Acute lymphoblastic leukemia (ALL)

- Clonal proliferation and accumulation of blast cells in blood, bone marrow and other organs
- Disorder arises from a single lymphoid progenitor cell that has undergone genetic damage leading to dysregulated growth and arrested differentation
- Heterogenous disease with different biological subtypes
- Incidence in adults :
  - The overall incidence 1-1,5/100 000
  - 20% of acute leukemias
- Etiology - unknown

Acute leukemias - clinical features

1. Bleeding
2. Fever/infection
3. Bone/joint pain
4. Hepatomegaly
5. Splenomegaly
6. Lymphadenopathy
7. CNS involvement

Symptoms and signs	Patients (%)
Infection/fever	36
Hemorrhages	33
Lyphadenopathy	57
Splenomegaly	56
Hepatomegaly	47
Mediastinum mass	14
CNS infiltration	7
Other organ involvement	9
Pleura	2.9
Bone	1.2
Pericardium	1.0
Retina	1.0
Skin	0.6
Tonsils	0.6
Lung	0.5
Kidney	0.4
Testes	0.3

Acute leukemias - laboratory findings (1)

1. Blood examination
   - anemia
   - thrombocytopenia
   - variable leukocyte count, usually increased
   - blood morphology: presence of blast cells
2. Bone marrow morphology
   - presence of blast cells
   - suppression of normal hematopoiesis

Laboratory findings in patients with ALL at diagnosis

	Patients (%)
Leukocytes (×106/L)	
<5,000	27
5000-10,000	14
10,000-50,000	31
50,000-100,000	12
>100,000	16
Lymphoblasts in blood smear	
present	92
absent	8
Limphoblasts in bone marrow smear	
<50%	3
51%-90%	51
>90%	46
„empty” bone marrow aspiraation	16

Laboratory findings in patients with ALL at diagnosis

Neutrophils (×106/L)	Patients (%)
<500	23
500-1000	14
1000-1500	9
>1500	54
Platelet (X 106/L)	
<25,000	30
25,000-50,000	22
50,000-150,000	33
>150,000	15
Hemoglobin (g/dL)	
<6	8
6-8	20
8-10	27
10-12	24
>12	21

Acute leukemias - Laboratory findings (2)

3. Cytochemical stains
4. Immunophenotyping
5. Cytogenetics
6. Molecular studies

Morphologic subtypes of acute lymphoblastic leukemias (FAB classification)

Subtype	Morphology	Occurrence (%)
L1	Small round blasts clumped chromatin	75
L2	Pleomorphic larger blasts clefted nuclei, fine chromatin	20
L3	Large blasts, nucleoli, vacuolated cytoplasm	5

