

A map of Africa is shown in the background, with a stethoscope resting on it. The stethoscope is silver and black, with its chest piece on the left and its tubing extending towards the right. The map shows various countries including Nigeria, Chad, Sudan, South Sudan, Central African Republic, and others. The text is overlaid on the map.

Relapsed acute lymphoblastic leukemia

Lymphoma Tumor Board

July 21, 2017

Diagnosis - Adult Acute Lymphoblastic Leukemia (ALL)

- Symptoms/signs include:
 - Fever
 - Increased risk of infection (especially bacterial infections such as pneumonia)
 - Thrombocytopenia
 - Anemia
 - Pallor
 - Tachycardia
 - Fatigue, Weakness, Breathlessness
 - Headache
 - Bone pain, joint pain (caused by the spread of "blast" cells to the surface of the bone or into the joint from the marrow cavity)
 - Enlarged lymph nodes, liver, and/or spleen
 - Pitting edema (swelling) in the lower limbs and/or abdomen
 - Petechiae
- Characteristics are quite similar to acute lymphoblastic lymphoma (ALL)
 - Comprises about 2% of all NHLs in adults
 - Sub-type of lymphoma that is generally of T-cell origin
- Patients with predominately nodal disease at presentation are classified as LBL whereas those with primarily disease in the marrow or peripheral blood are classified as ALL.
 - Historically, no standard of care treatment specifically designed for LBL
- Only 20-40% of adults with ALL are cured

ALL Classification

ALL – CLASSIFICATION WHO

- Uses immunophenotypic classification :
 - Acute lymphoblastic leukemia/lymphoma (Former Fab L1/L2)
 - **Precursor B** acute lymphoblastic leukemia/lymphoma.
 - Cytogenetic subtypes:
 - t(12;21)(p12,q22) TEL/AML-1
 - t(1;19)(q23;p13) PBX/E2A
 - t(9;22)(q34;q11) ABL/BCR
 - T(V,11)(V;q23) V/MLL
 - **Precursor T** acute lymphoblastic leukemia/lymphoma
 - Burkitt's leukemia/lymphoma (Former FAB L3)
(mature B cell ALL)
 - Biphenotypic acute leukemia (2 to 5%)

ALL Classification – (2)

TABLE 2: WHO 2008 classification of acute lymphoblastic leukemia (ALL)

Precursor lymphoid neoplasms

B-cell lymphoblastic leukemia/lymphoma, not otherwise specified

B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities

B-cell lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*

B-cell lymphoblastic leukemia/lymphoma with t(v;11q23); *MLL* rearranged

B-cell lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22);

TEL-AML1 (ETV6-RUNX1)

B-cell lymphoblastic leukemia/lymphoma with hyperploidy

B-cell lymphoblastic leukemia/lymphoma with hypoploidy (hypodiploid ALL)

B-cell lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32); *IL3-IGH*

B-cell lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);

E2A-PBX1 (TCF3-PBX1)

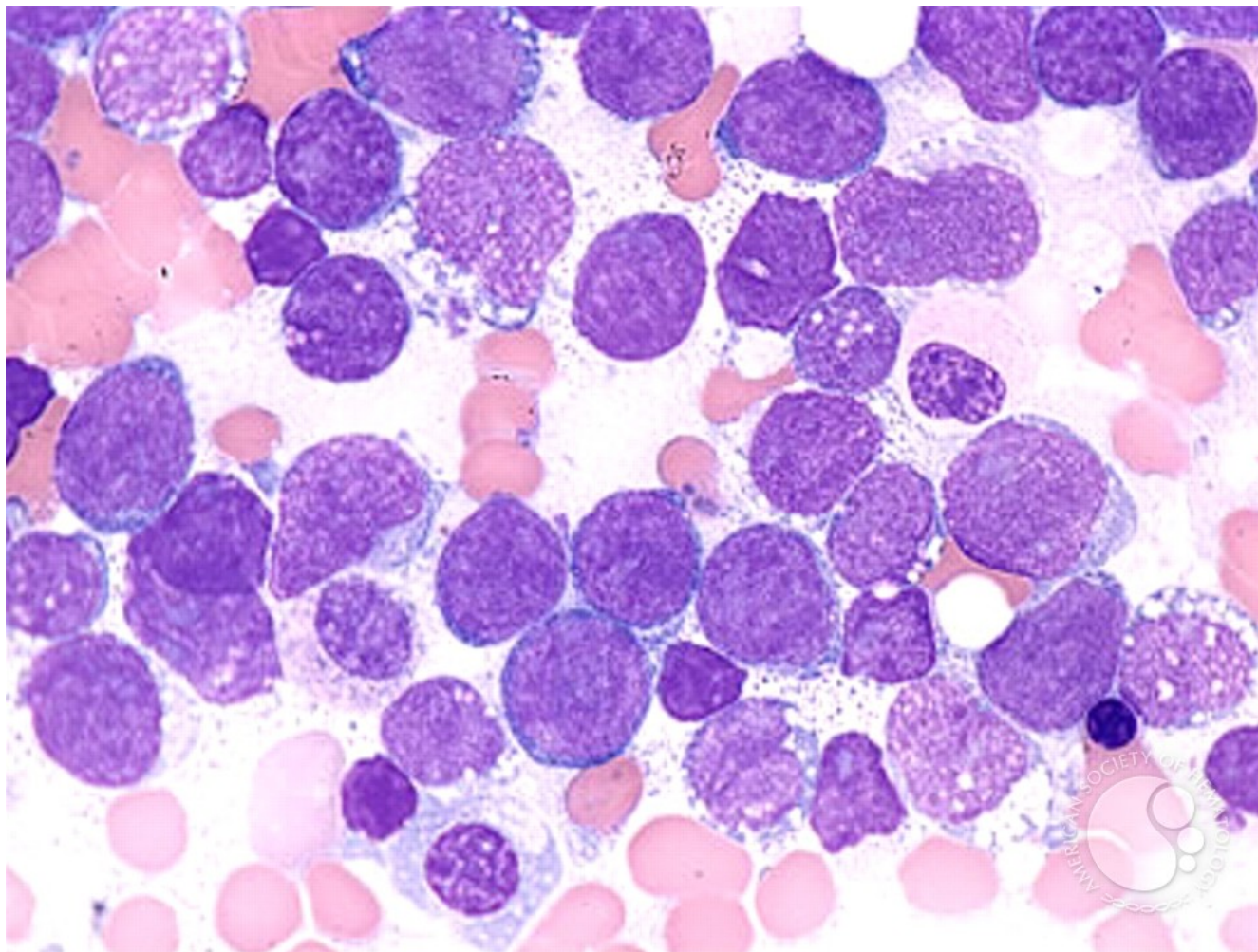
T-cell lymphoblastic leukemia/lymphoma

WHO = World Health Organization

Swerdlow SH, Campo E, Harris NL, et al (eds): WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press; 109–138, 2009.

