



Advances in Acute Myelogenous Leukemia

Novel Perspectives on Molecular Pathogenesis
and Clinical Applications



A microscopic image showing various cells, likely from a bone marrow biopsy, stained with a blue/purple dye. The cells are of different sizes and shapes, some with prominent nuclei.

STRATEGIES FOR THE ELDERLY PATIENT WITH AML

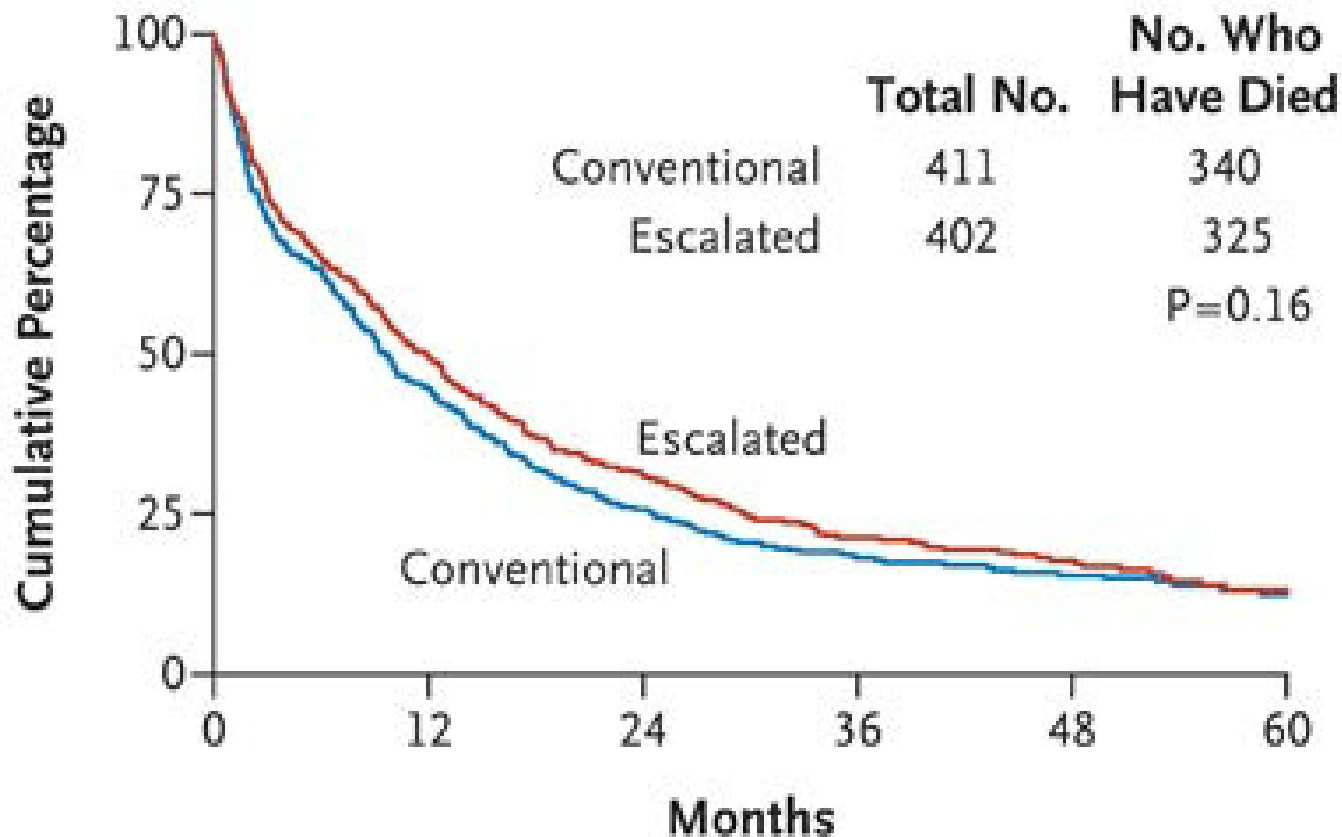
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High-Dose DNR in Older AML

- 813 pts; median age 67 yrs (60-83)
- Randomization to Ara-C 200 mg/m² CI/Dx7 and **DNR 45 vs 90** mg/m² daily x 3
- Consolidation HD Ara-Cx1

Parameter	DNR 45	DNR 90	P value
- % CR	54	64	0.002
- % CR post course 1	35	52	< 0.0001
- % 4-wk mortality	11	12	NS

