Acute myeloid leukemia

Post – ASH meeting 09/01/2015

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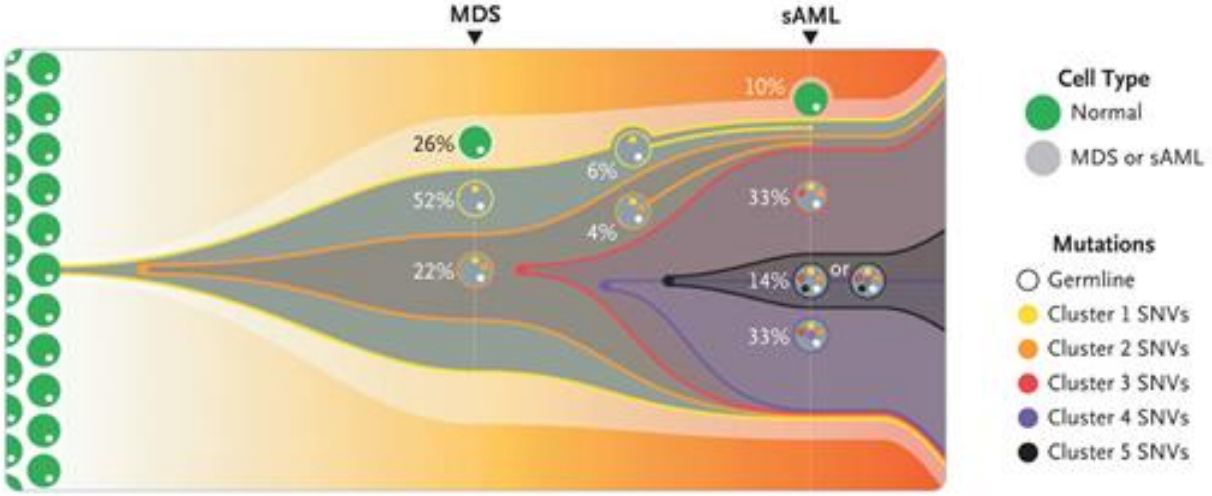
AML at ASH 2014

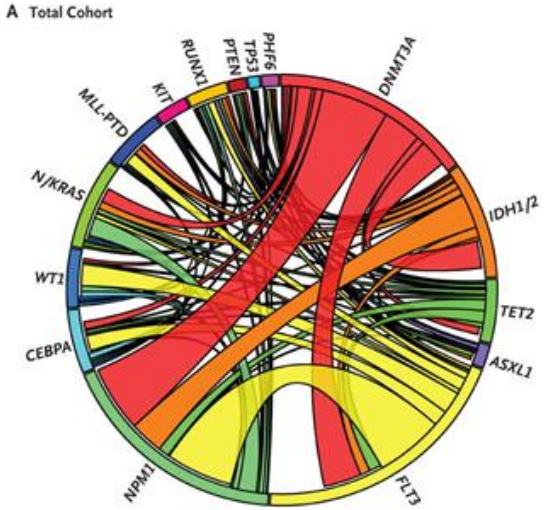
- Biology
- Risk stratification
- Treatment
- MRD assessment
- APL

AML BIOLOGY

AML Biology



Walter et al NEJM 2012



Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

Patel et al NEJM 2012

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AML Biology

- DNMT3a:
  - → Epigenetic regulator
  - → Essential for normal HSC differentiation
  - → Ablation leads to maturation arrest
  - → Additional mutations needed for leukemic transformation:
    - c-KIT
    - Flt3 ITD
  - → Mutation arises early in pre-leukemic phase

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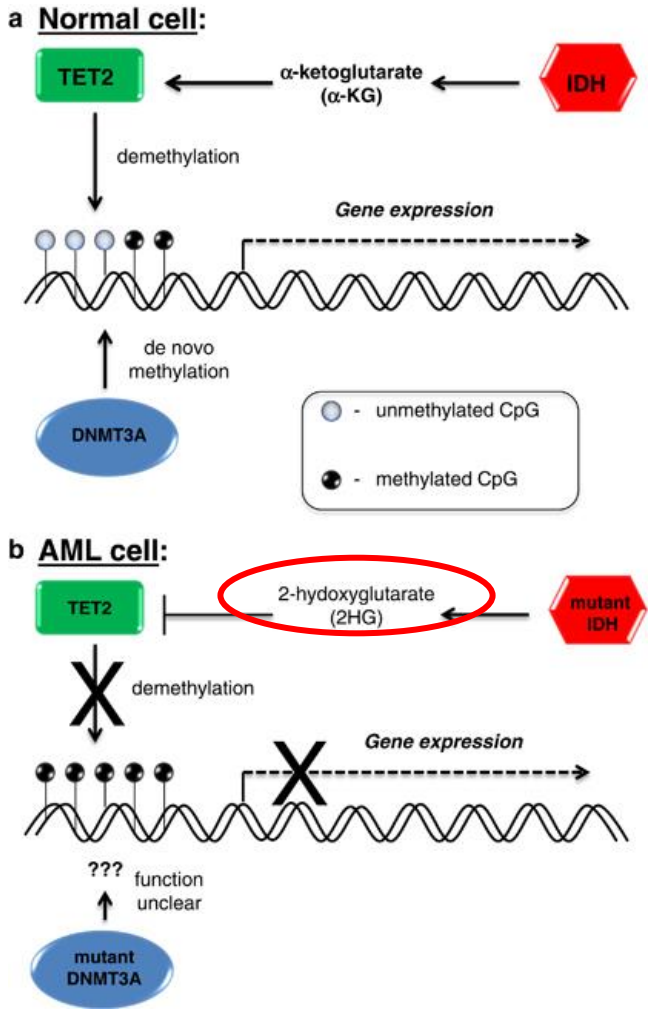
Celik H, et al ASH 2014 abstract # 837 // Poitras JL, et al ASH 2014 abstract #3568