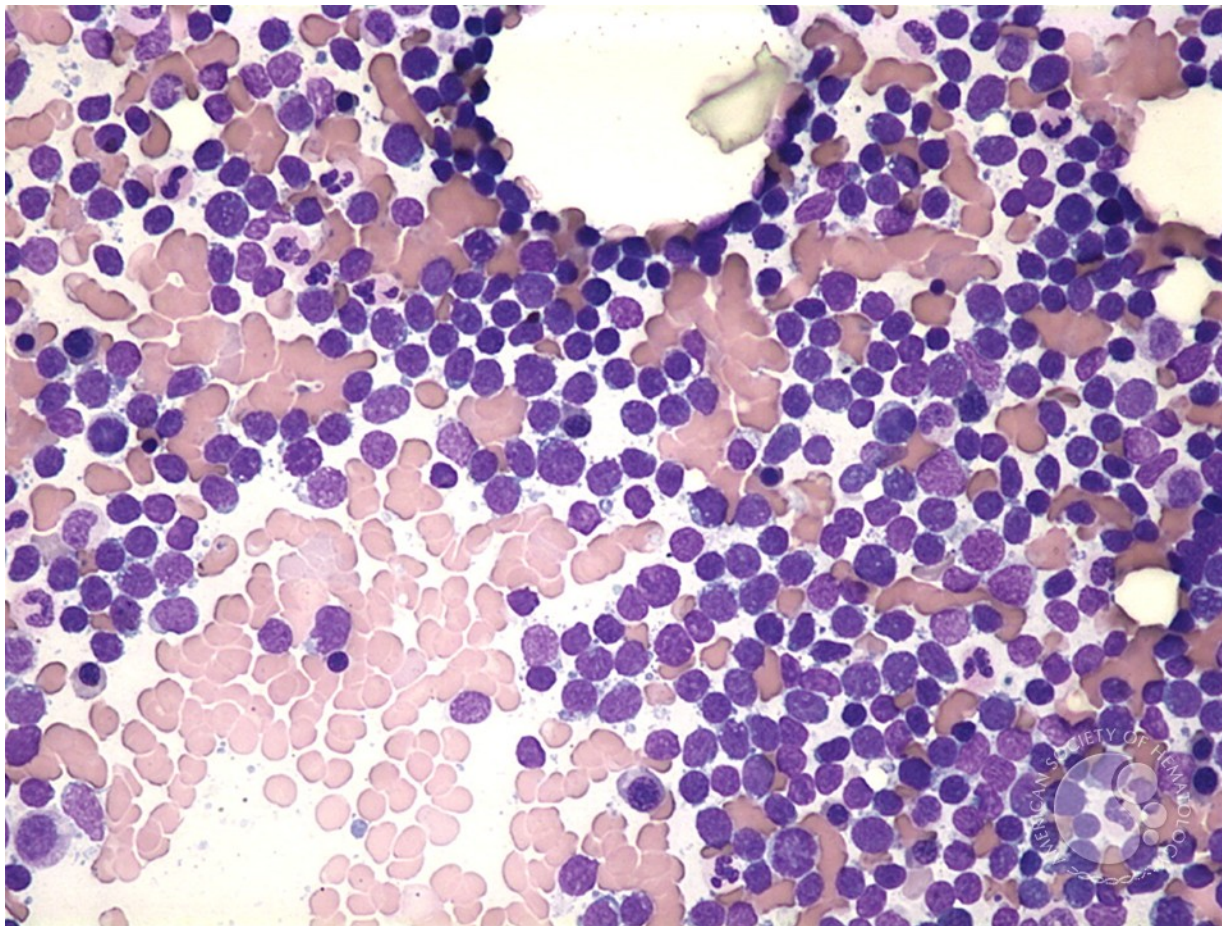
Relapsed ALL - 2.

Category: Myeloid Neoplasms and acute leukemia (WHO 2016) > Precursor Lymphoid Neoplasms



Relapsed T-cell ALL - 1.

Category: Myeloid Neoplasms and acute leukemia (WHO 2016) > Precursor Lymphoid Neoplasms > T-lymphoblastic leukemia/lymphoma

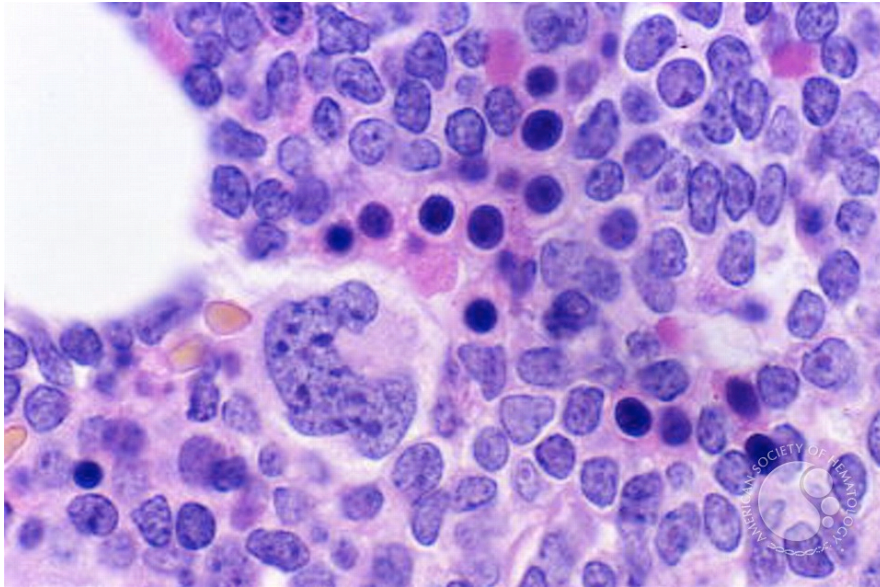


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Pathology – T lineage ALL

- Pathology:
 - IHC panel: CD45 (LCA), CD19, CD20, CD79a, CD3, CD2, CD5, CD7, TdT, CD1a, CD10, or Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, TdT, CD13, CD33, CD1a, cytoplasmic CD3, CD22, myeloperoxidase

A.



B.

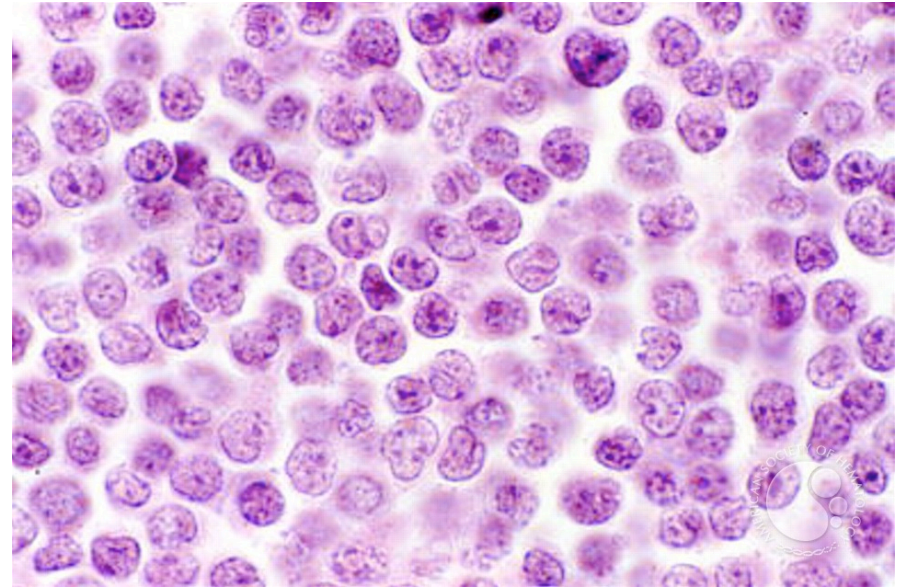
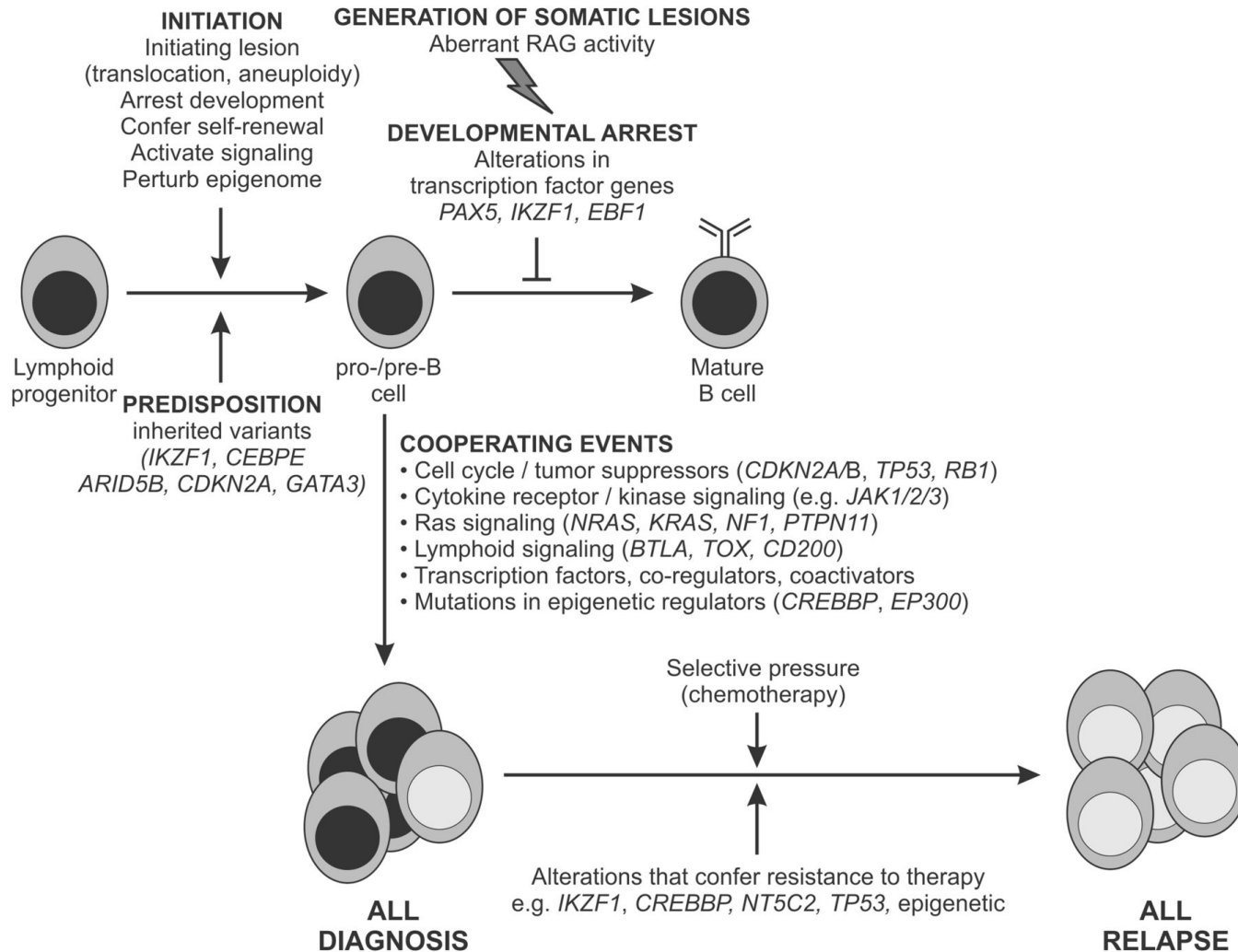