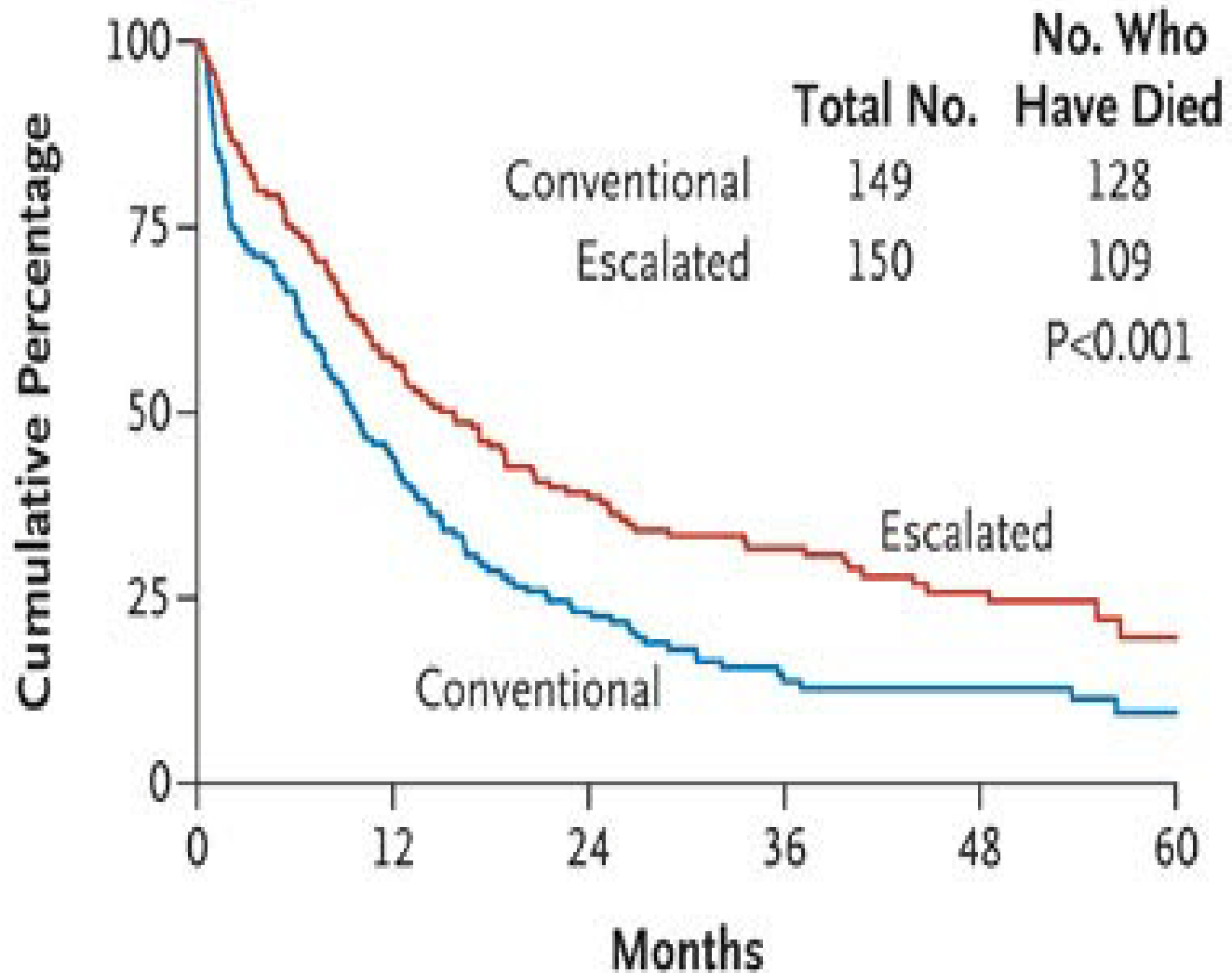
HD DNR in Older AML – Survival



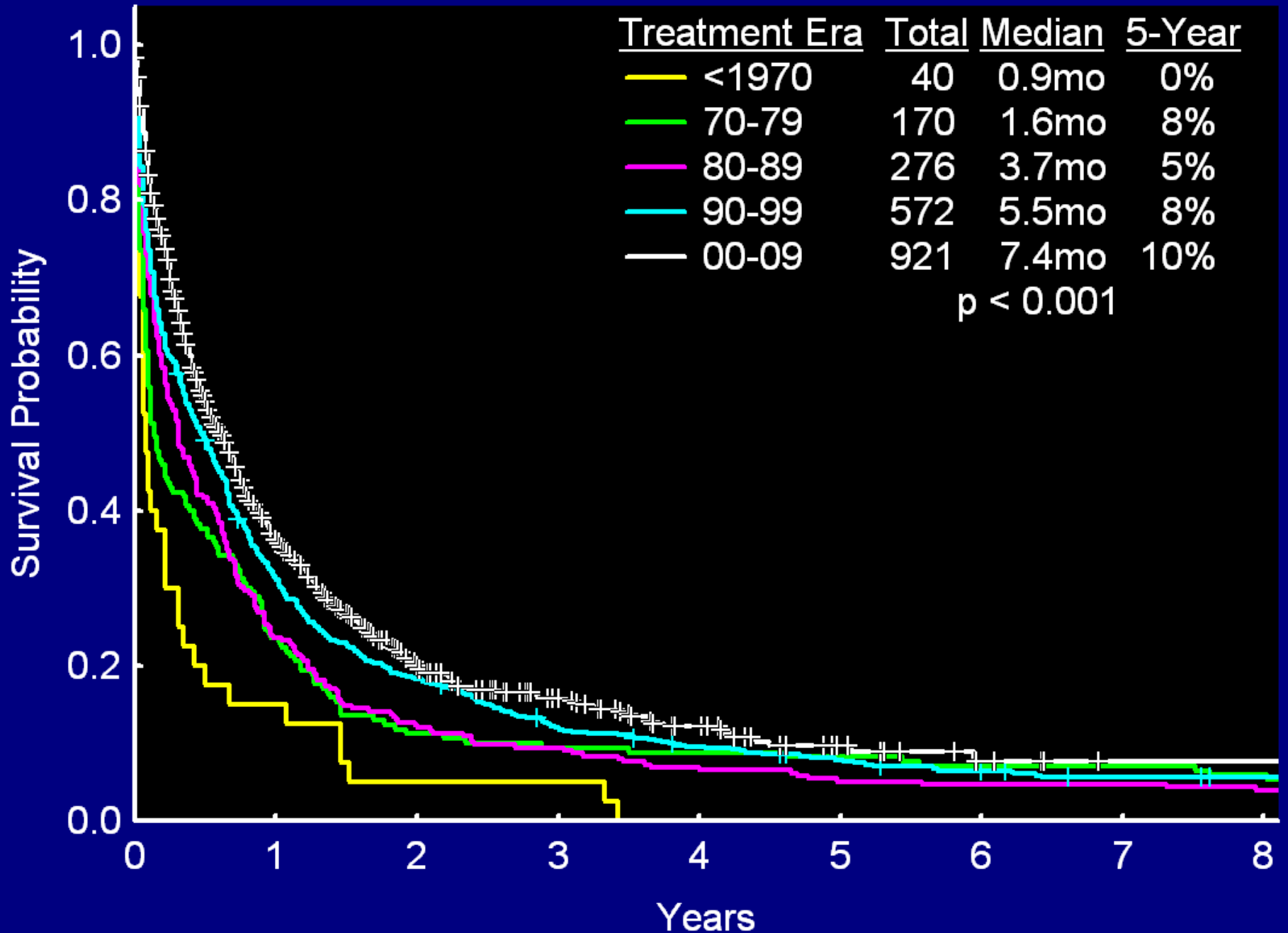
No. at Risk

