Treatment Breakthroughs In AML

Martin S. Tallman, M.D.
Chief, Leukemia Service
Memorial Sloan-Kettering Cancer Center
Weill Cornell Medical College
New York, NY

Hong Kong 2012

Outline

- Introduction
- Overview of current therapy
- Breakthroughs
- Future Directions

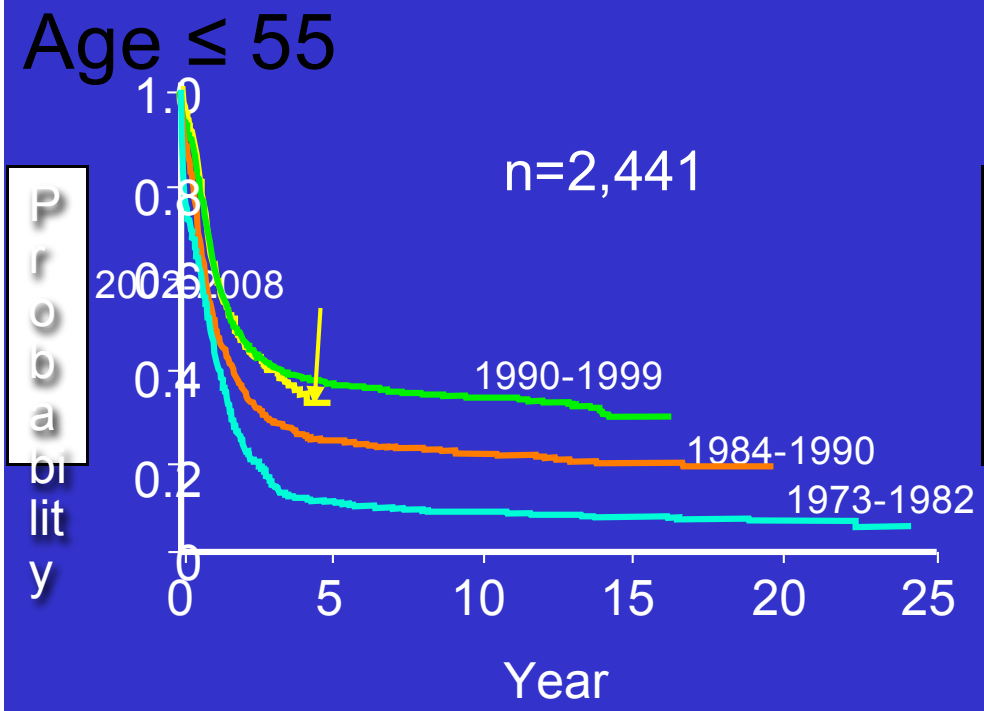
Introduction

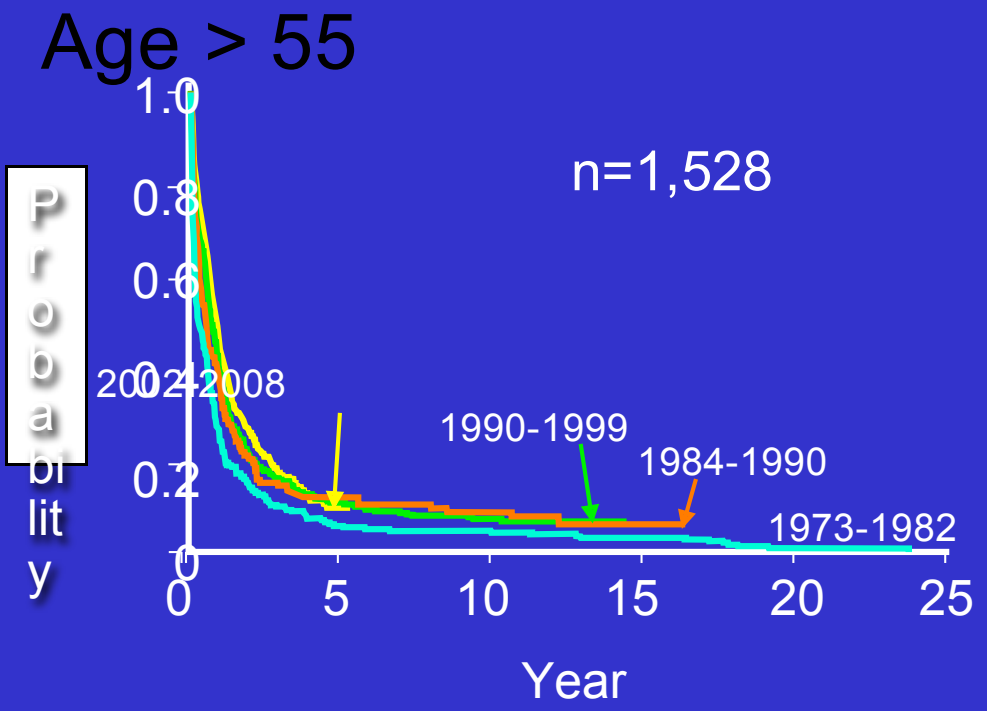
- Median age of AML: 72 years
- New patients/deaths in 2011: 13,400/9,000
- De novo or therapy-related or evolved from MDS or MPN
- Outcome varies by prognostic factors
- Heterogeneity in genetics and clinical manifestations

Ca for Clinicians, 2009; Juliusson Blood, 2009

Overview of Current Therapy

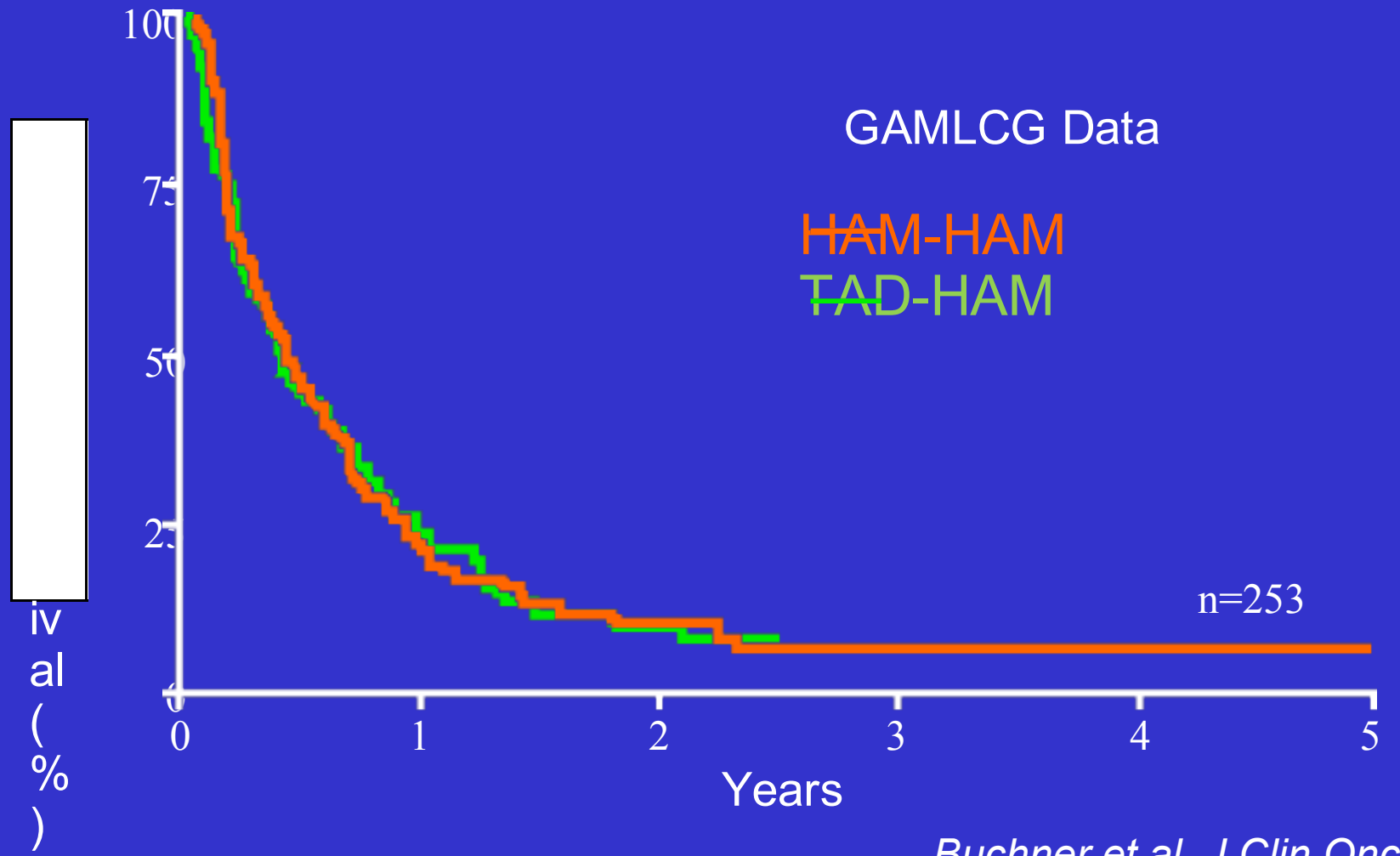
Survival of Newly Diagnosed AML Consecutive ECOG Frontline Trials





Tallman, Gilliland, Rowe et al. Blood, 2005 and update

AML in Older Adults (>60)
Overall Survival
with Unfavorable Cytogenetics



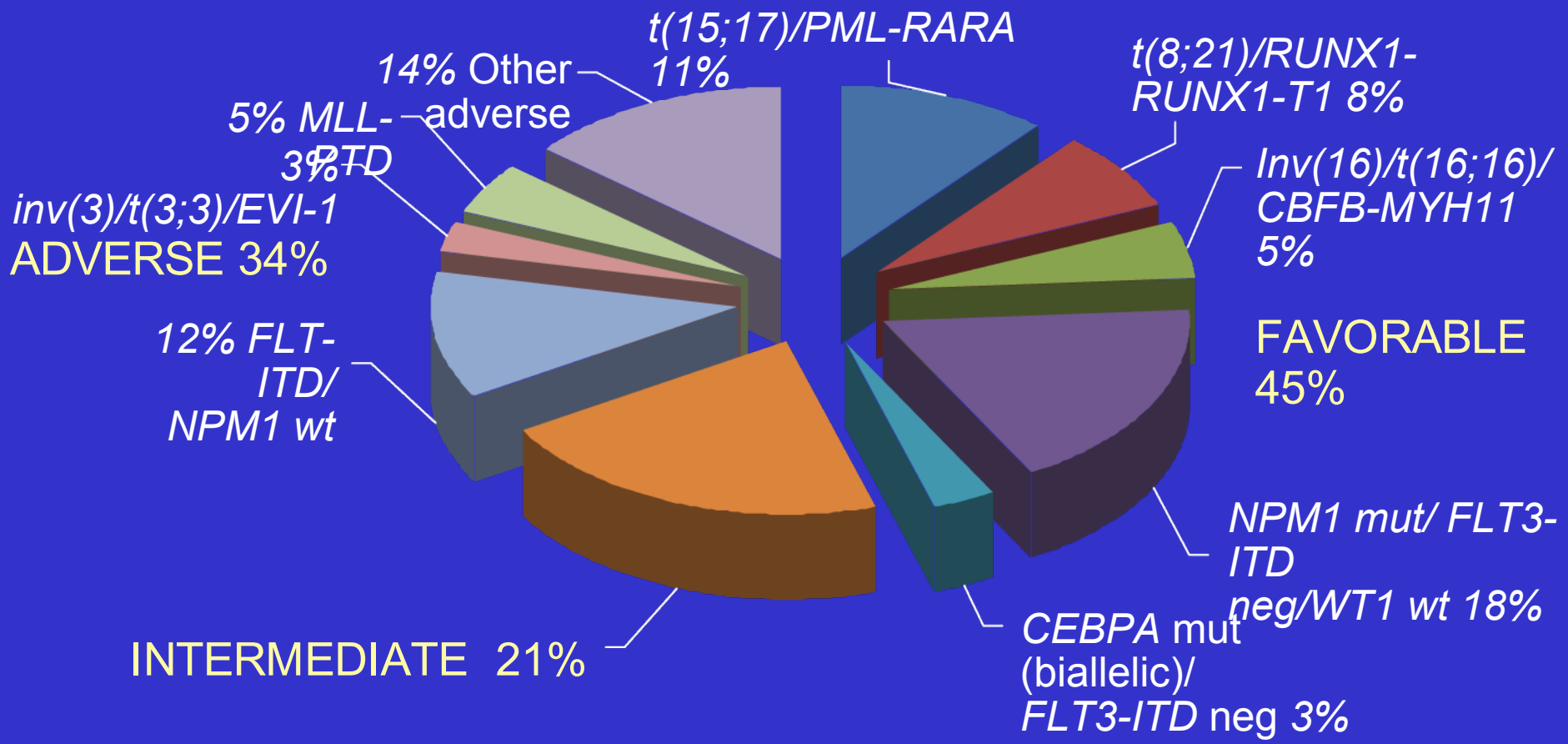
Buchner et al. J Clin Oncol, 2006

Breakthroughs

- Gene discovery/prognostic factors
- Acute promyelocytic leukemia (ATRA/ATO)
- Drug development
- Induction/postremission
- Minimal residual disease
- Less intense treatment of older adults
- Transplantation/alternative donors

