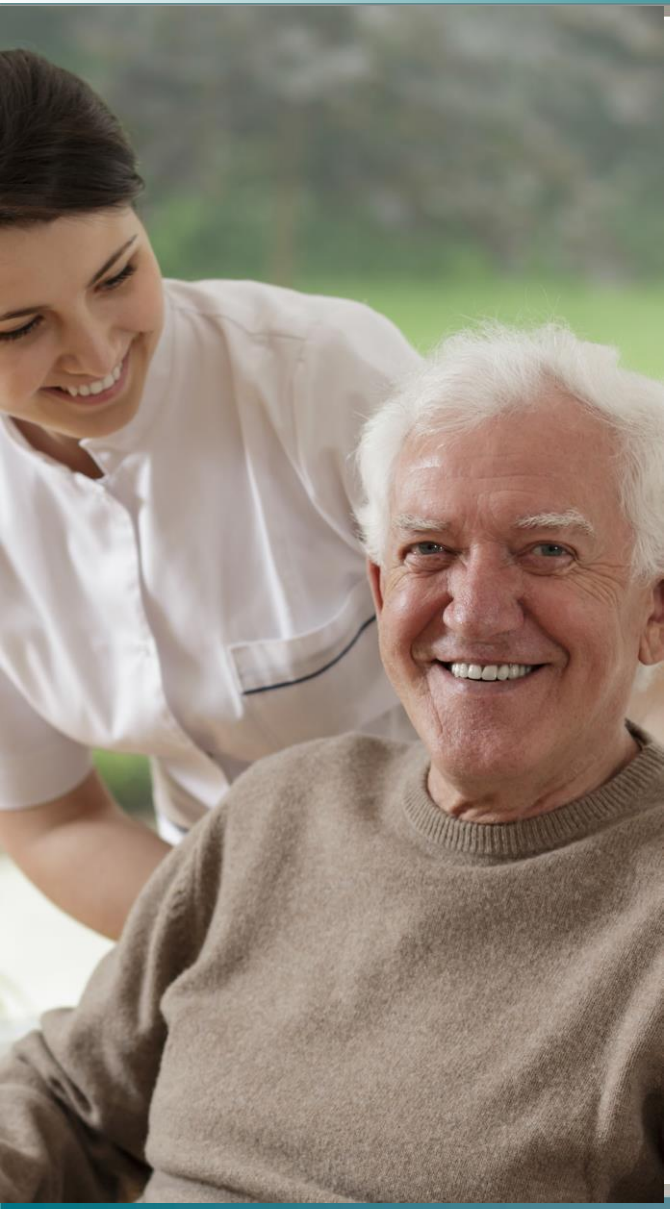


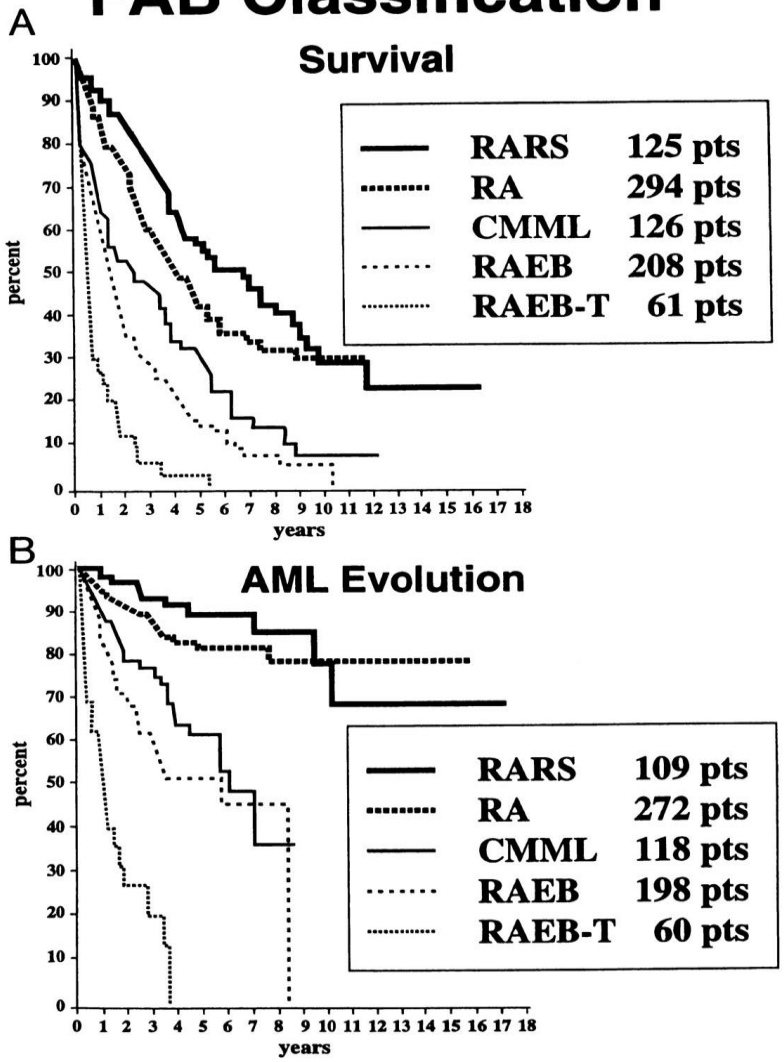
LAM 20-30%

Cristina Papayannidis, MD, PhD
DIMES, Istituto di Ematologia L. e A. Seràgnoli
Università di Bologna

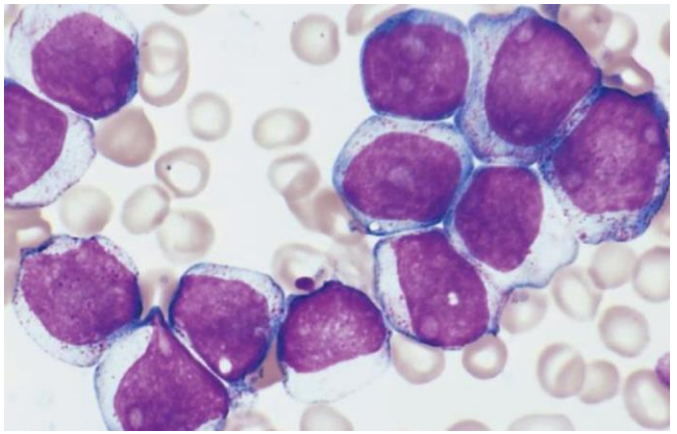
FAB CLASSIFICATION OF MYELODYSPLASTIC SYNDROME

