Are we ready for targeted therapy in AML

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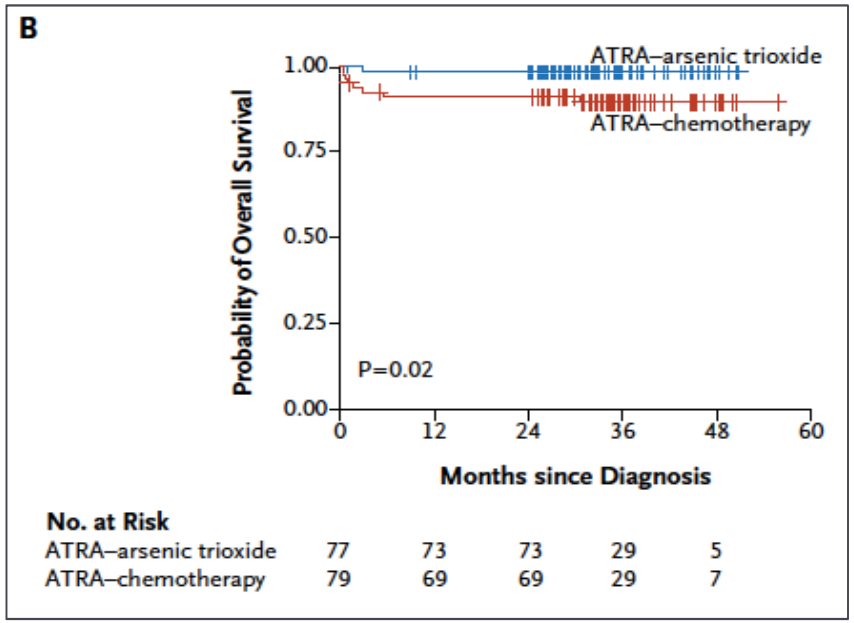
Targeted therapy in hematology

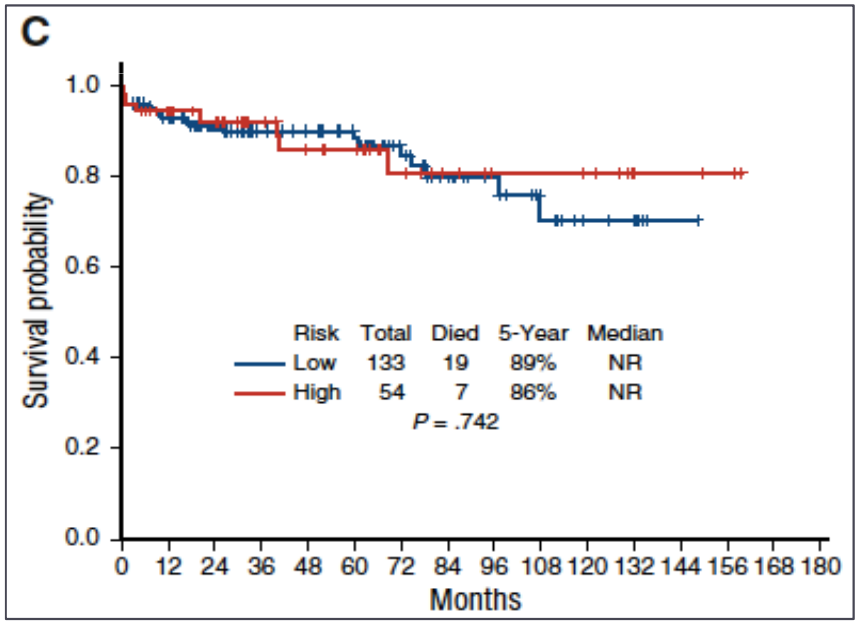
- **Fundametal shift in the treatment of malingnant blood diseases is under way**
- **Classical cytotoxic chemotherapy may not be a component of therapy in multiple myeloma, chronic lymphocytic leukemia, acute lymphoblastic leukemia**

- **Does cytotoxic therapy still have a place in the management of acute myeloid leukemia (AML)**

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 – acute myeloid leukemia

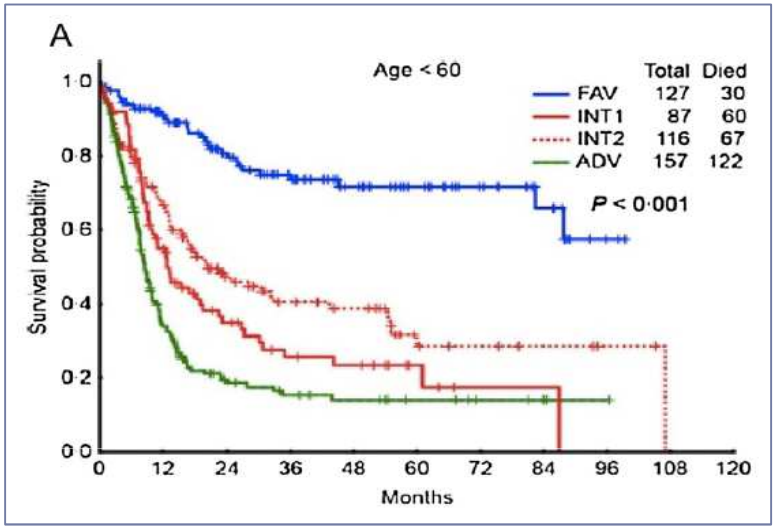
AML and related neoplasms	AML and related neoplasms (cont'd)
AML with recurrent genetic abnormalities	Acute myelomonocytic leukemia
AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	Acute monoblastic/monocytic leukemia
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	Pure erythroid leukemia#
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	

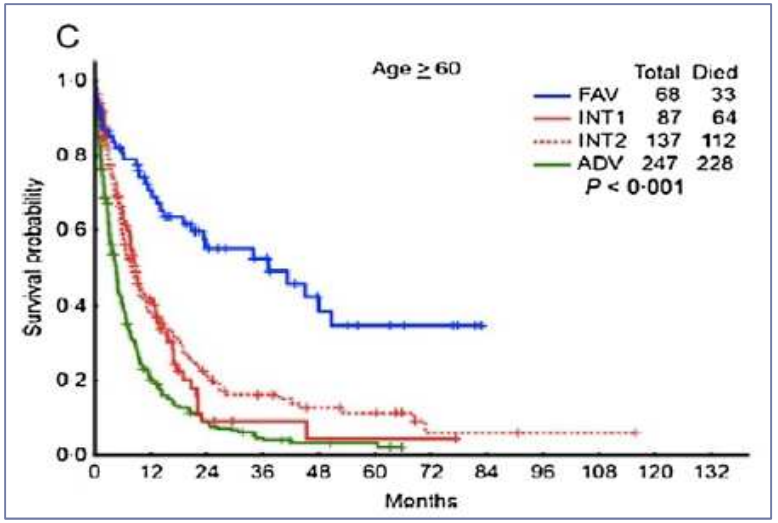
WHO 2016. Arber et al. Blood 2016

AML

- **Prognostic factors in AML**
  - **Age**
  - **Performance status**
  - **Functional and cognitive status**
  - **Comorbid condition**
  - **Antecedent haematologic al disorder**
  - **WBC at presentation**
  - **Cytogenetics**
  - **Molecular abnormalities**

