Acute leukemias

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Acute leukemias

- **Heterogenous group of hematological malignant diseases with clonal proliferation and accumululation of blast cells in blood, bone marrow and/or other organs**
- **The pathogenesis of the disease is multistep and multifactorial**
- **Etiology is not know**
  - Genetic predisposition
  - Irradiation
  - Viruses
- **The cure is possible**
  - Aggressive chemotherapy
  - Targeted therapy
  - Allogeneic stem cell transplantation

Acute leukemias – clinical picture

- **General symptoms**
  - Fatique, loss of weight, fever
- **Symptoms of cytopenia**
  - Anemia: pallor, palpitation, vertigo
  - Neutropenia: bacterial or fugal infection
  - Thrombocytopenia: bleeding, petechie, ecchymoses
- **Signs related to organ infiltration**
  - Hepatosplenomegaly
  - Lymphadenopathy
- **Symptoms of leukostasis**
  - Respiratory distress
  - Altered mental status

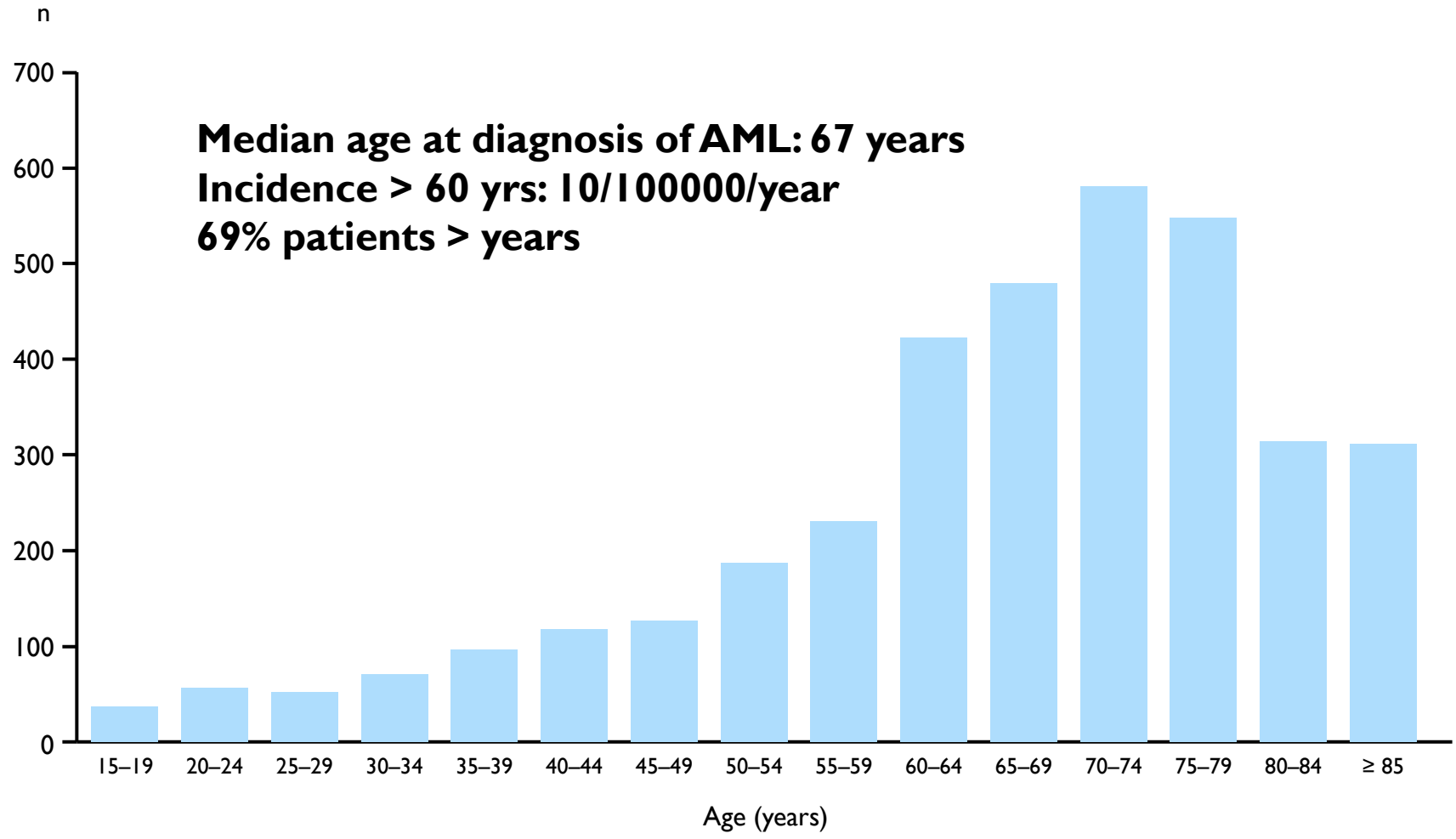
Acute leukemias

- **Acute myeloid leukemia** **>85%**
  - **Myelodysplastic syndrome**
- **Acute lymphoblastic leukemia** **<15%**

Acute myeloid leukemia (AML)

- **Definition**
  - **Heterogenous group of diseases characterized by clonal cells that exhibit maturation defect that correspond to stages in hematopoietic differentiation**
- **Diagnostic criteria**
  - **Bone marrow blast cells >20%**
  - **Clonal, recurrence cytogenetic abnormalities t(8;21), inv(16), t(16;16), t(15;17) regardless of blast cell percentage**

AML – incidence



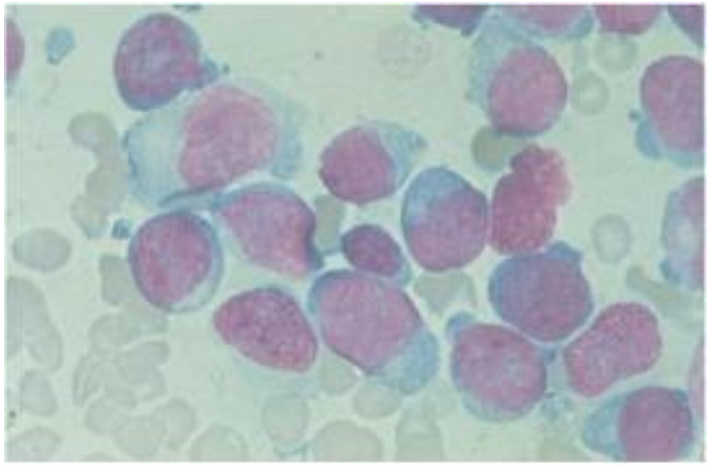
http://www.onkodin.de/e2/e51675/e52389/e52390/

AML - diagnosis

- **Test to establish the diagnosis**
  - Complete blood count with differential count
  - Bone marrow aspiration and biopsy
  - Immunophenotyping
- **Genetic analysis**
  - Cytogenetics
  - Screening for gene mutations
  - Screening for gene rearrangements
- **Additional tests/procedures**
  - Biochemistry, coagulation test, urine analysis
  - Viral test
  - Chest radiograph, abdominal sonography, ECG, ECHO
  - Demographic and medical history with comorbidites analysis
  - Detailed family history
  - Performance status (WHO)

AML - diagnosis

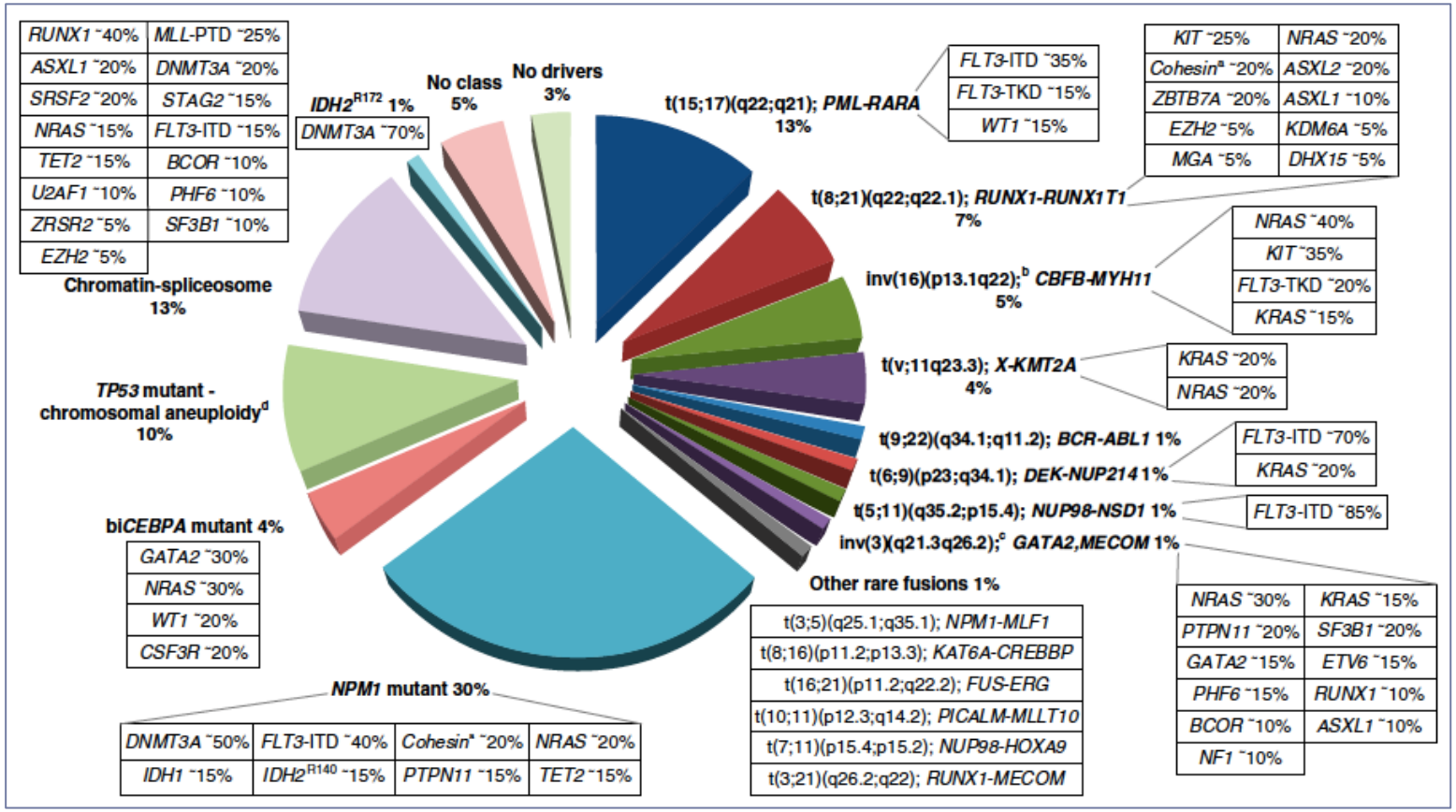
- **Complete blood count**
  - Anemia
  - Thrombocytopenia
  - Leukocytosis with neutropenia
- **Blood smear**
  - Blast cells
- **Bone marrow aspiration and biopsy**
  - Blast cells > 20%



AML - immunophenotyping

Expression of cell-surface and cytoplasmic markers	
Diagnosis of AML*	
Precursors†	CD34, CD117, CD33, CD13, HLA-DR
Granulocytic markers‡	CD65, cytoplasmic MPO
Monocytic markers§	CD14, CD36, CD64
Megakaryocytic markers‖	CD41 (glycoprotein IIb/IIIa), CD61 (glycoprotein IIIa)
Erythroid markers	CD235a (glycophorin A), CD36
Diagnosis of MPAL¶	
Myeloid lineage	MPO (flow cytometry, immunohistochemistry, or cytochemistry) or monocytic differentiation (at least 2 of the following: nonspecific esterase cytochemistry, CD11c, CD14, CD64, lysozyme)
T-lineage	Strong# cytoplasmic CD3 (with antibodies to CD3 ε chain) or surface CD3
B-lineage**	Strong# CD19 with at least 1 of the following strongly expressed: cytoplasmic CD79a, cCD22, or CD10 or weak CD19 with at least 2 of the following strongly expressed: CD79a, cCD22, or CD10

Genetic abnormalities in AML



Dohner et al. Blood 2017

AML classification

AML and related neoplasms	AML and related neoplasms (cont'd)
AML with recurrent genetic abnormalities	Acute myelomonocytic leukemia
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	Acute monoblastic/monocytic leukemia
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	Pure erythroid leukemia#
Acute promyelocytic leukemia with *PML-RARA**	Acute megakaryoblastic leukemia
AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*†	Acute basophilic leukemia
AML with t(6;9)(p23;q34.1); *DEK-NUP214*	Acute panmyelosis with myelofibrosis
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*	Myeloid sarcoma
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*‡	Myeloid proliferations related to Down syndrome
Provisional entity: AML with *BCR-ABL1*	Transient abnormal myelopoiesis
AML with mutated *NPM1*§	Myeloid leukemia associated with Down syndrome
AML with biallelic mutations of *CEBPA*§	Blastic plasmacytoid dendritic cell neoplasm
Provisional entity: AML with mutated *RUNX1*	**Acute leukemias of ambiguous lineage**
AML with myelodysplasia-related changes‖	Acute undifferentiated leukemia
Therapy-related myeloid neoplasms¶	MPAL with t(9;22)(q34.1;q11.2); *BCR-ABL1***
AML, NOS	MPAL with t(v;11q23.3); *KMT2A* rearranged
AML with minimal differentiation	MPAL, B/myeloid, NOS
AML without maturation	MPAL, T/myeloid, NOS
AML with maturation	