Conventional	411	179	99	55	36	13
Escalated	402	193	115	63	40	16

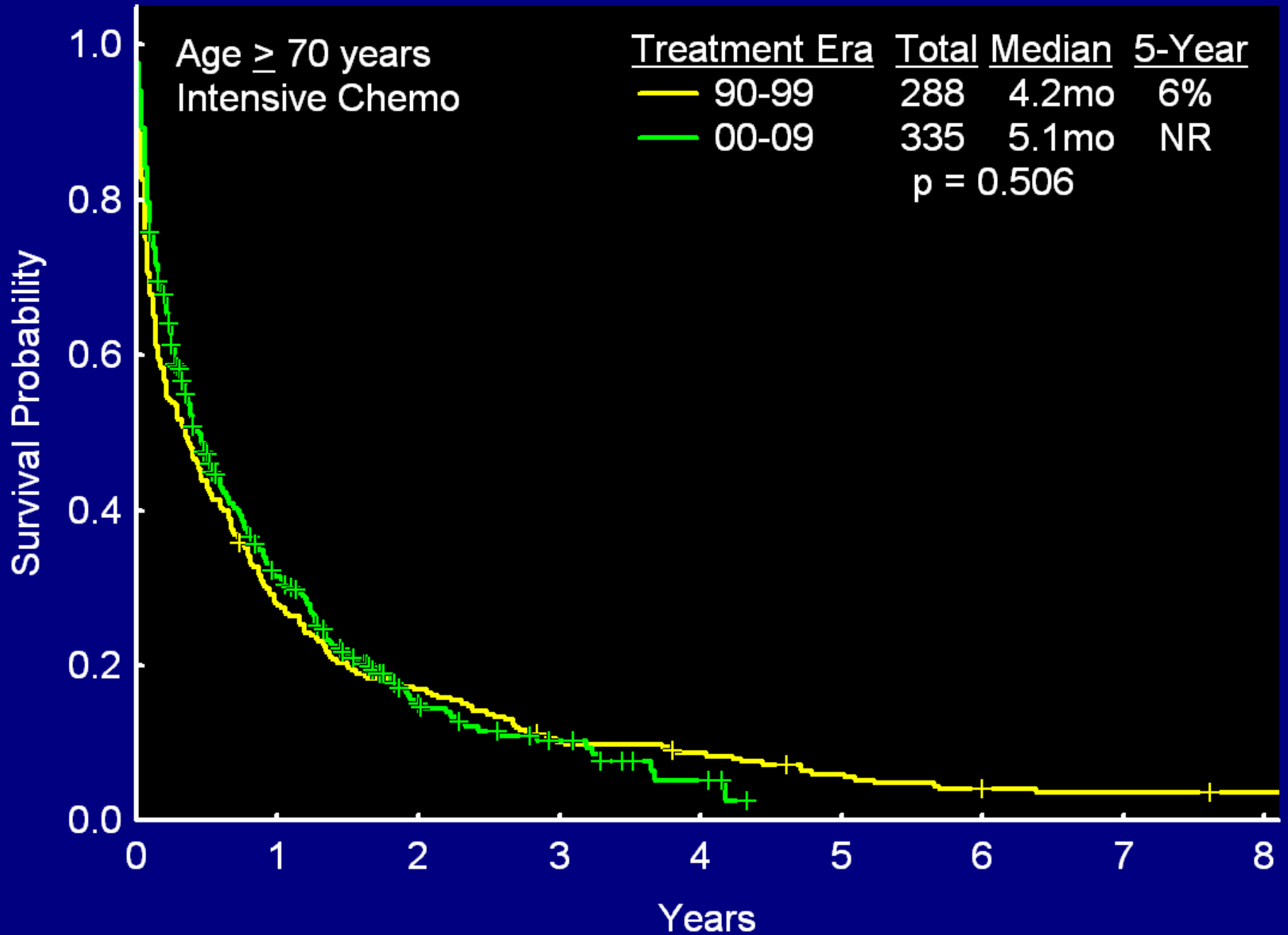
HD DNR in Older AML – Survival Age 60-65 Yr