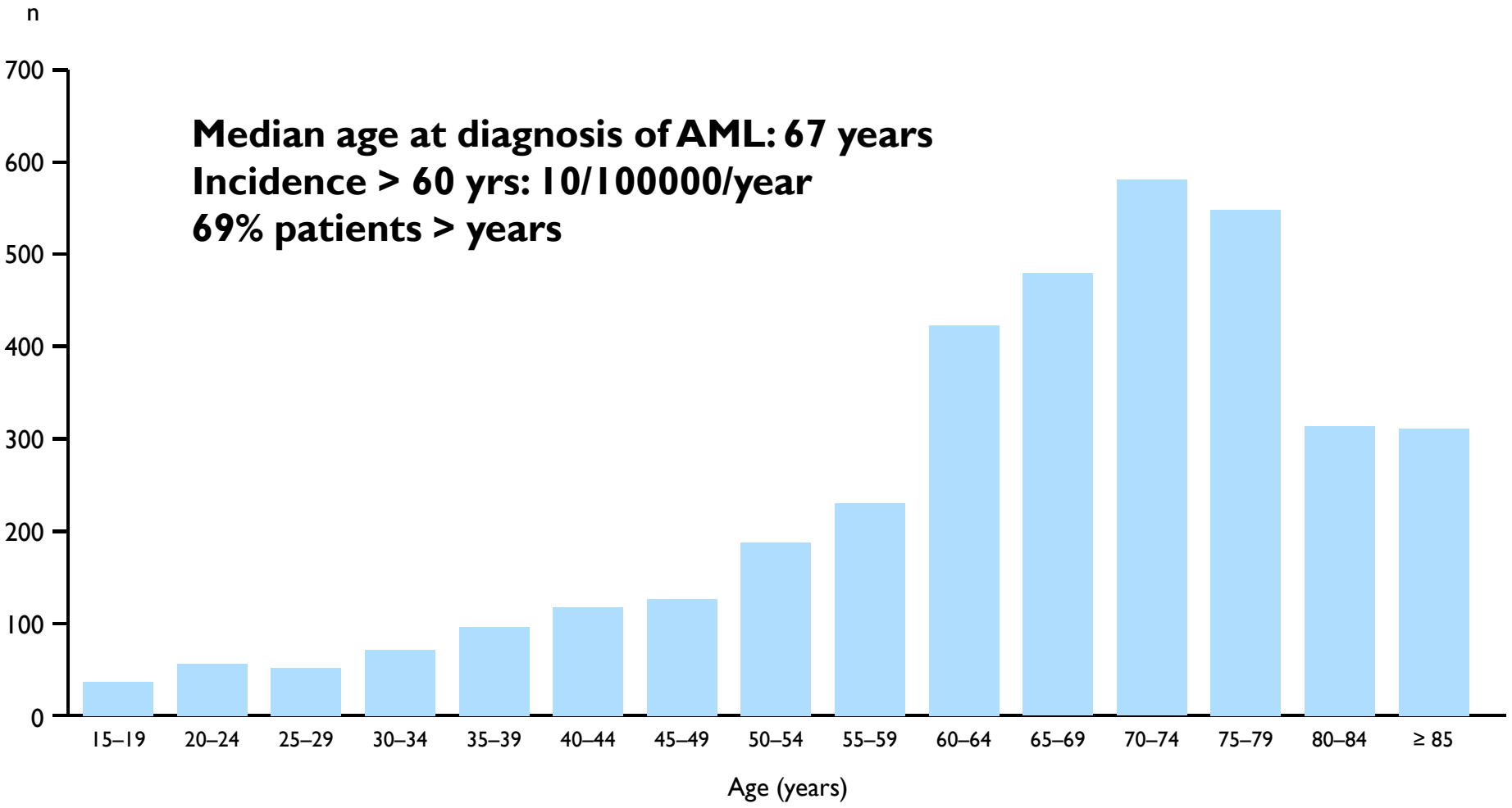
Risk Profile	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD (normal karyotype) Biallelic mutated *CEBPA* (normal karyotype)
Intermediate-I†	Mutated *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse‡
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *GATA2–MECOM (EVI1)* t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23); *KMT2A* rearranged –5 or del(5q); –7; abnl(17p); complex karyotype§





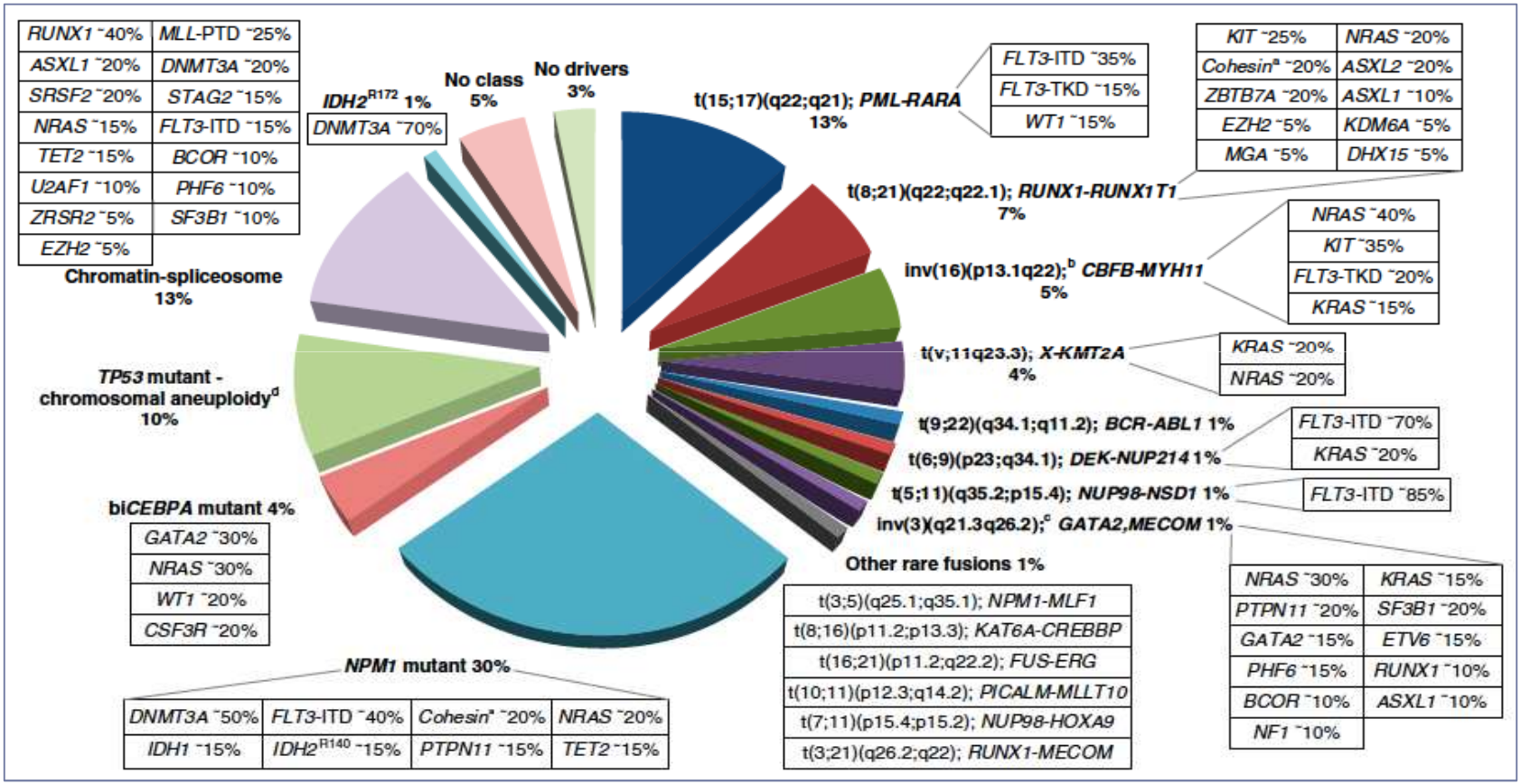
Dohner et al. NEJM 2015, Blood 2017 Tamamyan et al. Critical Rev Oncol/Hematol 2017