Image A. T-cell lymphoblastic lymphoma/leukemia in bone marrow biopsy. Neoplastic lymphocytes surround residual megakaryocytes and erythroid precursors. H&E section of formalin fixed tissue.

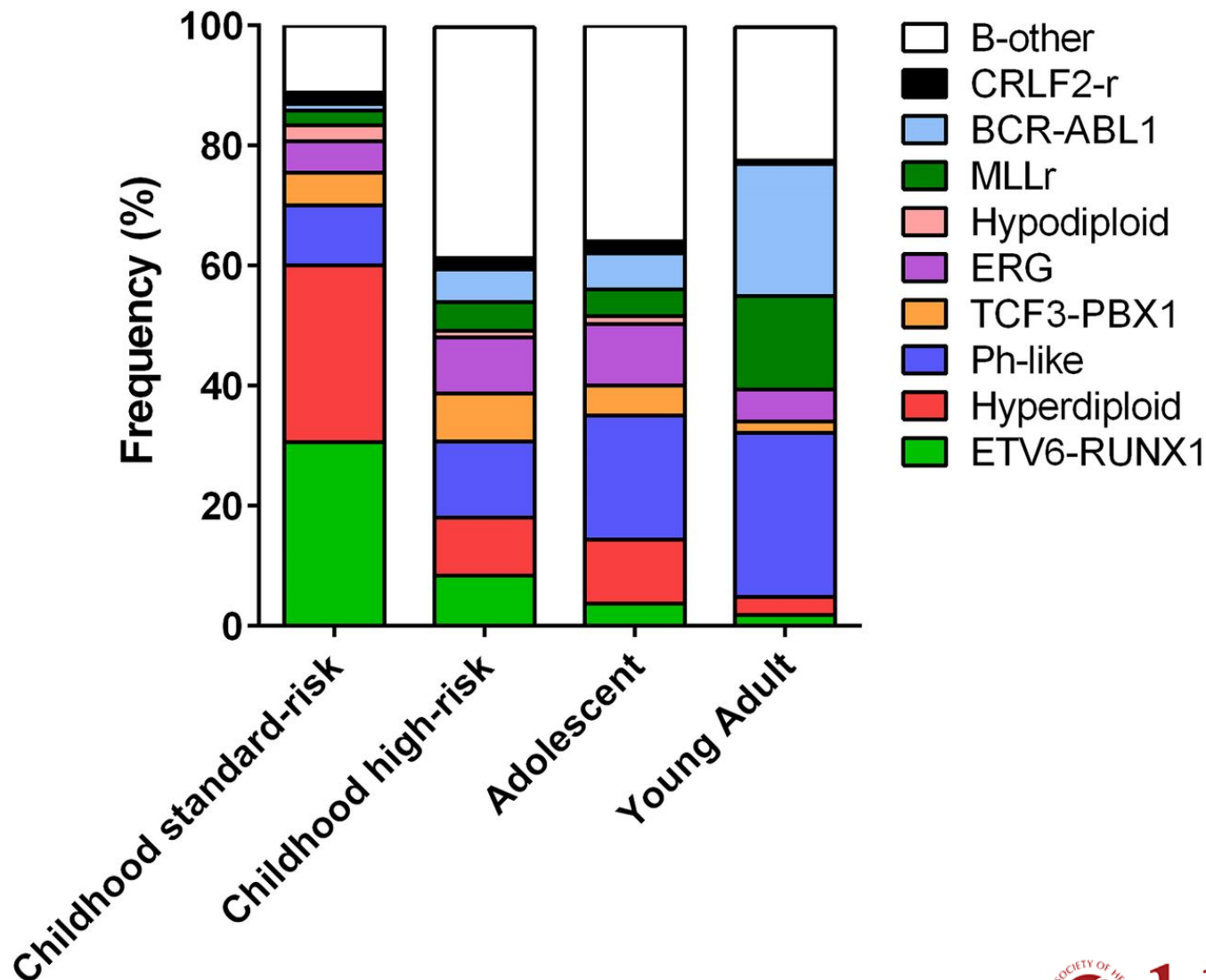
Image B. T-cell lymphoblastic lymphoma/leukemia. Cytology of lymphoblasts reveals medium sized cells with delicate unclumped chromatin, convoluted nuclear membrane and small but distinct nucleoli.

Schema for the genetic pathogenesis of B-ALL



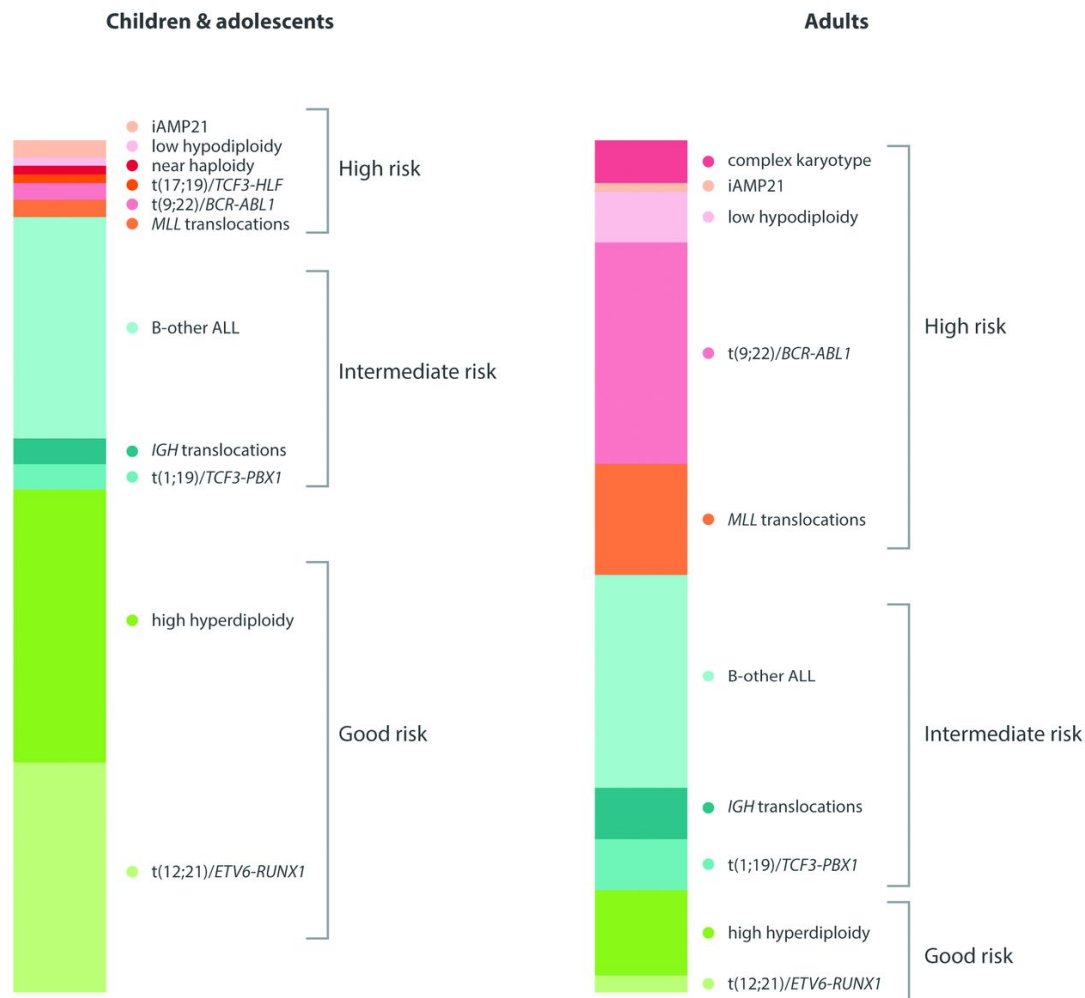
Stephen P. Hunger, and Charles G. Mullighan *Blood* 2015;125:3977-3987