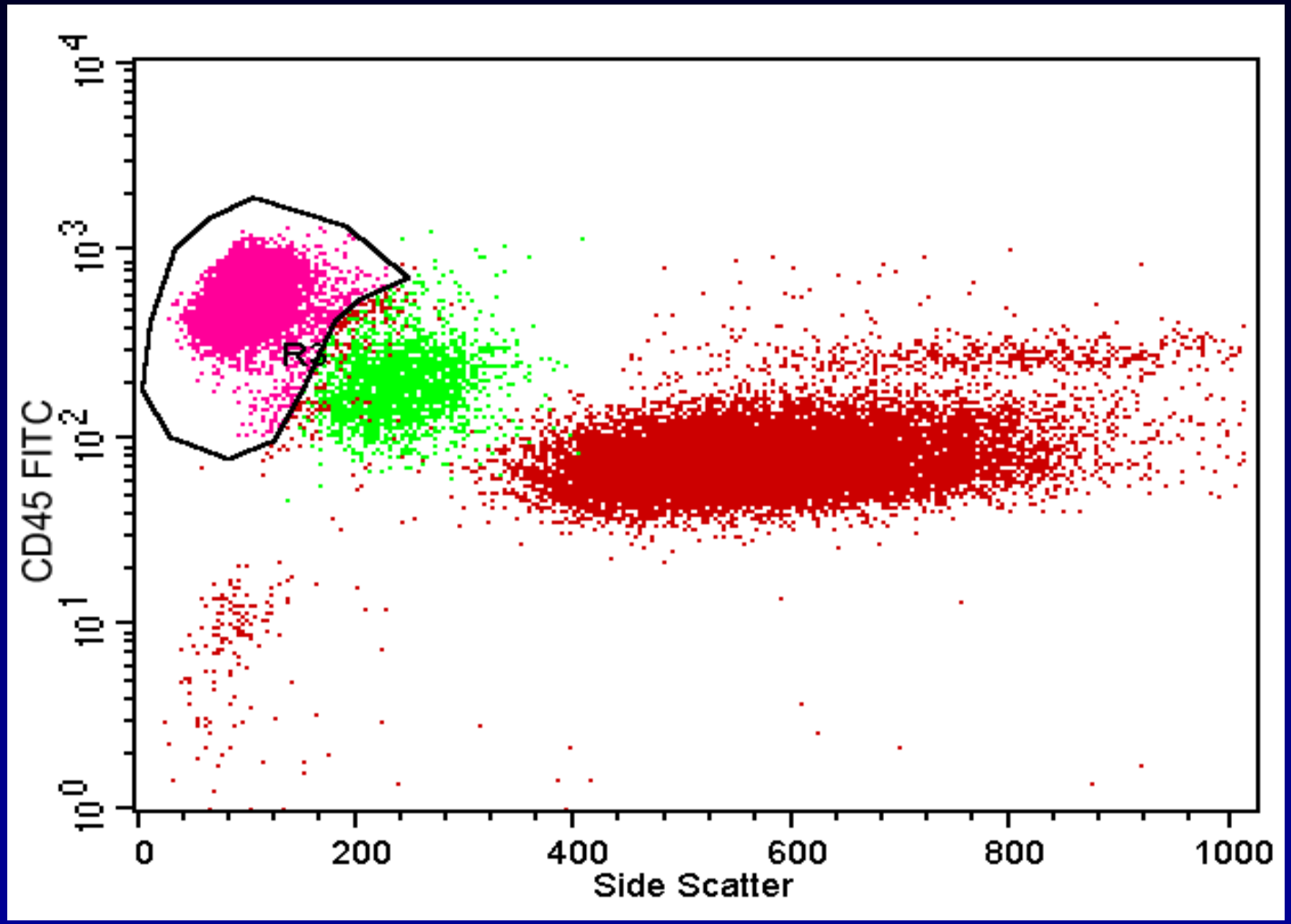
Acute lymphoblastic leukemias - reactivity with special stains

