Frontline Induction Therapy in 2017

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Ravenna, October 2017

Standard of Care

- Induction: 7+3 Ara-C / Daunorubicin
- Consolidation: High Dose Ara-C (3g doses)
- Total of 4 courses.
- Myeloablative allograft for young high risk groups

2017 marks the 44th anniversary of "3+7"

- DNR 45 mg/m^2, D 1-3
- Ara-C 100 mg/m^2, D 1-7

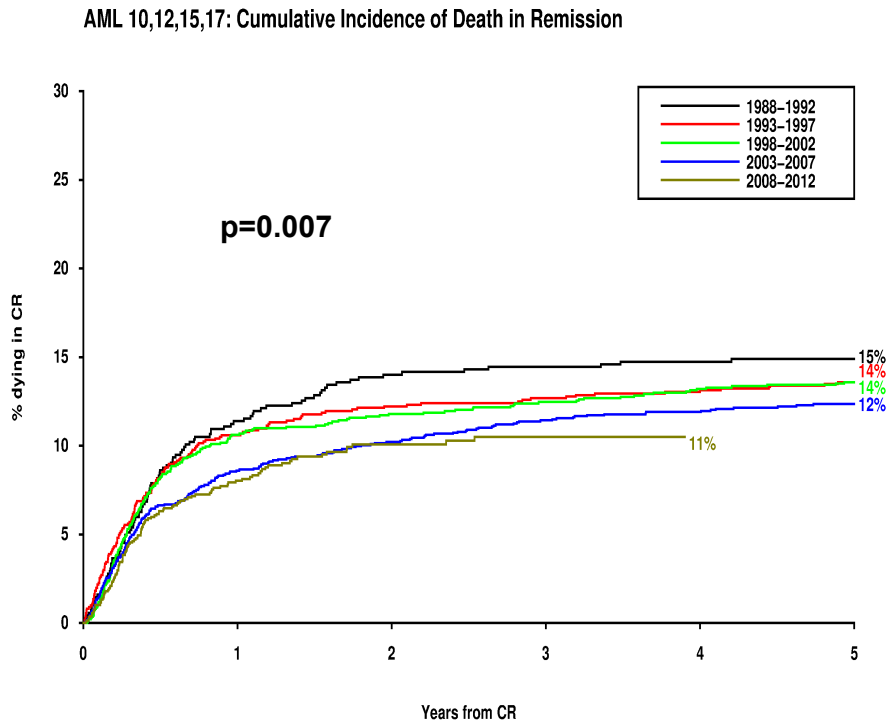
Yates JW et al, Cancer Chemother Rep 1973

Changes in outcome with time: remission rates

Age (years)	Pre-1980	1980–84	1985–89	1990–94	1995–99	2000–05
< 15	39%	82%	90%	92%	92%	93%
15–59	40%	73%	76%	79%	83%	85%
60–69	25%	52%	47%	58%	60%	65%
≥ 70	18%	36%	40%	48%	47%	62%
All	34%	66%	70%	74%	77%	79%

Changes in Early Mortality

Time Period	30 day mortality	60 day mortality
1988-1992	8%	12%
1993-1997	7%	10%
1998-2002	6%	8%
2002-2007	5%	8%
2008-2012	4%	7%



All non-APL patients aged 15-59 enrolled in trials for younger patients

SAB – a promising new treatment for AML in the elderly?

Treatment	Number of pts	CR rate	Induction deaths	Resistant disease
DAT	167	47%	30%	23%
SAB	284	61%	15%	24%

p=0.00007

Wheatley K et al.

Beyond “3+7”: Which Induction Treatment?

A) Daunorubicin/Ara-C (3+7)

B) Idarubicin/Mitoxantrone + Ara-C

C) Which dose of Ara-C

D) Above + a third drug

E) An alternative nucleoside analogue

F) Addition of an immuno-conjugate

Might some anthracyclines be better than others?

- Mitoxantrone 8-12 mg/m^2 compared to DNR 30-50 mg/m^2
  - superior CR rate in some studies[1,2] but not in others[3]
- Idarubicin 12-13 mg/m^2 compared to DNR 45-50 mg/m^2
  - superior CR rate and possibly longer OS[4]

[1]Lowenberg et al, JCO 1998; [2]Arlin et al, Leukemia1990; [3]Mandelli et al, JCO 2009; [4]Berman et al, Cancer 1997

Daily Ara-C Dose?

A) 100mg/m^2/day

B) 200mg/m^2/twice daily

C) 1.0g/m^2/day

D) 3.0g/m^2/day

Daunorubicin Dose

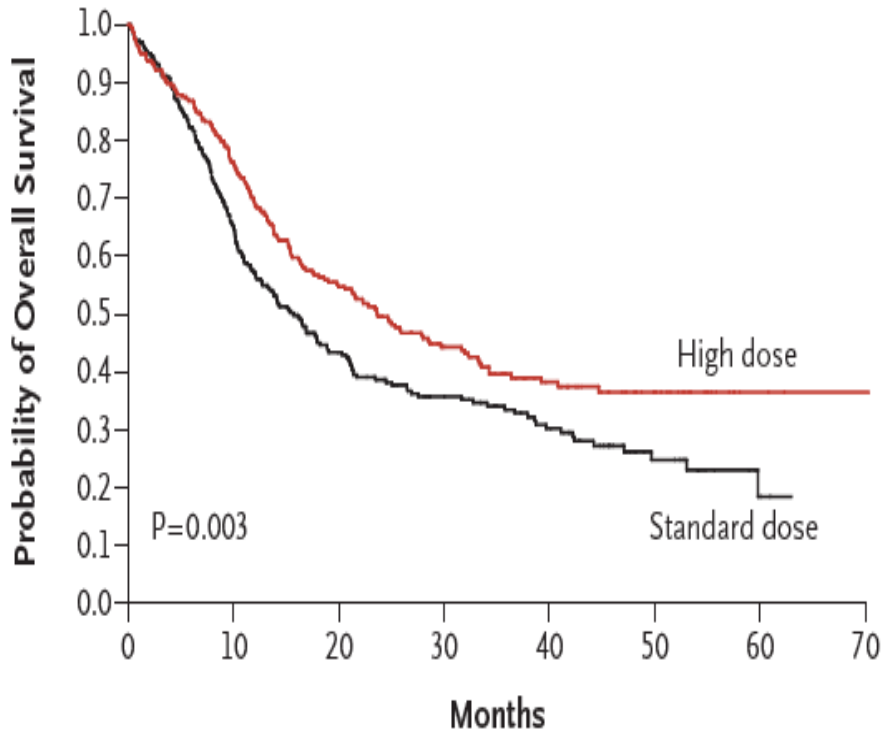
A) 45mg/m^2

B) 60mg/m^2

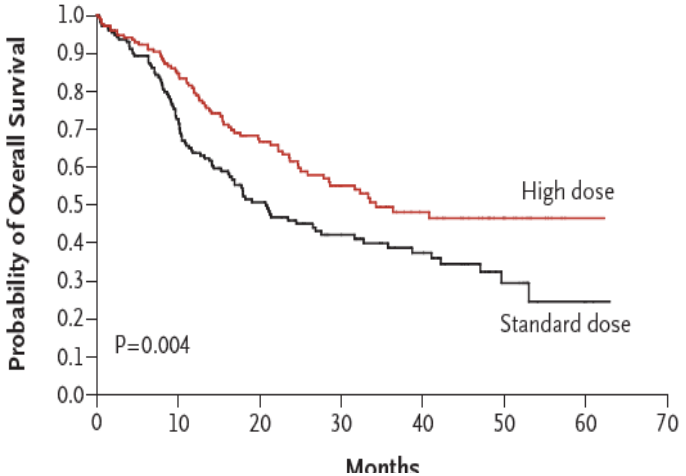
C) 90mg/m^2

ECOG E1900 (90mg vs 45mg)