AML



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

Genetic abnormalities in AML

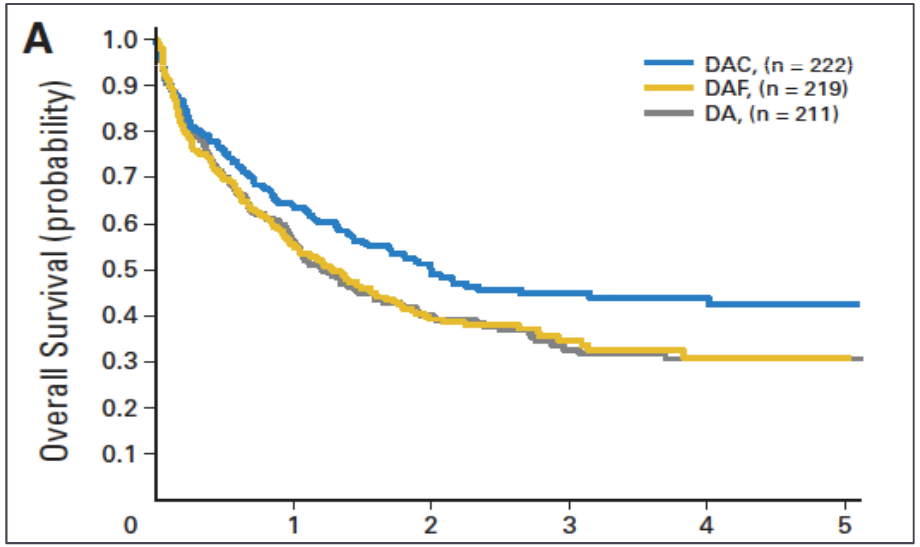


Dohner et al. Blood 2017

Treatment of AML

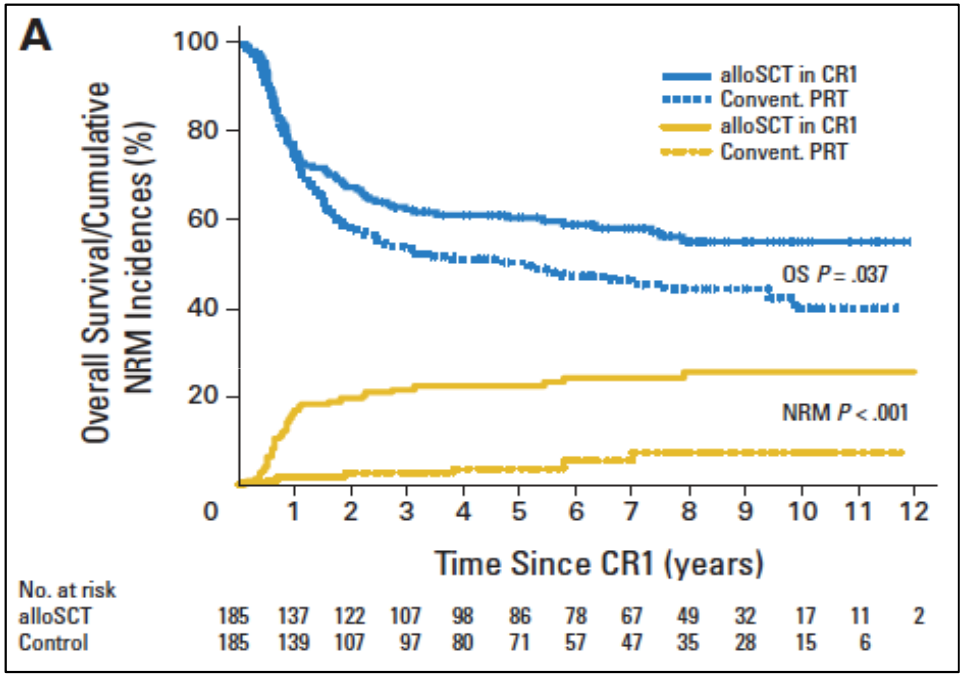
ELN, NCCN, PALG RECOMMENDATION

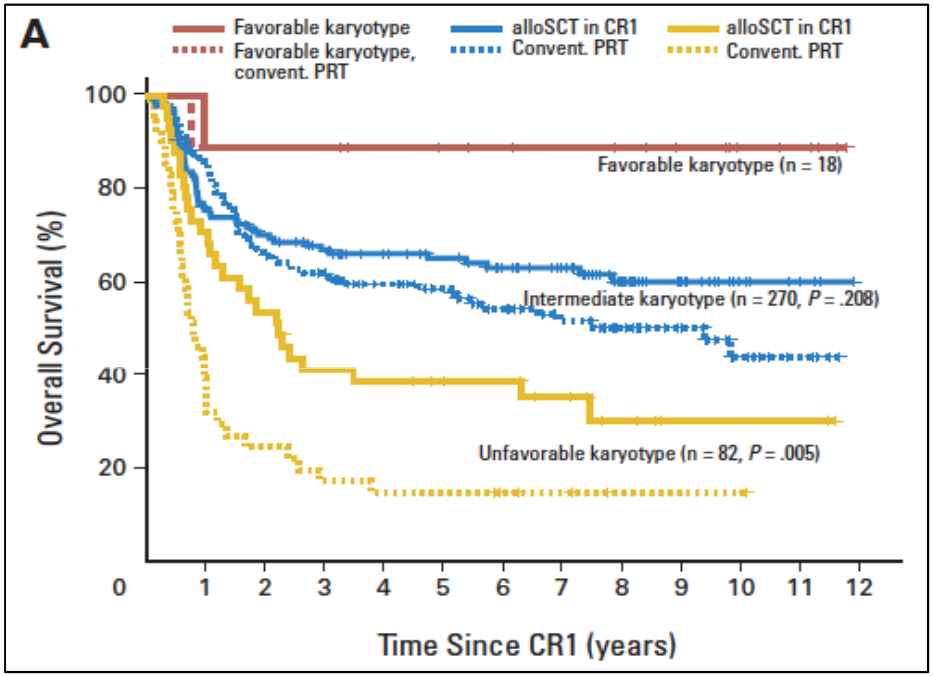
- **Induction chemotherapy**
  - **Regimen „3+7" (daunorubicin + cytarabine): CR 60-85%**
  - **Variants**
    - Dose and type of anthracycline
    - Dose of cytarabine
    - Nucleoside analogue
- **Post-remission therapy**
  - **Consolidation**
    - Chemotherapy based on HiDAC
  - **HSCT**
  - **Maintenance therapy?**



Hołowiecki et al. JCO 2012

AlloSCT in AML treatment

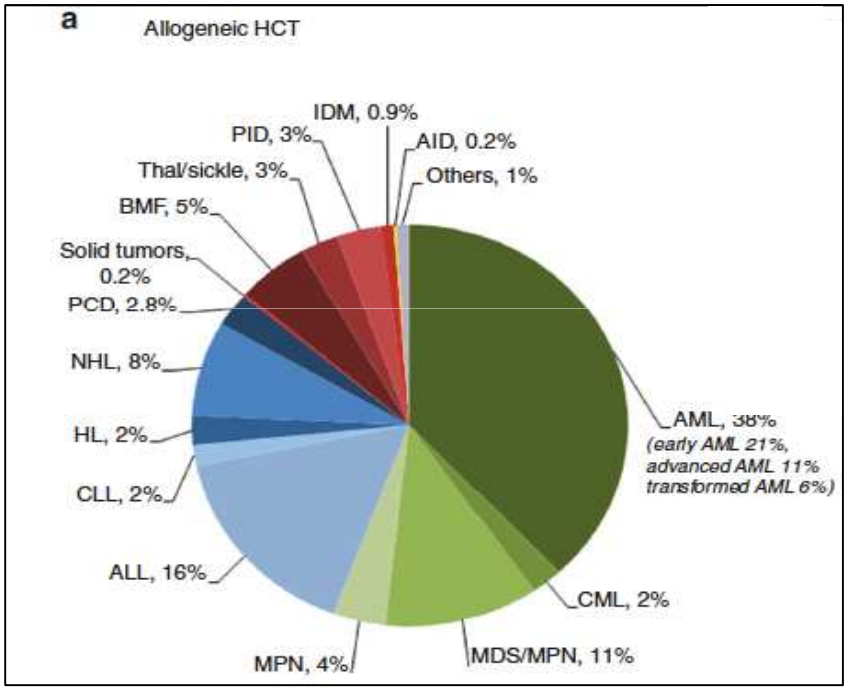


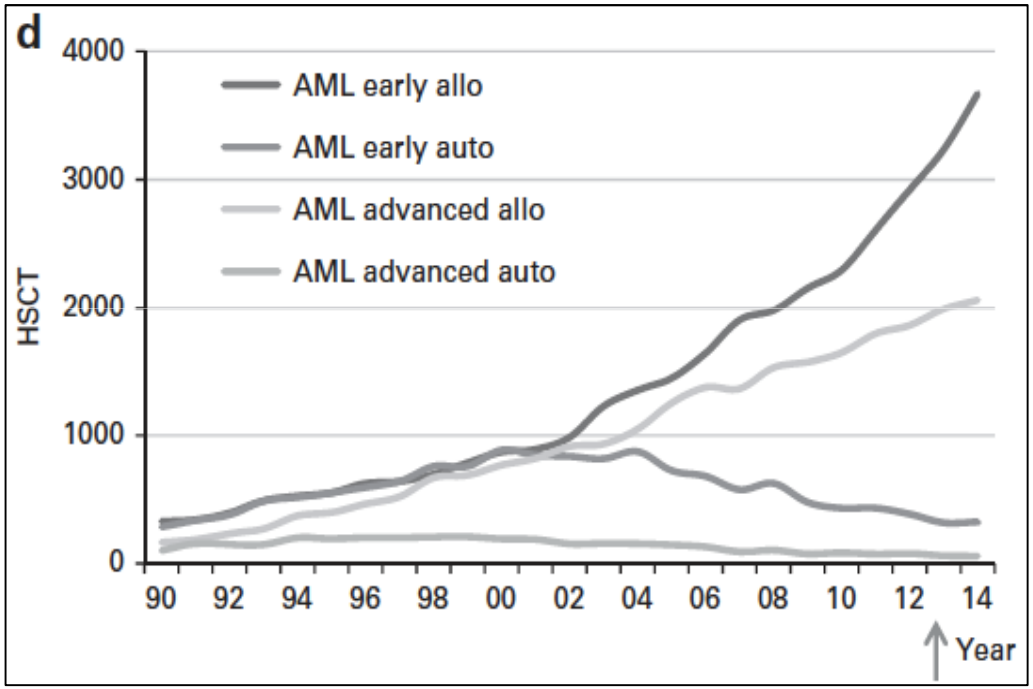


OS and NRM according to post-remission therapy and cytogenetic risk
AlloSCT vs conventional treatment