AML Biology: IDH1/2 mutations:



- Elevated 2-HG levels in IDH1/2 mut vs WT pt in:
  - → Serum
  - → Urine
  - → Marrow aspirate
- Regardless mutation type
- Allows for identification of IDH1/2 mut pt

Brunner A, et al ASH 2014 abstract #1045

AML Biology

- Persistence of clonal hematopoiesis in AML patients in CR

→ ALFA 0701:

- 15pt NPM1mut+/DNMT3a mut+
- Persistence of DNMT3a mut+ clone in 40% of patients remaining in CR

→ SAL:

- 48pt NPM1mut+/DNMT3a mut+
- Persistence of DNMT3a mut+ at CR/FU in 87,5%

→ Associated with inferior outcome?

→ SURVIVAL OF PRE-LEUKEMIC HSC AFTER CHEMOTHERAPY

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Otto A, et al ASH 2014 abstract # 121 // Debarri H, et al ASH 2014 abstract #2327

AML Biology

- Genetic evolution of (relapsed) AML
  - → Significant differences, dependent on cytogenetic risk groups
  - → Favorable:
    - Defining aberrations persist at relapse
    - Changes in karyotype 46%
    - Changes in mutational pattern 47%
  - → Intermediate:
    - Predominantly instable at molecular level
  - → Unfavorable:
    - High karyotype instability

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Hartmann L, et al ASH 2014 abstract # 17 // Meggendorfer M, et al ASH 2014 abstract #1029

AML RISK STRATIFICATION

Risk stratification

- 2012 revised risk stratification integrating genetic profiling

Cytogenetic Classification	Mutations		Overall Risk Profile
Favorable	Any		Favorable
Normal karyotype or intermediate-risk ctyogenetic lesions	*FLT3*-ITD-negative	Mutant *NPM1* and *IDH1* or *IDH2*	Favorable
	FLT3-ITD-negative	Wild-type *ASXL1*, *MLL*-PTD, *PHF6*, and *TET2*	Intermediate
	FLT3-ITD-negative or positive	Mutant *CEBPA*	Intermediate
	FLT3-ITD-positive	Wild-type *MLL*-PTD, *TET2*, and *DNMT3A* and trisomy 8–negative	Intermediate
	FLT3-ITD-negative	Mutant *TET2*, *MLL*-PTD, *ASXL1*, or *PHF6*	Unfavorable
	FLT3-ITD-positive	Mutant *TET2*, *MLL*-PTD, *DNMT3A*, or trisomy 8, without mutant *CEBPA*	Unfavorable
Unfavorable	Any		Unfavorable

Patel et al NEJM 2012

Risk stratification

- Development of new scores for CN AML:
  - → Marcucci et al: 7 gene score for CN AML
    - NGS to determine demethylated regions
    - Identification of 7 genes with expression associated with OS: lower score = higher CR rate
  - → Pastore et al: molecular + clinical markers
    - Clinical: age, PS, wbc count
    - Molecular: NPM1, CEBPA, flt3
    - 3 risk groups (OS, RFS)
  - → Thangavelu et al: 8 gene panel
    - Flt3, NPM1, IDH1/2, CEBPA, WT1, RUNX1, TP53

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Marcucci G, et al JCO 2014; 32: 548-556 // Pastore F, et al JCO 2014; 32: 1586-1594 // Thangavelu M, et al ASH 2014 abstract #2333

Risk stratification: flt3

- Impact of WT/mutant allelic ratio
  → Cut-off 0,51
  → Higher ratio = low CR rates
- Impact of ITD insertion site in TKD1
  → Low CR rates
- allelic ratio > 0,51 after post remission therapy (chemo/autoHCT) = unfavorable RFS (p 0,0008) and OS (p 0,004)
- Multivariate analysis: high allelic ratio predictive for beneficial effect alloHCT, IS in TKD1 remains unfavorable