Subtype	%	Blood Myeloblasts	Bone Marrow Myeloblasts	Average Survival	AML progression
RA	25%	<1%	<5%	32 months	15%
RARS	15%	<1%	<5%	76 months	5%
RAEB	35%	<5%	5%-20%	10 months	40%
RAEB-t	10%	5%-30%	20%-30%	5 months	50%
CMML	15%	<5%	<20%	22 months	35%

FAB Classification



WHO 2008 AML CLASSIFICATION



Bone marrow blast cells >20%

Peter Greenberg et al. Blood 1997;89:2079-2088

Acute myeloid leukaemia with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
- APL with t(15;17)(q22;q12); *PML-RARA*
- AML with t(9;11)(p22;q23); *MLLT3-MLL*
- AML with t(6;9)(p23;q34); *DEK-NUP214*
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
- AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
- Provisional entity: AML with mutated *NPM1*
- Provisional entity: AML with mutated *CEBPA*

Acute myeloid leukaemia with myelodysplasia-related changes

Therapy-related myeloid neoplasms

Acute myeloid leukaemia, not otherwise specified
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukaemia
- Acute monoblastic/monocytic leukaemia
- Acute erythroid leukaemias
  - Pure erythroid leukaemia
  - Erythroleukaemia, erythroid/myeloid
- Acute megakaryoblastic leukaemia
- Acute basophilic leukaemia
- Acute panmyelosis with myelofibrosis

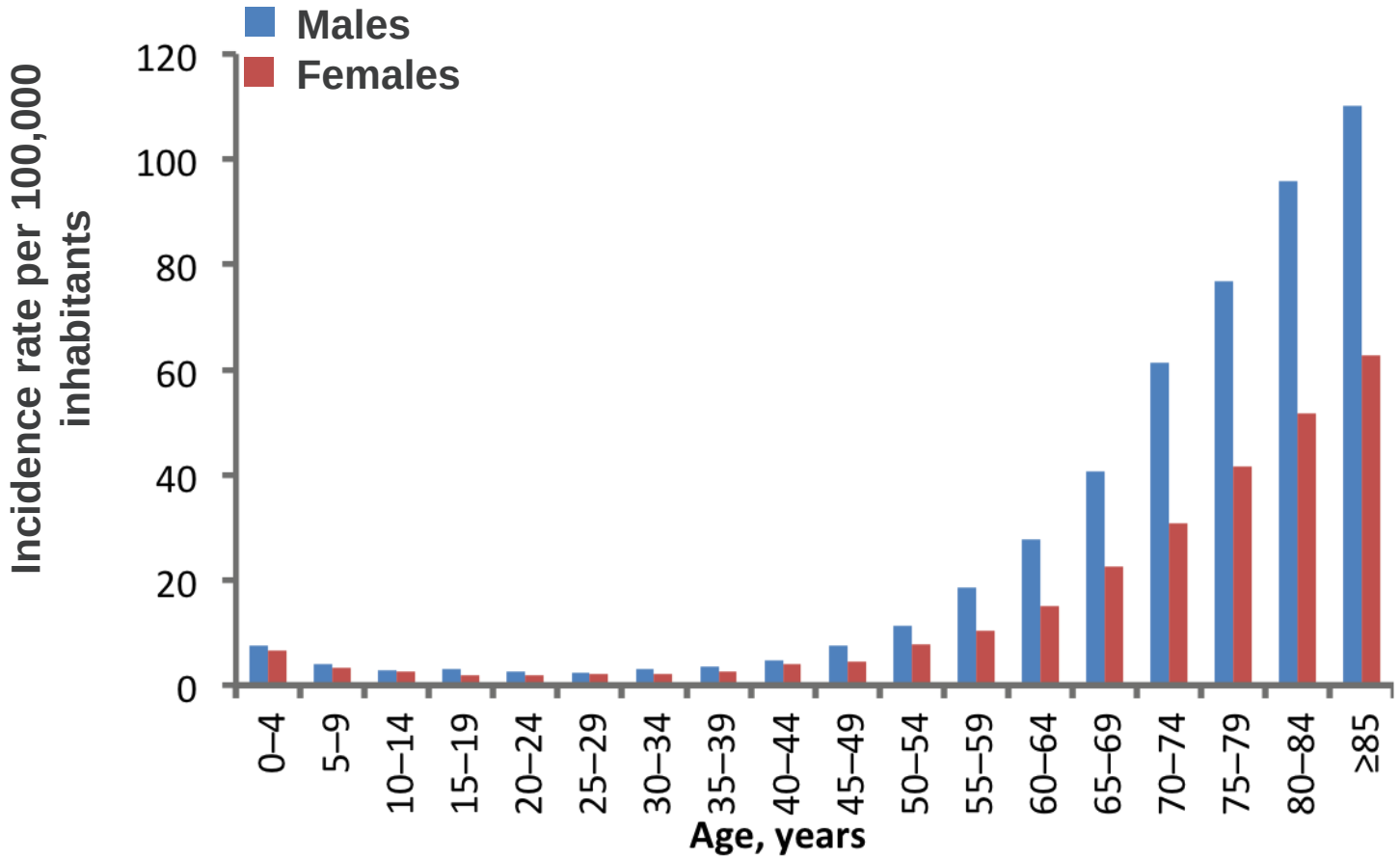
Myeloid sarcoma

Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis
- Myeloid leukaemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasms

CB 20-30%
Secondary to previous MDS or MPN
Multilineage dysplasia
Specific MDS-related cytogenetic abnormality

