

Höhepunkte des Amerikanischen Hämatologie-Kongresses San Francisco, 2008

MDS / Akute Leukämien

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Abt. Onkologie / Hämatologie**



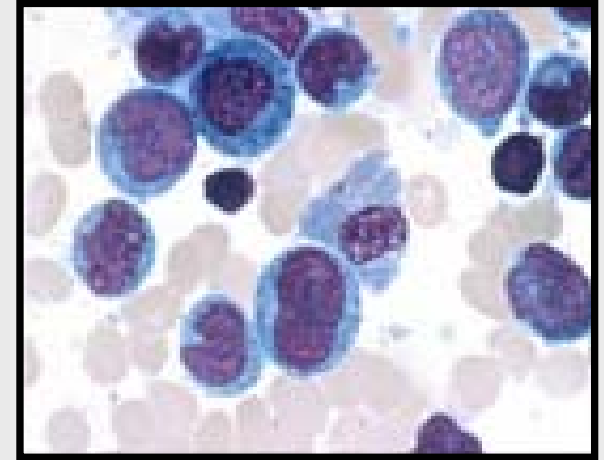
MDS Hintergrund und Epidemiologie

Heterogene Gruppe von klonalen Erkrankungen der hämatopoetischen Stammzellen

Charakterisiert durch

- Ineffektive, dysplastische Hämatopoese
- Periphere Zytopenien
- Variable Rate an Progress zur AML (ca. 30% insges.)

- Häufigste maligne hämatologische Erkrankung:
Jährliche Inzidenz USA (SEER): 10.000



US Medicare Population Datenanalyse (2003-2005): Jährliche Inzidenz MDS 40.000-70.000

(ASH 08; # 636)



Klassifikation bislang

FAB Klassifikation

- RA: <5% Blasten KM, <1% PB
- RARS: <5% Blasten KM, \leq 1% PB, zusätzl. >15% Ringsideroblasten
- RAEB: 5-20% Blasten KM, <5% PB
- RAEB-t: >20-30% Blasten KM, \geq 5% PB
- CMML: <5-30 Blasten KM, <5% PB, zusätzl. Monozytose $1 \times 10^9/L$

WHO Klassifikation 2001

- RA: Dysplasie* nur rote Reihe
- RARS: zusätzl. >15% Ringsideroblasten
- RCMD: Bi/Panzytopenie, Dysplasie* mind. 2 Reihen
- RAEB-1: 5-9% Blasten im KM
- RAEB-2: 10-19% Blasten
- MDS mit 5q-: isolierte del 5q, Blasten <5%
- MDS unklassifiziert: Blasten <5%, nicht RA/RARS

* in mind. 10% der Zellen



WHO Klassifikation 2008

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- MDS unklassifiziert: Blasten <5%, nicht RA/RARS

* in mind. 10% der Zellen

WHO Klassifikation 2008

- **RCUD + :**
 - Refraktäre Anämie (RA)**
 - Refraktäre Neutropenie (RN)**
 - Refraktäre Thrombozytopenie (RT)**
- RARS: zusätzl. >15% Ringsideroblasten
- RCMD: Bi/Panzytopenie, Dysplasie* mind. 2 Reihen
- RAEB-1: 5-9% Blasten im KM
- RAEB-2: 10-19% Blasten
- **MDS mit isolierter del (5q), Blasten <5%**
- MDS,U (unklassifiziert): Blasten <5%, nicht RA/RARS

+ gelegentlich Bizytopenie



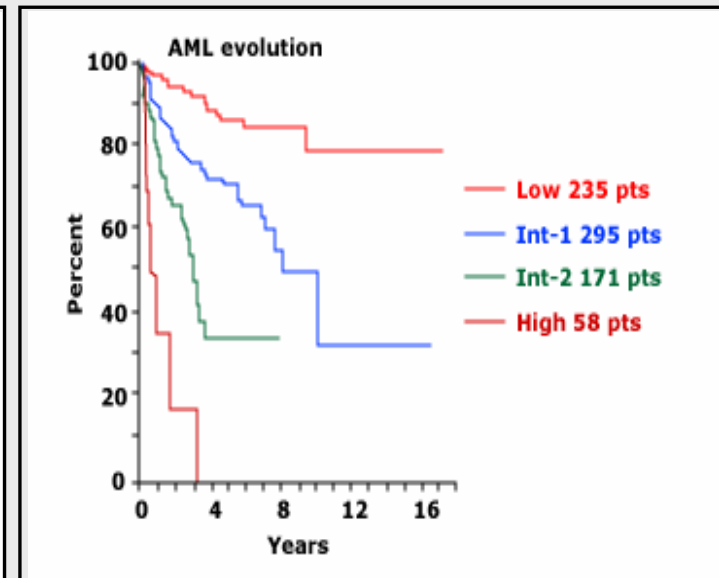
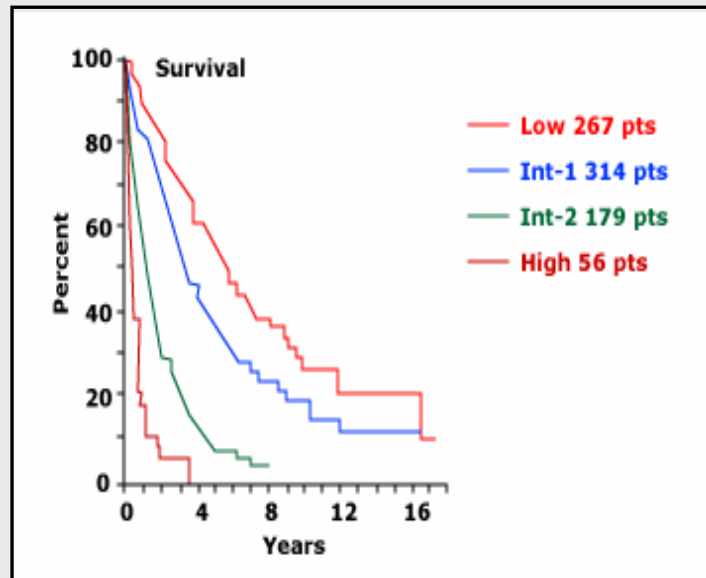
Prognose (IPSS, 1997)

Punkte	0	0,5	1	1,5	2
KM-Blasten [%]	<5	5-10	-	11-20	21-30
Karyotyp* (Risiko)	niedrig	mittel	hoch	-	-
Zytopenie**	0-1	2-3	-	-	-

* **niedrig:** normal: 5q-, 20q-, -Y **hoch:** komplex, Chr. 7-Veränd. **mittel:** andere

** Hb <10 g/dl Granulozyten <1500 /ul Thrombo <100.000 /ul

Low: 0
Int-1: 0,5-1
Int-2: 1,5-2
High: ab 2,5



IWG Response Criteria in MDS

Complete Remission (CR)

- <5% BM blasts
- No dysplasia
- Hgb > 11
- PMN > 1.5
- PLT > 100K

Partial Remission (PR)

- Same as CR
- 50% ↓ blasts

Hematologic Improvements

•RBC (HI-E)

Major: Transfusion independence or >2g/dL ↑ in Hgb

Minor: 50% ↓ transfusion requirement or 1-2 g/dL ↑ in Hgb

•Platelets (HI-P)

Major: Plat transfusion independence or ↑ by 30K if baseline <100K

Minor: 50% ↑ in plat count (at least 10K) if baseline <100K

•PMN (HI-N)

Major: ANC <1500, a 100% ↑ or 500/μL ↑ (whichever is greater)

Minor: ANC >1500, a 100% ↑ but <500/μL

Cheson 2000



Additional chromosomal abnormalities in del(5q) MDS

¹Database analysis of 305 patients with del(5q) MDS (all subtypes) treated with BSC

- Median age: 66 years; 52% WHO RA;

Cytogenetics	n (%)	Median survival, mos
del(5q) alone	204 (67)	69
▪ + 1 abnormality	52 (17)	55
▪ + ≥ 2 abnormalities	49 (16)	8

- No significant difference between del(5q) alone and del(5q) + 1 abnormality (<-> WHO)
- No single additional abnormality with particularly better or worse prognosis

²Meta-analysis of MDS studies from 1966-2008 (n = 2743, <20% blasts); del(5q): n = 287 (10%)

- Median age: 66 years; 3.4% low/int-1 MDS

Cytogenetics	Median survival, mos
Deletion 5q	9
▪ Alone	33
▪ + 1 abnormality	17
▪ + = 2 abnormalities or -7	6-12
▪ + IPSS low-intermediate 1	29

(ASH 08; #1649¹; #1644²)



Prognostic value of iron overload in MDS

- RBC transfusion dependency (TD) is prognostic in MDS patients (Malcovati JCO 2007).
 - Influence of iron overload: yet small patient numbers!
- > Retrospective analysis of 2994 (FAB) / 2107 (WHO) de novo MDS patients.

