Mixed-Lineage & Biphenotypic Acute Leukemia

Lymphoma Tumor Board

Friday, September 30, 2016

Background

- Mixed-phenotype acute leukemia (MPAL) is rare
- Heterogeneous group of rare leukemias where assigning a single lineage of origin is not possible
- Defined by limited set of lineage-specific markers
- Multipotent progenitor cells can differentiate into both myeloid and lymphoid lineages
- Factors possibly related:
  - Viral infection
  - Hereditary factors
  - Radiation exposure
  - Chemical exposure
- Association with several mutations, most common being t(9;22) and *MLL* gene rearrangement at 11q3.

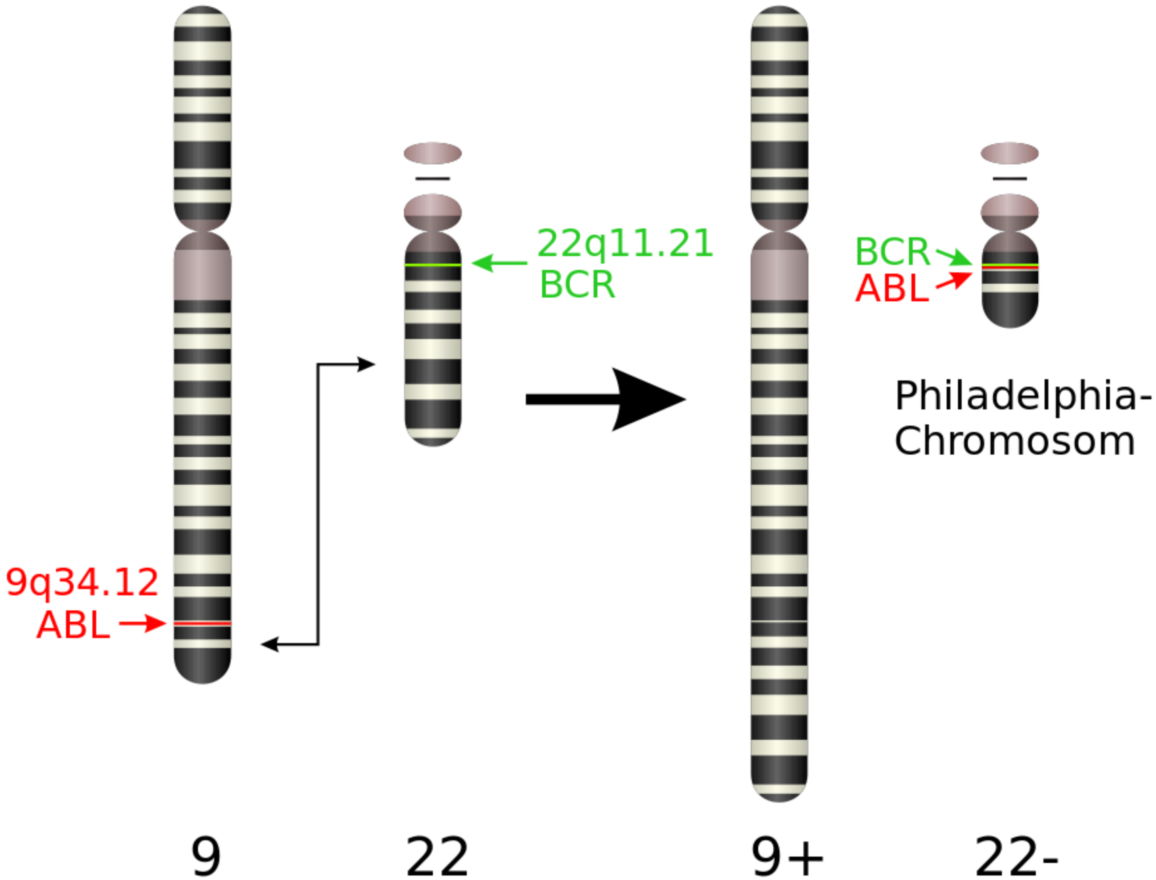


Figure 1. T(9,22) translocation

https://en.wikipedia.org/wiki/Biphenotypic_acute_leukemia

Diagnosis

- Patients diagnosed have >20% blasts in blood or marrow (or less in cases of chromosomal translocations and extramedullary presentation).
- "Sometimes the immature cells display cytochemical and/or immunophenotypic features of both lineages (**biphenotypic**) or there are different populations of leukemia cells (**bilineal**)."
- Symptoms due to bone marrow damage:
  - Bruising
  - Anemia
  - Persistent fever
  - Septicemia
- Symptoms due to leukemic cells infiltrating into tissues:
  - Lymphadenopathy
  - Joint pain
  - Swelling of the gums
  - Heptoslenomegaly
  - Headache/vomiting
  - Skin nodules or "lumps"
- Diagnosis **cannot** be based on morphology alone