INCIDENCE OF AML INCREASES WITH AGE

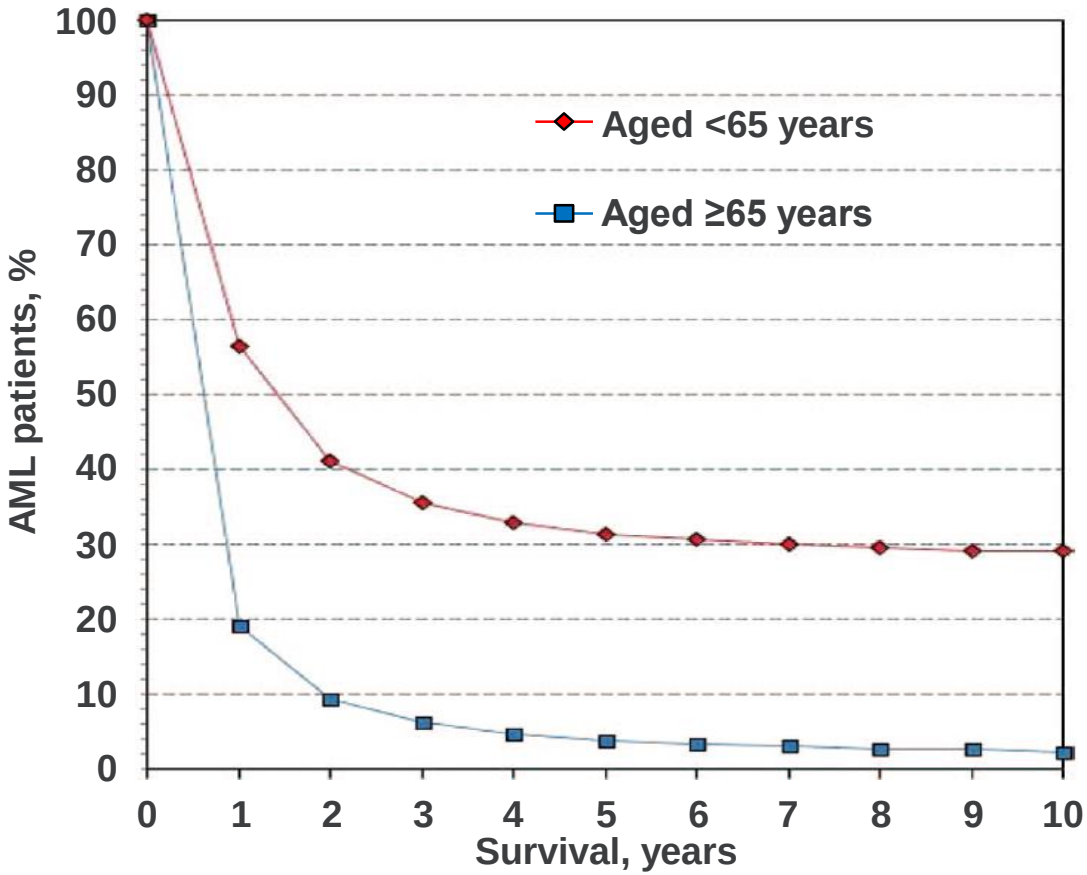


AML is predominantly a disease of older patients with a slight prevalence in males; the majority of cases occur in patients ≥65 years of age

1. Cancer Research UK. Leukaemia incidence statistics. Available at: http://www.cancerresearchuk.org/ cancer-info/cancerstats/types/leukaemia/incidence/uk-leukaemia-incidence-statistics

Advanced age is a poor prognostic factor in patients with AML

Age at diagnosis[1,2]



1. Klepin HD, et al. Oncologist 2009;14:222–32
2. National Cancer Institute. SEER Cancer Statistics Review 1975–2005

Age is associated with poor prognosis in patients with AML

Presentation

Younger patients

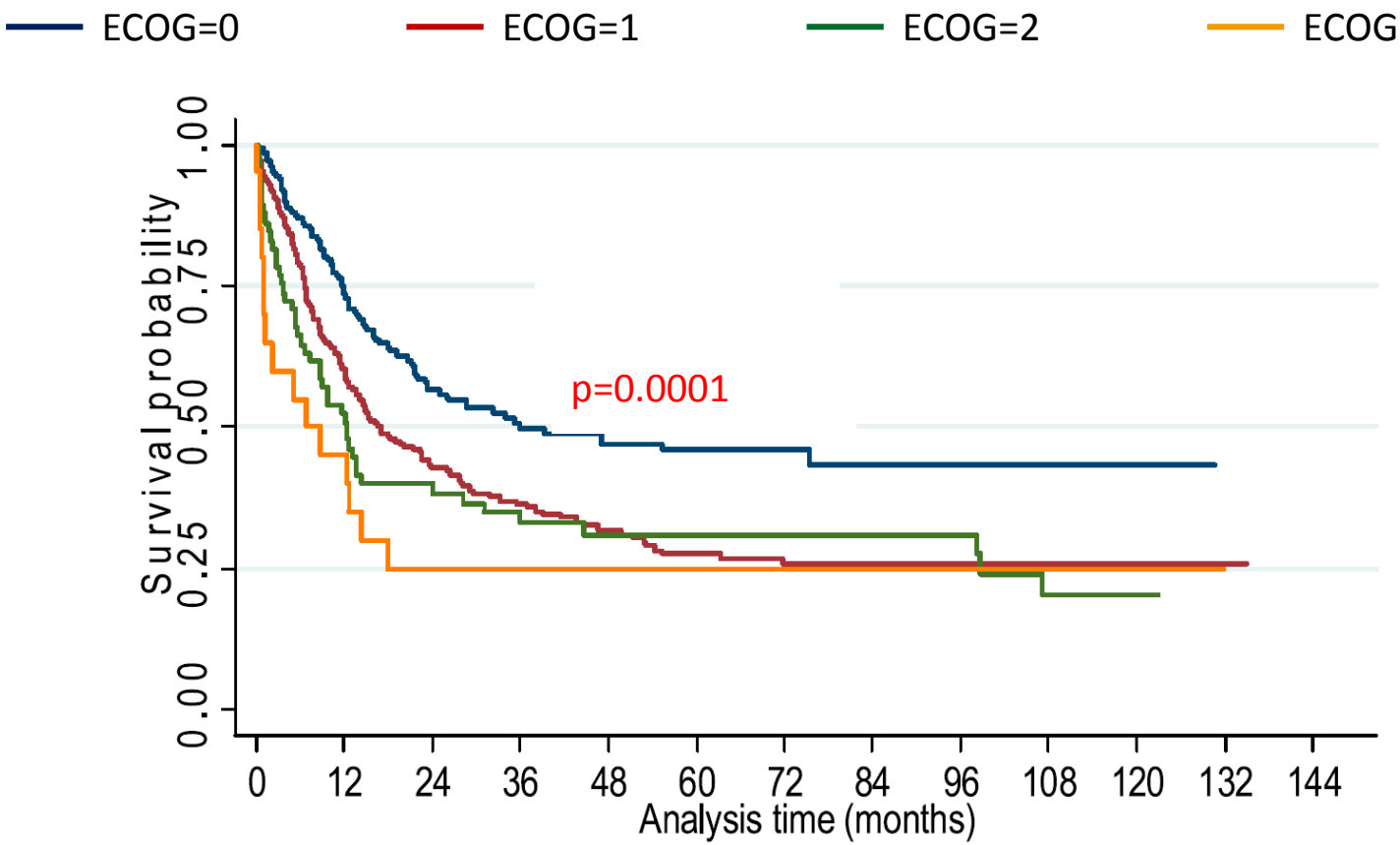
- Better performance scores
- Less comorbidities
- More likely to have favourable cytogenetics