Stelljes et al. JCO 2014

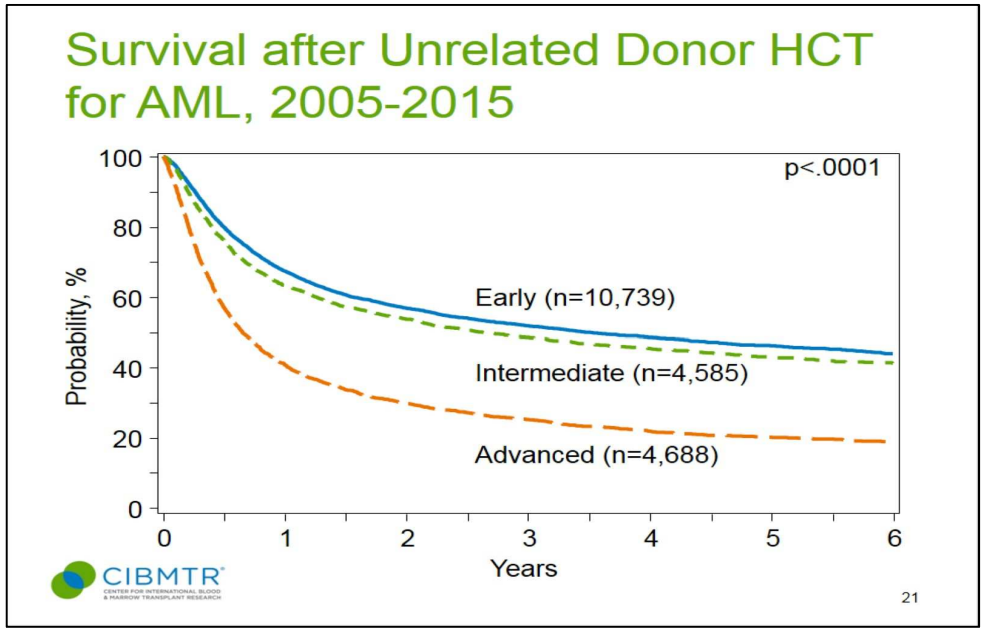
AlloSCT for AML

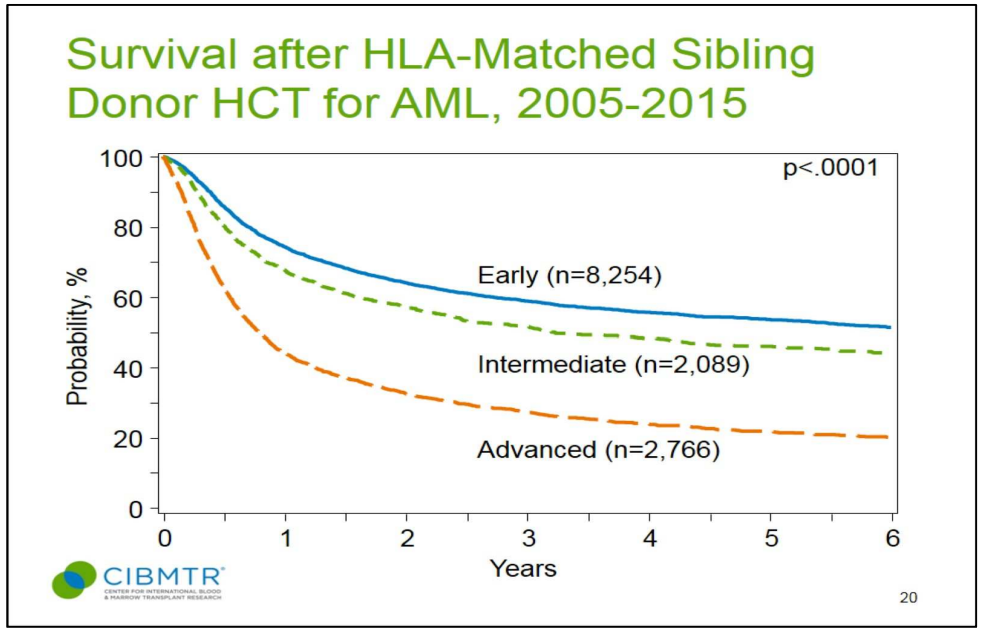




Passweg et al. BMT 2017, BMT 2018

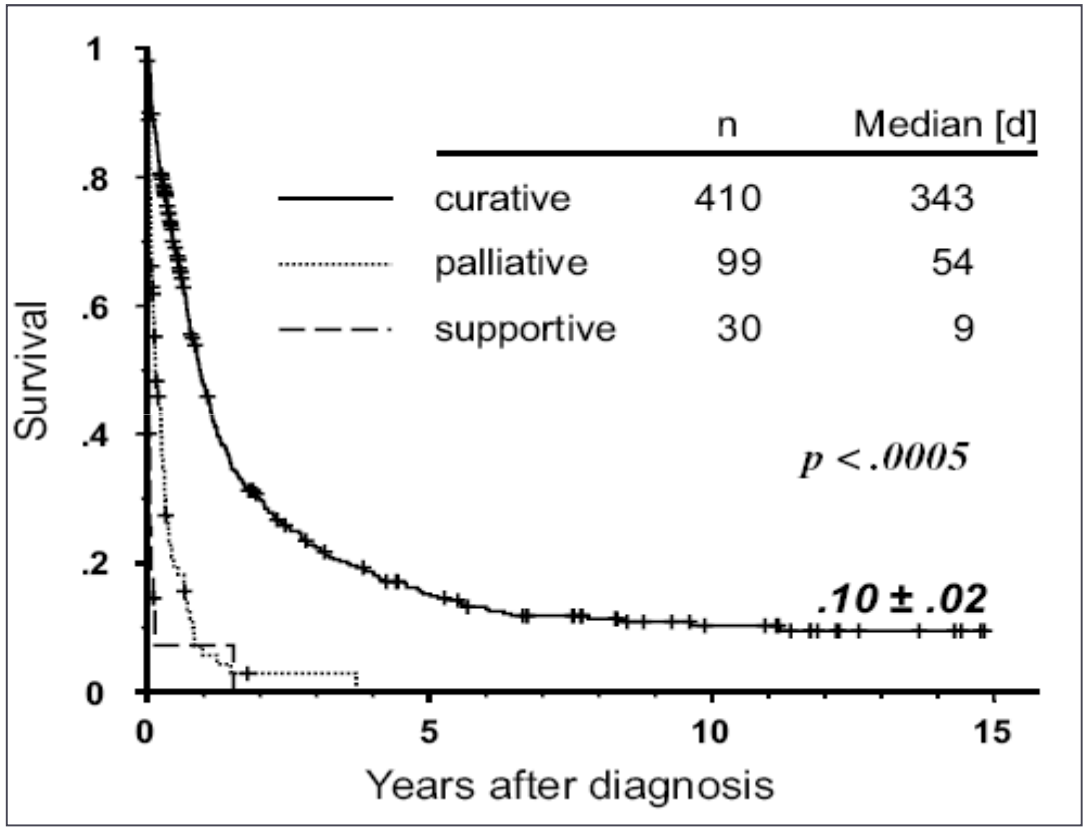
AlloSCT in AML treatment





CIBMTR Newsletter 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

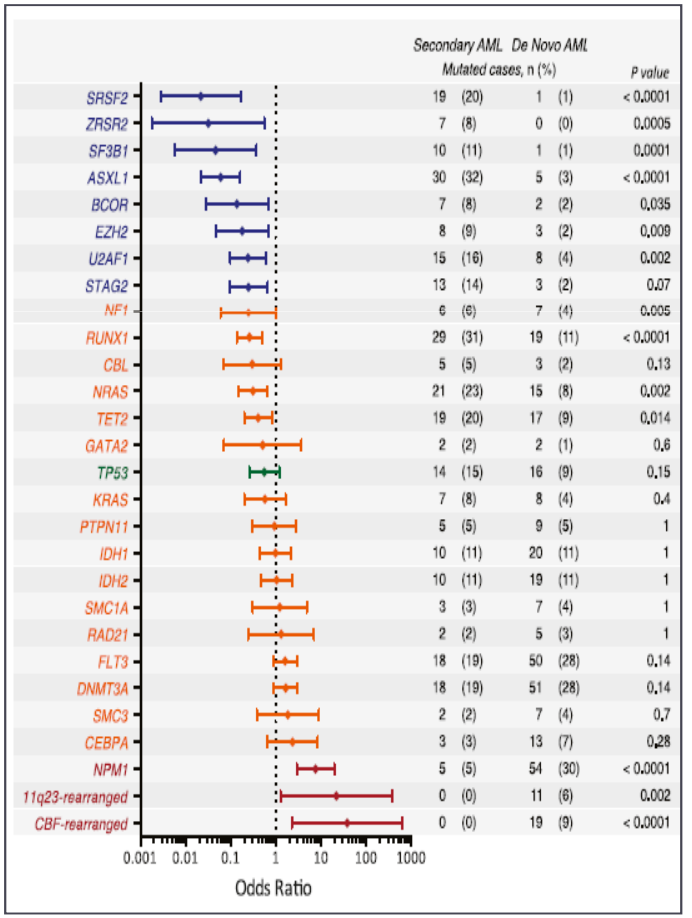
Etoposide

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

Kahl et al. J Cancer Res Clin Oncol 2016

AML – genomic and epigenomic landscape

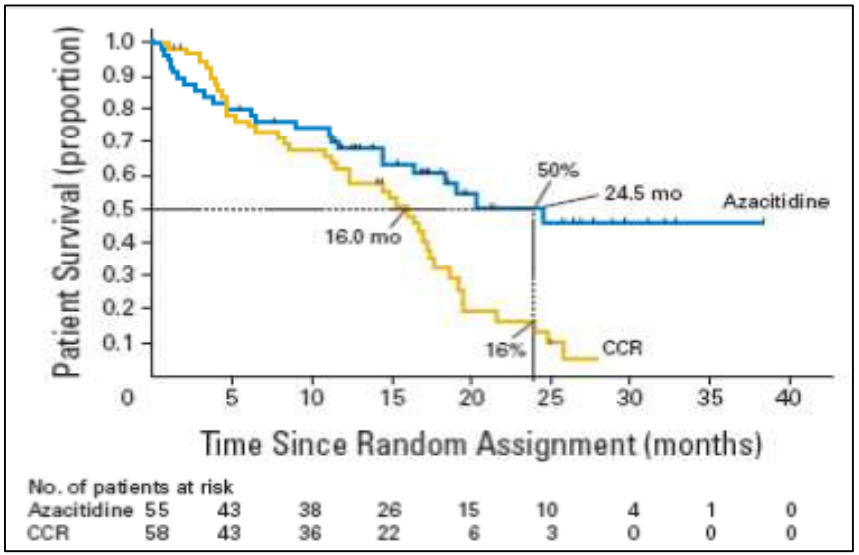
- **Targeted mutational analysis s-AML, t-AML and *de novo* AML >60 years old**