Diagnostic criteria for BAL and MPAL

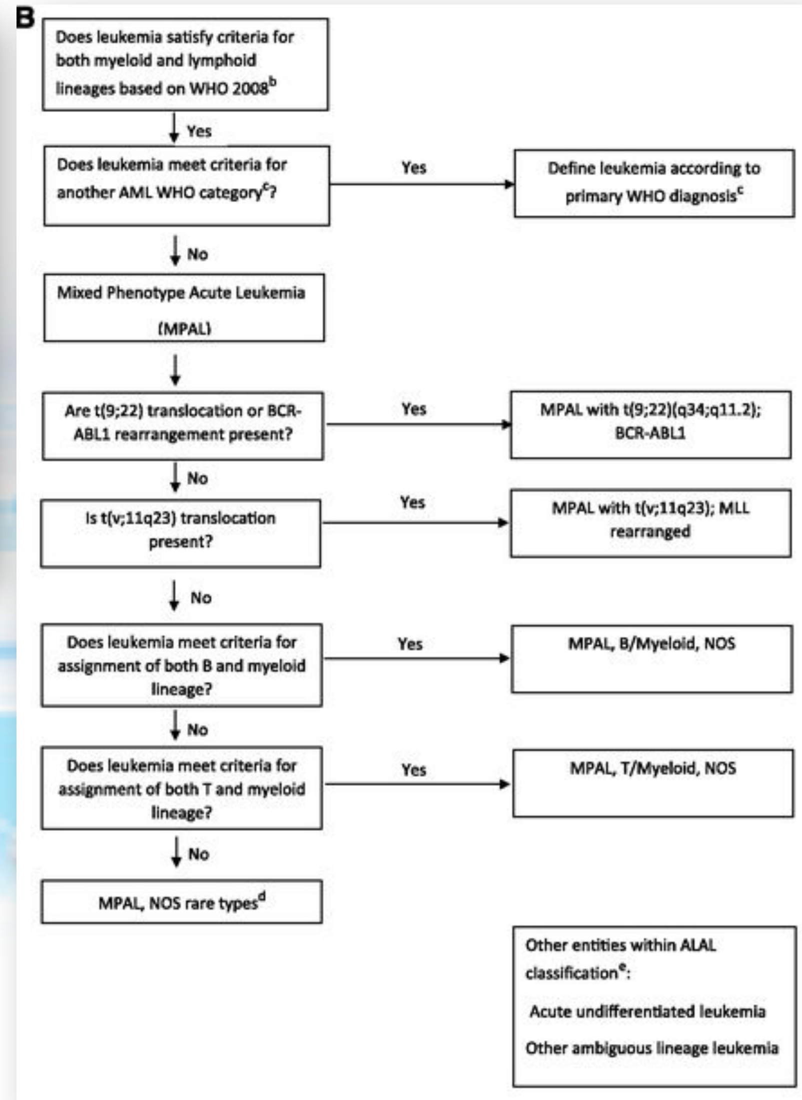
A

Points	B lineage	T lineage	Myeloid lineage
2	CD79a	CD3 (cyt/m)	Anti-MPO
	cyt IgM	anti-TCR α/β	
	Cyt CD22	anti-TCR γ/δ	
1	CD19	CD2	CD13
	CD10	CD5	CD33
	CD20	CD8	CDw65
		CD10	CD117
0.5	TdT	TdT	CD14
	CD24	CD7	CD15
		CD1a	CD64

[a]According to the EGIL criteria, biphenotypic leukemia (BAL) is diagnosed when scores are >2 for the myeloid and one of the lymphoid lineages. A marker is considered positive if more than 20% of cells stain positive with a monoclonal antibody; a lower threshold of 10% was set for MPO, CD3, CD79a and TdT.

Abbreviations: cyt, cytoplasmatic; m, membrane; MPO, myeloperoxidase; TCR, T-cell receptor; TdT, terminal deoxynucleotidyl transferase.

B



[b]The following lineage defining markers are required for assigning more than one lineage to a single blast population:

1) Myeloid lineage: myeloperoxidase (by flow cytometry, immunohistochemistry or cytochemistry) or monocytic differentiation (diffuse positivity for non-specific esterase or expression of at least 2 of the following: CD11c, CD14, CD36, CD64, lysozyme).

2) T-lineage: cytoplasmatic CD3 (flow cytometry with antibodies to CD3 epsilon chain; caution when using polyclonal anti-CD3 in immunohistochemistry as it may not be specific) or surface CD3.

3) B-lineage: strong CD19 with at least 1 of the following strongly expressed: CD79a, cytoplasmatic CD22, CD10 or weak CD19 with at least 2 of the following strongly expressed: CD79a, cytoplasmatic CD22, CD10.

For bilineal MPAL the myeloid component can be recognized when there are 2 or more distinct populations of blasts, one of which would meet the criteria for AML (need not comprise >20% of nucleated cells).

[c]The following subgroups of leukemia should be defined primarily by their genetic or clinical features even if they satisfy the above requirements for mutli-lineage expression. A secondary notion regarding their mixed phenotype should be added: AML with recurrent cytogenetic abnormalities such as t(8;21), t(15;17) or inv(16), leukemia with FGFR1 mutations, chronic myeloid leukemia in blast crisis, myelodysplasia-related AML and therapy related AML.

