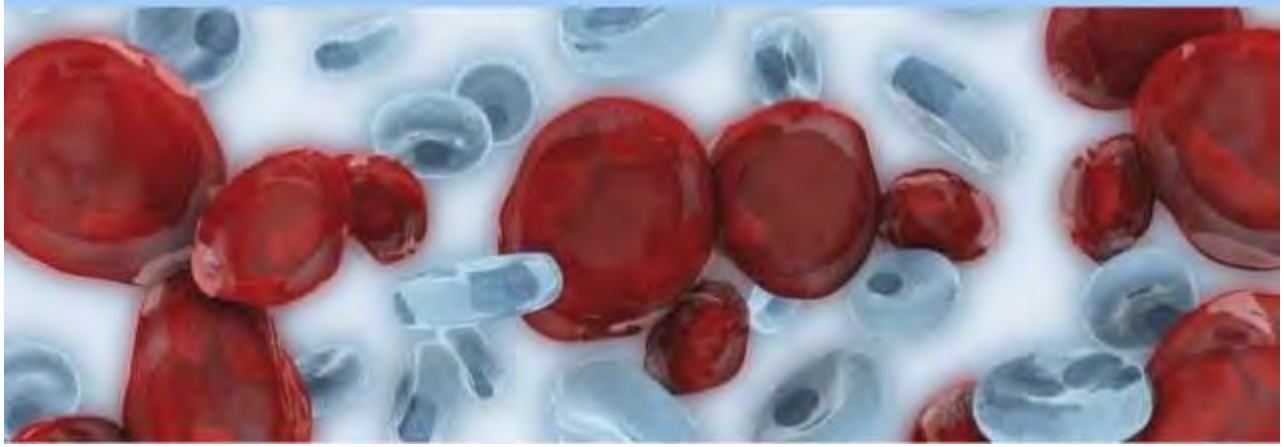
LEUCEMIE ACUTE

Leukemia

- Is a group of malignant (neoplastic) disorders , characterized by the clonal expansion and accumulation of one or more blood cell line(s) , with eventual involvement of all hematopoietic organs and other organs.



Leukemia

Tow or more Mutations within the genome of HSC or multipotential progenitors/precursors

↓

Activation of specific proto-oncogene
De-activation of tumor suppressor genes

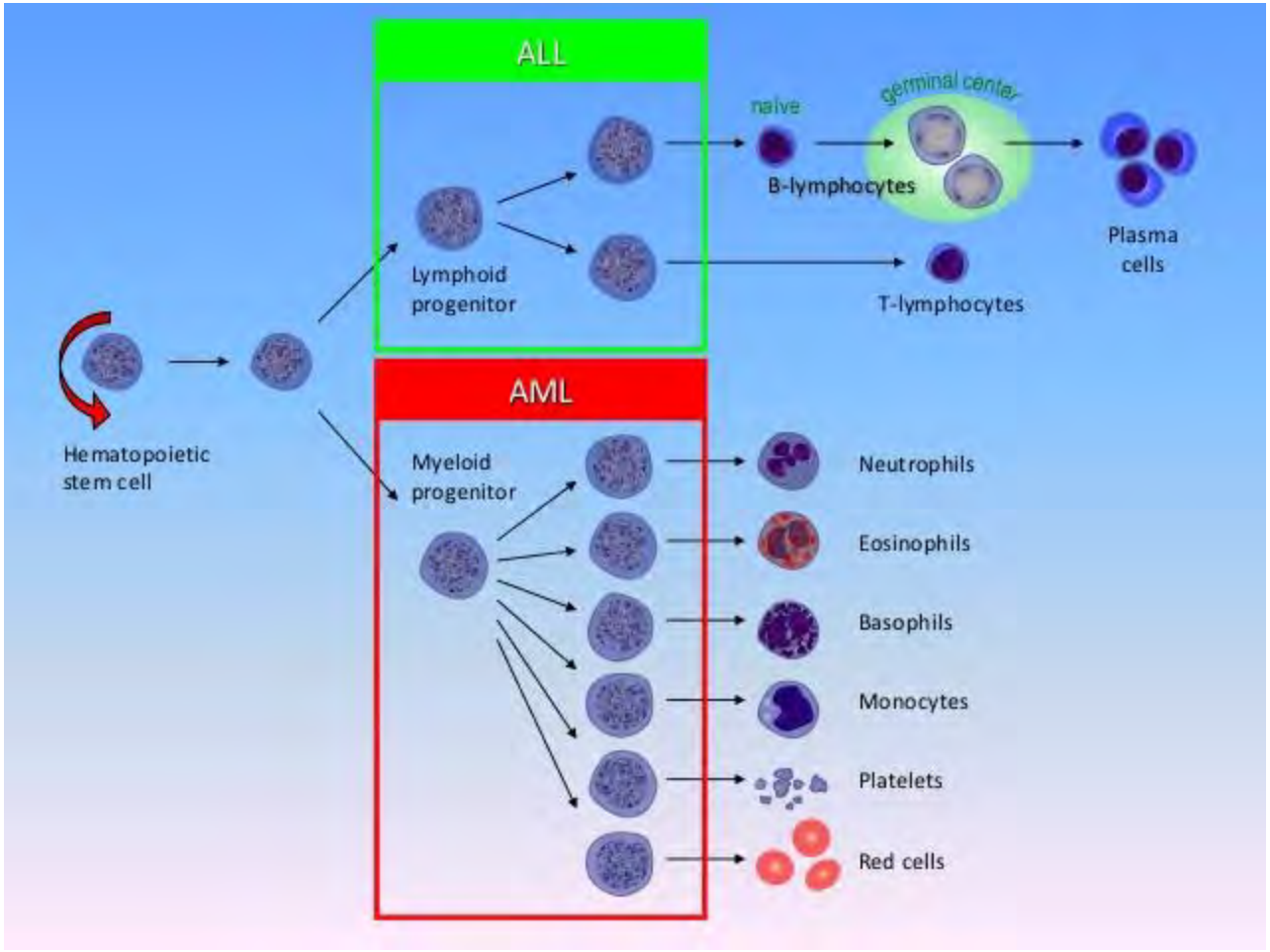
↓

Clone of cells with characteristics of a malignant cell

- Prolonged life (immortal) resistant to apoptosis
- Growth factor independent growth
- Insensitivity to growth-inhibitory signals
- Ability to invade and metastasize
- Blockage of intracellular differentiation

Incidence

- ~3.5 per 100,000 people per year
- higher in men than in women (4.5 vs 3.1)
- increases with age
  - 1.7 in individuals age <65 years
  - 15.9 in those age >65 years
- The median age at diagnosis is 67 years.


ALL
naive
germinal center
B-lymphocytes
Plasma cells
Lymphoid progenitor
T-lymphocytes
AML
Hematopoietic stem cell
Myeloid progenitor
Neutrophils
Eosinophils
Basophils
Monocytes
Platelets
Red cells

Acute Myeloid Leukemia

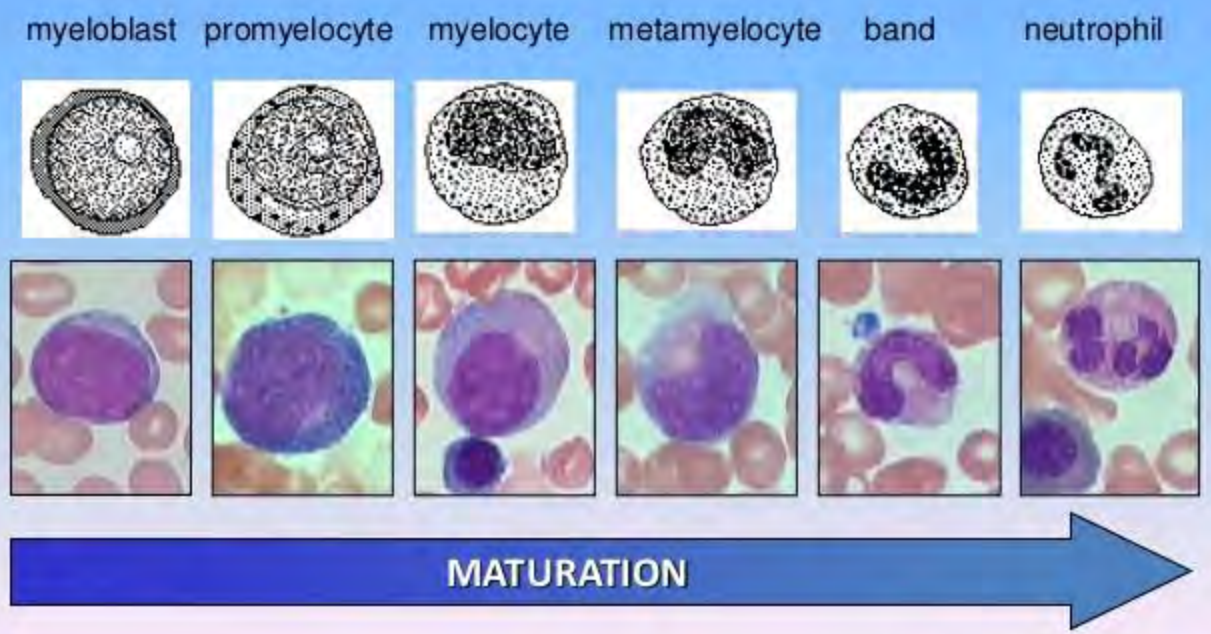
- Malignant neoplastic proliferation and accumulation of immature and nonfunctional myeloid line of blood cells in the bone marrow .

- Also known as acute myelogenous leukemia or acute nonlymphocytic leukemia (ANLL)

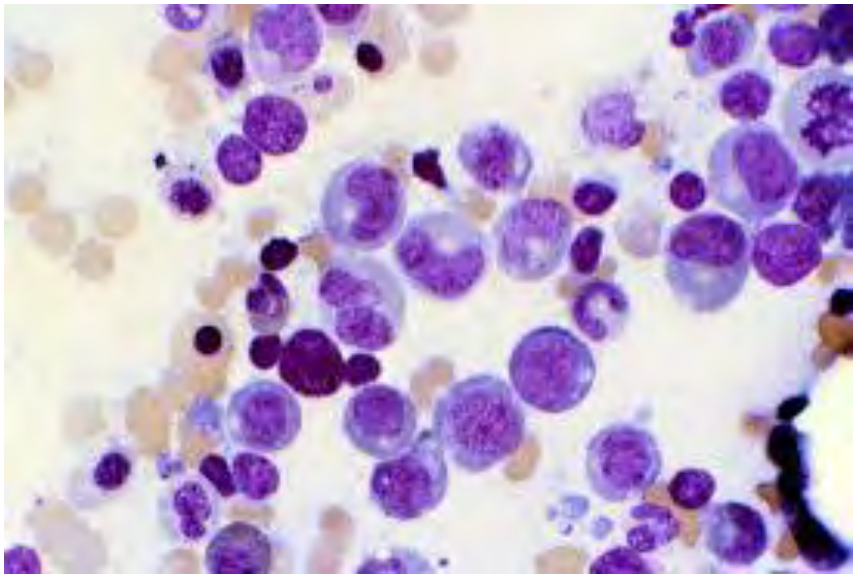
- Most common Acute Leukemia affecting adults.

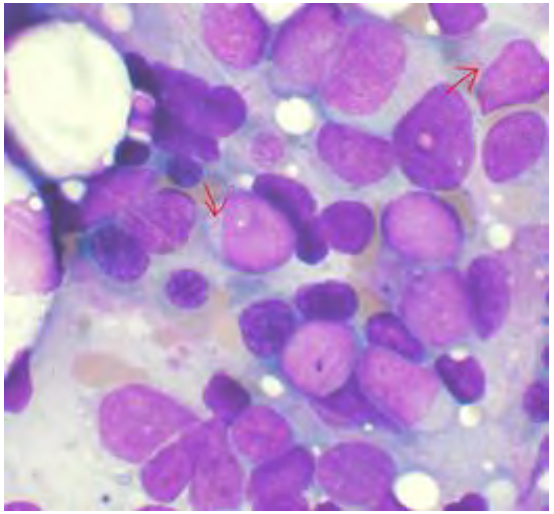
- As an Acute Leukemia, AML progresses rapidly and is typically fatal within weeks or months if left untreated .