Prevalence of ALL subtypes across age groups



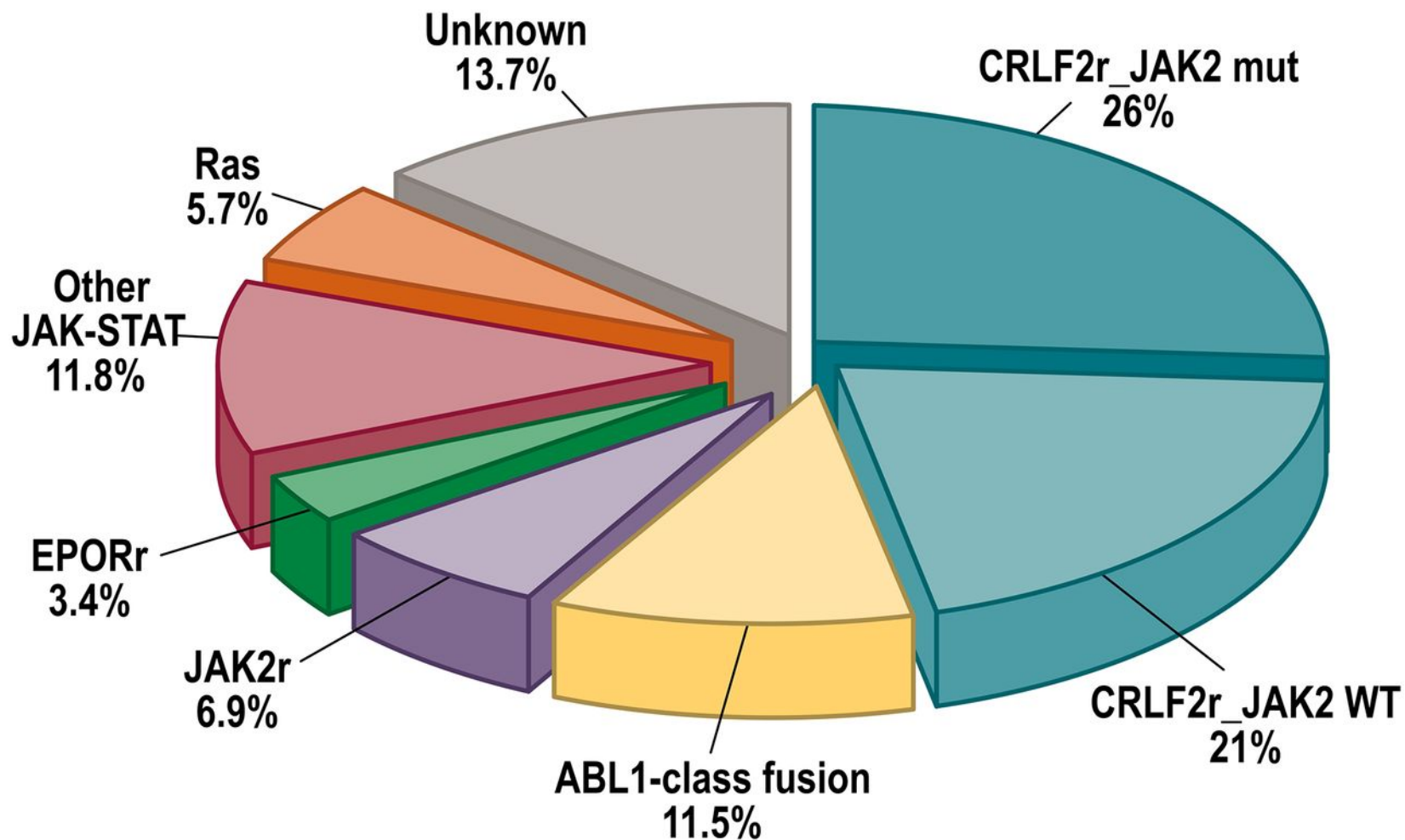
Stephen P. Hunger, and Charles G. Mullighan *Blood* 2015;125:3977-3987

Frequency of primary chromosomal abnormalities in children and adults with B-cell precursor ALL



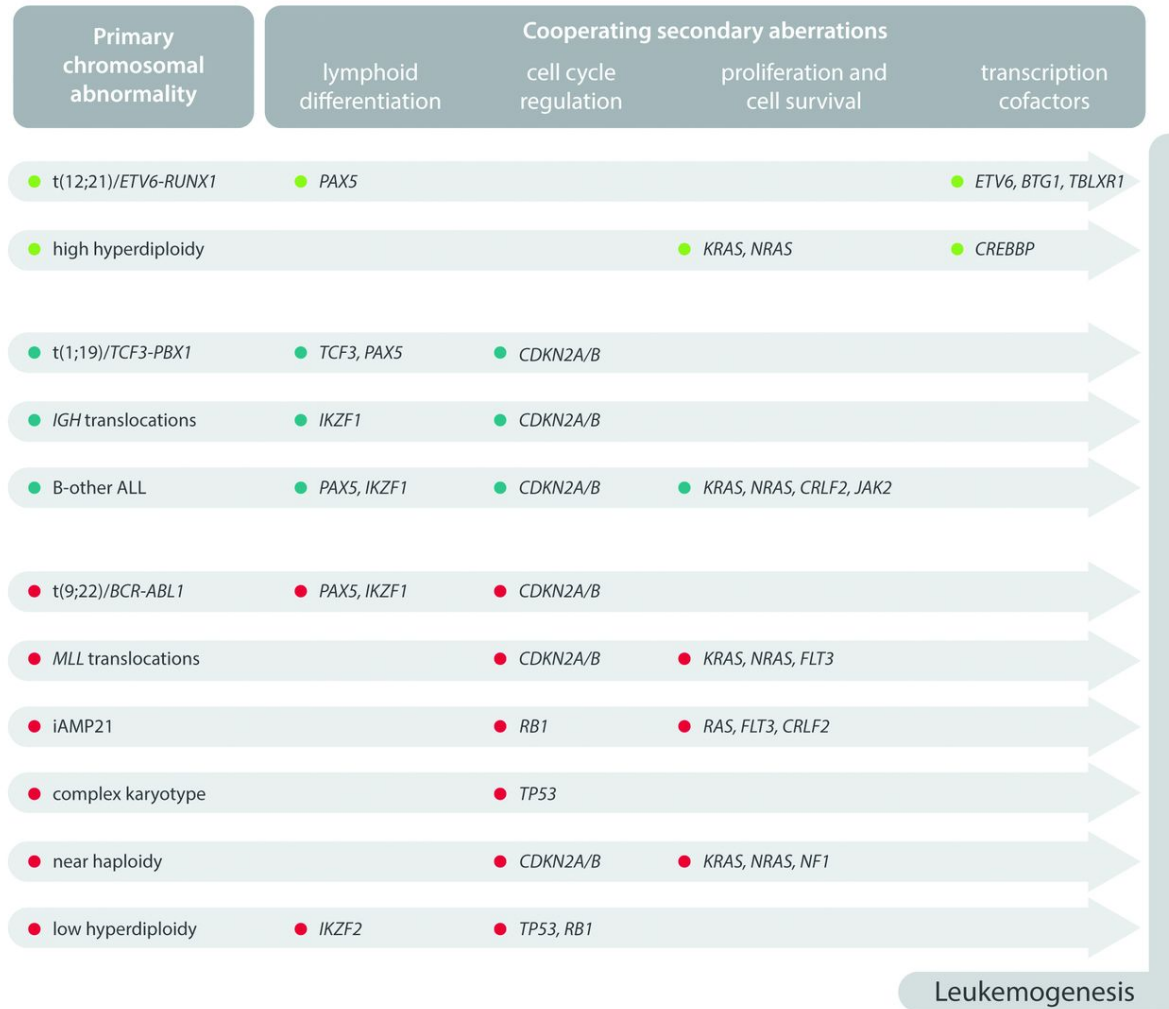
Anthony V. Moorman *Haematologica* 2016;101:407-416