Univariate analysis:

OS significantly dependent on TD:

TD at diagnosis: Median 19M

TD during evolution: Median 60M

Not TD: Median 96M

Multivariate analysis:

Independent prognostic value of

- iron overload (Ferritin >1000ng/ml)
- TD

Prognostic Factor	HR*	P Value
OS		
▪ Iron overload	2.1	< .0001
▪ Transfusion dependency	7.2	< .0001
LFS		
▪ Iron overload	1.6	.04
▪ Transfusion dependency	2.9	< .0001

*Multivariate analysis on cases with complete transfusion and serum ferritin records (n = 731).

-> avoiding or reducing iron overload by chelation may improve OS and reduce risk of AML

(ASH 08; # 640)



Iron chelation in MDS I

EPIC trial: Multicenter, open-label, single-arm, 1-year trial of deferasirox in transfusion dependent MDS patients (n = 341);

Inclusion criteria: Baseline serum ferritin \geq 1000 ng/mL, > 20 units red blood cell transfusions

- Treatment: deferasirox 10-30 mg/kg daily for 12 months
- Median age: 68 years (range: 11-89)
- Mean transfusion dependency duration: 3.6 years
- Previous chelation: 52%
- Discontinued treatment due to drug-related AE: 13%

Serum ferritin decrease over time:

Mo	Median Serum Ferritin, ng/mL
0	2730
3	2358
6	2210
9	2076
12	1904

Drug-related AE, all grades:

- Diarrhea: 32%
- Nausea: 13%
- Vomiting: 8%

(ASH 08; # 633)



Iron chelation in MDS II

US03: Phase II, open-label, multicenter, single-arm, 3-year trial of deferasirox in IPSS Low or Int-1 MDS patients (n = 176);

Inclusion criteria: Baseline serum ferritin \geq 1000 ng/mL, > 20 units red blood cell transfusions

- Treatment: deferasirox initially 20mg/kg KG daily, up to 40mg/kg (tolerability and response)
- Median age: 70 years (range: 21-90)
- Mean duration of transfusions: 3.5 years
- Discontinued treatment due to drug-related AE: 13%

Serum ferritin decrease over time:

Month	Serum Ferritin, ng/mL (N = 176)
0	3397
3	3057
6	2802
9	2635
12	2501

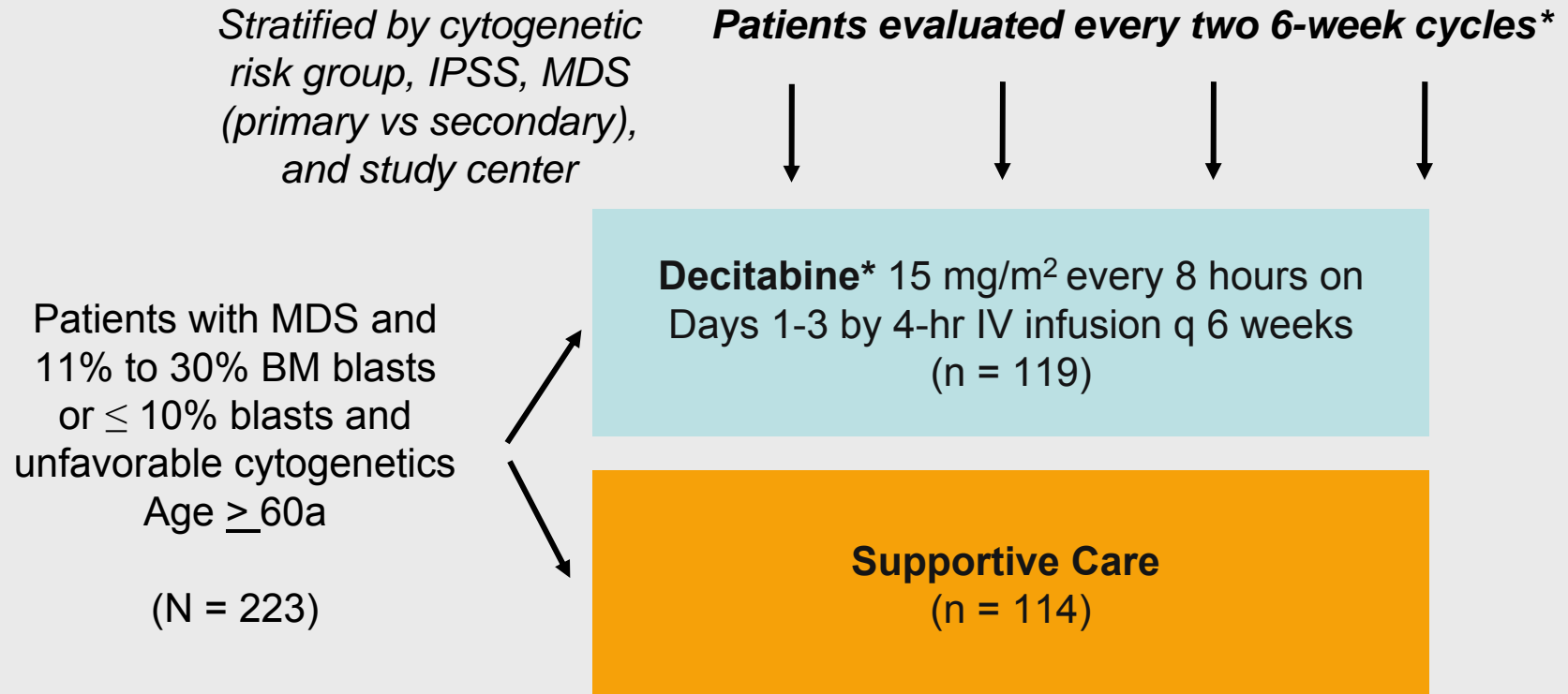
-> HI by IWG criteria: 8/176 (5%)

(ASH 08; # 634)



Decitabine vs BSC in intermediate or high risk MDS

Randomized international multicenter phase III study



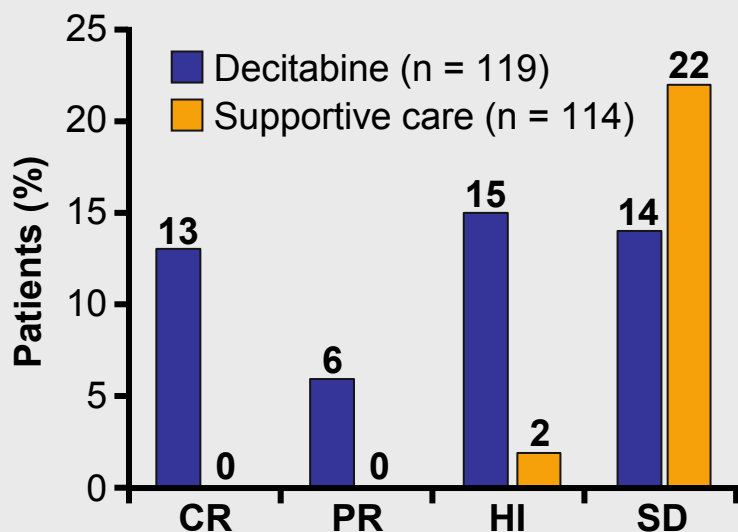
*Patients with hematologic improvement, SD, PR, or CR continued treatment (up to 8 cycles) except those with CR duration ≥ 2 cycles.

(ASH 08; # 226)



Decitabine vs BSC in intermediate or high risk MDS (cont.)