Myeloid maturation



Adapted and modified from U Va website





Etiology

- Heredity
  - Down syndrome
  - Fanconi anemia
  - Bloom syndrome
  - ataxia-telangiectasia
  - Congenital neutropenia (Kostmann syndrome)
- Radiation
  - High-dose radiation (atomic bombs survivors)

- chemical and occupational exposures
  - Benzene
  - petroleum products
  - Paint
  - embalming fluids
  - ethylene oxide
  - Herbicides
  - smoking
- Drugs
  - Alkylating agent
  - Topoisomerase II inhibitor
  - Chloramphenicol
  - Phenylbutazone
  - Chloroquine
  - methoxypsoralen

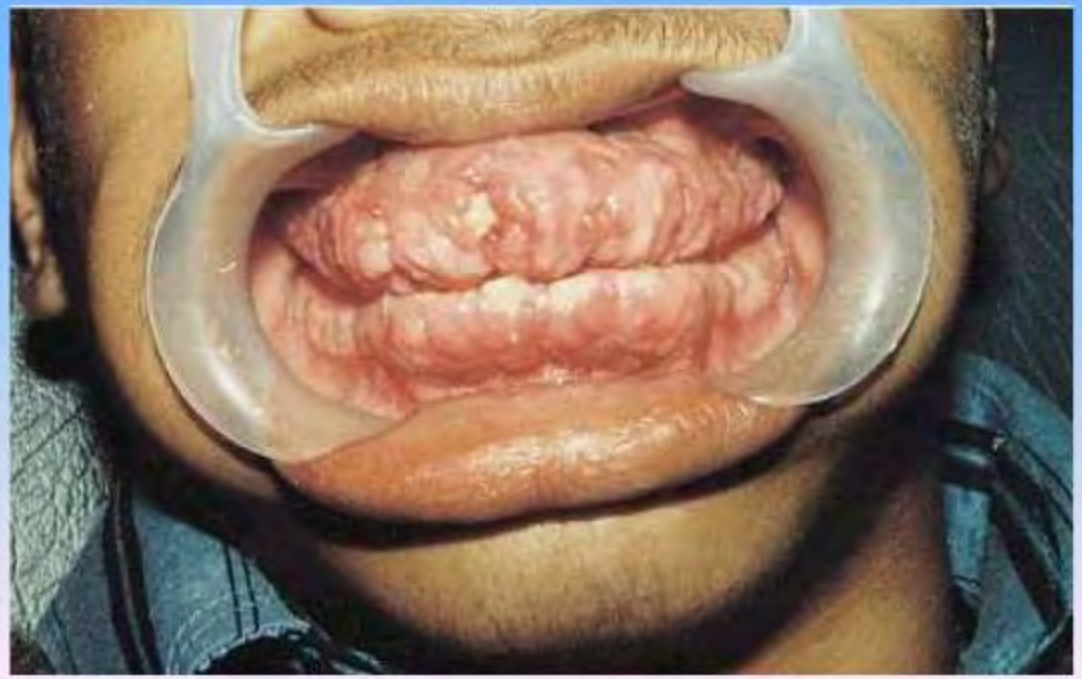
Clinical Presentation

- Nonspecific symptoms
- Fatigue
- Anorexia
- Weight loss
- Fever
- Bleeding, easy bruising
- Bone pain, lymphadenopathy, nonspecific cough, headache, or diaphoresis

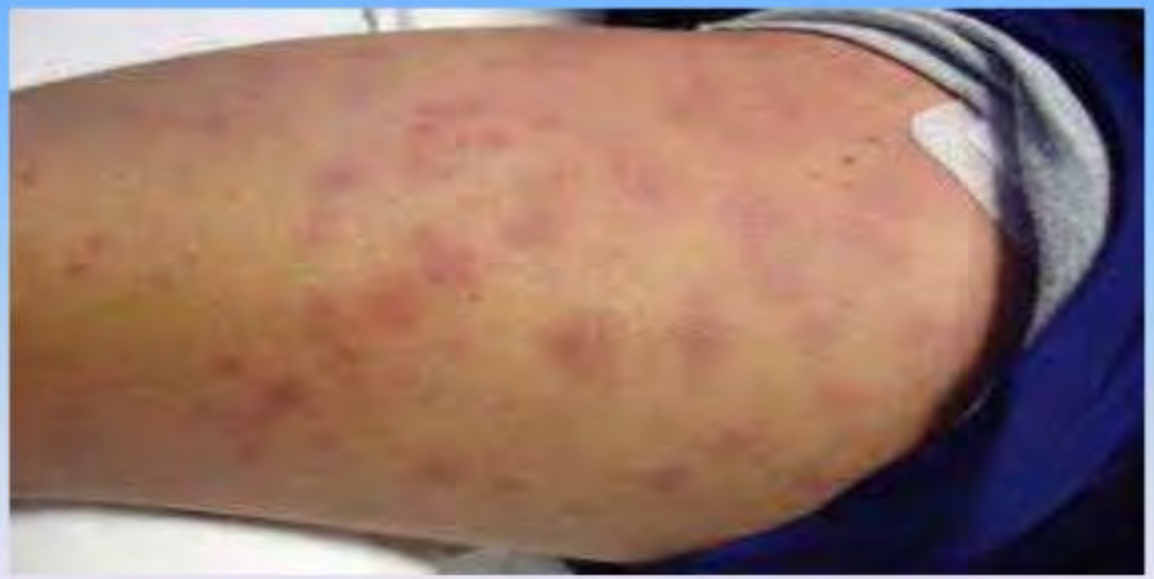
Physical Findings

- Fever
- Splenomegaly
- Hepatomegaly
- Lymphadenopathy
- Sternal tenderness
- Evidence of infection and hemorrhage

Gum hypertrophy



Leukemia cutis



FAB Classification: AML

M0 AML with no Romanowsky or cytochemical evidence of differentiation
M1 Myeloblastic leukemia with little maturation
M2 Myeloblastic leukemia with maturation
M3 Acute promyelocytic leukemia (APL)
M3h APL, hypergranular variant
M3v APL, microgranular variant
M4 Acute myelomonocytic leukemia (AMML)
M4eo AMML with dysplastic marrow eosinophils
M5 Acute monoblastic leukemia (AMoL)
M5a AMoL, poorly differentiated
M5b AMoL, differentiated
M6 "Erythroleukemia"
M6a AML with erythroid dysplasia
M6b Erythroleukemia
M7 Acute megakaryoblastic leukemia (AMkL)

STEM CELL

M0

MYELOID

COMMITTED CELL

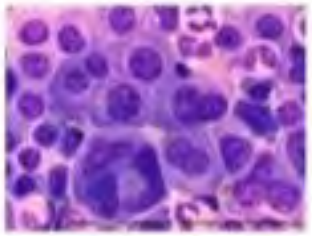
MONOBLAST

M5

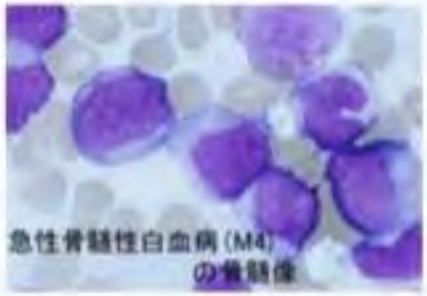
ERYTHROID

COMMITTED CELL

M6



M4 Myelomono



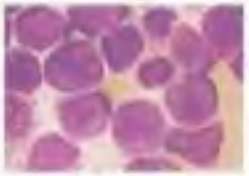
MYELOBLAST

M1

M2

PROMYELOCYTE

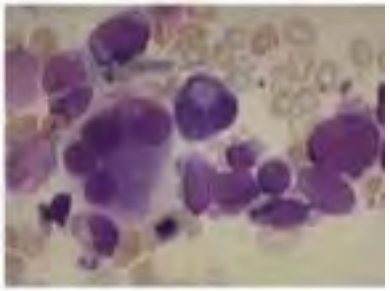
M3



MEGAKARYOCYTIC

COMMITTED CELL

M7



PRACTICE AID

Tools for Characterizing and Diagnosing AML and Higher-Risk Subtypes

PeerView Pathology

MLI

The WHO released an updated classification of AML in 2016[1]

AML and Related Neoplasms

AML with recurrent genetic abnormalities

- AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
- APL with *PML-RARA*
- AML with t(9;11)(p21.3;q23.3);*KMT2A-MLLT3*
- AML with t(6;9)(p23;q34.1);*DEK-NUP214*
- AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM*
- AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
- *Provisional entity: AML with* BCR-ABL1
- AML with mutated *NPM1*
- AML with biallelic mutations of *CEBPA*
- *Provisional entity: AML with mutated RUNX1*

AML with myelodysplasia-related changes

Therapy-related myeloid neoplasms

AML, NOS

- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Pure erythroid leukemia
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

Note: these cytogenetic abnormalities are sufficient to diagnose AML-MRC when ≥20% PB or BM blasts are present and prior therapy has been excluded

Cytogenetic Abnormalities

Complex karyotype (≥3 abnormalities)

Unbalanced abnormalities

- –7/del(7q)
- del(5q)/t(5q)
- i(17q)/t(17p)
- –13/del(13q)
- del(11q)
- del(12p)/t(12p)
- idic(X)(q13)

Balanced abnormalities

- t(11;16)(q23.3;p13.3)
- t(3;21)(q26.2;q22.1)
- t(1;3)(p36.3;q21.2)
- t(2;11)(p21;q23.3)
- t(5;12)(q32;p13.2)
- t(5;7)(q32;q11.2)
- t(5;17)(q32;p13.2)
- t(5;10)(q32;q21.2)
- t(3;5)(q25.3;q35.1)

Access the activity, "Pathology Insights on Innovation in AML: The Rapid Emergence of Precision Diagnostics & Novel Therapy Across the Spectrum of Care," at **PeerView.com/YCF40.**

Acute Myeloid Leukemia

WHO Classification of AML

1- AML with recurrent Cytogenetic abnormalities

- usually translocation, in most cases the chromosomal rearrangement create a fusion gene, encoding a novel fusion protein.

I. AML with t(8;21)(q22;q22);(ETO/AML1):

- Present morphological as AML with maturation.

- The fusion protein blocks the normal function of CBF, and induce abnormal gene activation and gene repression, this will lead to increase proliferation with blocked differentiation.

Acute Myeloid Leukemia

WHO Classification of AML

II. AML with abnormal B.M eosinphils

inv (16)(p13;q22) or t(16;16)(p13;q22)(CBFB/MYH11):

- Present morphology as AML with monocytic and granulocytic maturation and presence of abnormal eosinphils in B.M.

- Combination of acute myelomonocytic leukemia (AMML) with abnormal eosinphilis is morphologically AMML Eo.

- Abnormal immature (basophilic) granules in the eosinphils, promyelocyte, and myelocyte stages.

-

Acute Myeloid Leukemia

WHO Classification of AML

III . AML with t(15;17)(q22;q12)(PML/RARa) and variants:

- it is acute promyelocytic leukemia(APL), an AML in which abnormal promyelocyte predominate.

- The presenting signs are DIC and bleeding .

- The typical t(15;17) gene rearrangement result in the fusion of (PML/RARa) gene and reciprocal (RARa/PML) gene.

Acute Myeloid Leukemia

WHO Classification of AML

IV. AML with 11q23(MLL) abnormalities:

- These leukemia associated with monocytic features (monoblasts and promonocyte).

- The MLL protein is a DNA binding protein that interact with other nuclear protein and permits the association of transcription factor which regulate transcription.

Acute Myeloid Leukemia

WHO Classification of AML

2- AML with multilinage Dysplasia (with or without prior MDS)

-It is an Acute leukemia (>20% blast) with dysplasia in more than 50% of the cells in two or more myeloid cell lines.

-It is occurs with or following MDS / MPD.

-examples of dysplasia include: hypogranular PMNs, psuedo-pelger-Huet anomaly, megaloblastic erythrocyte, ringed sideroblast.

- - poor prognosis.

Acute Myeloid Leukemia

WHO Classification of AML

3- AML and Myelodysplastic syndrome, therapy releated:

-These disorder arise as a result of cytotoxic chemotherapy and / or radiation therapy.

Two major subtypes:

I. Alkylating agent/ radiation treatment: initially it start with MDS and eventually evolving AML.

II. Topoisomerase II inhibitor treatment.

Acute Myeloid Leukemia

WHO Classification of AML

4- Acute Myeloid leukemias not otherwise categorized:

- Include all AML cases that not fulfill criteria for any of other described.

- The subtypes of this AML are classified according to differentiated on morphology and cytochemical features.

I. AML Minimally Differentiated
II. AML without Maturation
III. AML with Maturation
IV. Acute Myelomonocytic leukemia (AMML)
V. Acute monoblastic leukemia and Acute monocytic leukemia
VI. Acute Erythroid leukemia (AEL)
VII. Acute Megakaryoblastic leukemia

Acute Myeloid Leukemia

WHO Classification of AML

VIII. Acute Basophilic leukemia

- The most characteristic feature by cytochemistry is metachromatic positivity with toluindine blue.

IX. Acute panmyelosis with mylofibrosis

- it is occur with or following chemo and radio therapy.

X. Myeloid Sarcoma

- a tumor of myeloblast or immature myeloid cells occures in the extramedullary site or in the bone.

