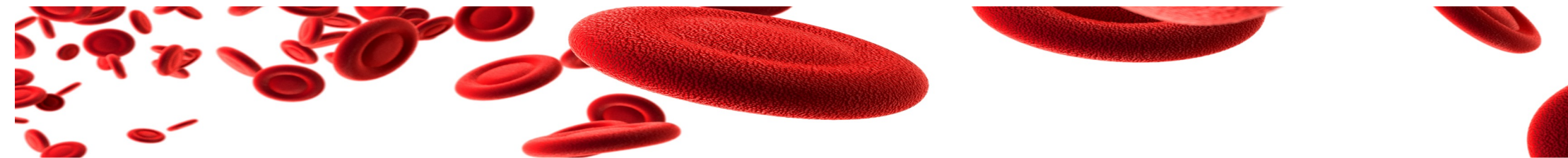
invaginazione nel nucleo a forma di coppa se viste di profilo; se viste dall'alto, invaginazione può simulare un nucleolo gigante

le tasche nucleari all'ultrastruttura risultano un insieme di mitocondri, lisosomi e reticolo endoplasmatico.

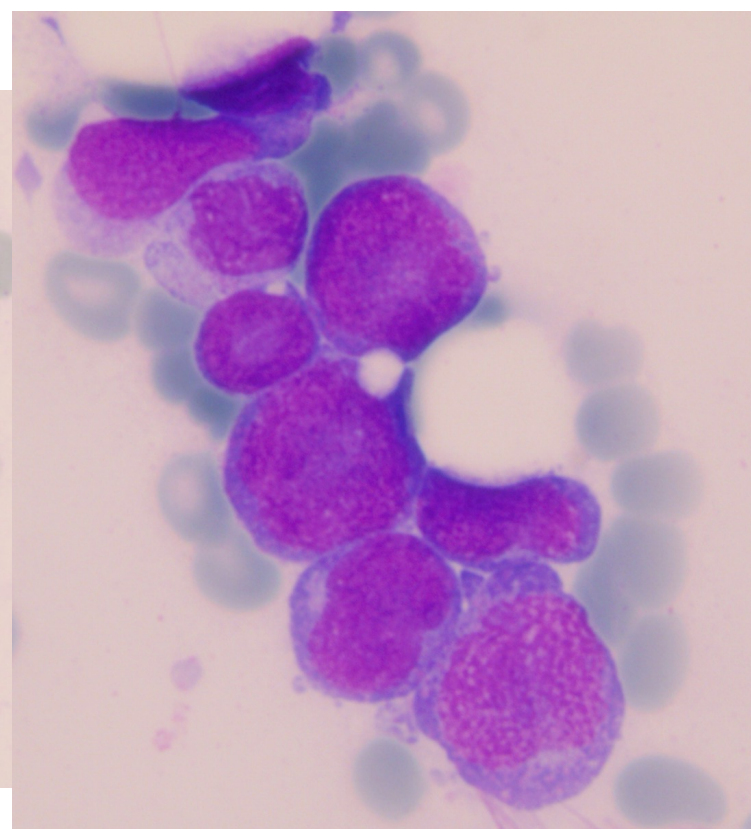
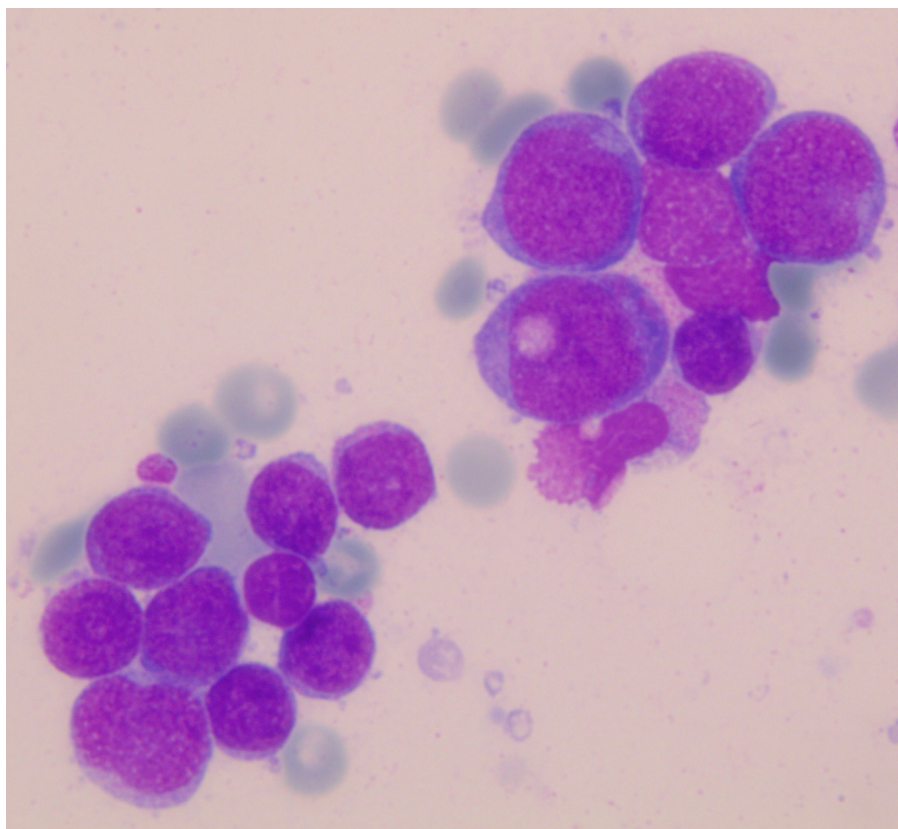


LAM NPM1 mutata FLT3+ in PB

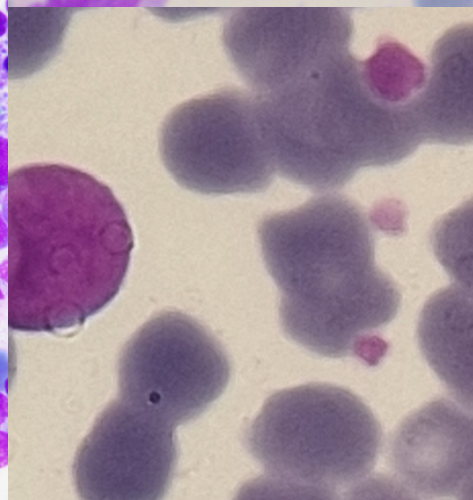
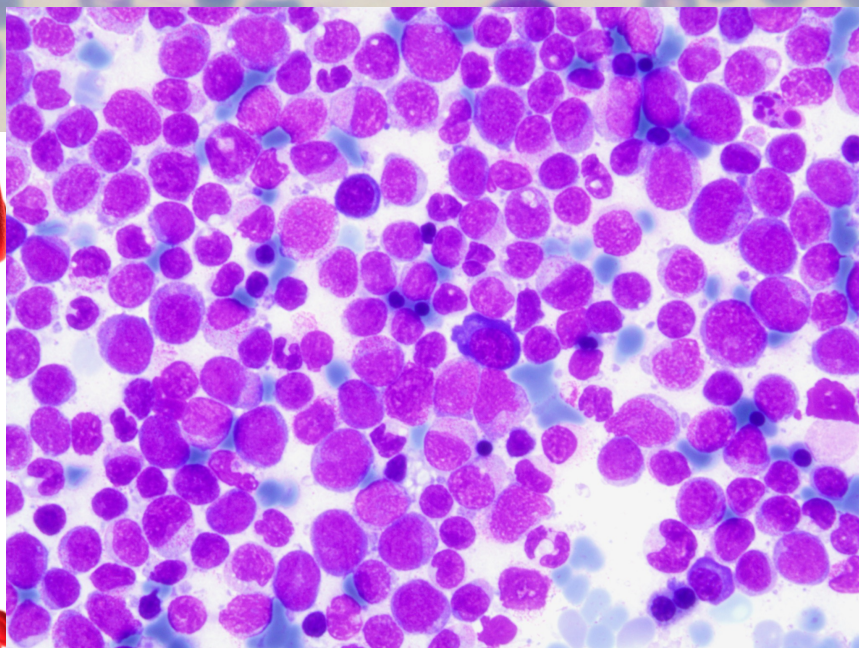
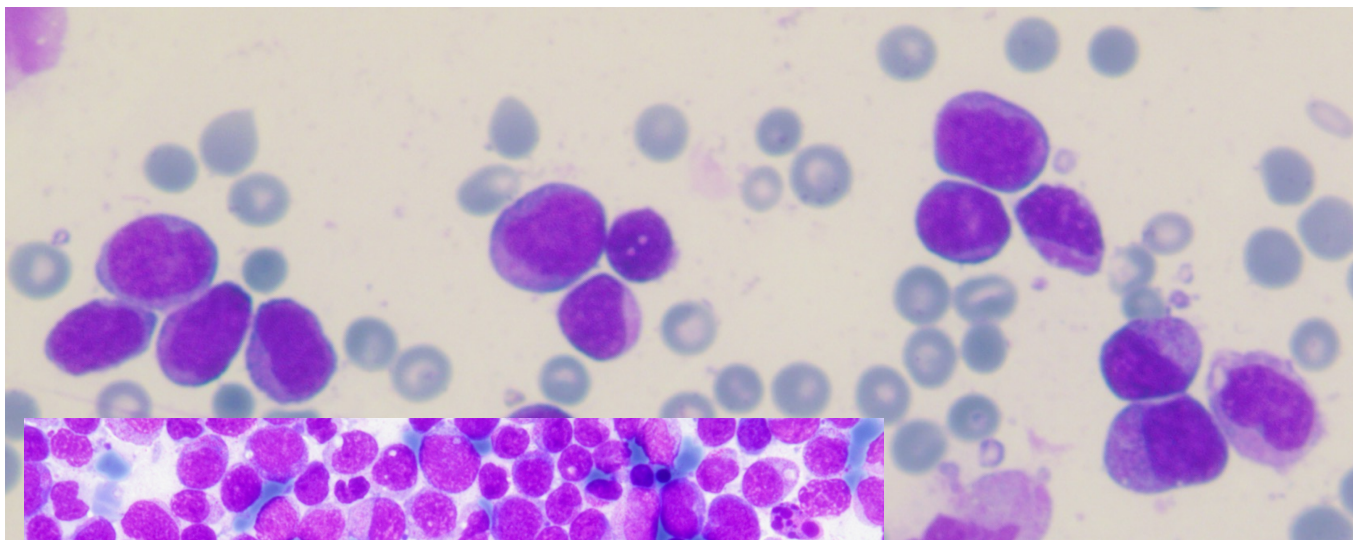