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Schlenk F, et al Blood 2014; 124: 3441-3449

Risk stratification: TP53

- 172 pt / 886 pt analyzed for TP53mut
- Sanger sequencing 29/172 TP53mut+

  → 36 different types of mutations

  → 7 pt with 2 mutations
- 79% of TP53mut pt also had complex karyotype
- Worse OS

  → Median survival 4,3m vs 31m
- Worse RFS

Papayannidis C, et al ASH 2014 abstract #484 // Ferrari A, et al ASH 2014 abstract #2379

Risk stratification

- DNMT3a:
  - → 30% of CN AML
  - → Loss of function mutation
  - → Associated with inferior outcome regardless type of mutation
  - → Persistence after treatment
- ASXL1
  - → Worse OS
- RUNX1 mutation
  - → Worse OS

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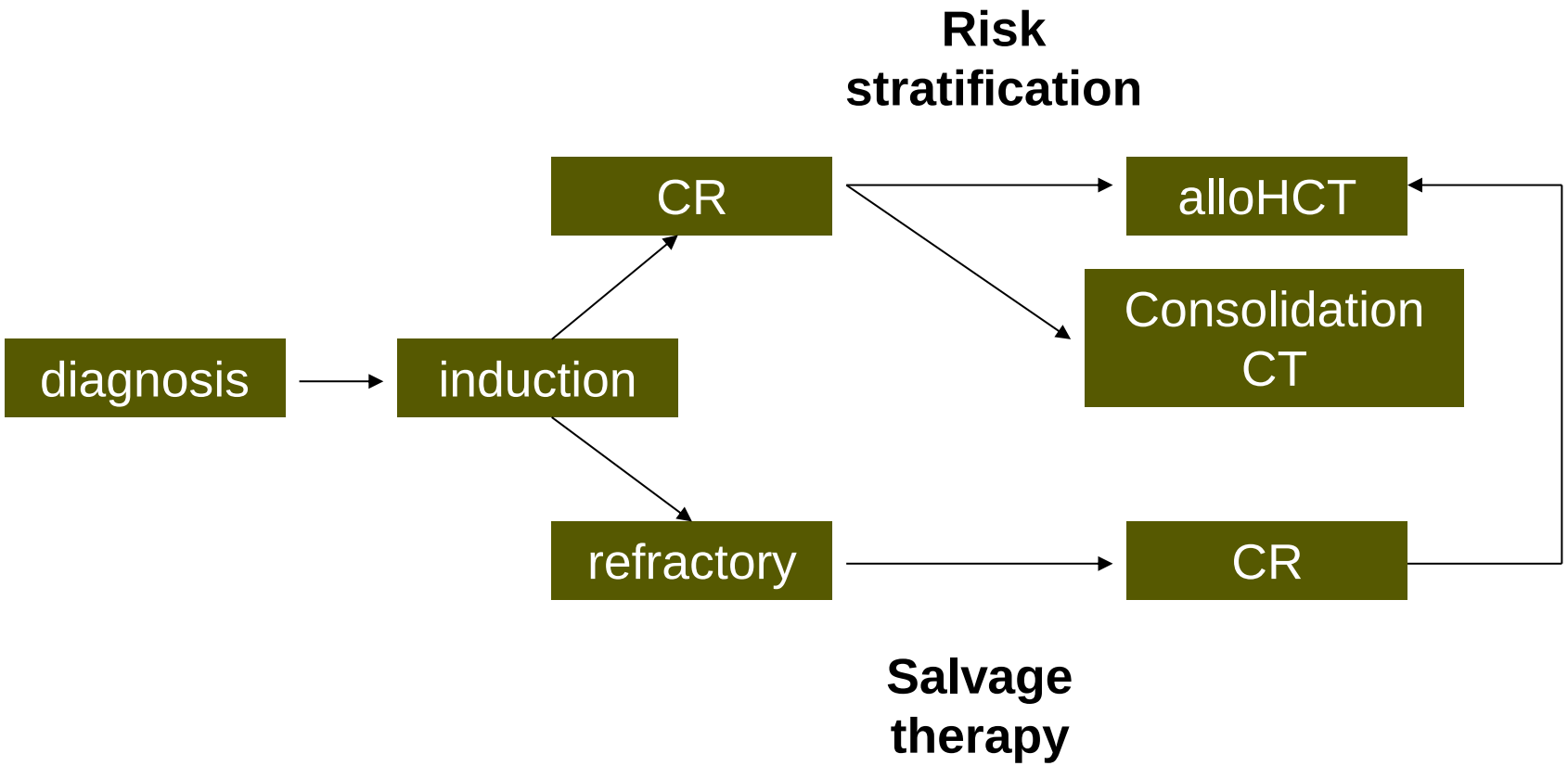
Schnittger S, et al ASH 2014 abstract #122 // Gale RE, et al ASH 2014 abstract #67 // Dohner K ASH Education Program 2014