AML
Cytogenetics & Prognosis

- **Favorable**
  t(8;21), t(15;17), inv(16)
- **Intermediate** (Most patients)
  normal, +8, +21, +22, del(7q), del(9q),
- **Adverse**
  -5, -7, del(5q), abnormal 3q,
  complex karyotype (> 3 - 5 abnormalities)

Group	CR	5 year survival
Favorable	91%	65-75%
Intermediate	86%	40-50%
Adverse	63%	<15%

Next Generation Sequencing

Group	Stratification criteria
Low risk	t(8;21)(q22;q22); RUNX1-RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11
	Mutation in NPM1 without FLT3-ITD
	Biallellic mutations in CEBPA*
Intermediate risk	Mutations in NPM1 with FLT3-ITD
	Wild type for both NPM1 and FLT3-ITD
	t(9;11) (p22;q23); MLLT3-MLL
	Cytogenetic abnormalities not classified as favorable or adverse
High risk	inv(3)(q21q26.2) or t(3;3)(q21;q26.2);RPN1-EVI1
	t(6;9)(p23;q34); DEK-NUP214
	t(v;11)(v;q23); MLL partners
	t(9;22)(q34,q11); BCR-ABL1†
	-5 or del(5q)
	-7
	abn(17p)
	Complex karyotype (defined by presence of >3 abnormalities)†
	Monosomal karyotype‡
	Mutation in FLT3-ITD without NPM1
	Total white blood cell count $>50 \times 10^9$/L†,§

*Biallelic mutations in CEBPA were investigated only in 24 samples; all were negative.
†Modifications to the proposed European LeukemiaNet 2010.[1]
‡Defined by the presence of 1 single monosomy in association with ≥1 additional

AML Treatment:
Induction Chemotherapy

- Anthracycline (Idarubicin) for 3 days and Cytosine arabinoside (Ara-C) for 7 days (3+7, Younger/fit patients only)

- Supportive care red cell and platelet transfusions, prophylactic antibacterial, antifungals and antivirals

AML:

Response to Induction

- Remission status determined by bone marrow at end of month following induction therapy (e.g. Day 14 & 28)

Complete remission:CR is defined-

- Blood neutrophil count -1000/L
- Platelet count 100,000/L.
- Circulating blasts - absent.
- The bone marrow <5% blasts
- Auer rods -absent.
- Extramedullary leukemia -absent

AML Treatment:
Consolidation

Following induction into Complete Remission

- 3-4 cycles of high dose cytosine arabinoside (HiDAC) administered approximately every 5-6 weeks

OR

- Bone marrow (peripheral blood stem cell) transplant (Depends on degree of risk)

In general, patients with **favorable risk disease will not benefit from HCT in first complete remission (CR1)** due to their relatively low risk of relapse balanced against the risk of transplant-related mortality (TRM) [1], [7]. Such patients would be candidates for HCT in a second complete remission (CR2) if that were achieved after relapse [1], [8]. However, patients aged over 60 may have poorer outcome in general and might benefit from HCT earlier in the course of their disease [1], [7], [8].

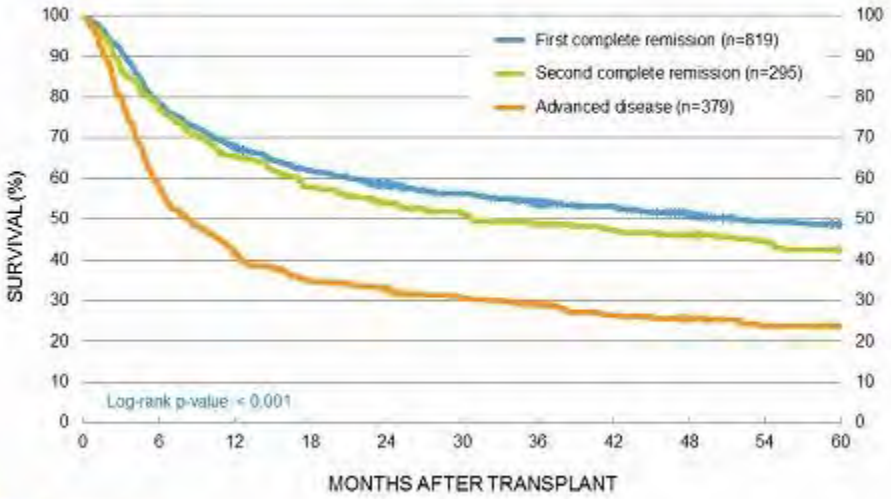
Patients **with adverse risk disease at high risk of relapse of about 70–90%** should be offered HCT in an effort to improve their chances of survival [8]. Waiting until a second remission is detrimental as a second CR is by no means assured, and outcomes of HCT in CR2 are generally poorer than those performed in CR1 [1], [9], [10].

Decisions about **HCT in intermediate-risk AML were less clear-cut** in the past and nowadays most patients are considered for HCT in CR1. Patient fitness, availability of a sibling donor or an alternative donor, a clinical trial option, as well as the transplant center experience must be considered when making a decision about HCT.

Acute Myeloid Leukemia Overall Survival

Bone Marrow Transplants for Adult Patients by Disease Status at Transplant

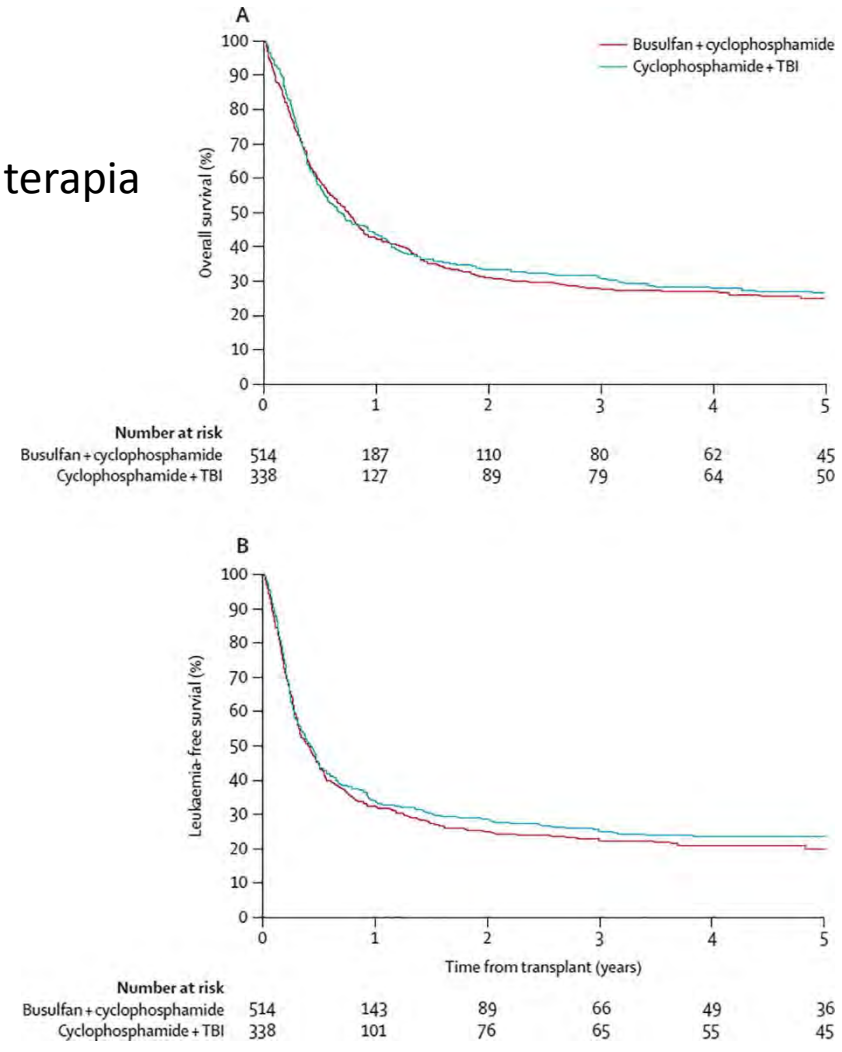
Unrelated Transplants Facilitated by NMDP/Be The Match (2006–2015)



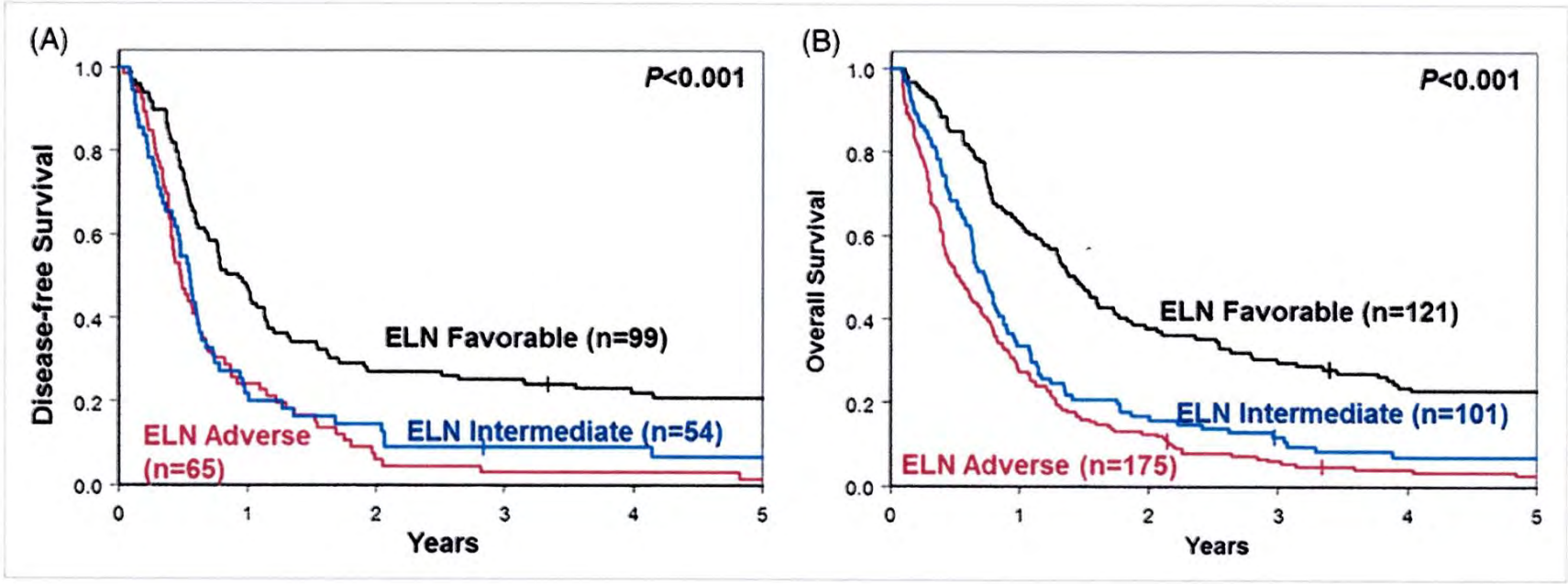
CIBMTR

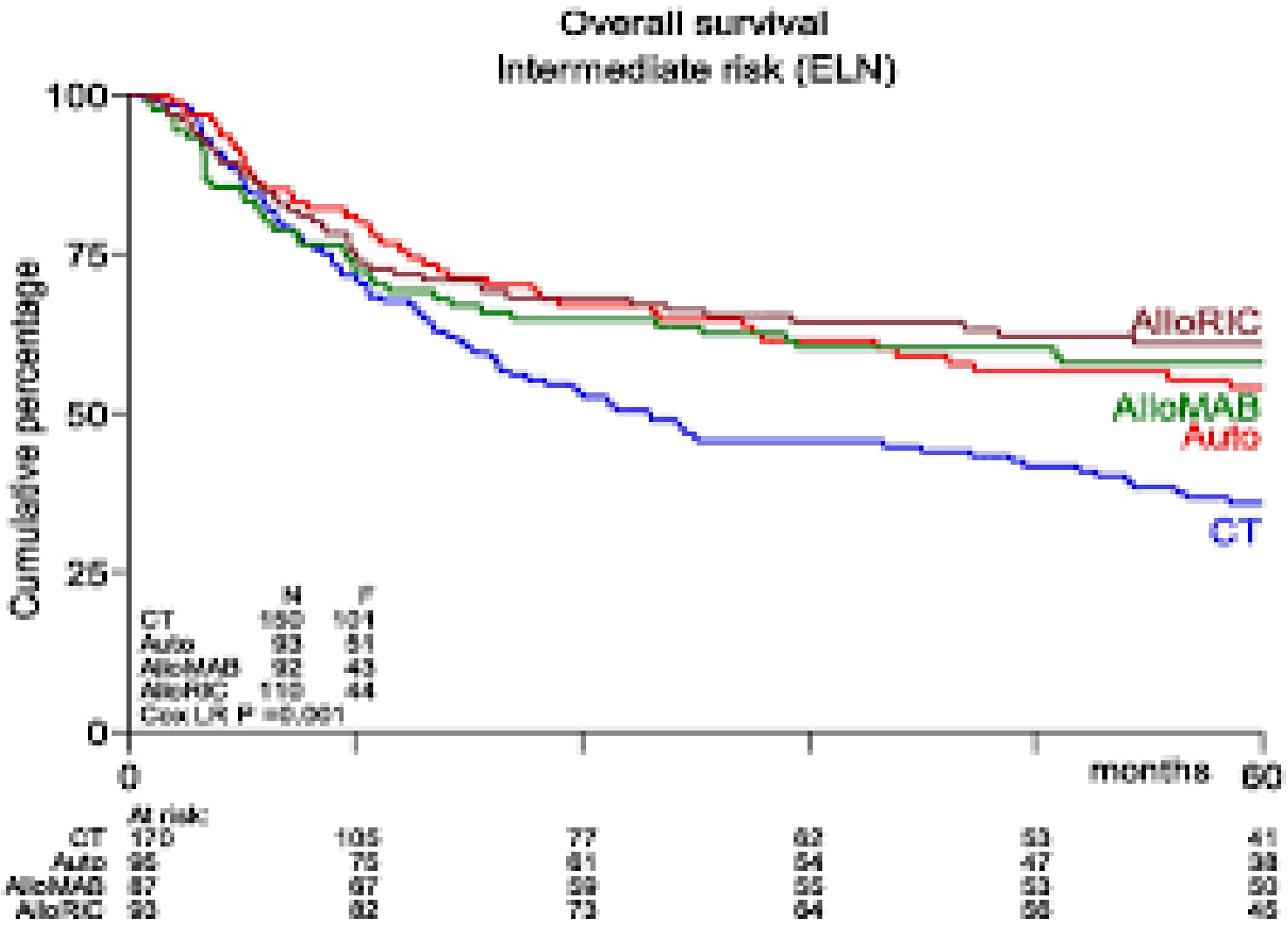
SOURCE: CIBMTR®, the research program of NMDP/Be The Match