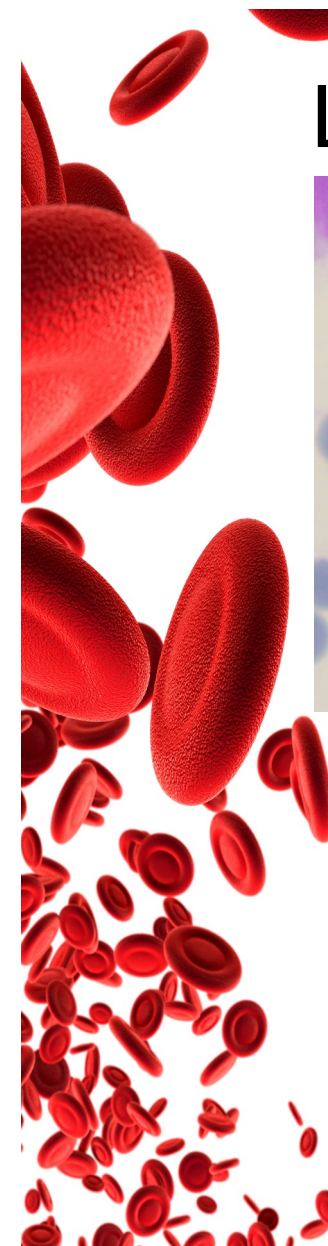
LAM NPM1 mutata FLT3+ in BM



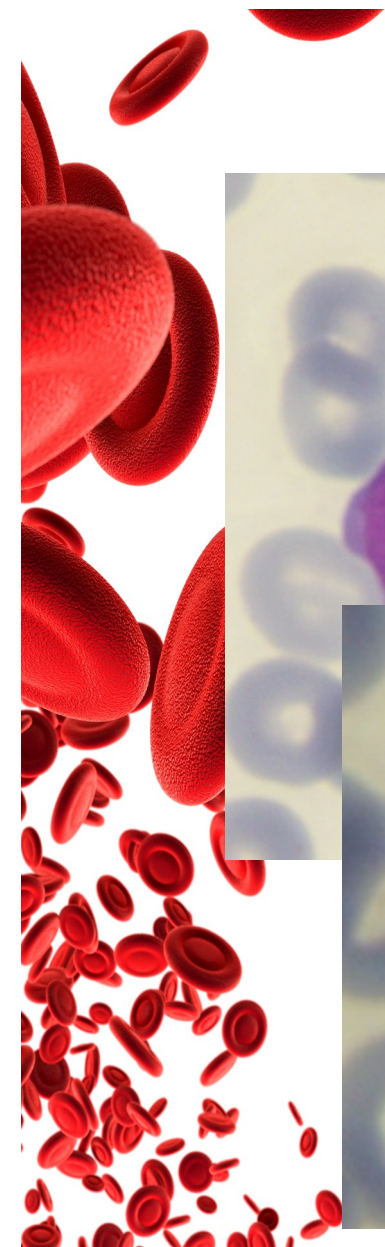
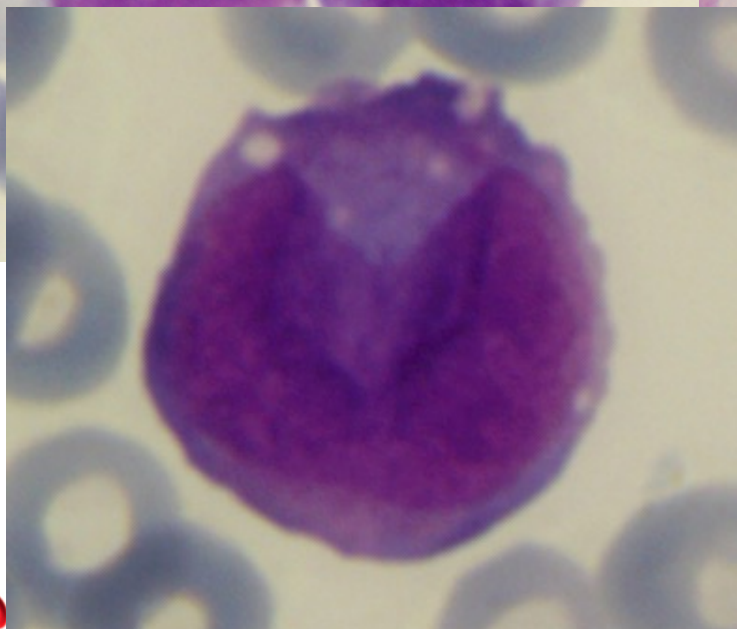
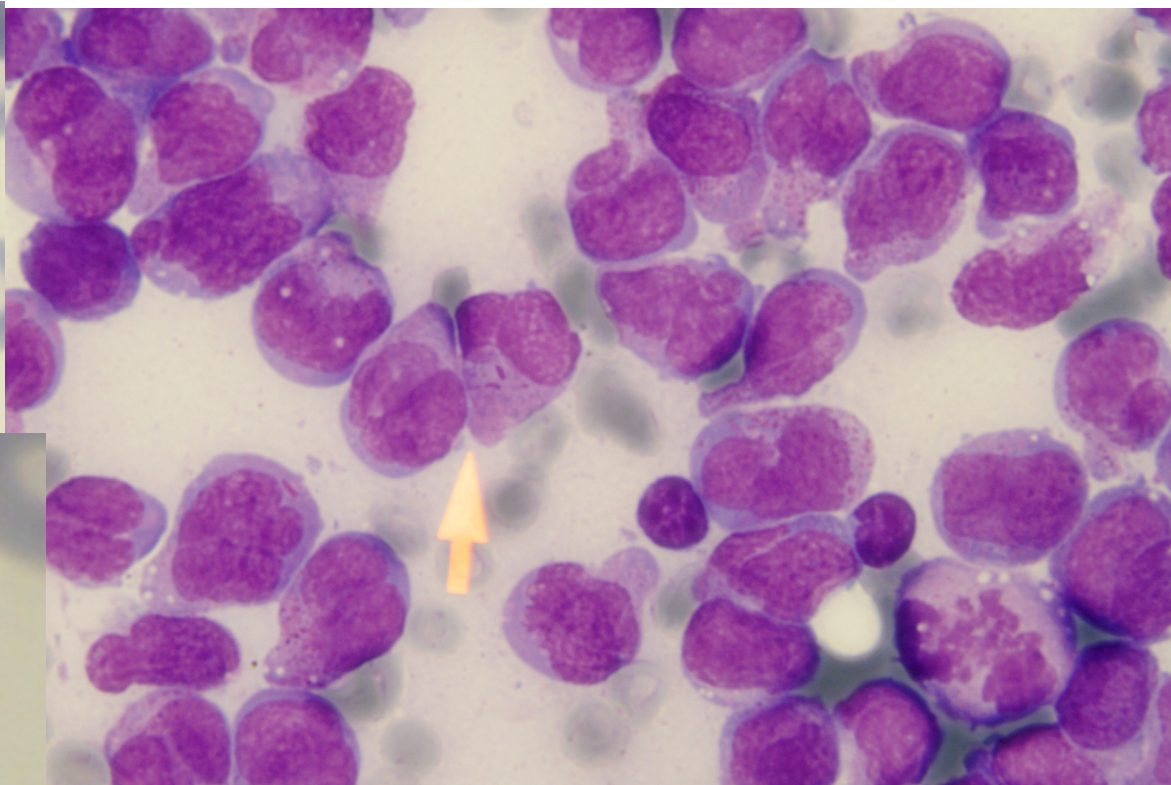
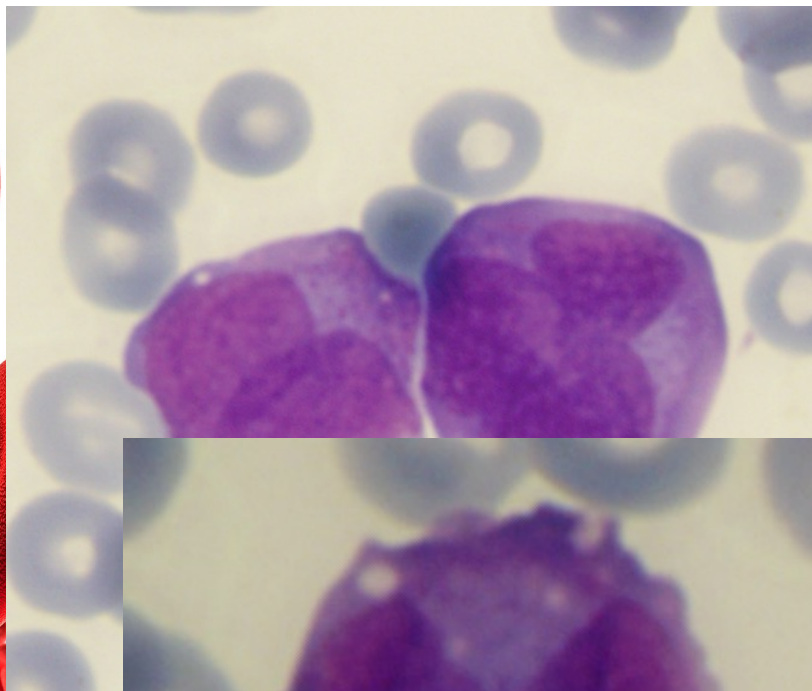
LAM NPM1 mutata: variabilità tra PB e BM