Older patients

- Poorer performance scores
- More comorbidities
- More likely to have unfavourable cytogenetics

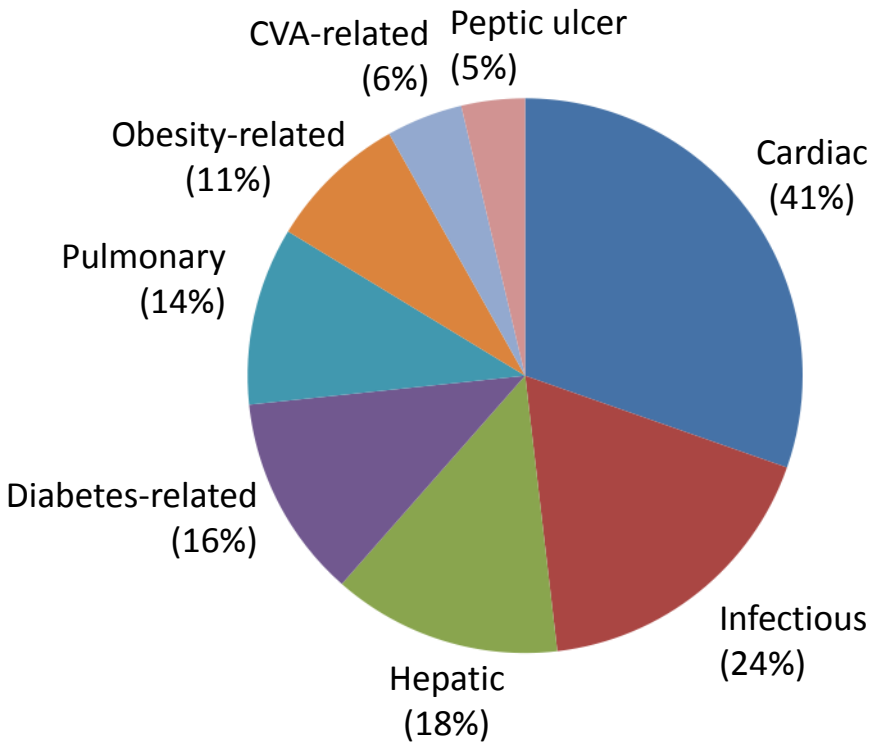
A high ECOG PS is a poor prognosis factor in patients with AML

Retrospective analysis of 599 patients with newly diagnosed AML treated with IC between 2000–2009



Analysis of 177 patients with AML >60 years old

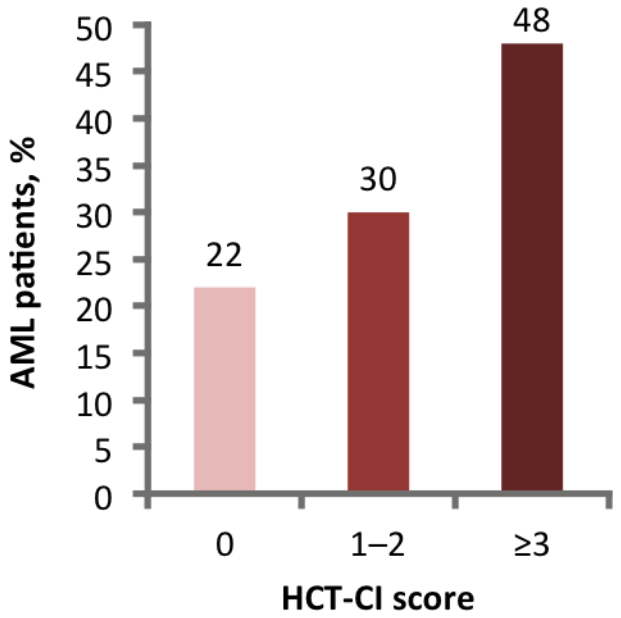
The most common comorbidities in older patients with AML



CVA = cerebrovascular accident
HCT-CI = Hematopoietic Cell Transplantation-Comorbidity Index

Proportions of patients with HCT-CI scores of 0, 1–2, or 3

HCT-CI is a composite scoring system for comorbidities; a higher score indicates more severe and/or a higher number of comorbidities[2]