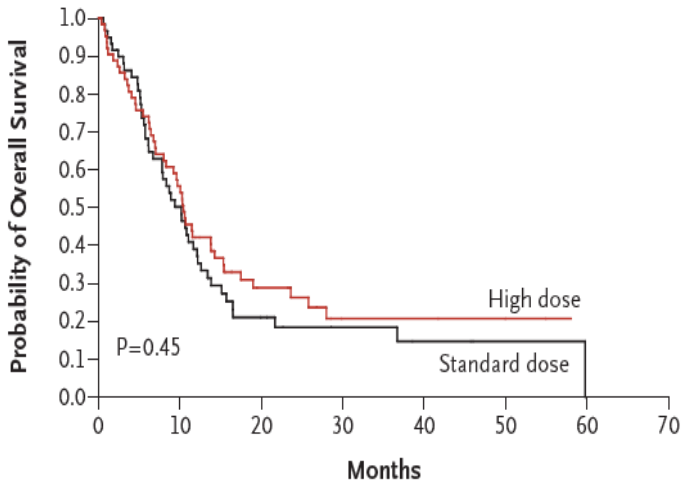
All Patients



Favorable or Intermediate Cytogenetic Profile

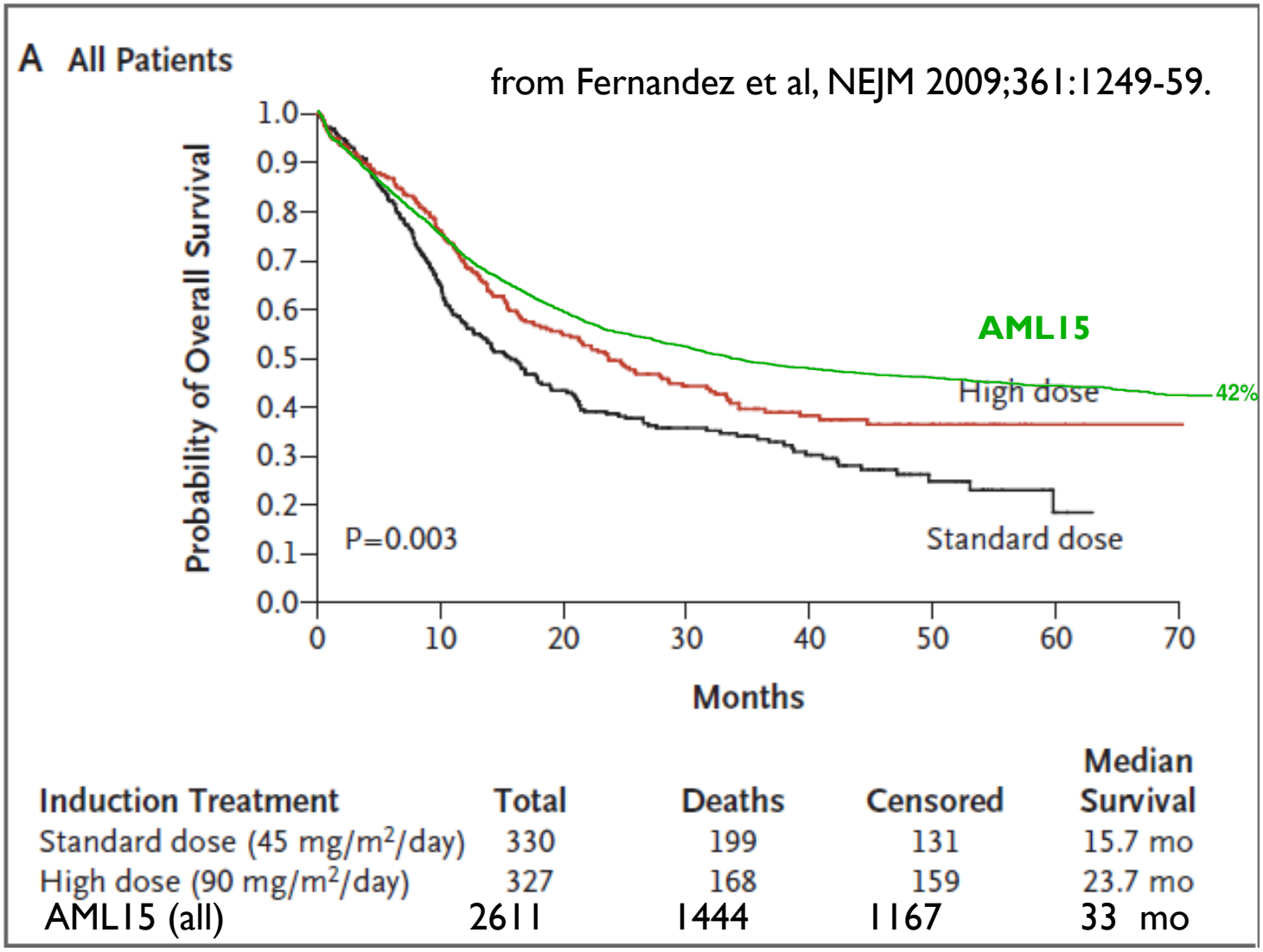


Unfavorable Cytogenetic Profile



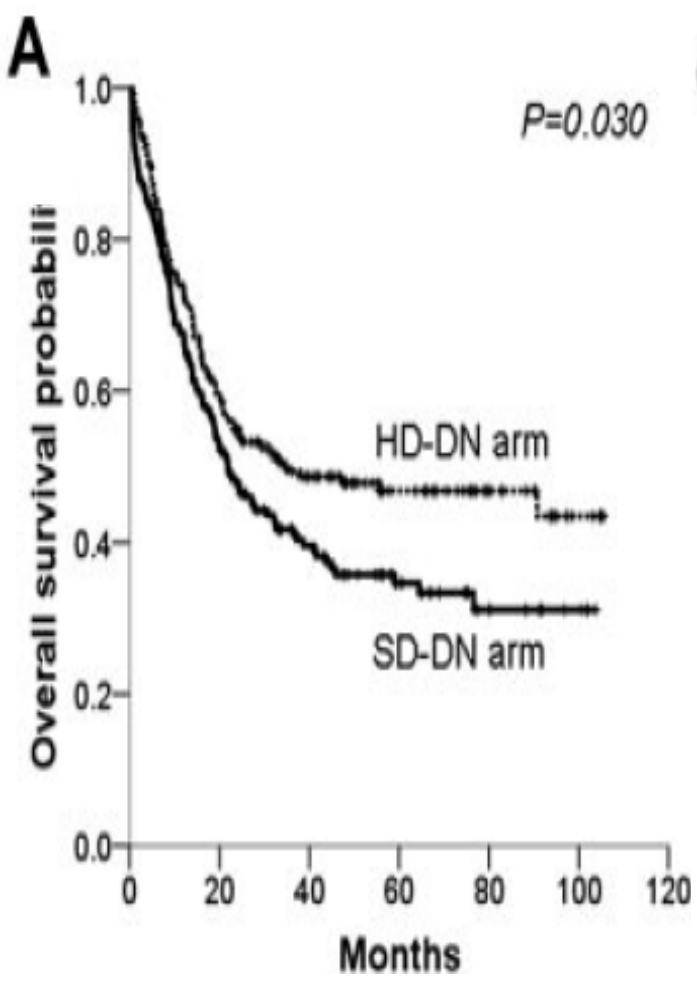
Fernandez et al, NEJM 2009

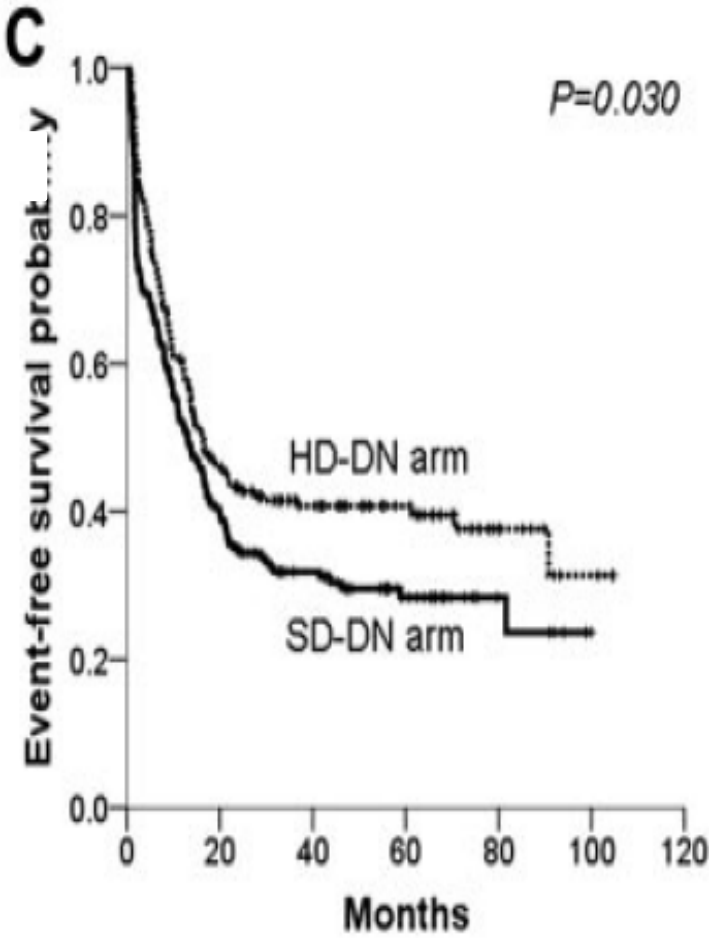
DA 90mg vs 45mg in younger patients

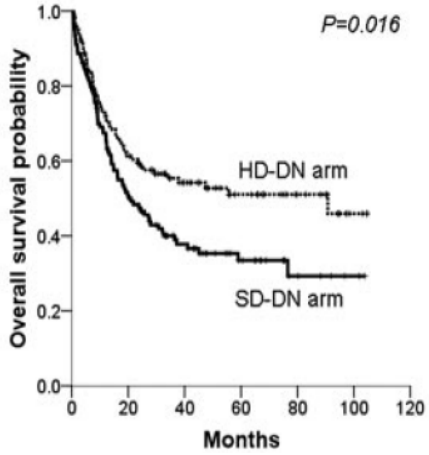


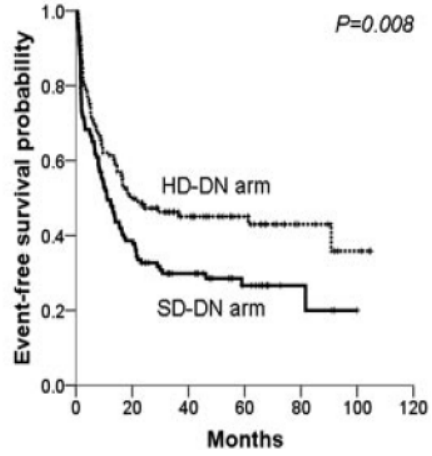
Induction Treatment	Total	Deaths	Censored	Median Survival
Standard dose (45 mg/m^2/day)	330	199	131	15.7 mo
High dose (90 mg/m^2/day)	327	168	159	23.7 mo
AML15 (all)	2611	1444	1167	33 mo

Korean Study



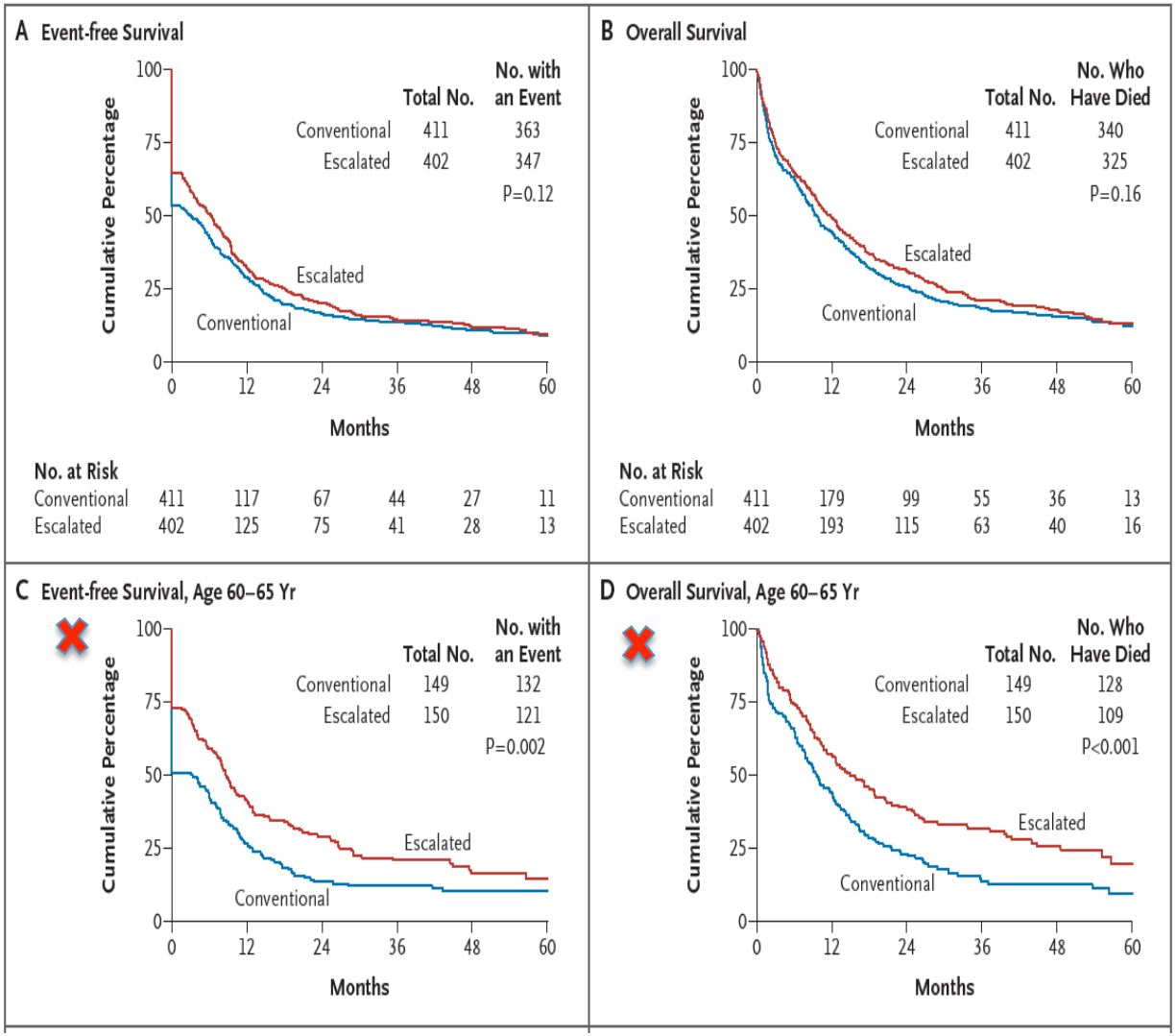


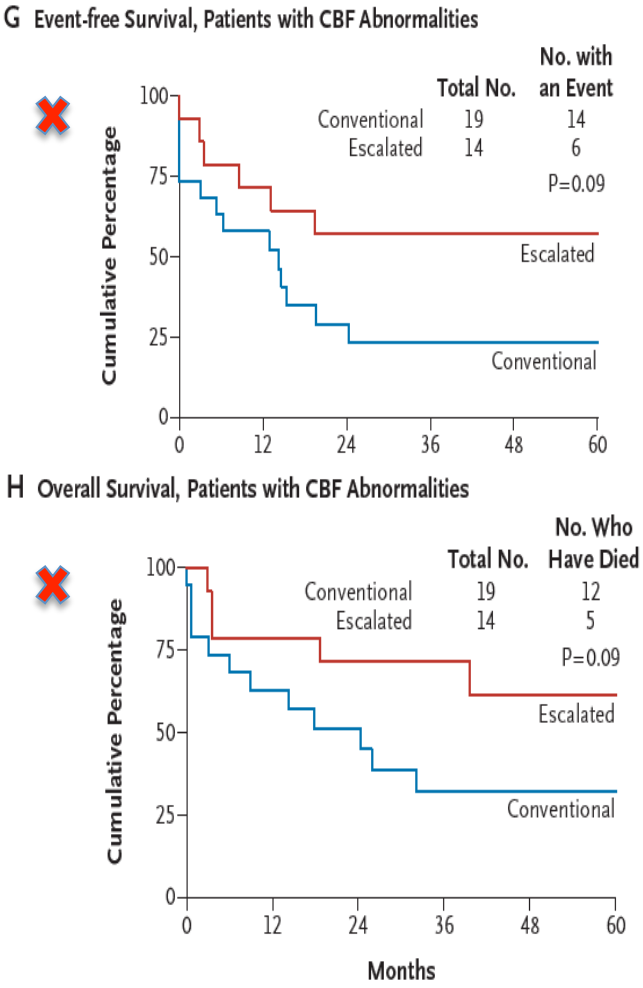




Lee et al, Blood 2011

HOVON-SAKK-AMLSG STUDY





Löwenberg et al, NEJM 2009

Randomised Trials of Escalated Daunorubicin

- **E1900 trial**: CR 70% vs 57%/ OS 38% vs 23%
- **HOVON trial**: CR 64% vs 54%/ OS: no difference
- **Korean Trial**: CR: 82% vs 72%/OS: 47% vs 35%

Randomised Trials of Escalated Daunorubicin

- **E1900 trial**: CR 70% vs 57%/ OS 38% vs 23%

  -benefit in <50's, intermediate cytogenetics

- **HOVON trial**: CR: 64% vs 54%/ OS: no difference

  - benefit in 60-65 yrs/ trend in CBF subgroup (35% vs 23%)

- **Korean Trial**: CR 82% vs 72%/OS 47% vs 35%

  - OS benefit due to intermediate risk (51% vs 34%)