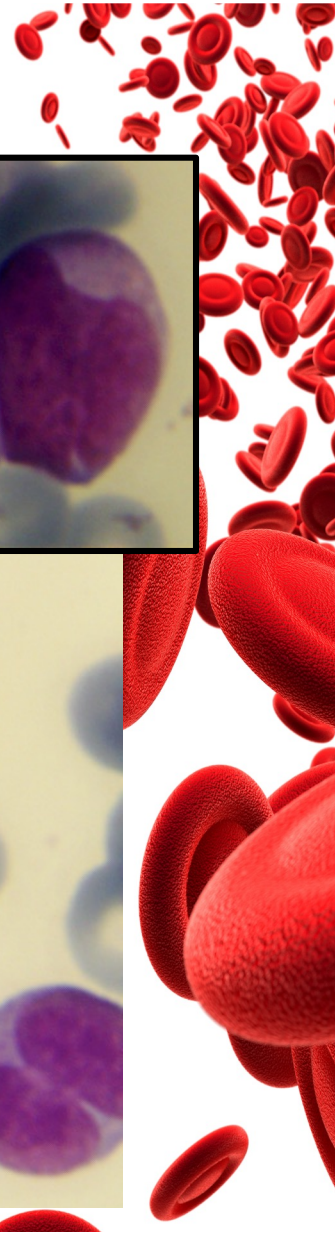
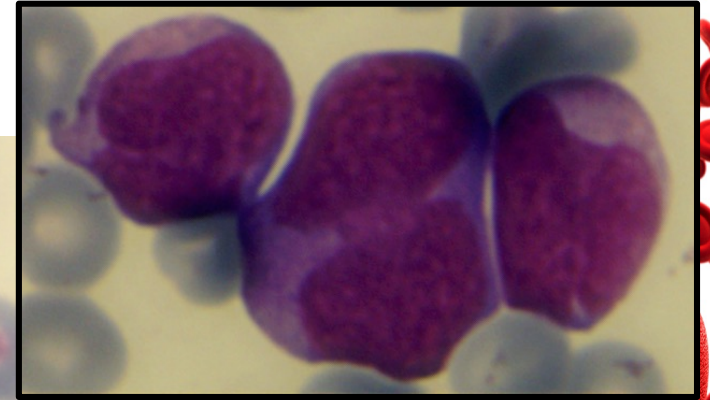
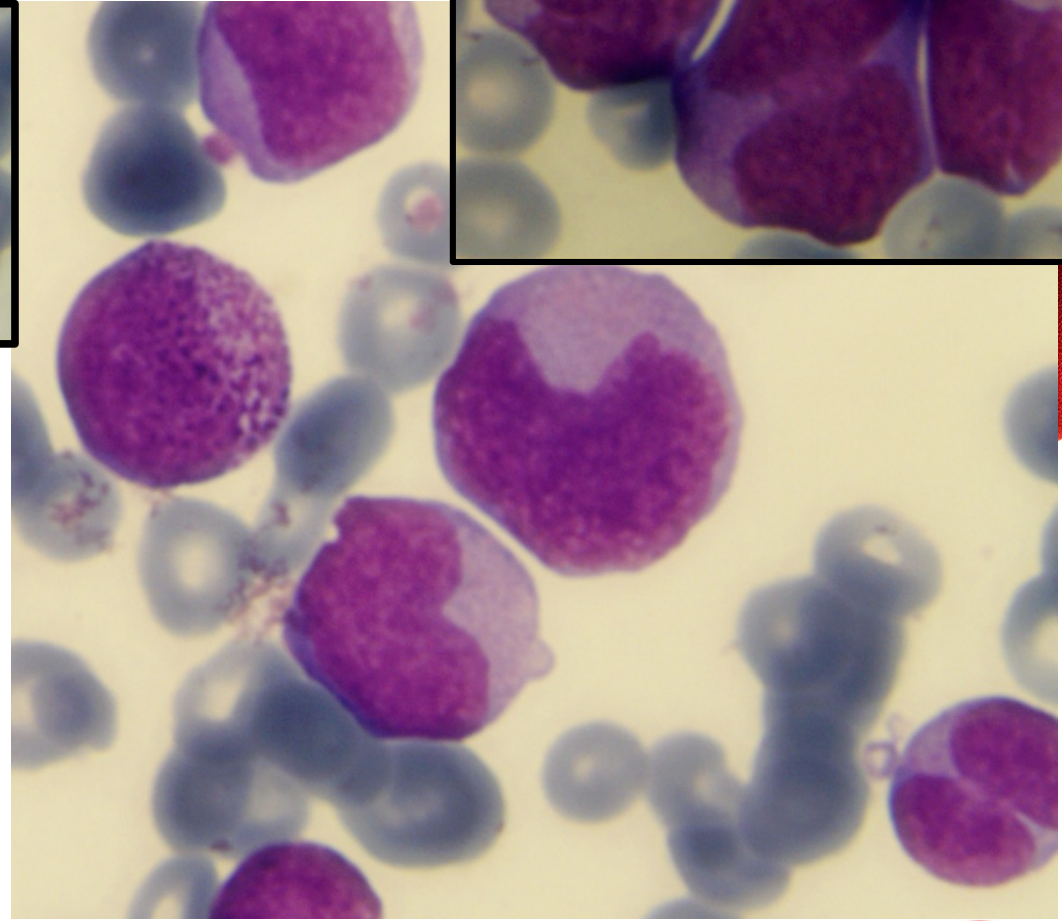
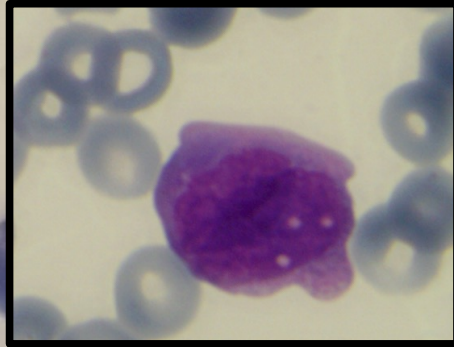
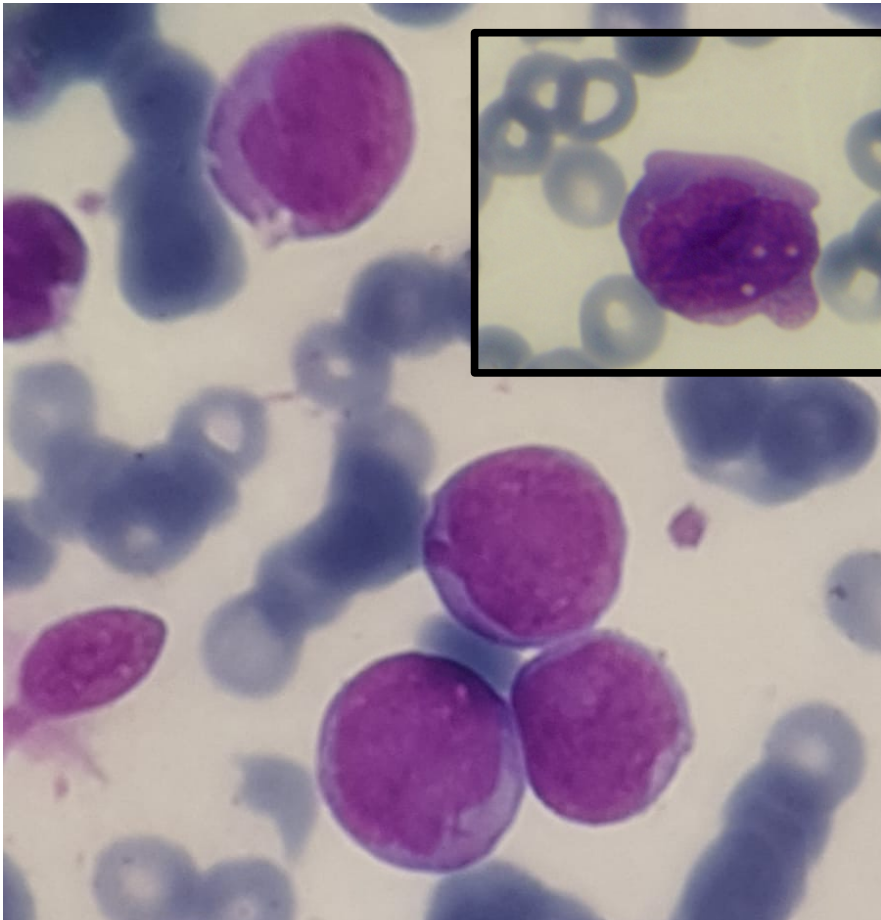
BM