Pazienti resistenti alla prima linea di terapia



PAZIENTI ANZIANI (>65°)




Overall survival
Intermediate risk (ELN)
Cumulative percentage
100
75
50
25
0
0
months
60
AlloRIC
AlloMAB
Auto
CT
N P
CT 150 101
Auto 93 51
AlloMAB 92 43
AlloRIC 110 44
Cox LR P =0.001
At risk:
CT 120 105 77 62 53 41
Auto 95 75 61 54 47 38
AlloMAB 87 67 59 55 53 50
AlloRIC 93 82 73 64 58 45

AML-M3 or APL

- Acute Promyelocytic Leukemia (APL M3)
- Blasts and promyelocytes heavily granulated, Auer rods often abundant
- Disseminated intravascular coagulation (DIC) common
- Treatment differs from all other AML subtypes once had the worst prognosis now the best prognosis

APL morphology: Hypergranular

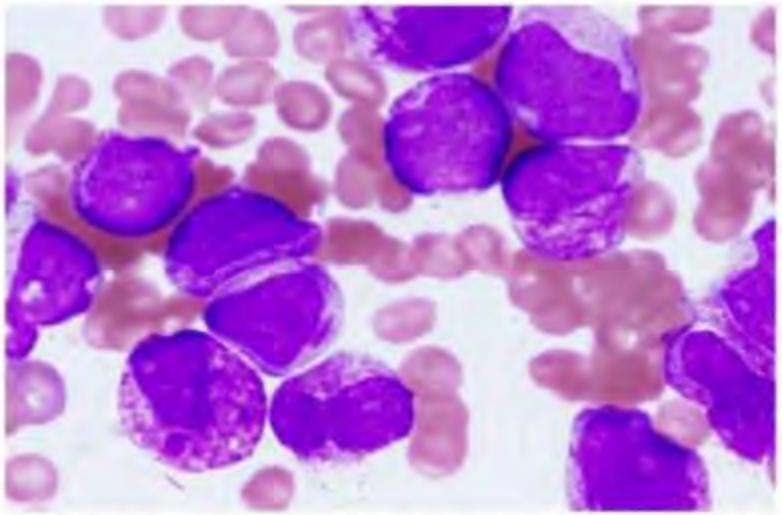
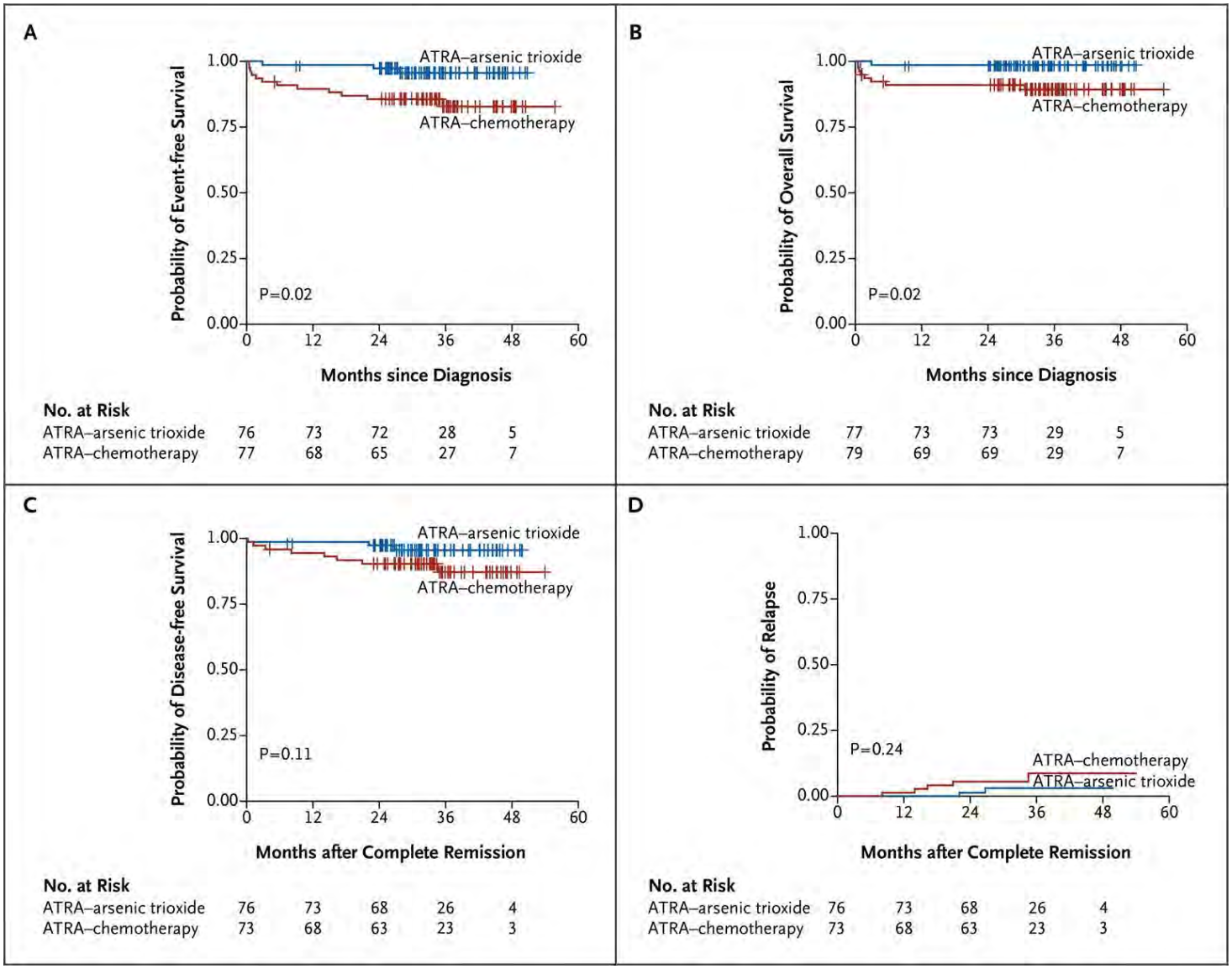


Figure 1. The bone marrow aspirate shows numerous abnormal promyelocytes with prominent cytoplasmic granules, characteristic of hypergranular acute promyelocytic leukemia. Some of these cells exhibit reniform or bilobed nuclei, and

Tallman, Blood, 2009


A
Probability of Event-free Survival
1.00
0.75
0.50
0.25
0.00
ATRA–arsenic trioxide
ATRA–chemotherapy
P=0.02
0
12
24
36
48
60
Months since Diagnosis
No. at Risk
ATRA–arsenic trioxide 76 73 72 28 5
ATRA–chemotherapy 77 68 65 27 7
B
Probability of Overall Survival
1.00
0.75
0.50
0.25
0.00
ATRA–arsenic trioxide
ATRA–chemotherapy
P=0.02
0
12
24
36
48
60
Months since Diagnosis
No. at Risk
ATRA–arsenic trioxide 77 73 73 29 5
ATRA–chemotherapy 79 69 69 29 7
C
Probability of Disease-free Survival
1.00
0.75
0.50
0.25
0.00
ATRA–arsenic trioxide
ATRA–chemotherapy
P=0.11
0
12
24
36
48
60
Months after Complete Remission
No. at Risk
ATRA–arsenic trioxide 76 73 68 26 4
ATRA–chemotherapy 73 68 63 23 3
D
Probability of Relapse
1.00
0.75
0.50
0.25
0.00
P=0.24
ATRA–chemotherapy
ATRA–arsenic trioxide
0
12
24
36
48
60
Months after Complete Remission
No. at Risk
ATRA–arsenic trioxide 76 73 68 26 4
ATRA–chemotherapy 73 68 63 23 3

- older patients may be considered for single-agent therapies with clofarabine or hypomethylating agents (i.e., 5-azacitidine or decitabine)

LAM FTL-3 MUTATA

Consider mutation status in your treatment strategy

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by a high degree of recurrent genetic mutations, several of which have been linked to poor prognosis.[1,9] These mutations include:

Among the most common of these is *FLT3*-ITD, one of the two major classes of activating mutations that can occur within *FLT3*.[1,9,48,49]

FLT3-ITD mutation: one of the worst molecular prognostic factors in AML[1,16]

FLT3-ITD mutation constitutively activates FLT3 kinase activity, inhibits cell differentiation, and drives .iferation and survival of leukemic cells.[16] **Patients with AML harboring a *FLT3*-ITD mutation typically have a ıificant disease burden presenting as leukocytosis, with high infiltration of bone marrow.[50]**

The *FLT3*-ITD mutation in AML has been associated with significantly shorter[51-56,a]:

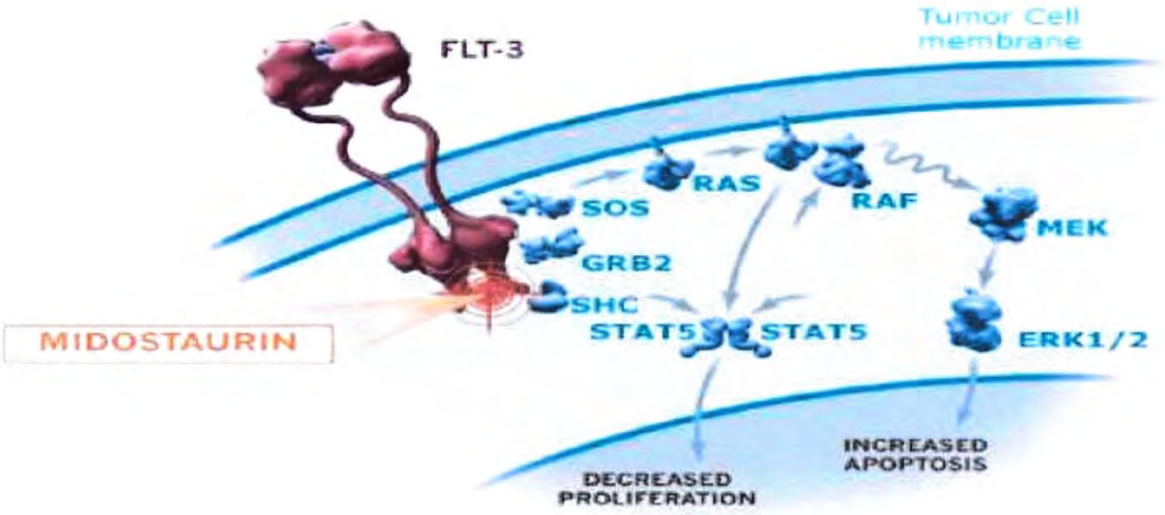
- **Overall survival (OS)**
- **Remission duration**
- **Disease- or event-free survival**

Median survival from relapse for patients with *FLT3*-ITD–mutated or *FLT3* WT AML[60,a]

[a] As reported in a single-center study of patients with normal karyotype AML whose *FLT3* status was determined at diagnosis. Data is reported from a subset of 127 relapsed patients.

Le novità per la Leucemia Mieloide Acuta. Per questa malattia del sangue si profila la prima importante novità terapeutica dopo oltre 25 anni: **midostaurina ,**designato come "breakthrough therapy" dalla FDA statunitense, utilizzato insieme alla chemioterapia negli studi clinici dimostra un aumento significativo della sopravvivenza.