WHO 2016

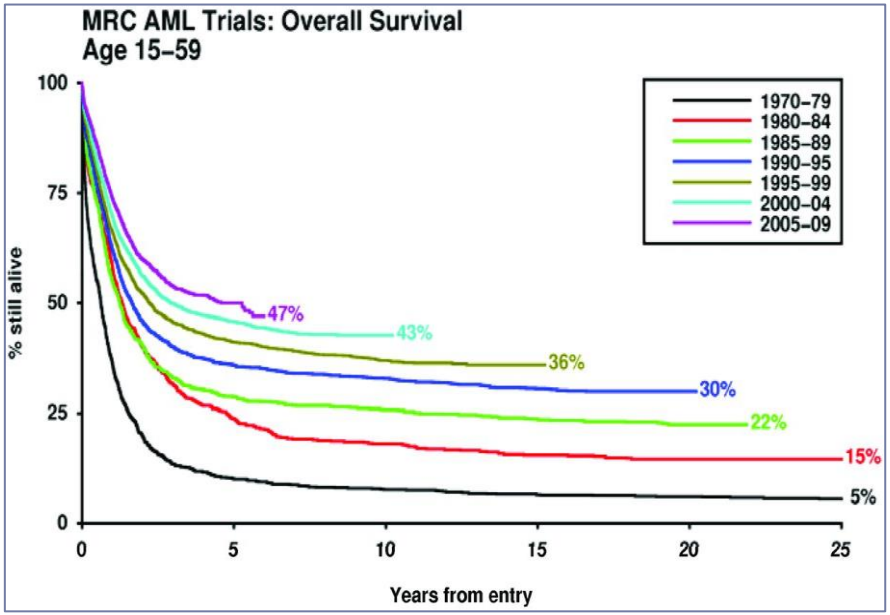
AML classification

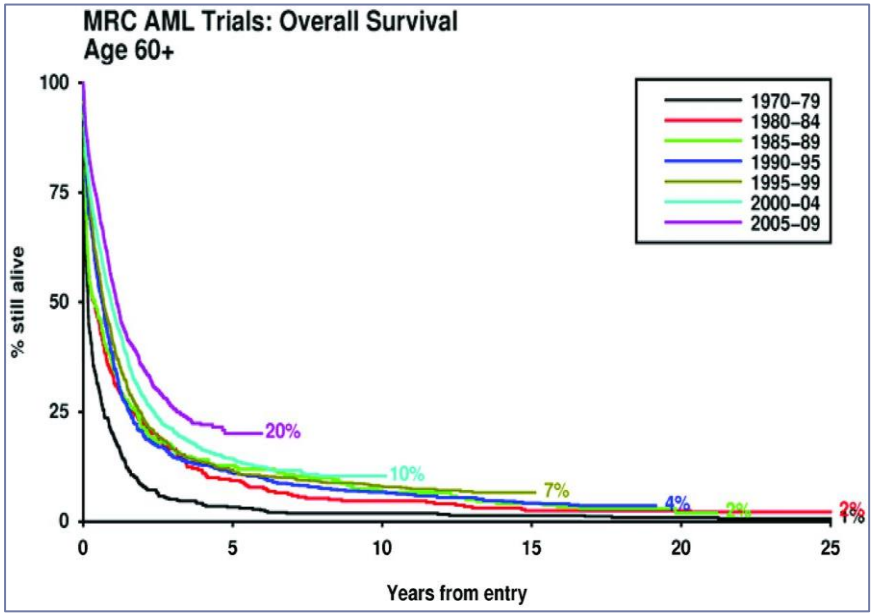
WHO classification
Classification*
Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction
AML with germ line *CEBPA* mutation
Myeloid neoplasms with germ line *DDX41* mutation†
Myeloid neoplasms with germ line predisposition and preexisting platelet disorders
Myeloid neoplasms with germ line *RUNX1* mutation†
Myeloid neoplasms with germ line *ANKRD26* mutation†
Myeloid neoplasms with germ line *ETV6* mutation†
Myeloid neoplasms with germ line predisposition and other organ dysfunction
Myeloid neoplasms with germ line *GATA2* mutation
Myeloid neoplasms associated with bone marrow failure syndromes
Juvenile myelomonocytic leukemia associated with neurofibromatosis, Noonan syndrome, or Noonan syndrome-like disorders
Myeloid neoplasms associated with Noonan syndrome
Myeloid neoplasms associated with Down syndrome†
Guide for molecular genetic diagnostics‡
Myelodysplastic predisposition/acute leukemia predisposition syndromes
CEBPA, *DDX41*, *RUNX1*, *ANKRD26*, *ETV6*, *GATA2*, *SRP72*, 14q32.2 genomic duplication (*ATG2B*/*GSKIP*)
Cancer predisposition syndromes§
Li Fraumeni syndrome (*TP53*)
Germ line *BRCA1*/*BRCA2* mutations
Bone marrow failure syndromes
Dyskeratosis congenita (*TERC*, *TERT*)
Fanconi anemia

AML – risk factors

- **General characteristic**
  - Age
  - Secondary AML to MDS or MPN
- **Cytogenetic factors**
  - Chromosomal anomalies
- **Gene mutation**
- **Gene expression**
  - Multidrug resistance: MRD1; MRP1&2
  - WT1 gene expression
  - BCL-2&Bax
  - Topoizomerase II

AML – OS according to age



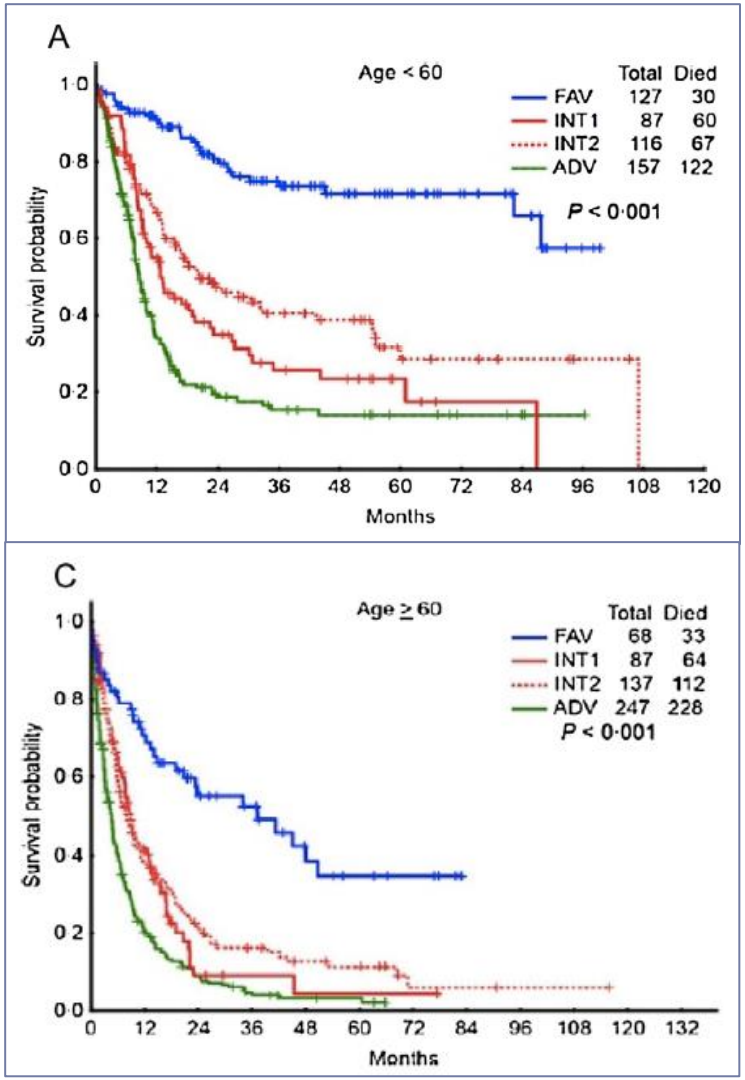


Burnett et al. Hematology 2012

Cytogenetic abnormalities in AML

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Dohner et al. Blood 2017



Tamamyan et al CROH 2017

Treatment strategy in AML

Goal of treatment – complete remission

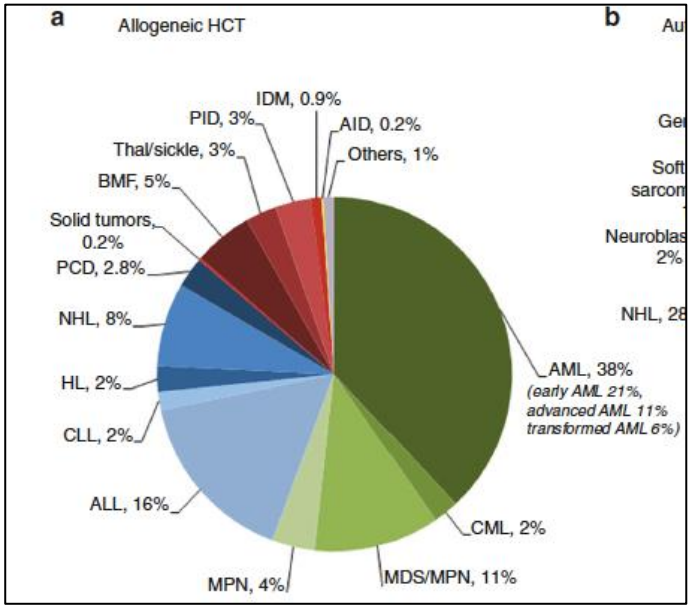
- No blast cell in bone marrow and peripheral blood (MRD-)
- Blood count: normal

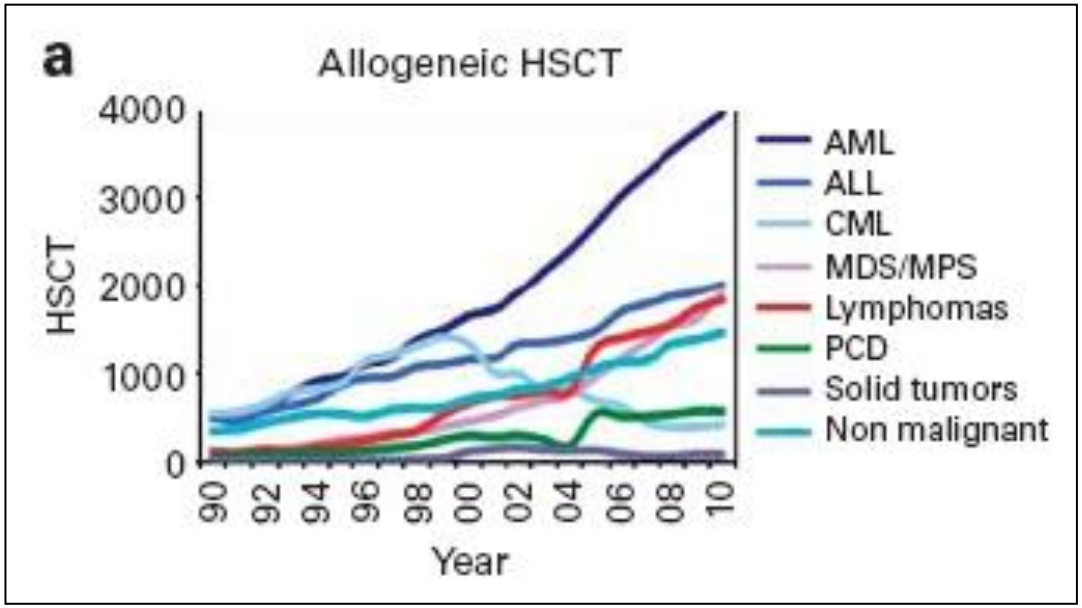
- **Remission induction therapy**
- **Post-remision therapy**
  - consolidation
  - hematopoietic stem cell transplantation
- **Treatment of refractory/relapsed disease**
- **Treatment of complication**

AML treatment

- **Patients eligible to intensive chemotherapy**: complete remission in 75%
  - Induction chemotherapy: daunorubicine + cytarabine (3+7)
    - variants
  - Consolidation therapy
    - Favorable risk group: 2-4 cycles of HD-AraC
    - Intermediate risk group: HD-AraC + alloSCT (or 2-4 cycles of HD-AraC or autoSCT)
    - High risk group: HD-AraC + alloSCT
- **Patients not qualified for intensive chemotherapy**
  - Azacitidine
  - Decitabine
  - Low-dose AraC
  - Best supportive care