LAP variante ipogranulare

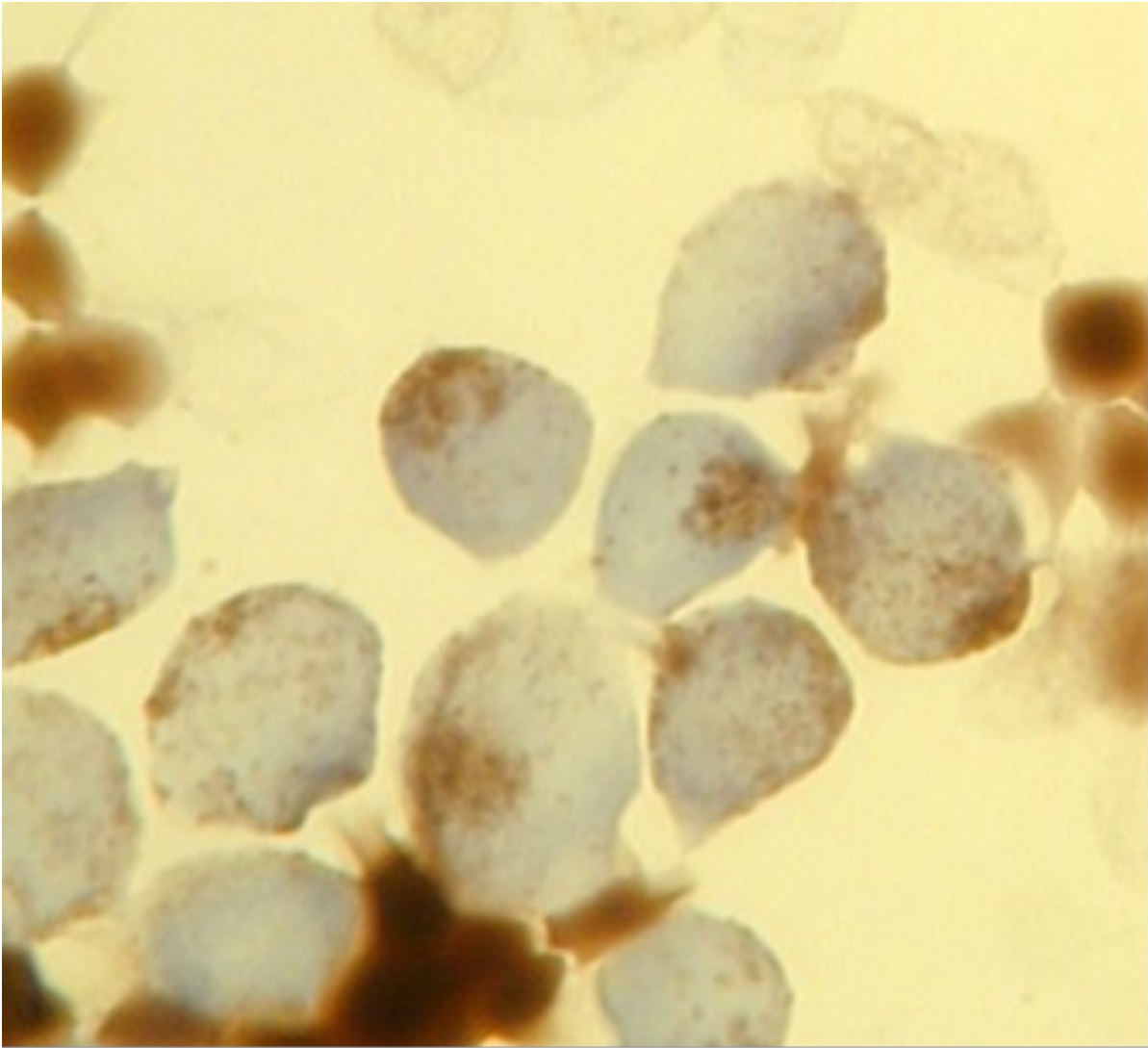


LAM NPM1 mutata o LAP variante ipogranulare?