AML TREATMENT

Treatment


Risk stratification
CR
alloHCT
Consolidation CT
diagnosis
induction
refractory
CR
Salvage therapy

Treatment: new cytotoxic agents

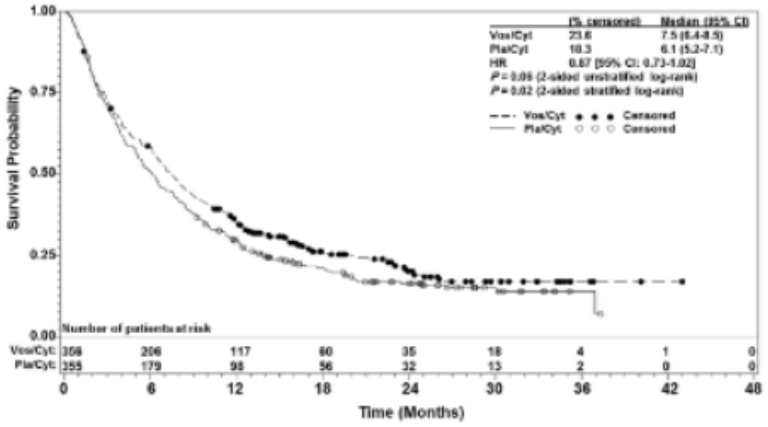
- Vosaroxin
  - → First-in-class anti-cancer quinolone derivative, topo-II-inhibitor
  - → VALOR:
    - Phase III, RCT
    - Cytarabine ± vosaroxin/placebo in R/R AML
    - 711pt
    - Signficantly higher CR rate in vosaroxin arm: 30,1% vs 16,3%

Ravandi F, et al ASH 2014 abstract #LBA-6

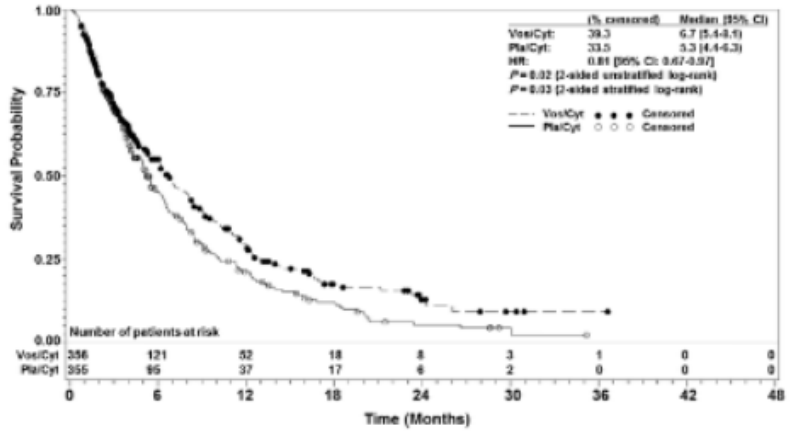
Treatment: VALOR

Figure. OS in patients with R/R AML treated with vosaroxin plus cytarabine vs placebo plus cytarabine

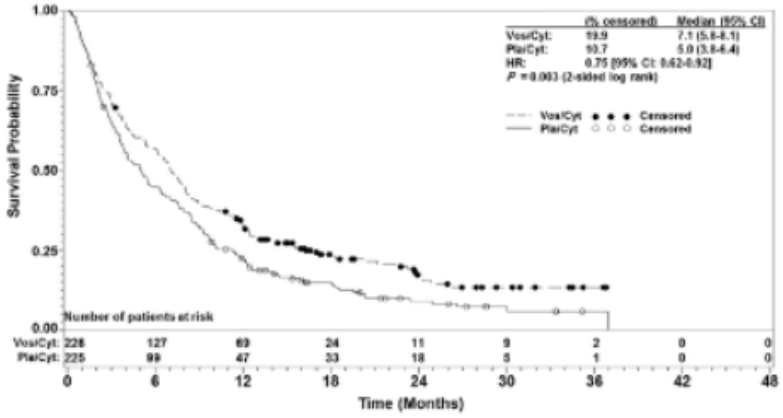
A. OS by treatment arm (N=711)