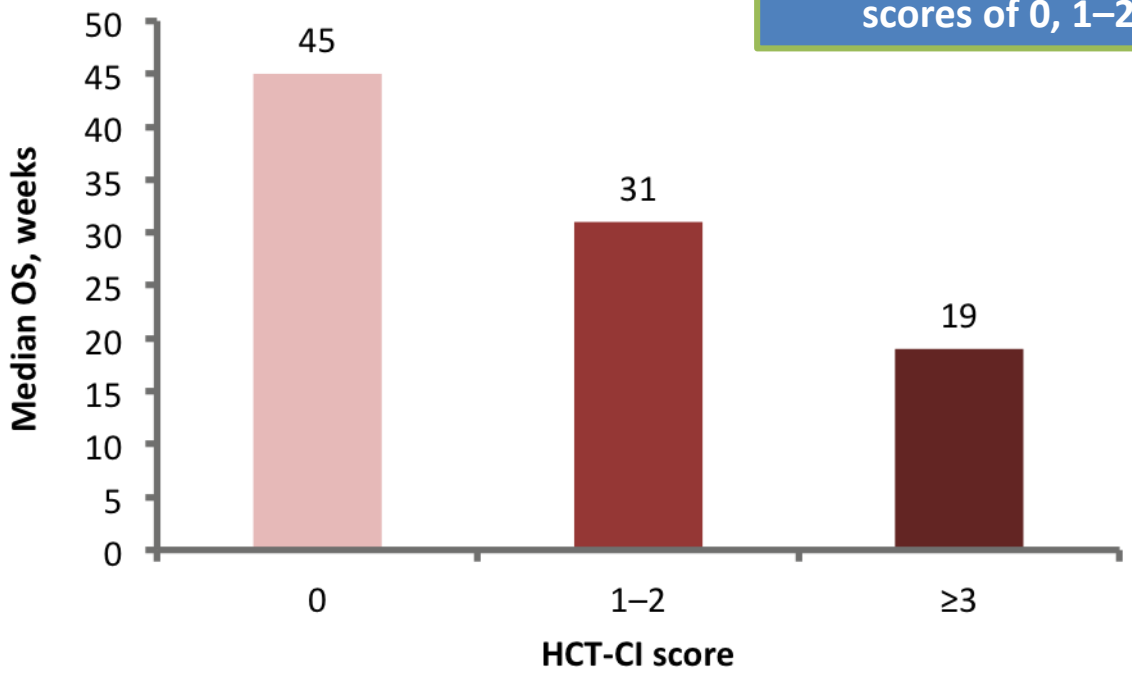


1. Giles FJ, et al. Br J Haematol 2007;136:624–7
2. Sorror ML, et al. Blood 2005;106:2912–9

A high comorbidity burden is a poor prognosis factor in patients with AML

p=0.04

OS of patients with HCT-CI scores of 0, 1–2, or 3

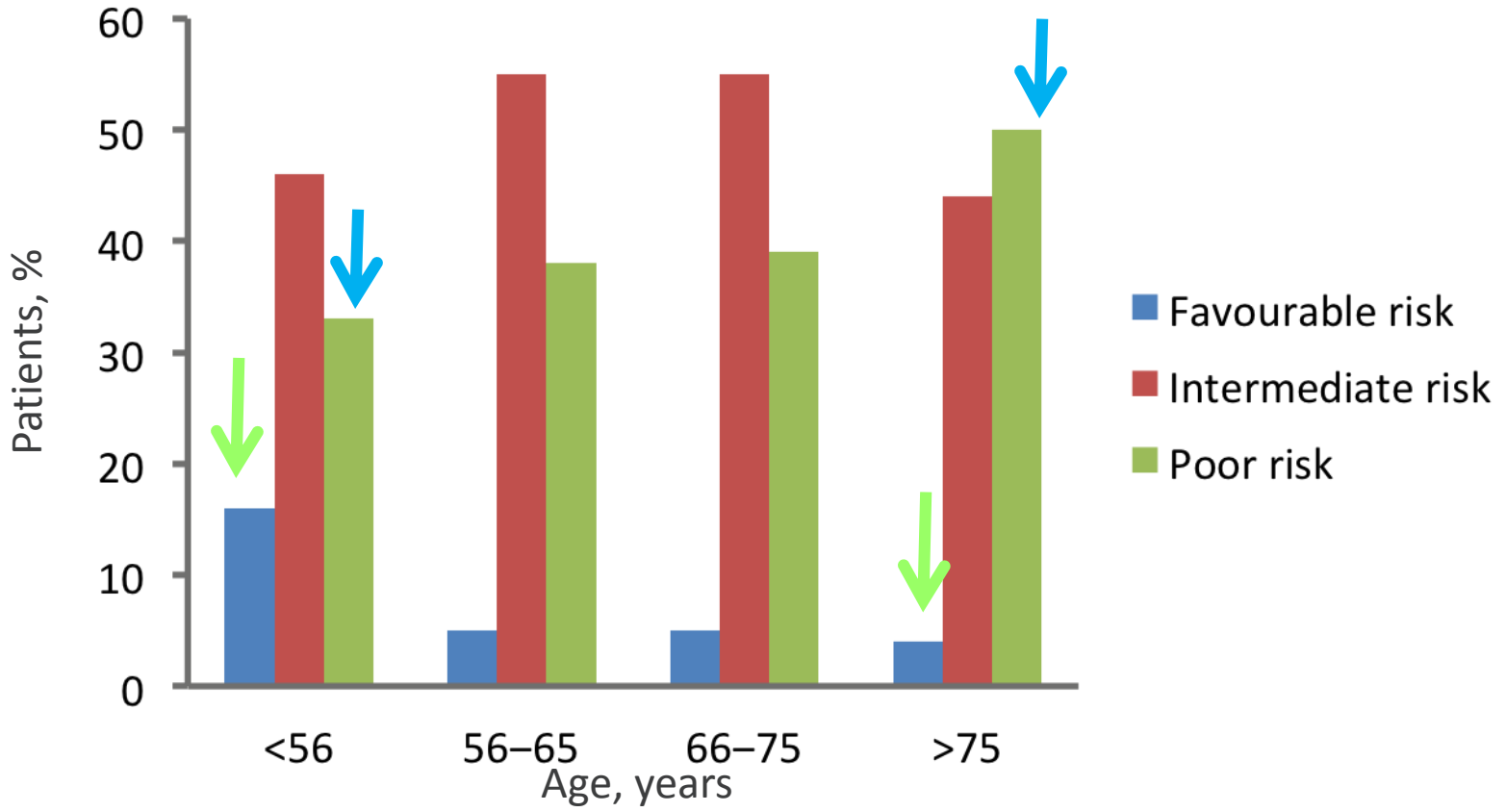


HCT-CI score was predictive of OS in older patients with AML treated with IC

Giles FJ, et al. Br J Haematol 2007;136:624–7

The incidence of poor risk cytogenetics increases with age

Retrospective analysis of 968 patients with AML[1]



*The cytogenetic scoring system used was devised by the SWOG/ECOG intergroup study, E3489/S9034[2]

1. Appelbaum FR, et al. Blood 2006;107:3481–5
2. Slovak ML, et al. Blood 2000;96:4075–83

Complex karyotype*	Unbalanced abnormalities	Balanced abnormalities
	-7 or del(7q)	t(11;16)(q23;p13.3) **
	-5 or del (5q)	t(3;21)(q26.2;q22.1) **
	i(17q) or t(17p)	t(1;3)(p36.3;q21.1)
	-13 or del(13q)	t(2;11)(p21;q23) **
	del(11q)	t(5;12)(q33;p12)
	del(12p) or t(12p)	t(5;7)(q33;q11.2)
	del(9q)	t(5;17)(q33;p13)
	idic(X)(q13)	t(5;10)(q33;q21)
		t(3;5)(q25;q34)

* Three or more unrelated abnormalities, none of which are included in the "AML with recurrent genetic abnormalities" subgroup; such cases should be categorized in the appropriate cytogenetic group.

** Abnormalities that most commonly occur in "therapy-related AML": the latter should be excluded before using such abnormalities as evidence for diagnosis of AML with myelodysplasia-related changes.