AML Survival in Older Patients (Age ≥ 60) by RX Era



AML Survival in Older Patients (Age ≥ 70) by RX Era



Remission Rate by Age – MDACC (1980-Present)

<u>Age</u>	<u>Remission Rate</u>
<60 years	72%
≥60 years	48%
≥70 years (Intensive Chemo, 1990+)	47%

Remission Rate in AML Patients by Age and Rx Era

Rx Era	Age <60	Age >60
<1970	35%	18%
1970-79	60%	38%
1980-89	70%	44%
1990-99	71%	52%
2000-09	74%	46%

Why Do Elderly Patients with AML Do Worse?

- Poor tolerance and ↑ mortality with intensive chemoRx
- Poor PS and co-morbid conditions
- Different disease biology
 - ↑ MDR
 - ↑ incidence of adverse CG
 - ↑ other adverse molecular events

Survival in Elderly AML (SEER – Medicare)

- 3439 pts age \geq 65 yrs; median age 76 yrs; median survival 2.4 mos
- 1164 (34%) received chemoRx (younger, less co-morbidities)

Survival

Median (mos)

% 1 yr

- | | | |
|-----------|-----|------|
| • Overall | 2.4 | |
| • ChemoRx | 6.8 | ≈ 30 |
| • No Rx | 1.7 | ≈ 10 |

Lang K, et al. *Drugs Aging*. 2005;22:943.

Menzin J, et al. *Arch Intern Med*. 2002;162(14):1597-1603.

Adverse Prognostic Factors with Intensive ChemoRx in Elderly AML

- Age \geq 75 yrs
- Unfavorable karyotype
- ECOG performance \geq 2
- AHD $>$ 6-12 mos; prior MDS
- Creatinine $>$ 1.3 mg/dL
- Poor supportive care (“Rx outside LAFR”)

Outcome of Elderly AML by Adverse Factors

No Adverse Factors	% CR	% 8-wk Mortality	% 1-yr Survival
0-1	60-70	10-20	50
2-3	40-50	30-40	20-35
≥ 4	20	60-65	< 10

Low Dose Ara-C vs Hydrea ATRA in Elderly AML-HR MDS

- 217 pts; 155 age > 65 yr; 53 secondary; 28 HR MDS
- Ara-C 20 mg/BID x10 Q4-6 wks vs hydrea

	Ara-C	HU	P value
—No Rx treated	94	92	
—% CR	17	1	0.0003
—% 1 yr surv	27	3	0.0004
→hazard ratio 0.61 (0.45-0.82; P = 0.001)			

Nucleoside Analogues

Adenosine	Thymidine-Uracil	
FAMP DCF	5-FU	
CDA Clofarabine	AZT	
8 chloroadenosine		
8 aminoadenosine		
Guanosine	Cytosine	
6MP, 6TG	Cytarabine	Decitabine
Tiazofurin	Gemcitabine	Azacitidine
Nelarabine	Troxacitabine	Zebularine
Forodesine	Sapacitabine	
	4-thio-ara-C	

Activity of Hypomethylating Agents in AML

Agent	No	% CR	% Response
Azacitidine	103	7-12	35-48
Decitabine	155	15	54
Decitabine	27	11	26
Decitabine	33	24	52
VPA			

→ Median survival: AZA 19 mos; support 13 mos

Azacitidine Prolongs Survival in WHO AML

- 358 pts AZA-001; 113 had $\geq 20\%$ blasts (WHO AML)
- 55 randomized to AZA, 58 to CCR (IC 10, LDAC 18, BSC, 25)
- Median age 70 yr, poor CG 24 %
- Median FU 20 mos; median cycles 8 (1-39)

Parameter	AZA	CCR	P value
- Median OS (mos)	24	16	0.004
- % 2-yr survival	50	16	0.004
- % CR	18	16	NS
- Hospitalization (pt-yr)	3.4	4.3	0.03
- Infection (pt-yr)	0.58	1.14	0.003