- Median age: 70 years (60-90); RAEB-t in 32%;
- IPSS: int-2 55%; high-risk 38%
- Poor cytogenetics: 46%
- Previous treatment: 20%



Response, mos	Dec (n = 119)	BSC (n = 114)	P Value
Median OS	10.1	8.5	.38
Median PFS	6.6	3.0	.004
Median time to AML or death	8.8	6.1	.24

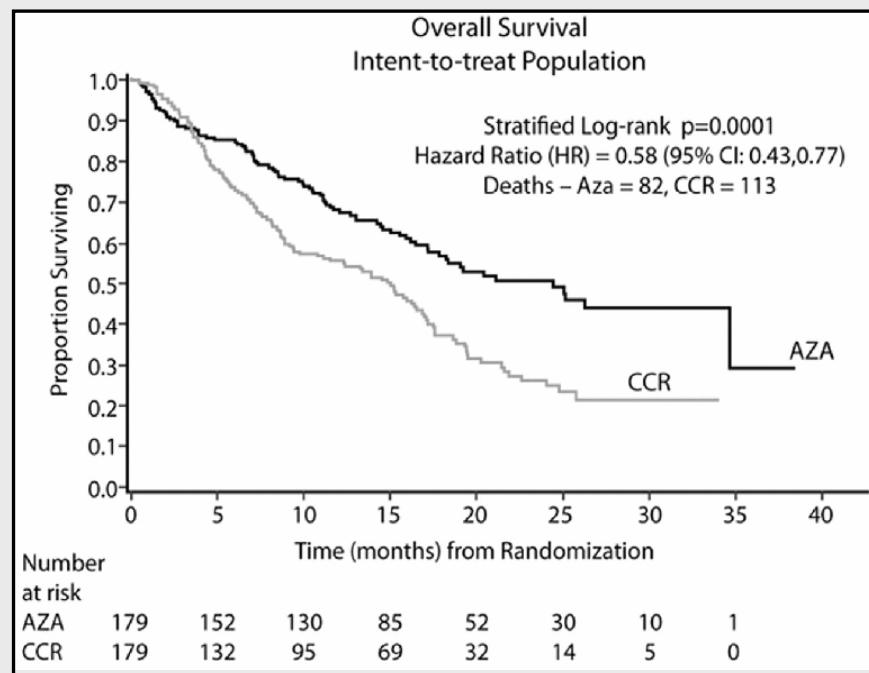
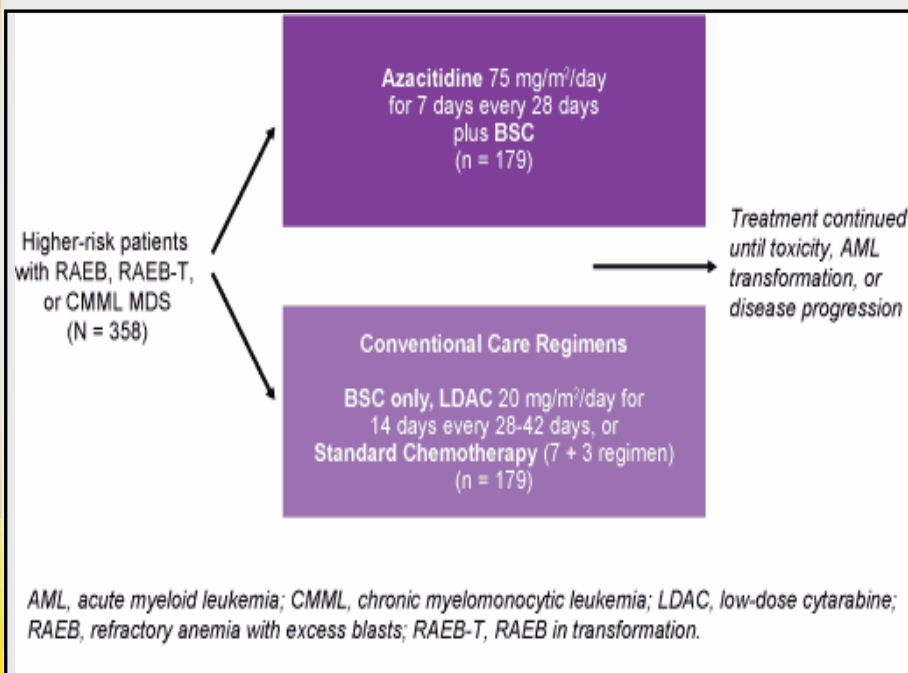
- > RR of 34% similar to previous studies
- > Difference between Decitabine and BSC regarding OS and AML development not significant (treatment duration? subsequent treatments?)

(ASH 08; # 226)



2007 AZA-001: Azacitidine vs CCR in Higher-Risk MDS

- International, multicenter, randomized, controlled, phase III study
- Methyltransferaseinhibition: Demethylation, i.e. activation of tumorsuppressorgenes
- Azacitidine (75 mg/m²/d for 7d q 28d vs. CCR



2 year survival 51% vs. 26%, p=0.001;

(ASH 07; # 817)

Continued Azacitidine in higher risk MDS: Response

91 of 179 Aza patients (51%) achieved IWG 2000 response \geq hematologic improvement

Response	Patients Achieving Response, n	Median Azacitidine Cycles, n (range)
OR	91	14.0 (2-30)
▪ CR	30	16.5 (5-30)
▪ PR	21	14.0 (2-27)
▪ HI	40	11.5 (3-25)

Median cycles to first response: 2 (range 1-22)

87% achieved first response by cycle 6, 90% by cycle 9

First response as best response: 57%

Response improved after first response: 43% (median: additional 4 courses; range: 1-11)

(ASH 08; # 227)



Azacitidine + Lenalidomide in Higher-Risk MDS

Rationale: Lenalidomide and AZA have single agent activity

Multicenter phase I trial: -> Improved response by combination?

N = 19 patients with higher risk MDS enrolled, 1 excluded for diagnosis of AML

Charakteristika		Median (Range), n=18
Alter (Jahre)		68 (52-78)
? /? (n)		6/12
Zeit seit Diagnose		5 Wochen (2-106)
Baseline:	Hgb	9,9
	Plt	69K
	ANC	832
	Epo	95
	Blasten (%)	11
IPSS (n):	Int-1	3
	Int-2	9
	High	6

(ASH 08; # 221)



Azacitidine + Lenalidomide in Higher-Risk MDS (cont.)

ORR 72% (13/18) (7 CRs, 1 PR, 3 HI, 2 BM CR)

Dosing for phase II studies: AZA 75 mg/m² SC. d1-5 and Lenalidomid 10 mg PO d1-21

Kohorte	AZA Dose	Rev Dose	IPSS Categories	Grade 3/4 non-heme toxicities	Maximum Response
1	75 mg/m ² SC days 1-5	5 mg PO days 1-14	1 Int-1 2 Int-2	1	2 CR 1 progression
2	75 mg/m ² SC days 1-5	5 mg PO days 1-21	2 Int-2 1 High	2	1 CR, 1 PR, 1 HI
3	75 mg/m ² SC days 1-5	10 mg PO days 1-21	1 Int-2 2 High	0	2 CR, 1 stable disease
4	50 mg/m ² SC days 1-5, 8-12	5 mg PO days 1-14	1 Int-1 2 Int-2	2	2 CR, 1 stable disease
5	50 mg/m ² SC days 1-5, 8-12	5 mg PO days 1-21	2 Int-2 1 High	2	1 HI 1 stable disease 1 progression
6	50 mg/m ² SC days 1-5, 8-12	10 mg PO days 1-21	1 Int-1 1 Int-2 1 High	2	1 HI 2 BM CR

(ASH 08; # 221)

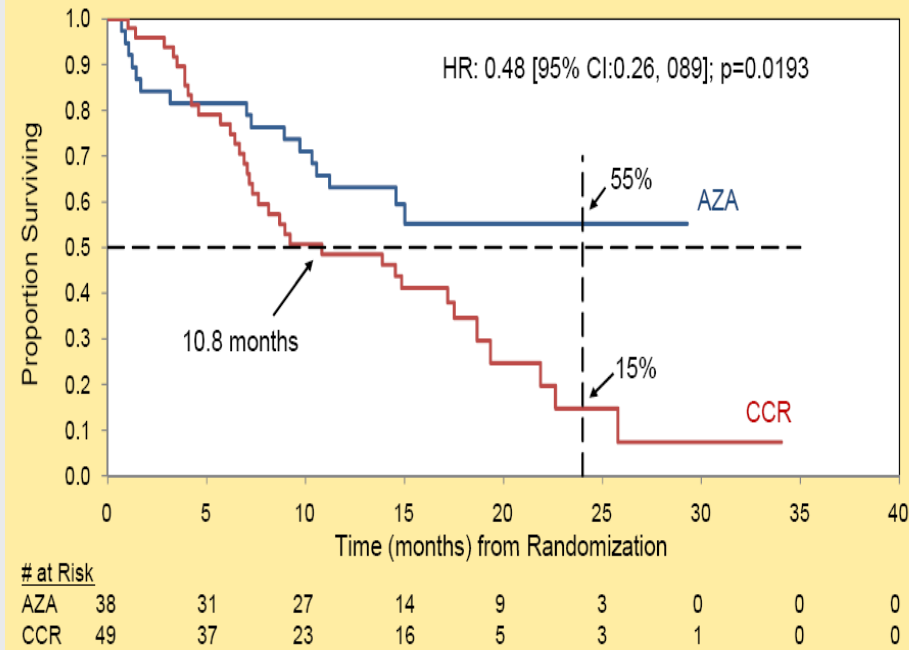


Azacitidine in elderly MDS patients ($\geq 75a$)