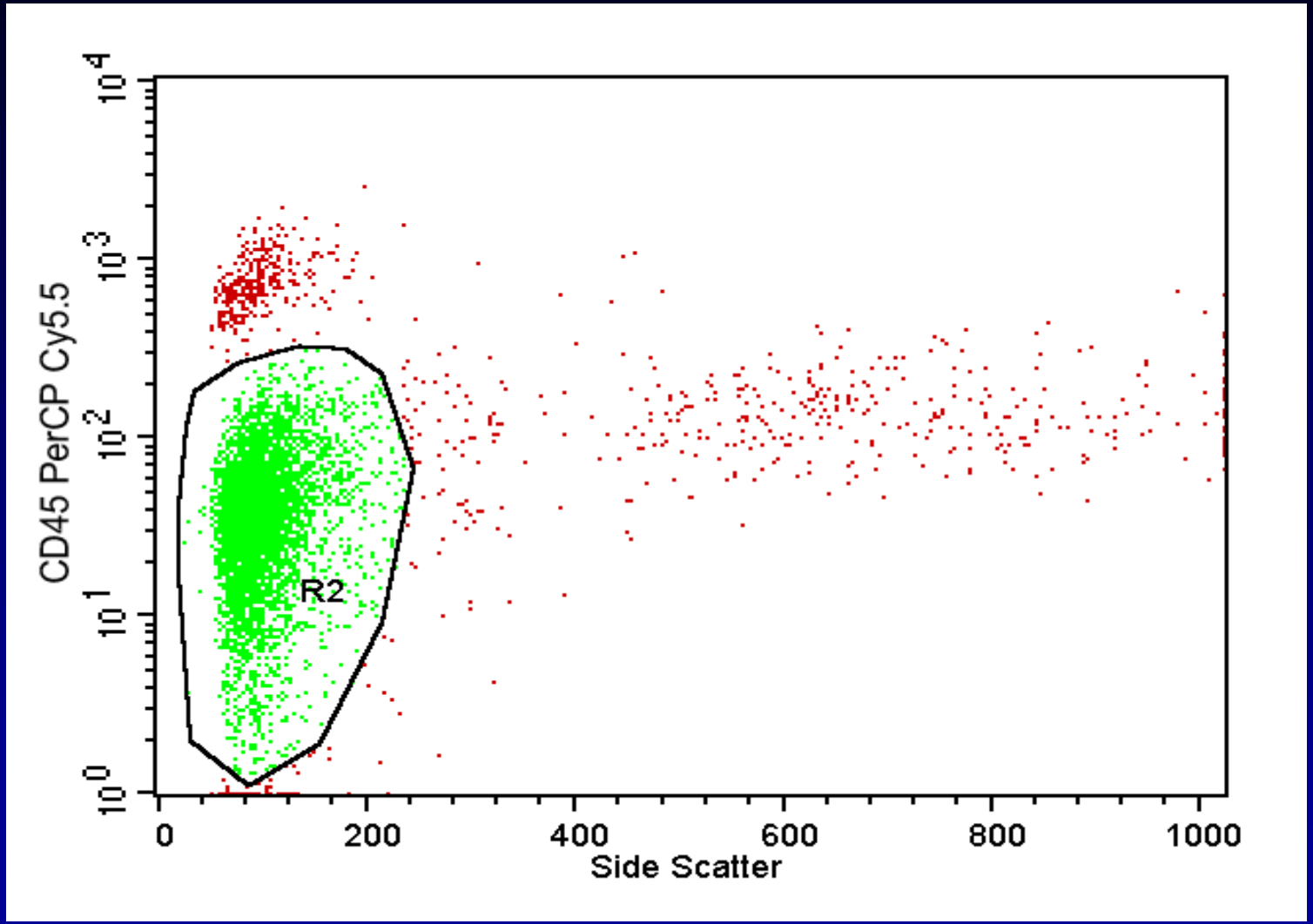
Subtype	Peroxidase or Sudan black	Non-specific esterase	Periodic acid-Schiff
L1	-	-	+++
L2	-	-	+++
L3	-	-	+++