Who Benefits from 90mg vs 45mg

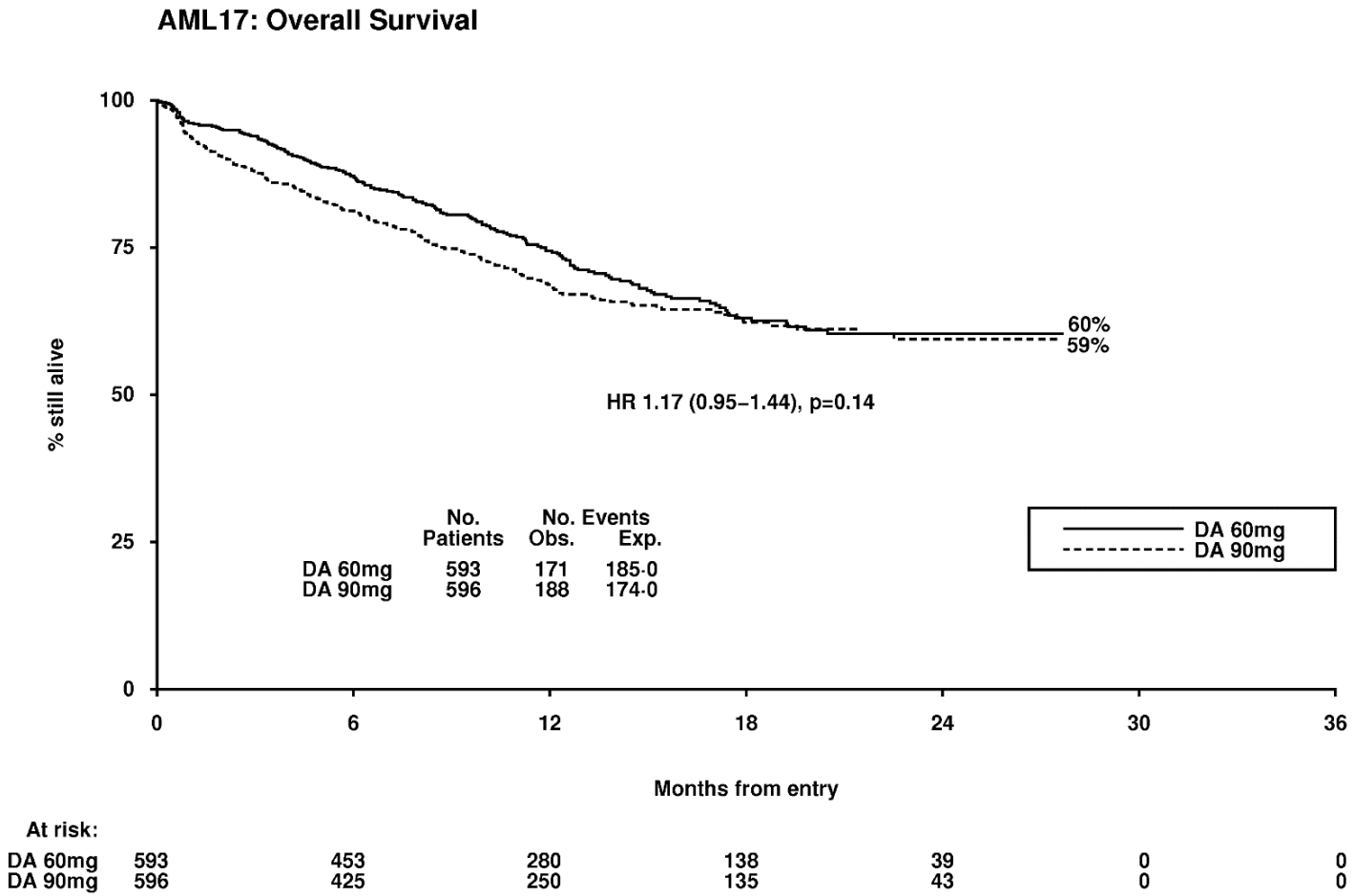
- Patel JP, Gonen M, Figueroa ME, et al. Prognostic relevance of integrated Genetic profiling in acute myeloid leukemia. *N.Engl J Med*. 2012; 366 (12): 1079-1089.

  DNMT3A, NPM1*, and *MLL-PTD

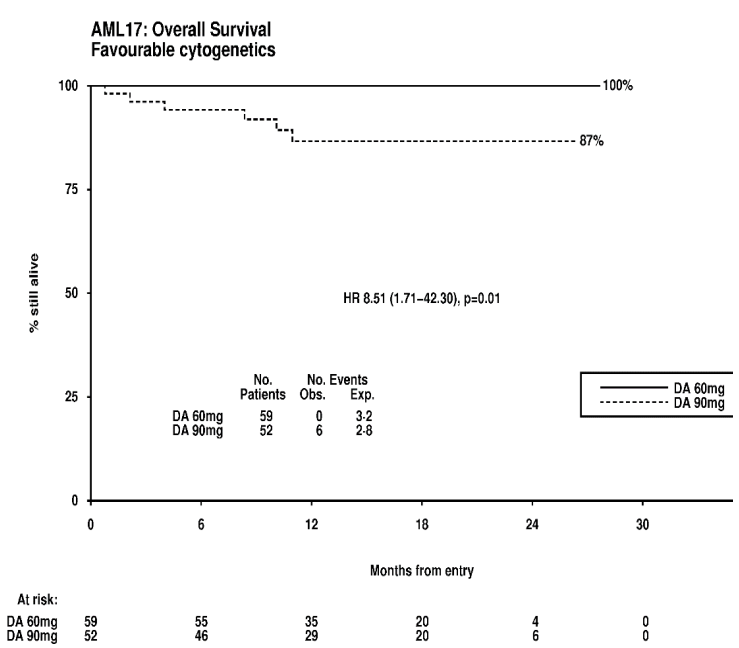
- Luskin MR, Lee J-W, Fernandez HF et al., Benefit of high dose daunorubicin in AML induction extends across cytogenetic and molecular groups: updated analysis of E1900 Blood 2016 Blood-2015-07-657403.

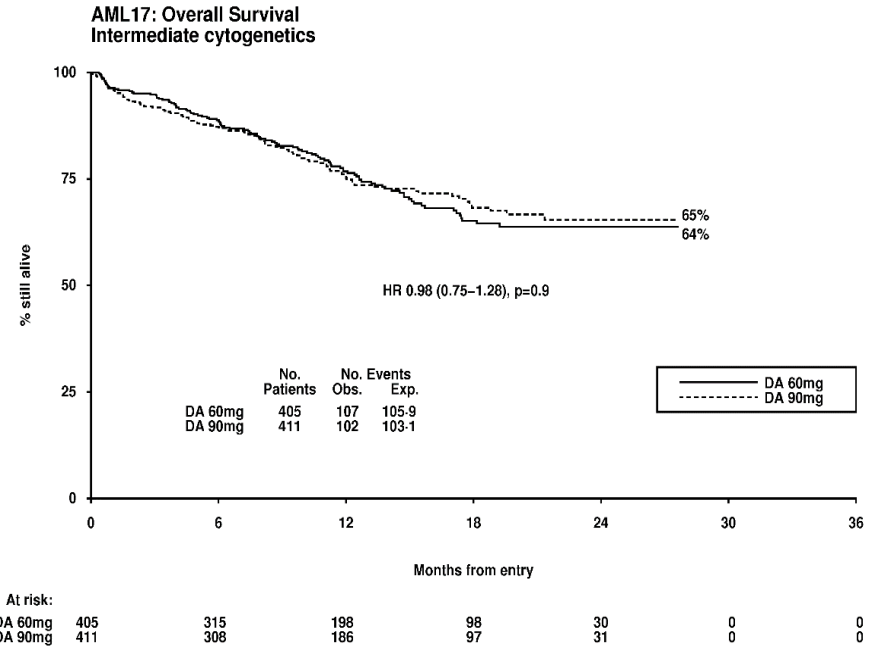
  <50 years, not adverse cytogenetics, not *FLT3, MLL-PTD and NMP1c if no FLT3*

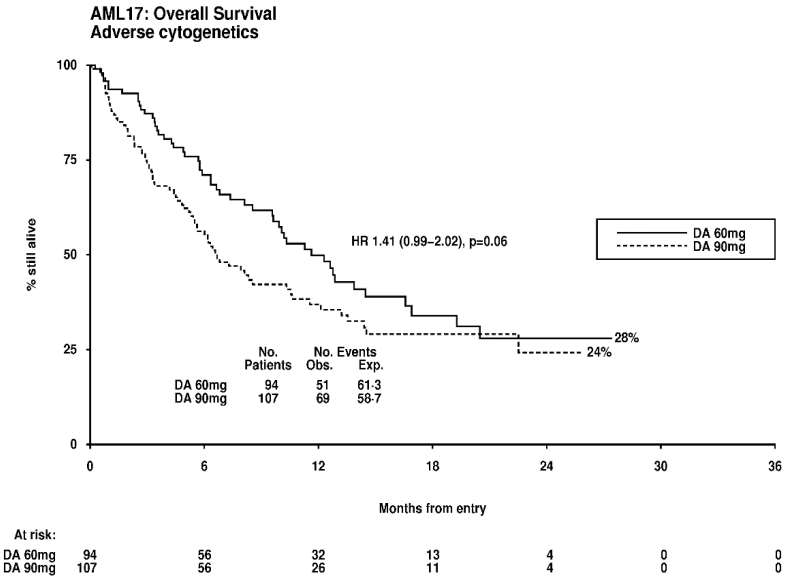
AML17: 90mg/m^2 vs 60mg/m^2: OS



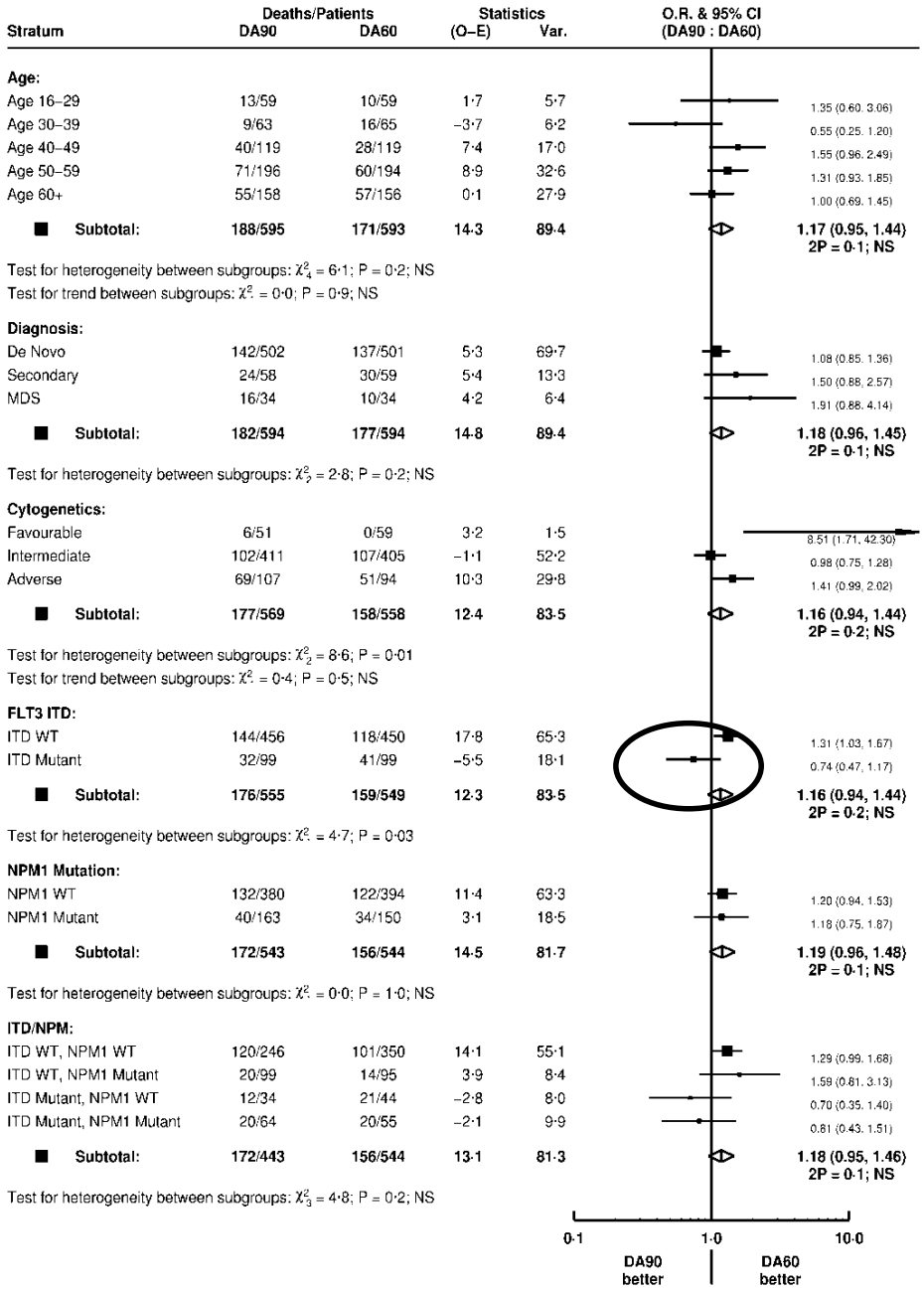
AML17: 90mg/m² vs 60mg/m²: OS by Risk Group