- Survival better in int CG not in unfav CG

Phase III Decitabine vs Best Support or Low-Dose Ara-C in Elderly AML

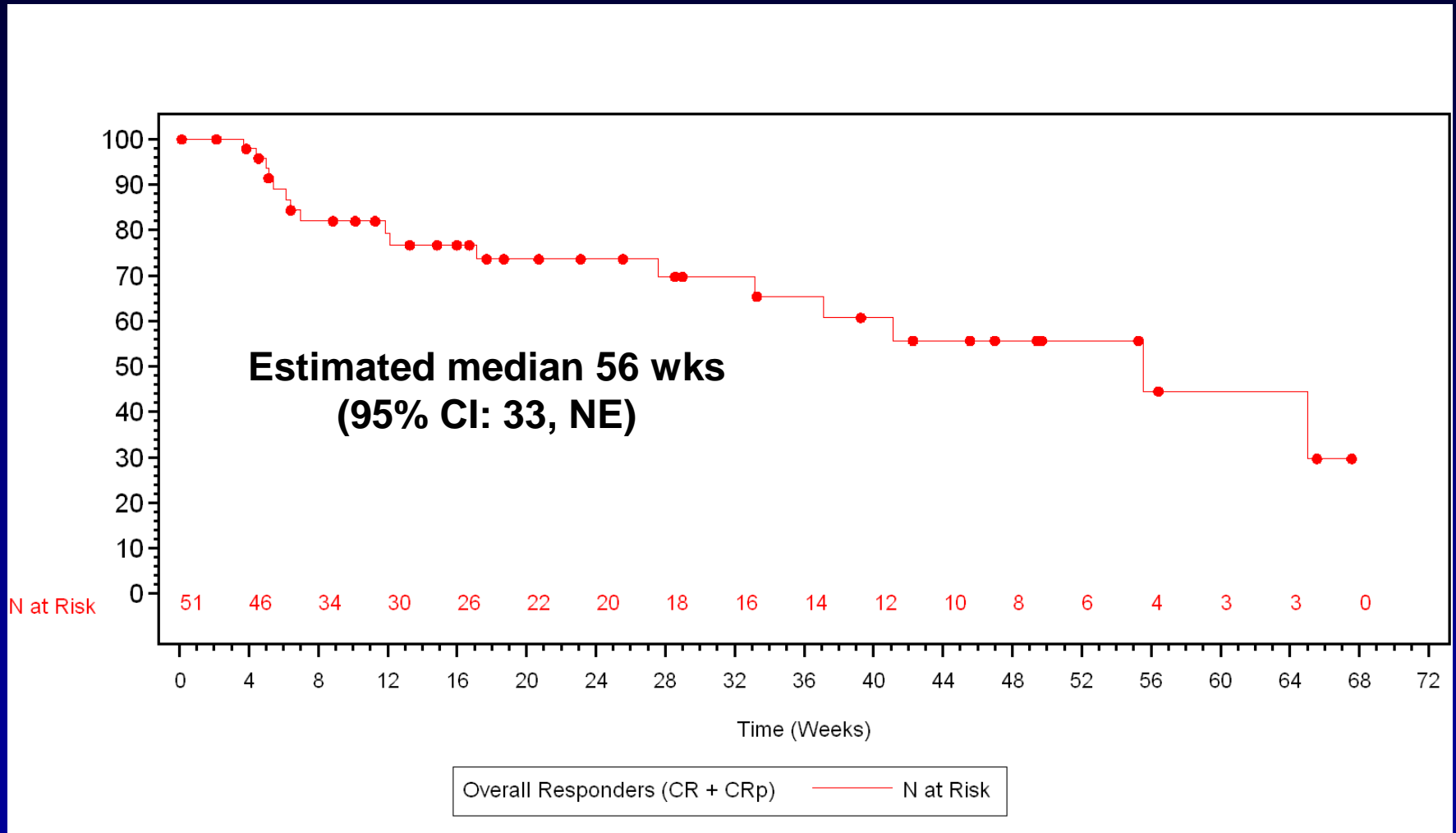
- Multinational study; 77 institutions
- Elderly (age \geq 65 yrs) AML unfit for intensive chemo Rx
- Randomization to:
 - Decitabine 20 mg/m² IV daily x 5 Q4 wks x 2 yrs
 - Ara-C 20 mg/m² SQ daily x 5 Q4 wks x 2 yrs
- Endpoints: CR, survival
- Planned accrual 480; accrual completed