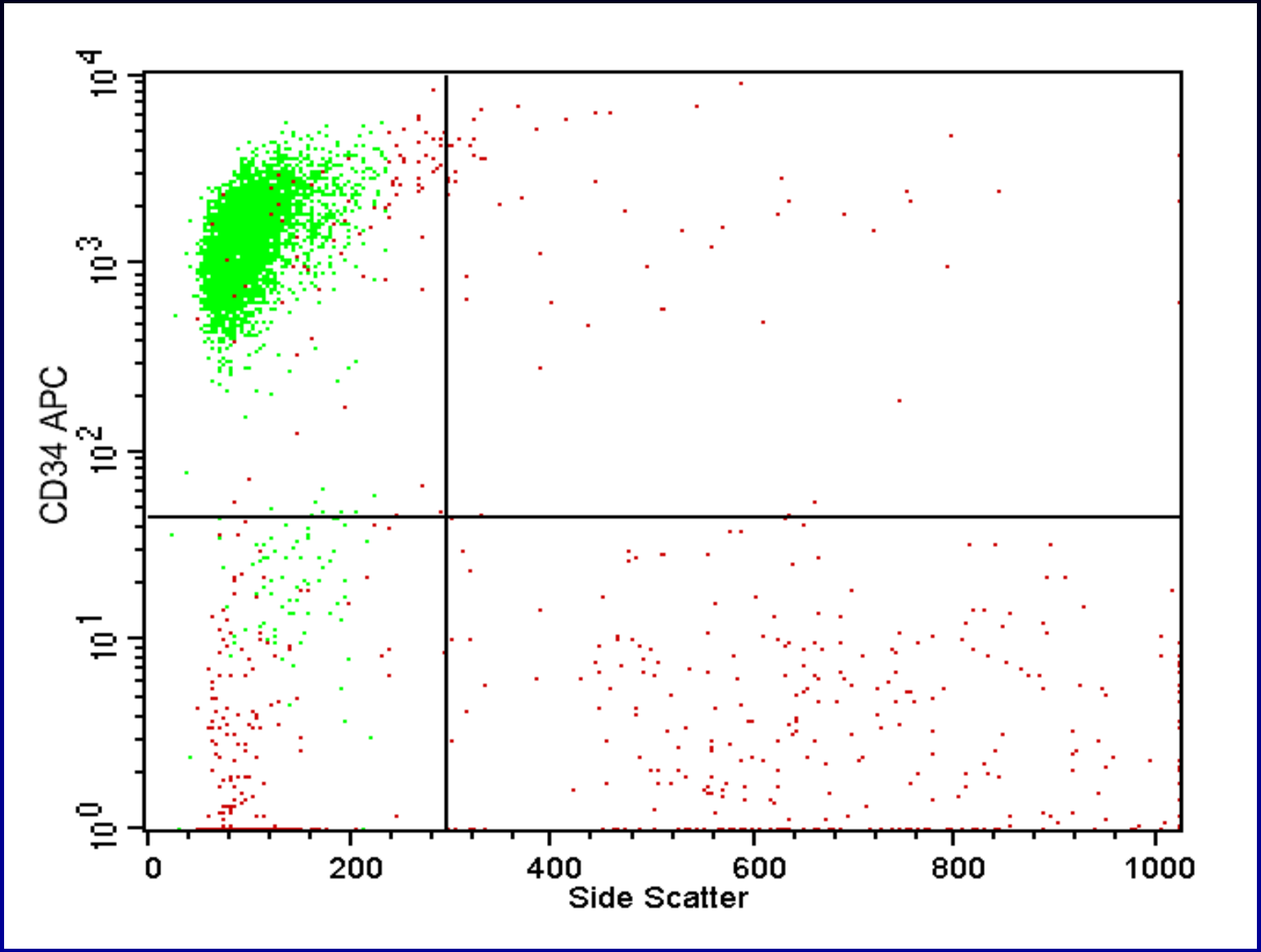
Immunologic classification of acute lymphoblastic leukemias