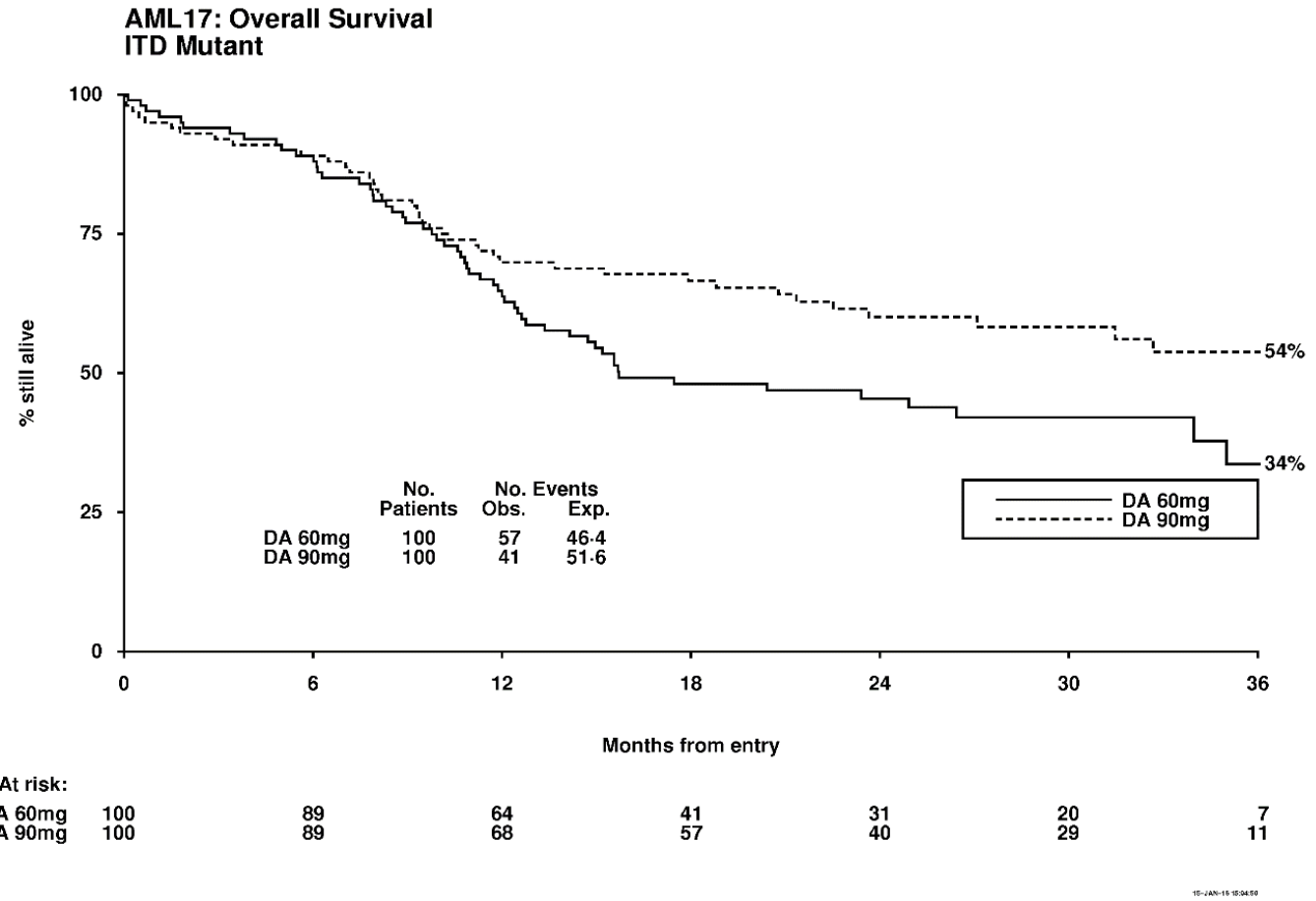




AML17: 90mg/m² vs 60mg/m²: Stratified Analysis of survival



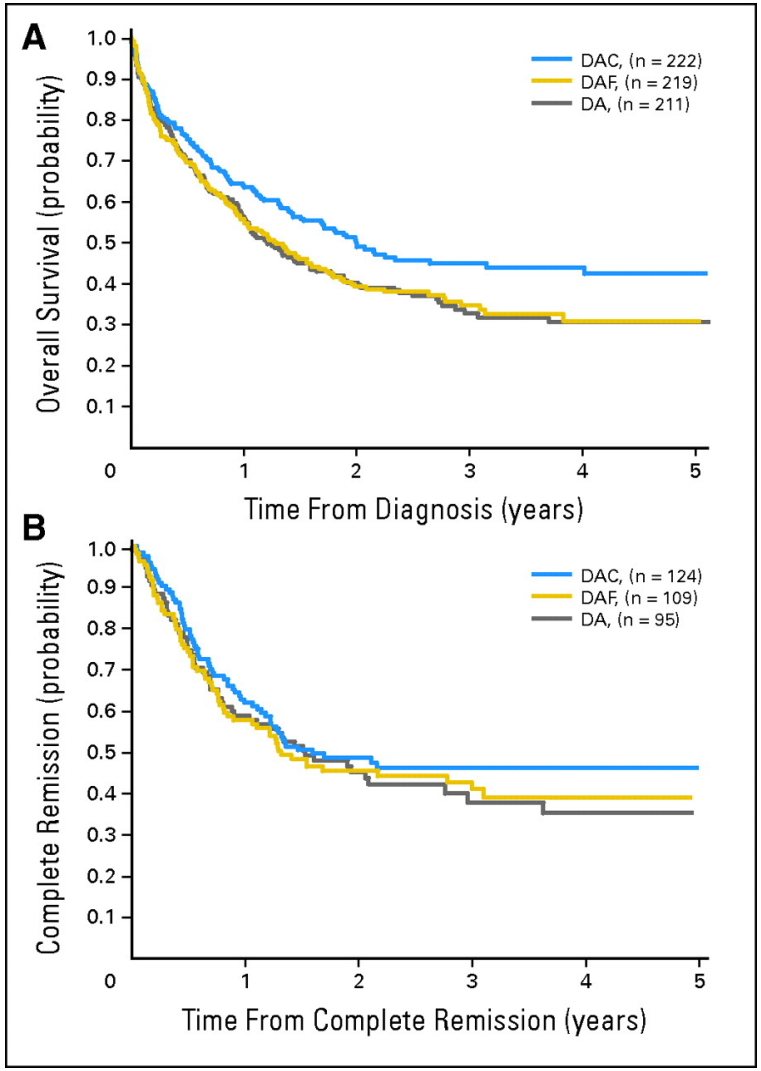
AML17 FLT3 Mutants: Dauno 90 vs. 60: Update



Addition of a Third drug

A) Etoposide
B) Cladrabine / Fludarabine/ Clofarabine
C) Gemtuzumab Ozogamicin (GO) – mylotarg
D) FLAG-Ida

Addition of Cladrabine to DA: (A) overall and (B) leukemia-free survival.



Holowiecki J et al. JCO 2012;30:2441-2448

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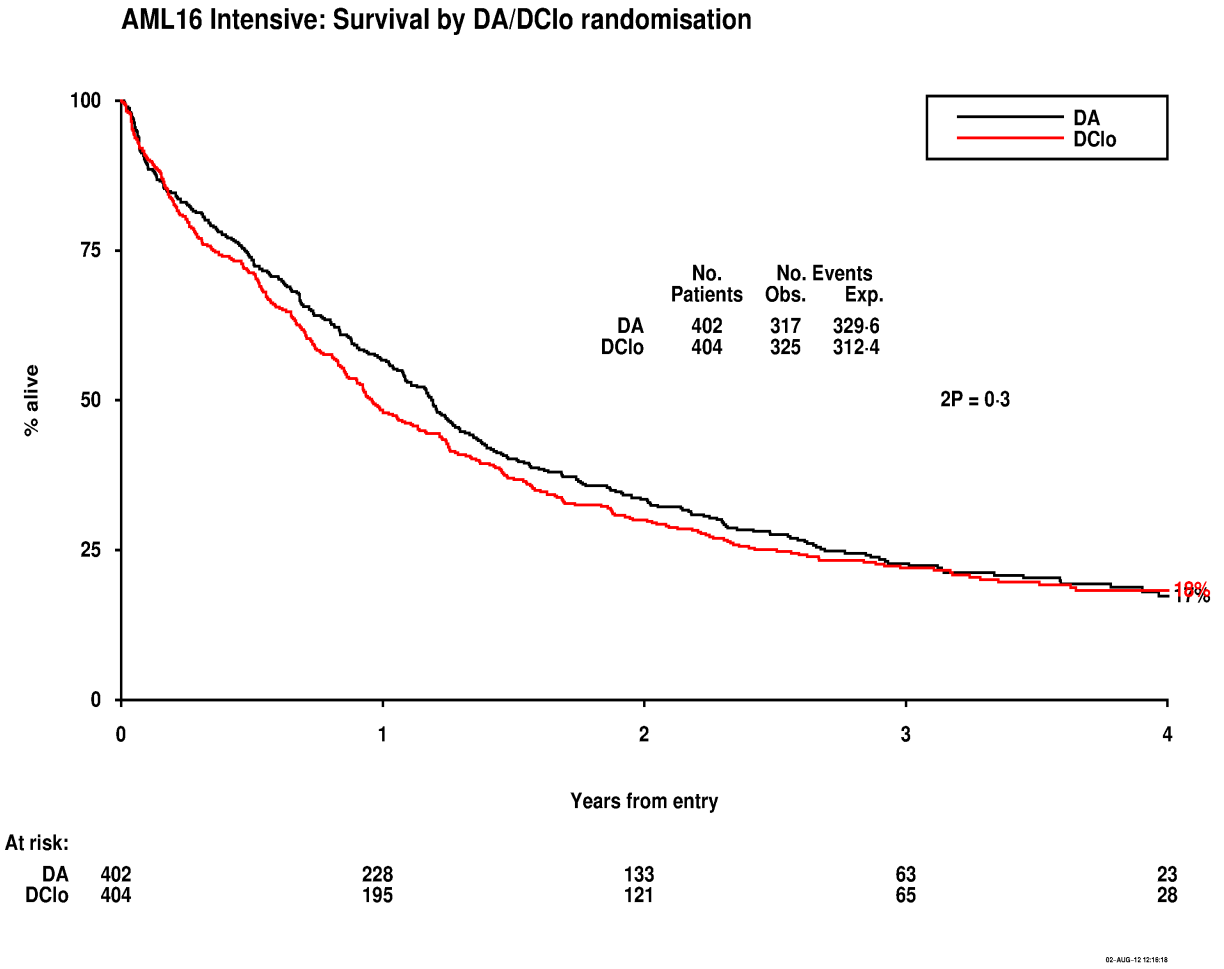
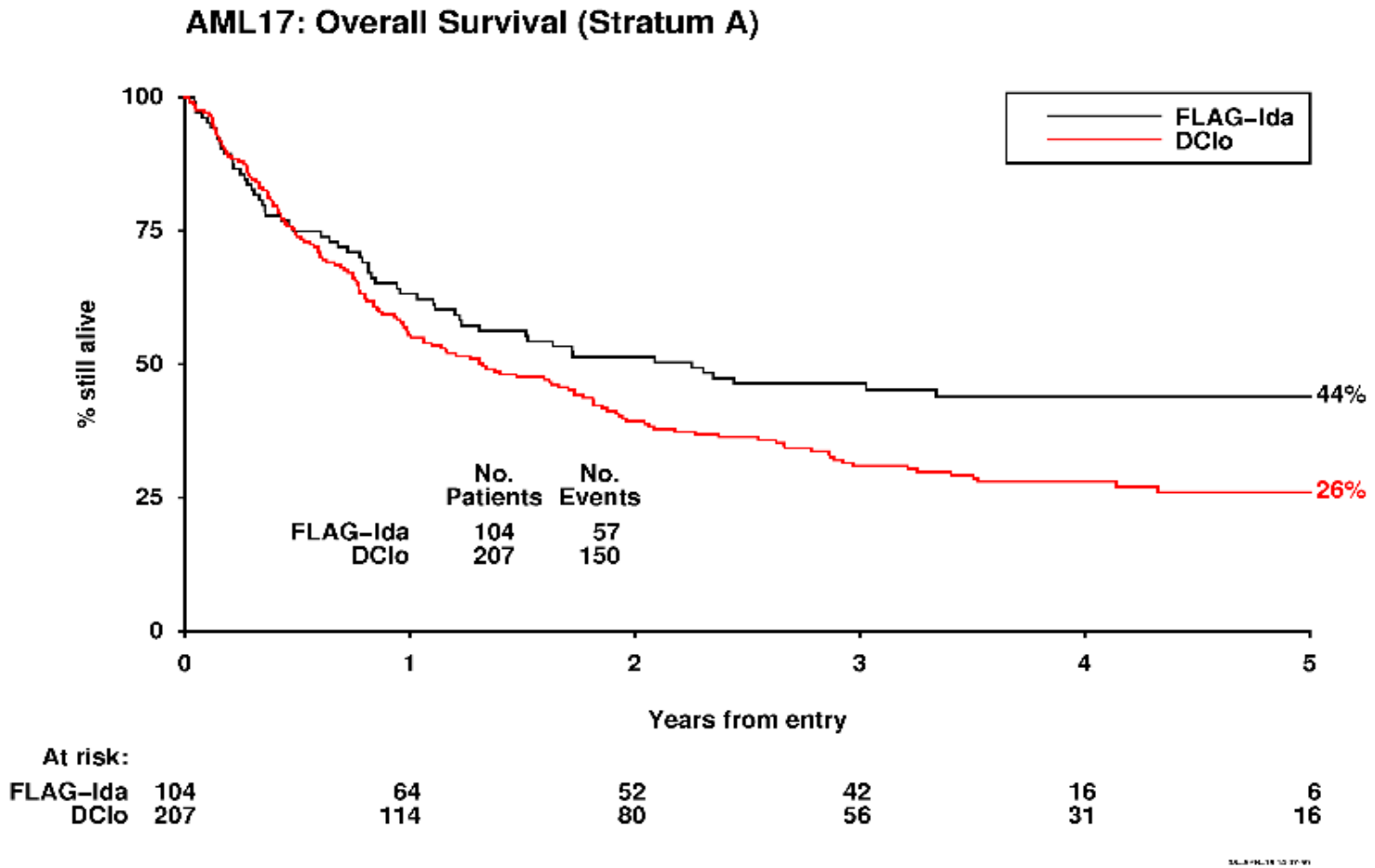
DA vs D-Clofarabine OS (n=806)