Clofarabine in Older Untreated AML

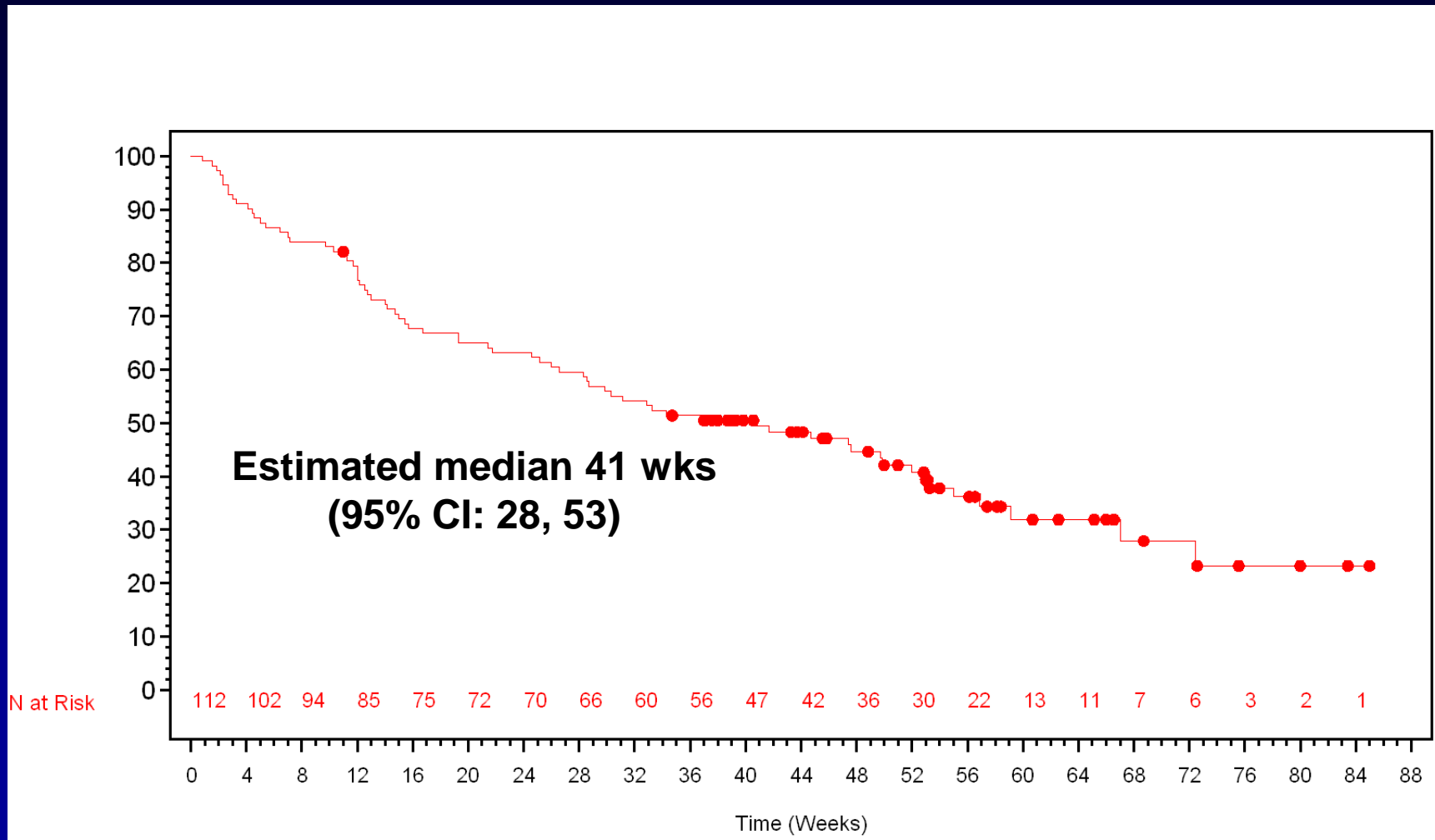
- Multi-institutional; 20 sites; age \geq 60 yrs; prior AHD and secondary AML allowed
- 112 pts; median age 71 yrs (60-88)
- CG adverse 55%; AHD 50%; age \geq 70 62%; ECOG 2 22%-78% with 2 or more adverse factors
- **CR 38%; OR 46%**
- **4-wk mort 9.6%; 8-wk mort 16%**