Gene Discovery/Prognostic Factors

Distribution of Cytogenetically and Molecularly Defined Risk Groups in AML



Grimwade Hematology Am Soc Hematol Educ Program, 2009

Mutation Frequencies
398 Patients on ECOG Protocol E1900
For Younger de novo AML

Mutation	Frequency
IDH1	6%
IDH2	8%
TET2	10%
ASXL1	4%
FLT3	37%*
NPM1	24%
KIT	14%
CEBP	9%
WT1	10%
KRAS	2.5%
NRAS	10%

*ITD 30%,TKD 7%

Patel et al. N Engl J Med 2012 (in press)

Mutation Frequencies in Normal Karyotype AML

Mutation	Frequency
NPM1	53% (fav)
FLT3-ITD	31%
FLT3-TKD	11%
CEBP	15% (fav)
MLL-PTD	8%
NRAS	13%
IDH1/2	10/3%

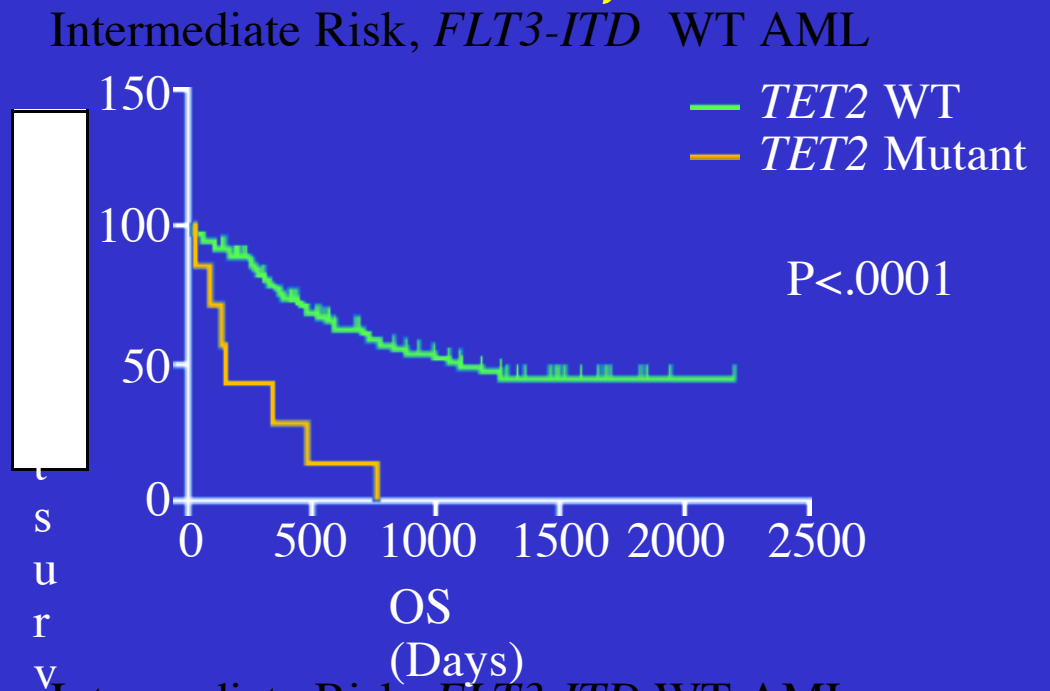
Schlenk et al N Engl J Med, 2008; Boissel et al. J Clin Oncol, 2010

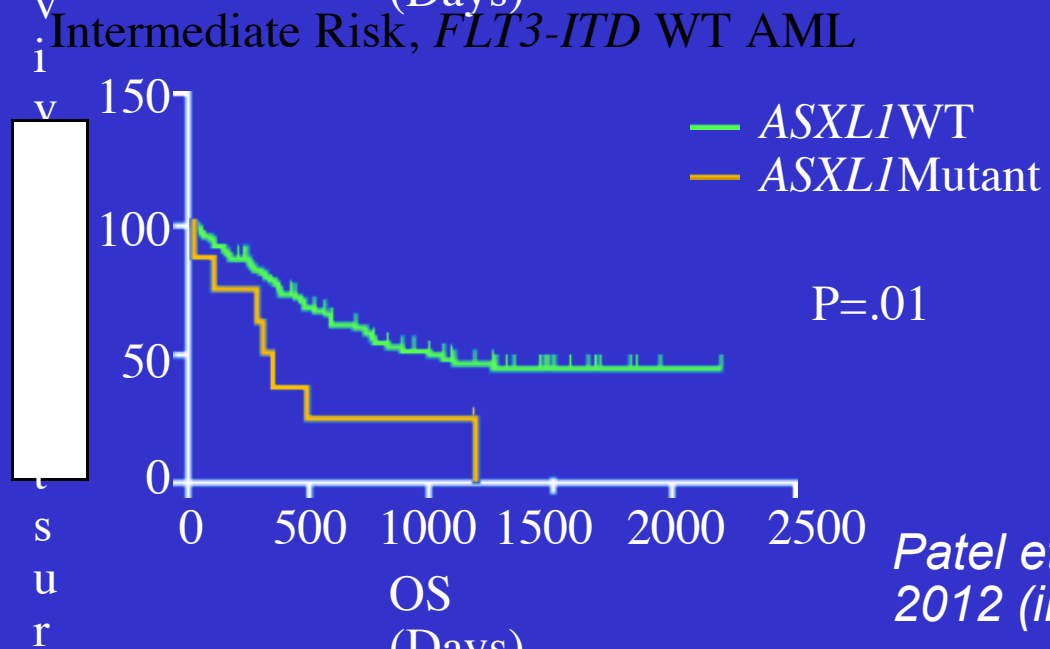
Novel Mutations in AML

Mutation	Freq	Associations	Outcome
IDH1/2	6%/8%	Older age, NK, *NPM1*+	Decreased OS in *FLT3-/NPM1-*
DNMT3A	22%	Enriched in intermed-risk, absent in fav-risk	Decreased OS
TET2	10%	May be assoc. with *NPM1*+	Decreased OS in intermed-risk, *FLT3-*
ASXL1	4%	Older age, *RUNX1*, trisomy 8 and not complex cyto, *FLT3, NMP1, WT1; CEBP*	Decreased OS in intermed-risk, *FLT3-*

Abbas et al. Blood, 2010; Ley et al. N Engl J Med, 2010; Nibourel et al. Blood, 2010; Chou et al. Blood, 2010; Patel et al. ASH, 2010

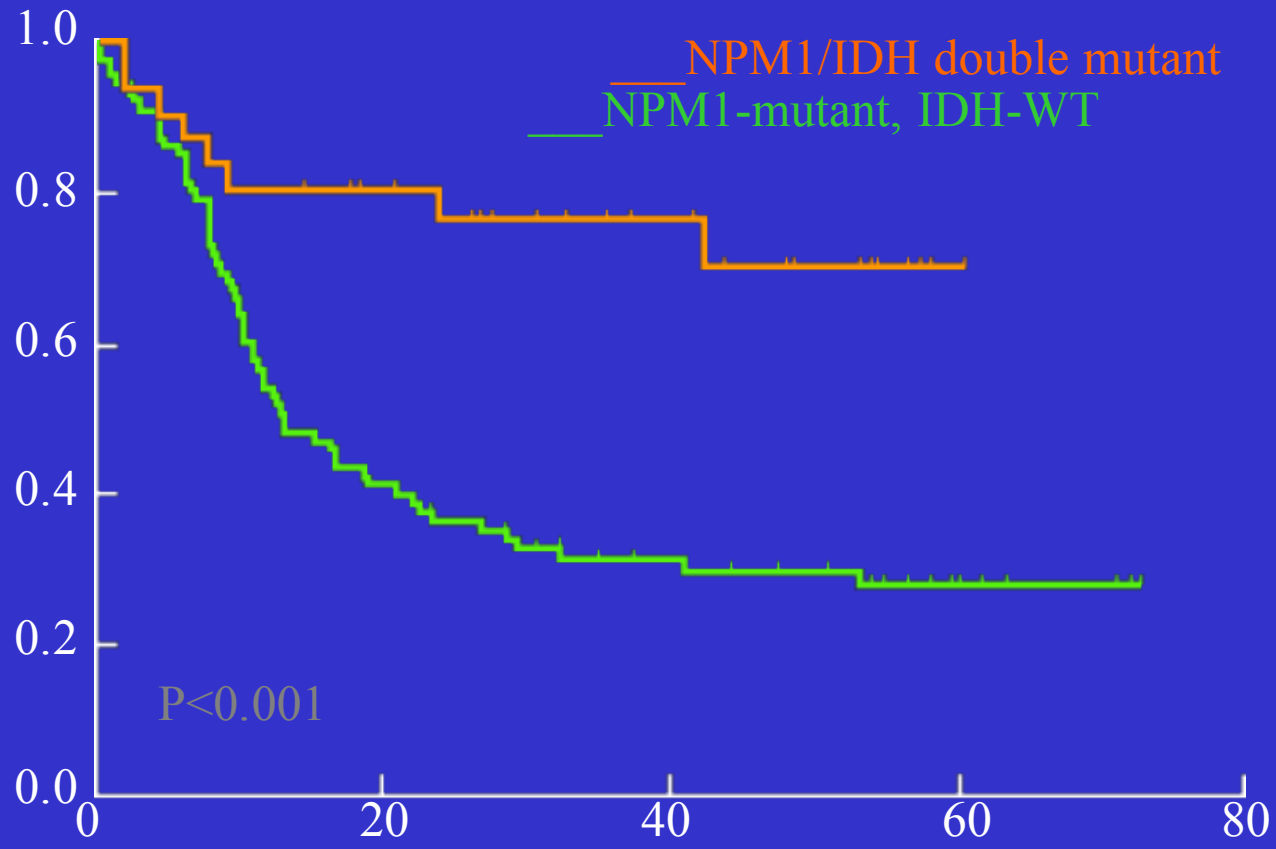
TET2 and *ASXL1* Mutations Associated With Adverse Outcon in Intermediate-Risk, *FLT3-ITD* WT AML





Patel et al. N Engl J Med, 2012 (in press)