  - RNA splicing: 55%
  - DNA methylation: 46%
  - Chromatin modification: 42%
  - RAS pathway signaling: 42%
  - Transcriptional regulation: 34%
  - The cohesin complex: 22%
- **„Secondary-type" mutations**
  - 95% specificity for s-AML
  - Elderly AML: 33,3% of secondary type mutation
  - Change approach to management of AML – use of HMA?



Lindsley et al. Blood 2015

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

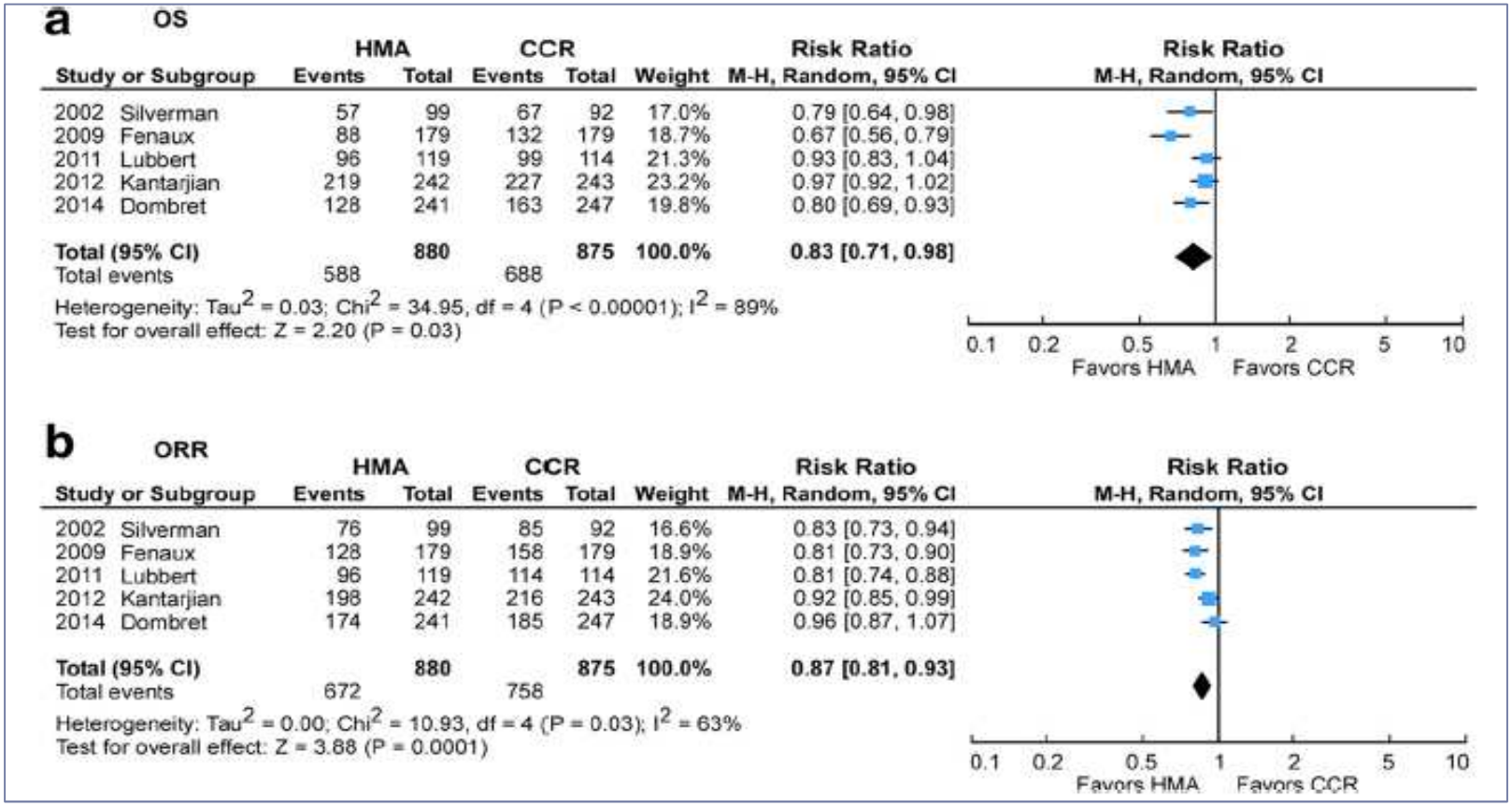


AML 20-30% blasts. 113 patients; edian age 70 years.

AZA vs CCR. 2-yrs OS 50% vs 16%.