<u>No. risk factor</u>	<u>% OR</u>
1	48
2	51
3-4	38

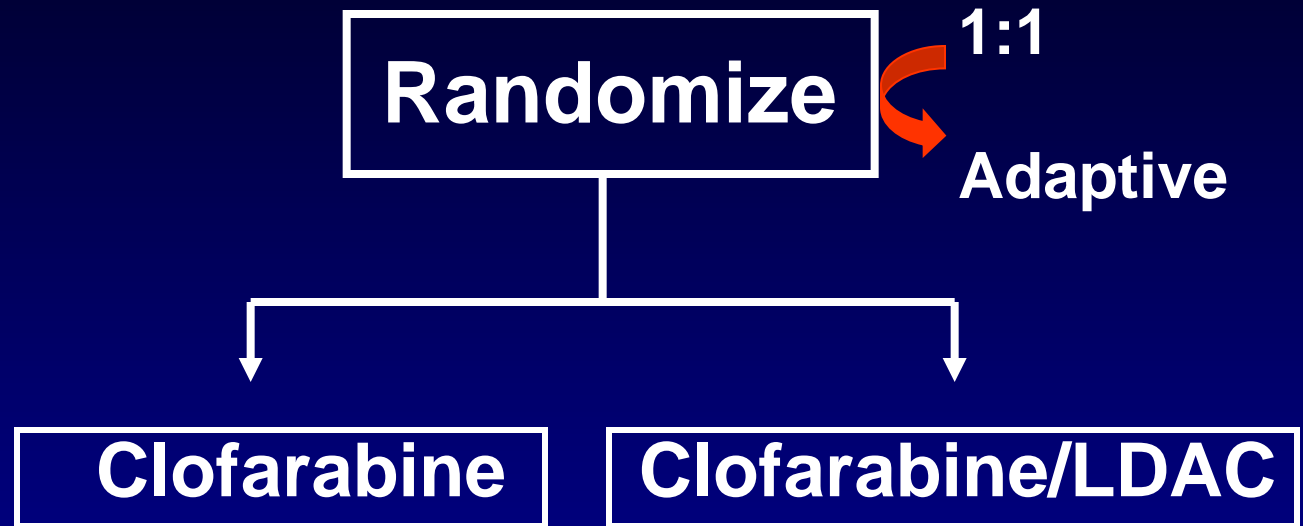
Clofarabine in Elderly AML – DOR



Clofarabine in Elderly AML – Survival



Clofarabine + Low-Dose Ara-C in AML Frontline Pts ≥ 60 yrs



Induction

C 30 mg/m² x 5

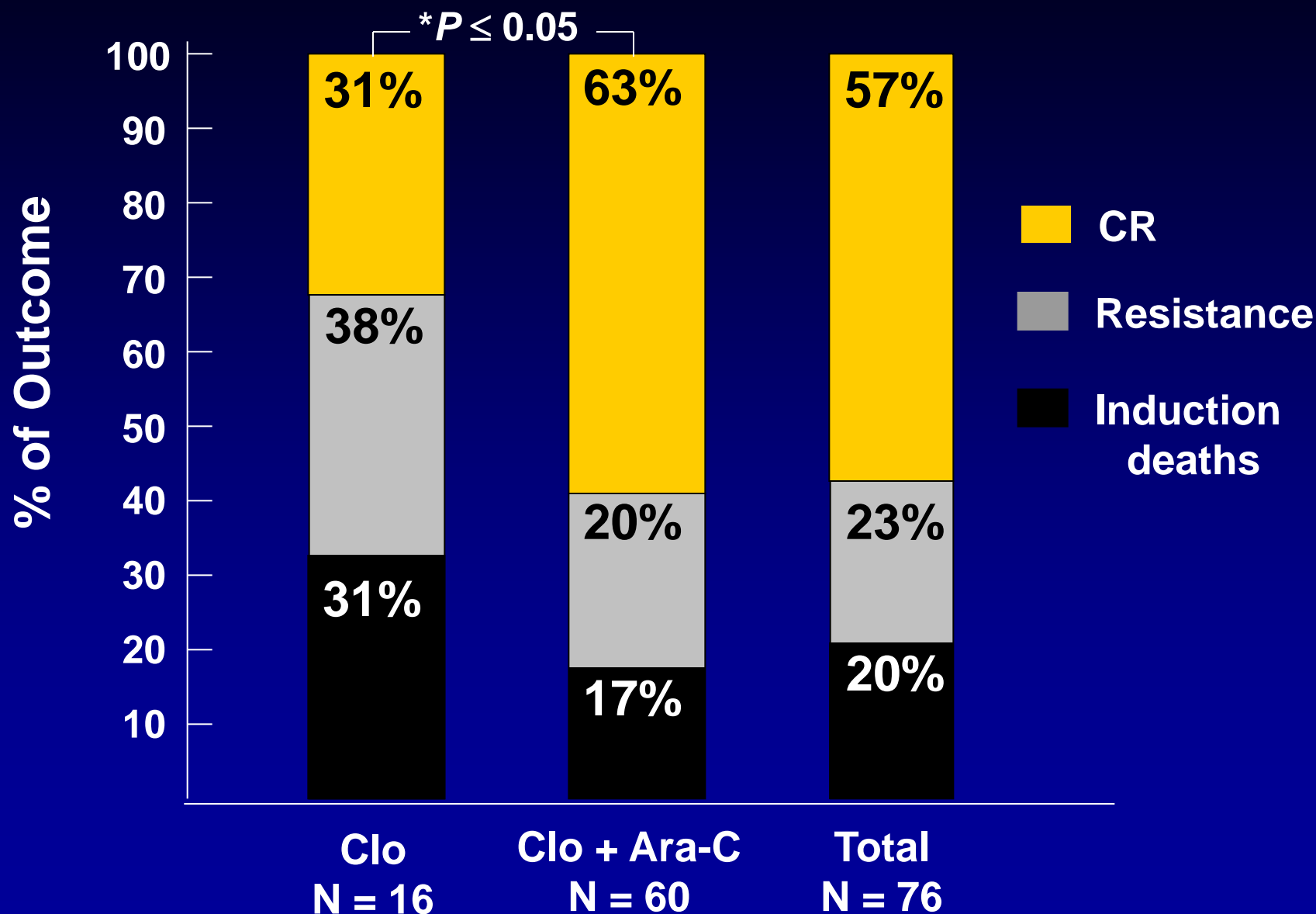
C 30 mg/m² x 5
A 20 mg/m² x 14

Consolidation

C 30 mg/m² x 3

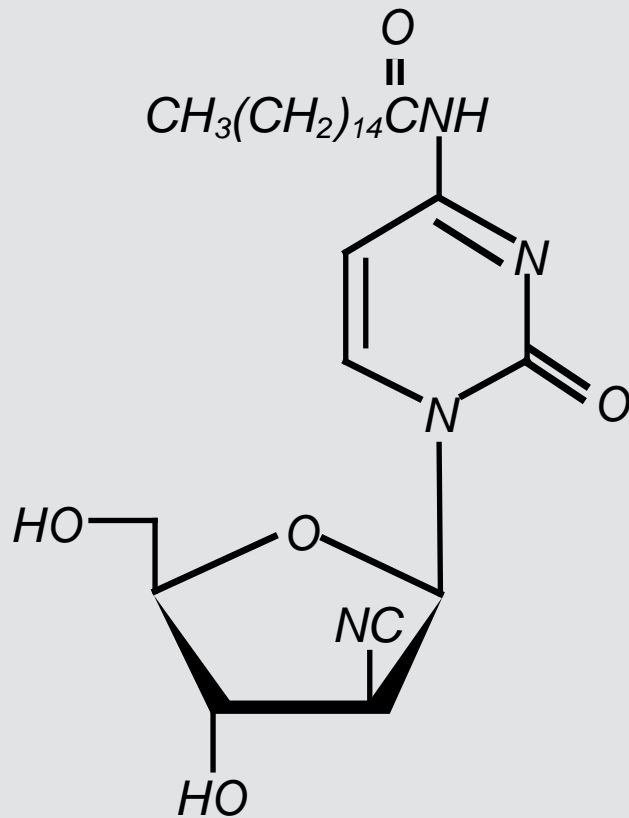
C 30 mg/m² x 3
A 20 mg/m² x 7

Clofarabine + LDAC: Outcome (N = 76)



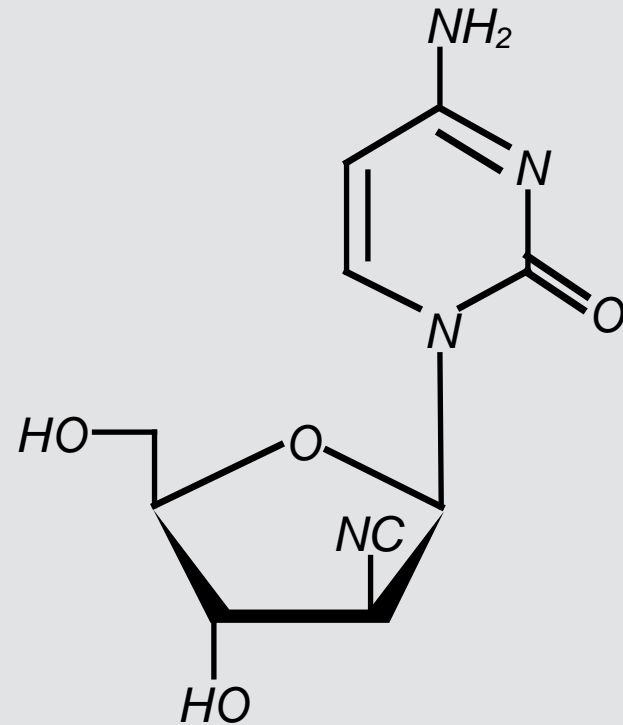
CS-682, CYC-682, Sapacitabine

An Orally Bioavailable Prodrug of CNDAC



CS-682

1-(2-C-cyano-2-deoxy-β-D-arabino-pentofuranosyl)-N⁴-palmitoylcytosine



CNDAC

1-(2-C-cyano-2-deoxy-β-D-arabino-pentofuranosyl)cytosine

Phase I Sapacitabine – Summary

- 47 pts: 42 AML, 4 MDS, 1 ALL
- Sapacitabine:
 - 75-375 mg BID x 7 days Q mo (n = 35)
 - 375-475 mg BID D1-3, D8-10 (n = 12)
- DLT – GI; MTDs – 375 mg BID x 7 days; 425 mg BID D1-3, D8-10
- Median cycles 3 (1-16)
- **Response: 13 (28%); 4 CRs; 9 marrow CR**
20 pts (43%) had 1 log ↓ blasts (n = 12) or ≥ 50% ↓ marrow blasts (n = 8). Favorable antileukemic effect in 33/47 = 70%

Aurora Kinase Inhibitors

Agent	AK	T315I	JAK2	FLT3
MK0457	+	+	+	+
KW2499	+	+	-	+