Maurillo L et al, Med J of Hemat 2013

Take home messages (I)

Age-specific assessment is required when evaluating therapies for AML

- Performance Status
- Comorbidities evaluation
- Cytogenetics and molecular biology assessment

…..which therapy? Which aim?

Improvement of quality of life (and survival)

Disease eradication ???

- Conventional Chemotherapy
- Hypomethylating Agents (5 Azacitidine, Decitabine)
- Investigational Drugs

Conventional Chemotherapy

Study	Age (range)	N°	Induction and post-remission	CR	ED	OS
HOVON-SAKK[31]	67 (60-83)	813	*INDUCTION* ARAc 200 mg/m^2 + DNR (45 mg/m^2 vs. 90 mg/m^2) x 3 days ARAc 1g/m^2 q 12 h x 6 days *POSTREMISSION* Allogeneic SCT or GO or no treatment	P=0.002 54% vs 64%	P = NS 12% vs 11%	30% (2-yrs)
ALFA-9801[32]	60 (50-70)	478	*INDUCTION* DNR 80 mg/m^{2}x 3d vs IDA 12 mg/m^2 x3d vs IDA 12 mg/m^2 x 4d +ARAc 200 mg/m^{2}x 7 days *POSTREMISSION* ARAc 1 g/m^2 q 12 h x 4d + induction anthracycline x 2d	P = NS 70% vs 83% vs 78%	P = NS 8% vs 3% vs 6%	38% (2-yrs)
ALFA-9803[42]	72 (65-85)	429	*INDUCTION* DNR 45 mg/m^2 x 4d or IDA 9 mg/m^2 x 4d + ARAc 200 mg/m^{2}x 7 days *POSTREMISSION* ARAc 1 g/m2 q 12 h x 5d + induction anthracycline x1d for 6 months vs ARAc 200 mg/m^2 x 7d + anthracycline x 4d	57%	10%	27%
AML HD98[43]	65 (61-78)	329	*INDUCTION* ICE 2 cycles +- ATRA *POSTREMISSION* HAM 1 cycle Random IEiv 1 cycle or 1-year oral maintenance therapy IEpo	46%	-	24% (4-yrs)
AML14[33]	67 (44-88)	1273	*INDUCTION* DAT x 2 courses +- PSC833 *POSTREMISSION* Random: MIDAC ± ICE	54%	18%	13% (5-yrs)

CR rate: 46-57%

OS @ 2 years: <25%

Maurillo L et al, Med J of Hemat 2013

Clinical outcomes of patients with CK (≥3 abnormalities)

Reference	Median age, years (range)	CR rate, %	Median OS, months	Early death* rate, %	Relapse rate, %
Older patients					
Farag SS, et al. Blood 2006;108:63–73	68 (60–86)	25	–	25	90
Fröhling S, et al. Blood 2006;108:3280–8	67 (61–84)	10	3.1	28	100
Schoch C, et al. Br J Haematol 2001;112:118–26	68 (60–81)	44	8.0	18	90
Van der Holt B, et al. Br J Haematol 2007;136:96–105	67 (60–78)	39	5.0	–	79

*Includes hypoplastic death
CR = complete remission

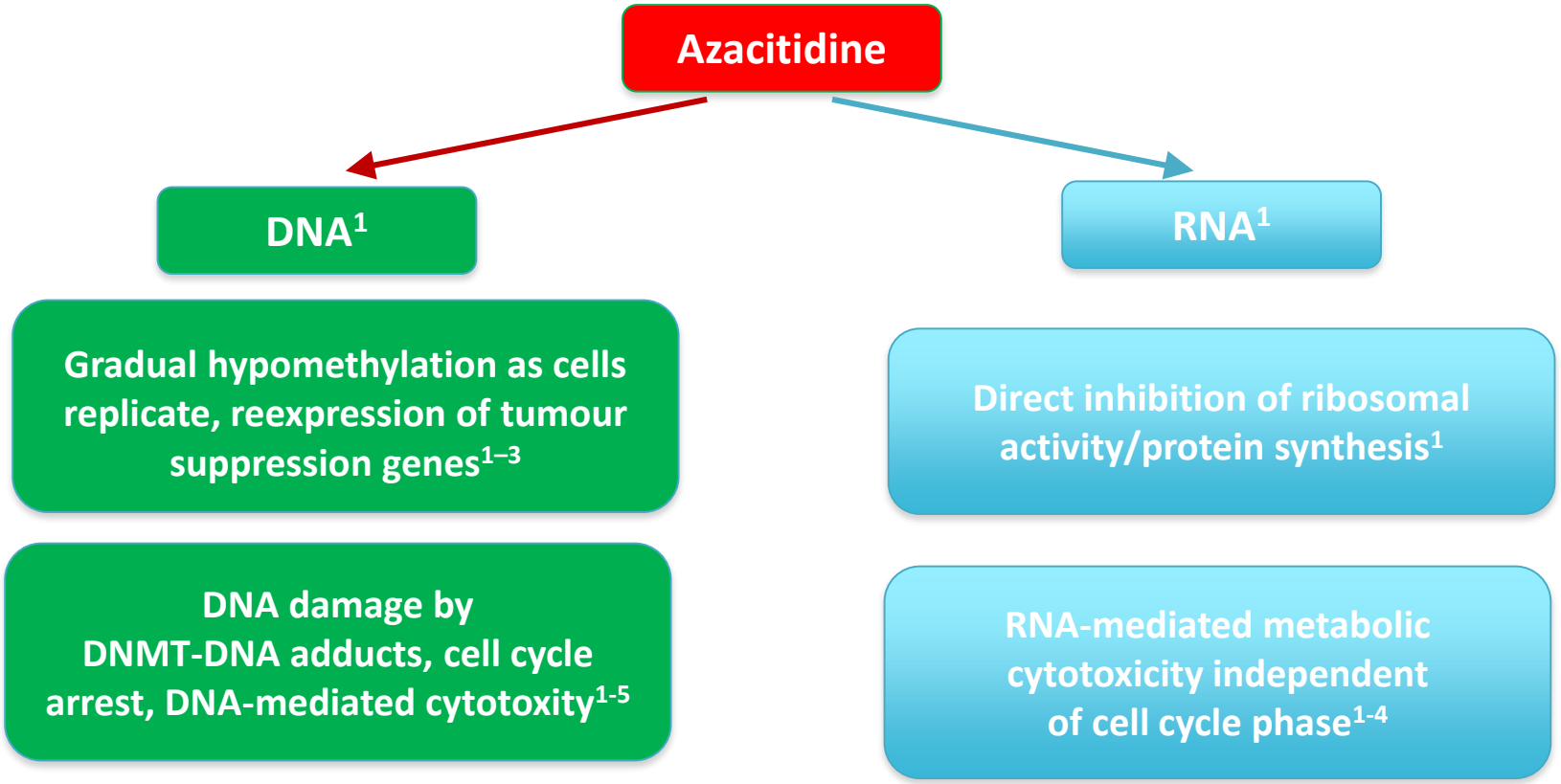
Azacitidine approved in EU

- Int-2-/High-risk MDS (IPSS)
- CMML with 10–29% bone marrow blasts without myeloproliferative disease
- World Health Organization-classified AML with 20–30% blasts and multilineage dysplasia
- not eligible for allogeneic stem cell transplantation