Subanalysis: Patient age ≥ 75 , n = 87 (24%); AZA vs. CCR [BSC =33, LDAC =14, IC =2]

- AZA q 4-5 weeks tolerated in $> \frac{3}{4}$ of patients; discontinued due to AE: 13% AZA vs. 8% CCR

Figure 2. Overall Survival in Patients ≥ 75 Years of Age: AZA vs CCR



- Medianes OS: AZA: not reached ($>17.7M$) vs. 10,8M, p = 0.0193
- 2-year survival: 55 vs. 15%, p=0.0003

Figure 3. Transfusion Independence: Patients ≥ 75 Years of Age

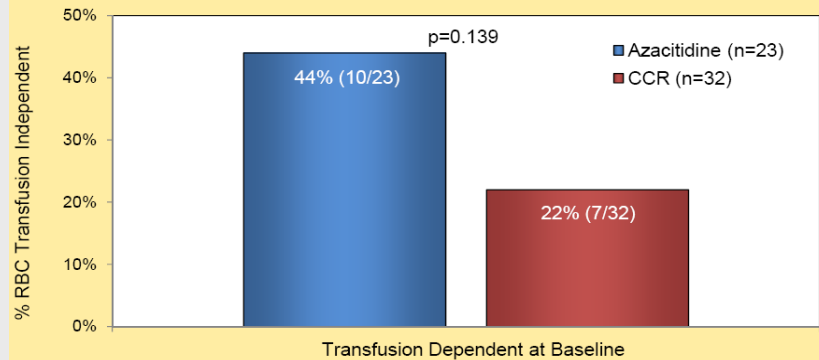
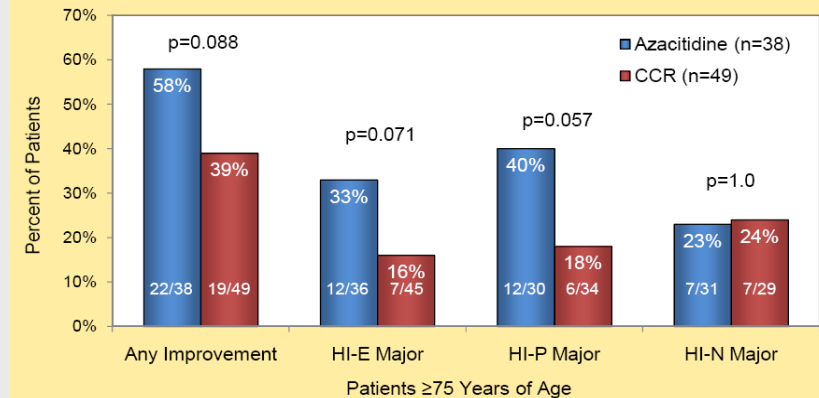


Figure 4. IWG 2000 Hematological Improvement



(ASH 08; # 3629)

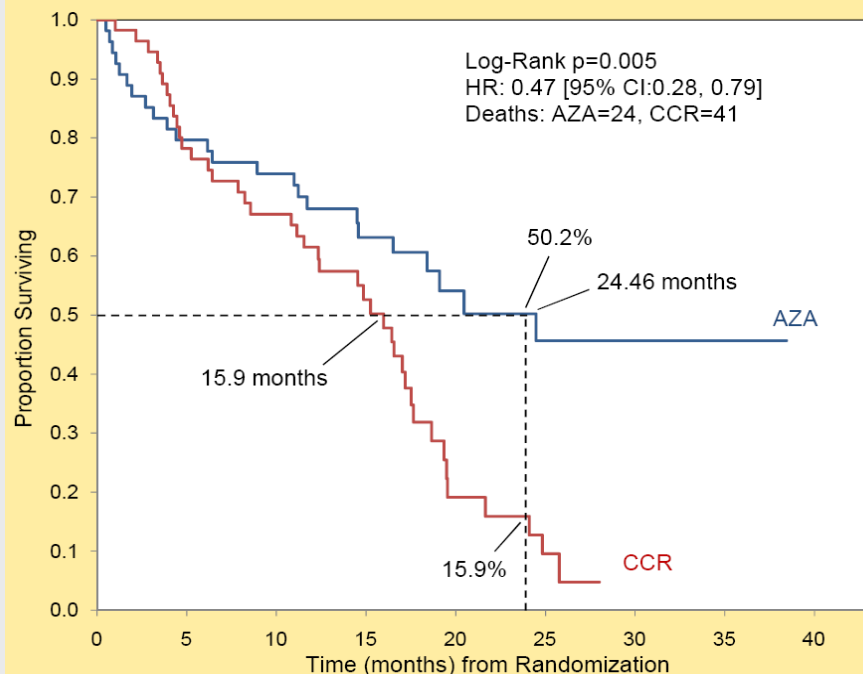
Azacitidine in AML

Subanalysis of AZA-001 study: Patients with $\geq 20\%$ blasts (WHO AML), n = 113

- Median 23% blasts
- Median age: 70 years
- Poor cytogenetics: 24%

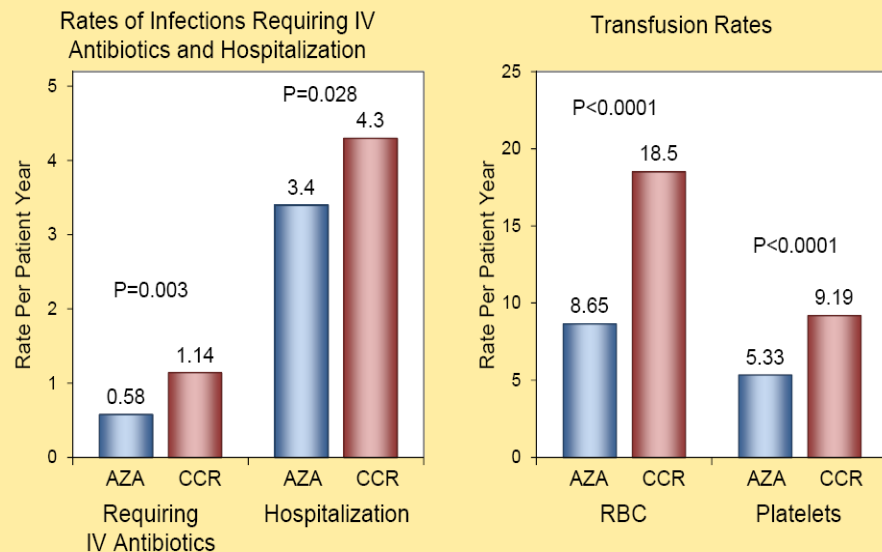
Azacitidine (75 mg/m²/d for 7d q 28d; median 8 cycles vs. CCR(IC: 10; LDAC: 18; BSC: 25))

Figure 1. Overall Survival: AZA vs CCR



# at Risk	0	5	10	15	20	25	30	35	40
AZA	55	43	38	26	15	10	4	1	0
CCR	58	43	36	22	6	3	0	0	0

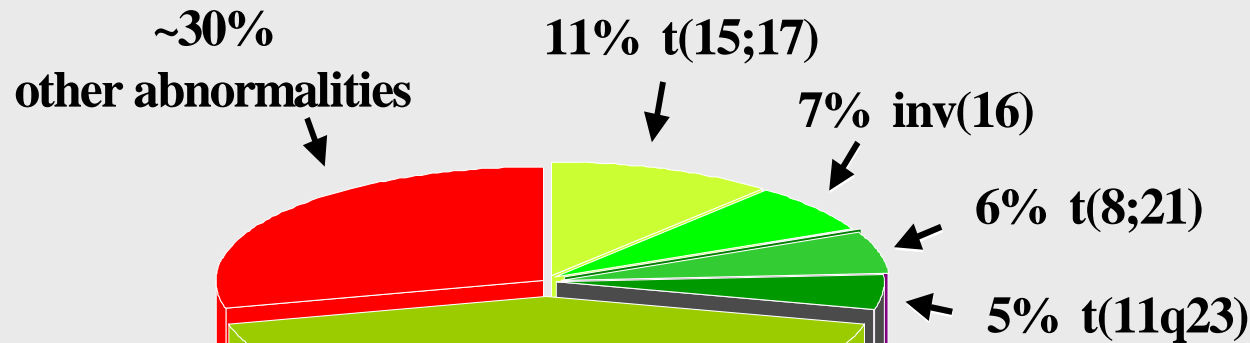
Figure 2.