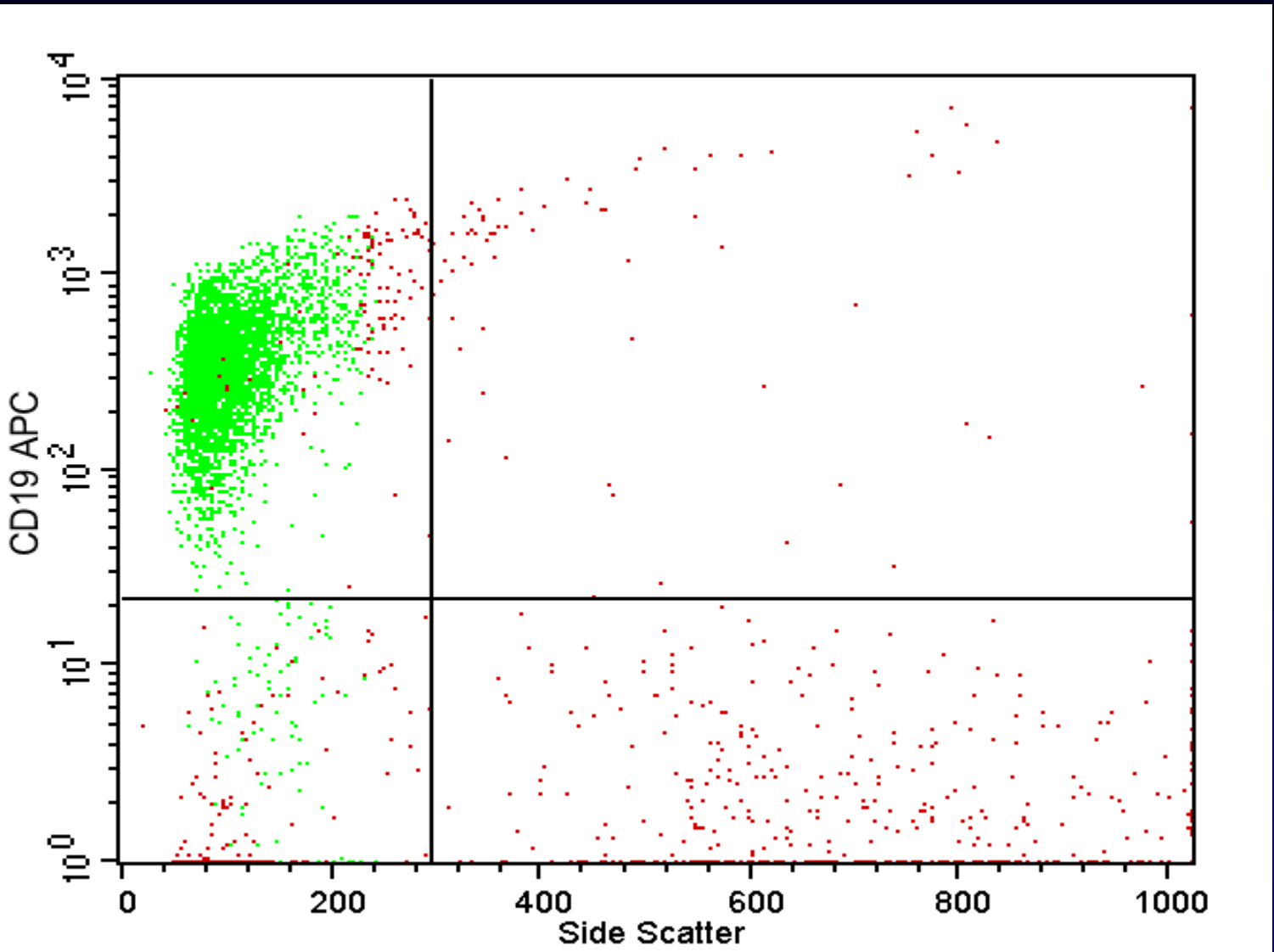
B- lineage (80%)	Markers
Pro-B	CD19(+),Tdt(+),CD10(-),CyIg(-),
Common	CD19(+),Tdt(+),CD10(+),CyIg(-),
Pre-B	CD19(+),Tdt(+),CD10(+),CyIg(+),SmIg(-)
Mature-B	CD19(+),CD10(±),CyIg(±),SmIg(+)

T-lineage (20%)	
Early-T	cCD3(+) CD7(+), CD2(+/-), Tdt(+), CD4(-) CD8(-)
Cortical-T	cCD3(+) CD7(+), CD2(+), CD1a(+) CD4(+) CD8(+)Tdt(+)
Mature-T	sCD3(+) CD4(+) OR CD8(+) CD1a(-)