Standard dosing

- 75 mg/m^2/day SC; 7 days of each 28-day treatment cycle
- minimum 6 cycles
- continue treatment as long as patient continues to benefit or until disease progression

Adapted from Vidaza SmPC EU, 2016.



azacitidine not only acts on blasts when DNA replication is ongoing, but also during all other phases of the cell cycle

1. Hollenbach PW, et al. PLoS One 2010;5:1–10; 2. Schaefer M, et al. Cancer Res 2009;69:8127–32; 3. Santos FP, et al. Expert Rev Anticancer Ther 2010;10:9–22; 4. Paul TA, et al. Blood 2010;115:3098–108; 5. Kuo HK, et al. Cancer Res 2007;67:8248–54

5 Azacitidine: results

Study	Patients (n)	AML with 20-30% blasts (n)	Median Age (yrs)	ORR (%)	CR rate (%)	2-year OS (% of patients)	Median survival (months)
Silverman [58,61]	91	91	66	36	9	NA	19.3
Fenaux [62]	Aza 55 CCR 58	Aza 55 CCR 58	70 70	NA NA	18 15 (LDAC), 55 (IC)	50 16	24.5 16.0
Seymour [64]	Aza 38 CCR 49	Aza 12 CCR 18	78 77	58 39	NA NA	55 15	NR 10.8
Thepot [65]	138	44	73	21	14	18	10.2
Maurillo [69]	82	16	77	48	19	13	9

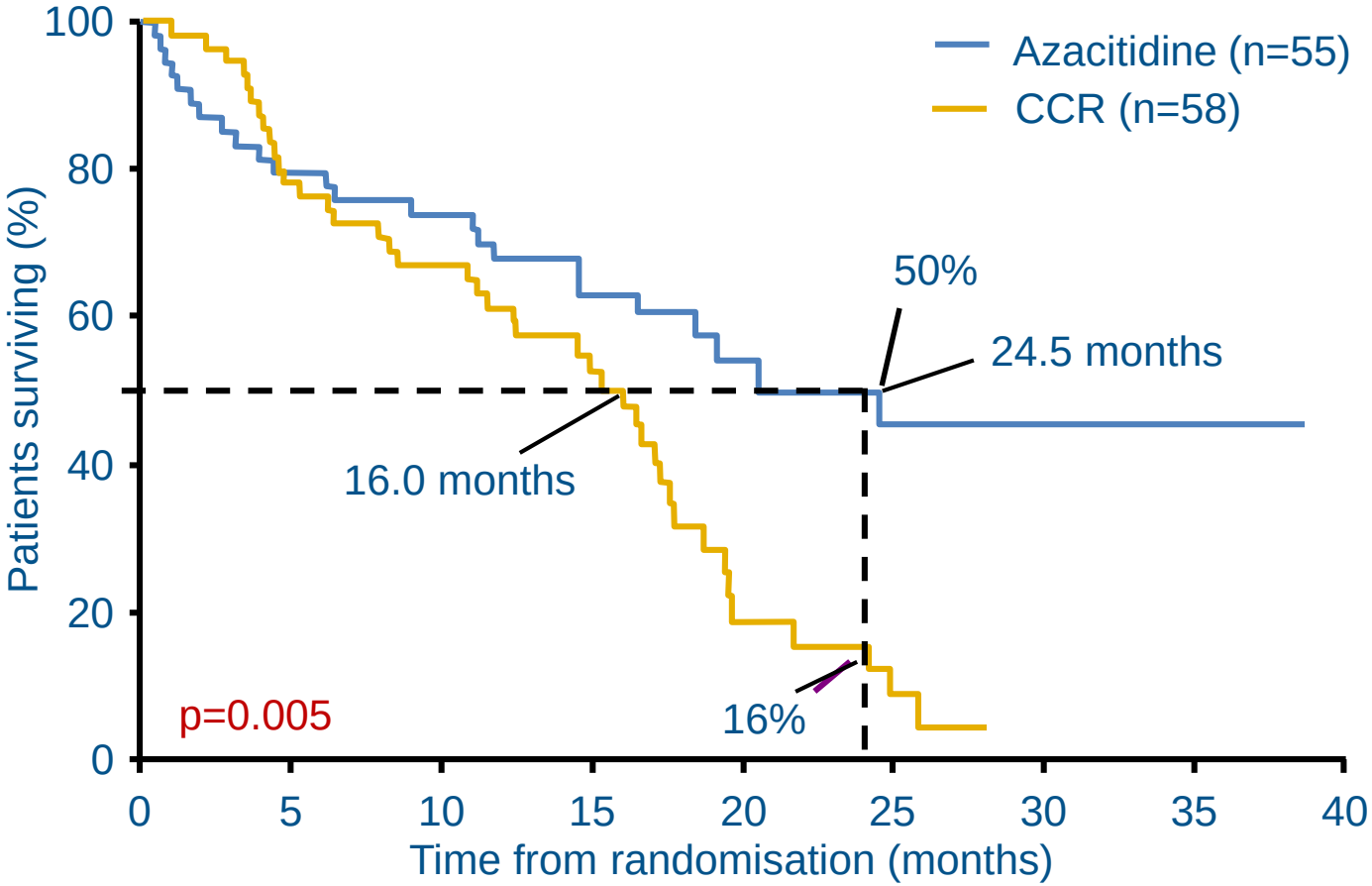
Maurillo L et al, Med J of Hemat 2013

AZA-001: baseline demographics of patients with AML 20–30% blasts

	Azacitidine (n=55)	CCR (n=58)
Median age, years (range)	70 (52–80)	70 (50–83)
ECOG status, %		
0	29.1	37.9
1	63.6	58.6
2	7.3	0
Cytogenetics, %		
Intermediate	69.1	74.1
Normal	34.5	56.9
unfavourable	25.5	22.4