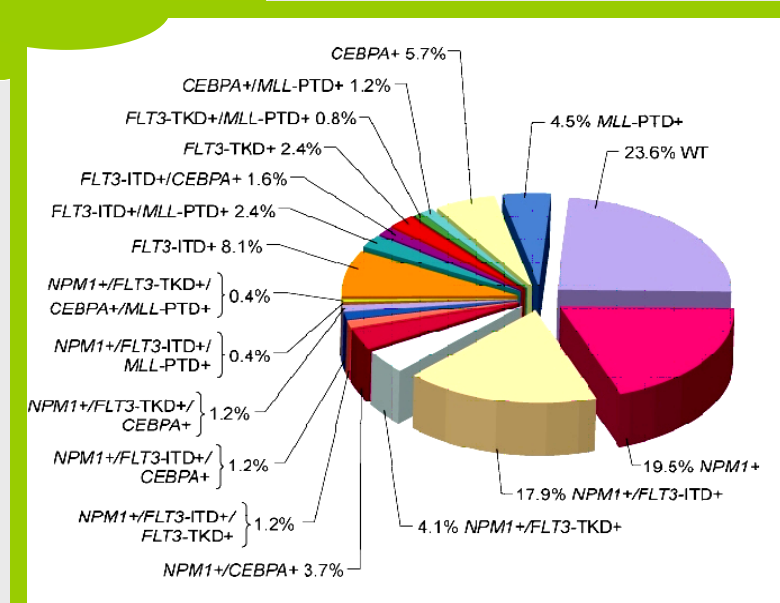
(ASH 08; # 3636)



Genetische Untergliederung der AML



~45%
normal karyotype



(Döhner, ASH 07 Educational)



Neue WHO Klassifikation der AML

WHO Classification (2001)

AML with recurrent genetic abnormalities

- t(8;21), (CBF)
- inv(16) or t(16;16) and abnormal bm eosinophils (CBF)
- t(15;17) and variants (APL)
- 11q23 (MLL)

AML with multilineage dysplasia

- Following MDS
- Dysplasia in $\geq 50\%$ of cells in ≥ 2 myeloid lineages

AML and MDS, therapy related

- Alkylating agent / radiation-related
- Topoisomerase II inhibitor-related
- Others

AML, not otherwise categorized

- Classify as:
 - AML minimally differentiated
 - AML without maturation
 - AML with maturation
 - Acute myelomonocytic leukemia
 - Acute monoblastic / Acute monocytic leukemia
 - Acute erythroid leukemia (pure / mixed)
 - Acute megakaryoblastic leukemia
 - Acute basophilic leukemia
 - Acute panmyelosis with myelofibrosis
 - Myeloid sarcoma

Undifferentiated or biphenotypic acute leukemias

WHO Classification (2008)

AML with recurrent genetic abnormalities

- t(8;21), (CBF)
- inv(16) or t(16;16) and abnormal bm eosinophils (CBF)
- t(15;17) and variants (APL)
- t(9;11), (MLLT3-MLL) 11q23 (MLL)
- t(6;9)
- inv(3) or t(3;3) assoc. with megakaryoblastic leukemia
- t(1;22), associated with megakaryoblastic leukemia
- **Gene mutations:** mutated NPM1 & CEBPA (provisional)

AML with myelodysplasia-related changes

- Following MDS
- MDS-related cytogenetic abnormality
- Dysplasia in $\geq 50\%$ of cells in ≥ 2 myeloid lineages

AML and MDS, therapy related

- Alkylating agent/radiation-related
- Topoisomerase II inhibitor-related
- Others

AML, not otherwise categorized

- *no change*
- *some pts. may be re-classified as AML w/ gen.abnorm.*
- *some pts. may be re-classified as AML w/ myelodyspl.*

Myeloid sarcoma

Myeloid proliferations related to Down syndrome

Blastic plasmacytoid dendritic cell neoplasms

Acute leukemias of ambiguous lineage

HOVON/SAKK AML Prognosescore (< 60 y)

Risk (% of cases*)	From diagnosis			From start of consolidation		
	CR1†, %	EFS§ at 5 y, %	OS‡, %	EFS2‡ at 5 y, %	OS2¶, %	
Good (30)						
GR1	t(8;21), WBC ≤ 20	94 *	51	65	58	76
GR2	inv(16)/t(16;16)	94	59	68	66	75
GR3	no MK, <i>CEBPA</i> ^{mut}	93	44	68	50	77
GR4	no MK, <i>FLT3ITD</i> ^{neg} / <i>NMP1</i> ^{mut} CRe	84	48	61	59	67
GR4	no MK, <i>FLT3ITD</i> ^{neg} / <i>NMP1</i> ^{mut} CRe	100 *	51	57	59	61
Intermediate (20)						
IR1	t(8;21), WBC > 20	99 *	42	51	48	55
IR2	CN -X -Y, WBC ≤ 100 CRe	87	32	46	35	50
IR2	CN -X -Y, WBC ≤ 100 CRe	100 *	43	51	48	55
Poor (30)						
PR1	CN -X -Y, WBC ≤ 100 not CRe	75 *	19	25	27	
PR1	CN -X -Y, WBC ≤ 100 not CRe	69 *	17	23	24	31
PR2	CN -X -Y, WBC > 100	74 *	23	27	32	37
PR3	CA, non CBF, no abn3q26, <i>EV11</i> ⁻	79	20	25	27	33
Very Poor (20)						
VPR1	Monosomal karyotype (MK)	60	3	7	7	12
VPR1	Monosomal karyotype (MK)	48	2	4	6	9
VPR2	abn3q26	65	8	19	8	12
VPR3	<i>EV11</i> ⁺	79	10	17	10	16

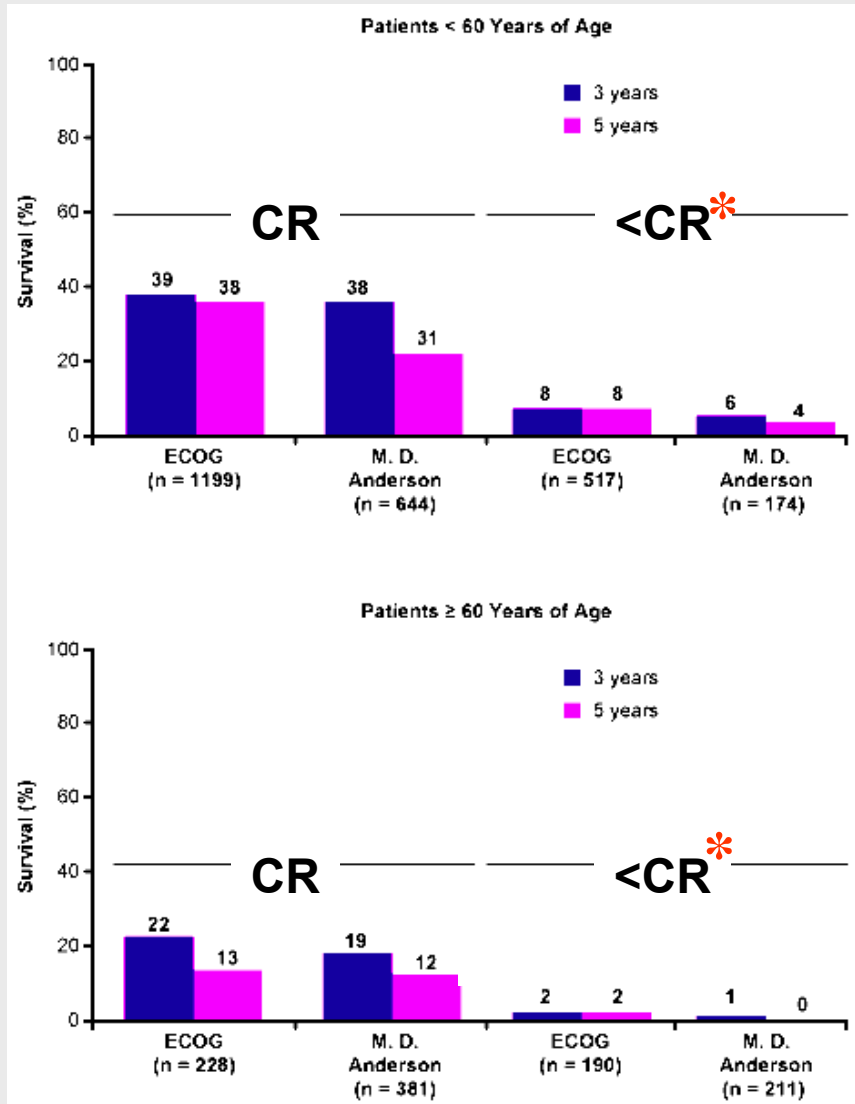
*, % distribution of each risk subgroup of all patients at diagnosis
 † % patients reaching a first CR after cycle I or cycle II
 § EFS actuarial probability of event-free survival 5 years from diagnosis
 ‡ OS actuarial probability of overall survival 5 years from diagnosis
 ‡EFS2 actuarial probability of event-free survival 5 years from start consolidation
 ¶ OS2 actuarial probability of overall survival 5 years from start consolidation