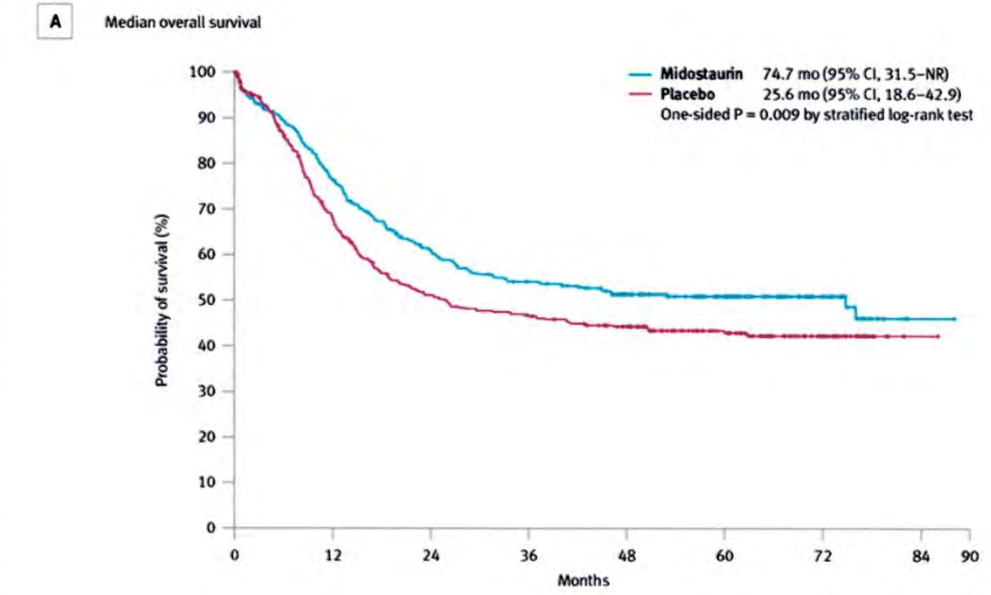
FLT3 è un recettore della tirosin-chinasi, posto sulla superficie cellulare, che svolge un ruolo nella proliferazione, o nell'aumento del numero di alcune cellule ematiche.

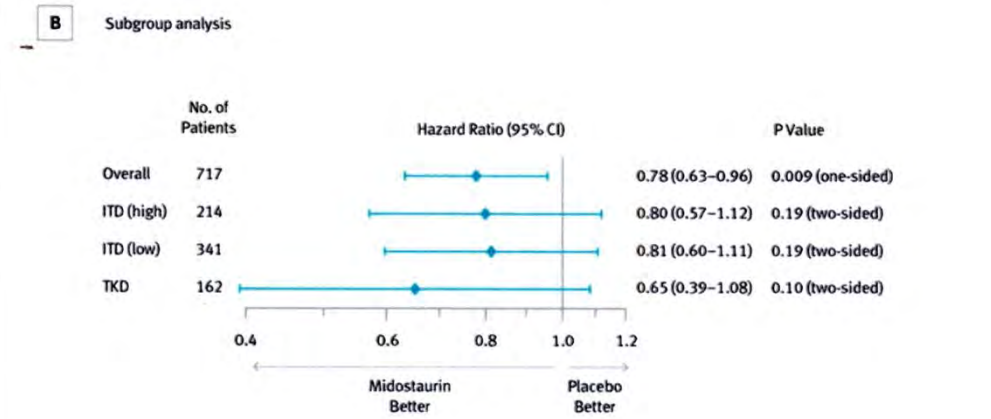


La midostaurina inibisce la mutazione genetica FLT3, presente in circa 1/3 dei pazienti con Leucemia Mieloide Acuta. Usata in combinazione con la chemioterapia, riduce in maniera significativa il rischio di recidiva offrendo una maggiore probabilità di lunga sopravvivenza.
La nuova molecola dovrebbe essere disponibile in Italia dal 2017.

MIDASTAURINA

Figura 1.





A. *Curva di Kaplan-Meier per la overall survival mediana nel gruppo trattato con midostaurin e con placebo;* ***B.*** *Analisi overall survival nei sottogruppi in base allo stato di FLT3 (mutazione puntiforme nel dominio TKD, internal tandem duplication con alto e basso rapporto di alleli wild-type). Mod. da Stone RM, et al. N Engl J Med 2017; 377: 454–464*


MYLOTARG

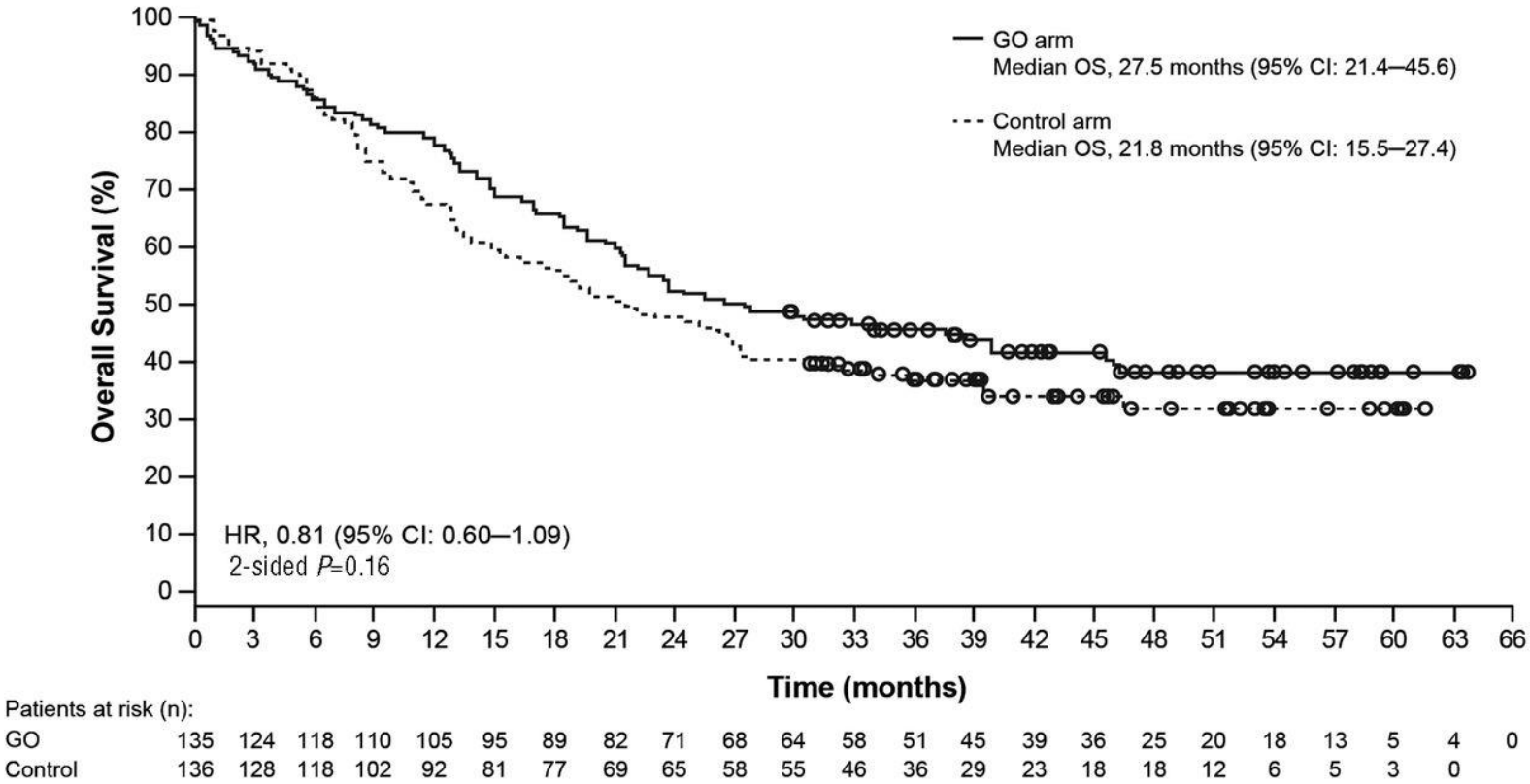
The Scenario

- **Background: Mylotarg** (gemtuzumab ozogamicin) – approved by FDA under its "Accelerated Approval" policy in 2000 for Acute Myeloid Leukemia (AML)
  - Surrogate endpoint -- response rate (i.e., the percentage of patients whose leukemia decreased or disappeared in laboratory tests) -- observed in 142 patients with AML across three clinical trials.
  - Condition of approval – do study whether adding Mylotarg to standard chemotherapy showed improvement in clinical benefit (survival time) to AML patients.

Scenario …

- Study results –
  - no improvement in clinical benefit was observed
  - a greater number of deaths occurred in the group of patients who received Mylotarg compared with those receiving chemotherapy alone.
  - At initial approval, Mylotarg was associated with a serious liver condition called veno-occlusive disease, which can be fatal.
    - This rate increased in the postmarket setting
- 2010 – Wyeth/Pfizer withdrew from market
  - Existing supplies not recalled; patients on medication allowed to continue
  - Future use – FDA said had to be under an Investigational New Drug (IND)

MYELOTARG in associazione a chemioterapia



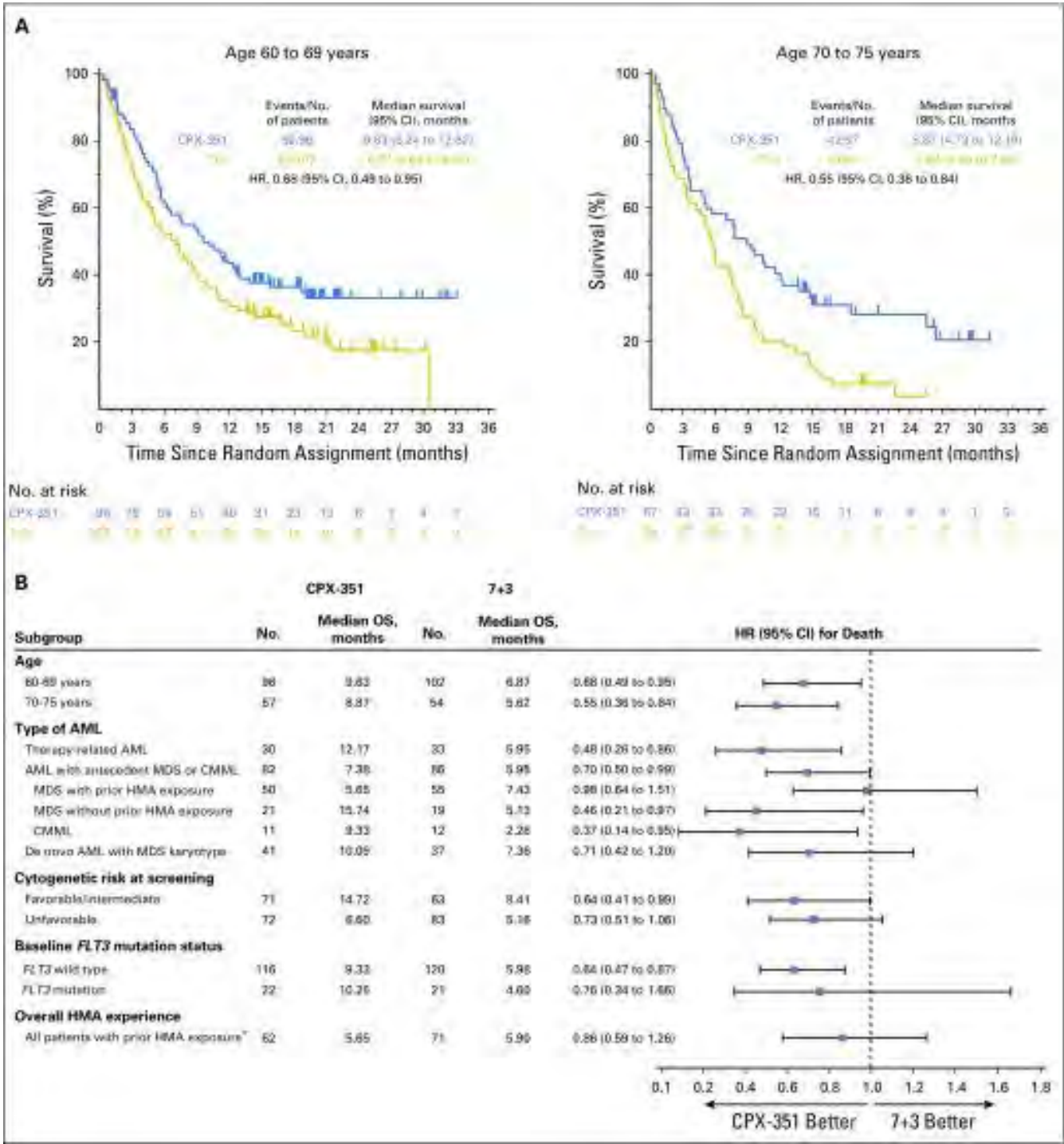
VIXEOS
(Daunorubicina liposomiale + citarabina)