AZD1152	+	-	-	-
AT9283	+	+	+	-

**Others: CYC11056; PHA739358 (AK + T315I);
Ro 4612910; TTP607**

Phase I-II AZD1152 in AML

- Selective aurora kinase inhibitor
- Phase I: 300-1600 mg CI over 7D/course
- DLT mucositis; phase II 1200 mg/course
- OR 20-25% in refractory relapse AML

Phase I CPX351 in Refractory Leukemia

- CPX351 = liposomal carrier with 5:1 fixed molar ratio Ara-C: DNR – optimal in vitro target and delivery
- 47 pts with refractory AML (n = 44), ALL (n = 3) Rx on phase I
- MTD and phase II 101 u (101 mg Ara-C + 44 mg DNR)/m²
- 3DLTs: LVEF, ↑ b.p, aplasia
- T 1/2 33 hr for Ara-C, 23 hr for DNR
- 11 CR + CRp = 23%

SNS 595 (voreloxin) in Leukemia

- Naphthyridine (novel class) analog; intercalates DNA; poisons topo II
- Phase I: DLT mucositis; MTD 72 mg/m²/wk
- Phase II; age ≥ 60 yrs; 72 mg/m² weekly x 2-3: CR16 (25%); OR 21 (33%)
- 20 pt Rx with SNS 72 mg/m² D1 and 4
- Plans: elderly AML; SNS + HD Ara-C

Elderly AML “Not Fit for Intensive ChemoRx” – Treatment Options

- Clofarabine LD Ara-C
- Decitabine VPA
- Cloretazine
- LD Ara-C GO or AS_2O_3
- Sapacitabine, bendamustine, others
- **Do not use hydrea or supportive care**

Leukemia Questions?

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