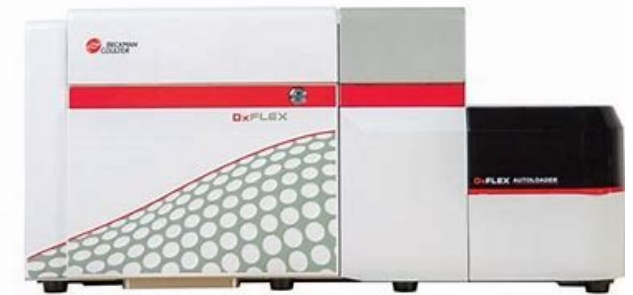
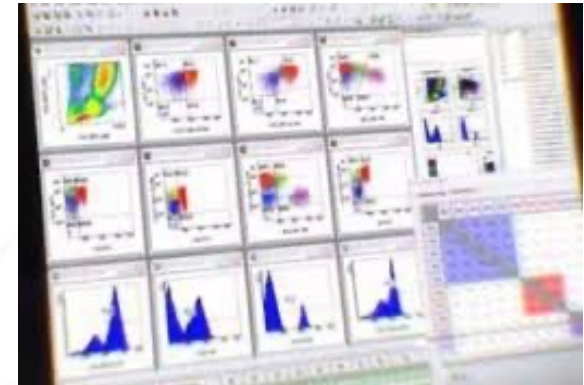




MPO



La parola alla citofluorimetria....



> [Leukemia](#). 2009 Jul;23(7):1361-4. doi: 10.1038/leu.2009.84. Epub 2009 Apr 16.

Flow cytometric identification of acute myeloid leukemia with limited differentiation and NPM1 type A mutation: a new biologically defined entity

W Kern, C Haferlach, U Bacher, T Haferlach, S Schnittger

PMID: 19369962 DOI: 10.1038/leu.2009.84

Comparative Study > [Leuk Res](#). 2013 Jul;37(7):737-41. doi: 10.1016/j.leukres.2013.03.009.

Epub 2013 Apr 16.

NPM1-mutated acute myeloid leukemia of monocytic or myeloid origin exhibit distinct immunophenotypes

Yan-Rong Liu¹, Hong-Hu Zhu, Guo-Rui Ruan, Ya-Zhen Qin, Hong-Xia Shi, Yue-Yun Lai, Yan Chang, Ya-Zhe Wang, Dan Lu, Le Hao, Jin-Lan Li, Ling-Di Li, Bin Jiang, Xiao-Jun Huang

Cytometry Part B (Clinical Cytometry) 96B:67-72 (2019)

Original Article

Pattern Associated Leukemia Immunophenotypes and Measurable Disease Detection in Acute Myeloid Leukemia or Myelodysplastic Syndrome with Mutated *NPM1*

Yi Zhou,* Andres Moon, Eric Hoyle, Jonathan R. Fromm, Xuayan Chen, Lori Soma, Stephen J. Salipante, Brent L. Wood, and David Wu

Department of Laboratory Medicine, University of Washington, Seattle, Western Australia, Australia

Received: 31 May 2020 | Revised: 2 September 2020 | Accepted: 17 September 2020
DOI: 10.1111/ijlh.13357

ORIGINAL ARTICLE

ISLH International Journal of Laboratory Hematology WILEY

Acute myeloid leukemia with mutated *NPM1* mimics acute promyelocytic leukemia presentation

Manuel J. Arana Rosainz¹ | Nghia Nguyen¹ | Amer Wahed¹ | Laura C. Lelenwa¹ | Nfn Aakash¹ | Karen Schaefer² | Adan Rios³ | Zeyad Kanaan³ | Lei Chen¹

Received: 2 June 2020 | Revised: 9 November 2020 | Accepted: 24 November 2020
DOI: 10.1002/cyto.b.21979

ORIGINAL ARTICLE

CLINICAL CYTOMETRY WILEY

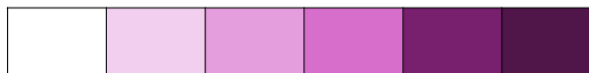
Radar plots facilitate differential diagnosis of acute promyelocytic leukemia and *NPM1*+ acute myeloid leukemia by flow cytometry

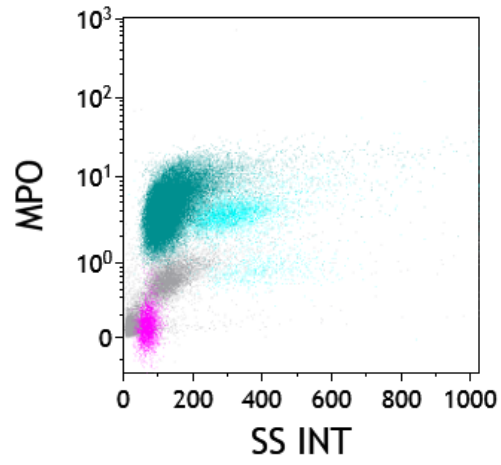
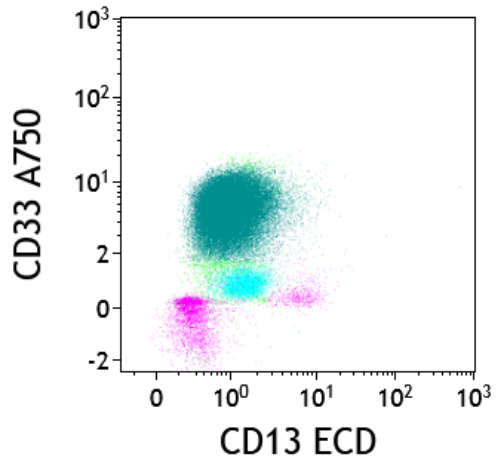
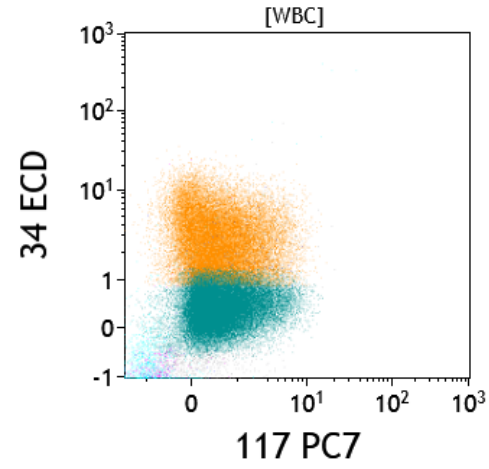
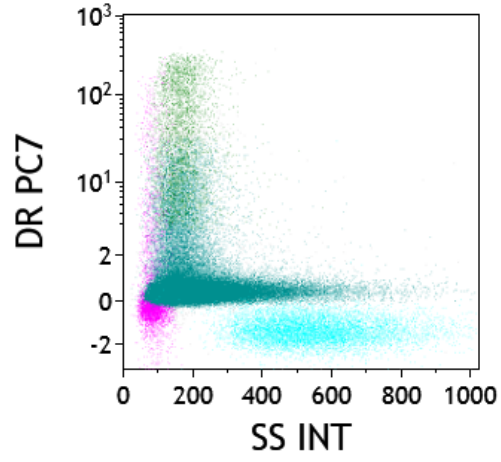
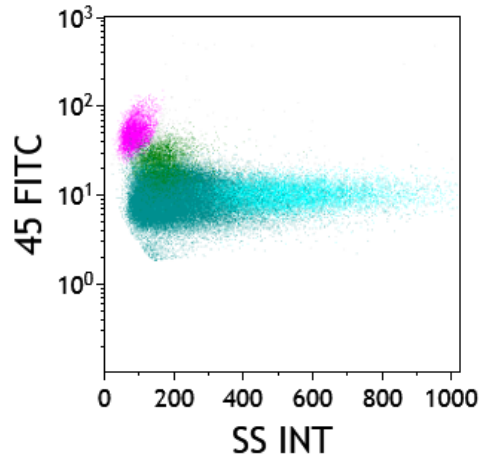
Monali Gupta^{1,2} | Katayoon Jafari^{2,3} | Amr Rajab^{2,4} | Cuihong Wei^{2,3} | Joanna Mazur^{5,6} | Anne Tierens² | Elizabeth Hyjek^{2,7} | Rumina Musani² | Anna Porwit^{2,8}

LAIP e ANOMALIE CITOGENETICHE

	t (8;21)	Inv (16)	t (15;17)	11q23	NPM1mut Monocitica	NPM1mut Cup-like
SSC						
CD34						
HLADR						
CD117						
MPO						
CD13						
CD33						
CD64						
CD15						
CD123						
CD19						
CD79a						
CD56						
NG2						