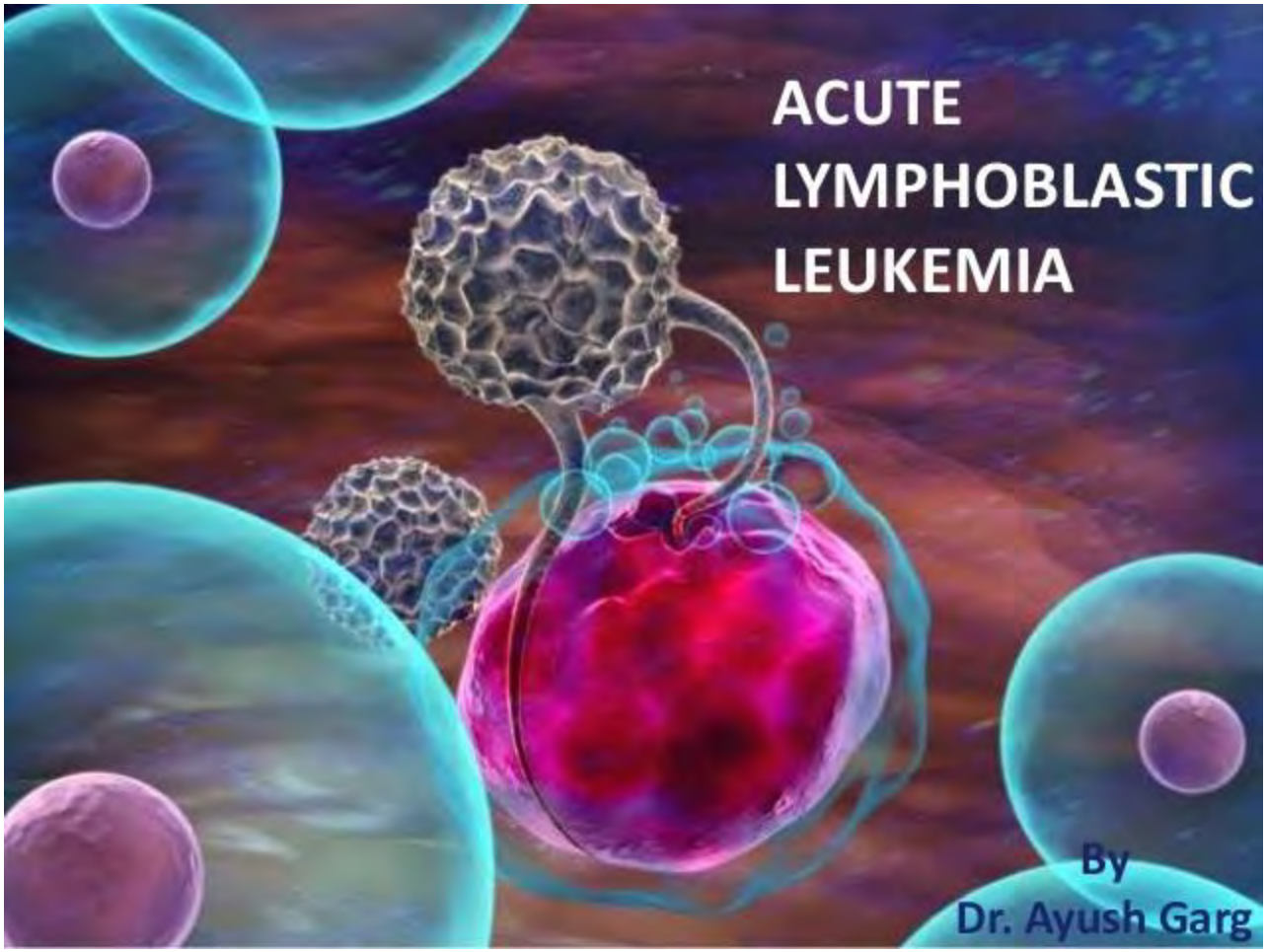
INDICAZIONE:

- Leucemia acute secondarie a pregressa chemioterapia

- Leucemia acute secondarie a mielodisplasia

Età: 60-75 anni




ACUTE
LYMPHOBLASTIC
LEUKEMIA
By
Dr. Ayush Garg

Definition

Acute lymphoblastic leukemia is malignant disease of marrow in which early lymphoid precursors proliferate and replace the normal haematopoietic cells.

EPIDEMIOLOGY

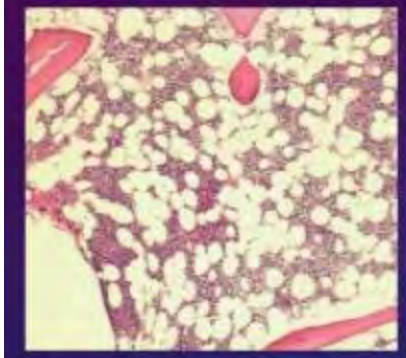
- Commonest form of malignancy in childhood.
- Majority are children of 2-10 yrs
- Peak incidence at 4 – 5 yrs of age.
- Acute onset with short history of duration.
- 85% are B cell

  15% are T cell
- 5 times more frequent in childhood than AML

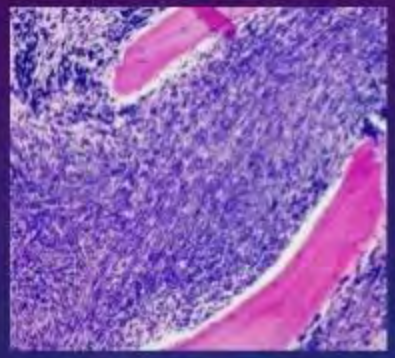
FACTORS PREDISPOSING ALL

GENETIC	ENVRONMENTAL
Downs,turner, klinefelter	Ionising Radiation
Fanconi,diamond blackfan	Drugs
NF Type1	Alkylating Agents
Ataxia telengiectasia	Nitrosourea
SCID	Epipodophyllotoxin
PNH	Benzene Exposure
Li-fraumeni syndrome	Advanced Maternal Age
Blooms syndrome	Paternal Smoking

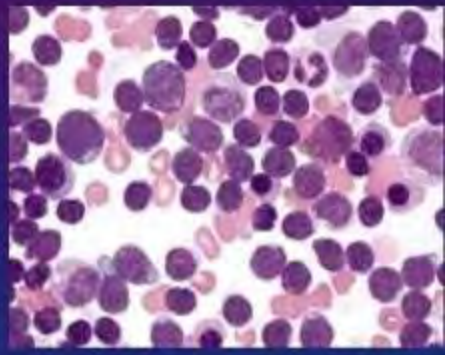
NORMAL MARROW



ENTIRE MARROW REPLACED BY BLAST



MARROW SHOWING BLASTS



FAB CLASSIFICATION OF ALL

Cytologic Features	L1	L2	L3
Cell Size	Small Cells Predominate, Homo Genous	Large, heterogenous In Size	Large Homogenous
Cytoplasm	Scanty	Variable,often Moderately Abundant	Moderately Abundant
Nucleoli	Small	One Or More, often Large	One Or More, prominent
Nuclear Shape	Homogenous	Variable, Heterogenous	Stippled, Homogenous
Nuclear Shape	Regular	Irregular Clefts	Regular
Cyt.Basophilia	Variable	Variable	Intensely Basophilic
Cyt.Vacuolation	Variable	Variable	Prominent

CLASSIFICATION OF ALL(WHO)

Immunologic Subtype	% Of Cases	FAB Subtype	Cytogenetic Abnormalites
Pre B ALL	75	L1,L2	t(9;22),t(4;11) t(1;19)
T cell ALL	20	L1,L2	14q11 Or 7q34
Mature Bcell All(burkitt Leukemia)	5	L3	t(8;14)

B CELL ALL (85%)

Type	Tdt	Calla	Surface Ig
Early Pro B ALL	Positive	Negative	Negative
Pre Bcell ALL	Positive	Positive	Negative
Mature B ALL	Negative	Positive	Positive

T CELL ALL(15%)

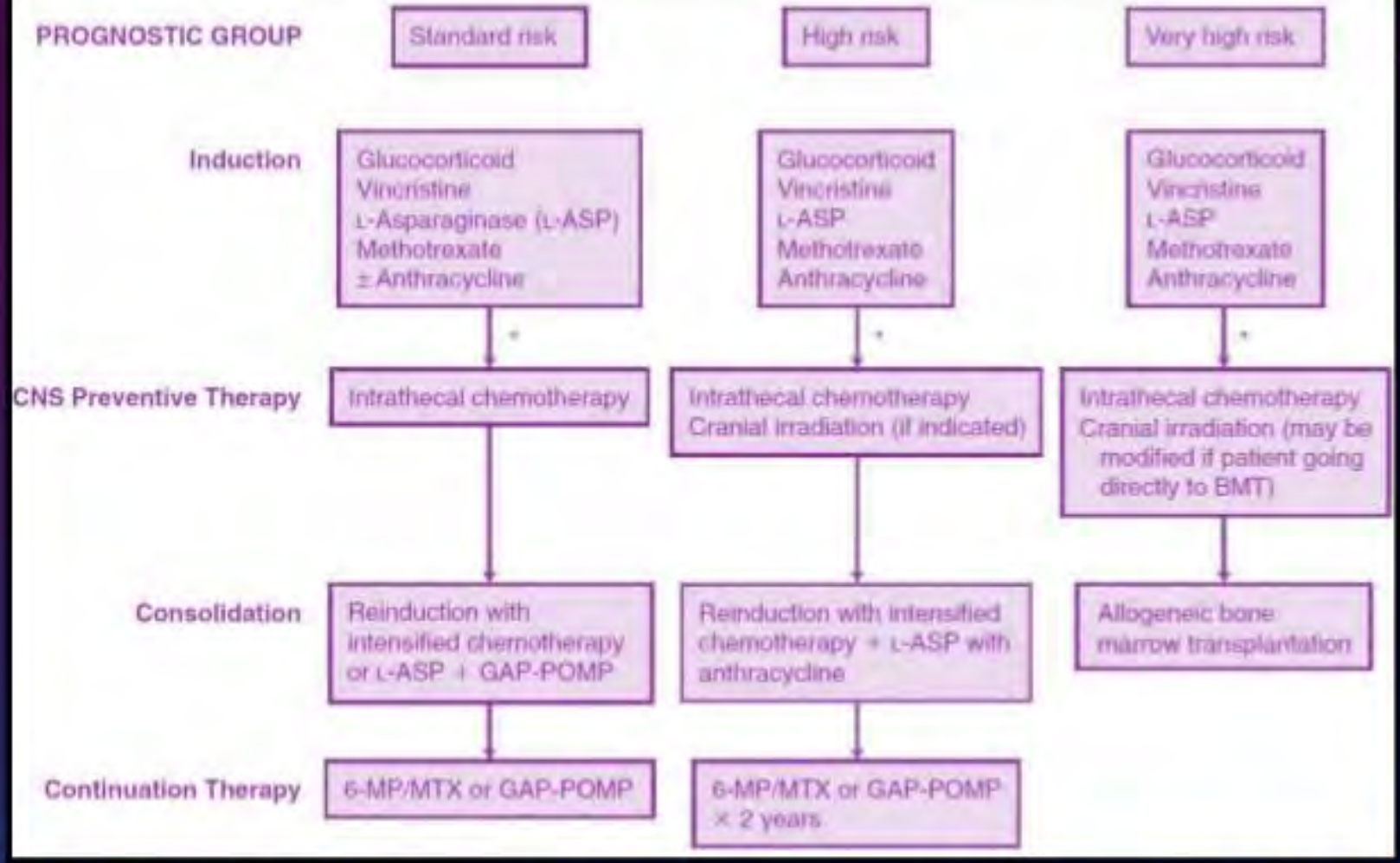
- Early subtype
- CD3 -, CD4-,CD8- or
- CD3-,CD4+,CD8+.
- Later subtype
- CD3+ with CD4+ or CD8+

PROGNOSTIC FACTORS IN ALL

Determinants	Favourable	unfavourable
WBC Counts	<10,000	>2,00,000
Age	2-10 years	<1yr,>10yr
Gender	female	male
Ethnicity	white	blac
Node,liver,splenomegaly	absent	massive
Testicular enlargement	absent	present
CNS involvement	absent	Csf blast and pleocytosis
FAB Type	L1	L2
Cytogenetics	T(12;21)(TEL-AML1) Trsomies 4,10,17	t(9;22)(bcr-abl) t(4;11)(MLL-AF4)
Ploidy	hyperdipoidy	hypodiploidy
Time to remission	<14days	>28days

PHYSICAL FINDINGS

Physical findings	Percentage
Splenomegaly	86
Lymphadenopathy	76
Hepatomegaly	74
Sternal Tenderness	69
Purpura	50
Fundic Changes	14



6-MP, 6-mercaptopurine; *BMT*, bone marrow transplant; *CNS*, central nervous system; *MTX*, methotrexate. *GAP-POMP* (GAP refers to the schedule of mercaptopurine administration given on 14 days of each 21-day cycle, thus a 7-day GAP) repeats a 3-week cycle until 2 years of continuous complete remission: vincristine, prednisone, mercaptopurine, methotrexate; high-dose cycle; vincristine, mercaptopurine, high-dose intravenous and intrathecal methotrexate.

TREATMENT OF ALL INDUCTION 1

Cycle	Chemotherapy	Dose and schedule
Induction	Prednisolone or	1mg/kg p.o days 1-28 days
	Vincristine	1.5mg/m2 i.v weekly one dose x 4 weeks
	Doxorubicin	30mg/m2 i.v weekly one dose x 4 weeks
	L-Asparginase	1,00,000 u/m2(total dose) in divided doses of 10,000 u daily for 10 days
CNS Preventive therapy	Methotrexate	12mg IT days 1,8,15,22

CNS PROPHYLAXIS

- In most regimens, CNS prophylaxis for patients at lower risk is achieved with systemic and intrathecal chemotherapy without cranial irradiation.
- Children with high-risk features are at an increased risk of CNS relapse and, historically, have received prophylactic cranial irradiation.
- These features include a presenting WBC count of 50,000/μL or greater; those with WBC counts over 100,000/μL are at particularly high risk of CNS relapse.
- Additional high-risk features that are indications on some treatment protocols for cranial irradiation are T-cell phenotype, Ph chromosome–positive ALL, and the presence of t(4;11).
- Infants younger than age 12 months with 11q23 abnormalities are at high risk of CNS relapse but because of their young age are usually treated without cranial irradiation, using intensified systemic and intrathecal chemotherapy to treat the CNS.