IDH/NPM1 Mutations Define Favorable Outcome in *FLT3*-Neg, Intermediate-Risk AML

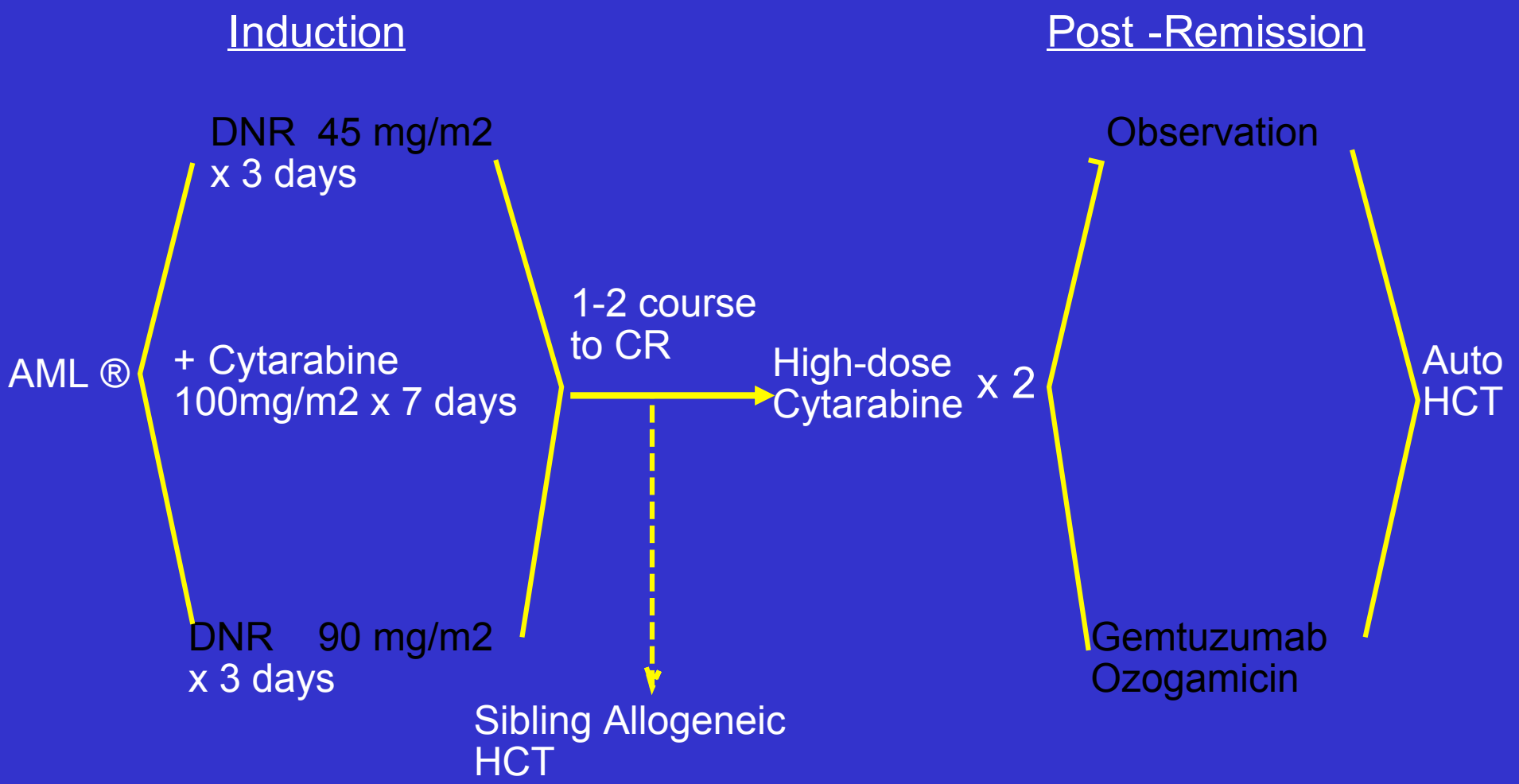


IDH/NPM1-mutant pts, but not *NPM1*-mutant/*IDH*-WT pts have a favorable outcome

Patel et al. N Engl J Med, 2012 (in press)

Inducton/Postremission

Dauno Dose Intensification
E1900 AML < 60 yrs



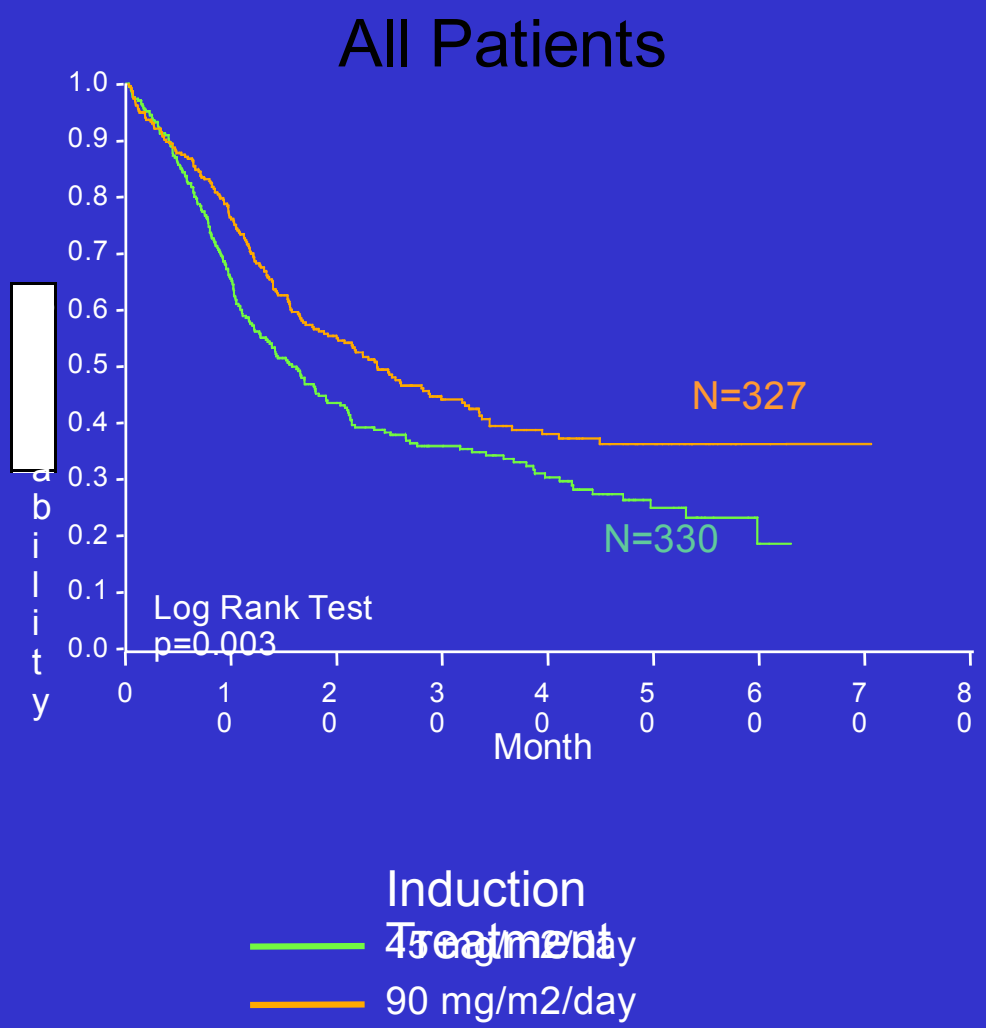
Fernandez et al. N Engl J Med, 2009

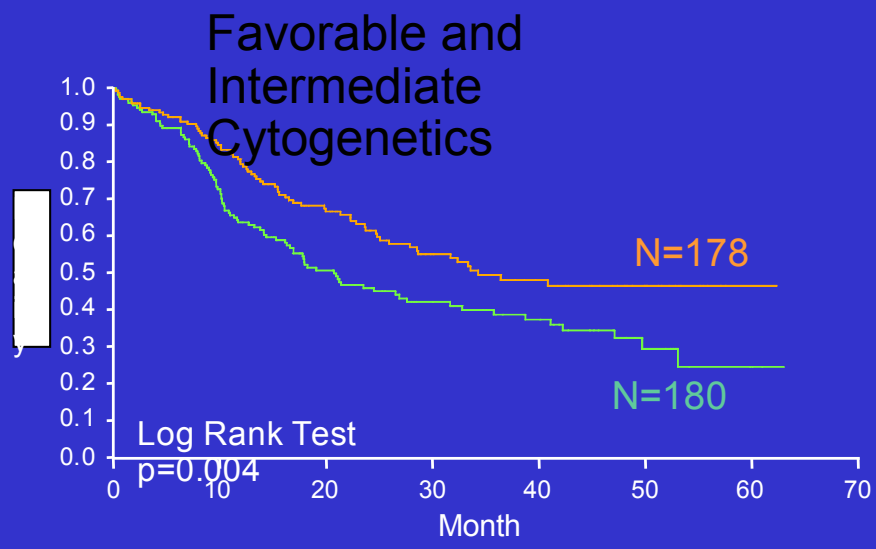
Intensified Induction in AML ECOG E1900

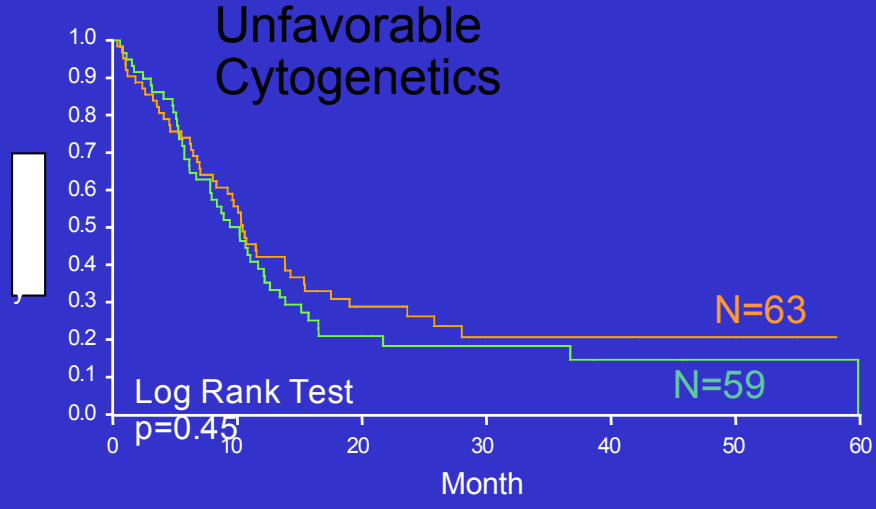
- 657 patients
- CR Dauno 45 - 57%
  Dauno 90 - 71% p=< .001
- Induction deaths
  Dauno 45 - 2.4%
  Dauno 90 - 4% p=.28