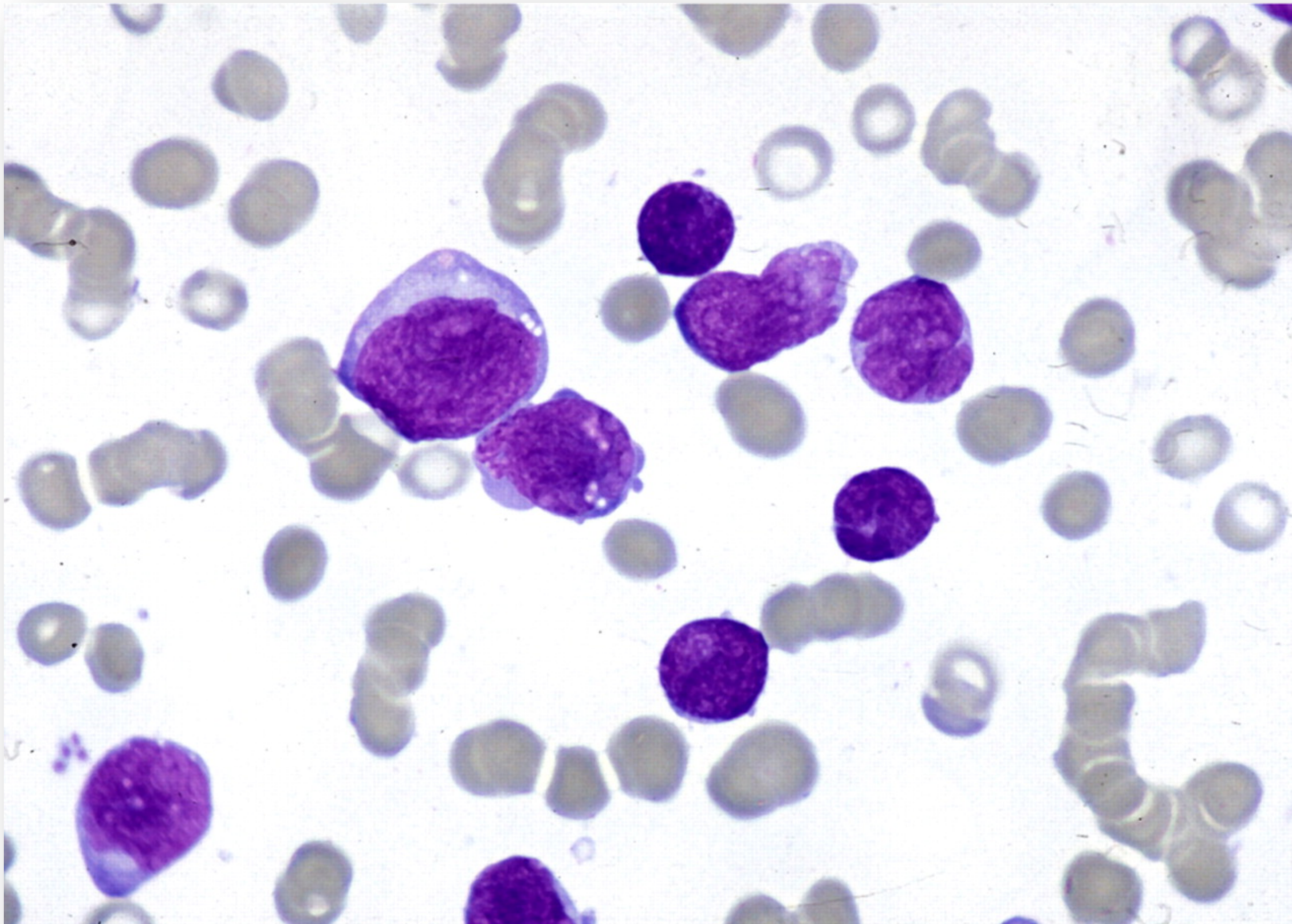
[d]Include rare cases where leukemic blasts show evidence of both T and B lineage, trilineage T, B and myeloid commitment or other rare combinations; CD79a and CD10 should not be considered as evidence for B cell differentiation in this setting as they lack specifity.

[e]These diagnostic entities are associated with lack of definitive lineage commitment. 'Acute undifferentiated leukemia' include leukemias that express no lineage specific markers. 'Other ambiguous lineage leukemia' subgroup encompass the rare cases of leukemia that express combination of lineage associated markers that are suggestive but not sufficient for lineage assignment (so called 'acute unclassifiable leukemias'); Natural killer cell lymphoblastic leukemia/lymphoma is regarded as a provisional entity in this category.

(A) EGIL criteria for the diagnosis of biphenotypic acute leukemia (B) 2008 WHO criteria

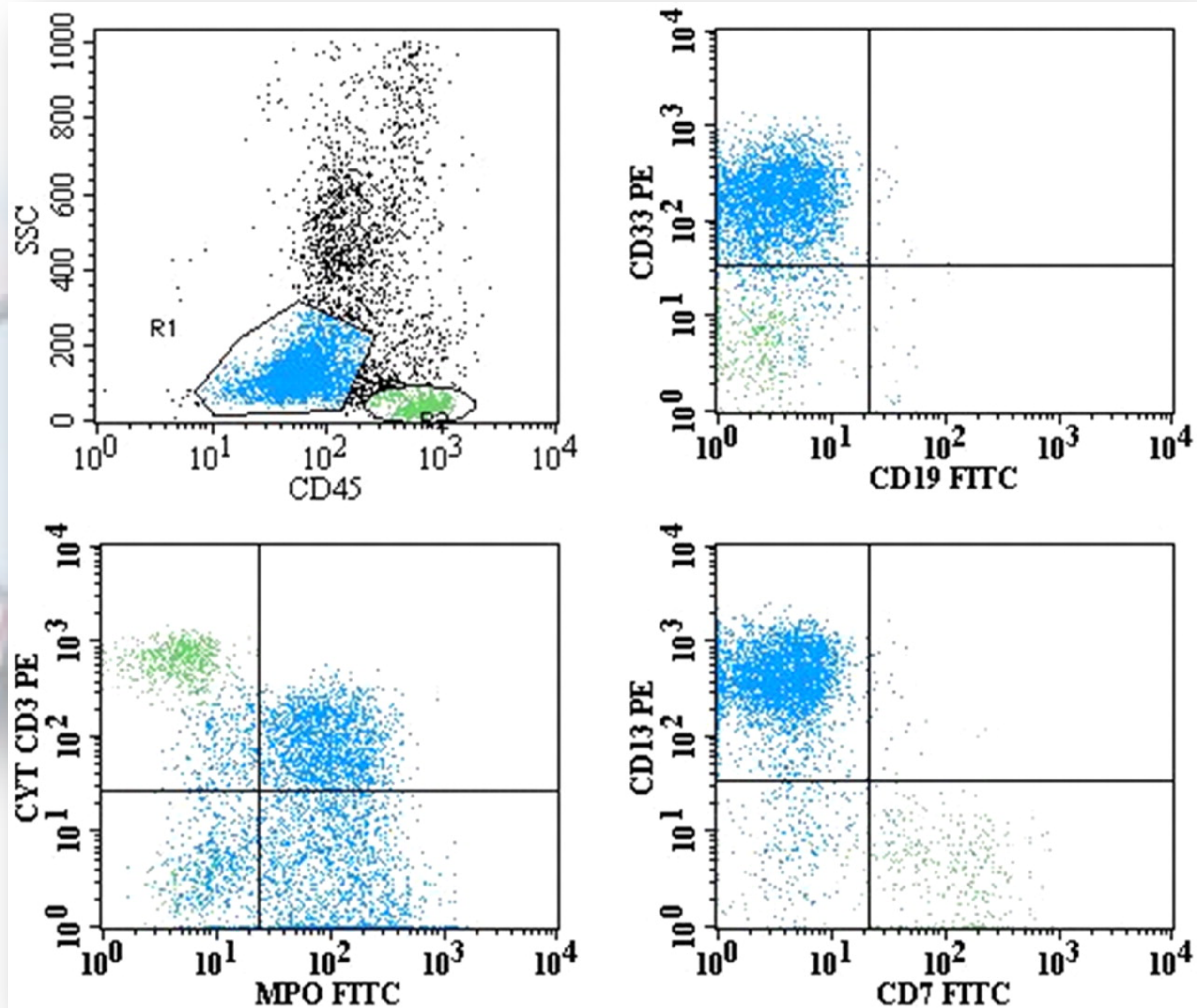
Ofir Wolach, and Richard M. Stone Blood 2015;125:2477-2485