L-ASPARAGINASE
L-ASPASE
Rx

L-ASPARAGINASI

- Utilizzata come supporto alla trasformazione di prodotti alimentari per prevenire la formazione di **acrilammide** nei prodotti amidacei come craker o biscotti

- Le cellule leucemiche soprattutto della leucemia acuta linfoide proliferano in presenza di asparagina.

- L-asparaginasi catalizza la conversione di L-asparagina in acido aspartico e ammoniaca

LOT/EXP
PAA091004

NDC 0008-0100-01
Rx only

BESPONSA™
(inotuzumab ozogamicin)
for Injection

0.9 mg/vial

For Intravenous Infusion Only

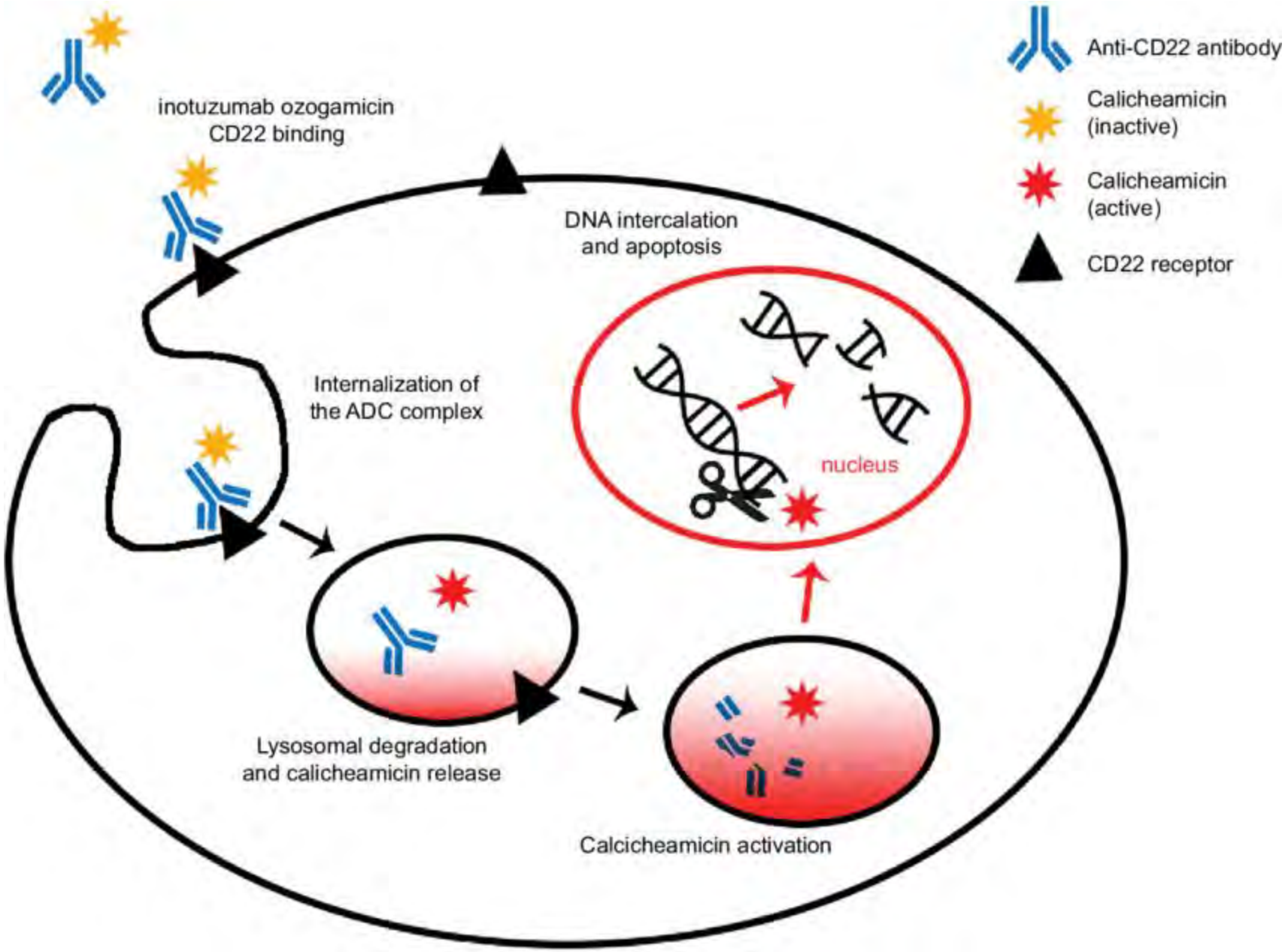
No Preservatives

Single-dose vial.
Discard unused portion.

Refrigerate vial at 2°C to 8°C (36°F to 46°F) in original carton to PROTECT FROM LIGHT. DO NOT FREEZE. See prescribing information for dosage, preparation and administration. Concentration is 0.25 mg/mL when reconstituted with 4 mL Sterile Water for Injection.

Mfg. by Wyeth Pharmaceuticals Inc
A subsidiary of Pfizer Inc
Philadelphia, PA 19101
US License No. 003

FPO 6.5" Data Bar Limited (RSS) - 10 mil
(01)00300080100011


Anti-CD22 antibody
Calicheamicin (inactive)
Calicheamicin (active)
CD22 receptor
inotuzumab ozogamicin CD22 binding
DNA intercalation and apoptosis
Internalization of the ADC complex
nucleus
Lysosomal degradation and calicheamicin release
Calcicheamicin activation

BESPONSA è indicato in monoterapia per il trattamento di pazienti adulti con leucemia linfoblastica
acuta (LLA) da precursori delle cellule B CD22-positivi, recidivante o refrattaria. I pazienti adulti con
LLA da precursori delle cellule B, recidivante o refrattaria, positiva per il cromosoma Philadelphia
(Ph+), devono aver fallito il trattamento con almeno un inibitore della tirosinchinasi (TKI) .

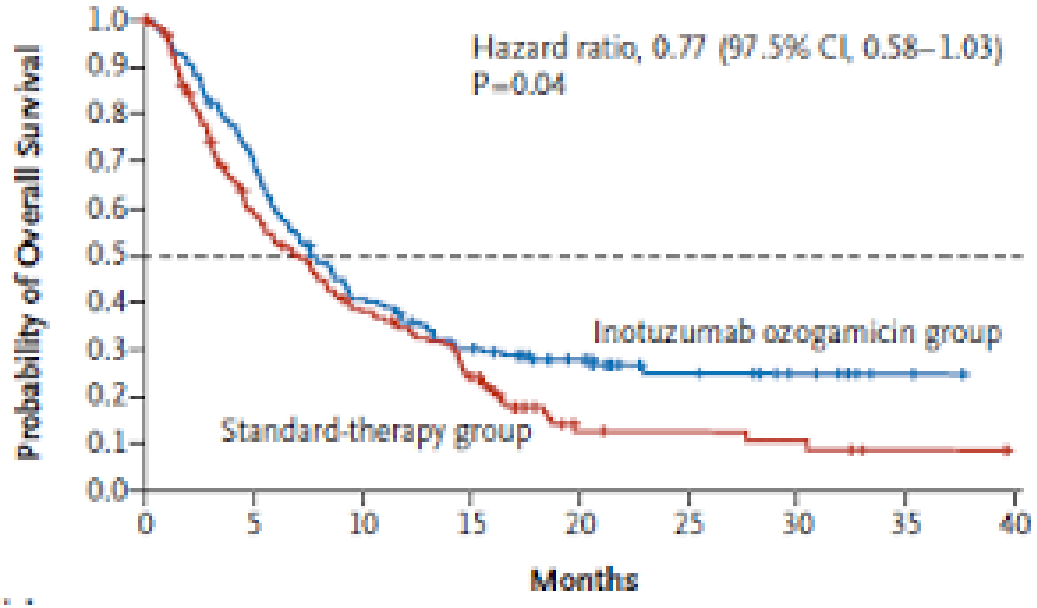
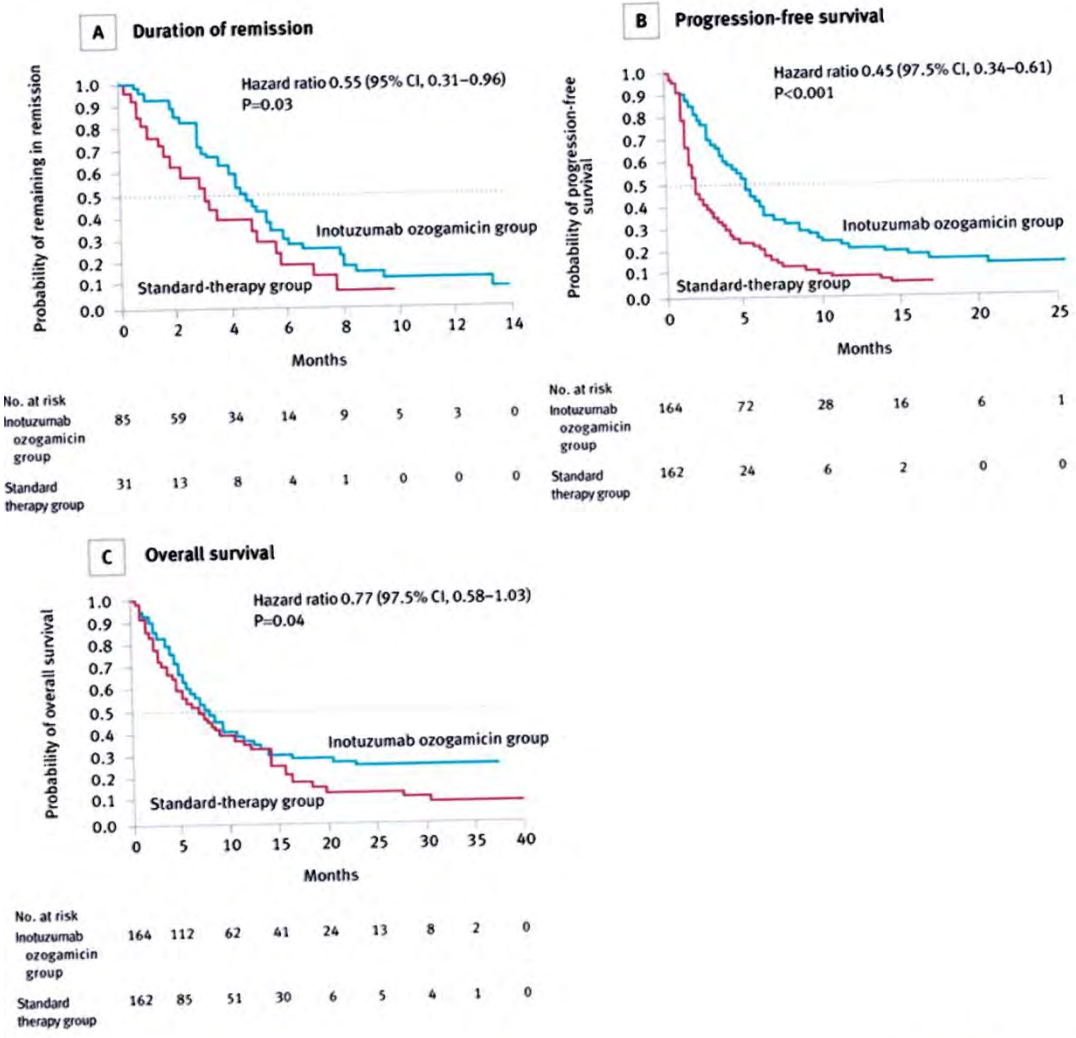

Probability of Overall Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
15
20
25
30
35
40
Months
Hazard ratio, 0.77 (97.5% CI, 0.58–1.03)
P=0.04
Inotuzumab ozogamicin group
Standard-therapy group

Tabella 1

	Inotuzumab ozagamicin (n=109)	Chemioterapia (n=109)	p
CR	80,7%	29,4%	<0,001
MRD–	78,4%	28,1%	<0,001
Durata della remissione	4,6 mesi	3,1 mesi	0,03
PFS	5 mesi	1,8 mesi	<0,001
OS	7,7 mesi	6,7 mesi	0,04