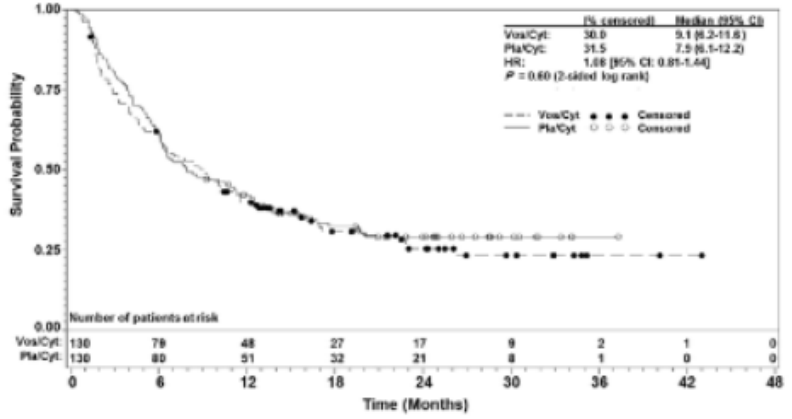
B. OS (censored for ASCT), by treatment arm (N=711)



C. OS in patients aged ≥ 60 years, by treatment arm (n=451)



D. OS in patients aged < 60 years, by treatment arm (n=260)



Ravandi F, et al ASH 2014 abstract #LBA-6

Treatment: cytotoxic agents

- ECOG E1900: final analysis
  - → 657pt, median FU 80m
  - → DNR 90 improves survival in AML up to 60y
  - → Across all (cyto)genetic risk groups
- ALFA 0701: final analysis
  - → 278pt, de novo AML 50-70y
  - → standard treatment ± GO
  - → No difference in CR+Cri
  - → Trend for fewer 1ary refractory pt (30 vs19)
  - → Significantly better EFS, RFS
  - → No difference in 3y OS (36 vs 44%)

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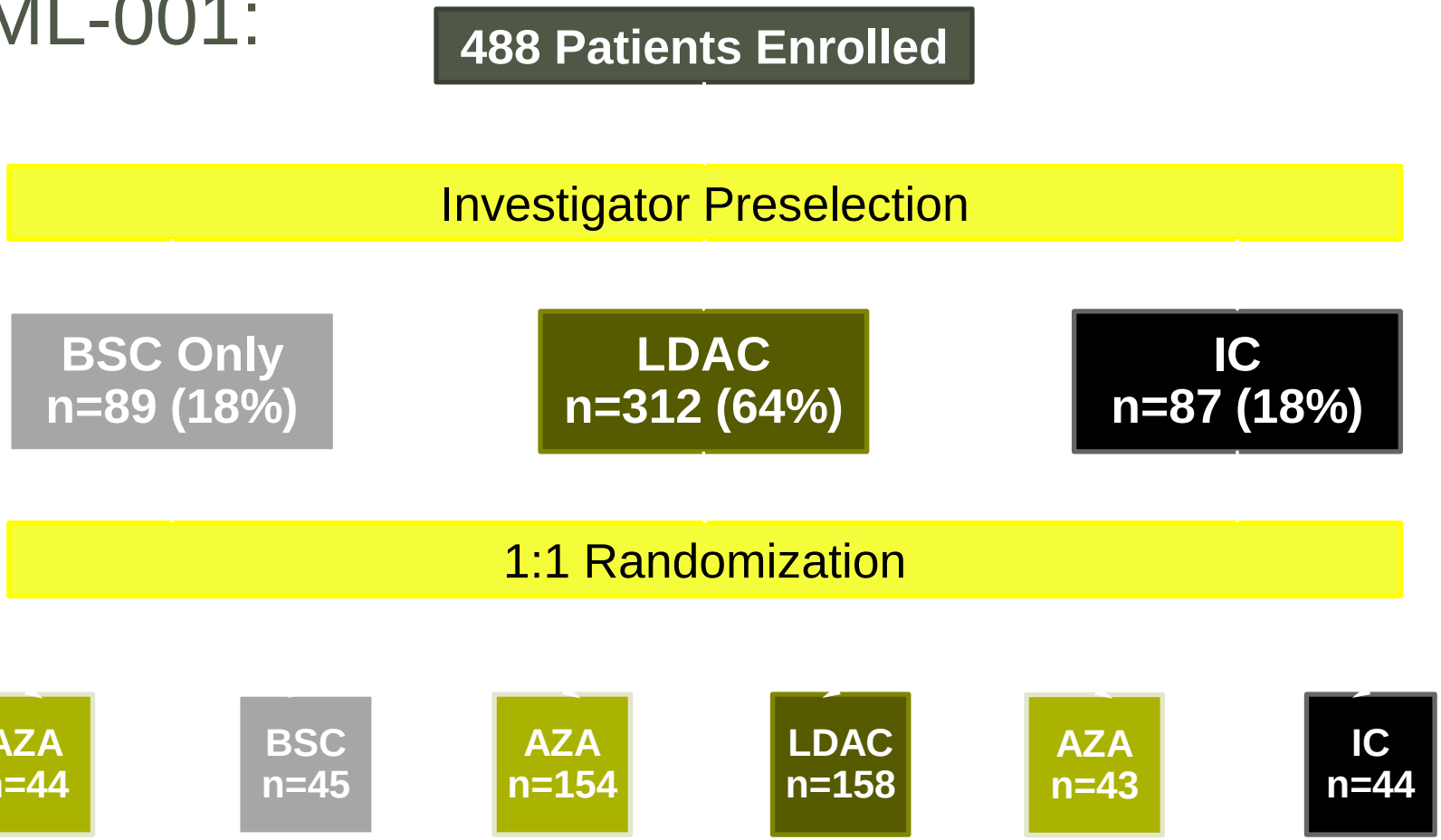
Luskin M, et al ASH 2014 abstract #373 // Castaigne S, et al ASH 2014 abstract #376