Intensità di espressione





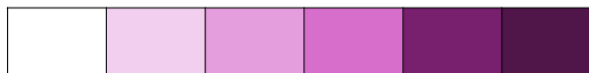
PML/RaR α

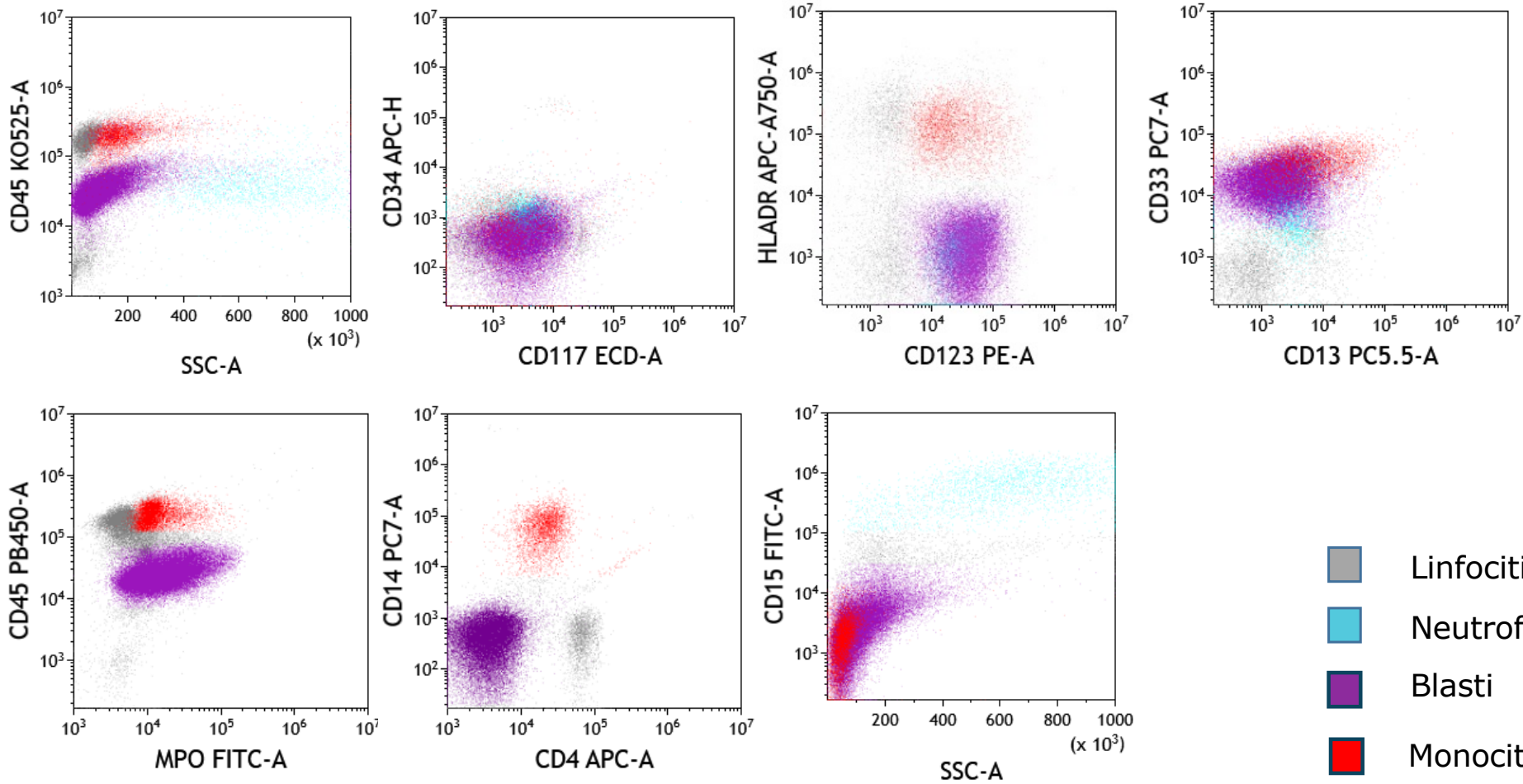


LAIP e ANOMALIE CITOGENETICHE

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CD13						
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NG2						

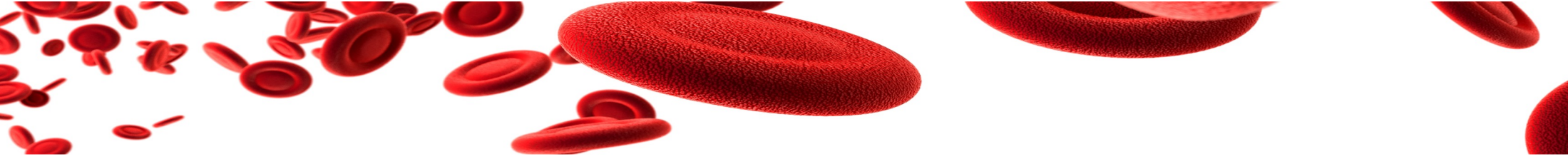
Intensità di espressione





NPM1 mut




$$SSC\ ratio = \frac{SSC(blasts)}{SSC\ (lymp)}$$

Caetano MB et al. ISLH Symposium 2022 (Poster)

AML NPM1mut: 1.98 (1.2-2.8)

Acute Promyelocytic Leukemia: 5.96 (3.1 – 8.11)

$p < 0.001$

Intensità di espressione MPO

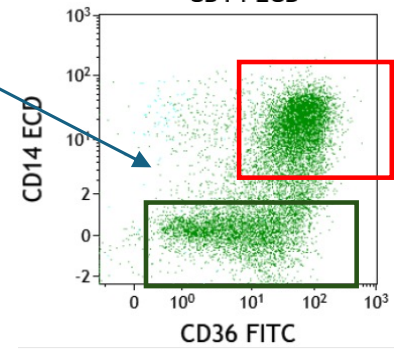
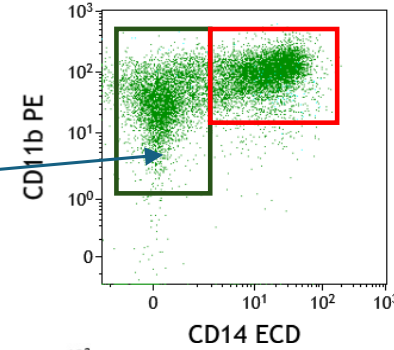
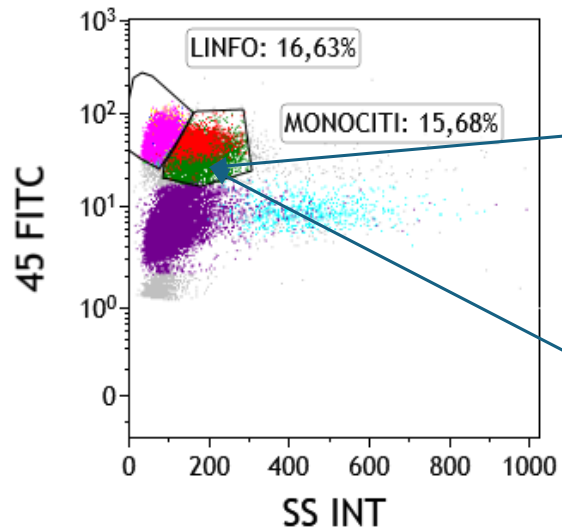
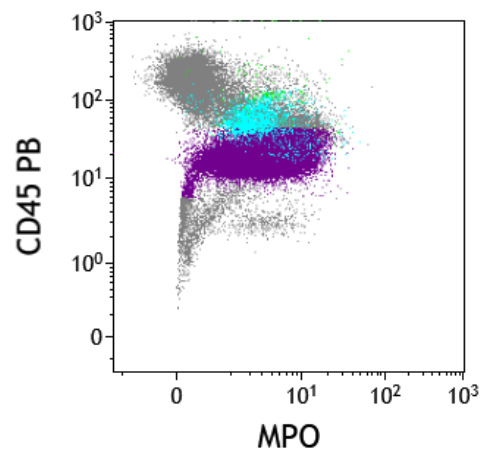
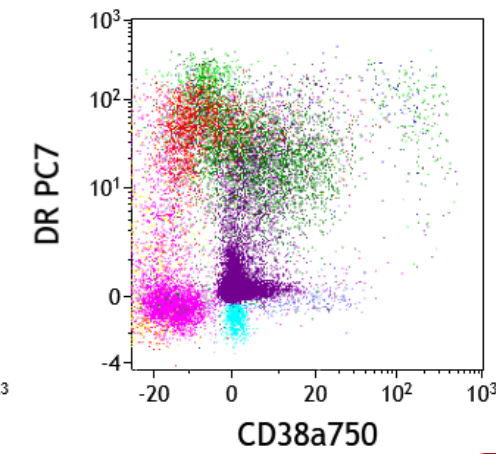
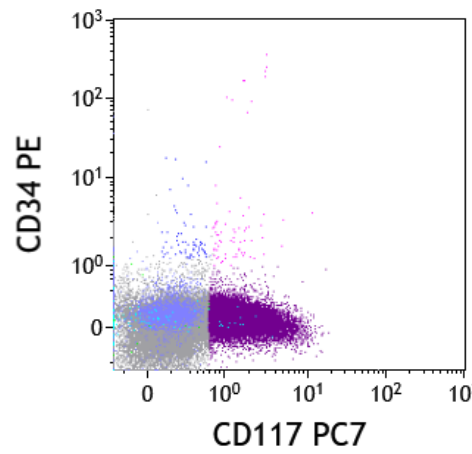
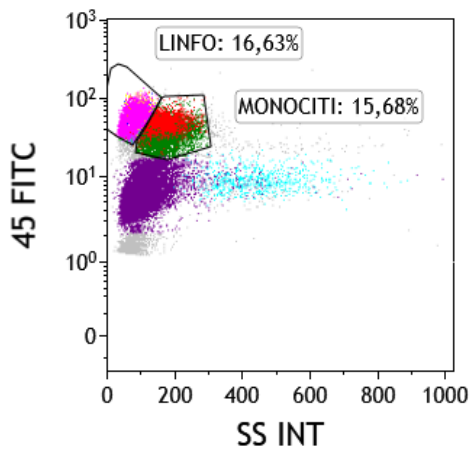
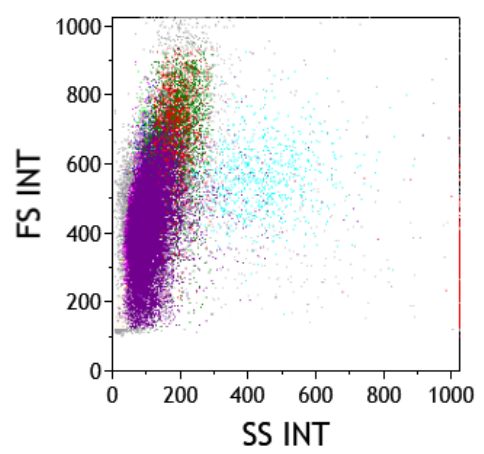