CBF core-binding factor (CBF): t(8;21)(q22;q22) or inv(16)(p13q22) or t(16;16)(p13;q22)
CN -X -Y cytogenetically normal or only loss of X or Y chromosome as the sole cytogenetic abnormalities
CA cytogenetically abnormal
CRe attainment of early CR, i.e., after cycle I
EV11+ high EV11 mRNA expression
FLT3ITDneg / NMP1mut no FLT3-internal tandem duplication but NPM1-mutant positive

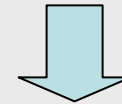
(Löwenberg, ASH 08
 Ham Wasserman Lecture)



Rationale zur Optimierung der AML Induktionstherapie



- * including alternative CR definitions as
 - CR without platelet recovery (CRp)
 - CR without blood count recovery (CRi)
- no difference of CRi vs. induction failure in overall survival (pts > 60 yrs.) §



„True“ Complete Response rates predicts increased long-term survival after Cytarabine Induction

(ASH 07: #298, § ASH 08: #2988)



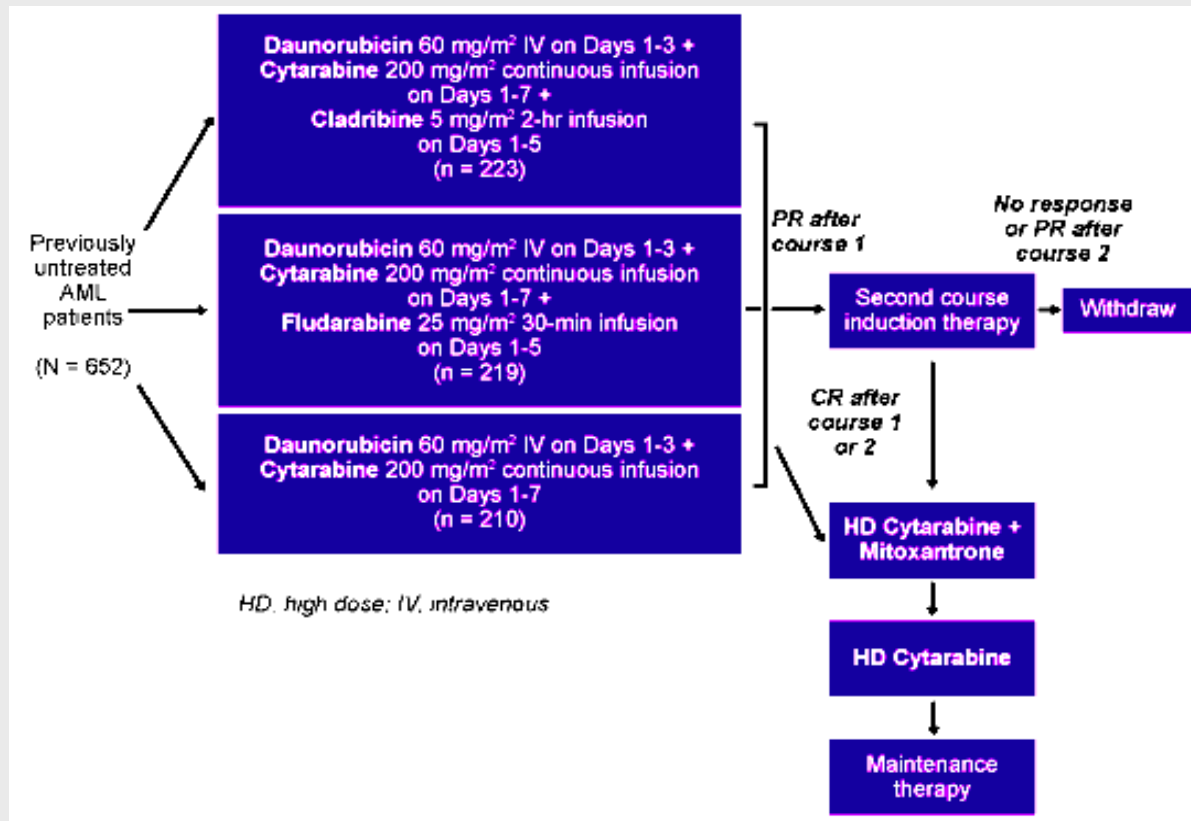
Cladribine + Daunorubicin + Cytarabine / < 60y

Background:

- Cladribine: purineanalogon
- Antiproliferation in cell cycle active and dormant cells by accumulation

Protocol:

- Eligibility criteria: previously untreated AML, 16 - 60 years



(ASH 08: #133)



Cladribine + Daunorubicin +Cytarabin / < 60y

<i>Outcome, %</i>	<i>DAF (n = 219)</i>	<i>DAC (n = 223)</i>	<i>DA (n = 210)</i>	<i>P Value (DAC vs DA)</i>	<i>P Value (DAC vs DAF)</i>
CR	59.0	68.0	56.0	.013	.08
CR after 1 cycle	55.0	62.0	50.5	.017	.16
OS	32.0	43.5	32.5	.02	.008
ED	8.5	11.0	10.5	NR	NR

<i>Outcome, %</i>	<i>DAF</i>	<i>DAC</i>	<i>DA</i>	<i>P Value</i>
CR				
▪ Favorable risk	80.0	93.0	62.5	NR
▪ Intermediate risk	65.0	71.0	70.0	NR
▪ Unfavorable risk	47.0	59.0	34.0	.05
OS				
▪ Favorable risk	66.0	80.0	37.0	.09
▪ Intermediate risk	32.0	47.0	38.0	.05
▪ Unfavorable risk	31.0	41.0	23.0	.7

Adverse events: similar between treatment arms

- 100% patients experienced grade 3/4 neutropenia and thrombocytopenia
- Other adverse events occurring in > 20% of pts. inkl. infection, vomiting, mucositis

(ASH 08: #133)



Sorafenib + Idarubicin / Cytarabine (AML < 65y)

Background:

- FLT3 mutations in 25% - 40% of AML: Confers worse prognosis vs. wild-type FLT3
- Sorafenib: multikinase inhibitor (RAF, FLT3, KIT, PDGFR)

Protocol:

- Eligibility criteria
 - Phase I: relapsed/refractory AML
 - Phase II: previously untreated AML
- Treatment plan
 - Induction
 - Idarubicin: 12 mg/m² on Days 1-3
 - Cytarabine: 1.5 g/m² CI on Days 1-4
 - Sorafenib: 400 mg twice daily
 - Postremission treatment / Consolidation (up to 5 cycles given every 4-6 weeks)
 - Idarubicin: 8 mg/m²/day IV over 1 hour for 2 days
 - Cytarabine: 0.75 g/m²/day over 24 hours for 3 days
 - Sorafenib: 400 mg twice daily for up to 28 days per cycle
 - Maintenance (every 4-6 weeks for up to 1 year)
 - Sorafenib: 400 mg twice daily for up to 28 days per cycle

(ASH 08: #768)



Sorafenib + Idarubicin / Cytarabin (AML < 65y)

<i>Response, %</i>	<i>Phase I (n = 10) "Salvage therapy"</i>	<i>Phase II (n = 38) "Front-line therapy"</i>
CR	40	72
CRp	0	11
Early death	20	6
Resistant	40	11