Targeted therapy: epigenetics: AZA

AML-001:



Seymour J, et al ASH 2014 abstract #10

Targeted therapy: epigenetics: AZA

- AML-001
- Vidaza® in newly diagnosed AML with >30% blasts
- Age ≥ 65years
- Inelegible for alloHCT
- AZA vs CCR (LDAC, BSC, ICT)
- No significant improvement in OS
- Pre-planned censoring at next treatment: significant better OS for AZA

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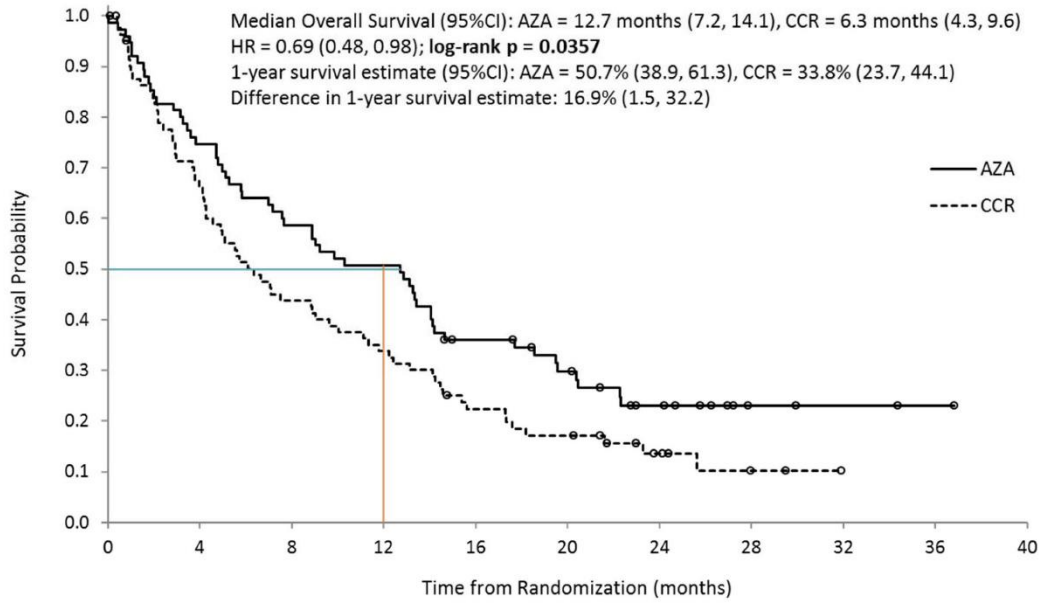
Seymour J, et al ASH 2014 abstract #10

Targeted therapy: epigenetics: AZA

- AML-001 subgroup analysis:

  → 1/ AML-MRC

Figure. Overall Survival in Patients with AML with Morphologic Dysplastic Changes Treated with AZA vs. CCR



Pts at risk											
AZA	75	56	44	38	25	19	11	4	3	2	0
CCR	83	53	35	27	17	13	6	2	0		

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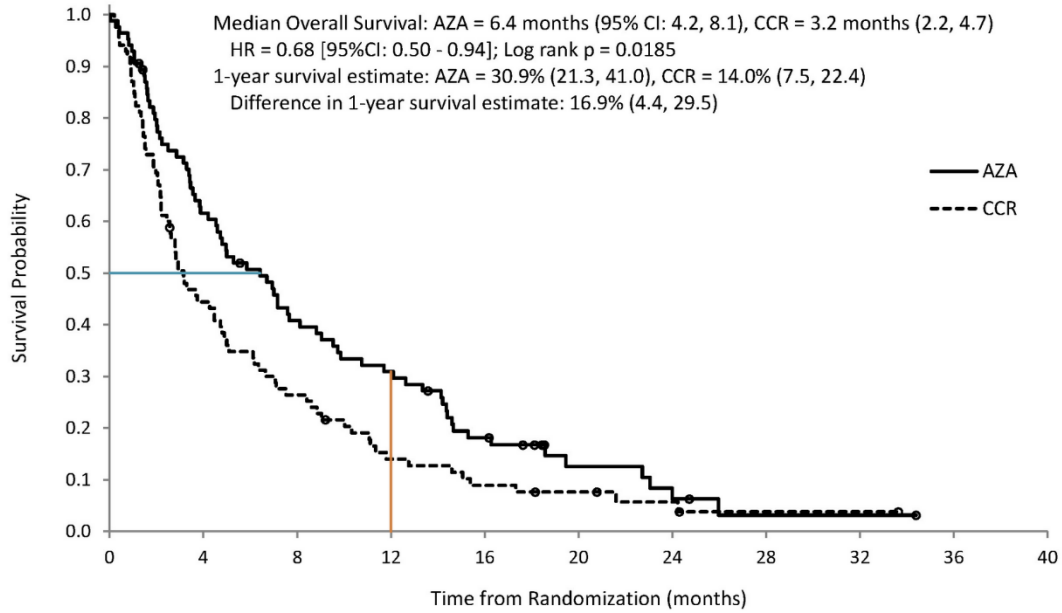
O Censored