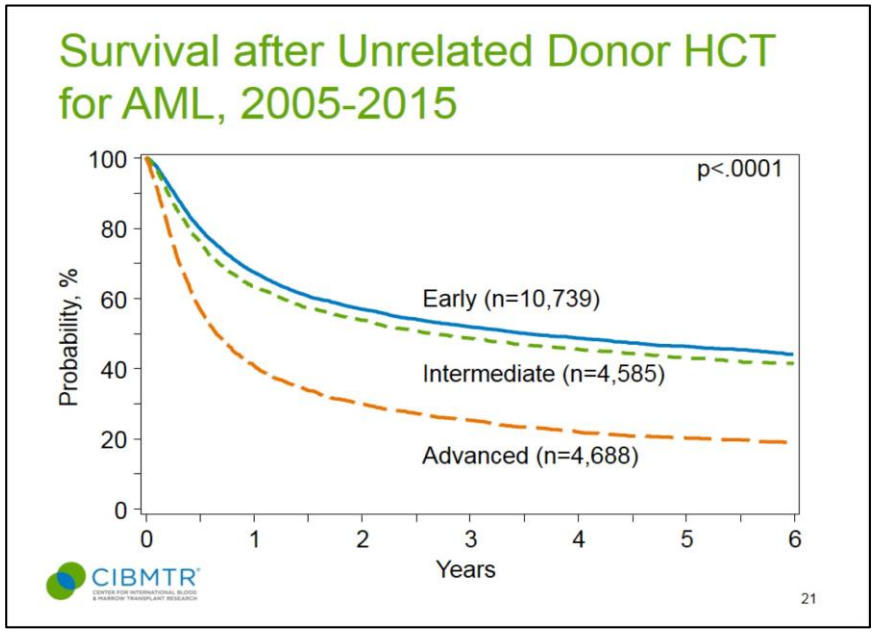
alloSCT in Europe - EBMT

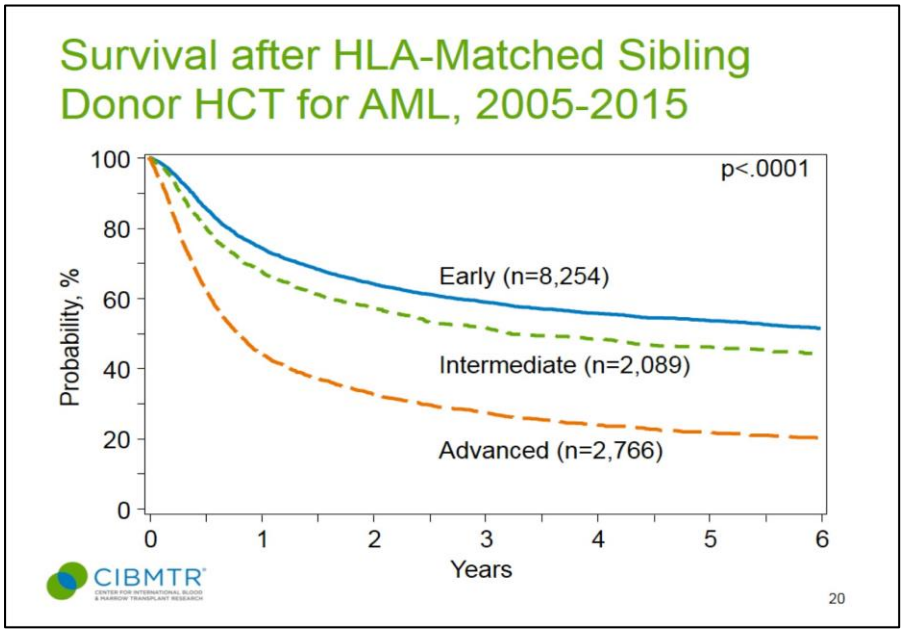




Passweg et al. BMT 2014, BMT 2018

AlloSCT for AML





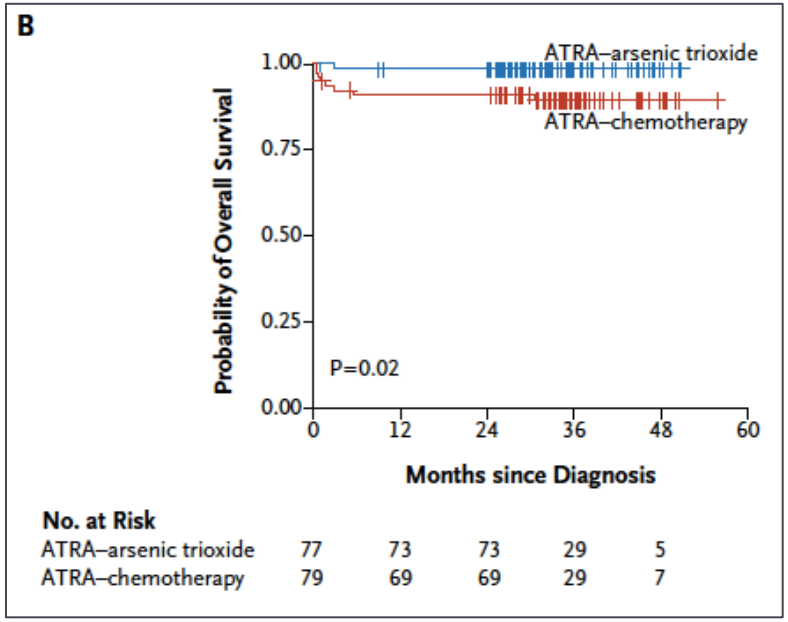
CIBMTR Newsletter 2017

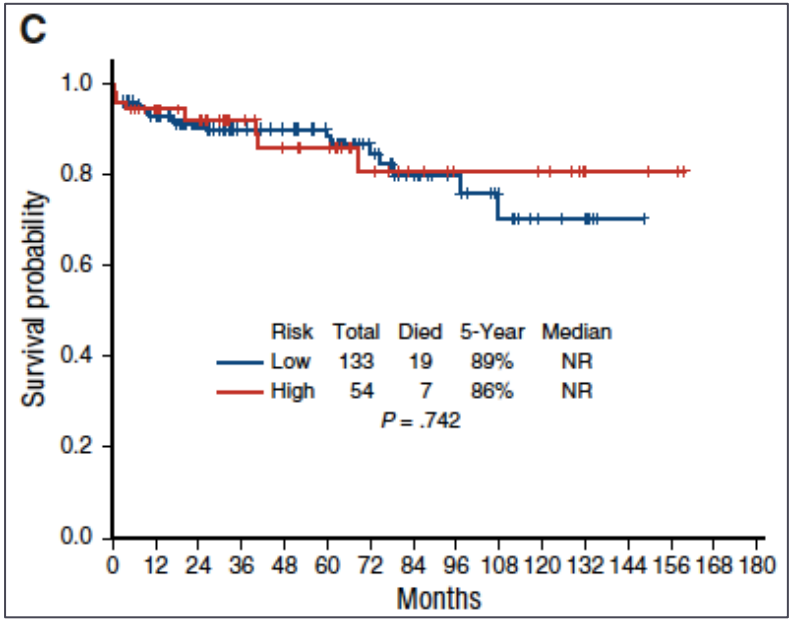
AML with t(15:17) PML/RAR-alfa

- **Induction, consolidation and maintenance is based on all-*trans* retinoid acid (ATRA) given in combination** (ATRA+ATO, ATRA+chemo, ATRA+ATO+GO)
- **CR >90% and cure rate >80%**
- **ATRA induces maturation of promielocytes and prevent DIC**
- **Refractory/relapsed disease: arsenic trioxide (ATO)**
- **AlloSCT only in patients MRD+ with relapsed disease**

Acute promyelocytic leukemia

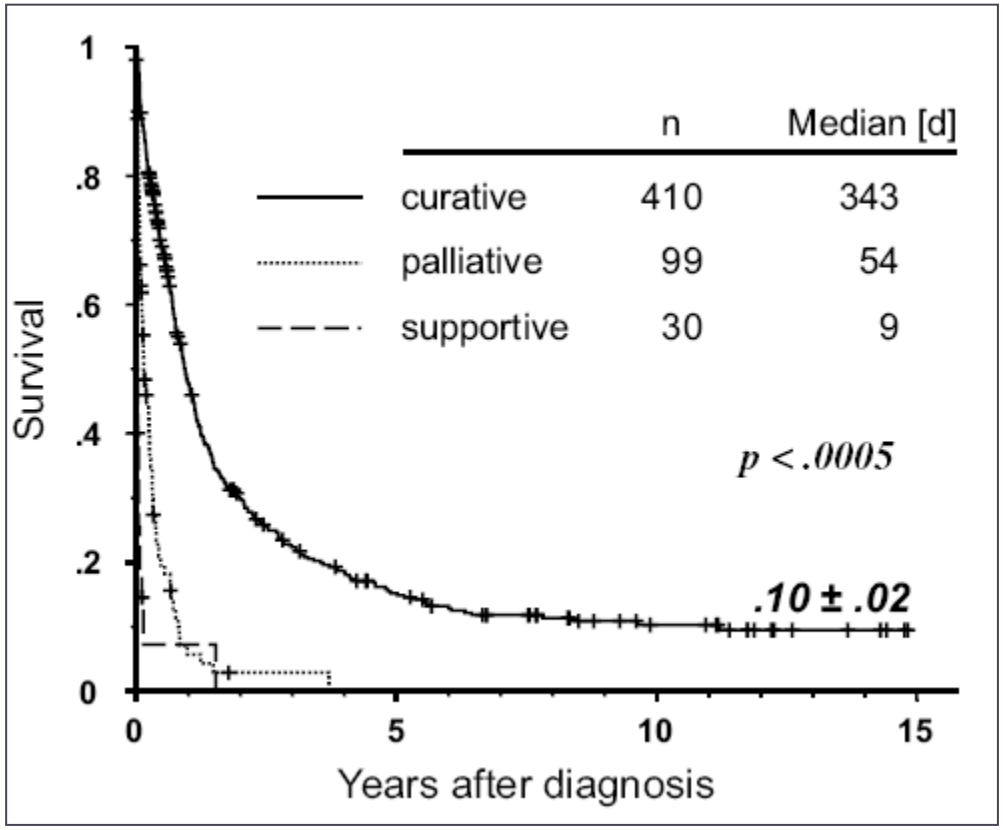
- **APL – t(15;17); *PML/RARA* gene**
- **Induction and consolidation based on all-*trans* retinoic acid (ATRA) in combination with arsenic trioxide (ATO) or anthracyclin (idarubicine)**
- **CR >95%**





Lo-Cocco et al. NEJM 2013, Abaza et al. Blood 2017

AML in older age



Intensive chemotherapy

CR: 66,8%

2 yrs OS: 30%

Risk factors

- performance status
- cytogenetics

Palliative treatment

LD-AraC

IDA + thioguanine

Etoposide

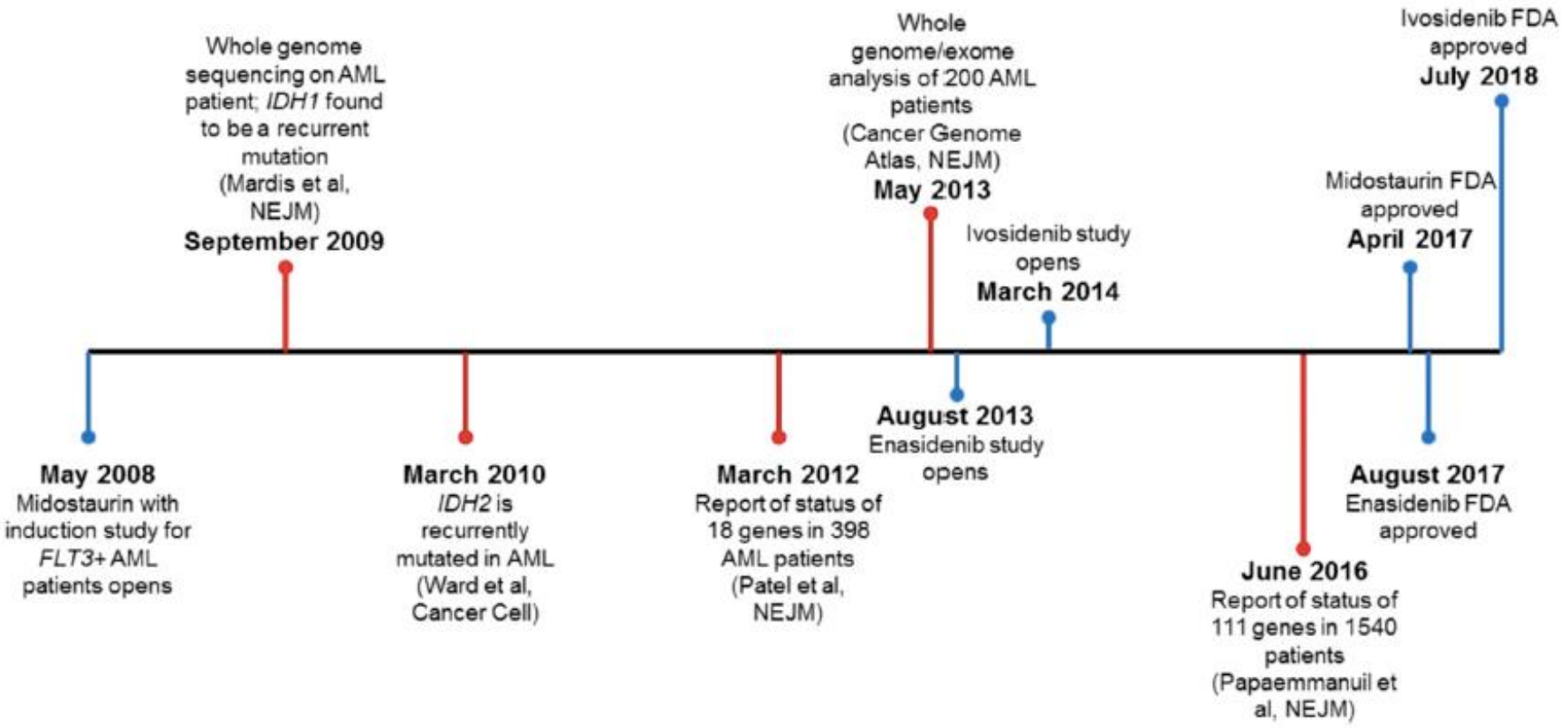
OS of AML pts >60 years according to treatment arm. AML97 OSHO Study.