May-Grunwald-Giemsa–stained BM smear showing a mixed-cell population of large and small blasts



Estella Matutes et al. Blood 2011;117:3163-3171

Dot plots with the blast population highlighted in blue (R1) and lymphocyte population in green (R2)



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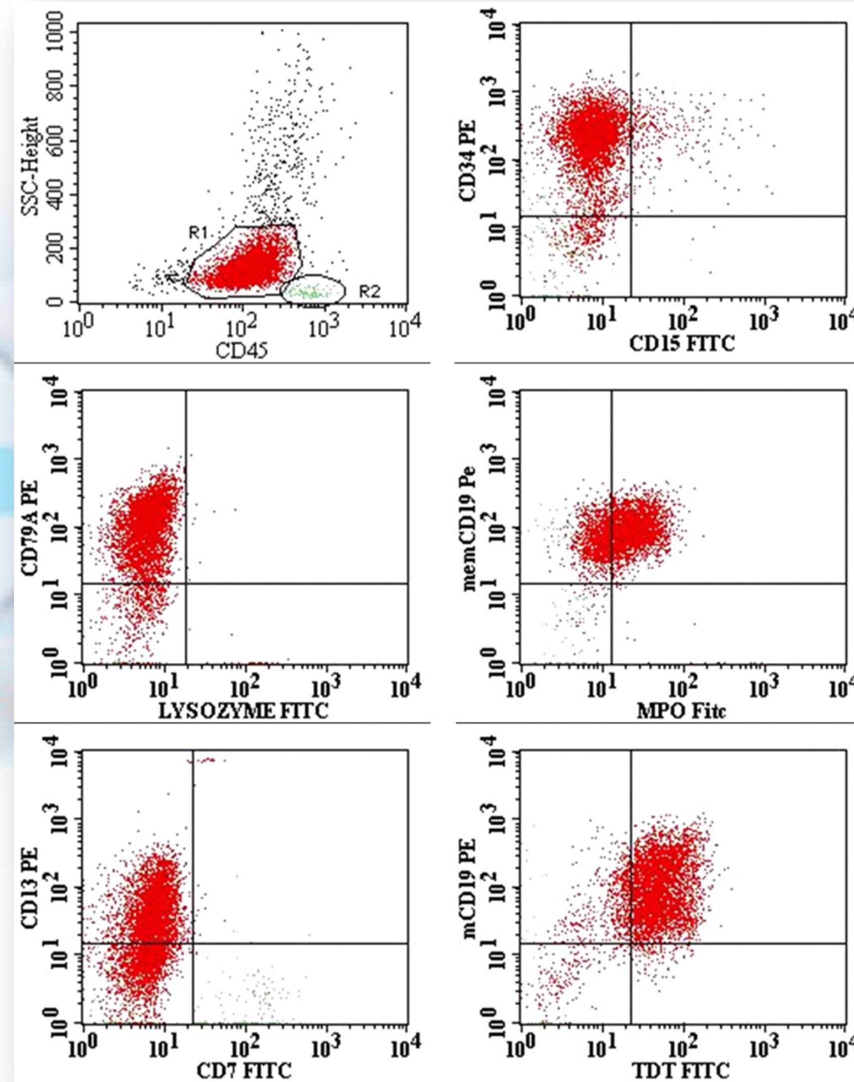
Dot plots with the blast population highlighted in red (R1) and lymphocyte population in green (R2)