Seymour J, et al ASH 2014 abstract #10

Targeted therapy: epigenetics: AZA

- AML-001 subgroup analysis:
  → 2/ cytogenetic risk group

Figure. OS in Patients with Poor-risk Cytogenetics



Pts at risk										
AZA	85	51	33	25	14	6	3	1	1	0
CCR	85	37	22	11	7	5	3	1	1	0

O Censored

Döhner H, et al ASH 2014 abstract #621

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Targeted therapy: epigenetics

- Decitabine:
  - → Priming before ICT
  - → Prolonged administration
- New molecules:
  - → AG-221: IDH 2 inhibitor
  - → EZP5676: DOT1L inhibitor
  - → OTX015: BET bromodomain inhibitor
  - → SGI-110: 2nd generation hypomethylating agent

Halpern AB, et al. ASH 2014 Abstract #3730 // Stein E, et al. ASH 2014 Abstract #115 // Stein E, et al. ASH 2014 Abstract #387 // Dombret H, et al. ASH 2014 Abstract #117 // Roboz G ASH Education Program 2014

Targeted therapy: flt3

- SORAML:
  - → 276 pt, final analysis, AML < 60y
  - → chemo + sorafenib/placebo followed by 12m maintenance
  - → Significantly prolonged 3y EFS, RFS
  - → No significance for OS
  - → Flt3 ITD+ pt trend for prolonged OS en RFS in favor of sorafenib

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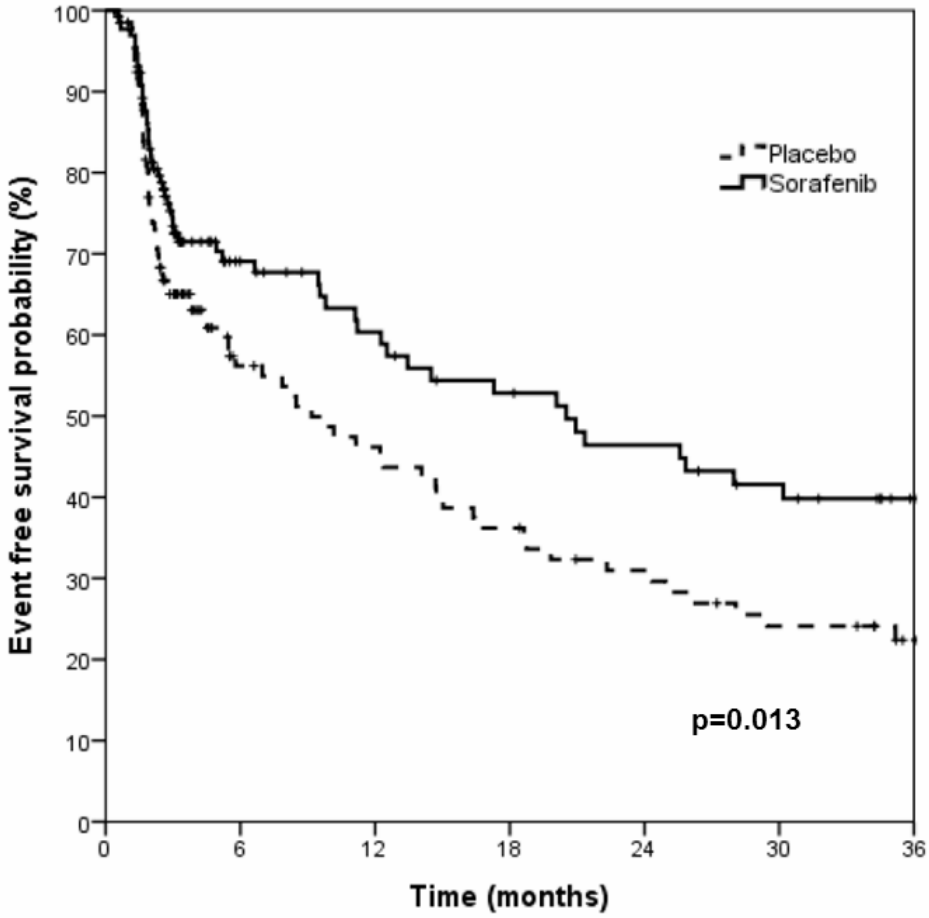
Röllig C, et al ASH 2014 abstract #6