CD45 FITC
10^0
10^1
10^2
10^3
10^4
R2
0
200
400
600
800
1000
Side Scatter


CD45 PerCP Cy5.5
10^0
10^1
10^2
10^3
10^4
R2
0
200
400
600
800
1000
Side Scatter


CD34 APC
10^0
10^1
10^2
10^3
10^4
0
200
400
600
800
1000
Side Scatter


CD19 APC
10^4
10^3
10^2
10^1
10^0
0
200
400
600
800
1000
Side Scatter

Risk classification in ALL

1. Standard risk
2. High risk
3. Very high risk

Very high-risk ALL
(modified by TKI treatment)

Chromosome Philadelphia - positive
or BCR/ABL (+)

High-risk ALL

1. Age > 35 years,
2. WBC > 30 G/L in B-ALL
   > 100 G/L in T-ALL
3. t(4;11); hipodiploidy

4. Detection of MRD (minimal residual disease) with flow cytometry or molecular methods- MRD positivity in post remission phase
5. No remission after 4 weeks of induction therapy

High risk ALL

The most important adverse prognostic factor:

Detection of MRD (minimal residual disease) with flow cytometry or molecular methods-

MRD positivity: 0.1-0.01% lymphoblasts in BM

Treatment phases in ALL

- Remission induction therapy
- Post-remission treatment
  - Intesification (consolidation) therapy
  - Haematopoietic stem cell transplantation
  - Maintance chemotherapy
- Prophylaxis / treatment of CNS involvement
- Treatment of refractory/relapsed ALL

Remission induction therapy in ALL

1. Antineoplastic treatment

- Drugs:
  prednisone, vincristine, antracycline, asparginase,
  cytosine arabinoside, cyclophosphamide
- Imatinib or dasatinib in combination with chemotherapy in Ph+ ALL!
- Treatment duration: 4-8 weeks

2. CNS prophylaxis: Mtx it, Ara-C it, steorids it
3. Supportive care
4. Treatment of complications

The objective of induction chemotherapy = complete remission

Definition of CR:

1. **Normocellular bone marrow with 5% or fewer blasts**
2. **Peripheral blood without blasts**
3. **Granulocyte count > 1,0 G/L, platelet count > 100G/L**
4. **The absence of any signs and symptoms od extramedulary leukemia**

Complete remission: 85-95 % of pts

Intensification therapy

- **8-12 weeks of chemotherapy**
- **high dose (HD) of cytosine arabinoside, HD methotrexate, HD cyclophosphamide, asparaginase, steroids**
- **Imatinib or dasatinib in Ph+ ALL**
- **CNS prophylaxis: Mtx it, Ara-C it, steroids it**
- **alternatively: radiotherapy 18 Gy**

Post-remission therapy in standard-risk ALL

1. **Chemotherapy**

   a/. Maintenance therapy:

   6-mercaptopurine, methotrexate - for 2-3 years.

   b/. Intensification treatment periodically

   repeated: daunorubicin/adriablastin,

   prednisone, vincristine, cyclophosphamide.

2. **CNS prophylaxis**

Post-remission therapy in high-risk ALL

1. Allogeneic hematopoietic stem cell transplantation
2. Autologous HSCT (donor-, MRD -)

Conditioning regimen:

TBI 12-13 Gy plus cyclophosphamide 120 mg/kg

Post-remission therapy in very high-risk ALL

- Allogeneic stem cell transplantation
- Maintance therapy after alloHSC in MRD+ pts: imatinib or the other TKI

Treatment results in ALL

- **Adults**
  - **Complete remission (CR)** **90-95%**
  - **Leukemia-free survival (LFS)** **40-60%**
- **Children**
  - **Complete remission (CR)** **95-99%**
  - **Leukemia-free survival (LFS)** **70-80%**

Chromosomal/molecular abnormalities with prognostic significance in ALL

Better prognosis

- normal koryotype
- hyperdiploidy

Poor prognosis

- t (8; 14)
- t (4; 11)

Very poor prognosis

- t (9; 22); BCR/ABL (+)