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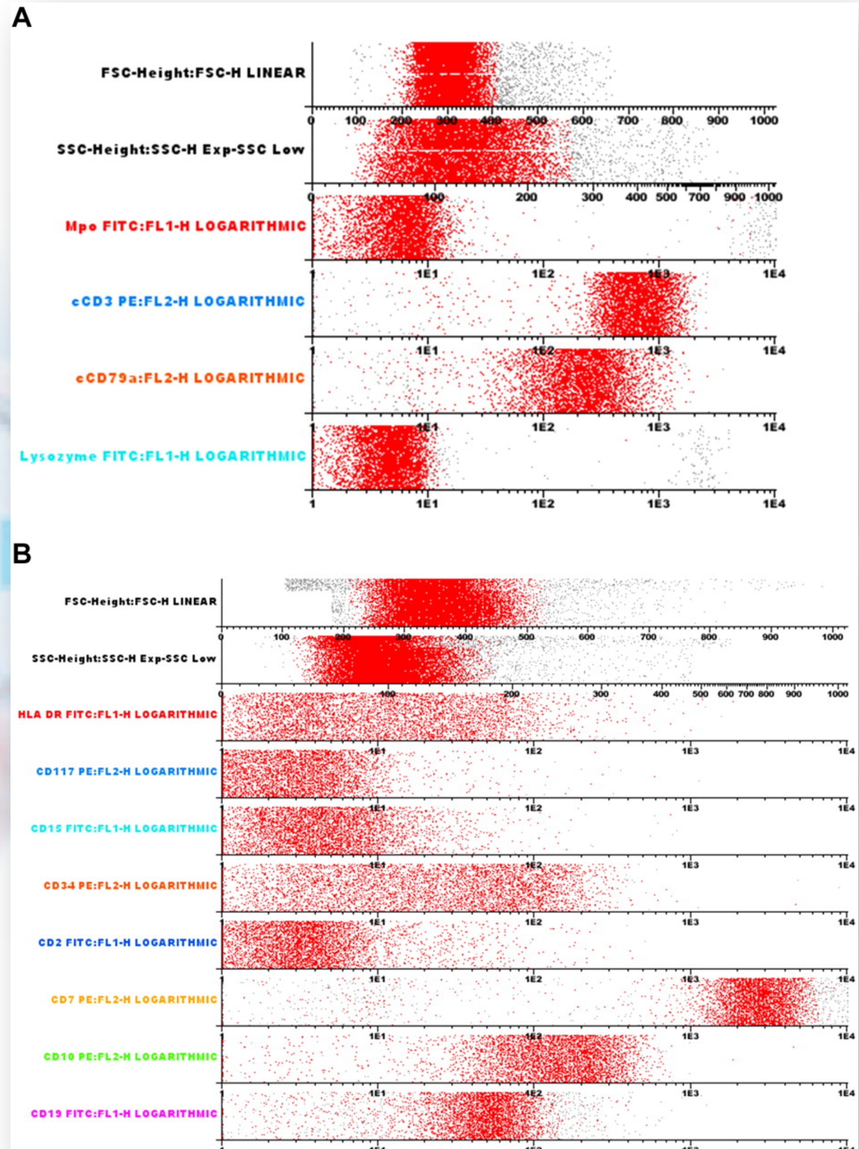
Infinicyte band representation



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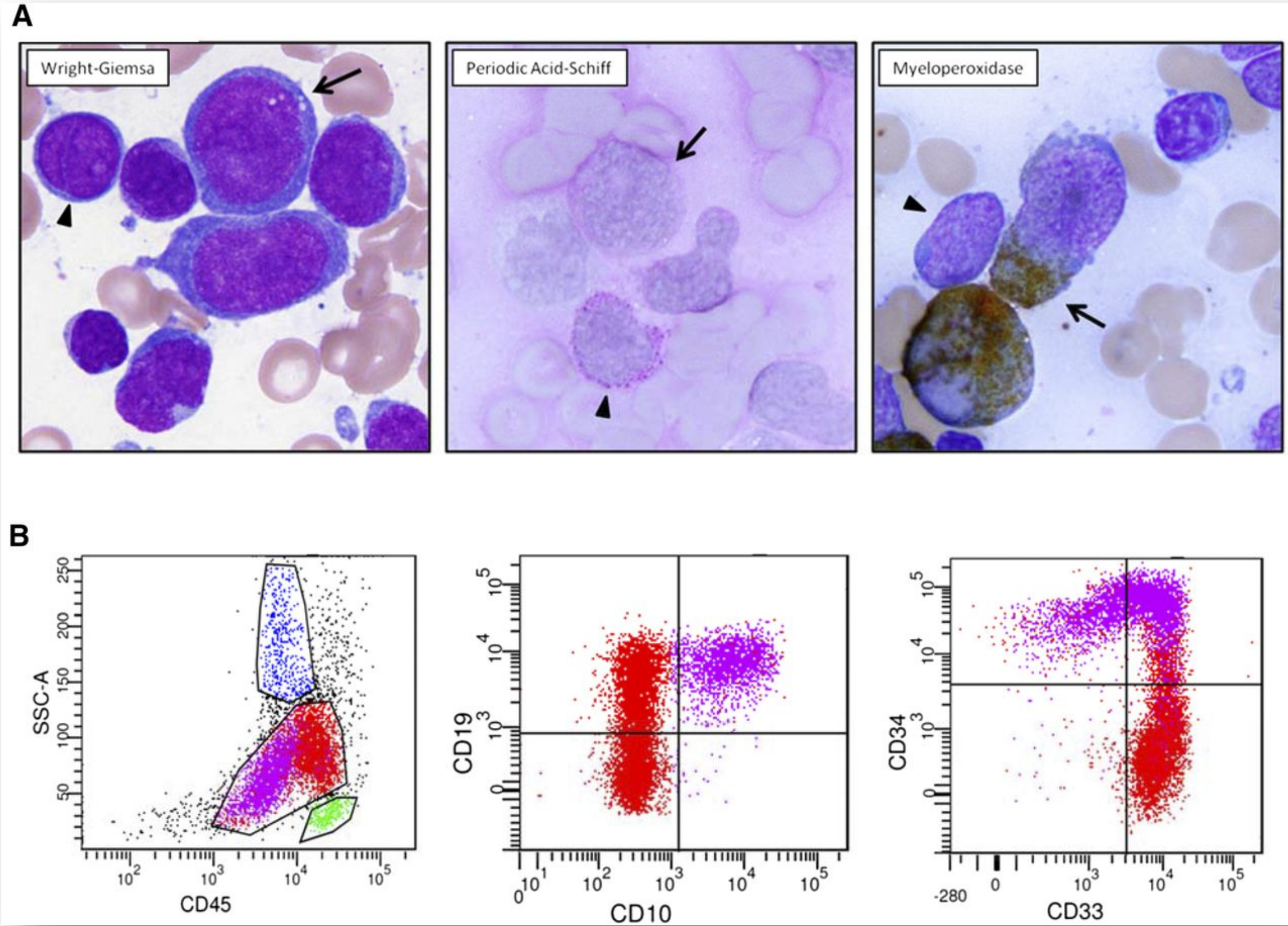
Characteristic morphology