Fenaux et al. JCO 2010

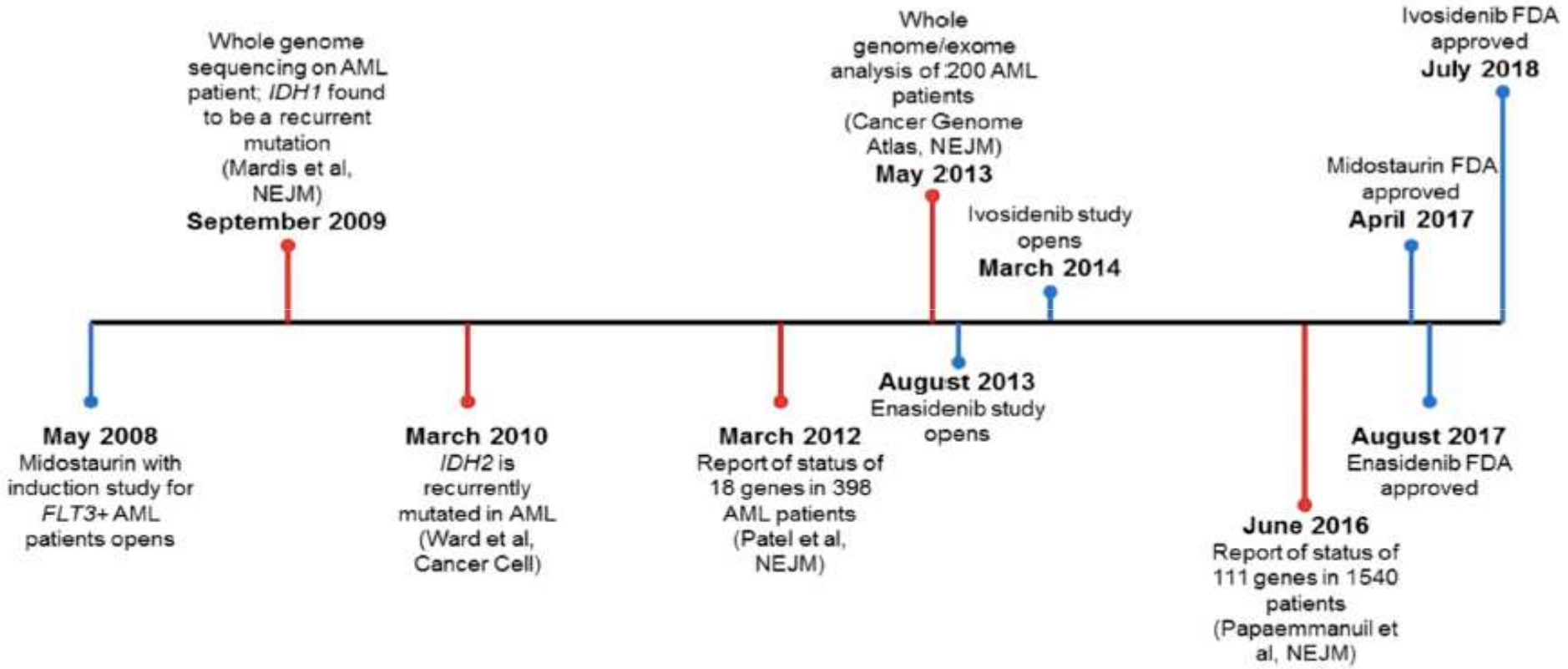
Azacitidine in MDS/AML treatment



Meta-analysis of randomised studies AZA vs conventional care regimen (CCR). 1775 patients. OS (a) ORR (b)

Yun et al. Clinical Epigenetics 2016

AML – novel therapies



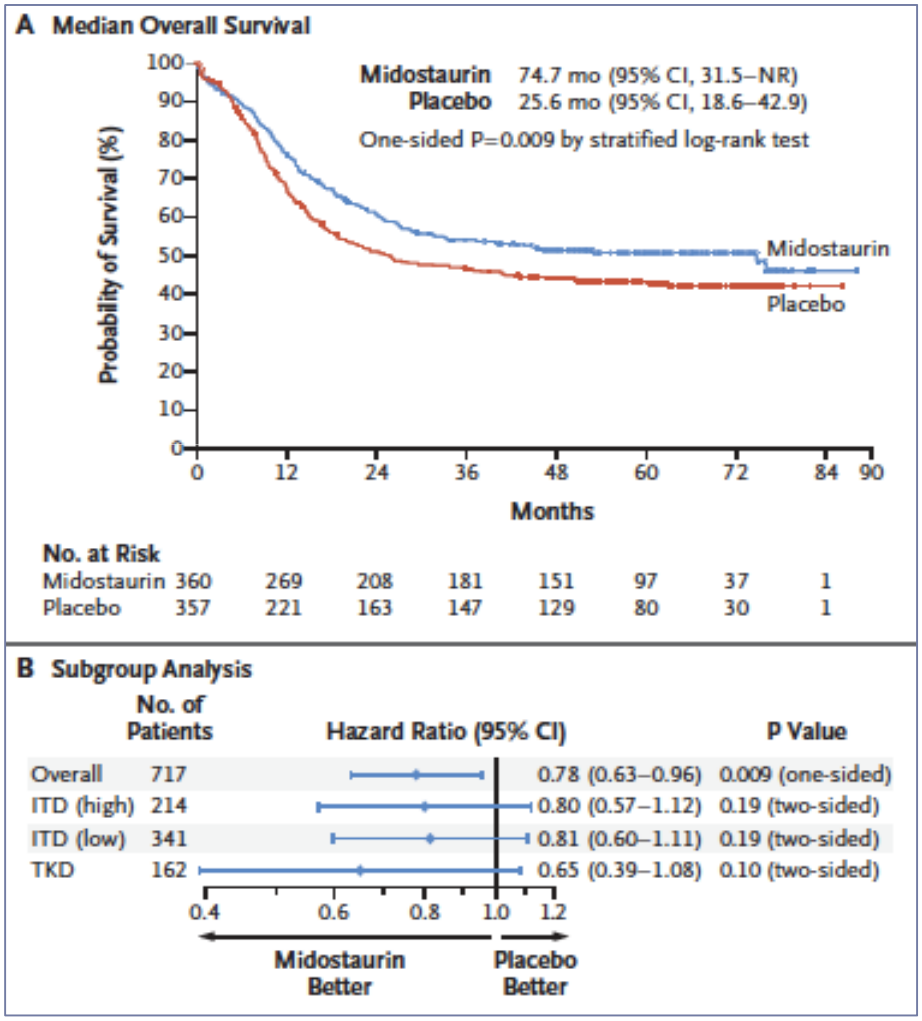
Daniel Pollyea. Hematology, ASH 2018

New drugs for AML

Drug and indication	Regulatory status
Midostaurin (Rydapt)	
Adult patients with newly diagnosed AML who are *FLT3*$^+$, as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.	FDA approval 28 April 2017
In combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single-agent maintenance therapy, for adult patients with newly diagnosed AML who are *FLT3*$^+$.	European Medicines Agency approval 20 September 2017
CPX-351 (Vyxeos)	
Treatment of adults with *t*-AML or AML with AML-MRC.	FDA approval 3 August 2017
Enasidenib (Idhifa)	
Treatment of patients with relapsed or refractory AML with an *IDH2* mutation detected with an FDA-approved assay.	FDA approval 1 August 2017
Gemtuzumab ozogamicin (Mylotarg)	
Adults with newly diagnosed AML whose tumors express the CD33 antigen (CD33$^+$ AML). Patients aged 2 y and older with CD33$^+$ AML who have experienced a relapse or who have not responded to initial treatment (refractory).	FDA approval 1 September 2017
Venetoclax (Venclexta)	
Venetoclax in combination with HMAs for the treatment of patients with untreated (treatment-naïve) AML who are ineligible to receive standard induction therapy (high-dose chemotherapy).	FDA breakthrough designation 28 January 2016
Venetoclax in combination with LDAC for elderly patients with previously untreated AML who are ineligible for intensive chemotherapy.	FDA breakthrough designation 28 July 2017