LAIP e ANOMALIE CITOGENETICHE

	t (8;21)	Inv (16)	t (15;17)	11q23	NPM1mut Monocitica	NPM1mut Cup-like
SSC						
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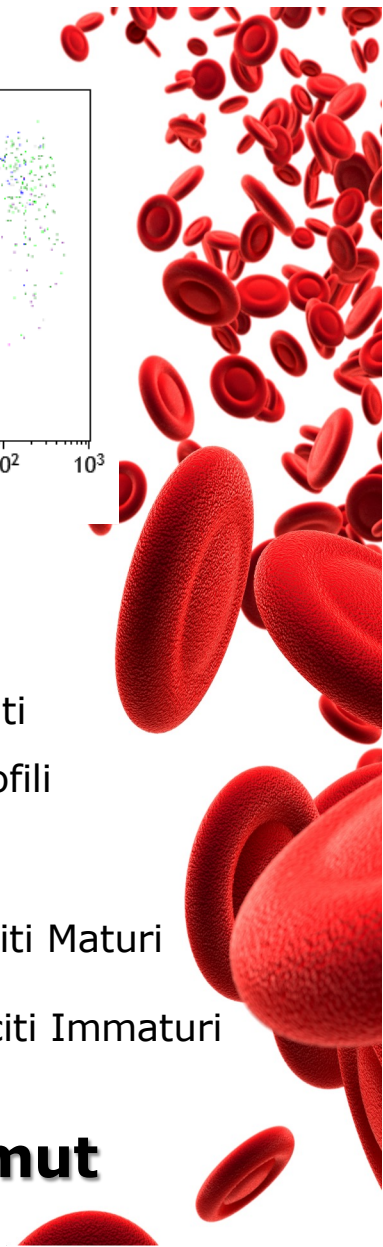
Intensità di espressione





- Linfofociti
- Neutrofili
- Blasti
- Monociti Maturi
- Monociti Immaturi

NPM1 mut



Original Article

Pattern Associated Leukemia Immunophenotypes and Measurable Disease Detection in Acute Myeloid Leukemia or Myelodysplastic Syndrome with Mutated *NPM1*

Yi Zhou,* Andres Moon, Eric Hoyle, Jonathan R. Fromm, Xueyan Chen, Lori Soma, Stephen J. Salipante, Brent L. Wood, and David Wu
Department of Laboratory Medicine, University of Washington, Seattle, Western Australia, Australia

...detection of leukemic blasts in 590 specimens collected from 152 patients in complete remission after induction for AML/MDS-EB with mutated *NPM1*.

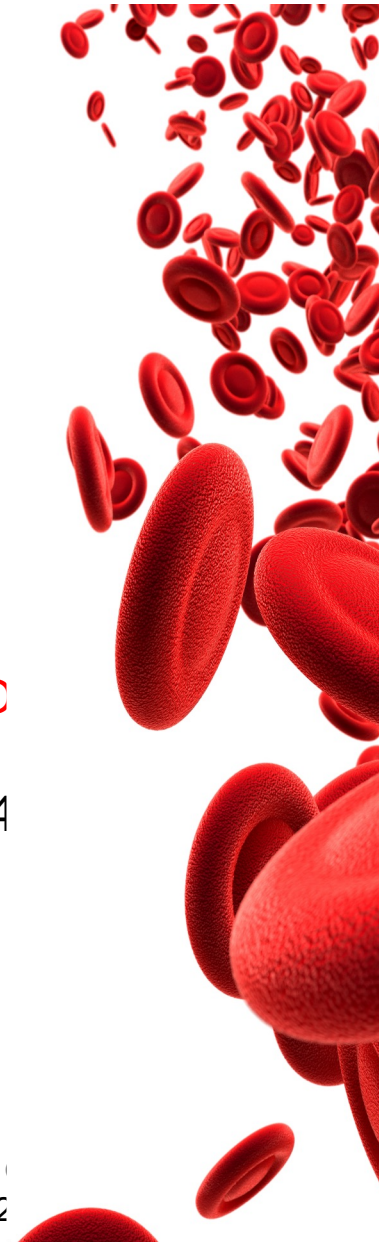
«LAIP-based difference-from-normal»

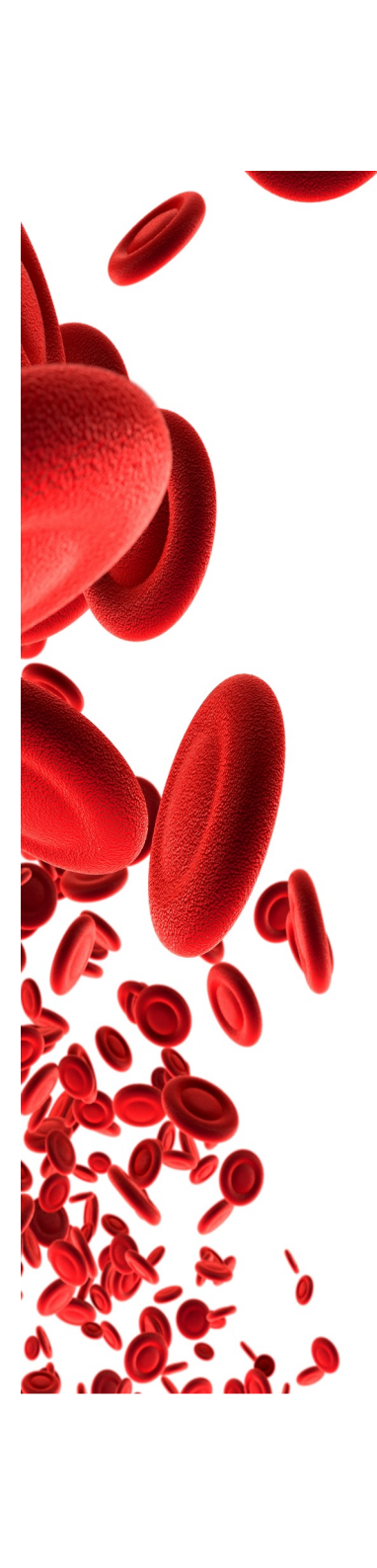
regenerative myeloid blasts having myelomonocytic differentiation (CD34+, CD117+, CD13+, CD15-, CD33+, CD64-, CD123+, HLA-D

promyelocytes (CD34-, CD117+, CD13++, CD15++, CD33+, CD64 CD123+, HLA-DR-)

immature monocytes (CD34-, CD117-, CD13-, CD15+, CD33++, CD64+, CD123+, HLA-DR++).