CCR = conventional care regimens
ECOG = Eastern Cooperative Oncology Group
WHO = World Health Organization

AZA-001: OS in patients with AML 20–30% blasts



Azacitidine significantly extended OS versus CCR

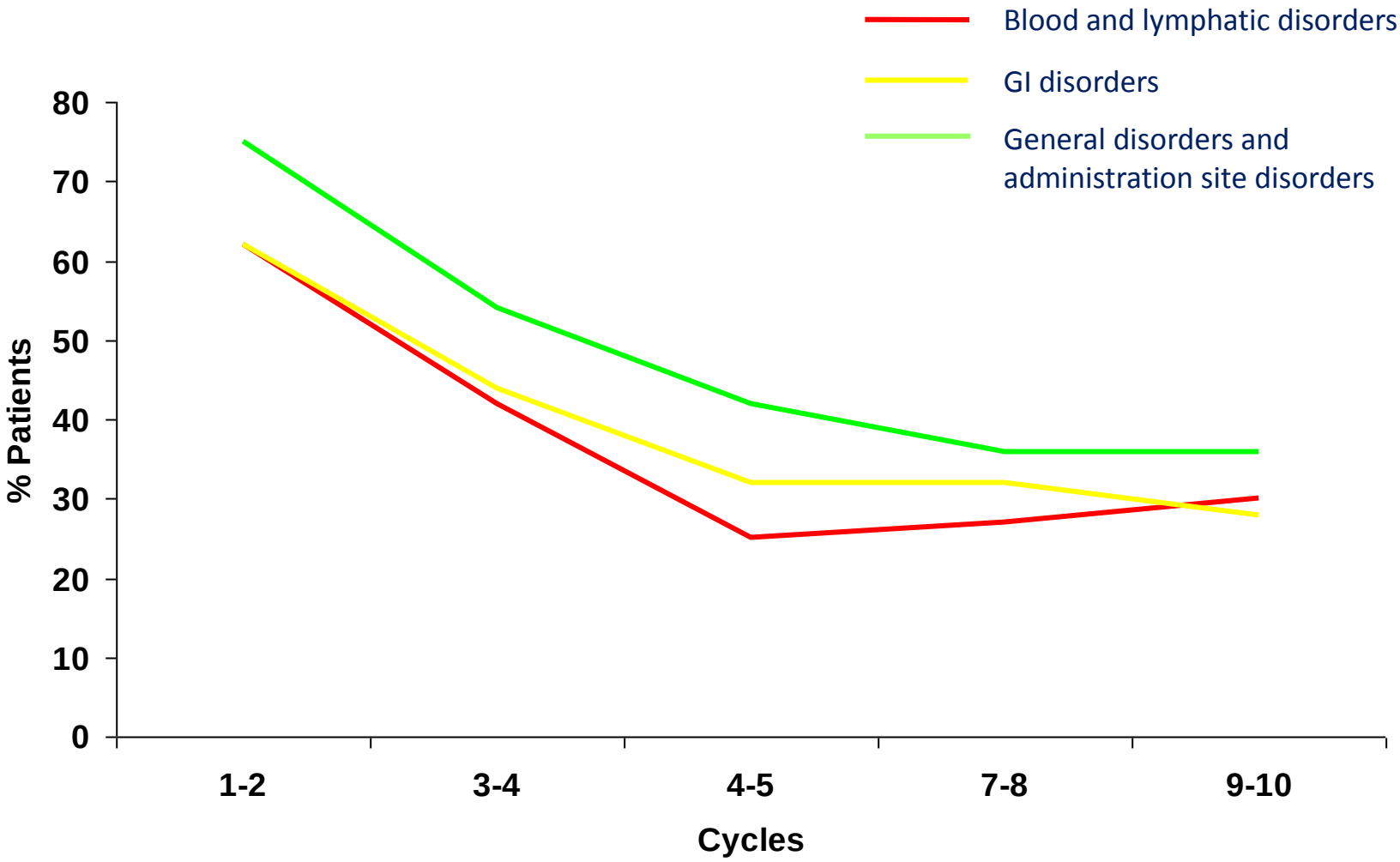
OS = overall survival

Management of AEs

AE	Suggested action	Suggested medication
Haematological[1]	• Monitoring • Delay of next cycle • Dose adjustment	• Prophylactic antibiotics • Growth factor support • Transfusions
Nausea, vomiting[2]	• Prevent prior to azacitidine	• Anti-emetics
Diarrhoea[2]	• Symptomatically treat as it occurs	• Anti-diarrhoeals
Constipation[2]	• Symptomatically treat as it occurs	• Laxatives, stool softeners
Injection-site reactions[2,3]	• Check injection technique is appropriate • Alleviate with medication	• Antihistamines • Corticosteroids • Analgesics

1. Vidaza [package insert]
2. Demakos EP, Linebaugh JA. Clin J Oncol Nurs 2005;9:417–23
3. Almeida A, Pierdomenico F. Leuk Res 2012;36:e211–3

Occurrence of AEs generally decreases over time



Adapted from Santini V, et al. Poster presented at ASH 2008. Abstract 1653

QUAZAR Trial in AML Maintenance

CC-486-AML-001 Phase 3 Trial Schema[1,2]

QUAZAR®
AML Maintenance

N = 460 planned

Transplant-ineligible AML

Within 90 days of first CR/CRi following induction ± consolidation

CC-486 maintenance
300 mg QD × 14 days
+
Best supportive care

Placebo maintenance
QD × 14 days
+
Best supportive care

Relapse with
> 5%-15% BM blasts:
Dose-escalate to CC-486 300 mg or placebo QD × 21 days

Relapse with
≥ 16% BM blasts:
Discontinue treatment

1. http://www.clinicaltrials.gov/ct2/show/NCT01757535. 2. Celgene data on file

Take home messages (II)

- The choice of therapeutic approach in AML elderly patients requires a multidisciplinary evaluation
- Adverse cytogenetics induces a low rate of response to standard chemotherapy
- 5 Azacitidine is well tolerated and has a crucial role in the treatment of 20-30% AML patients
- The identification of new genetic alterations in AML patients will lead to the development of innovative compounds with more “targeted” mechanisms of action

Thank you!

SEVENTH FRAMEWORK PROGRAMME

NEXT GENERATION SEQUENCING for Targeted Personalized Therapy of Leukemia

AIL Bologna