Frequency of subtypes of Ph-like ALL



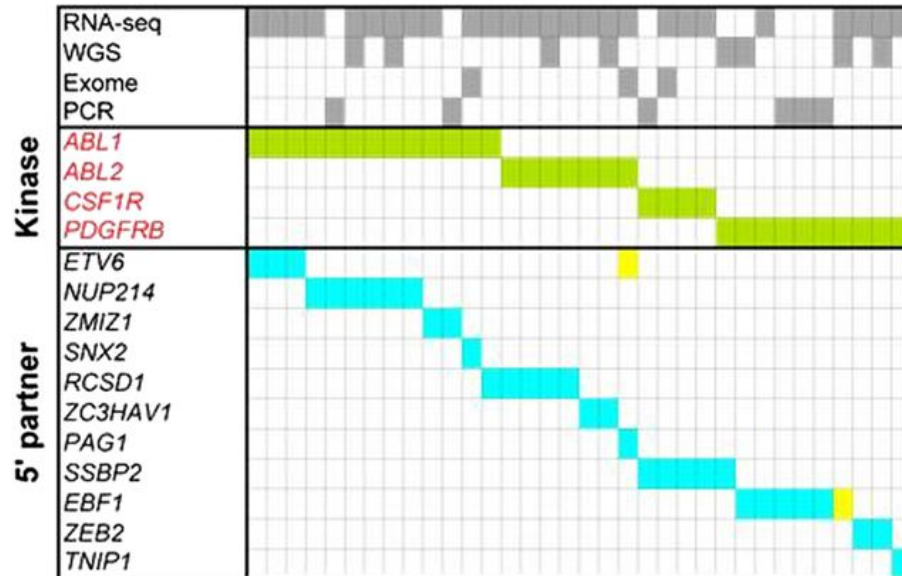
Stephen P. Hunger, and Charles G. Mullighan Blood 2015;125:3977-3987

Overview of key co-operating mutations in relation to distinct genetic subtypes of B-cell precursor ALL

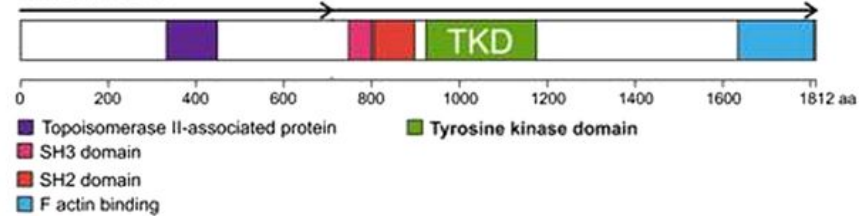


Anthony V. Moorman Haematologica 2016;101:407-416

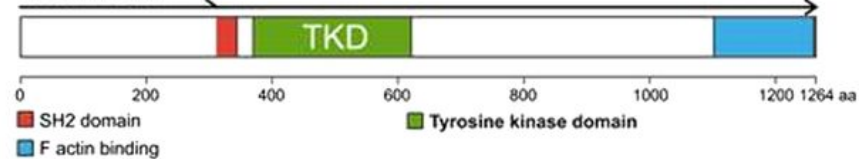
ABL1-class rearrangements in Ph-like ALL



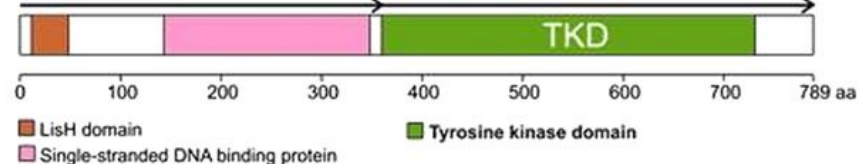
ZMIZ1-ABL1



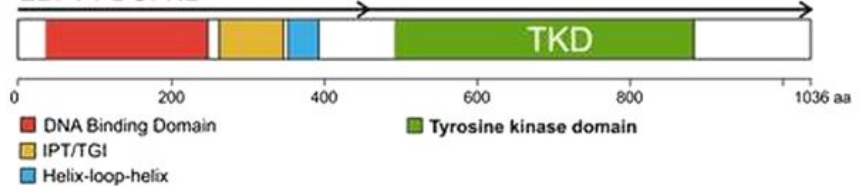
PAG1-ABL2



SSBP2-CSF1R



EBF1-PDGFRB



Stephen P. Hunger, and Charles G. Mullighan *Blood* 2015;125:3977-3987

The landscape of genetic alterations in T-ALL



Mark R. Litzow, and Adolfo A. Ferrando Blood 2015;126:833-841



ALL Treatment - General Principles

- Adaptation of pediatric protocols of intensive chemotherapy and CNS prophylaxis has led to marked improvements in outcomes in adults
- Numerous chemotherapy/radiotherapy regimens are similar in dose and schedule to ALL regimens
- Common features of these regimens include:
 - Induction therapy
 - CNS prophylaxis
 - Consolidation therapy
 - Subsequent maintenance therapy for 12 to 18 months
- Long-term disease-free survival rates between 40-70%

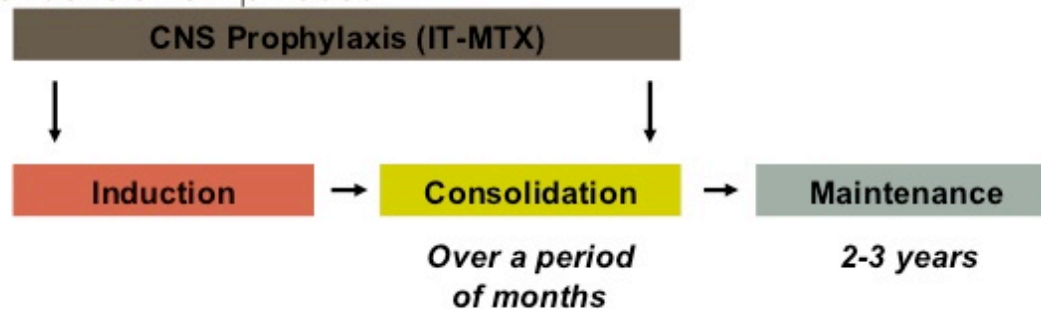
ALL Treatment – Overall Structure

- Remission induction – Defined as > 5% leukemic blasts in the bone marrow
 - Combination of prednisolone or dexamethasone, vincristine, asparaginase and daunorubicin to induce remission.
 - CNS prophylaxis - achieved by irradiation, cytarabine + methotrexate, or liposomal cytarabine
- Consolidation/intensification – uses high doses of IV multidrug chemotherapy. Can be delivered through an Ommaya reservoir
 - Vincristine, cyclophosphamide, cytarabine, daunorubicin, etoposide, thioguanine, or mercaptopurine
 - CNS – intrathecal methotrexate or cytarabine is combined with or without irradiation
- Maintenance therapy – Aim is to kill any residual cell that was not killed by remission induction
 - Daily oral mercaptopurine, once weekly oral methotrexate, once monthly 5-day course of IV vincristine and oral corticosteroids are used
 - Usually lasts 2 years for adults