Kahl et al. J Cancer Res Clin Oncol 2016

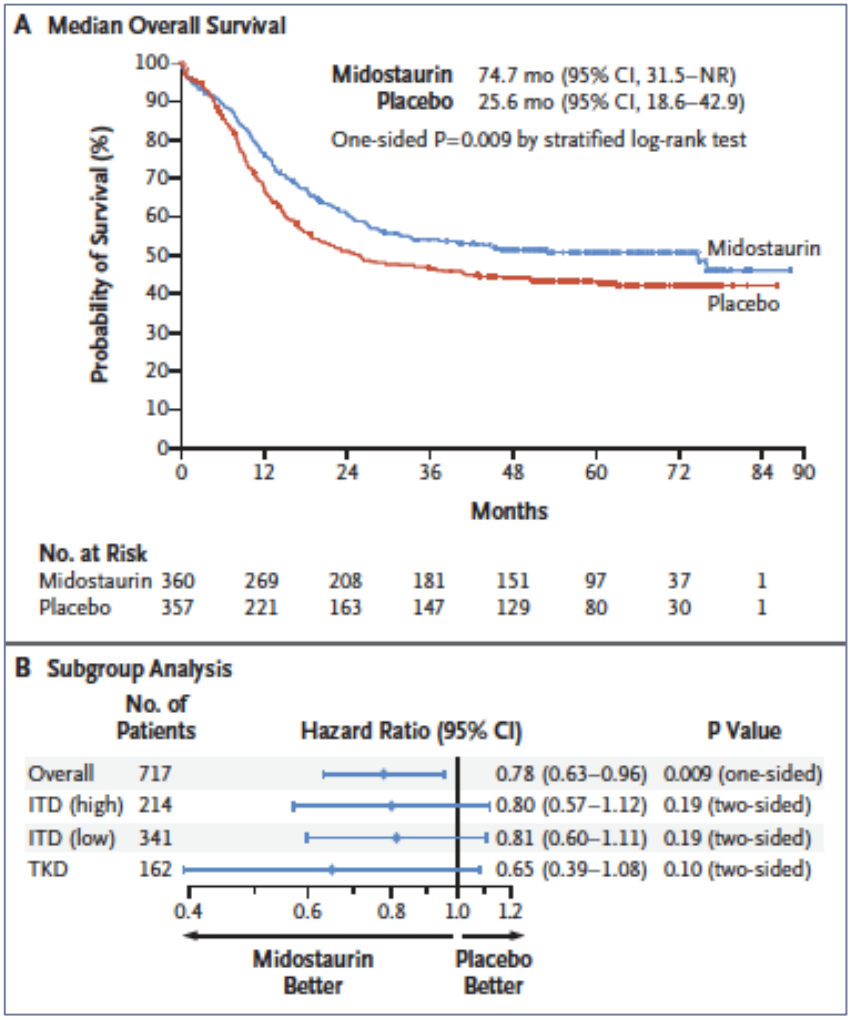
AML - therapy

Protein kinase inhibitors	• FLT3 inhibitors (midostaurin, quizartinib, gilteritinib, crenolanib) • KIT inhibitors • PI3K/AKT/mTOR inhibitors • Aurora and polo-like kinase inhibitors, CDK4/6 inhibitors, CHK1, WEE1, and MPS1 inhibitors • SRC and HCK inhibitors
Epigenetic modulators	• New DNA methyltransferase inhibitors (SGI-110) • HDAC inhibitors • IDH1 and IDH2 inhibitors • DOT1L inhibitors • BET-bromodomain inhibitors
Chemotherapeutic agents	• CPX-351 • Vosaroxin • Nucleoside analogs
Mitochondrial inhibitors	• Bcl-2, Bcl-xL, and Mcl-1 inhibitors • Caseinolytic protease inhibitors
Therapies targeting oncogenic proteins	• Fusion transcripts targeting • EVI1 targeting • NPM1 targeting • Hedgehog inhibitors
Antibodies and immunotherapies	• Monoclonal antibodies against CD33, CD44, CD47, CD123, CLEC12A • Immunoconjugates (eg, GO, SGN33A) • BiTEs and DARTs • CAR T cells or genetically engineered TCR T cells • Immune checkpoint inhibitors (PD-1/PD-L1, CTLA-4) • Anti-KIR antibody • Vaccines (eg, WT1)
Therapies targeting AML environment	• CXCR4 and CXCL12 antagonists • Antiangiogenic therapies

AML - therapy


Whole genome sequencing on AML patient; *IDH1* found to be a recurrent mutation (Mardis et al, NEJM)
September 2009
Whole genome/exome analysis of 200 AML patients (Cancer Genome Atlas, NEJM)
May 2013
Ivosidenib FDA approved
July 2018
Midostaurin FDA approved
April 2017
Ivosidenib study opens
March 2014
May 2008
Midostaurin with induction study for *FLT3*+ AML patients opens
March 2010
IDH2 is recurrently mutated in AML (Ward et al, Cancer Cell)
March 2012
Report of status of 18 genes in 398 AML patients (Patel et al, NEJM)
August 2013
Enasidenib study opens
August 2017
Enasidenib FDA approved
June 2016
Report of status of 111 genes in 1540 patients (Papaemmanuil et al, NEJM)

Midostaurin



Midostaurin – phase 3 study RATIFY

- Oral multitargeted kinase inhibitor
- AML *de novo* 717 patients
- *FLT3* 30%

Combination therapy

- Standard chemotherapy
- Midostaurin 2 x 50 mg 8-21 days or placebo

Maintenance therapy

Efficacy outcomes

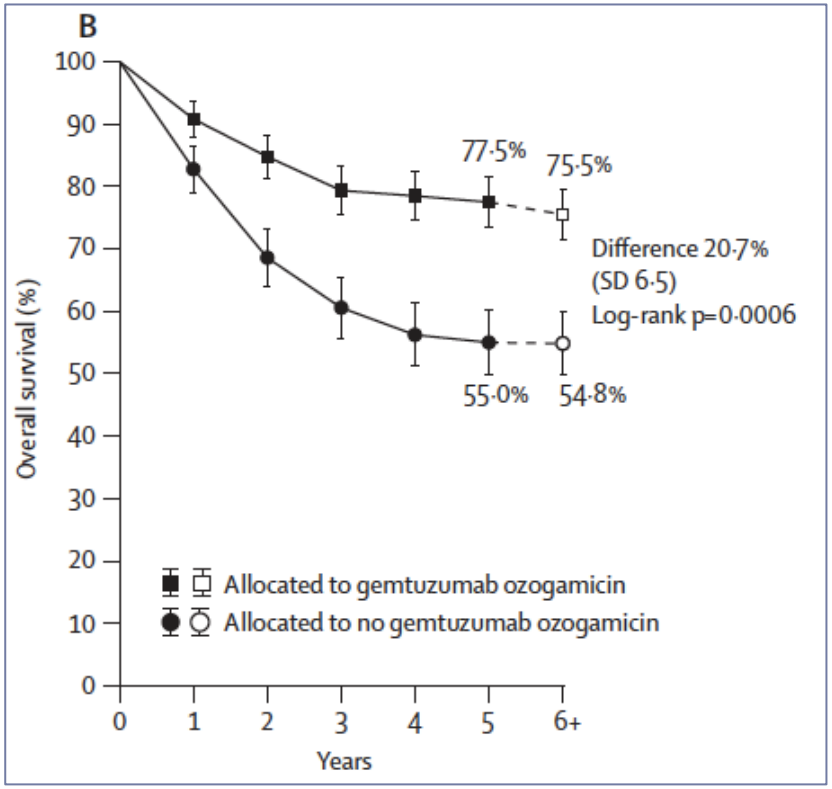
- CR 58.9% vs 53.5%
- Median OS 74.7 vs 25.6 months
- 4-yrs OS 51.4% vs 44.3%

Safety and tolerance

- Anemia
- Nausea
- Skin rash

Stone et al. NEJM 2017

Gemtuzumab ozogamycin



Gemtuzumab ozogamicin

- Monoclonal antibody to CD33 linked to calicheamicin
- AML *de novo*
- Combination therapy

Efficacy

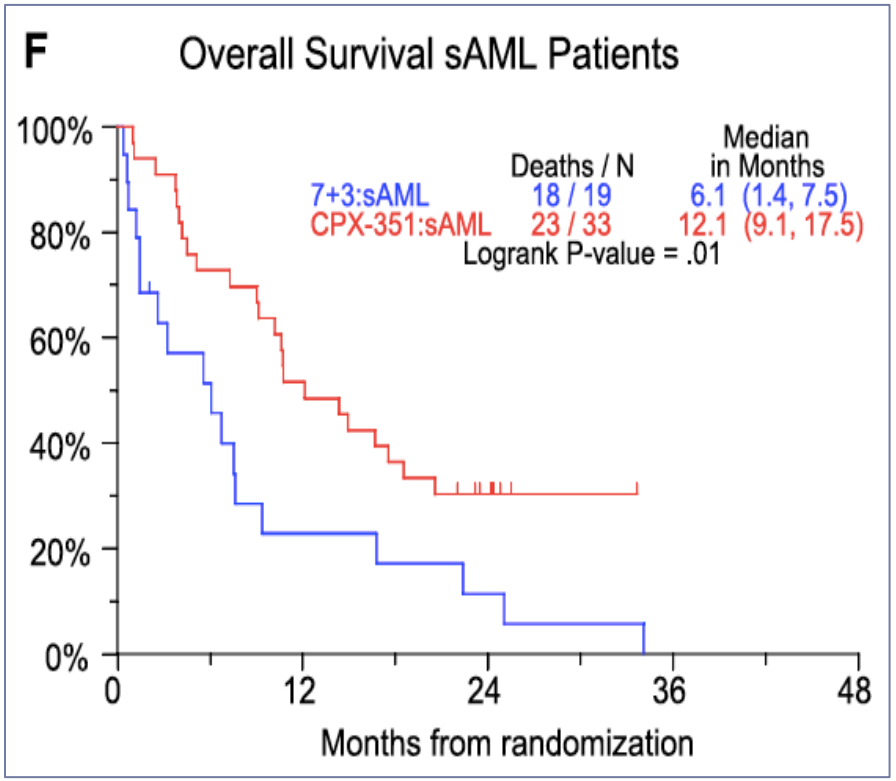
• 6-yrs OS	32.2 vs 35.6%
• 6-yrs OS LR-IR	54.8 vs 75.5%

Safety: 3 mg/m²

• VOD	0.5%
• Increase AlAT	7%
• Nephrotoxicity	1%
• Hematuria	1%

Hills et al. Lancet Oncol 2014. Burnett et al. Heamatologica 2016

CPX-351



CPX-351

- Liposomal formulation of cytarabine:daunorubicin (1:5) vs 3+7
- AML – phase 2 126 patients
- AML >60 yrs – phase 3 309 patients

Efficacy

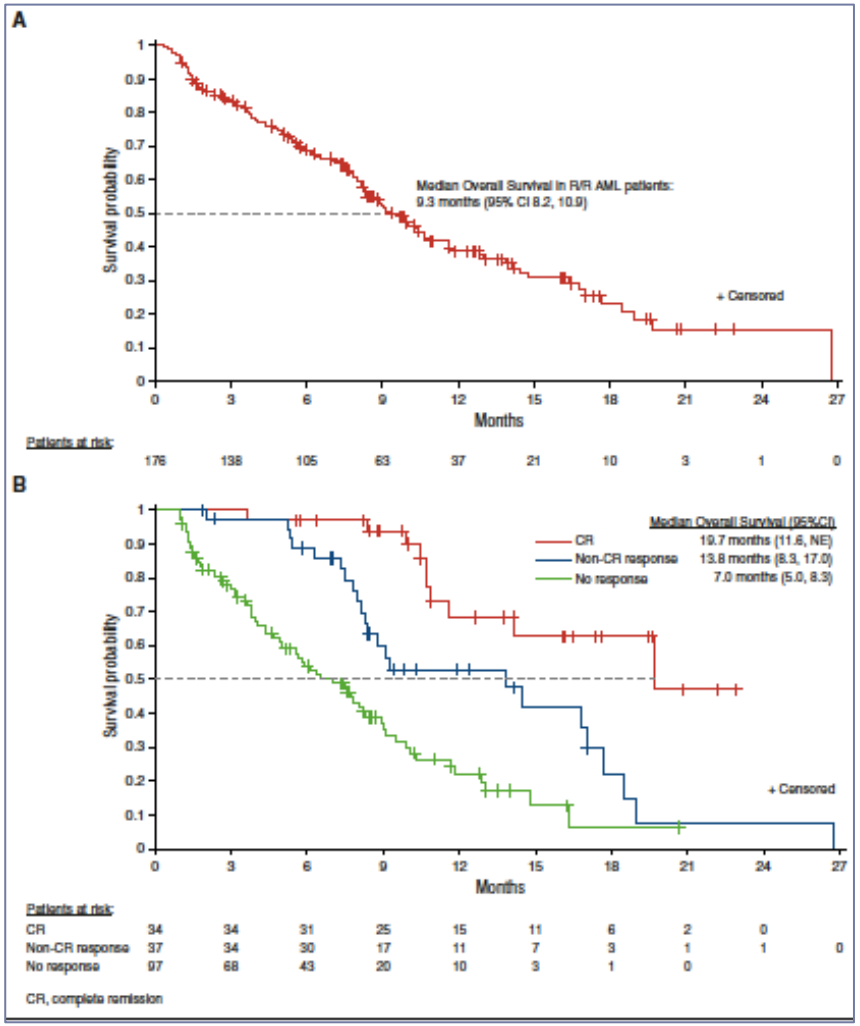
- ORR 66.7 vs 51.2%
- OS 14.7 vs 12.9 mo
- OS for sAML 12.1 vs 6.1 mo

Safety

- Slow hematologic recovery
- Infection complication

Lancet et al. Blood 2014. Lancet et al. JCO suppl 2016

Enasidenib



Enasidenib – phase ½ study

- Oral selective inhibitor of mut *IDH2* enzymes
- AML relapsed/refractory
- mut*IDH2* 12%
- Dosing: 100 mg selected

Efficacy

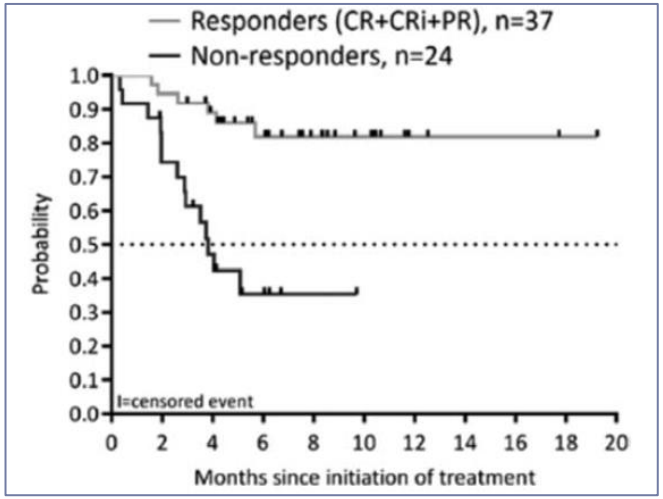
- ORR 40.3%
- CR 19.3%
- Early response 1.9 mo
- Median response duration 5.8 mo
- Median OS 9.3 mo
- OS for patients with CR 19.7 mo
- 1-yr OS 39%