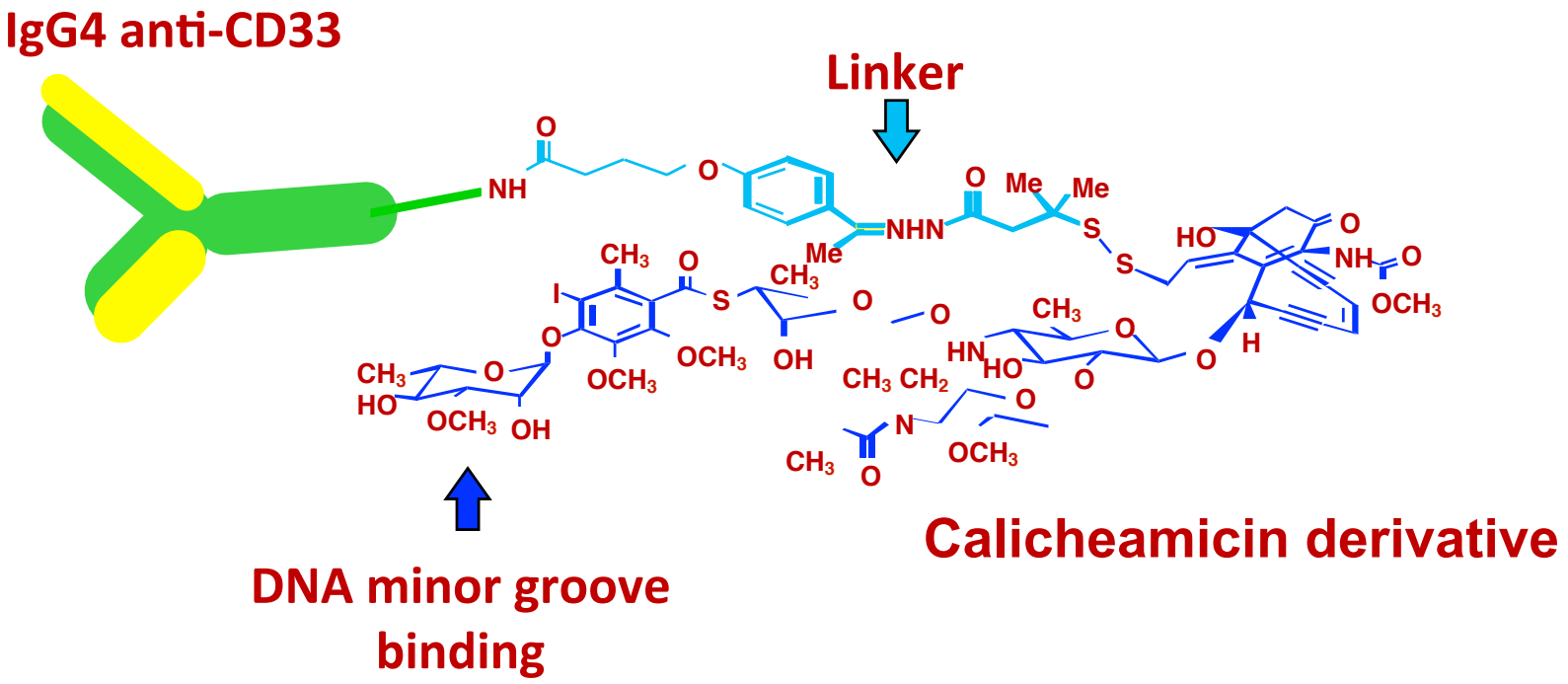


DClo vs FLAG-Ida for high risk



Mylotarg® (gemtuzumab ozogamicin)

First antibody-targeted chemotherapeutic agent for the treatment of relapsed acute myeloid leukemia in older patients

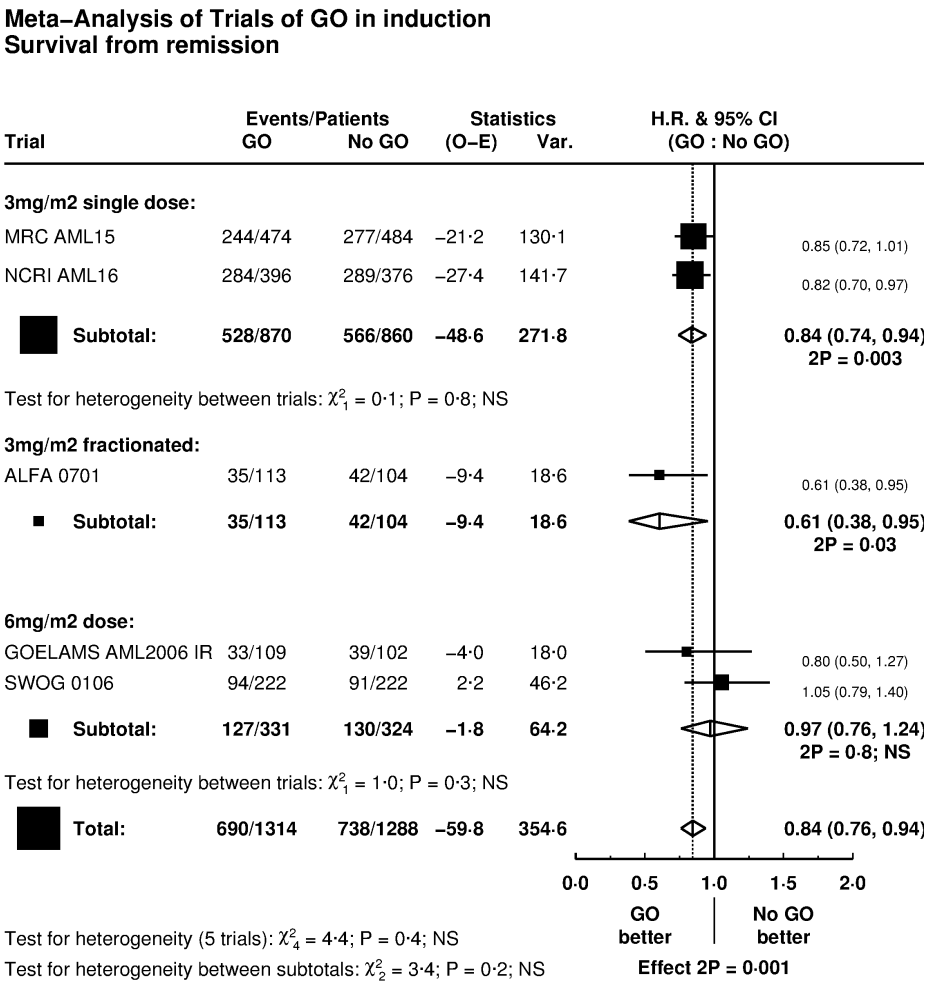


GO+IC: meta-analysis of RCT

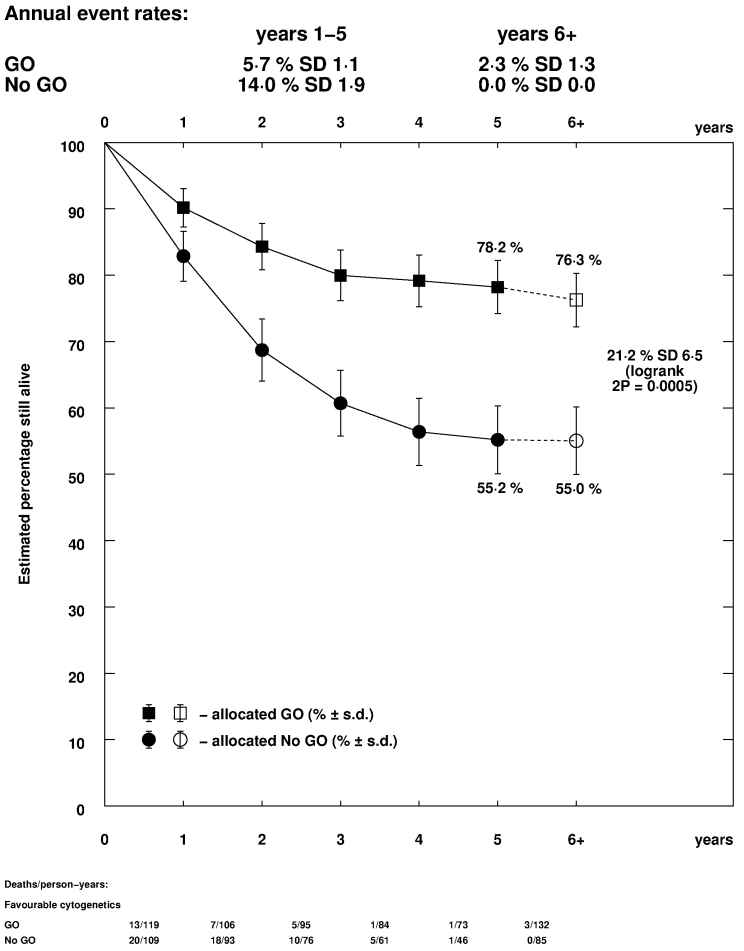
Trial	GO dose/sched	Induction Chemo	No. of patients	Median age (years)	CG Risk (MRC)
MRC AML15	**3 mg/m² d1**	ADE,DA, FLAG-Ida	1099	50 (15-71)	All
NCRI AML16		DA, DClo	1115	67 (51-84)	All
SWOG-0106	**6 mg/m² d4**	DA (3+7)	595	47 (18-60)	All
GOELAMS AML2006/IR		DA (3+7)	238	50.5 (18-60)	Inter
ALFA-0701	**3 mg/m² d1,4,7**	DA (3+7)	278	62 (50-70)	Inter/Adv

Hills RK et al. Lancet Oncol.

Results: Survival post remission



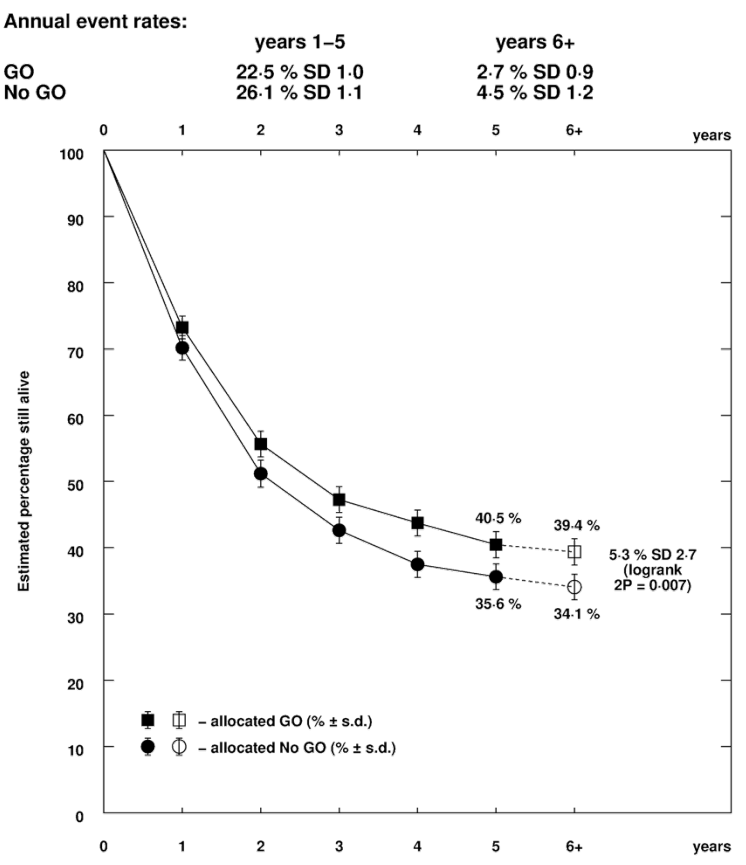
Overall Survival: Favourable, Intermediate Cytogenetics



Deaths/person–years:

Favourable cytogenetics

GO	13/119	7/106	5/95	1/84	1/73	3/132
No GO	20/109	18/93	10/76	5/61	1/46	0/85



Deaths/person–years:

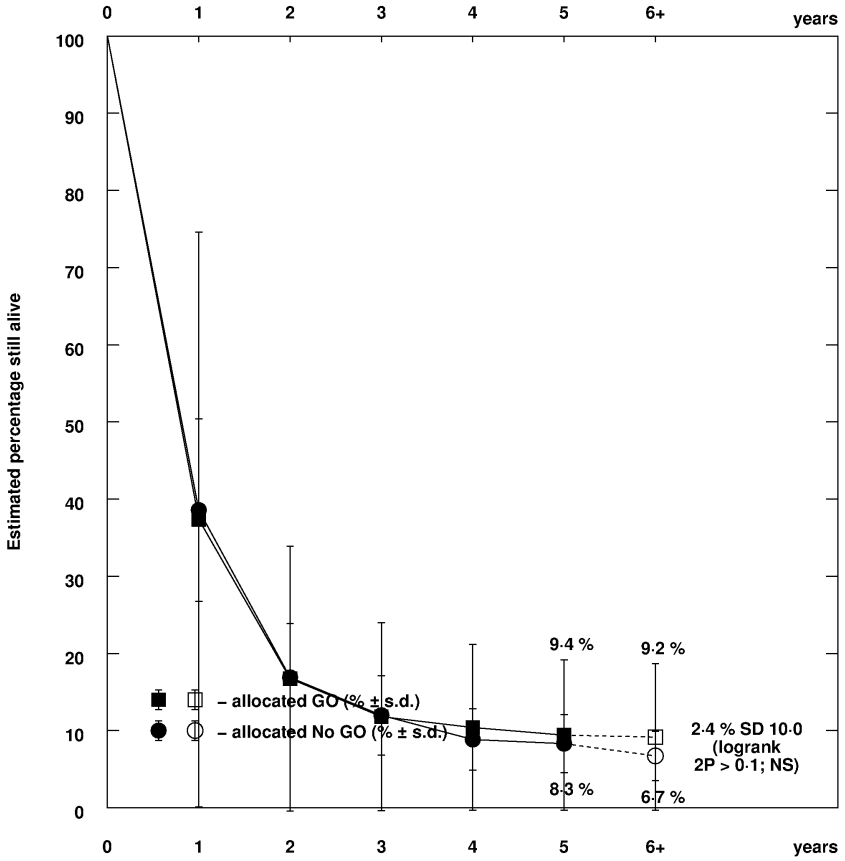
Intermediate cytogenetics

GO	248/806	158/575	70/418	24/293	16/202	9/336
No GO	284/793	166/524	67/373	33/262	9/186	14/308

Overall Survival: Adverse

Annual event rates:

	years 1–5	years 6+
GO	74·9 % SD 4·8	3·0 % SD 3·0
No GO	75·3 % SD 4·8	26·3 % SD 11·8



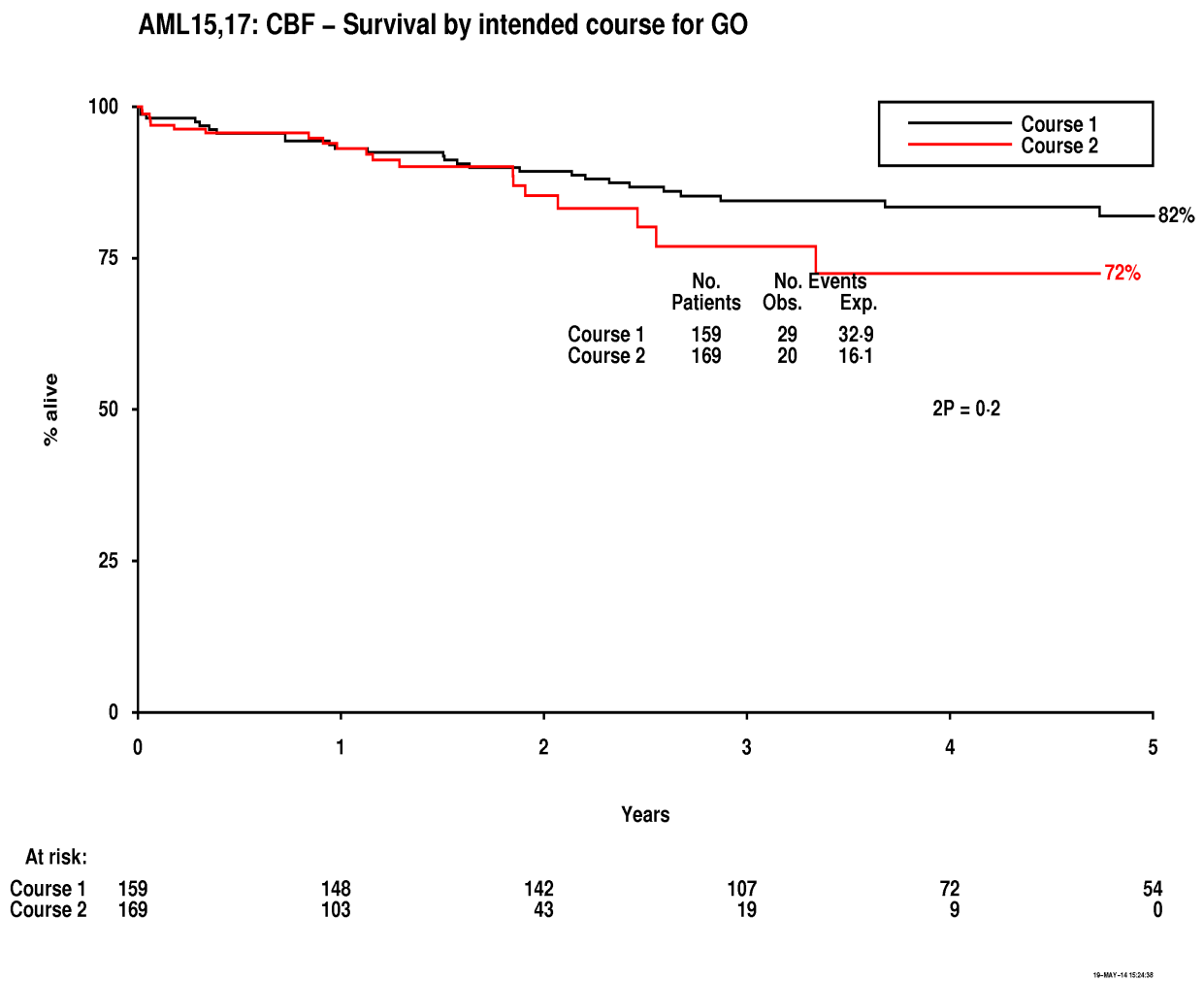
Deaths/person–years:

Adverse cytogenetics						
GO	172/173	54/68	14/40	3/27	2/19	1/33
No GO	166/176	56/67	13/38	8/25	1/18	5/19

CBF Subset: Results of regression analysis

Variable listed in order of importance	Hazard ratio	95% Confidence Interval	P-value
GO	0.47	0.30 to 0.71	<0.0001
Performance status (per category)	1.18	1.06 to 1.33	0.002
Age (per 10 years)	1.18	1.07 to 1.31	0.002
Ara-C consolidation	0.81	0.68 to 0.98	0.02
Male sex	1.30	1.03 to 1.63	0.03

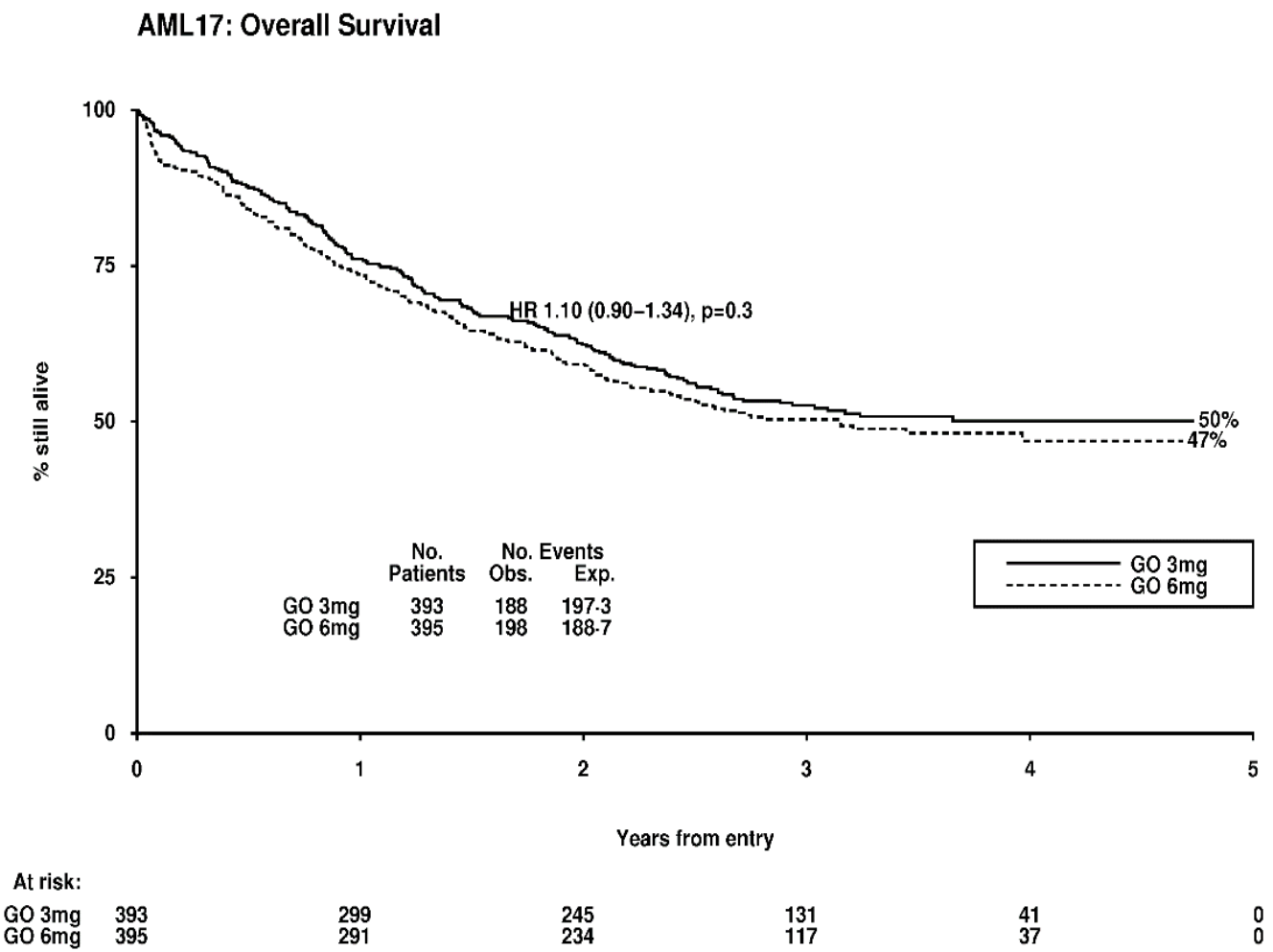
GO for CBF in course 1 or course 2?



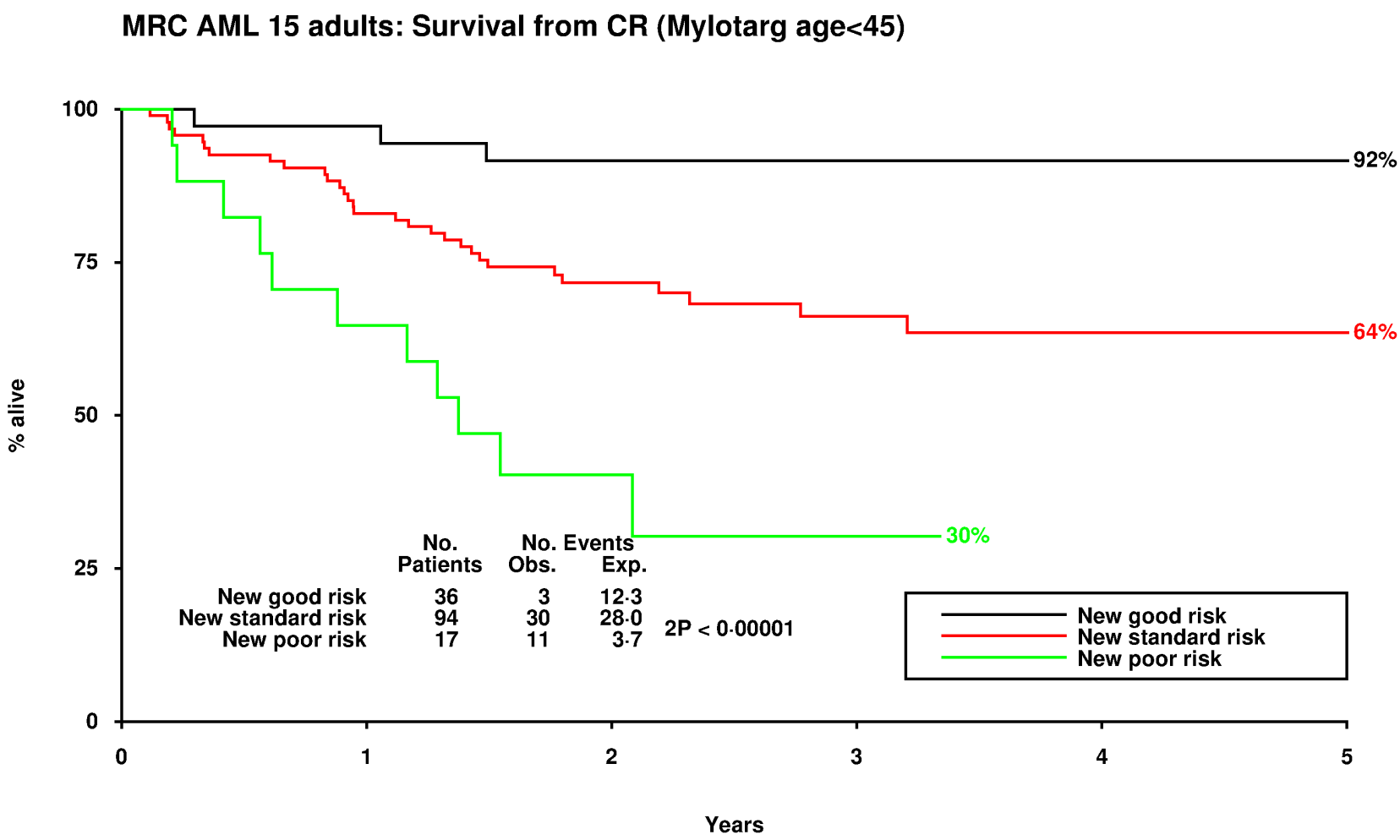
Mylotarg: Remaining Issues

- Optimum dose
- Schedule
- Use in consolidation
- Use in APL
- Availability/ approval