Fernandez et al. N Engl J Med, 2009

Dauno Dose Intensification: E1900
Overall Survival

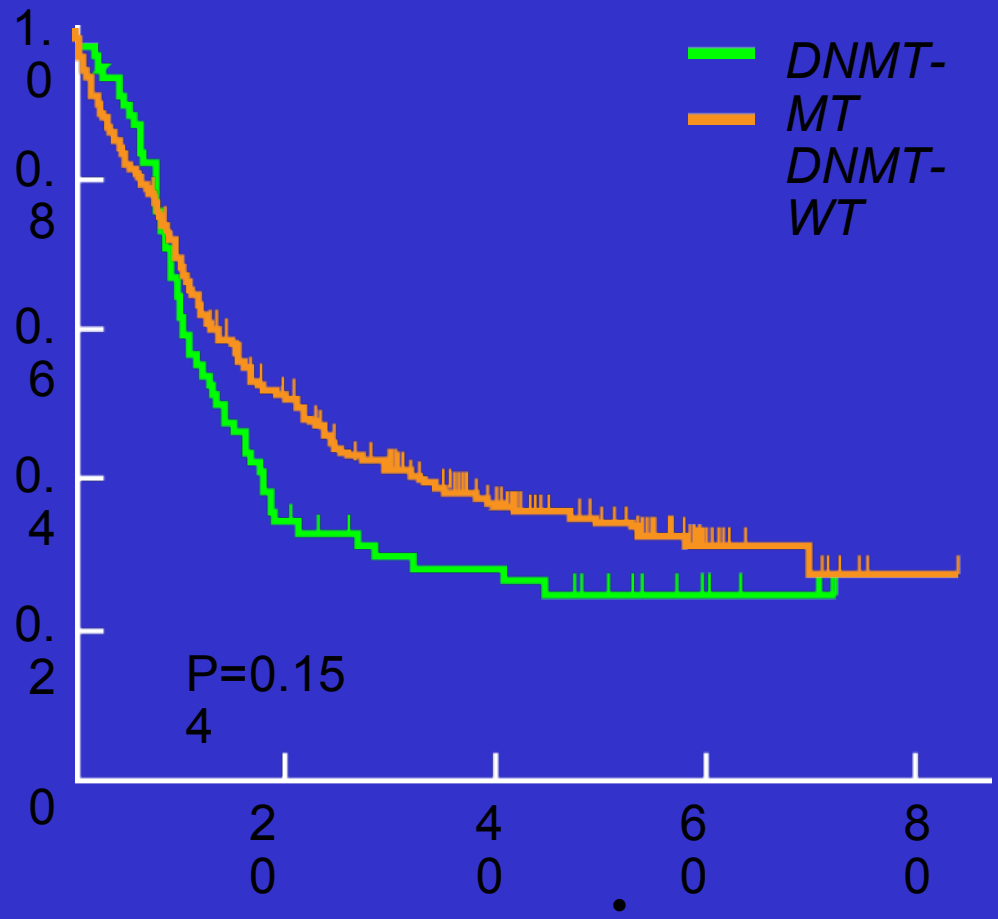






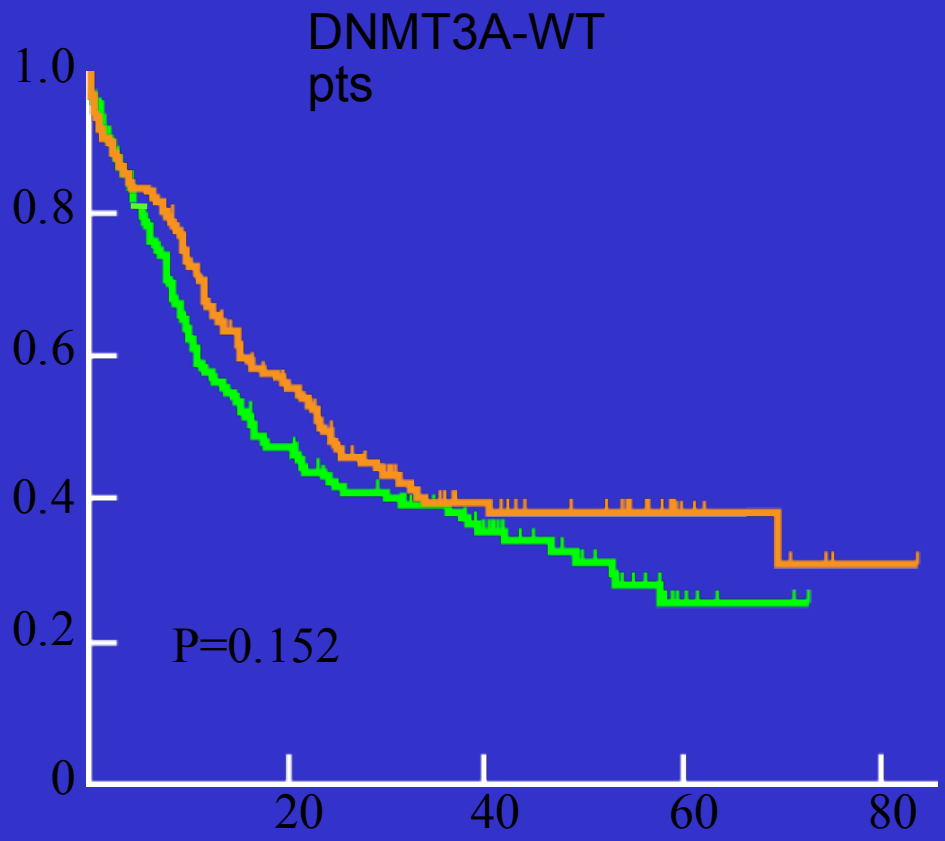
Fernandez et al. N Engl J Med,

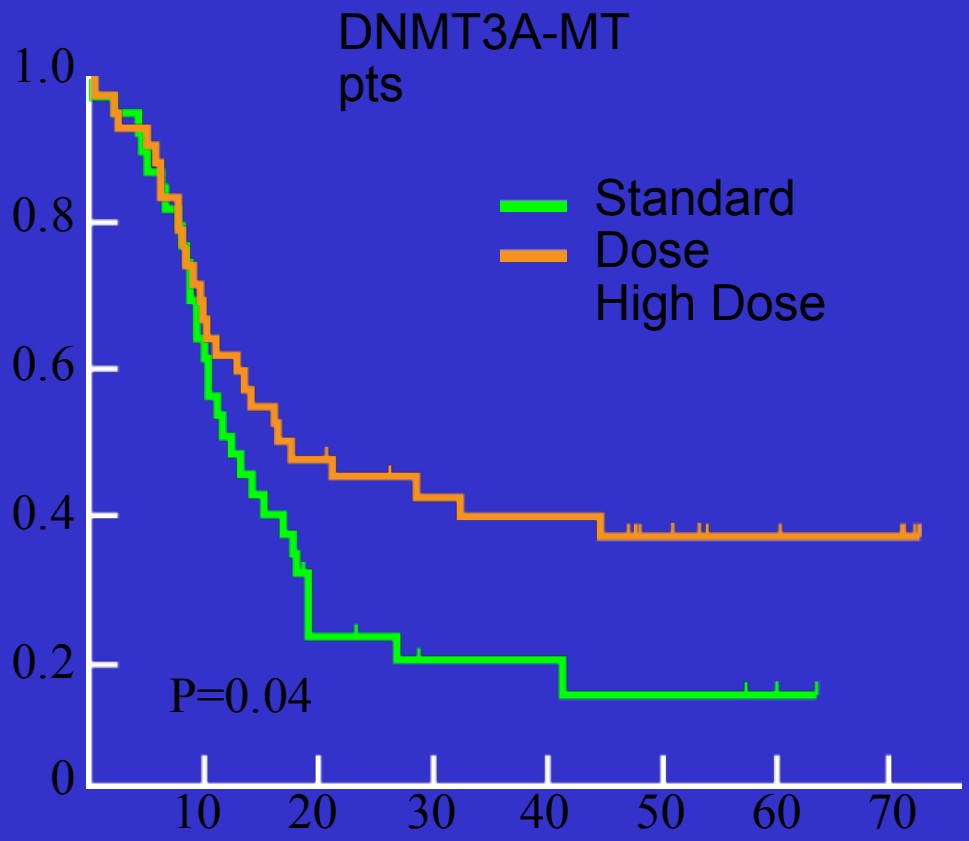
DNMT Mutational Status Does Not Affect Outcome in E1900 Cohort



Patel et al. N Engl J Med, 2012 (in press)

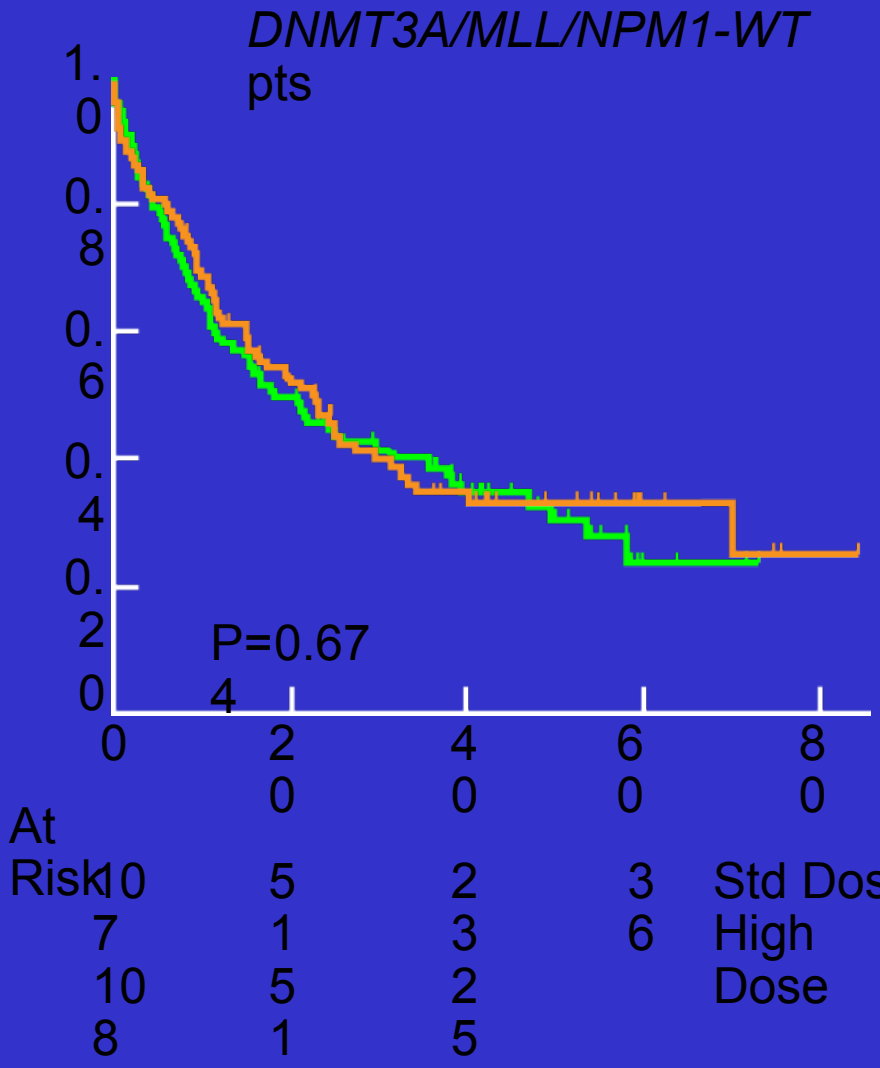
High Dose Daunorubicin Improves Outcome in *DNMT3A* Mutant Patients, But Not *DNMT-WT* patients

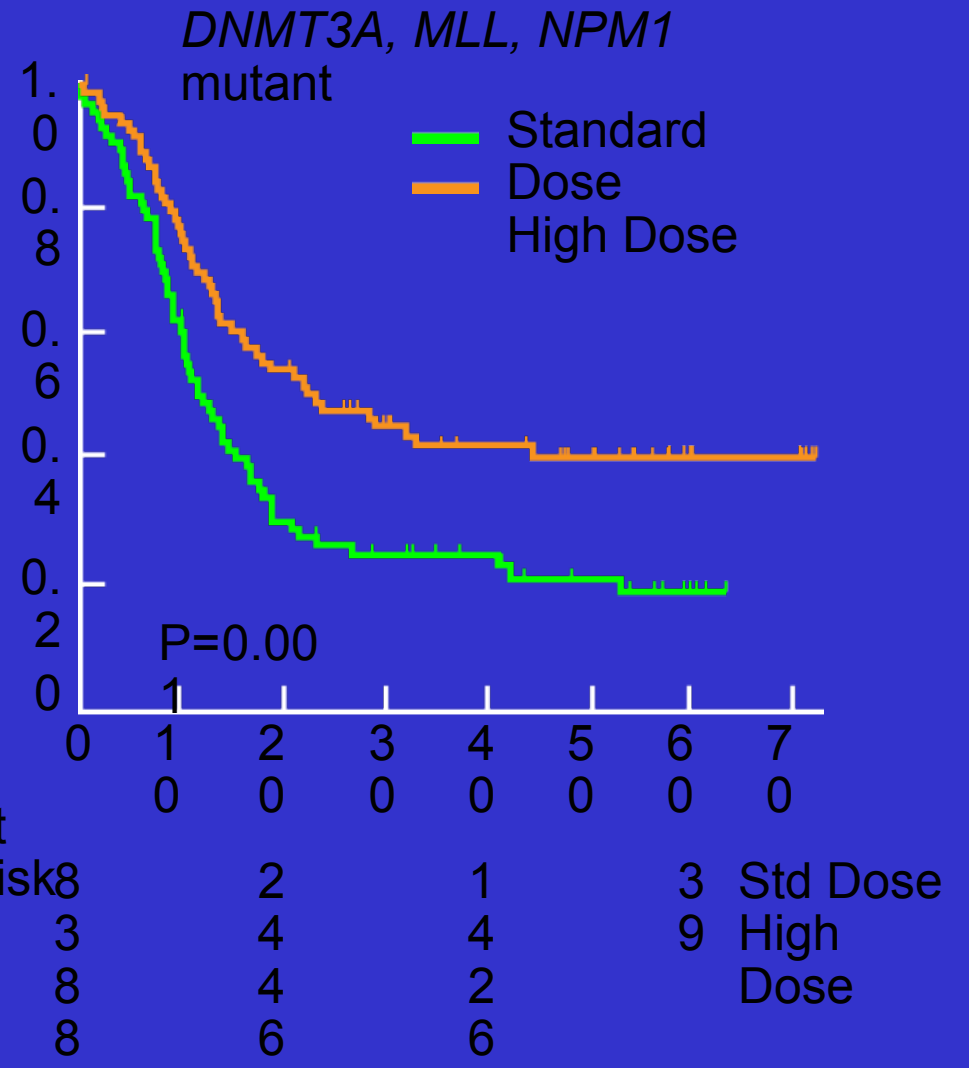




Patel et al. N Engl J Med, 2012 (in press)

High Dose Daunorubicin Improves Outcome in Patients With *DNMT3A* Mutations, *MLL* Fusions, or *NPM1* Mutations





Patel et al. N Engl J Med, 2012 (in press)