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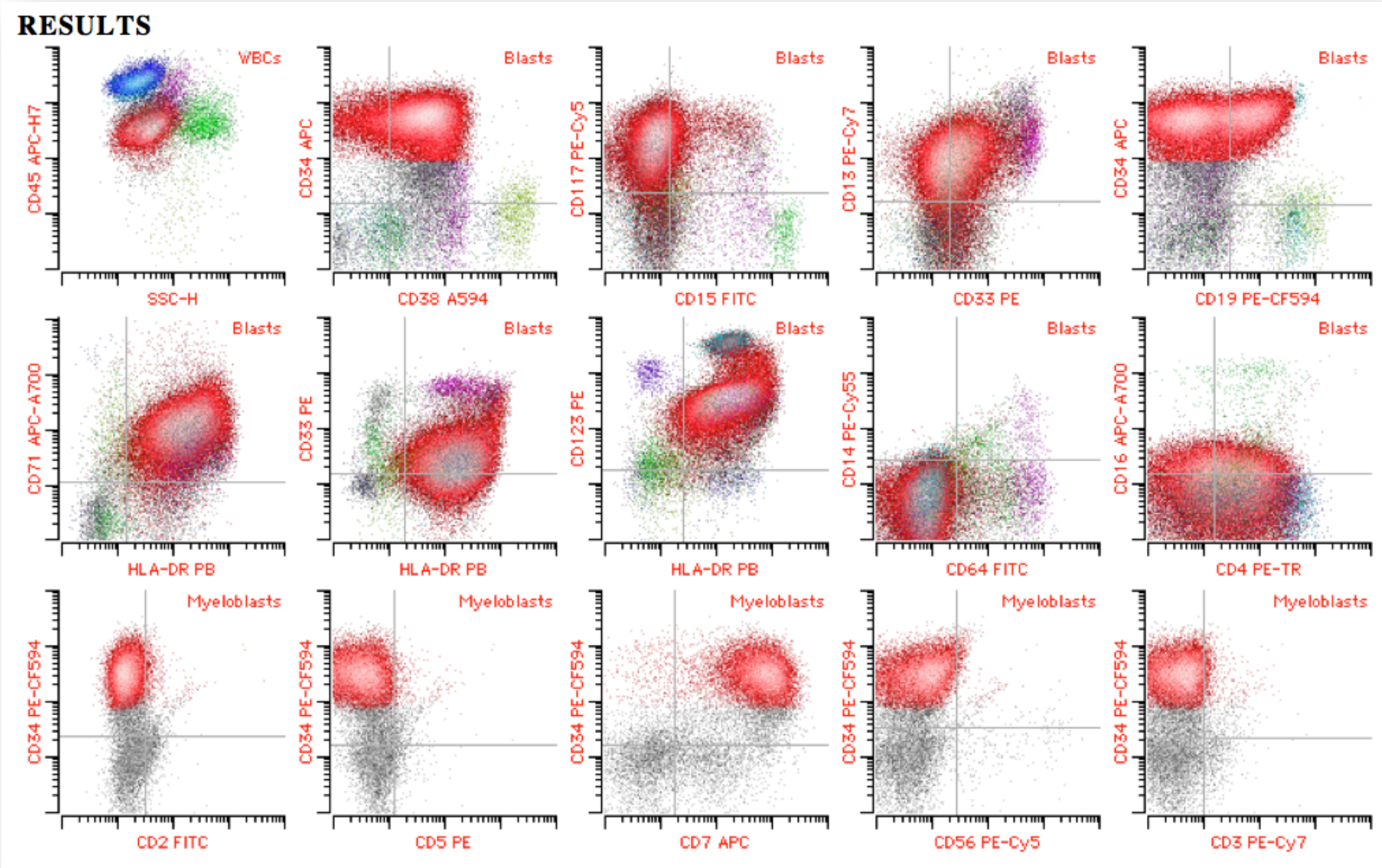
MPAL case study (FHCRC): Bone marrow aspirate