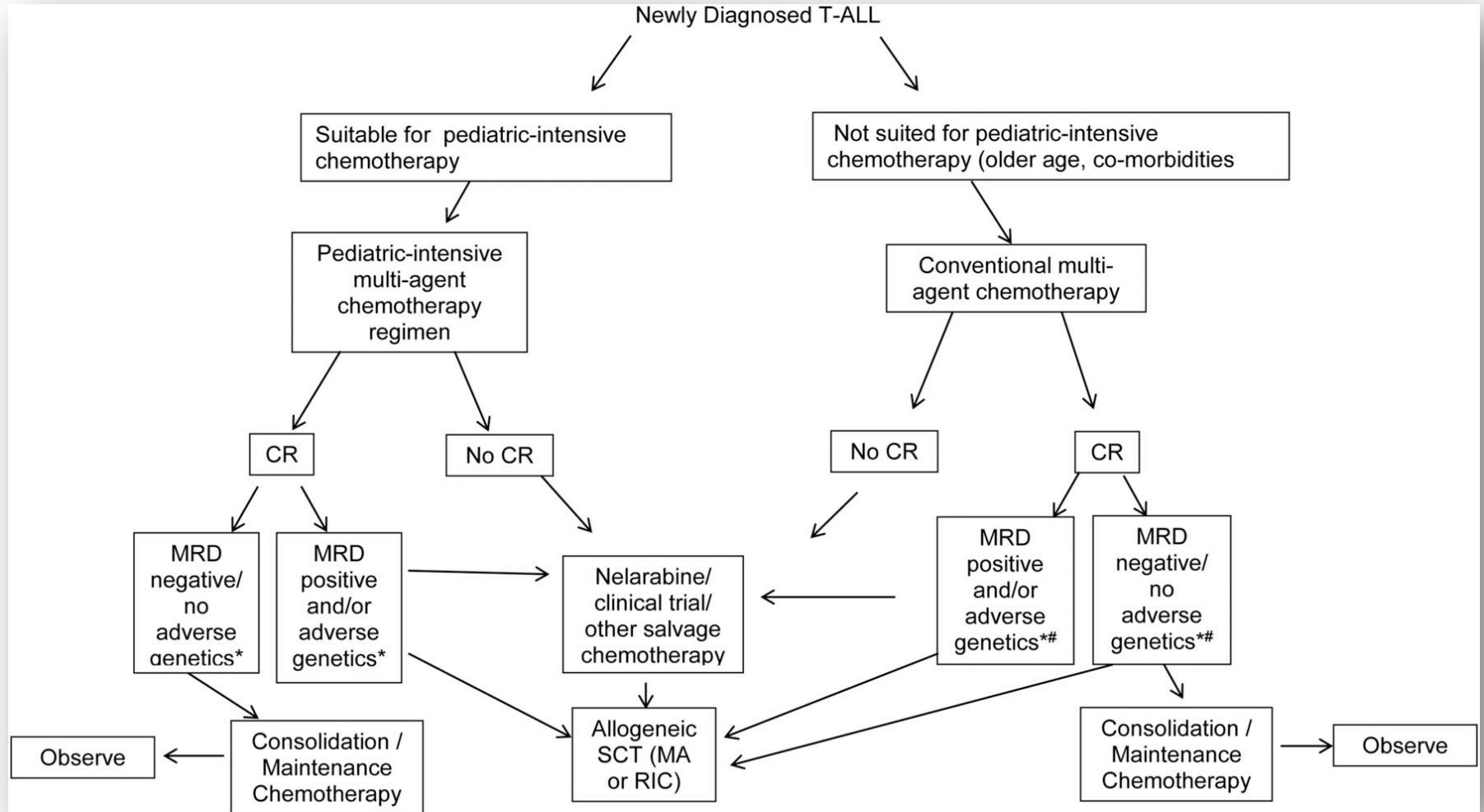
ALL – Frontline Treatment

ALL: TYPICAL TREATMENT

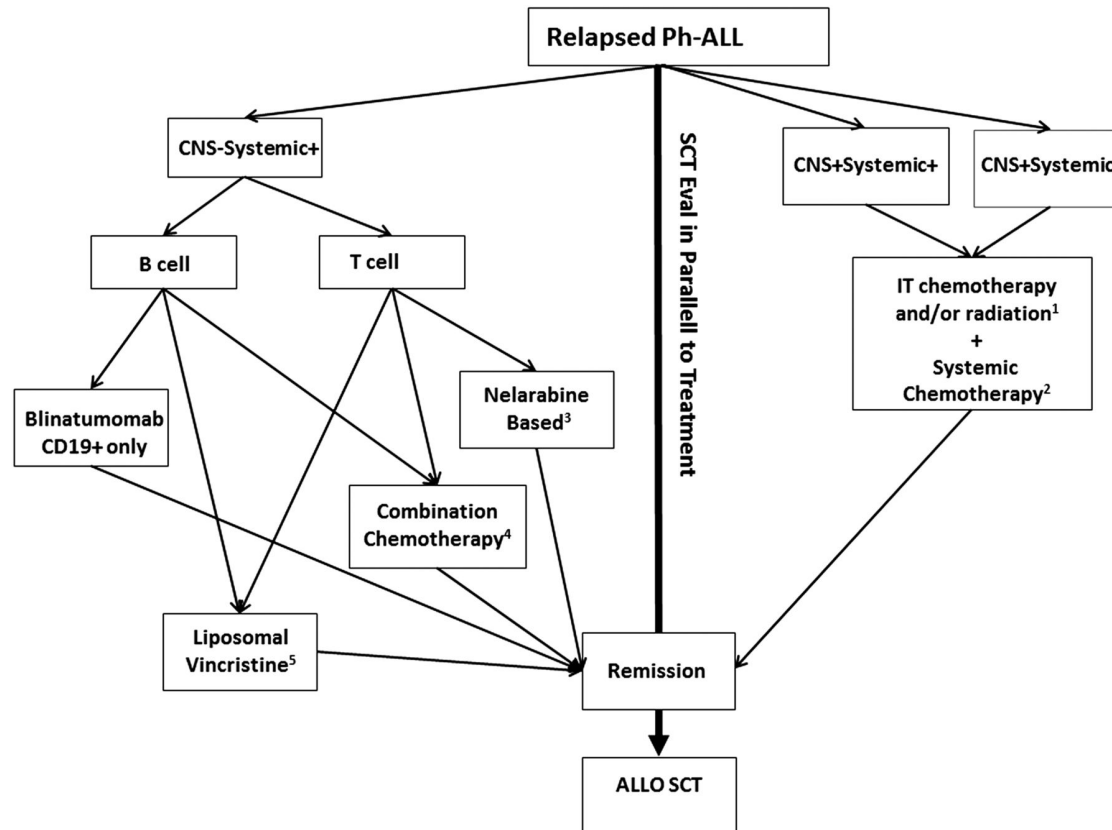
- Primary objective : to achieve and maintain a complete remission (CR)
- Induction, consolidation, maintenance phases
 - CNS prophylaxis with IT-MTX during induction and consolidation phases



Treatment Algorithm – T-lineage ALL



Treatment approach to adult patient with relapsed Ph⁺ B-ALL.



¹Radiation: Consider over IT chemotherapy if cranial nerve palsies or focal neurologic deficits. Note: Allow window between Radiation and systemic or IT methotrexate

²Consider regimens with CNS penetration (such as high dose methotrexate and/or AraC.

³Consider Nelarabine if no neuropathy or CNS deficits

⁴Choice of combination chemotherapy dependent on 1) prior therapy (asparaginase containing regimen?) and duration of prior remission

⁵Consider if multiple relapse, poor candidate systemic chemotherapy.