Gemtuzumab Ozogamicin

Structure

Humanized anti-CD33 antibody linked to calicheamicin

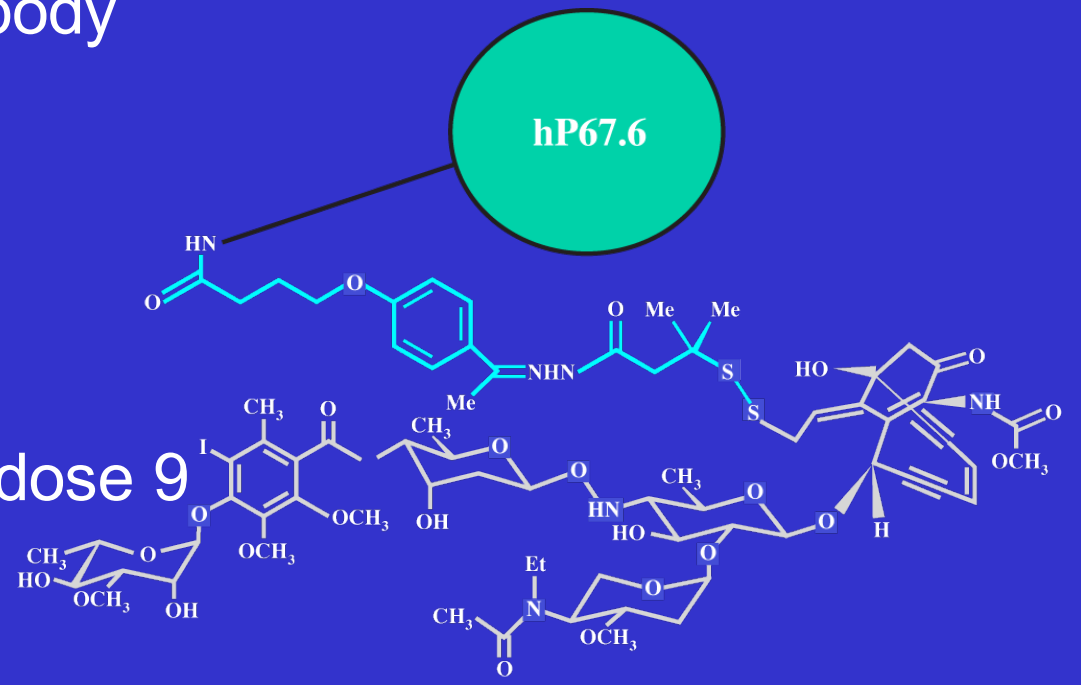
History

Induces CR/CRp ~ 30%

Approved for adults ≥ 60 in first relapse in 2000 (dose 9 mg/m2 twice)

Rare VOD/SOS

Withdrawn from market in 2010

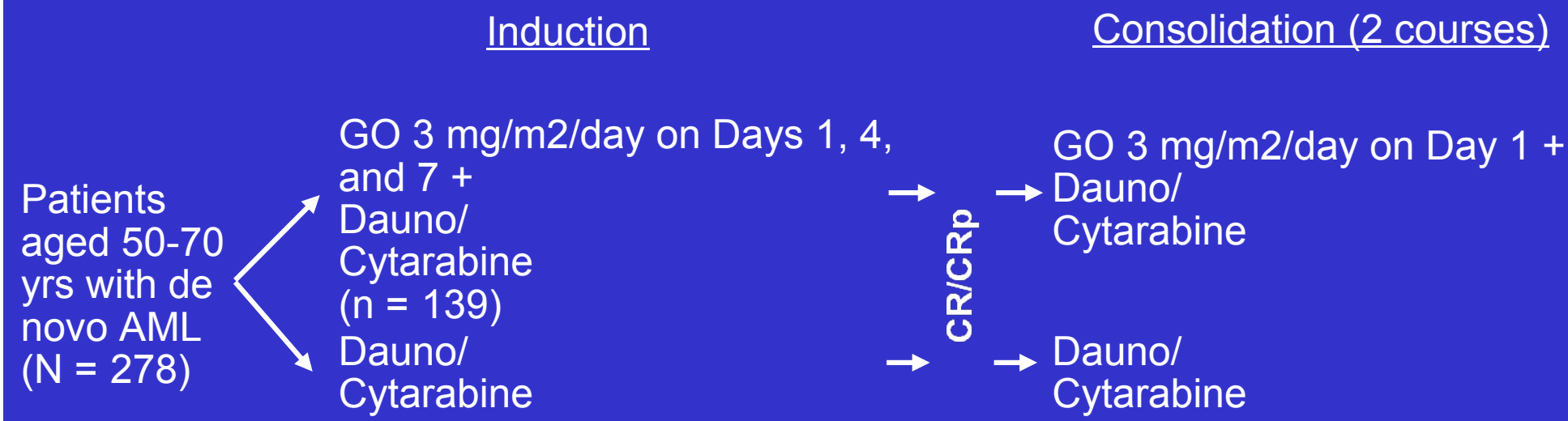


Variable Results From Randomized Trials of Gemtuzumab Ozogamicin in AML (age <60)

- MRC AML15 (3 mg/m2/dose/cycle)
  - No increase in induction mortality
  - Survival benefit in fav-risk
  - Trend for survival benefit in intermed-risk
- SWOG S0106 (6 mg/m2/dose/cycle)
  - Increased induction mortality
  - Trend for survival benefit in fav-risk

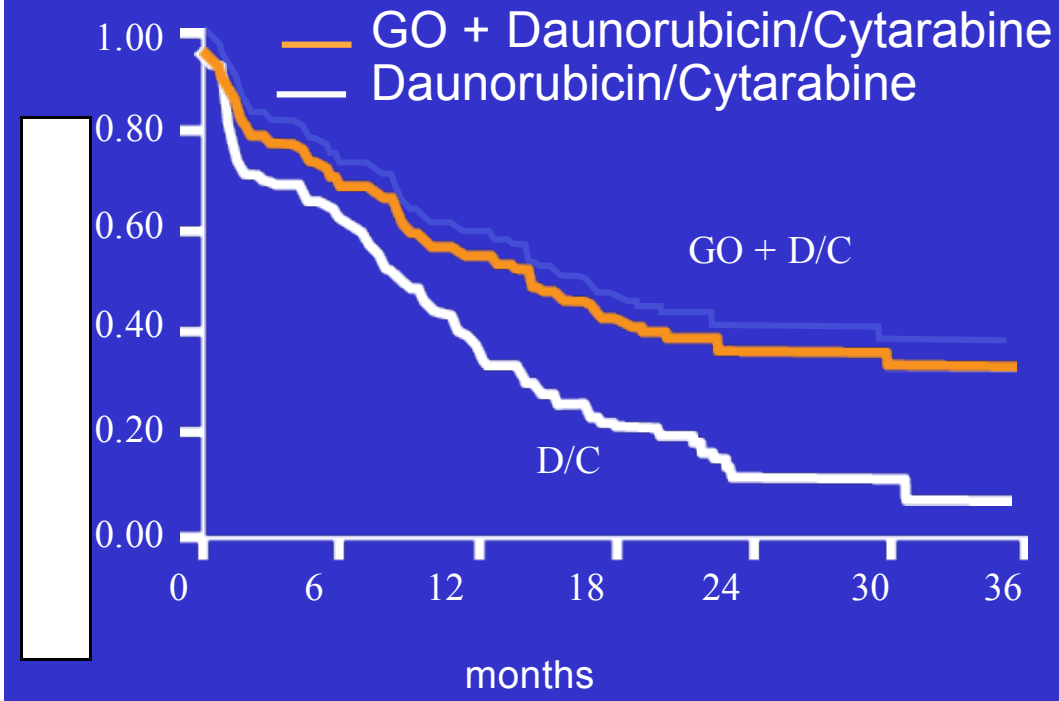
Burnett et al. J Clin Oncol, 2011; Petersdorf et al. Blood, 2009 (abstr)

Fractionated Gemtuzumab Ozogamicin + Chemotherapy in De Novo AML ALFA 0701



Castaigne et al. ASH 2011 (abstr)

ALFA 0701
EFS



EFS	D/C (n=139)	GO + D/C (n=139)
Events	104	76
Median	11.9 mo	19.6 mo
2-year	16.5%	41.1%

P = .00018

Castaigne et al. ASH 2011 (abstr)

ALFA 0701

- GO + dauno/cytarabine improved EFS, OS, RFS in AML aged 50-70 (fav and interm cyto)
- Safety profile of GO acceptable despite increase in hematologic and liver toxicity

Castaigne et al. ASH 2011 (abstr)

emtuzumab Ozogamicin (GO) In Induction
RC AML15

Induction

DA □ GO
vs
ADE □ GO
vs
FLAG-Ida □ GO

Consolidation

MACE-MiDAC □ GO
vs
HiDAC □ GO
(3.0 vs 1.5 mg/m2)

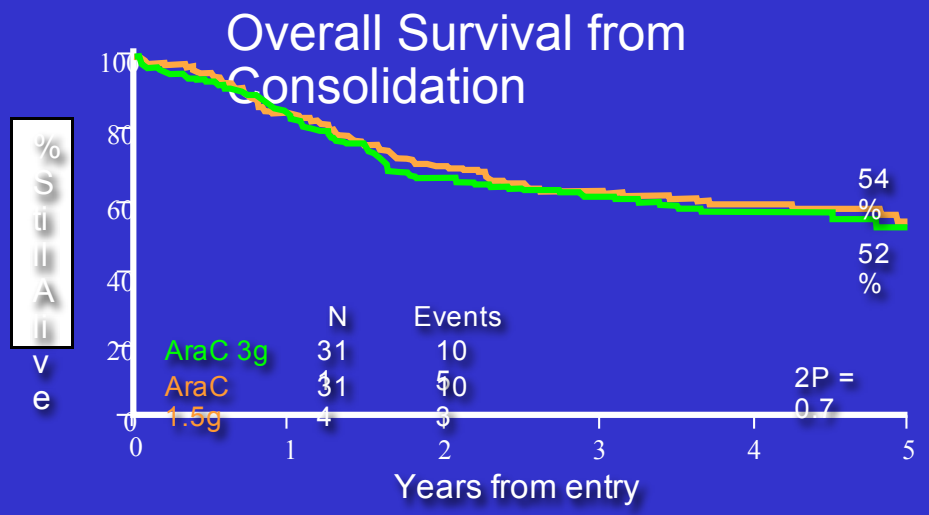
Burnett et al. Blood, 2009 (abstr)

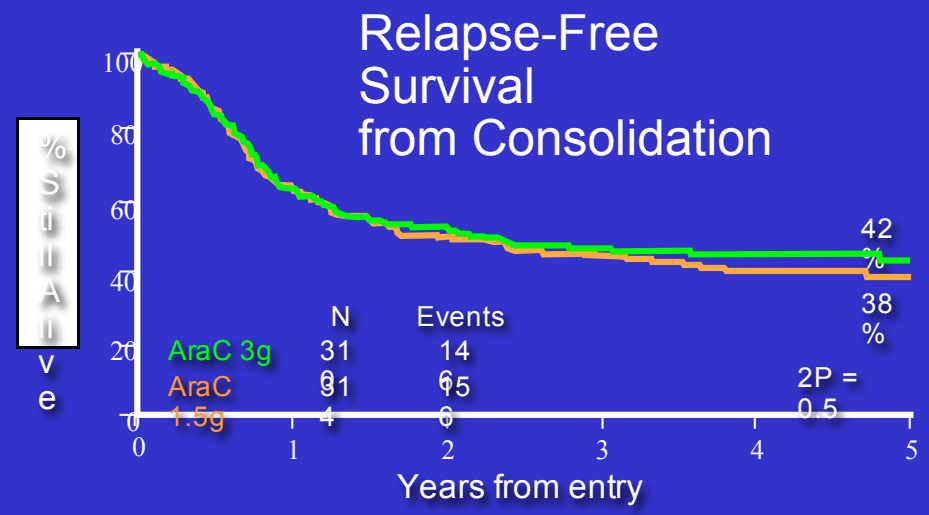
MRC AML15
Post-remission Outcomes

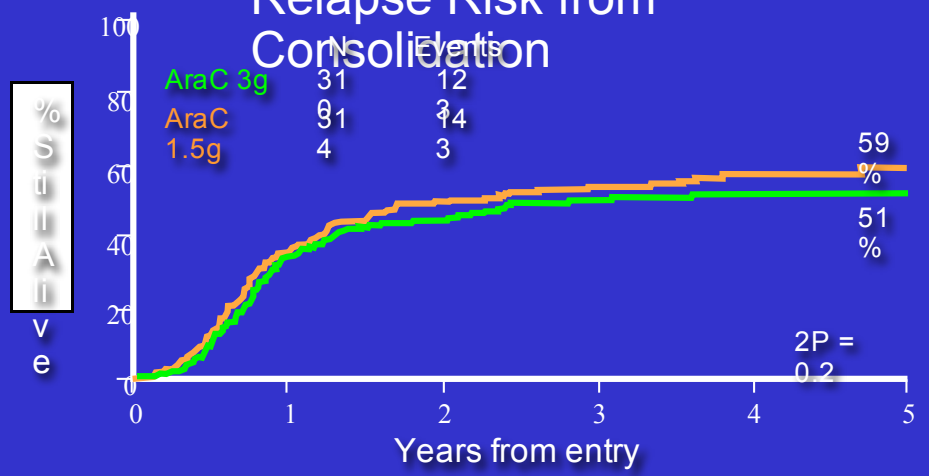
	5-yr death in CR	5-yr relapse rate	5-yr RFS	5-yr OS
Ara-C	10%	53%	42%	54%
MRC	15%	51%	42%	52%
Ara-C 1.5 gm	9%	58%	38%	54%
Ara-C 3 gm	14%	51%	43%	52%
5 courses	0%	58%	42%	60%
4 courses	1%	53%	46%	58%