AML17: GO 6mg vs 3mg (n=788)



Role for Transplant? The Mylotarg Impact

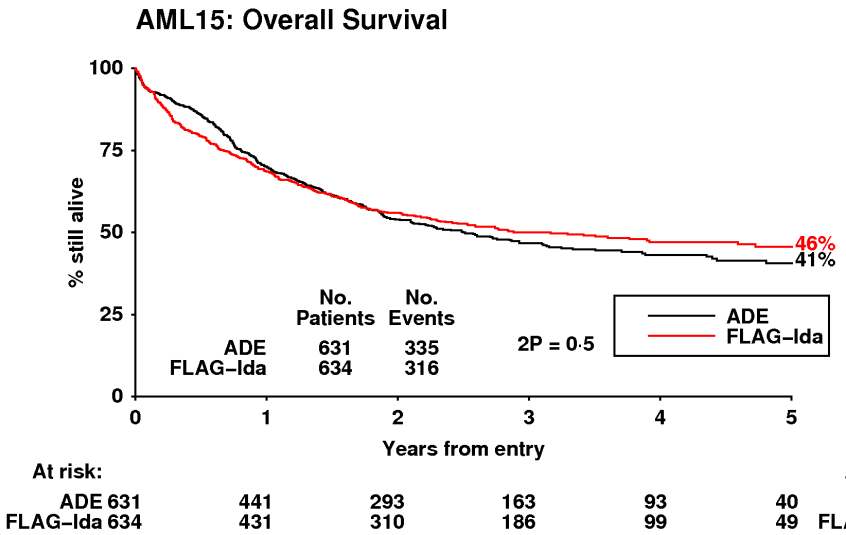


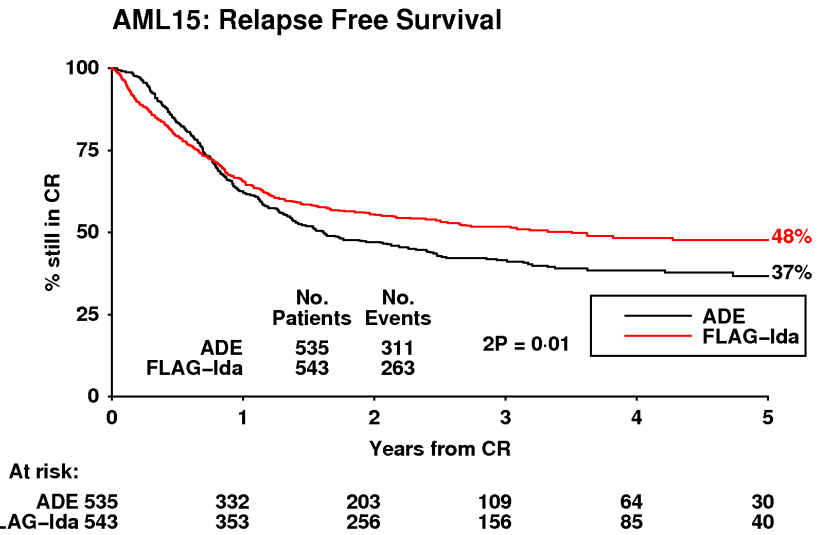
FLAG-Ida

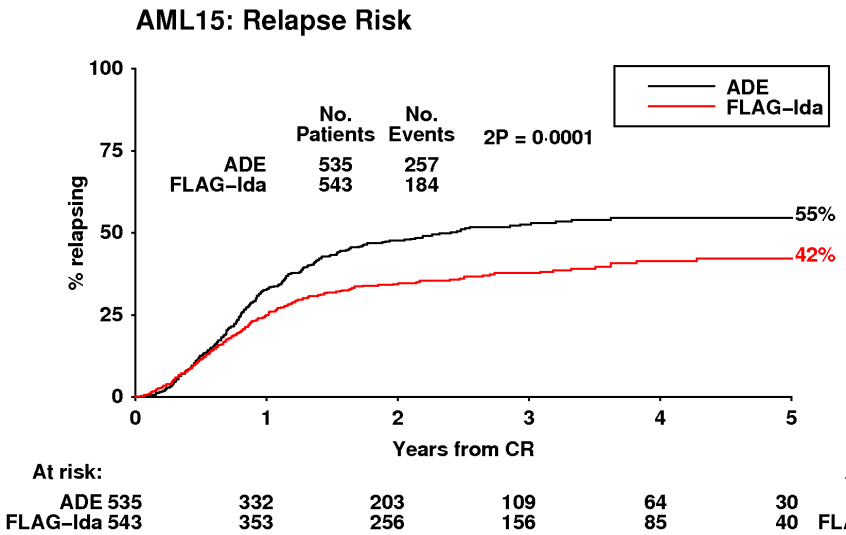
AML 15 Patients <60 yrs: Remission Rates

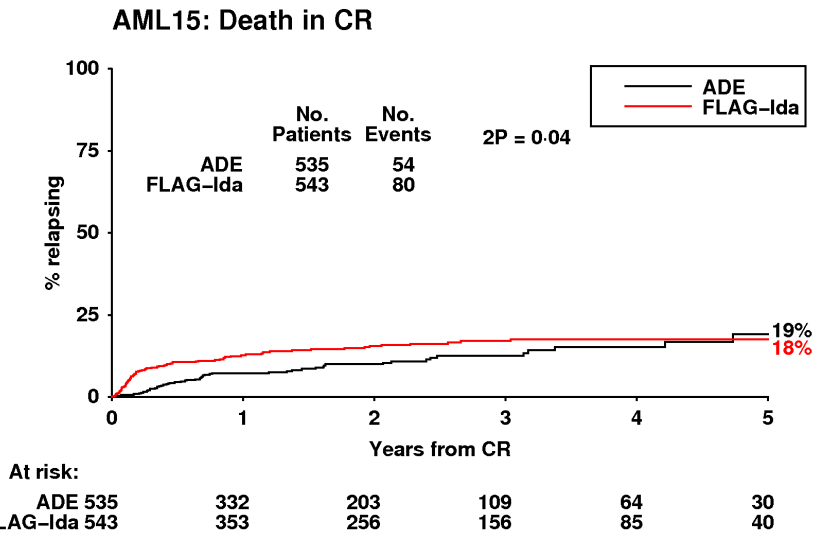
	DA vs ADE		ADE vs FLAG-Ida		DA(90)
Overall (%)	78	82	81	84	71
Course 1	63	69	67	**77**	59
% of remitters	81	84	83	**92**	83