Noelle V. Frey, and Selina M. Luger *Blood* 2015;126:589-596

Treatment

Table 1

Intensive Induction Regimens for Adult Lymphoblastic Lymphoma

Author	Regimen	N	Response Rate	Failure-Free Survival/ Relapse-Free Survival	Overall Survival
Coleman et al [11]	Two ALL-type protocols with intensified CNS	44	100%	3-yr FFS = 56%	NA
Slater et al [12]	Various ALL protocols	51	80% CR for "nonleukemic"; 77% CR for leukemic	NA	5-yr actuarial OS = 45%
Bernasconi et al [13]	Various ALL protocols	31	77% OR	3-yr RFS = 45%	3-yr OS = 59%
Levine et al [16]	Modified LSA ₂ L ₂	15	73% CR; 27% PR	5-yr actuarial FFS = 35%	5-yr actuarial OS = 40%
Weinstein et al [17]	APO	21	95% CR	3-yr actuarial FFS = 58%	5-yr actuarial OS = 69%
Hoelzer et al [18]	Two ALL-type protocols, both including CNS and	45	93% CR	7-yr actuarial DFS = 62%	7-yr actuarial OS = 51%
Thomas et al [19]	HyperCVAD	33	91%	3-yr PFS = 66%	3-yr OS = 70%
Jabbour et al [20]	LMT-89 (ALL-type induction regimen derived	27	85% OR	5-yr FFP = 44%	5-yr OS = 63%
Song	"Hybrid" NHL/ALL regimen	34	100% OR	4-yr EFS = 68%	4-yr OS = 72%

ALL = acute lymphoblastic leukemia; APO = doxorubicin (Adriamycin), prednisone, vincristine (Oncovin); CHOP = cyclophosphamide, hydroxydaunomycin, vincristine, prednisone; CNS = central nervous system; CR = complete response; DFS = disease-free survival; EFS = event-free survival; FFP = freedom from progression; FFS = failure-free survival; HyperCVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, methotrexate; IPI = International Prognostic Index; NA = not available; NHL = non-Hodgkin lymphoma; OR = overall response; PR = partial response; RFS = relapse-free survival; SCT = stem cell transplantation.

Treatment of relapsed/refractory ALL - Blinatumomab

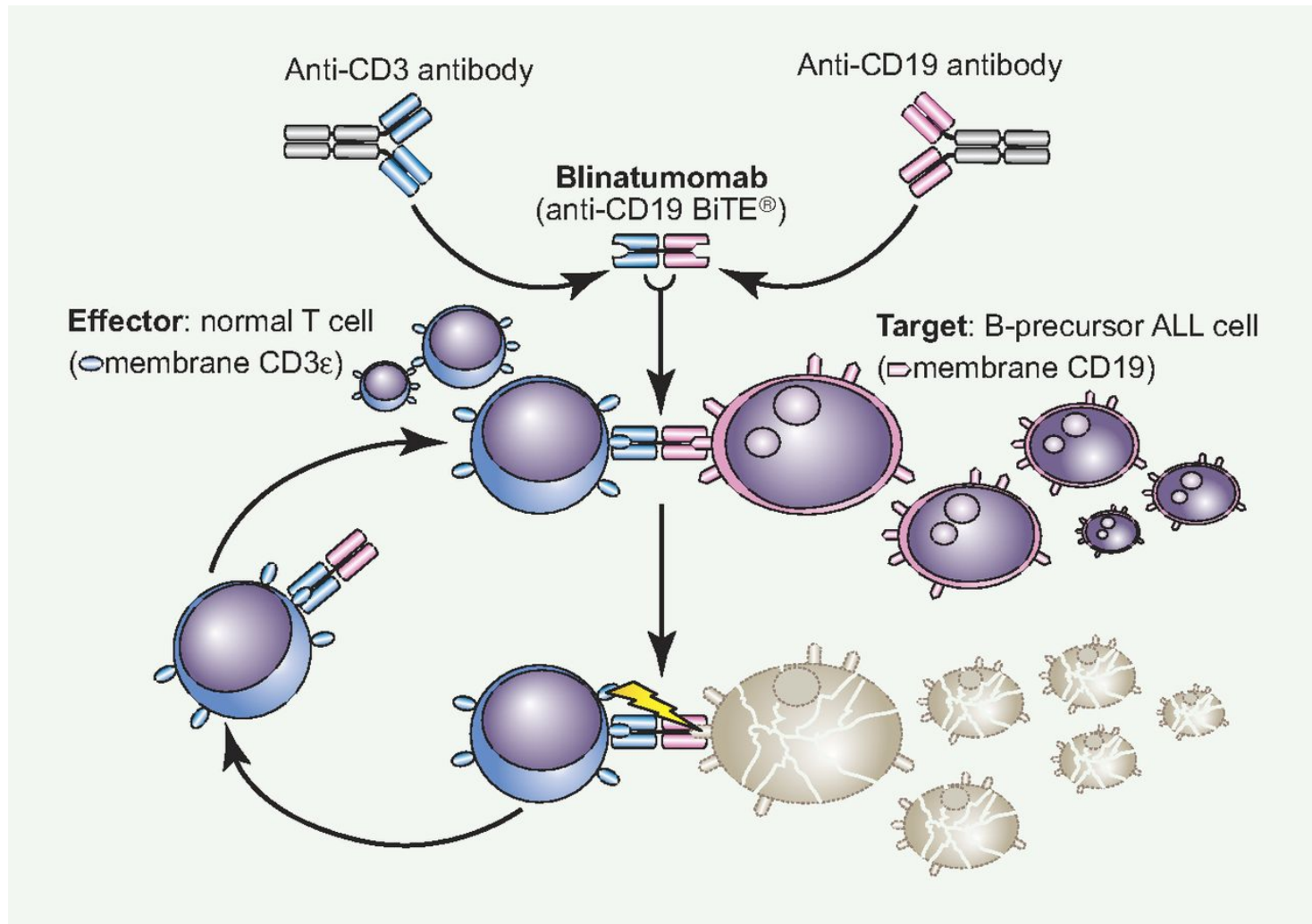


In collaboration with the Food and Drug Administration (FDA), and as a service to our members, the American Society of Hematology provides information about newly approved therapies and other important FDA actions (e.g., updated safety information, new prescribing information) for patients. This allows the agency to inform hematologists and professionals in hematology-related fields of recent approvals in a timely manner. Included in the message below is a link to the product label, which provides the relevant clinical information on the indication, contraindications, dosing, and safety. In providing this information, ASH does not endorse any product or therapy and does not take any position on the safety or efficacy of the product or therapy described. The following is a message from the FDA Oncology Center of Excellence.

On July 11, 2017, the U.S. Food and Drug Administration approved blinatumomab (BLINCYTO[®], Amgen Inc.) for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.

Blinatumomab received accelerated approval in December 2014 for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. This current supplement provides the confirmation of clinical benefit required under the accelerated approval and also expands the indication to include Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL.

Blinatumomab: a novel bispecific construct that reacts simultaneously to normal CD3⁺ T cells and CD19⁺ ALL cells, creating a tight intercellular connection followed by T cell-mediated cytotoxicity exerted on CD19⁺ blast cells (BiTE mechanism)



Renato Bassan Blood 2012;120:5094-5095

ALL - Supportive care

- Allopurinol is recommended for the first 10 days of induction therapy to prevent hyperuricemia.
- Antimicrobial prophylaxis, antiviral and *Pneumocystis jiroveci* pneumonia prophylaxis throughout treatment.
- Fungal prophylaxis should include mold coverage throughout induction therapy.
 - Broader spectrum azole antifungals should be used with caution when using vincristine.
- Asparaginase-related toxicities
 - Asparaginase-related hypersensitivity reactions can occur in 20% of children and adults.