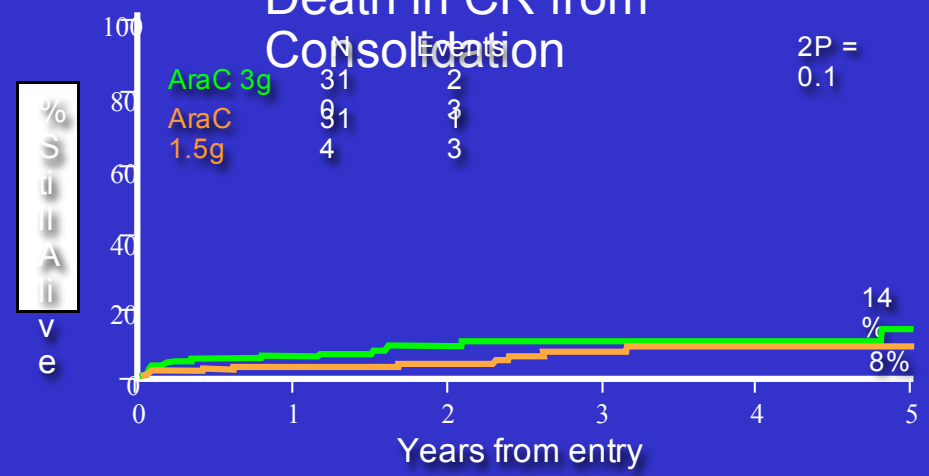
Burnett et al. Blood, 2009 (abstr)

MRC AML 15
Ara-C dose



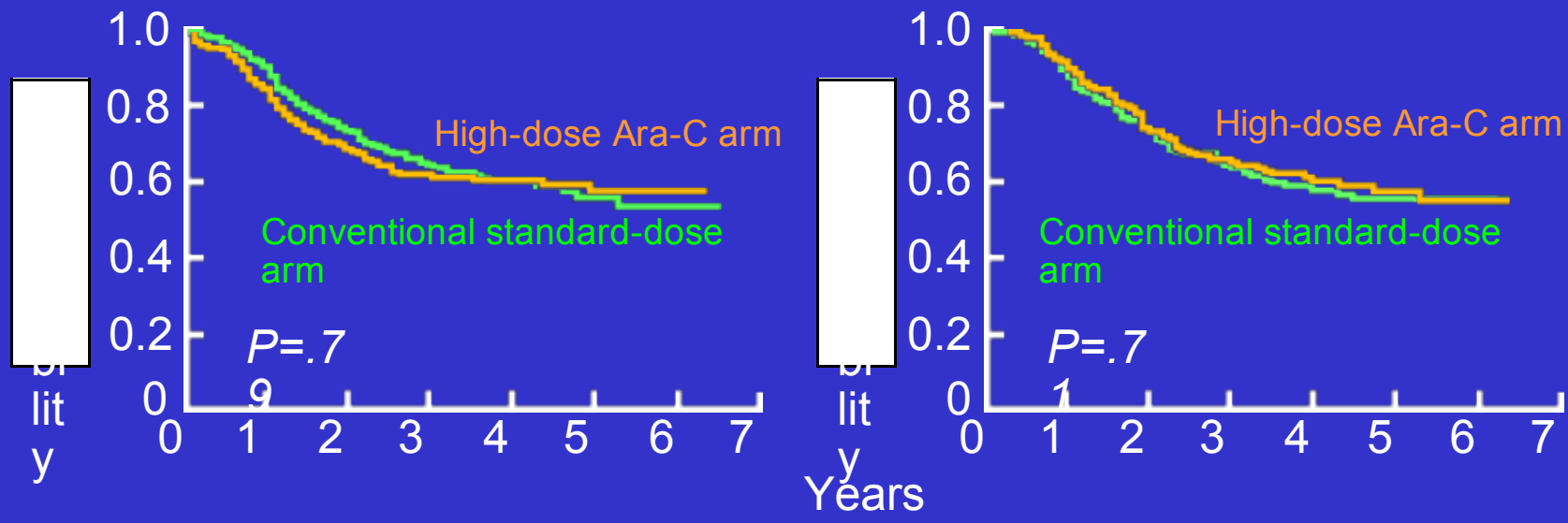






Burnett et al. Blood, 2009 (abstr)

OS of CR Patients Randomized to Receive Consolidation Therapy



Conventional standard-dose=200 mg/m2 D1-5 x 4

High-dose Ara-C= 2.0 gm/m2 q12h D1-5 x 3

Ohtake et al. Blood, 2011

Induction and Postremission Strategies

- High-dose daunorubicin appears better for younger patients in induction
- GO may benefit CBF AML/fav-risk
- Lower doses of ara-C appear as good as standard HiDAC for consolidation and potentially less toxic
- HiDAC in consolidation may not benefit intermed- and high-risk patients

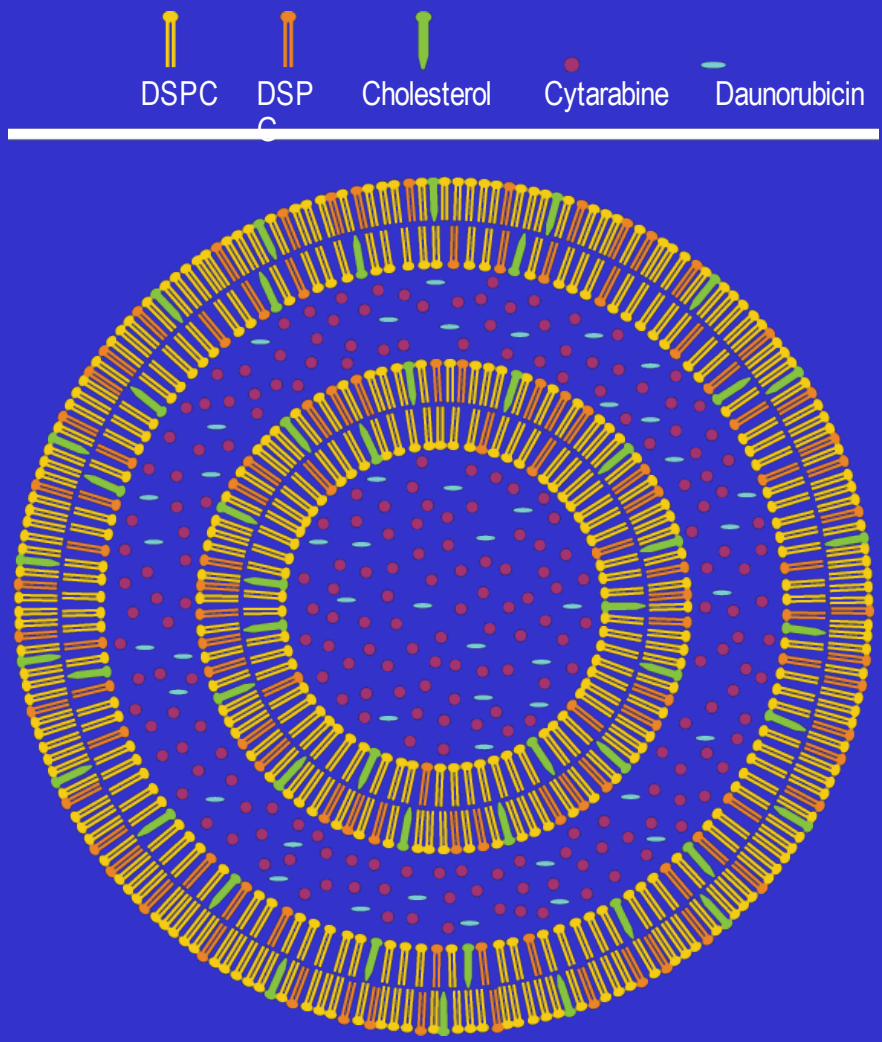
Drug Development

New Agents in AML

Agent	Mechanism	Comments
CPX-351	Liposomal fixed ratio of dauno/ara-C	High response rate and reduced mortality
DOT1L inhibitor	Histone H3K79 methyltransferase	Preclinical data against *MLL*
Sorafenib/AC220	Multikinase inhib	CRs w/single agent
Clofarabine	Nucleoside analog	Effective in older adults with unfav. prog. factors
Sapacitabine	Nucleoside analog	CRs w/single agent
Elacytarabine	Eliadic ester of ara-C	Modest remission in adv disease

Bayne J Pharm Sci, 2008; Pollock ASH, 2010; Metzelder Blood, 2009; Cortes Blood, 2009 (abstr); Erba J Clin Oncol, 2010; Kantarjian Blood, 2009 (abstr); O'Brien Blood, 2009 (abstr)

CPX-351
A Liposomal Carrier Containing Cytarabine and Daunorubicin in a Fixed Ratio



- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin
- Specifically designed drug delivery vehicle enables specific drug ratios to be maintained

Feldman et al. J Clin Oncol, 2011

CPX-351 vs 7 + 3 Remission Rates

	CPX-351 n=84	7+3 n=41	
CR+CRi	56 (66.7%)	21 (51.2%)	p=0.0712**
CR	41 (48.8%)	20 (48.8%)	
CRi	15 (17.9%)	1 (2.4%)	

**one-sided Fisher's Exact test

Lancet et al. ASH, 2010

CPX-351 vs 7 + 3
Early Deaths (all causes)

	CPX-351	7+3	
	n=85	n=41	
30-Day Mortality	3 (3.5%)	3 (7.3%)	p=0.35
60-Day Mortality	4 (4.7%)	6 (14.6%)	p=0.053

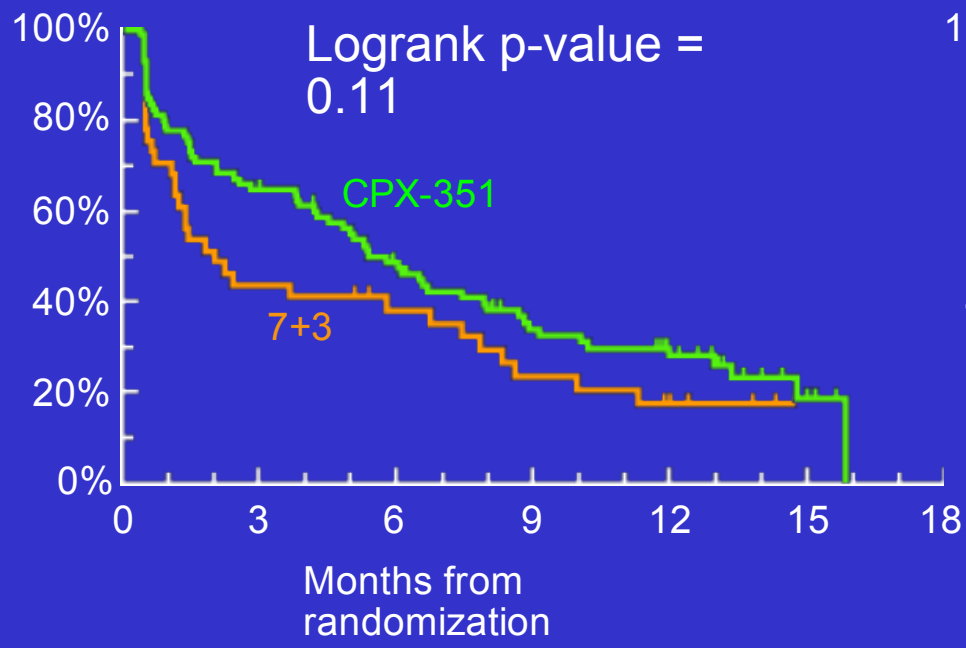
All early deaths occurred in the high risk group