Wei & Tiong. Blood 2017

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

FLT3 inhibitors

Reference	*FLT3 inhibitor used*	*Study design*	*Patients number*	*Median age, yr (range)*	*Response*	*Survival*
Cortes *et al.*[17]	Quizartinib for relapsed/refractory AML *FLT3*+ or WT	Phase 1	76	60 (23–86)	CR:10 (13%) PR: 13 (17%)	Median OS: 14 w (18 w for *FLT3*+10 w for WT)
Levis *et al.*[78]	Lestaurtinib (L) for relapsed/refractory AML *FLT3*+	Randomized	224 CT: 112 L +CT: 112	CT: 54 (21–79) L+CT: 59 (20–81)	CT: 23 (CR/CRp) L+CT: 29 (CR/CRp)	No difference in OS
Smith *et al.*[14]	Lestaurtinib for relapsed/refractory AML *FLT3*+	Phase 1/2	14	61(18–74)	50% PB blast reduction: 5 (36%)	—
Knapper *et al.*[77]	Lestaurtinib for untreated older patients with AML not fit for CT (*FLT3*+ or WT)	Phase 2	29 FLT3+: 5 WT: 24	73 (67–82)	BMR: 5 HR: 3	—
Stone *et al.*[75]	Midostaurin (M) versus placebo (P) for first-line *FLT3*+ AML added to ind/cons/main	RCT phase 3	717 M: 360 P: 357	48 (18–60)	CR: M 59%, P 54% (NS)	Median OS: M 74.7 m, P 26 m (S) Median EFS: M m, P 3 m (S)
Fischer *et al.*[74]	Midostaurin for relapsed/refractory AML *FLT3*+ or WT	Randomized phase 2	95 *FLT3*+: 35 WT: 60	*FLT3*+: 16 (46%) were >65 yr WT: 45 (75%) were >65 yr	ORR: *FLT3*+ 25 (71%), WT 32 (56%)	Median survival: *FLT3* +100 d, WT 159 d
Stone *et al.*[15]	Midostaurin for relapsed/refractory AML or MDS not candidates for CT *FLT3*+	Phase 2	20	62 (29–78)	50% PB blast reduction: 14 (75%)	—
Randhawa *et al.*[79]	Crenolanib for relapsed/refractory AML	Phase 2	38	61 (30–87)	ORR: 47%	Median EFS: 8 weeks Median OS: 19 weeks
Levis *et al.*[80]	Gilteritinib for relapsed/refractory AML	Phase 1/2	166	—	ORR: 57%	—

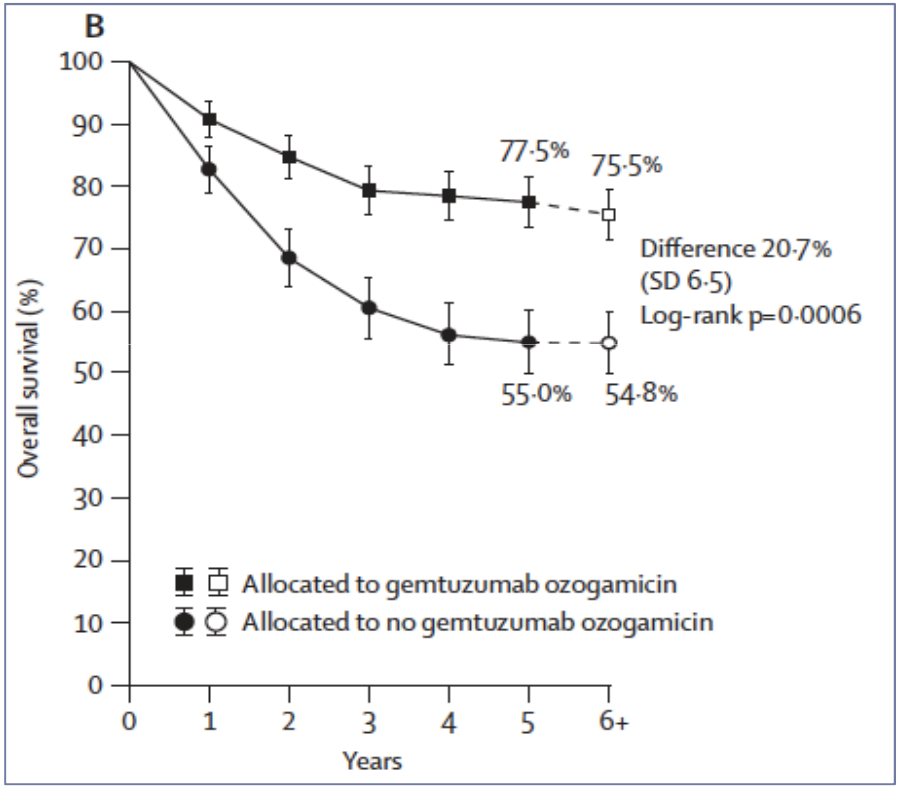
Antar et al. BMT 2017

Gemtuzumab ozogamycin

	Dates of recruitment	Number of patients	Eligibility criteria	Median age of patients in years (range)	Cytogenetic grouping by MRC[12] classification*	Chemotherapy given	Dose and dosing schedule of gemtuzumab ozogamicin	Median follow-up for survival	Time of last follow-up (original publication)	Time of last follow-up (data for meta-analysis)
MRC AML15†[5]	2002–06	1099	AML, either de novo or secondary; mostly aged <60 years	50 (15–71)	Favourable n=133 (15%); intermediate n=565 (63%); adverse n=196 (22%); unknown n=205	DA (3+10 then 3+8), ADE (3+10+5 then 3+8+5), or FLAG-Ida	3 mg/m² on day 1 of chemotherapy	86·0 months (IQR 76·6–99·4)	January, 2009	March, 2013
SWOG S0106[7]	2004–09	595	De-novo AML; aged 18–60 years	47 (18–60)	Favourable n=72 (17%); intermediate n=283 (67%); adverse n=67 (16%); unknown n=173	DA (3+7) plus G-CSF or GM-CSF	6 mg/m² on day 4 of chemotherapy	55·2 months (IQR 46·0–66·3)	February, 2013	June, 2013
NCRI AML16[6]	2006–10	1115	AML, either de novo or secondary, or high-risk myelodysplastic syndrome; mostly aged ≥60 years	67 (51–84)	Favourable n=33 (4%); intermediate n=576 (66%); adverse n=264 (30%); unknown n=242	DA (3+10 then 3+8) or daunorubicin (days 1, 3, and 5) plus clofarabine (days 1–5)	3 mg/m² on day 1 of chemotherapy	45·5 months (IQR 34·3–57·6)	July, 2011	March, 2013
GOELAMS AML 2006 IR[8]	2007–10	238	De-novo AML, aged 18–60 years	50·5 (18–60)	Favourable n=0; intermediate n=224 (100%); adverse n=0; unknown n=14	DA (3+7)	6 mg/m² on day 4 of chemotherapy	39·3 months (IQR 29·1–44·4)	..	January, 2013
ALFA-0701[11]	2008–10	278	De-novo AML; aged 50–70 years	62 (50–70)	Favourable n=9 (4%); intermediate n=179 (73%); adverse n=57 (23%); unknown n=33	DA (3+7)	3 mg/m² on days 1, 4, and 7 of chemo-therapy, up to 5 mg per dose	24·1 months (IQR 15·7–32·8)	August, 2011	August, 2011

Meta-analysis of randomised trials - 3325 patients. Hills et al. Lancet Oncol 2014

Gemtuzumab ozogamycin



Gemtuzumab ozogamicin

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

Efficacy

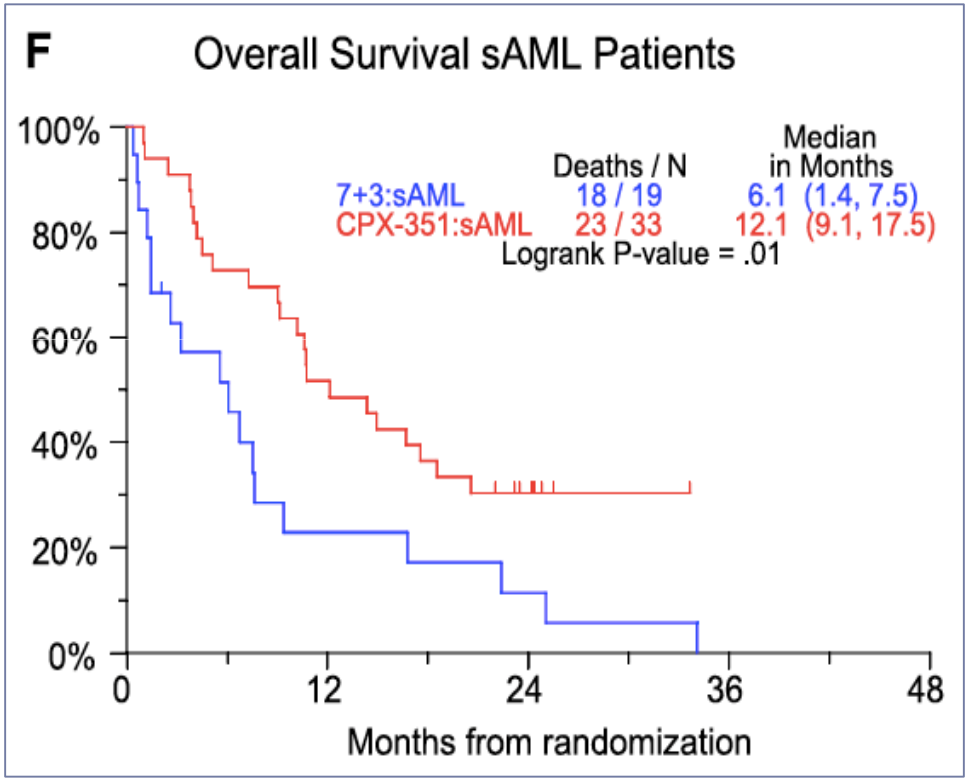
- 6-yrs OS 32.2 vs 35.6%
- 6-yrs OS LR-IR 54.8 vs 75.5%