ALL Prognosis

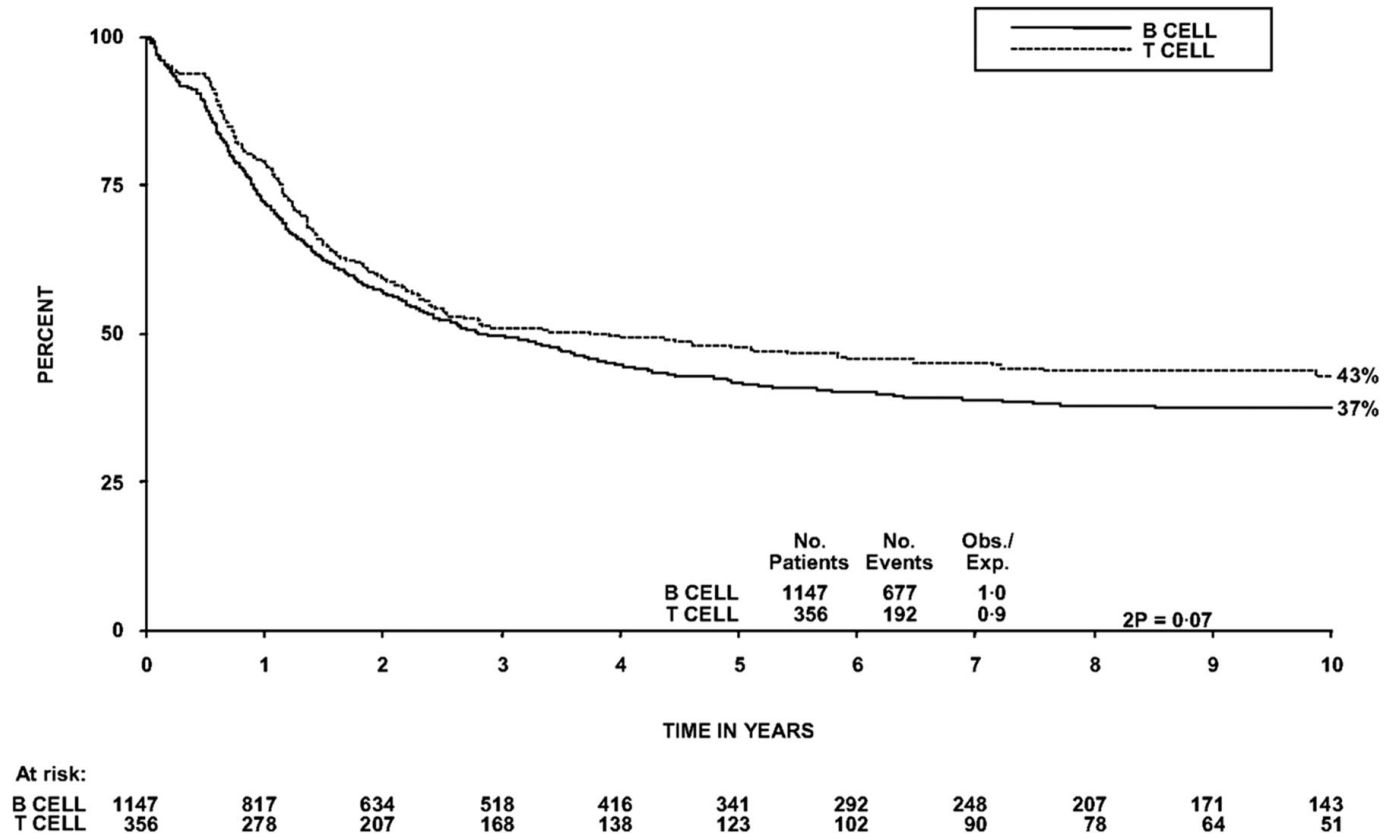
Cytogenetic change	Risk category
Philadelphia chromosome	Poor prognosis
t(4;11)(q21;q23)	Poor prognosis
t(8;14)(q24.1;q32)	Poor prognosis
Complex karyotype (more than four abnormalities)	Poor prognosis
Low hypodiploidy or near triploidy	Poor prognosis
High hyperdiploidy (specifically, trisomy 4, 10, 17)	Good prognosis
del(9p)	Good prognosis

Correlation of prognosis with bone marrow cytogenetic finding in acute lymphoblastic leukemia

Prognosis	Cytogenetic findings
Favorable	Hyperdiploidy > 50 ; t (12;21)
Intermediate	Hyperdiploidy 47 -50; Normal(diploidy); del (6q); Rearrangements of 8q24
Unfavorable	Hypodiploidy-near haploidy; Near tetraploidy; del (17p); t (9;22); t (11q23)

Unclassified ALL is considered to have an intermediate prognosis.^[60]

OS from diagnosis of patients with B- vs T-ALL in the UKALLXII/E2993 trial

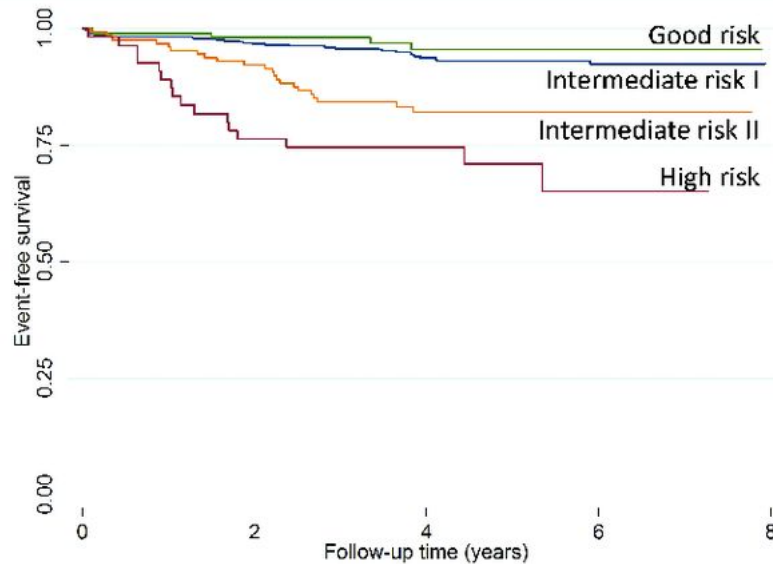


Outcome of ALL patients by genetic risk group

Children & Young Adults

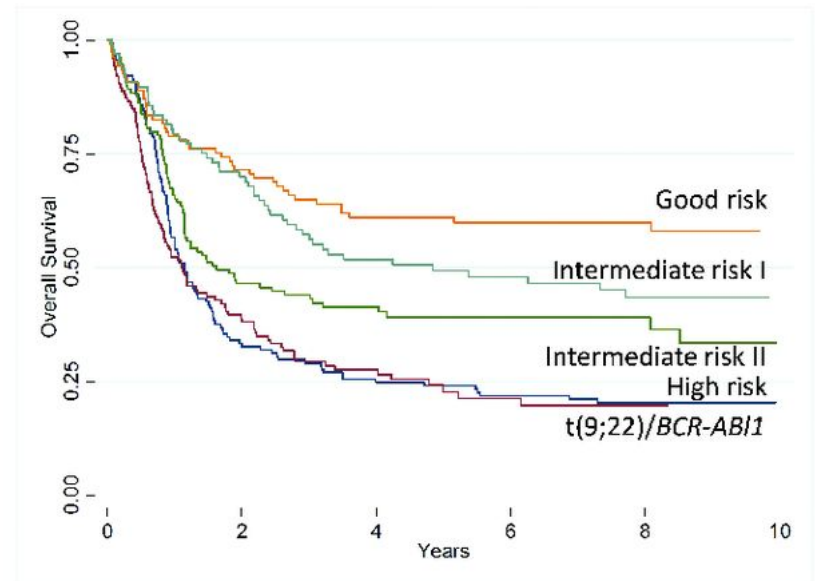
Adults

A



Good risk: $t(12;21)/ETV6-RUNX1$, High hyperdiploidy;
Intermediate Risk: B-other/ $t(1;19)/TCF3-PBX1/IGH$ translocations
 I - with good risk copy number alteration profile
 II: with intermediate/poor risk copy number alteration profile
High risk: iAMP21, *MLL* translocations, $t(17;19)/TCF3-HLF$, haploidy, low hypodiploidy

B



Good risk: High hyperdiploidy, abnormal 9p;
Intermediate Risk I: B-other, iAMP21
Intermediate Risk II: *IGH* translocations, *CRLF2* rearrangements, *IKZF1* deletions, $t(1;19)/TCF3-PBX1$
High risk: $t(4;11)/MLL-AF4$, low hypodiploidy, complex karyotype

Anthony V. Moorman *Haematologica* 2016;101:407-416

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