Lancet et al. ASH, 2010

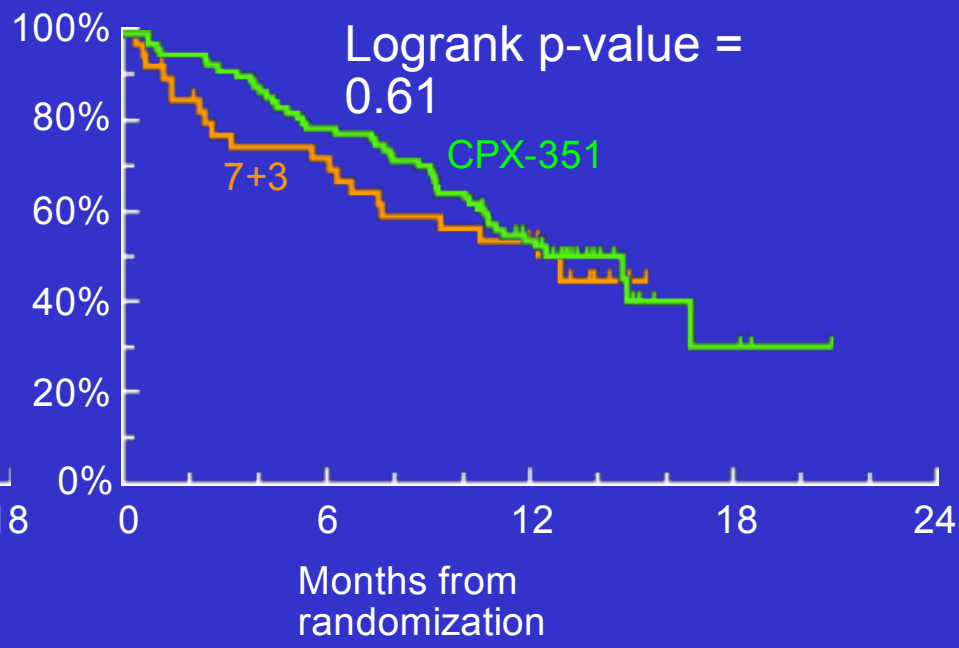
CPX-351 vs 7 + 3

Event-Free and Overall Survival

Event Free Survival



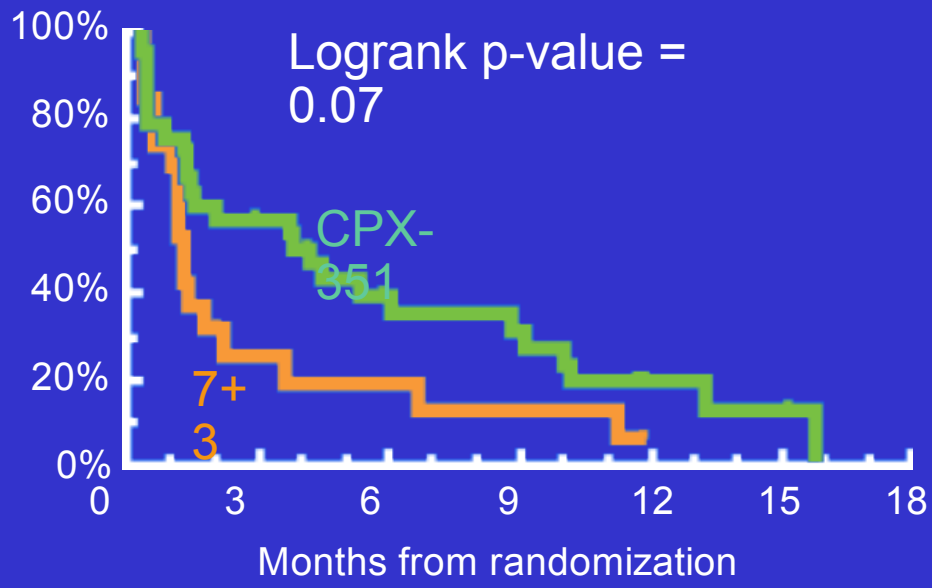
Overall Survival



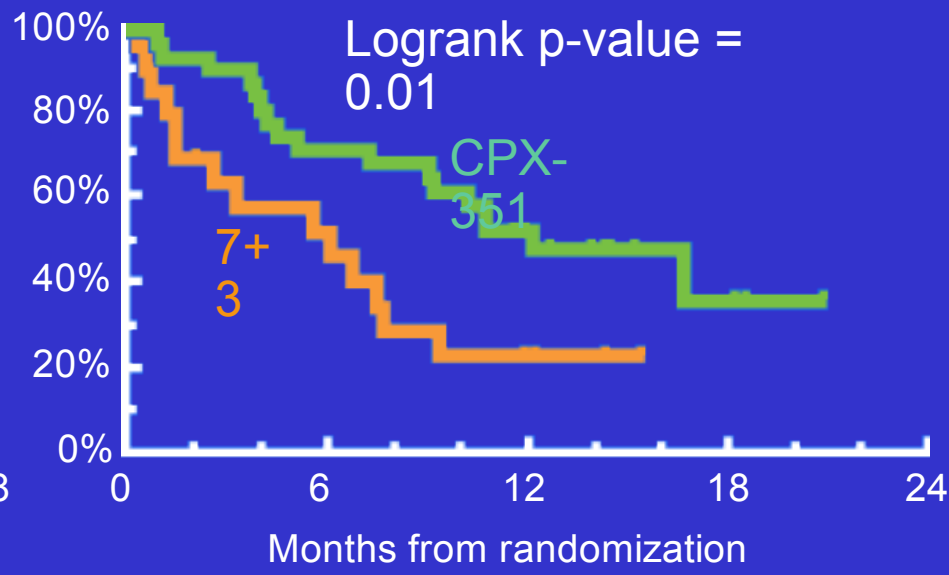
Lancet et al. ASH, 2010

CPX-351 vs 7 + 3
Event Free and Overall Survival
Secondary AML

Event-Free Survival



Overall Survival



Lancet et al. ASH, 2010

Quizartinib Monotherapy in Relapsed/ Refractory *FLT3-ITD*–Positive AML

- Quizartinib (AC220), a selective oral *FLT3* TKI active in *FLT3-ITD*–pos AML
- Nonrandomized phase II trial of quizartinib monotherapy ongoing
- 2 patient cohorts enrolled
  - Cohort 1
    - Relapsed/refractory to frontline chemo
    - Age ≥ 60 years
  - Cohort 2
    - Relapsed/refractory to second-line chemo or HSCT
    - Age ≥ 18 years

Cortes et al. ASH, 2011 (abstr)

Quizartinib in Relapsed/Refractory *FLT3*-ITD–Positive AML Efficacy

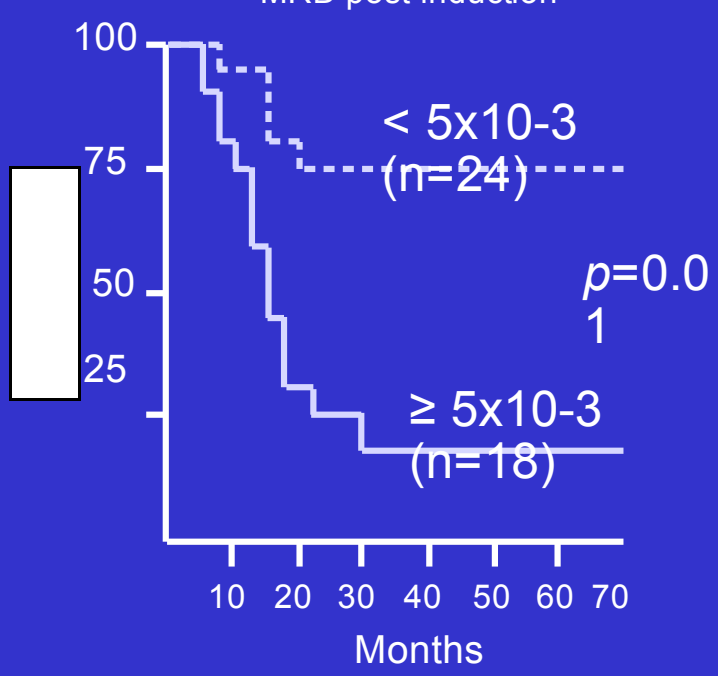
Best Response, %	Cohort 1 (n = 26)	Cohort 2 (n = 36)	Total (N = 62)
CRc (CR + CRp + CRi)	46	36	40
▪ CR	4	0	2
▪ CRp	4	0	2
▪ CRi	39	36	37
PR	15	22	19
NR	23	22	23
Unknown	15	19	18

Cortes et al. ASH 2011, (abstr)