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

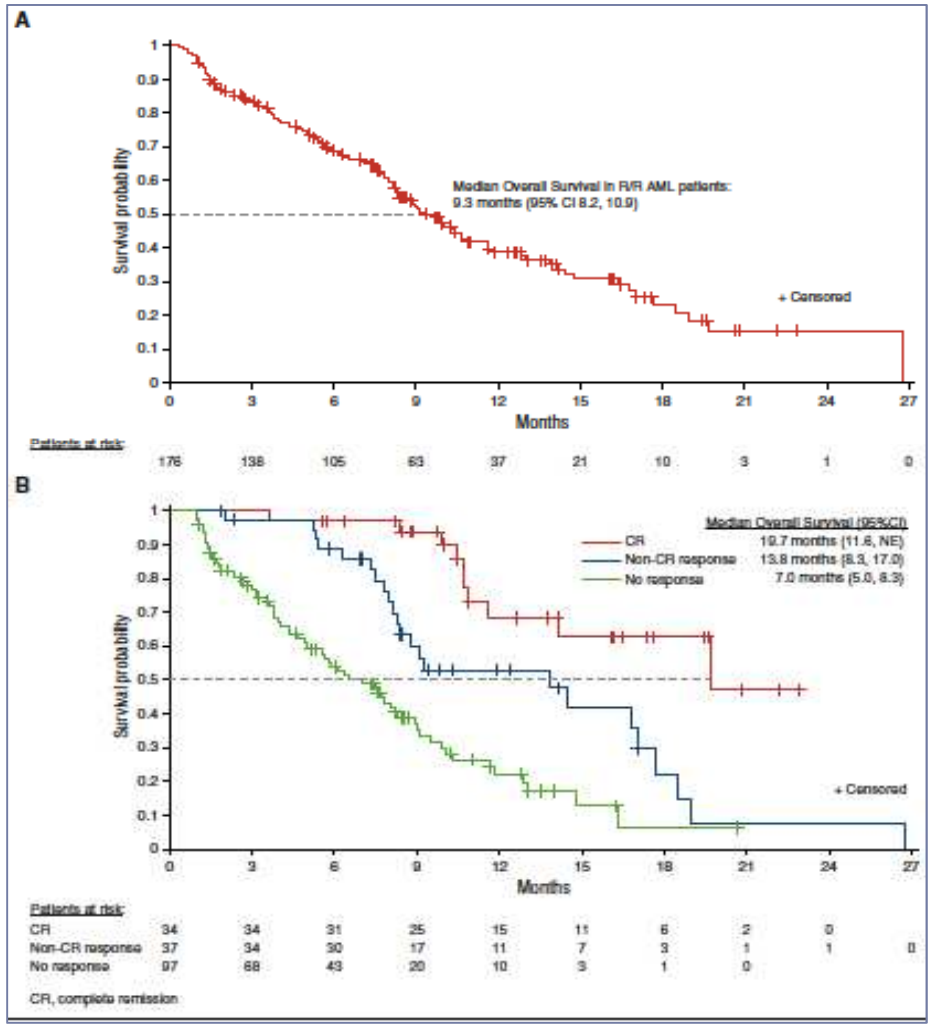
- ORR 66.7 vs 51.2%
- OS 14.7 vs 12.9 mo
- OS for sAML 12.1 vs 6.1 mo

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

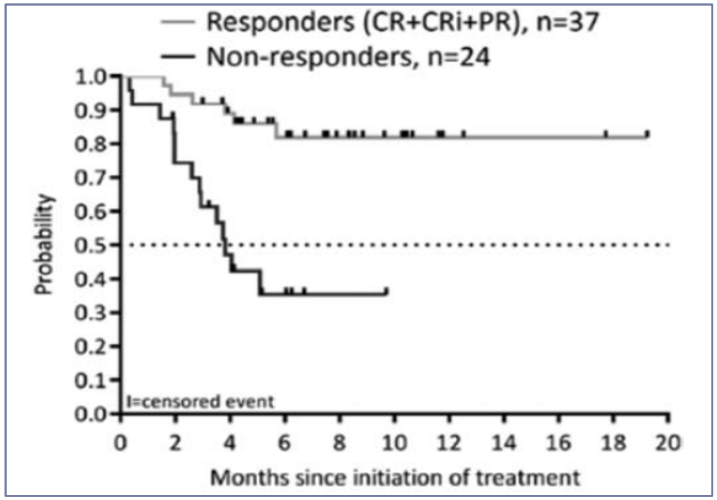
- ORR 40.3%
- CR 19.3%
- Early response 1.9 mo
- Median response duration 5.8 mo
- Median OS 9.3 mo
- OS for patients with CR 19.7 mo
- 1-yr OS 39%

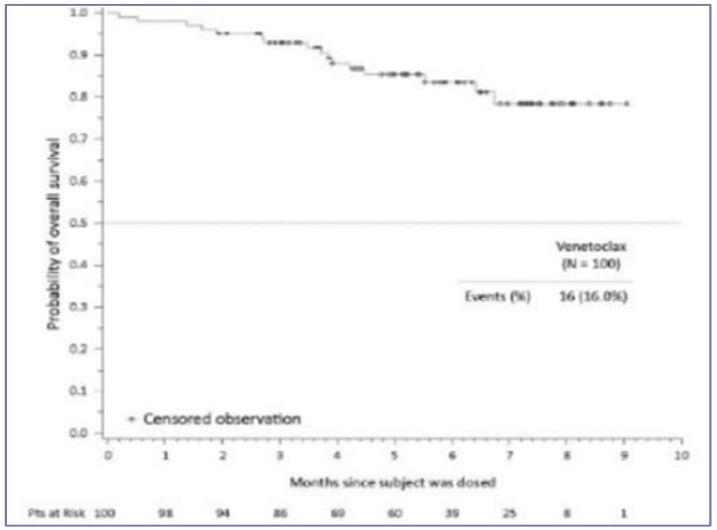
Safety

- 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

Untreated AML, fit patient

NGS–limited/rapid panel
(send full panel)
Gene fusion testing
(RT-PCR or FISH)
FLT3-PCR
Send cytogenetics
Immunophenotyping

48-72 hours

Diagnostic group	Therapeutic options
PML-RARA	ATRA/ATO ? GO
CBF fusion	7+ 3 ? fractionated/low dose GO ? KIT inhibitor (e.g.midostaurin or dasatinib)
TP53 mutation	CPX-351 HMA (or novel HMA) +/- additional agents (e.g. venetoclax)
FLT3-ITD+ or D835+	7+3 + midostaurin (especially if age ≤60) ? selective TKI (e.g. gilteritinib, crenolanib, quizartinib)
IDH1+ or IDH2+	7+3 ? IDH inhibitor (e.g.enasidenib, ivosidenib)
NPM1+ or CEBPa double mutation+	7+3 ? fractionated/low dose GO if no CR1 transplant planned
t-AML or AML with MRC (if known)	CPX-351 ?additional agents depending on mutational profile (e.g. ?LSD1, DOT1L, or BET inhibitor if MLL fusion+)

Perl A. ASH. Hematology 2017

Summary

- New targeted drugs are likely to re-shape the therapeutic landscape of AML
- Daunorubicin and cytarabine continue to play an important role in the treatment of AML