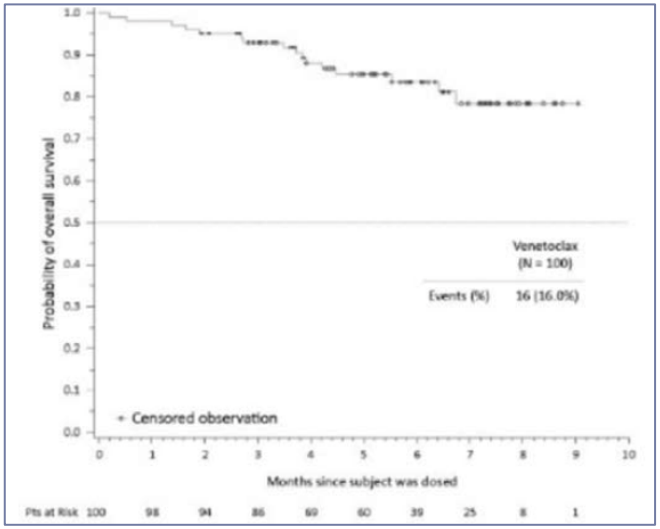
Safety

- Hyperbilirubinemia 12%
- Differentiation syndrome 7%

Stein et al. Blood 2017

Venetoclax





Venetoclax

- Oral bcl-2 inhibitor
- AML >65 yrs
  - HMA 61 patients
  - LDAraC 100 patients

Efficacy

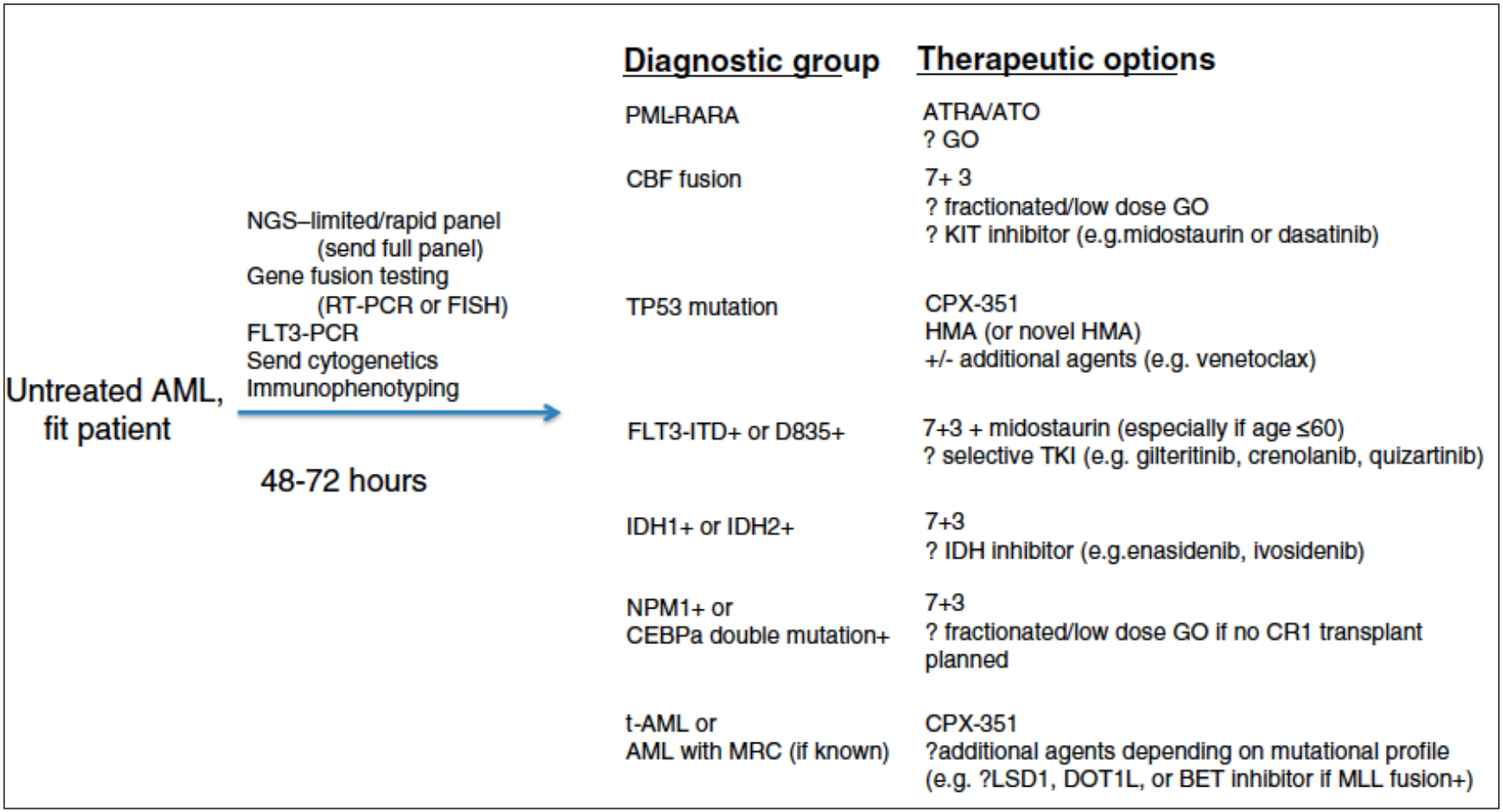
- HMA combination
  - ORR 68%
- LDAraC combination
  - ORR 61%

Safety

- Nausea
- Diarrhoea
- Neutropenic fever
- Hypertension

Pratz et al. Haematologica 2017 suppl. Wei al. Haematologica suppl 2017

Treatment of AML

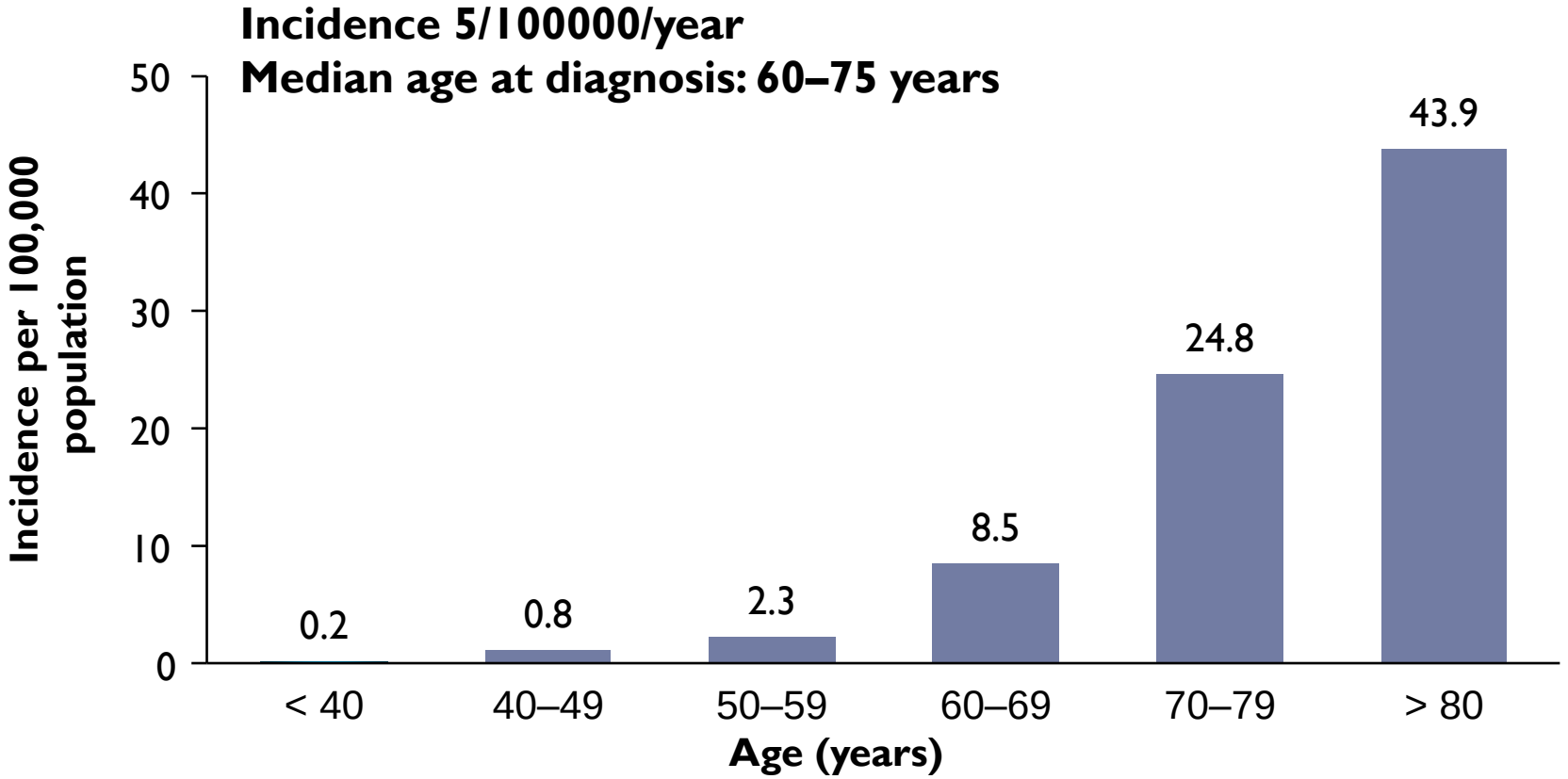


Perl A. ASH. Hematology 2017

Myelodysplastic syndrome (MDS)

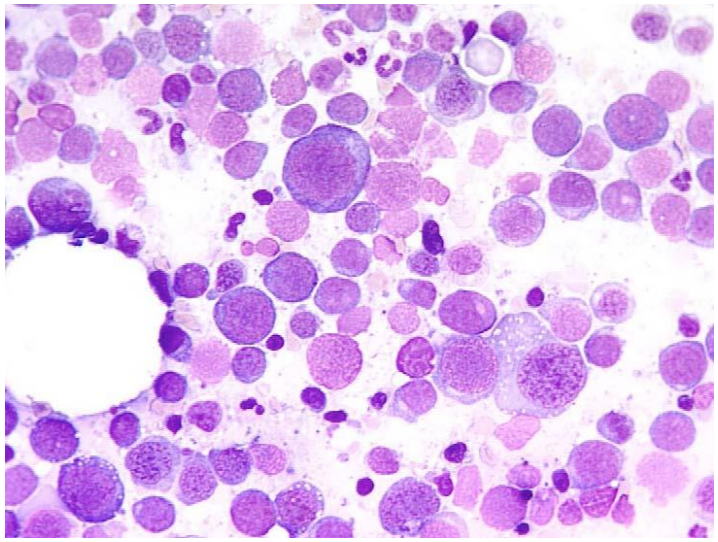
- **Group of hematological clonal diseases characterised by**
  - **Ineffective hematopoiesis**
  - **Peripheral blood cytopenia**
  - **Increased risk for AML transformation**
- **Blast cells in bone marrow < 20%**
- **Heterogenous clinical picture**
- **Heterogenous genetic profile**

MDS incidence



MDS - diagnosis

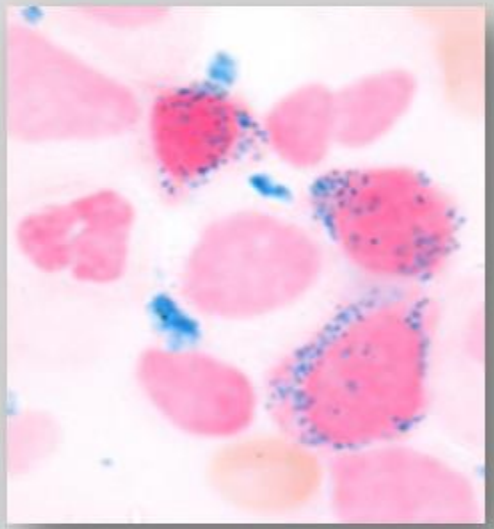
- **Complete blood count with differential count**
  - Cytopenia: anemia and/or thrombocytopenia and/or neutropenia
- **Peripheral blood smear**
  - Cell dysplasia
- **Bone marrow aspiration and biopsy**
  - Cell dysplasia
  - Blast cells <20%
- **Cytogenetics**
- **Immunophenotyping**
- **Screening for gene mutations**



Typical Manifestations of Dysplasia in MDS

Dysplastic erythropoiesis:

- Ring Sideroblasts

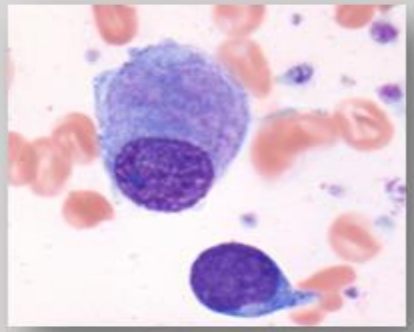


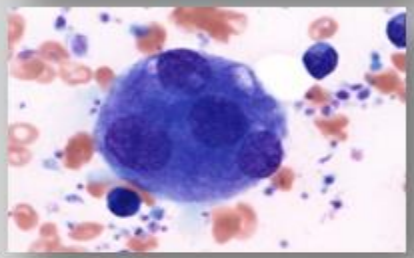
Dysplastic granulopoiesis:

- Pseudo-PelgerAnomaly

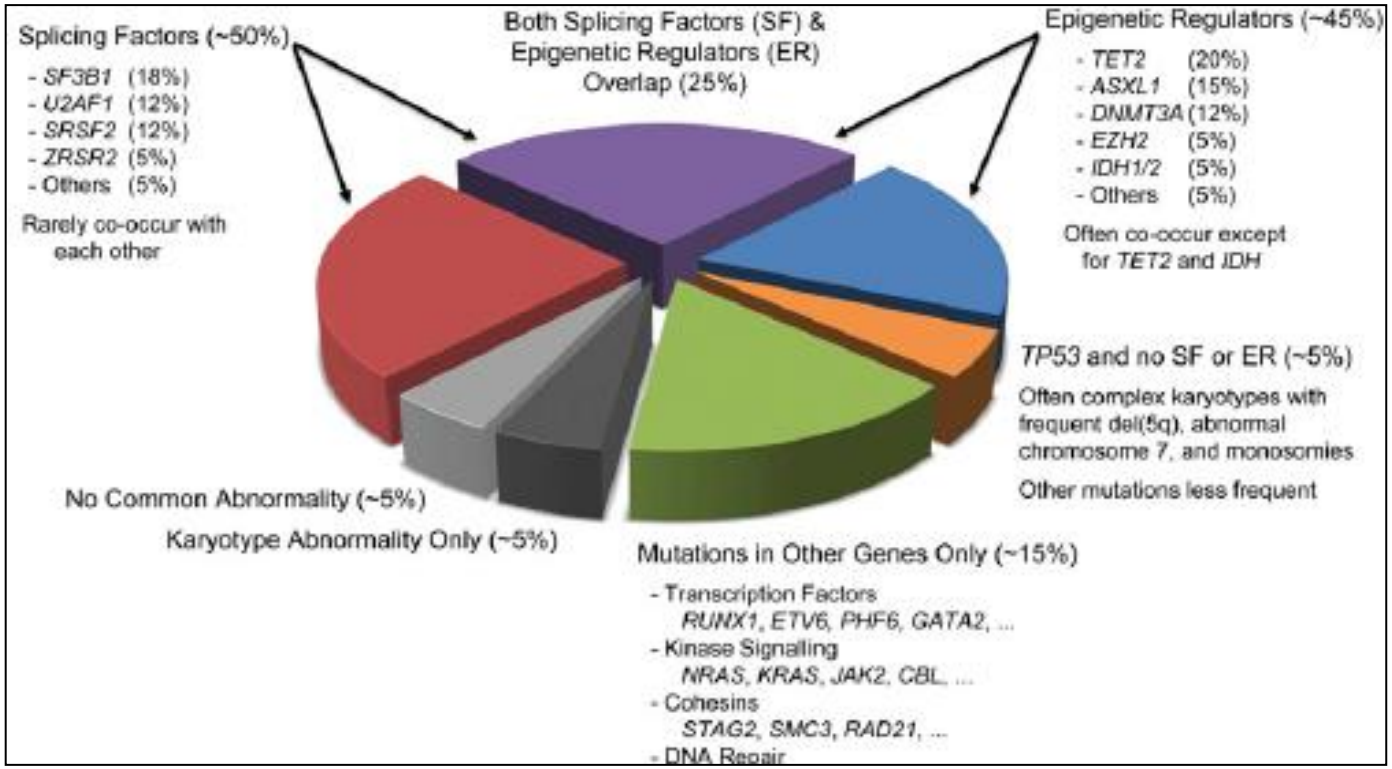
Dysplastic megakaryocytes:

- Microforms
- Mono- binucleated forms
- Separate nuclei





Genetic abnormalities in MDS



Mutations and karyotypic abnormalities in MDS > 80%.
Bejar&Steensma Blood 2014

MDS - classification

Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable

WHO. Arber et al. Blood 2016

Prognosis in MDS: IPSS-R

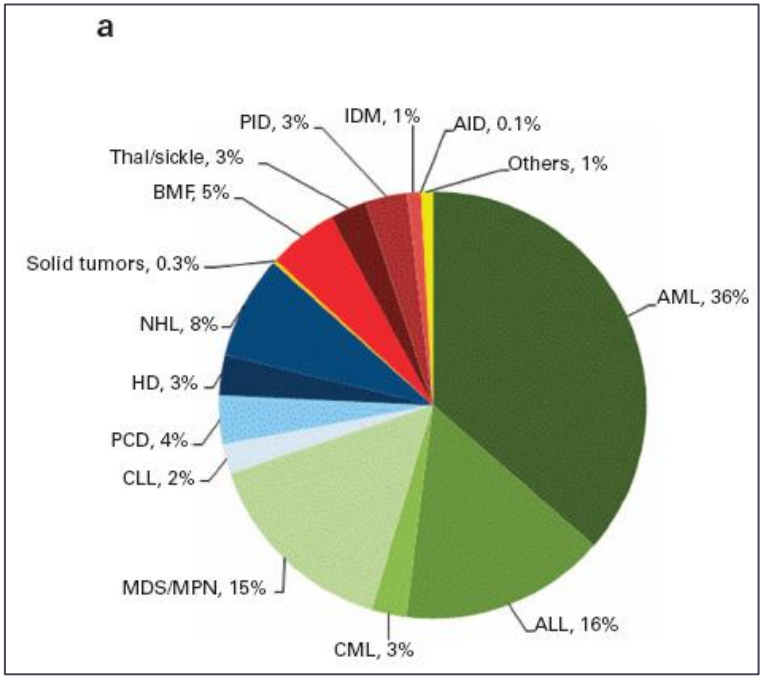
Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤ 2	—	> 2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50-< 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

Prognostic subgroups, % of patients	Cytogenetic abnormalities
Very good (4%*/3%†)	−Y, del(11q)
Good (72%*/66%†)	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate (13%*/19%†)	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor (4%*/5%†)	−7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex: 3 abnormalities
Very poor (7%*/7%†)	Complex: > 3 abnormalities

Greenberg et al. Blood 2012

MDS therapy

- **Conventional therapies**
  - Chemotherapy
    - Intensive
    - Low-dose
  - Hypomethylating agents
  - Immunomodulators
  - Growth factors
  - Blood products transfusion
- **AlloSCT - curative procedure**
  - **RIC alloSCT**
  - **Age of recipients**
  - **Alternative donors**
  - **Supportive care**



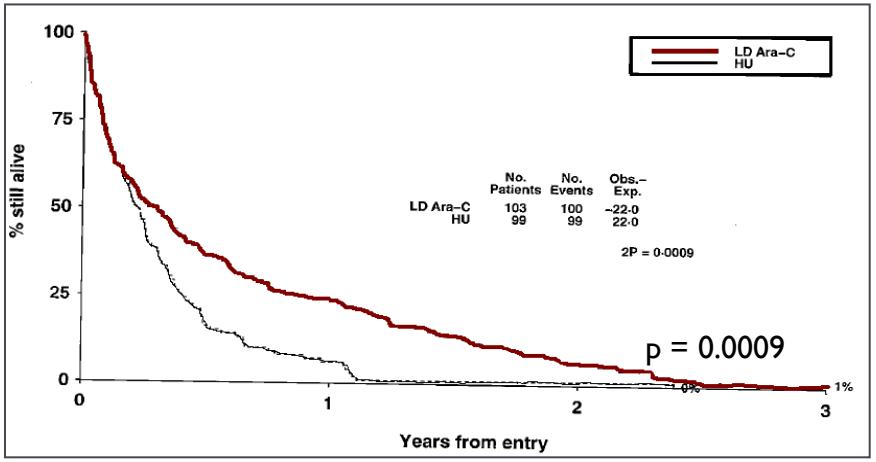
Passweg et al. BMT 2016

MDS – paliative therapy

Analysis of 36 studies (12370 pts) with AML/MDS (median age 70 years)

Treatment	Survival (weeks)
Low dose chemotherapy	12
Supportive chemotherapy	7.5

Median survival: LDAraC vs hydroxyurea: 4 months

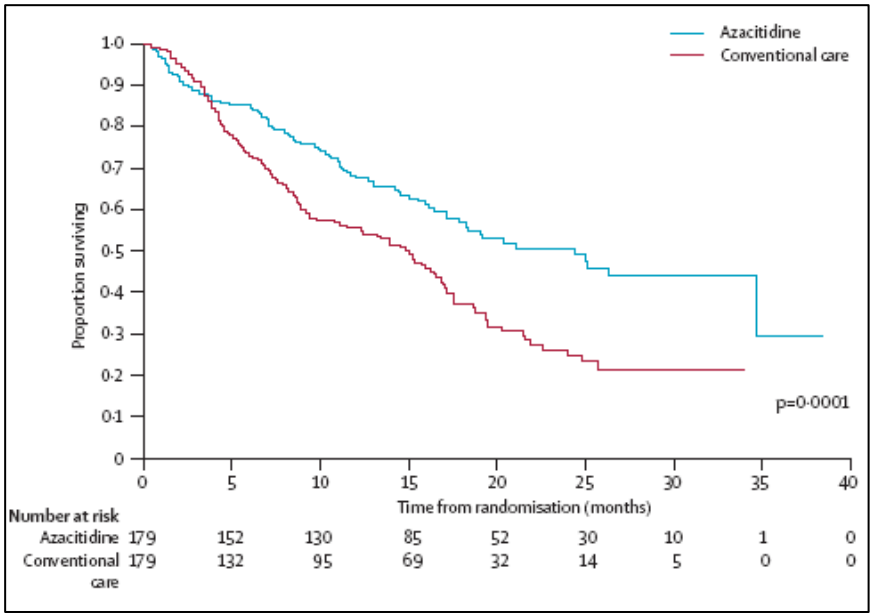


Deschler B, et al. Haematologica 2006
Burnett AK et al. Cancer 2007

Azacitidine

- **5-azacitidine – analog of cytosine, DNA methylotransferase inhibitor (DNMT)**
- **Mechanism of action**
  - Dose-dependent activity
  - Direct cytotoxicity and apoptotic effect on malignant cells (high dose)
  - DNA demethylation leading to re-expression of silenced tumor suppression genes (low dose)
- **Therapeutic profile**
  - Prolongs OS in MDS and selected AML patients
  - Responses seen in high risk patients (short-lived)
  - Well tolerated in comorbid and/or elderly patients

Azacitidine in MDS



Azacitidine

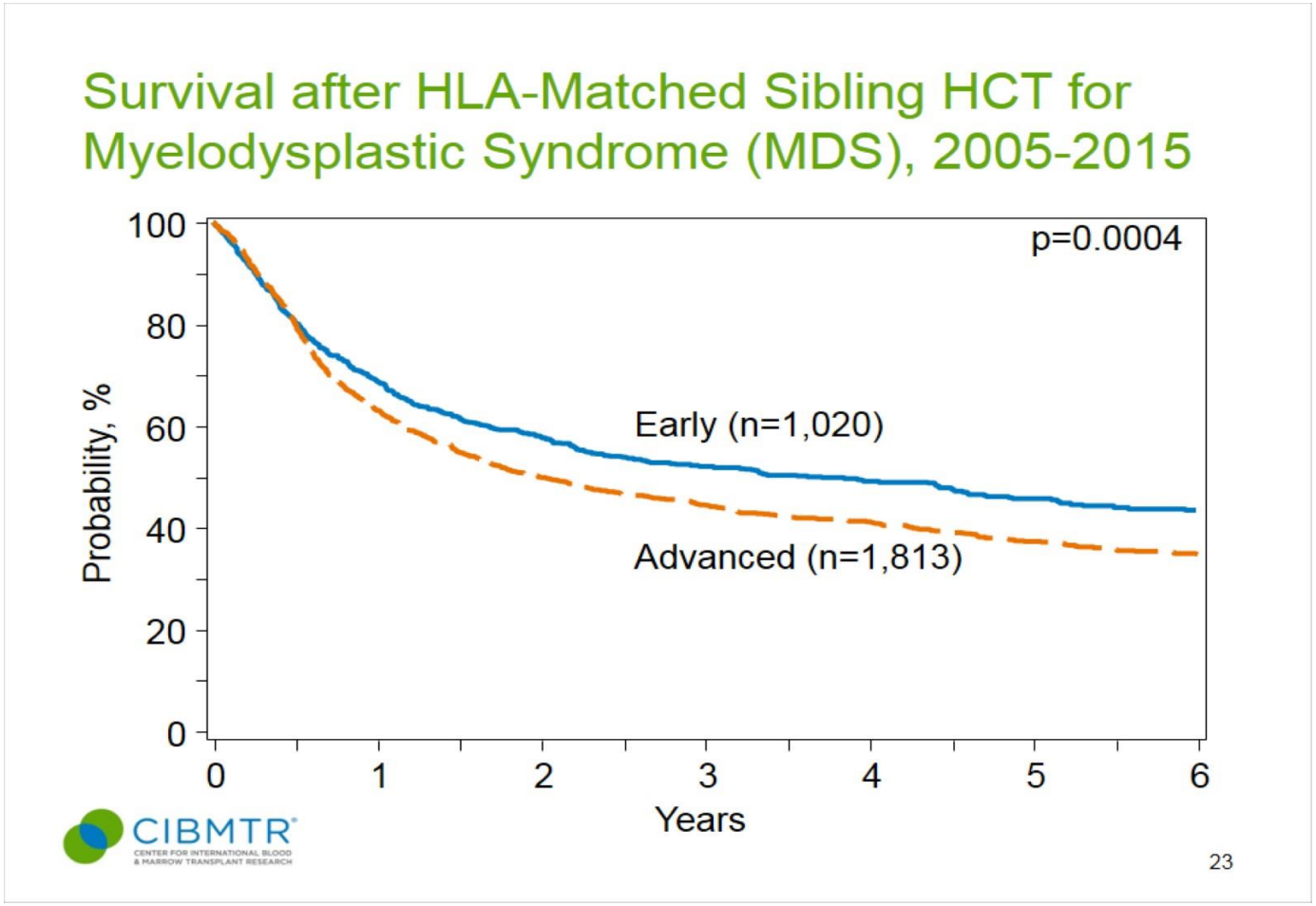
prolonged survival
reduced progression to AML
reduced transfusion need
reduced rate of infection