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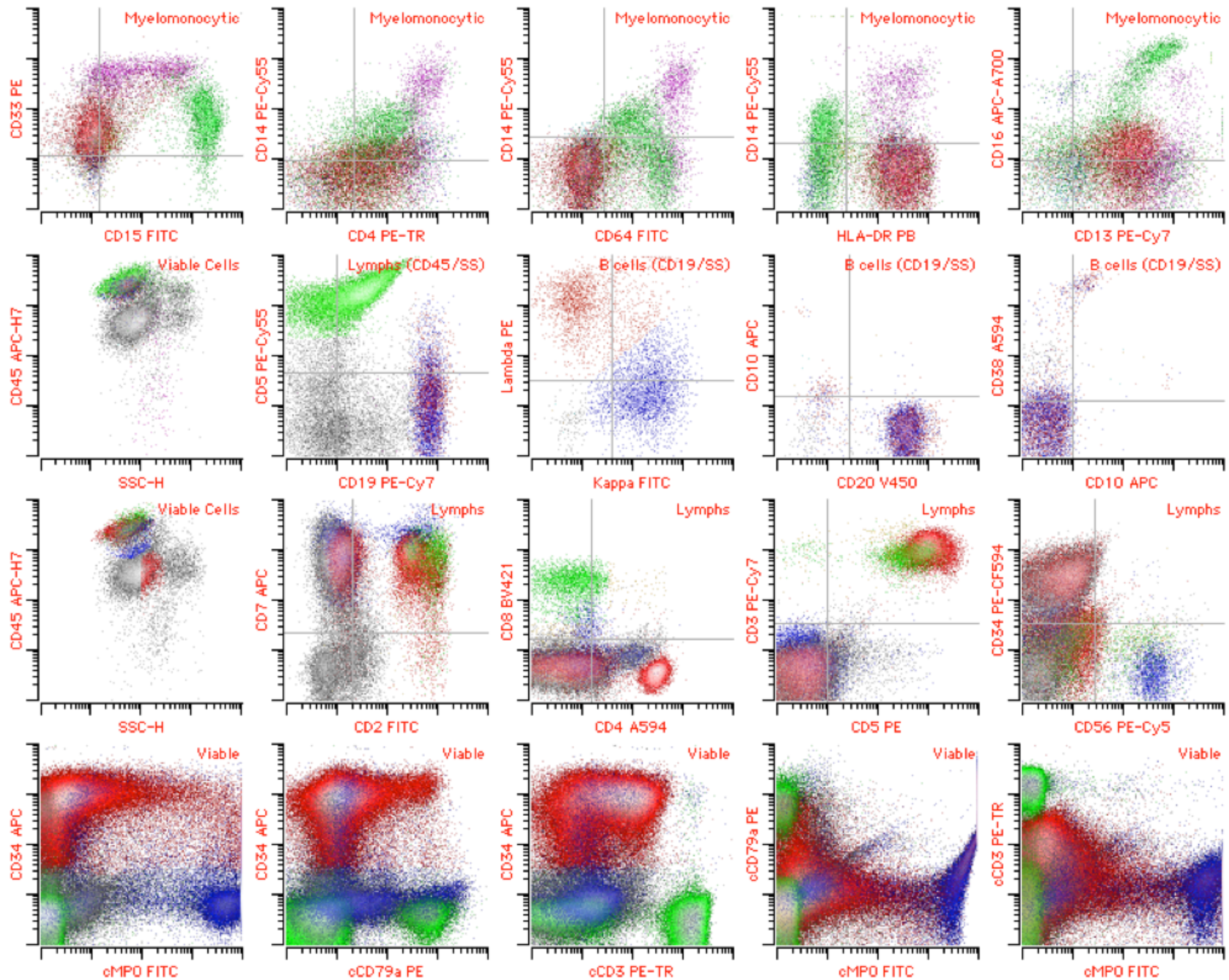
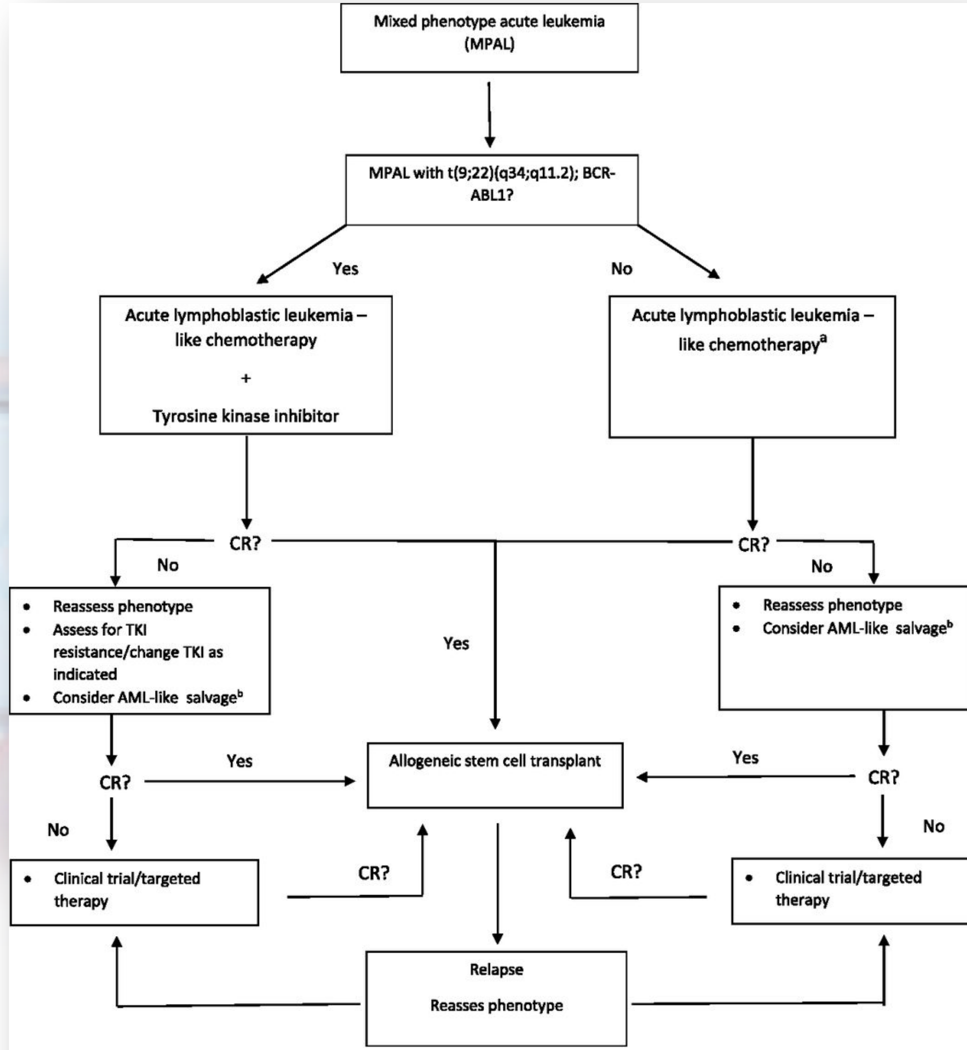


Immunophenotyping by flow cytometry after lysis of the erythroid cells reveals that the white blood cells consist of 51 % blasts (CD34+), 6.8 % maturing neutrophilic forms, 4.2 % monocytes, and 30.5 % lymphocytes. The lymphocytes consist of 20.0 % B cells (CD19+), 63.5 % T cells (CD3+) having a CD4:CD8 ratio of 3.3, and 16.5 % NK cells (CD3-, CD7+).