Early Detection of MRD as a Potential Tool For Risk-Stratification in AML

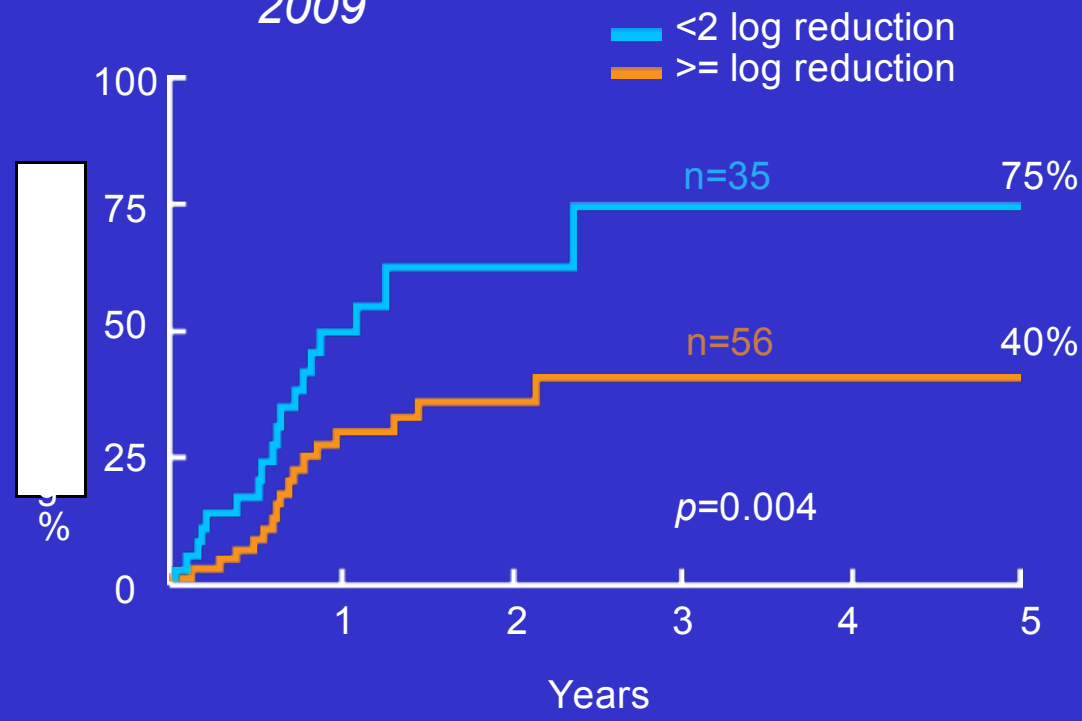
Flow cytometry

San Miguel et al. Blood 1997



RQ-PCR *(WT1)*

Cilloni et al. J Clin Oncol 2009



Treatment of Older Adults

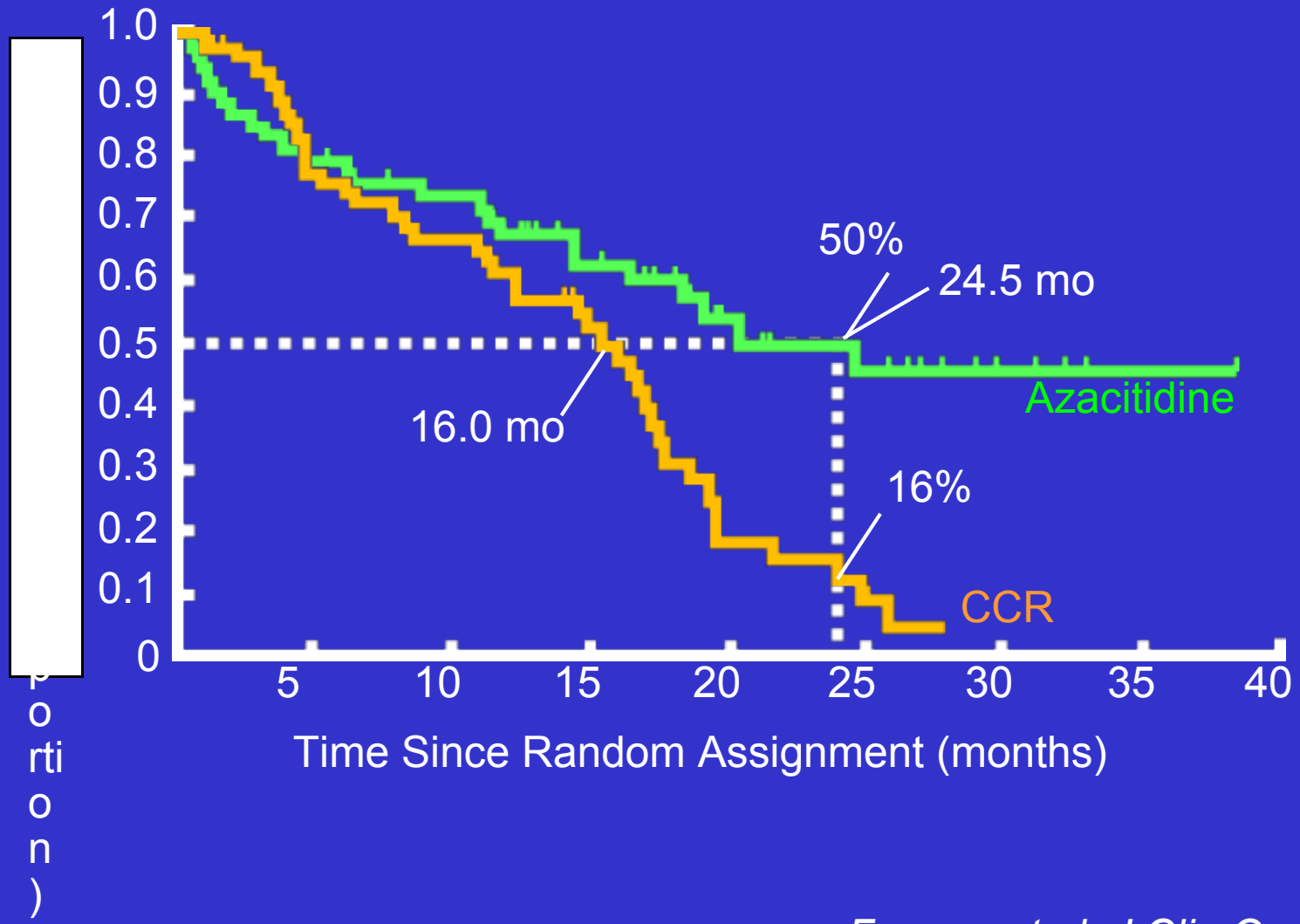
Treatment of Older Adults

Agent	N	Med Age	CR	Mortality	OS
5-azacitidine	55	70	18%	NA	25 mo
Decitabine	55	74	24%	7%	7.7 mo
Lenalidomide*	33	71	30%**	24%	4 mo
Clofarabine	112	71	38%	10%	10 mo

*50 mg/m2 for up to two 28-day cycles
**53% CR+CRi

aux et al. J Clin Oncol, 2009; Cashen et al. J Clin Oncol, 2010; Fehniger et al. Blood, 2010;
tarjian et al. Clin Oncol, 2010

Overall Survival in Patients Receiving Azacitidine or Conventional Care Regimens



Fenaux et al. J Clin Oncol, 2009

Treatment of Older Adults

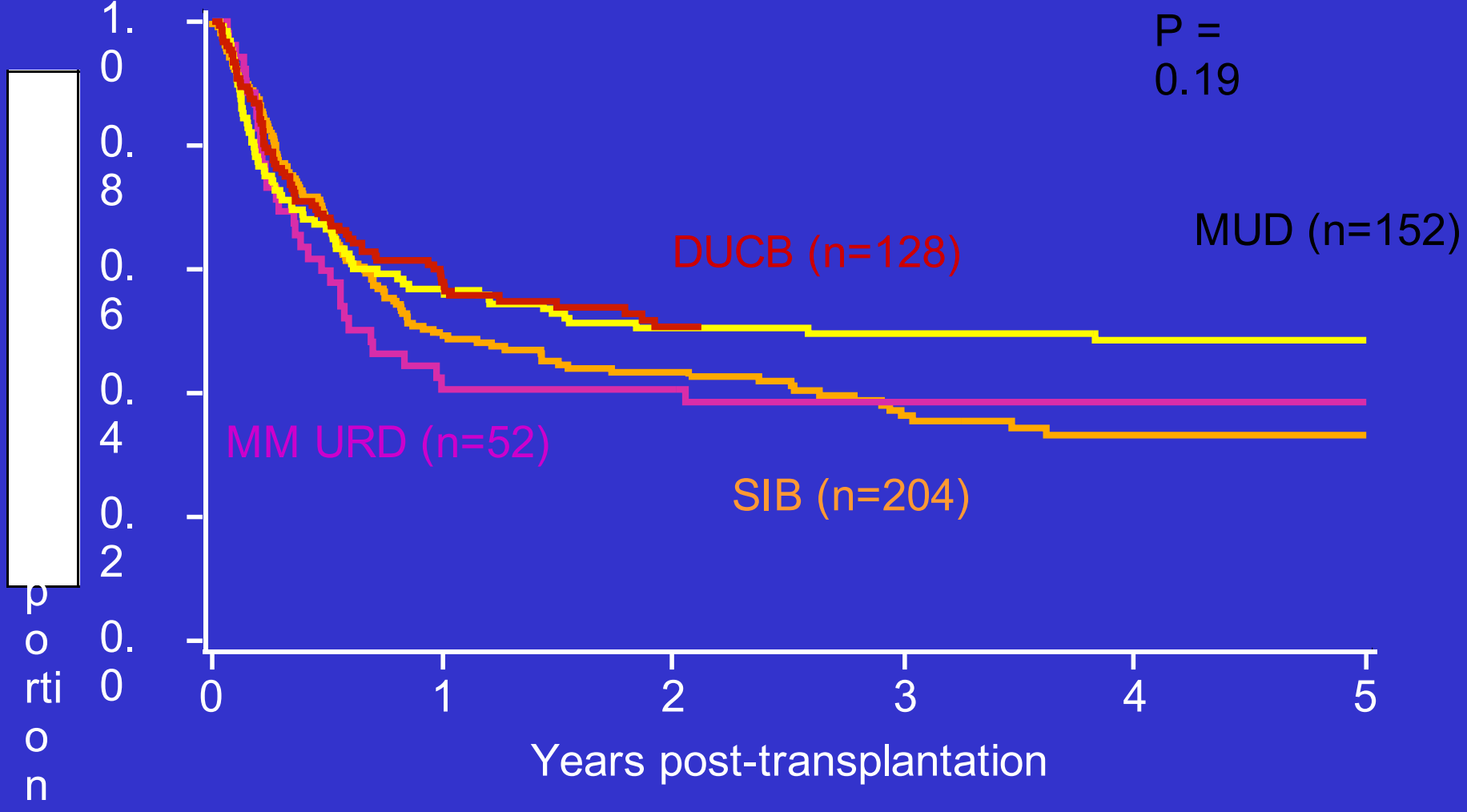
- Prognostic factor models exist to predict induction mortality, CR and OS
- Novel strategies exist with potentially less toxicity and unique mechanisms of action
- Further studies will define optimal dose and schedule and combinations
- Important shift away for conventional chemotherapy toward novel strategies-new standard of care

Transplantation/Alternative Donors

Advances in Transplantation

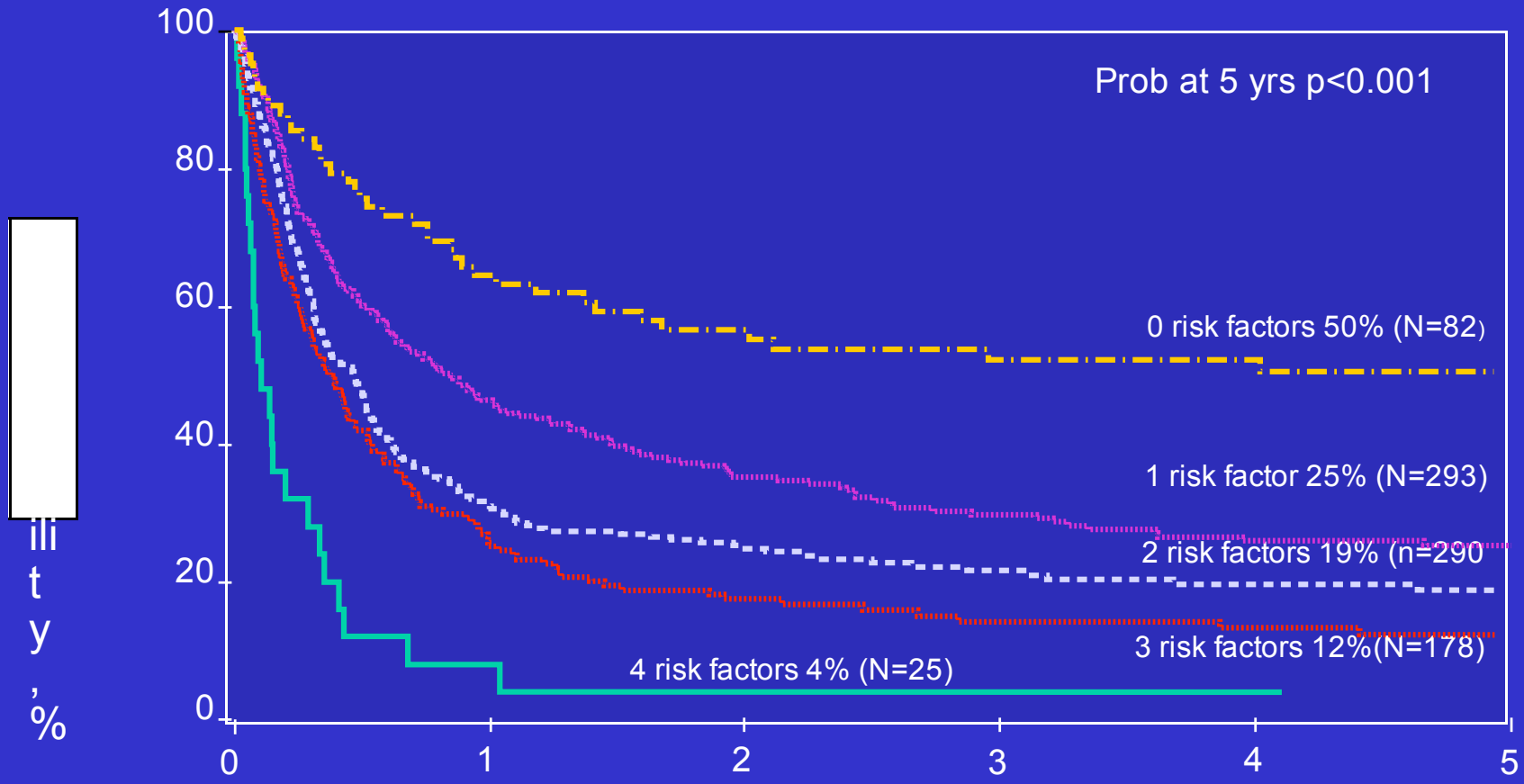
- Equivalent outcomes MSD and MUD
- Haploidentical transplantation
- Umbilical cord
- Reduced-intensity conditioning
- Outcome of t-AML

Leukemia-Free Survival by Donor Type For Patients With Heme Malignancy in CR 1,2 or 3



Brunstein et al. Blood,

Probability of Overall Survival After Allogeneic HCT for Therapy-Related AML and MDS by Risk Factors



Risk Factors
1. Age >35
2. Poor-risk cytogenetics
3. t-AML not in CR or adv MDS
4. Donor other than MDS or well-matched MUD

Litzow et al. Blood, 2010

Transplantation For AML in CR1

- Alternative donor sources expand pool of patients who may benefit
- Outcome for MUD transplants appears to approach that of MRD
- Umbilical cord transplantation increasing
- Identify pts with t-AML who may or may not benefit from transplant

Future Directions in AML

- Gene expression profiling for signatures characteristic of specific genetic subtypes, identify cooperating mutations and perturbed pathways and predict treatment response
- Risk-stratify therapy with specific targeted strategies
- Characterize mechanisms of action and off-target effects of putative molecularly targeted therapies
- Identify molecular markers of residual disease

Acknowledgments

ECOG Leukemia Committee

North American Intergroup Colleagues

European LeukemiaNet Colleagues

Leukemia Service
Memorial Sloan-Kettering Cancer Center