Improvement not related to

age
blast number
karyotype

AZA vs CCR. Fenaux et al. Lancet Oncol. 2009

AlloSCT w MDS

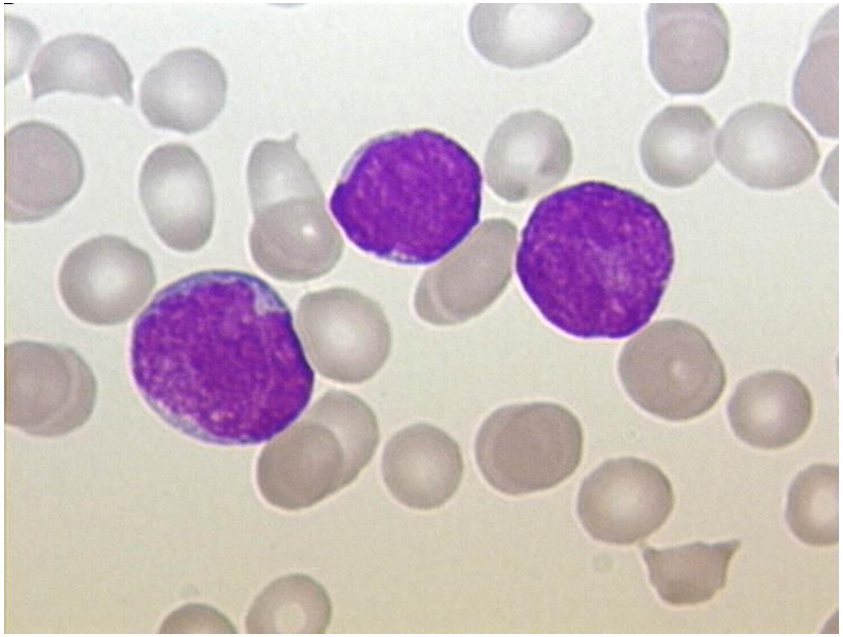


Acute lymphoblastic leukemia (ALL)

- **Clonal disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells**
- **Heterogenous disease with different biological subtypes**
- **ALL is the most common type of cancer and leukemia in children**
- **Incidence in adults**
  - 0.7-1.8/100000 per year
  - <15% of acute leukemias

ALL diagnosis

- **Diagnostic work-up**
  - Complet blood count with diferential
  - Bone marrow aspiration and biopsy
  - Immunochemistry
  - Immunophenotyping
  - Cytogenetics
  - Molecular studies
  - Gene expression profiling
  - Lumbar puncture
  - Chemistry profile
  - Viral tests
  - Coagulation of studies
  - Chest X-ray
  - Computed tomography
  - ECG, ECHO



Morphologic subtypes of ALL (FAB classification)

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

ALL - immunophenotyping

B- lineage (80%)	**Markers**
Pro-B	CD19(+),Tdt(+),CD10(-),Cylg(-)
Common	CD19(+),Tdt(+),CD10(+),Cylg(-)
Pre-B	CD19(+),Tdt(+),CD10(+),Cylg(+),Smlg(-)
Mature-B	CD19(+),Tdt(+),CD10(±),Cylg(±),Smlg(+)

T-lineage (20%)	
Pre-T	CD7(+), CD2(-), Tdt(+)
Mature-T	CD7(+), CD2(+), Tdt(+)

Risk classification in ALL

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

Risk factors in ALL

- **Conventional risk factors**
  - Age > 35 years
  - WBC > 30 G/L in B-ALL and > 100 G/L in T-ALL
- **Cytogenetical/moleular factors**
  - t(9;22)/ bcr-abl
  - t(4;11)/MLL
  - Hypodiploidy
  - Complex abnormalities
- **Response to therapy**
  - No remission after 4 weeks of induction therapy
  - Minimal residual disease (MRD)

Risk classification in ALL

Very high risk: Ph+/bcr-abl+

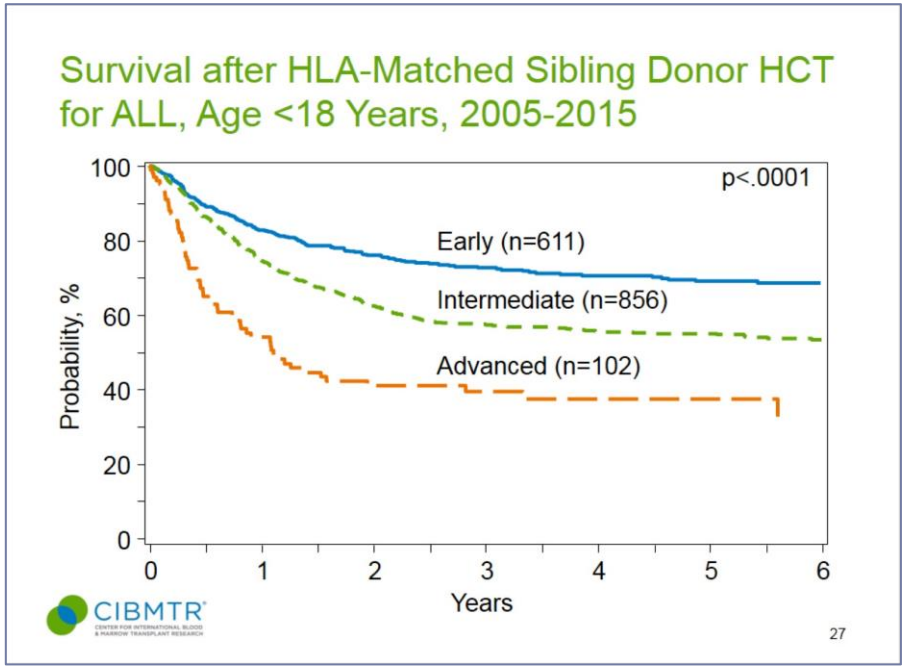
Treatment strategy in ALL

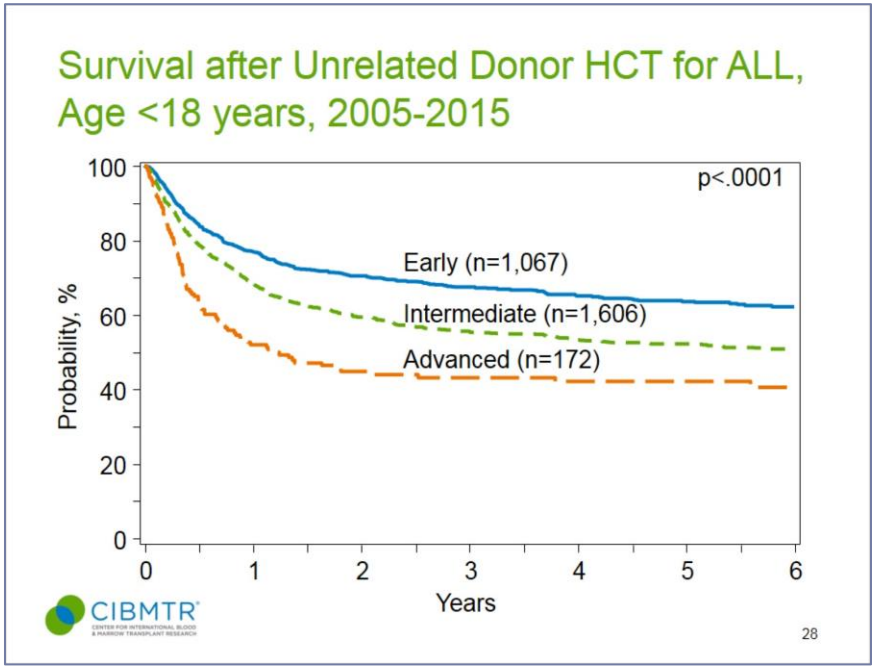
- **Remission induction therapy**
- **Post-remision therapy**
  - consolidation
  - hematopoietic stem cell transplantation
  - maintenance therapy
- **CNS involvement prophylaxis and treatment**
- **Treatment of complication**

Treatment strategy in ALL

- **Remission induction (4-8 weeks):**
  - prednison, vincristin, anthracyclin, L-asparaginaze, cyclophosphamid, cytarabine
  - CR 70-85%
- **Consolidation (8-12 weeks)**
  - HD Ara-C, Mtx, Cyclophosphamid, L-asparginaze
  - alloHSCT in high and very high risk group: LFS 51%
- **Maintenance**
  - Chemotherapy 2-3 yrs: 6-meraptopurine + methotrexate

AlloSCT for ALL





CIBMTR Newsletter 2017

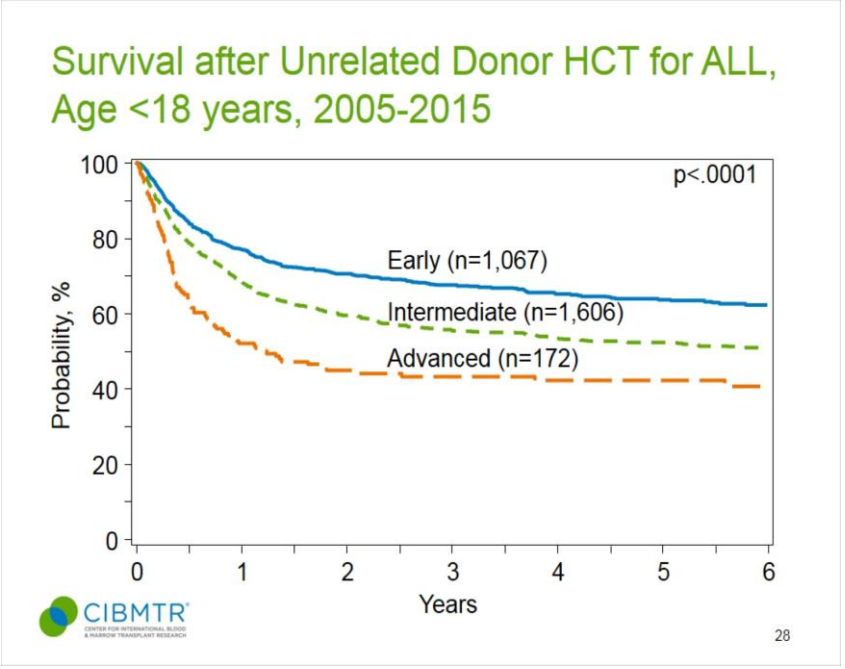
ALL bcr/abl+

- **Tyrosine kinase inhibitors:** imatinib, dasatinib, ponatinib
  - Remission induction in combination with chemotherapy
  - Maintenance after alloHSCT

  CR: 95%
  Molecular remission: 40% - 60%
  DFS 2 yrs: 50% - 65%

Treatment results in ALL

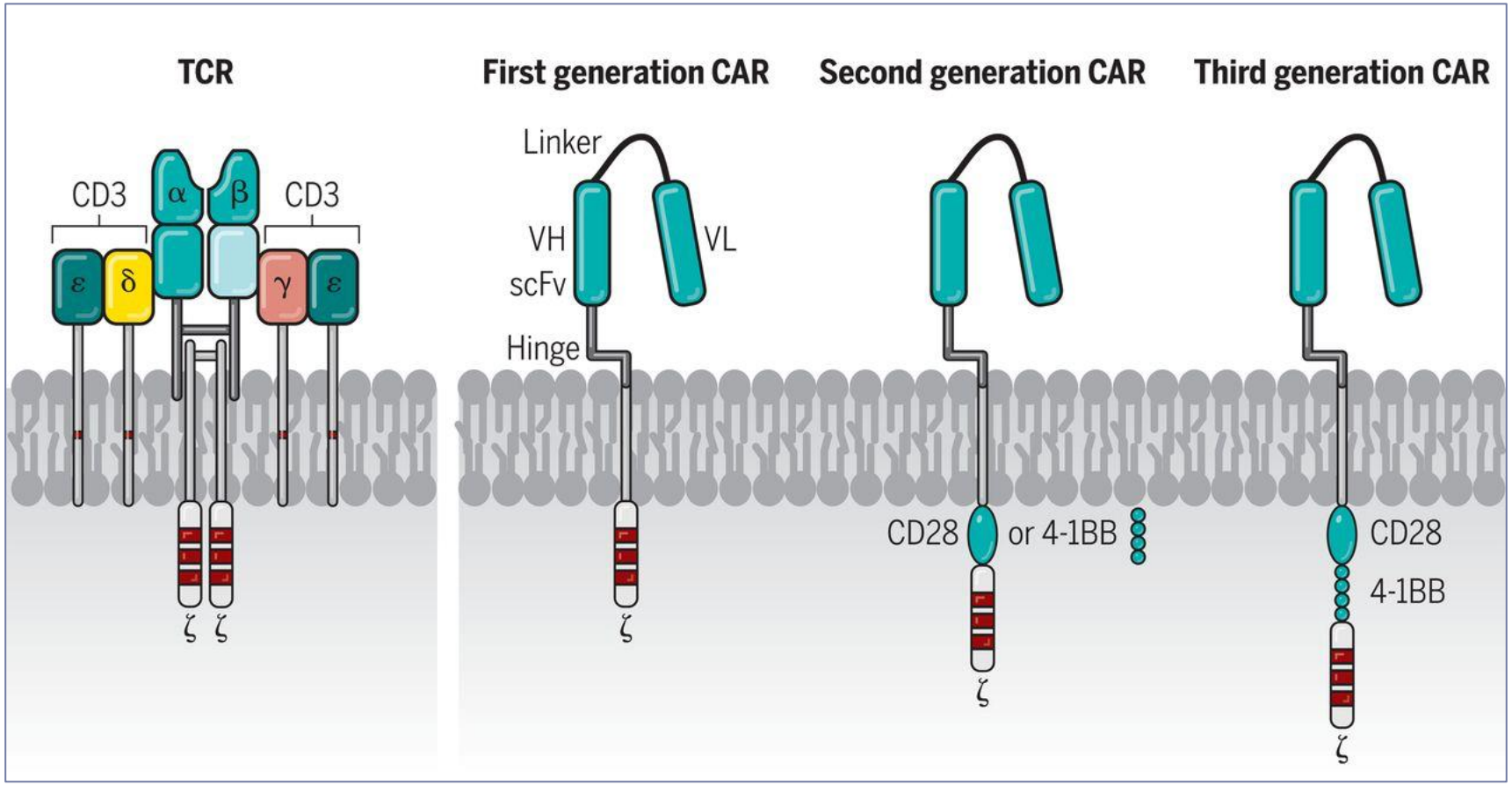
- **Adults**
  - Complete remission (CR) 80-85%
  - Leukemia-free survival (LFS) 30-40%
- **Children**
  - Complete remission (CR) 95-99%
  - Leukemia-free survival (LFS) 70-80%