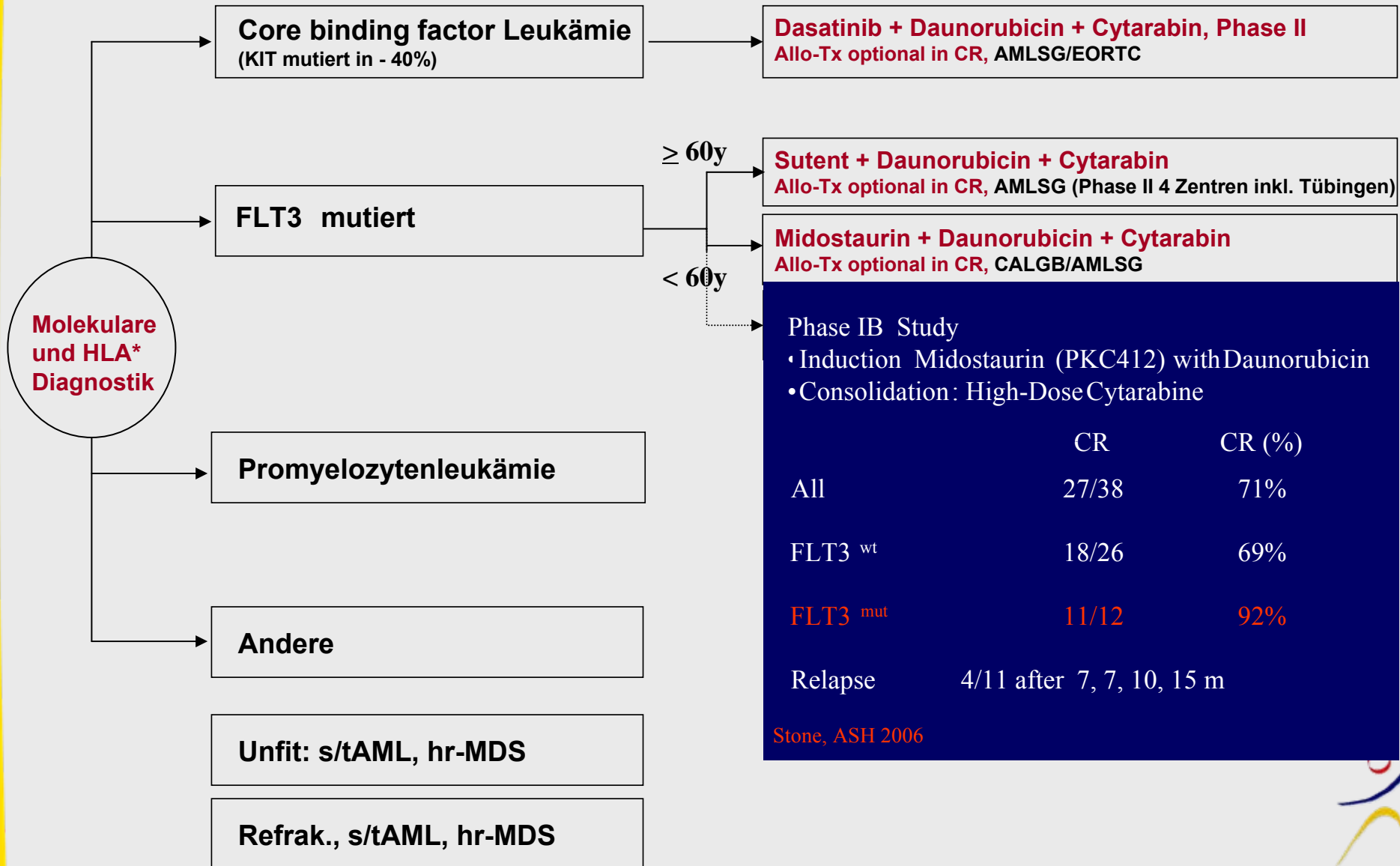
- > Inhibition of FLT3 phosphorylation:
 - FLT3 mutation: 100% inhibition, Wild-type: 47% inhibition
- > **All 13 patients with FLT3 mutations responded and remain alive**
- > 8-mo survival: 80%

<i>Adverse Event, %</i>	<i>Grade 1/2</i>	<i>Grade 3/4</i>
Gastrointestinal	58	11
Rash	21	5
Hepatic	13	18

(ASH 08: #768)



AML-Studienbaum am UKT



Dasatinib bei Ph-positiver ALL

Background:

- Dasatinib: potent inhibitor of BCR-ABL and most Imatinib-resistant point mutations
- *Imatinib +/- HyperCVAD in de novo Ph+ALL: OS (3y) 55% vs 15% (no Imatinib)* ¹

Protocol:

- 34 eligible patients with **de novo Ph+ALL** enrolled (24-76 years) ²
- Treatment plan:
 - Steroid prephase (7days)
 - Dasatinib 70 mg BID + Steroids up to 31 days
- Outcome:
 - PCR reduction $\leq 10^{-3}$ sole prognostic factor
 - No fatalities, 1 treatment stop due to toxicity

CHR	100% 94% after 1st determination at d 22
OS (10mths)	81%
Relapses	26%

Further Studies of Dasatinib + Chemotherapy: 93%-100% CR, follow up 3-6 m ³

(ASH 08: ¹ #2931, ² #305, ³ #2920, #2919, #2921)



Promyelozytenleukämie

Induction (good risk): ¹

ATRA duration during induction therapy predicts for CIR and OS (APL93/2000 trials)

– ATRA discontinuation due to side effects, ATRA syndrome, recovery (not CR)

• < 10 000 / μ l (n=263, 64%):

	ATRA <1500 mg	ATRA > 1500mg
CIR	31%	13%
OS	81%	95%

• > 10 000 / μ l (n=151, 36%): no change

Induction (high risk): ²

Risk-adapted treatment (LPA 2005 trial PETHEMA) - including addition of Anthracycline + **Cytarabine** with ATRA in high risk patients

DFS	94%	[88% (LPA99)]
OS	92%	[85% (LPA99)]
CIR (2y)	5%	[9% (LPA99)]

CIR - Cumulative Incidence of Relapse
OS - Overall Survival
DFS - Disease Free Survival
LPA99 trial: "no cytarabine in high risk pts"

	low risk WBC <10 t/ μ l, PLT >40 t/ μ l	intermediate risk WBC <10 t/ μ l, PLT <40 t/ μ l	high risk WBC >10 t/ μ l
CIR (2y)	0% [3% (LPA99)]	6% [4% (LPA99)]	8% [25% (LPA99)]

Note: UKT-Treatment strategy analogous AIDA2000 protocol (including cytarabine option in high risk pts)

(ASH 08: ¹ #139, ² #138)



Promyelozytenleukämie

Novel Agents

Outcome	ASH 2006/07	ATRA + ATS	ATRA + ATO	ATRA	P Value
		(n = 68)	(n = 60)	(n = 56)	
CR, n (%)		68 (100)	56 (93.3)	51 (91.1)	.737
Median time to CR, days (range)		29.5 (14-62)	27 (15-38)	32 (15-67)	< .001
4-year overall survival			98.1%	83.4%	P = .012
4-year event-free survival		94%	94.2%	45.6%	< .00001

→ ATRA plus AC provide greater 4-year OS and EFS compared to ATRA alone

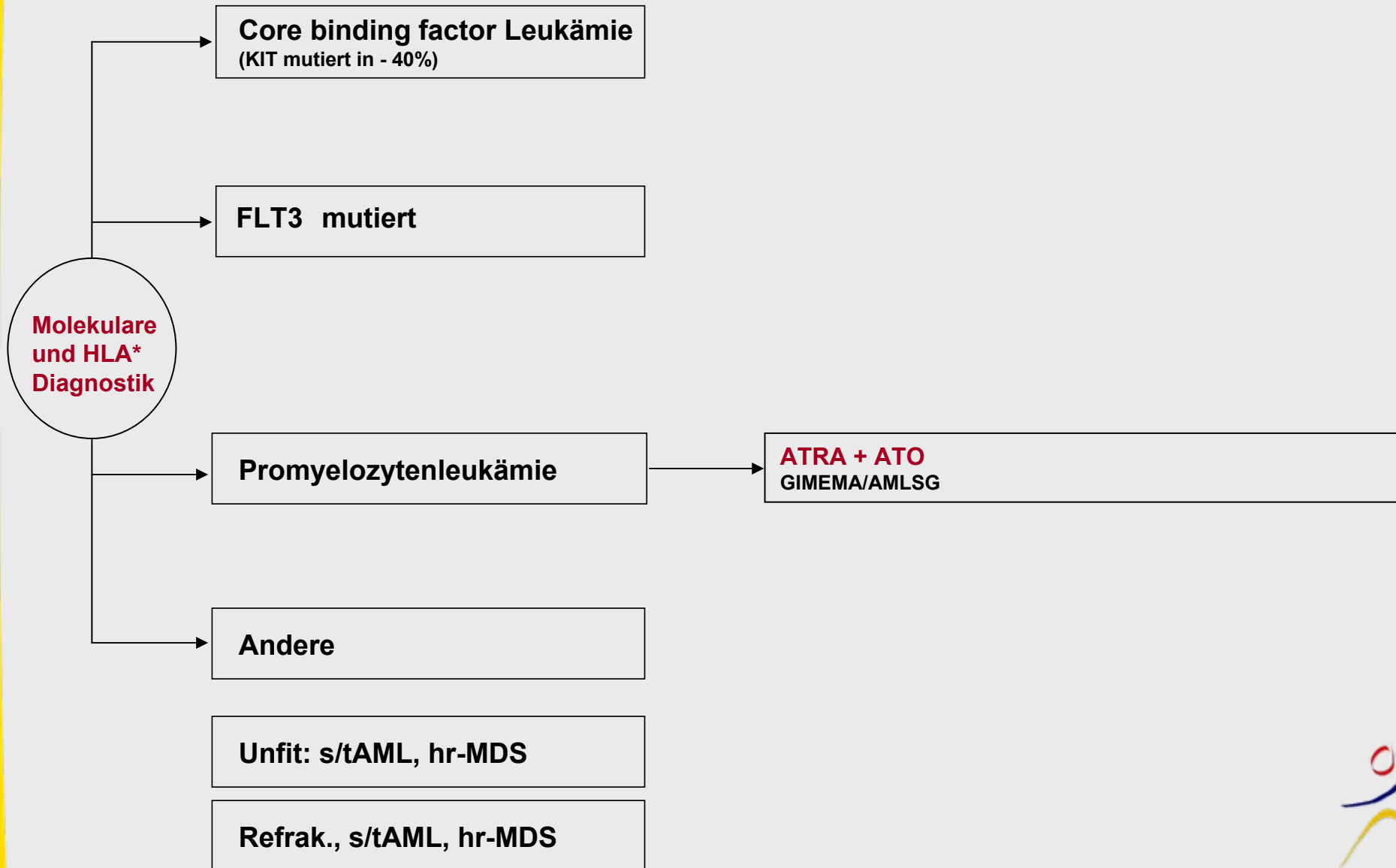
→ Rationale for Arsenic Trioxide (ATO) in APL:

- **ATO: Single most effective drug in APL** by degradation of PML-RAR α
- High remission rates in a recent ATO-monotherapy study (n=193) ¹
 - **CR 82%**
 - DFS at 2 years 86% - 3 years 79% - **5 years 66%**
 - Risk of relapse at 1 year 25% - 2 years 17% - 3 years 6% - 4 years 3%
 - Chance of survival at 1 year 82% - 2 years 89% - 3 years 95% - 4 years 100%

(¹ ASH 08: #140)



AML-Studienbaum am UKT



Epigenetics: Decitabine in AML (Elderly)

Background:

- Methyltransferaseinhibitor:>> Demethylation, i.e. activation of tumorsuppressorgenes

Protocol:

- Prospective, open-label, phase II study
 - Previously untreated AML
 - ECOG 0: 47%, 1: 35%, 2: 18%
 - Poor cytogenetics: 44%
 - AML transformed from MDS: 35%
- Treatment:
 - Decitabine 20 mg/m² on Days 1-5
 - every 4 weeks

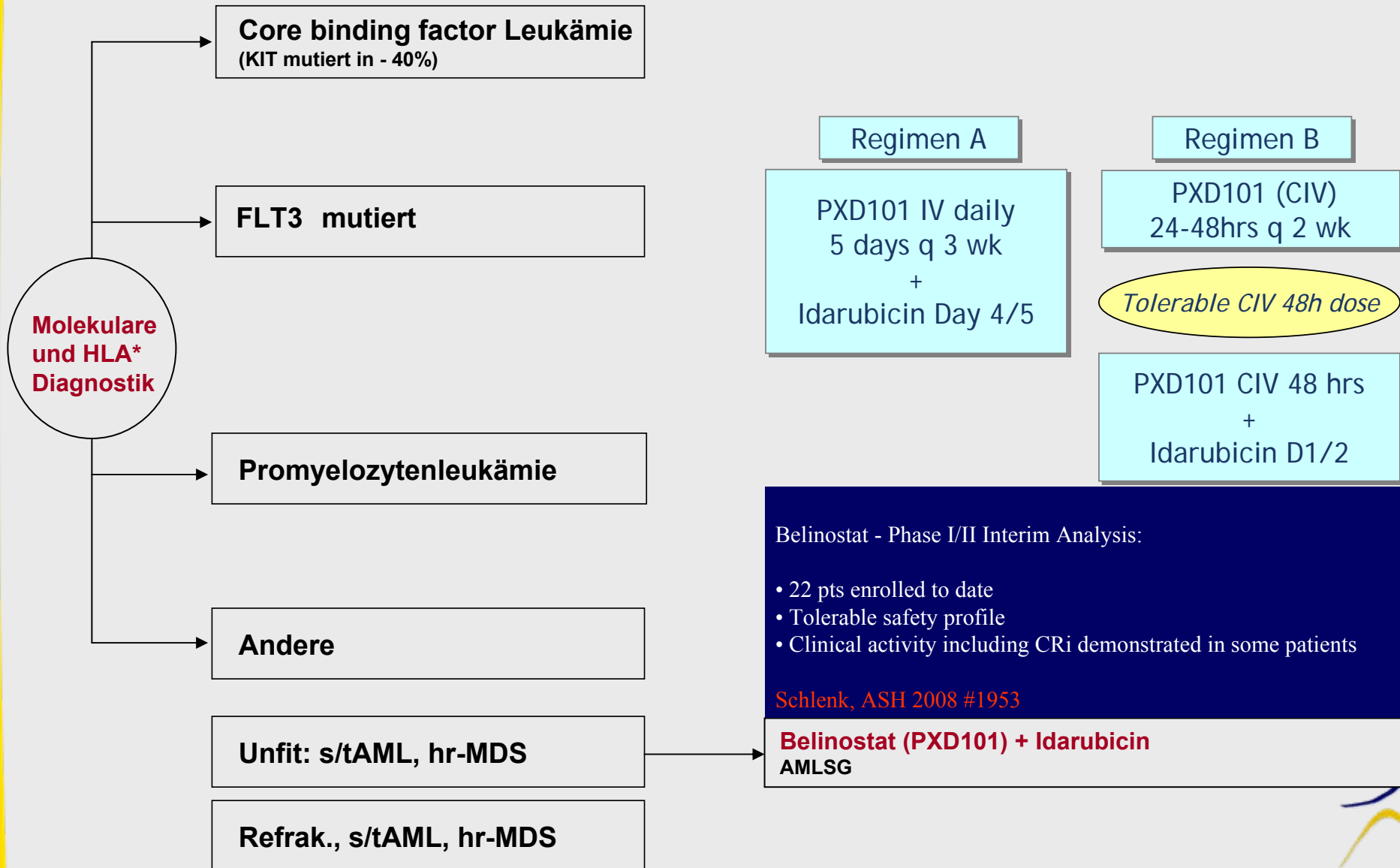
Response	Patient population (N = 55)
ORR, %	26 %
▪ CR	23 % (13pts)
▪ CR, poor cytogenetics	22 %
▪ CR, prior MDS	26 %
Median OS, months	7.7
Median time to CR, months (range)	4 (2-8)
Median DOR, months (range)	4 (2-18)
30-day mortality, %	4 %*

*Compare: Mortality rate in Elderly treated with standard induction is 20%

(ASH 08: #560)



AML-Studienbaum am UKT



Plerixaflor (AMD3100) bei Relaps / Refraktärer AML

Background:

- CXCR4 is expressed on AML (bone marrow) blasts
- Plerixaflor: Reversible CXCR4 small molecule antagonist (**approved as stem cell mobilizer** in combination with G-CSF for PBSCT in lymphoma/multiple myeloma)
- Mobilization and thereby chemosensitization of leukemic blasts in vivo and in vitro models (inkl. Ph+/- ALL) ¹

Protocol:

- Phase I/II study ²
 - 19 pts. treated
- Eligibility:
 - Relapsed or refractory AML
- Treatment:
 - Plerixaflor administered s.c. 4h prior to Cx (dose levels 80, 160, 240 mg/kg/d)
 - Mitoxantrone 8mg/m² / 5d, Etoposid 100 mg/m² / 5d, Cytarabine 1000 mg/m² / 5d
- Outcome:
 - 2-fold increase of leukemic and non-leukemic blasts after 6-8hrs after injection
 - **CR+CRi in 33% (dose level 80 & 160 mg/kg) and 75% (dose level 240 mg/kg)**
 - Safety profile: Well tolerated, no hyperleukocytosis, no delay in neutrophil recovery

(ASH 08: ¹ #2922, ² #1944)

AML-Studienbaum am UKT

Studienübersicht: <http://www.med-onk.de/ifa2.htm>