Mod. da Kantarjian HM, et al. N Engl J Med 2016; 375: 740–753

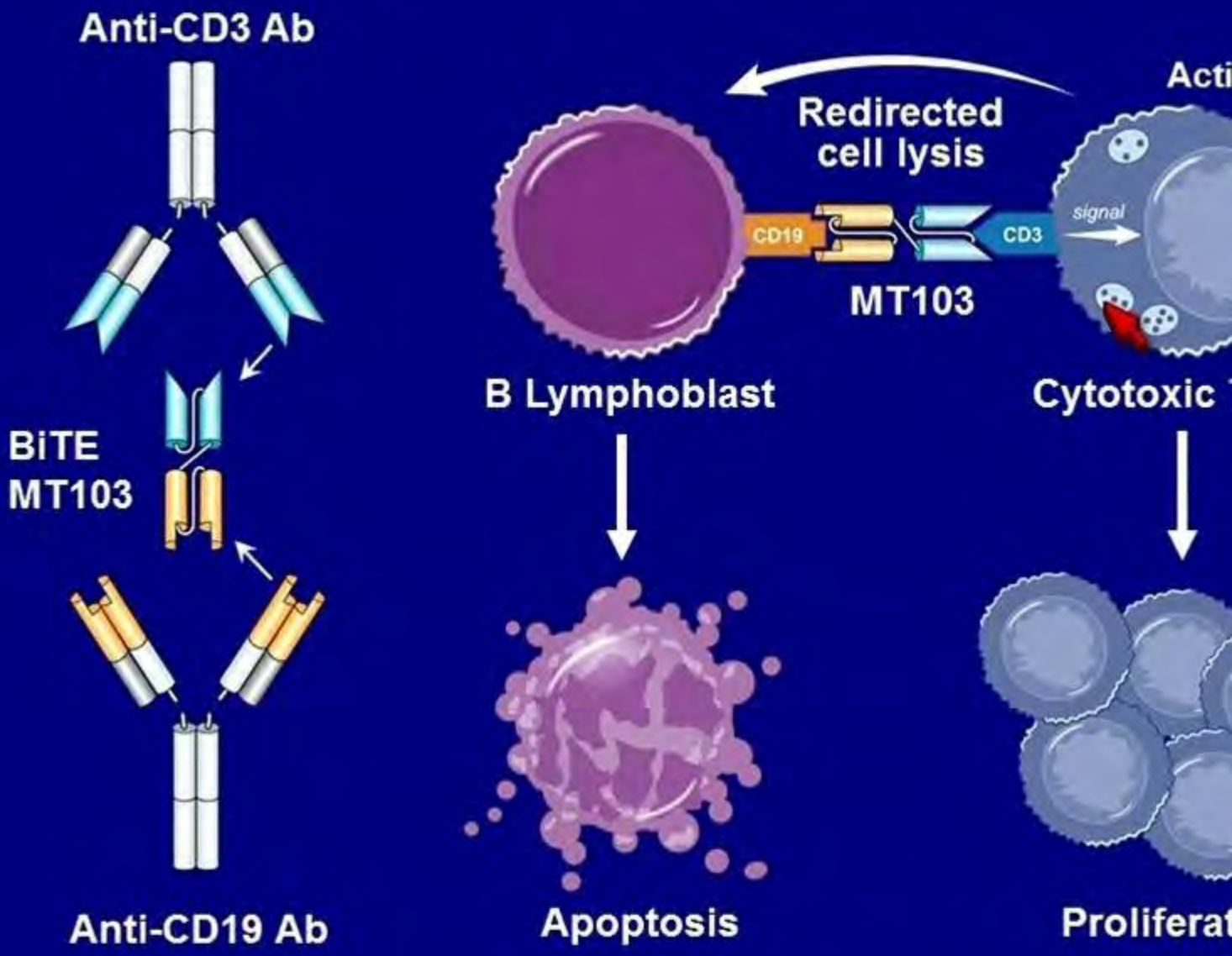
gura 1. Curve di Kaplan Meier



Probabilità di rimanere in remissione tra i pazienti che hanno conseguito la RC o la RCi. Hazard ratio: rischio di progressione o morte. ***B.*** *Progression-free survival. Hazard ratio: rischio di progressione, iniziare un nuovo trattamento, procedere a trapianto non in risposta o morte.* ***C.*** *Overall survival. Mod. da Kantarjian HM, et al. N Engl J Med 2016; 375: 740–753.*

Articolo successivo

Blinatumomab (MT103)® A T Cell-Engaging BiTE An



Adapted from: Nagorsen D et al; Blood 20

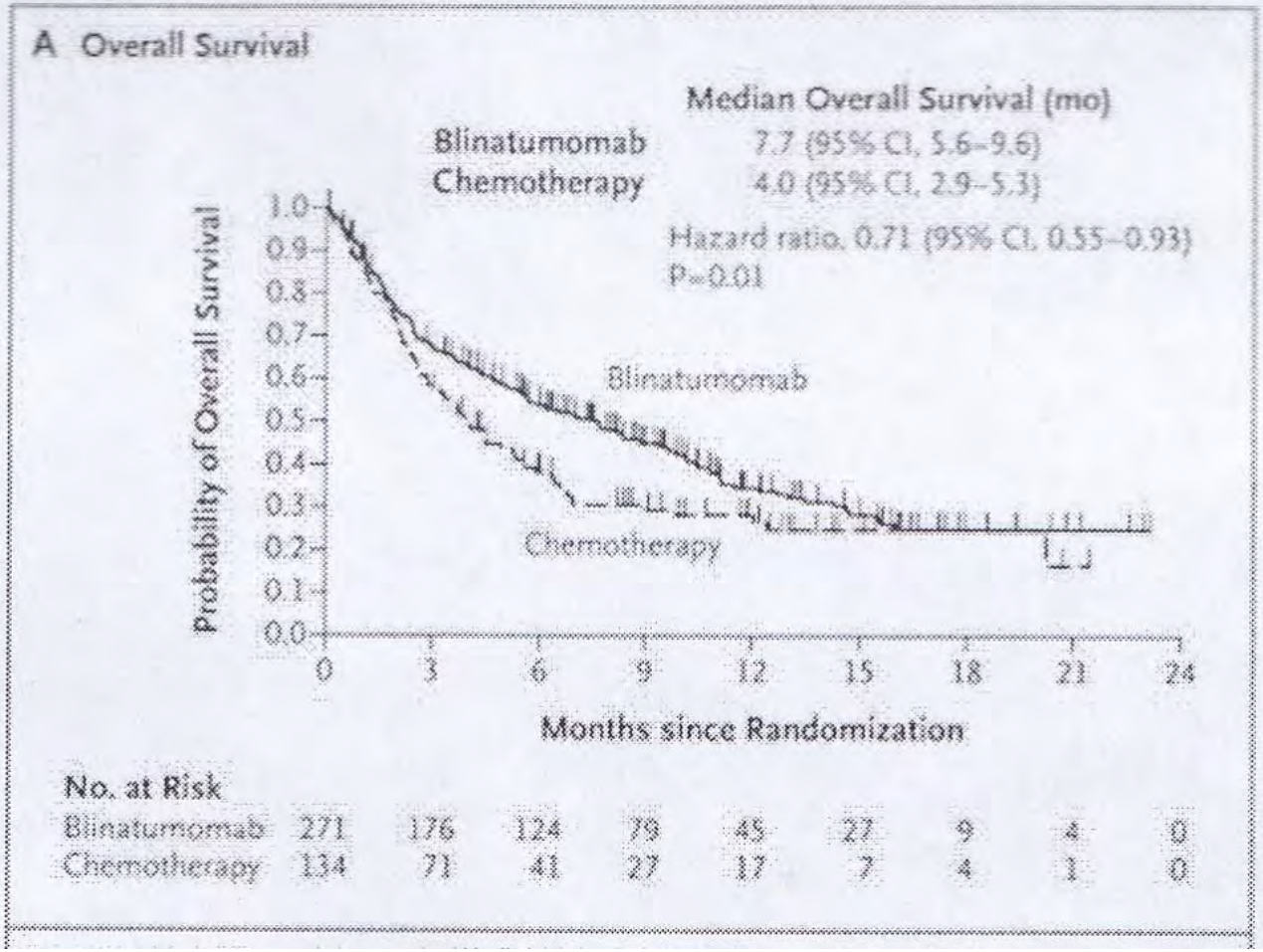

COME FUNZIONANO
GLI ANTICORPI BiTE
I BiTE conducono le cellule T
in prossimità delle cellule tumorali[2]
In questo modo le cellule T sono
in grado di riconoscerle e combatterle[2]
Una volta che le cellule T utilizzano
il ponte creato dai BiTE, si trovano vicine
alle cellule tumorali abbastanza
da poterle combattere[2]

BLINATUMOMAB

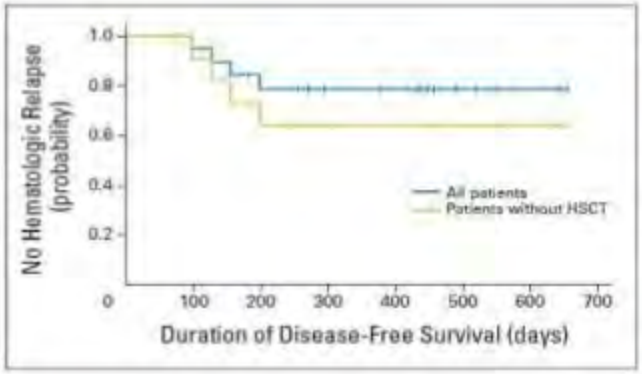
BLINCYTO è indicato in monoterapia per il trattamento di adulti con leucemia linfoblastica acuta (LLA) da precursori delle cellule B, recidivante o refrattaria, positiva per CD19, negativa per il cromosoma Philadelphia.

BLINCYTO è indicato in monoterapia per il trattamento di adulti con LLA da precursori delle cellule B negativa per il cromosoma Philadelphia, positiva per il CD19, in prima o seconda remissione completa con malattia minima residua (MRD), superiore o uguale allo 0,1%.

BLINCYTO è indicato in monoterapia per il trattamento di pazienti pediatrici di età pari o superiore a 1 anno con LLA da precursori delle cellule B, recidivante o refrattaria, positiva per CD19, negativa per il cromosoma Philadelphia, in recidiva dopo aver ricevuto almeno due precedenti terapie o in recidiva dopo allotrapianto di cellule staminali ematopoietiche.


A Overall Survival
Median Overall Survival (mo)
Blinatumomab 7.7 (95% CI, 5.6–9.6)
Chemotherapy 4.0 (95% CI, 2.9–5.3)
Hazard ratio, 0.71 (95% CI, 0.55–0.93)
P=0.01
Probability of Overall Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Blinatumomab
Chemotherapy
0 3 6 9 12 15 18 21 24
Months since Randomization
No. at Risk
Blinatumomab 271 176 124 79 45 27 9 4 0
Chemotherapy 134 71 41 27 17 7 4 1 0

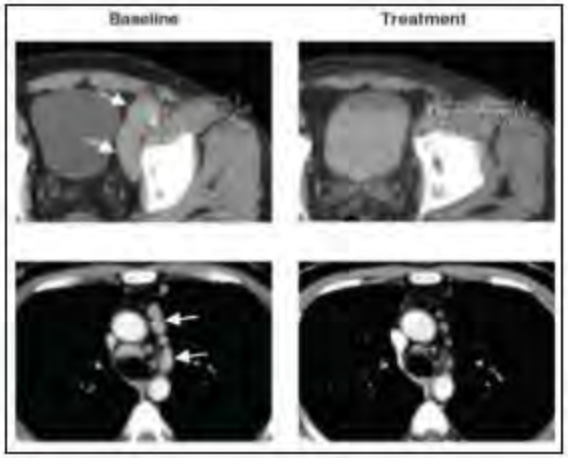
Blinatumomab in ALL & NHL



Blinatumomab on Chemotherapy-Refractory MRD in B-ALL

VOLUME 29 · NUMBER 18 · JUNE 20 2011

JOURNAL OF CLINICAL ONCOLOGY



Tumor Regression in Cancer Patients by Very Low Doses of a T Cell–Engaging Antibody

Ralf Bargou *et al.*
Science **321**, 974 (2008).
DOI: 10.1126/science.1158545

Science
AAAS

Blinatumomab in R/R ALL: Efficacy

Parameter, %	Pts (N = 64)	95% CI
Hematologic response		
▪ CR/CRh, first 2 cycles	45	33-58
• CR, first 2 cycles	28	18-41
• CRh, first 2 cycles	17	9-29
▪ CR/CRh, first cycle*	76	--
▪ Blast-free hypoplastic or aplastic BM	6	2-15
▪ Failure to respond	19	10-31
▪ Insufficient treatment duration	11	--
Treatment outcomes		
▪ AlloHSCT after CR or CRh*	24	--
▪ 100-day transplant-related mortality	14	2-67
Molecular response†	(n = 18)	
▪ MRD response	89	--
• Complete MRD response	83	--
▪ MRD nonresponse	6	--
▪ No MRD assessment	6	--

*n = 29. †Pts who achieved CR in first 2 cycles.

Stein AS, et al. ASH 2015. Abstract 861.

Slide credit: clinicaloptions.com

Blinatumomab in R/R ALL: RFS and OS

- Median RFS (n = 29): 7.4 mos (95% CI: 5.0-10.1)
- Median OS (N = 64): 8.5 mos (95% CI: 4.2-11.2)

Stein AS, et al. ASH 2015. Abstract 861.

Slide credit: clinicaloptions.com