Schuurhuis GJ, Heuser M, Freeman S, Bene MC, Buccisano F, Cloos J, et al. Minimal/measurable residual AML: A consensus document from the European LeukemiaNet MRD working party. Blood 2018;131(12):12

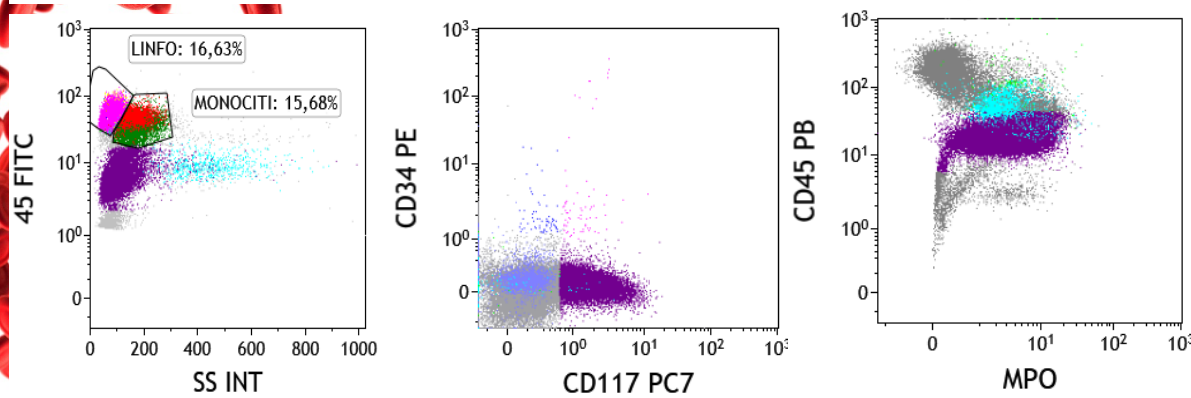
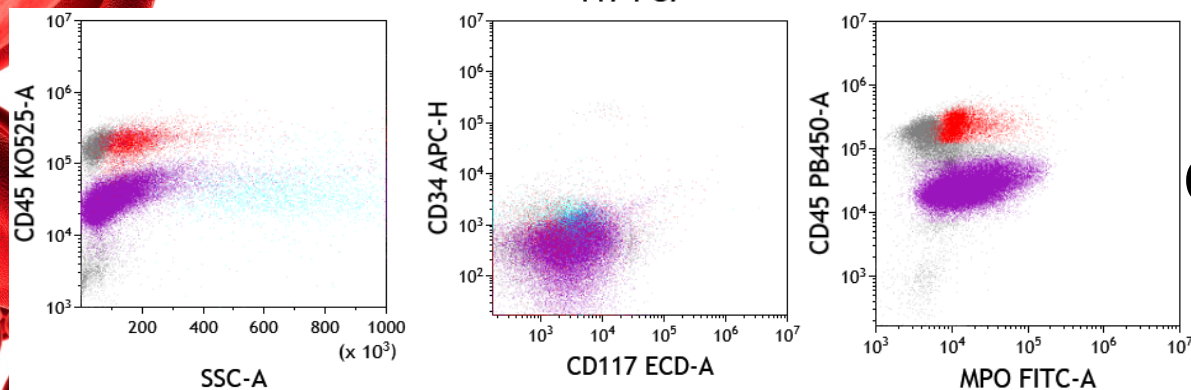
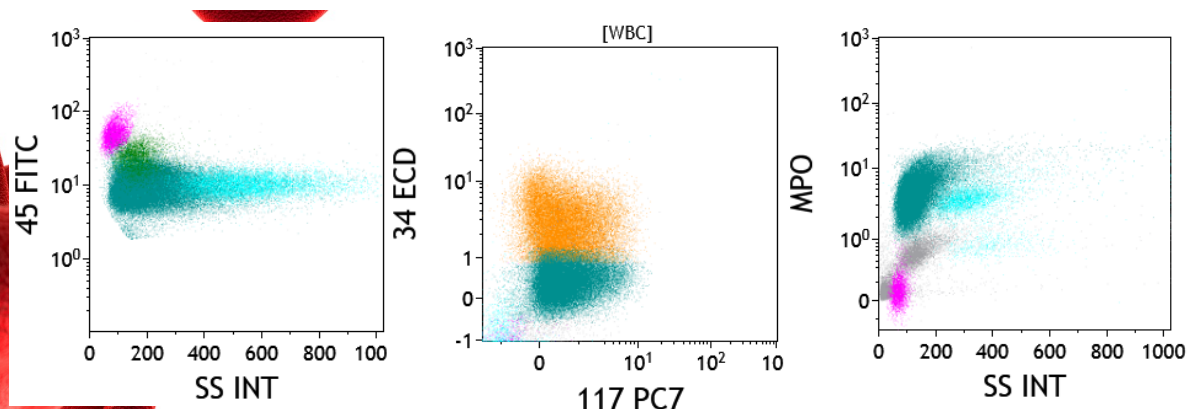




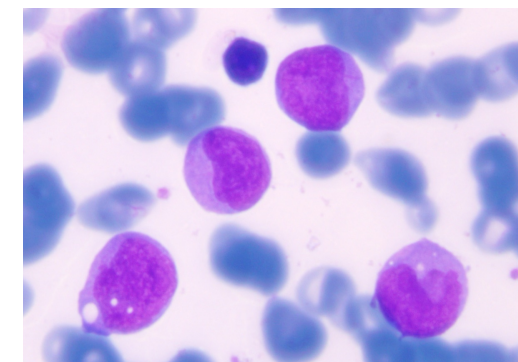
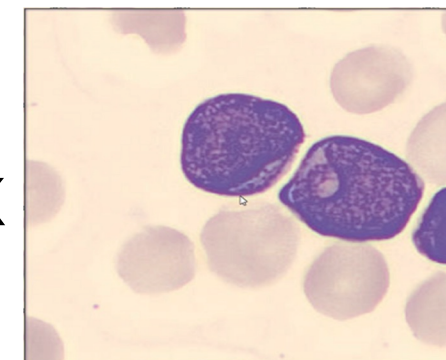
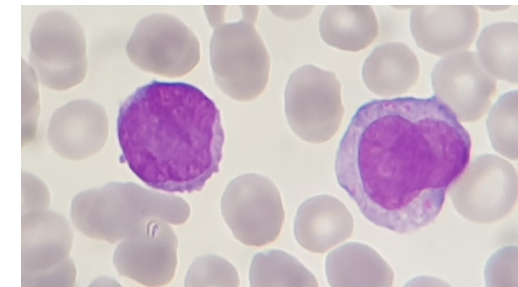
i blasti mieloidi con NPM1 mutato hanno LAIP non significativamente alterati (tranne l'espressione di CD34) dalla terapia, dalla presenza di FLT3 ITD o di anomalie citogenetiche

Blasti mieloidi sono presenti in quasi tutte le LAM o MDS-EB con NPM1 mutato, mentre la popolazione monocitica immatura è prevalentemente presente nella LAM con differenziazione monocitica, e tende a diminuire in caso di recidiva. Questi risultati suggeriscono che una popolazione di blasti mieloidi con un immunofenotipo di progenitori precoci anomali con differenziazione mielomonocitaria è il segno distintivo della NPM1 mutata; mentre l'espansione dei monociti immaturi è un segno dell'alterazione della maturazione mielomonocitaria causata dalla mutazione NPM1 e può variare nel corso della malattia

I blasti mieloidi leucemici possono essere rilevati nella MRD di un midollo osseo rigenerativo in pazienti in remissione completa. Al contrario, la quantificazione di monociti immaturi leucemici è difficile a causa della mancanza di un distinto pattern LAIP



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