Targeted therapy: flt3

- SORAML:



Röllig C, et al ASH 2014 abstract #6

Targeted therapy: flt3

- Crenolanib:
  - → Phase II in R/R AML flt3+
  - → Monotherapy
  - → Flt3 ITD or flt3 TKD
  - → 34 pt evaluable
  - → Significantly better response in TKI naive pt
    - Median OS 55w vs 13w
    - On target flt3 inhibition

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Randhawa JK, et al ASH 2014 abstract #389

Targeted therapy: c-KIT

- KIT mutations in ca 30% of CBF-AML
- In general poor prognosis
- Dasatinib:
  - → Multikinase-inhibitor
  - → Synergism with cytarabine
  - → Inhibition of WT and mutant KIT
  - → Inhibitor of AML stem/progenitor cell growth & survival

Targeted therapy: c-KIT

- CALGB 10801
- Update, median follow-up 21m

Table. Clinical outcomes

	All (n=59)	Younger (n= 45)	Older (n= 14)	RUNX1/RUNX1T1 (n= 20)	CBFB/MYH11 (n= 38)	*KIT*-wt (n=46)	*KIT*-mut (n=10)
CR* (%)	90	93	79	90	89	89	90
Relapseº (%)	17	13	29	20	16	17	20
2-yr DFS# (%)	72	74	65	79	67	72	70
2-yr OS¶ (%)	87	96	61	85	89	86	90

*CR, complete remission; º Relapse rate at any time #DFS, disease-free survival, ¶OS, overall survival

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Marcucci G, et al ASH 2014 abstract #8

Targeted therapy: cell cycle inhibitors

- Volasertib:
  - → Polo-like kinase 1 inhibitor
  - → Phase II
  - → Median EFS 2,3m vs 5,6m (p0,021) LDAC vs LDAC+volasertib
  - → Median OS 5,2m vs 8m (p0,047) LDAC vs LDAC+volasertib

Döhner H, et al Blood 2014; 124: 1426-1433

Targeted therapy: CXCR-4

- CXCR-4 anchors cells in BM via interaction with CXCL12/SDF-1
- Ulocuplumab = anti-CXCR-4 antibody
- Phase I
- R/R AML, 73pt
- Ulocuplumab + MEC
- CR+CRi 51%, 4pt in CR/CRi after 1 dose of ulocuplumab

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Becker S, et al ASH 2014 abstract #386

Treatment: new agents

- AMG-330
  → CD33/CD3 BiTE antibody
- ABT-199
  → Selective Bcl-2 inhibitor
- RG7388
  → MDM2 antagonist
- CPX-351
  → Cytarabine+daunorubicin liposome

MINIMAL RESIDUAL DISEASE

Minimal residual disease

- Discrepancies morphology-flow cytometry
- Heterogeneity of the disease:
  → Mean of 13 mutations in 1 AML pt
- Translocations:
  → Rare breakpoints
  → Comparison to household gene (abl)
  → MRD assessment by RT-qPCR provides indepent prognostic info
  → Guidance of treatment regardless flt3/NPM1/… status

Minimal residual disease

- WT1:
  - → Not unique
  - → Not universal: 46% OK in PB, 13% OK in BM
- NPM1 mutation
  - → Off the shelf kits, sensitivity 1/100000
  - → AML17 trial (NCRI):
    - PCR status in PB following 2nd chemotherapy
    - Most potent prognostic factor
    - Present in 98/100 relapses
- New techniques:
  - → NGS/digital PCR

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ACUTE PROMYELOCYTIC LEUKEMIA

Acute promyelocytic leukemia

- Long term follow-up of patients treated with ATRA-ATO
- 217 pt, treated between 2001-2010
- No late toxicities
- No significant arsenic retention
- Novel agents

→ Next generation retinoids

- tamibarotene

→ Next generation arsenic:

- Oral tetra-arsenic-tetra-sulfide

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Zhu H, et al ASH 2014 abstract #282 // Sanford D, et al ASH 2014 abstract #2751

Conclusions

- Further insight in AML biology
- Identification of new targets for treatment
- Efforts to improve risk stratification of intermediate risk AML, CN AML
- Targeted treatment
- MRD assessment

  → complicated by heterogeneity of the disease
- ATRA-ATO gaining ground

Questions?