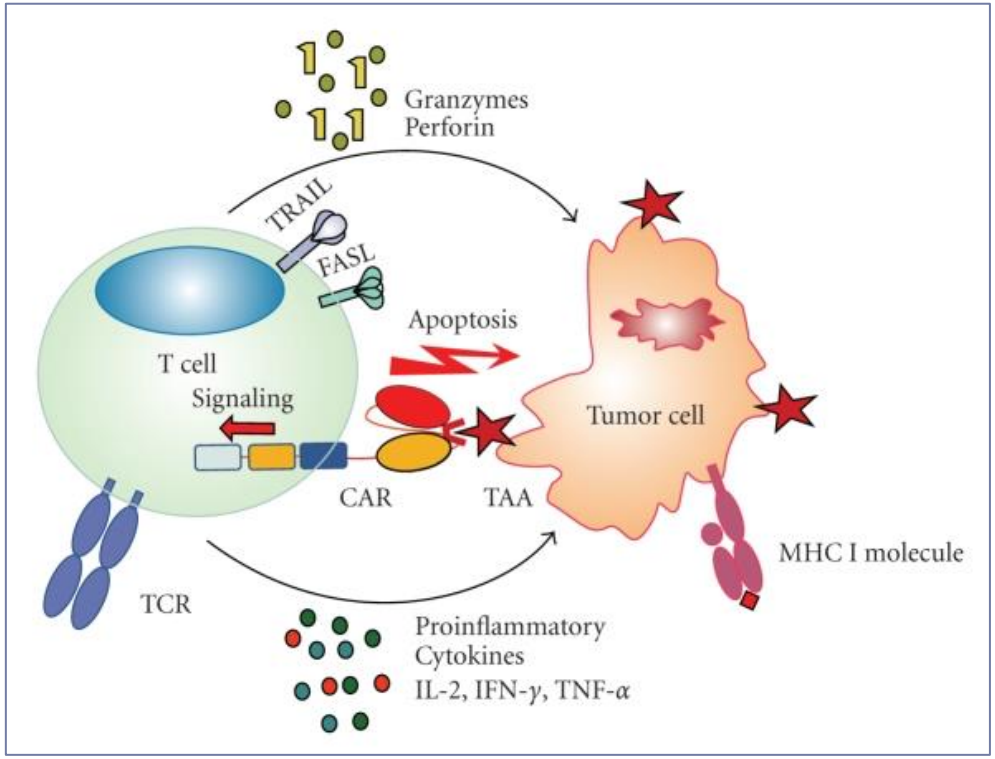
New drugs and methods

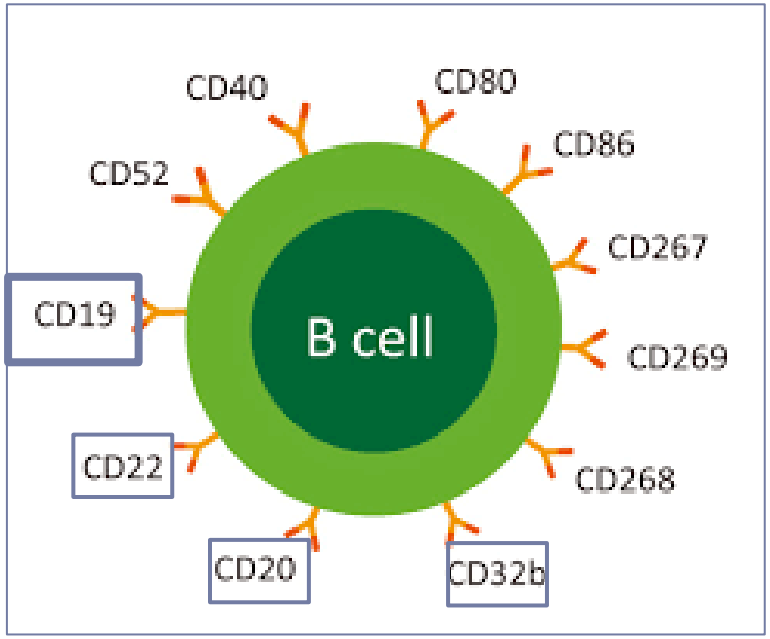
- **New drugs**
  - Tyrosine kinase inhibitors (imatinib, dasatinib)
  - Farnesyl transferase inhibitor (FTI)
  - Monoclonal antibodies
    - Inotuzumab
    - blinatumumab
  - Chemotherapy (nelarabine, clofarabine)
- **New methods**
  - RIC (reduced-intensity conditioning) + alloSCT
  - Haploidentical
  - GvL (graft versus leukemia)
  - CAR-T

CART – Chimeric Antigen Receptor T cells



CART – Chimeric Antigen Receptor T cells





Cartelleri et al. J Biomed Biotechnol. 2010

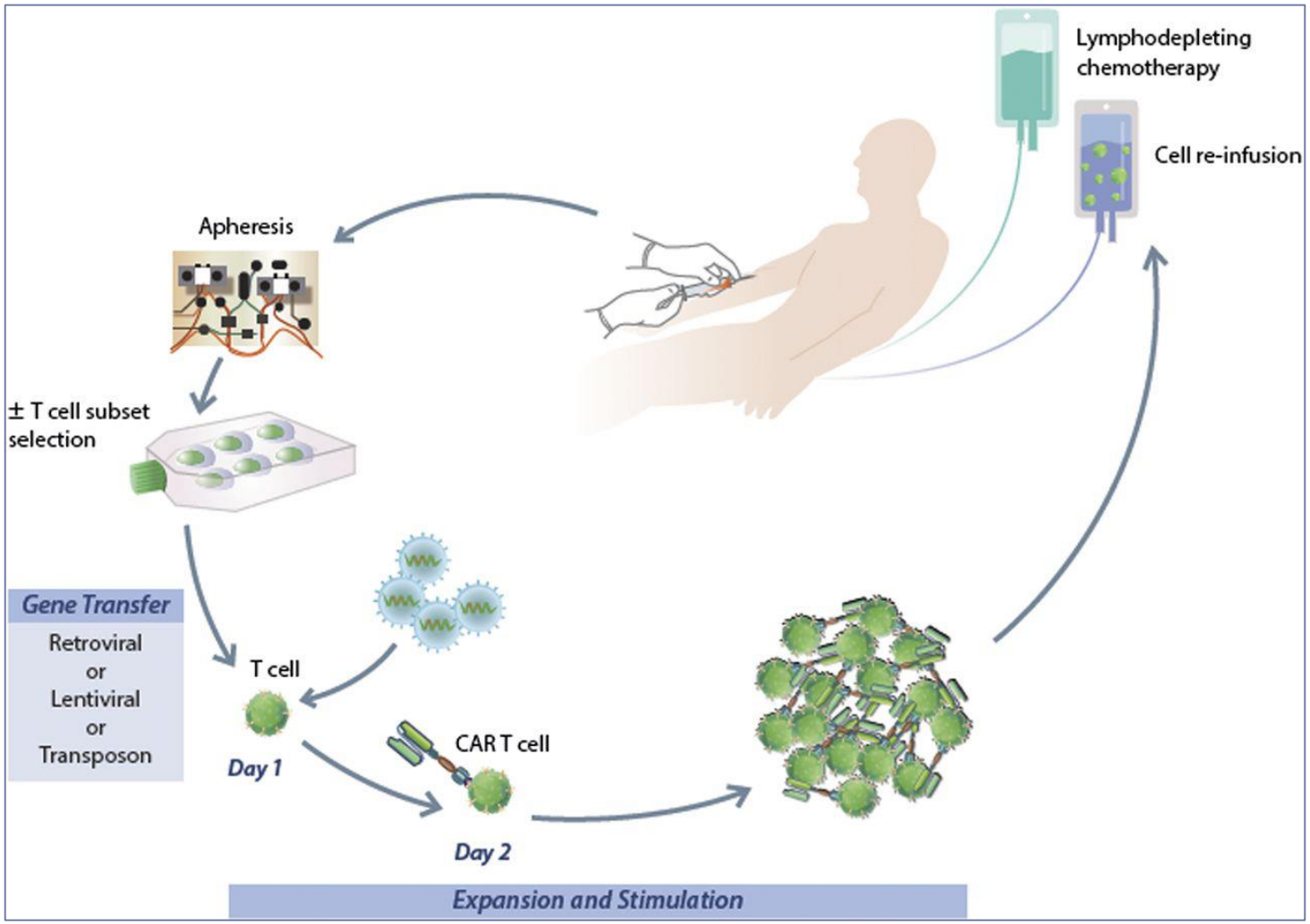
CART – Chimeric Antigen Receptor T cells

Tisagenlecleucel (*Kymriah*, Novartis) is approved for use in pediatric and young adult patients (age 3 to 25 years) with B-cell ALL that is refractory or in second or later relapse (August 30,2017)

Axicabtagene ciloleucel (*Yescarta*, Kite) is approved for use in adult patients with large B-cell lymphoma after at least two other kinds of treatment failed, including DLBCL, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma (October 18, 2017)

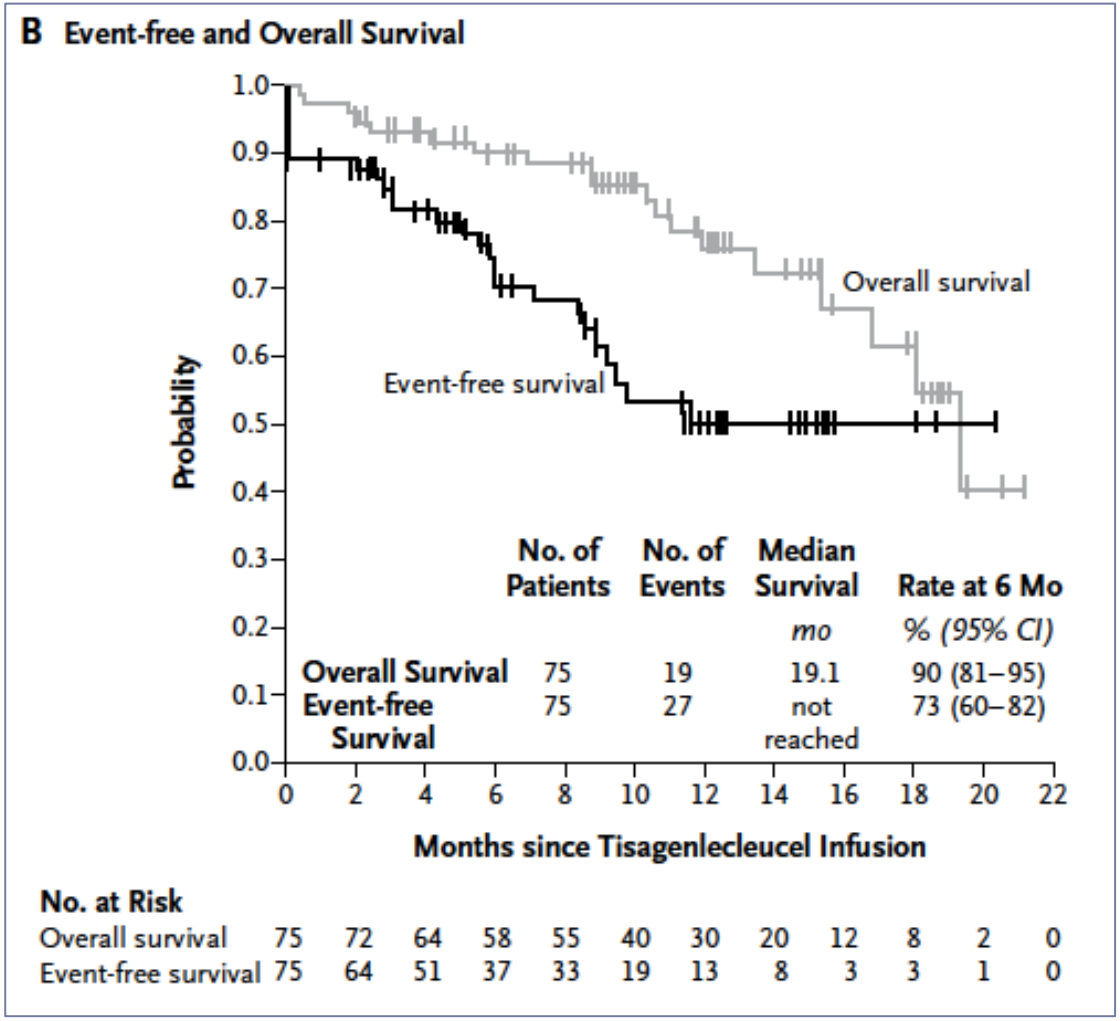
YESCARTA™
(axicabtagene ciloleucel) Suspension for IV infusion

CART – Chimeric Antigen Receptor T cells



Mato A, Porter DL Blood 2015

New drugs and methods



Maude et al. NEJM 2018

Acute leukemias

- **Infection prophylaxis**
  - enviromental
  - pharmacological
- **Infection treatment**
  - empirical antibiotic therapy
- **Blood products transfusion**
- **TPN**
- **Psychological support**