Treatment

- Optimal treatment is still undefined as MPAL is quite rare
- Treatment based on:
  - Patient age
  - Medical history
  - Comorbidities
  - Blast morphology
  - Cytogenetics
  - Immunophenotype
  - Molecular studies
- Patients with 11q23 are considered separate entities
- Critical to define the Ph^{+} patients so TKI can be added
- Most patients get either AML or ALL treatment
- AML induction: cytarabine, anthracycline
- ALL induction: prednisolone, dexamethasone, vincristine, asparaginase, daunorubicin
- Using both may be associated with superior outcome

Therapeutic approach in patients with MPAL



[a]Consider pediatric inspired protocol if <40 years old (in which case transplant in first remission not generally indicated)

[b]For example High-dose cytarabine and mitoxantrone (HAM).

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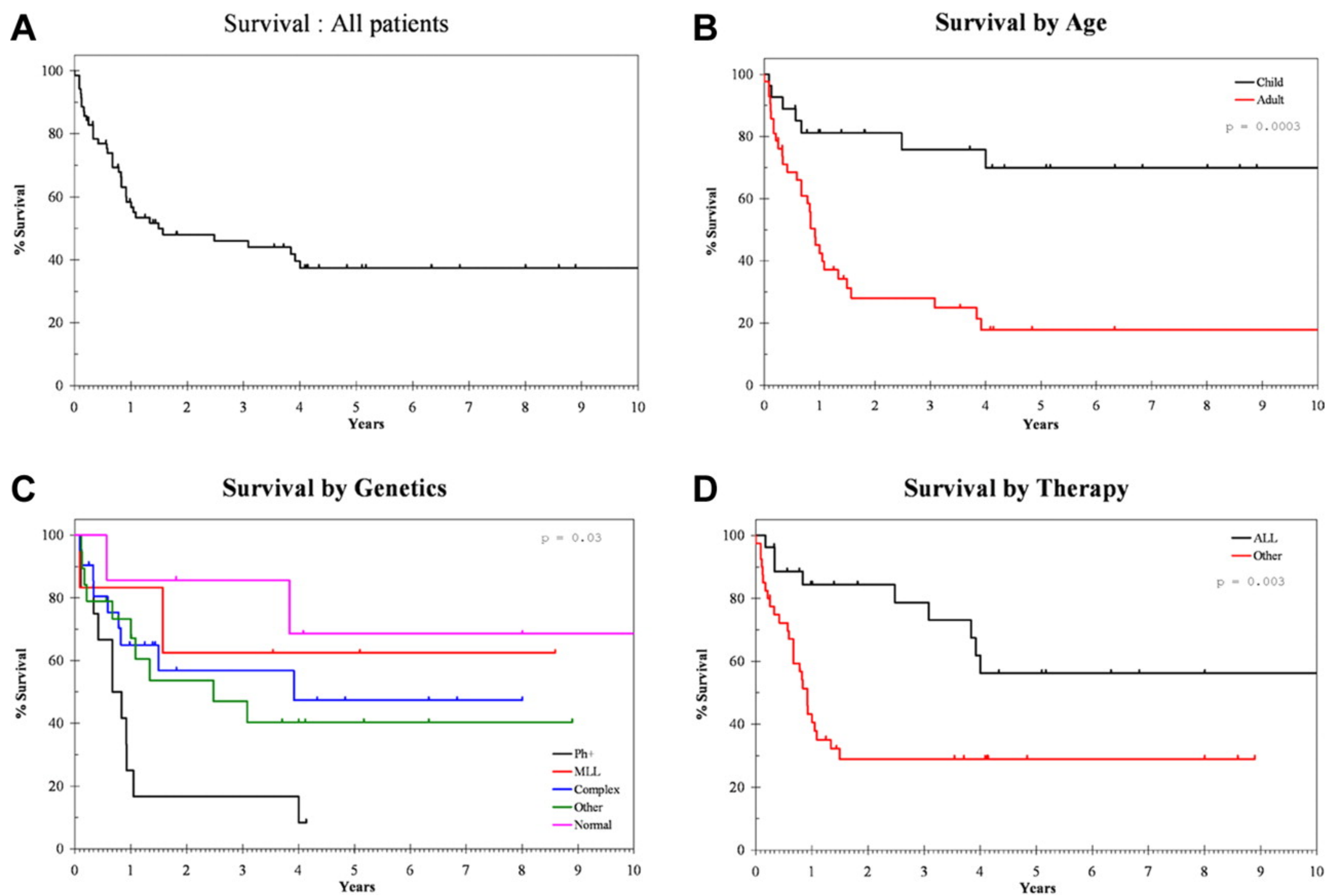
blood

Overall survival of MPAL patients



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References

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- https://en.wikipedia.org/wiki/Biphenotype_acute_leukemia
- Background photo: https://www.oriel.nhs.uk/Web/Content/images/sg2.jpg
- Jonathan Fromm, MD, PhD – University of Washington/Seattle Cancer Care Alliance