ADE vs FLAG-Ida

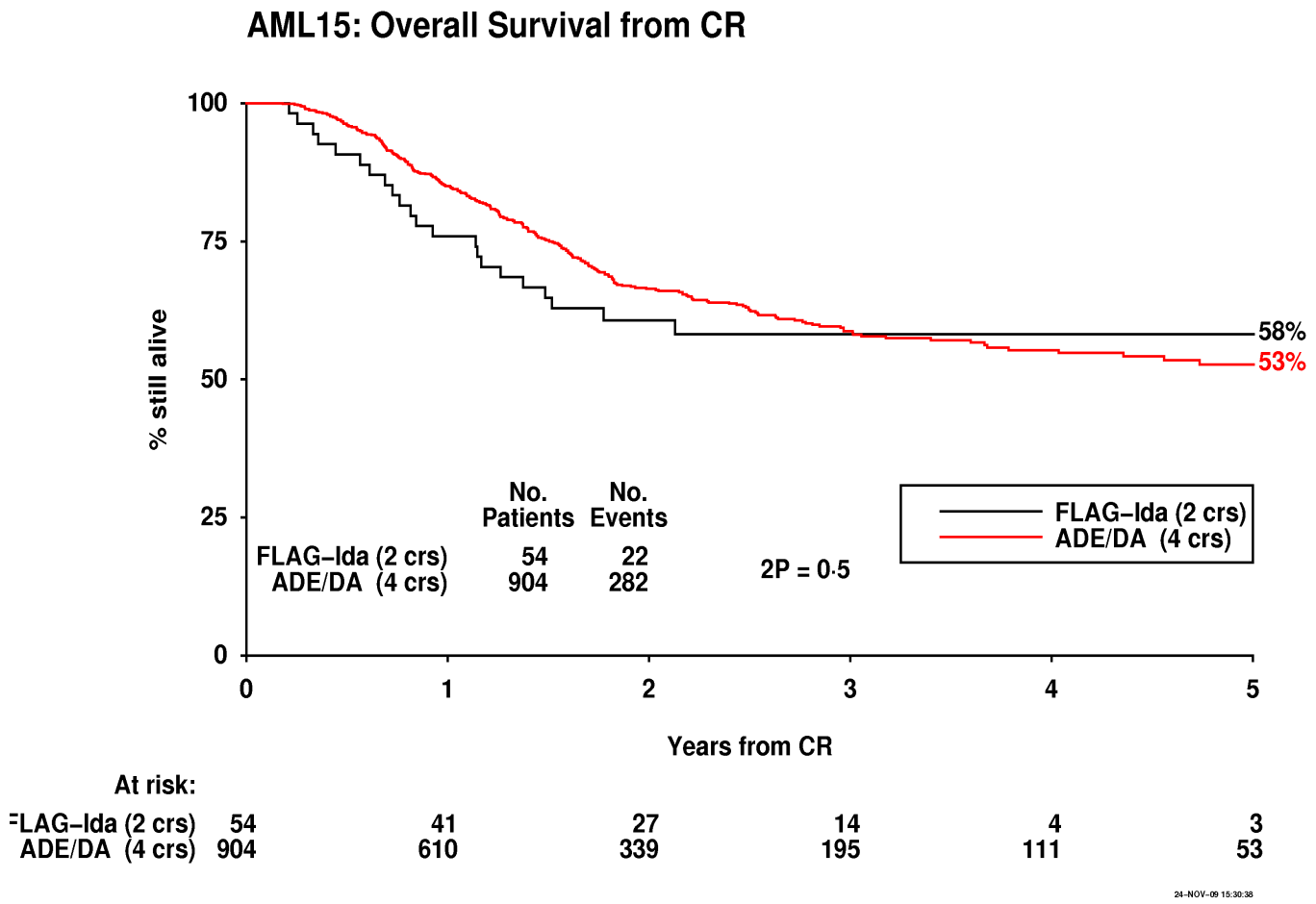




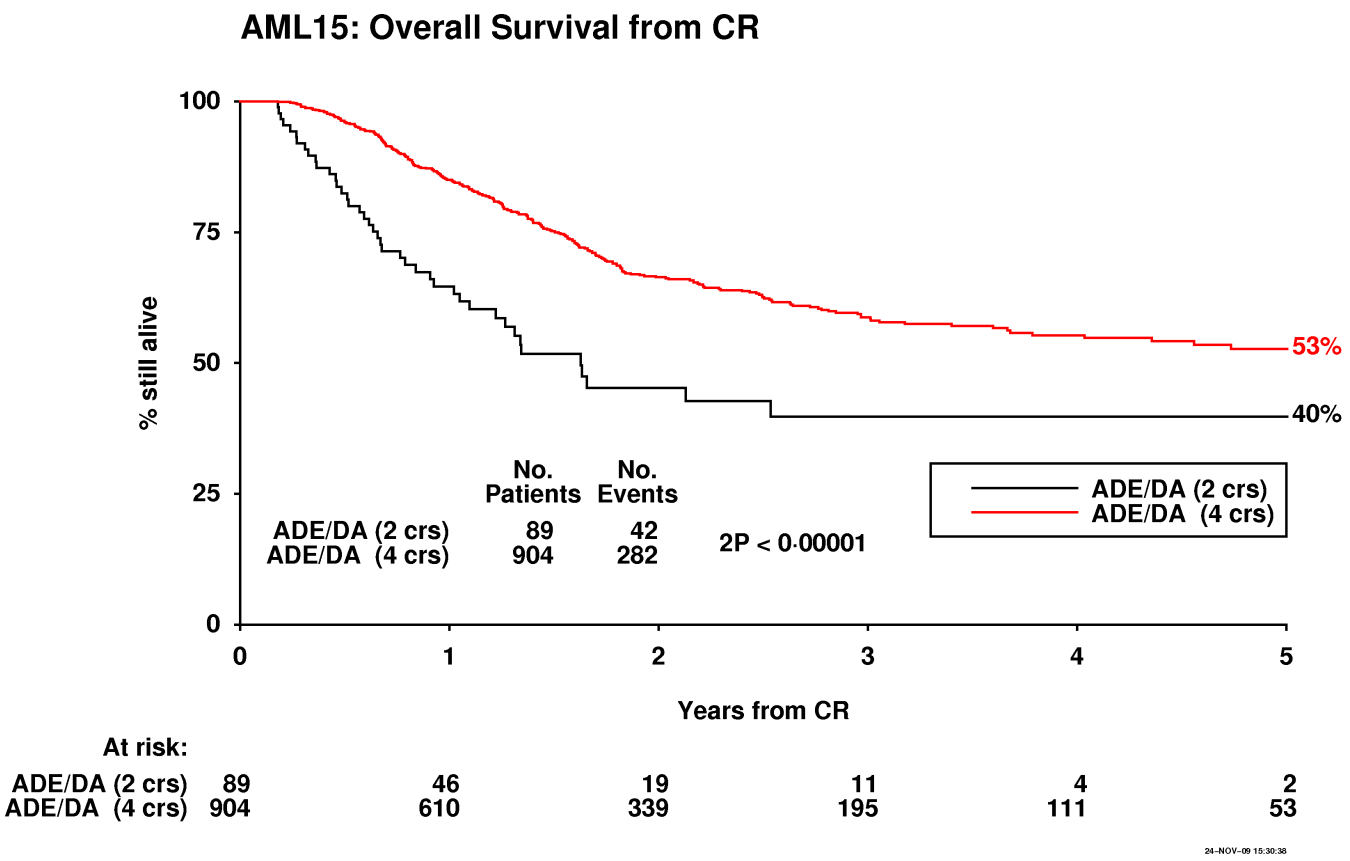




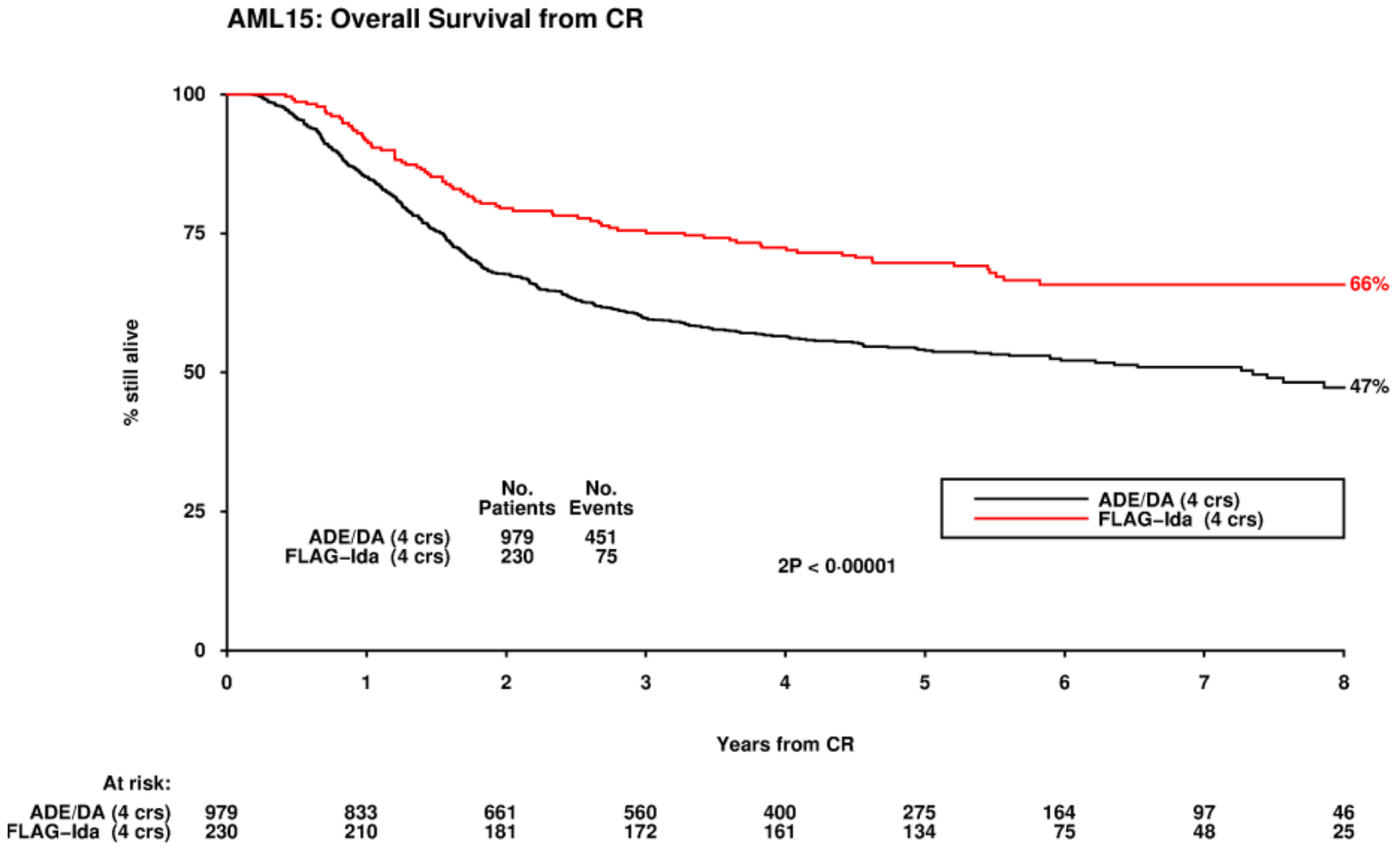
2 or 4 courses? FLAG v ADE/Ara-C



2 or 4 courses? ADE/DA

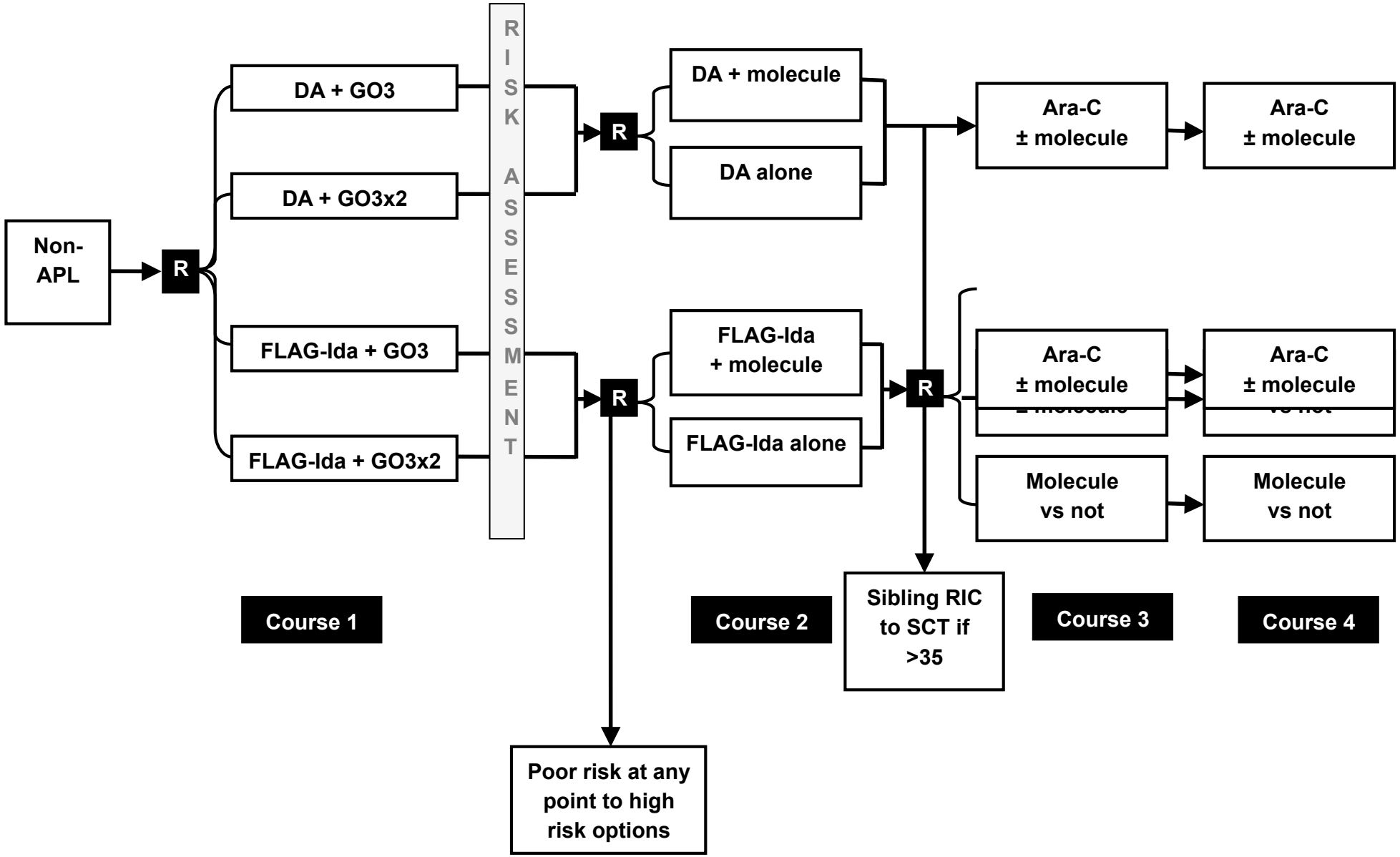


ADE/DA vs FLAG-Ida – 4 courses



p-value adjusted for age, WBC, cytogenetics, secondary disease p=0.004

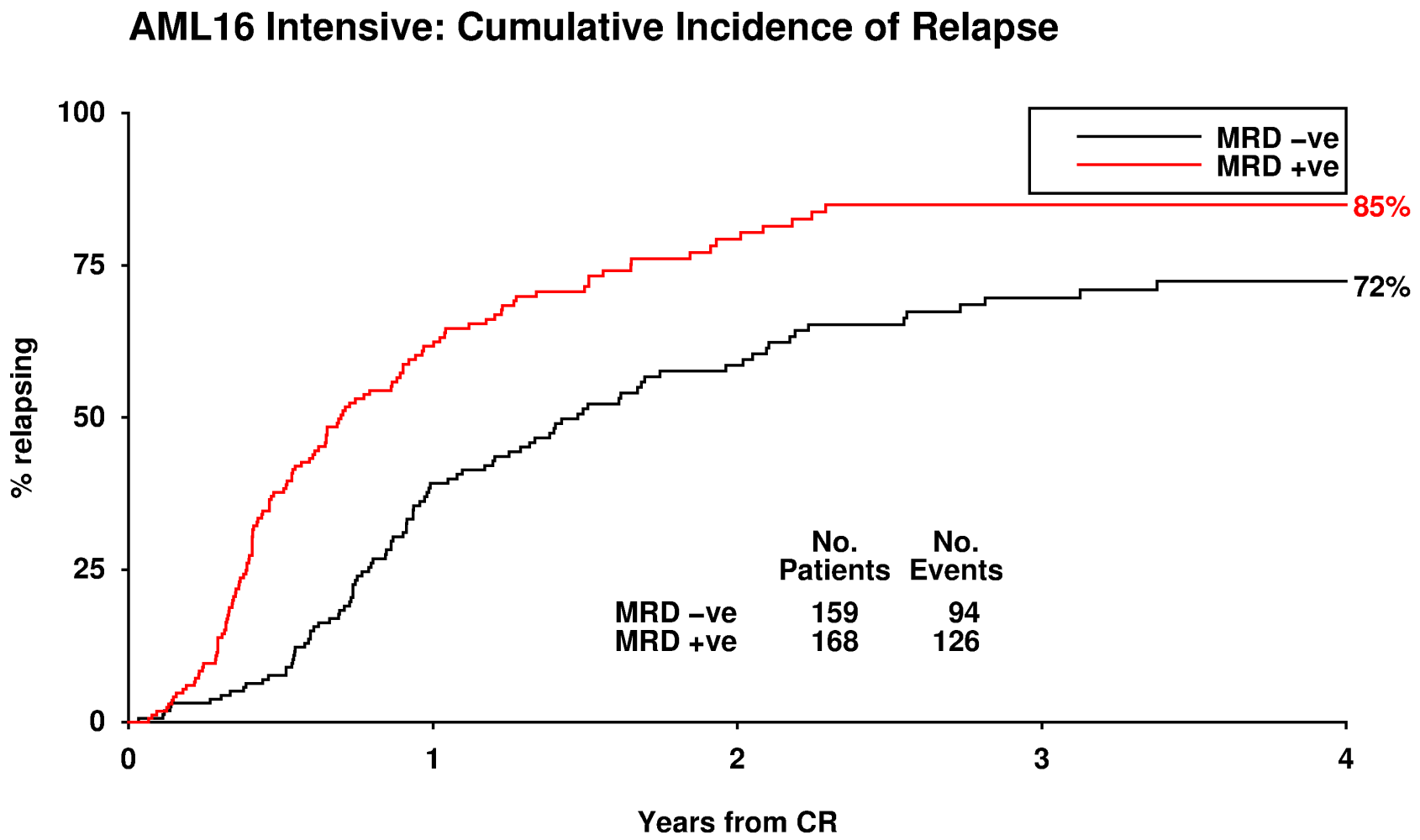
NCRI AML19 (2015-)



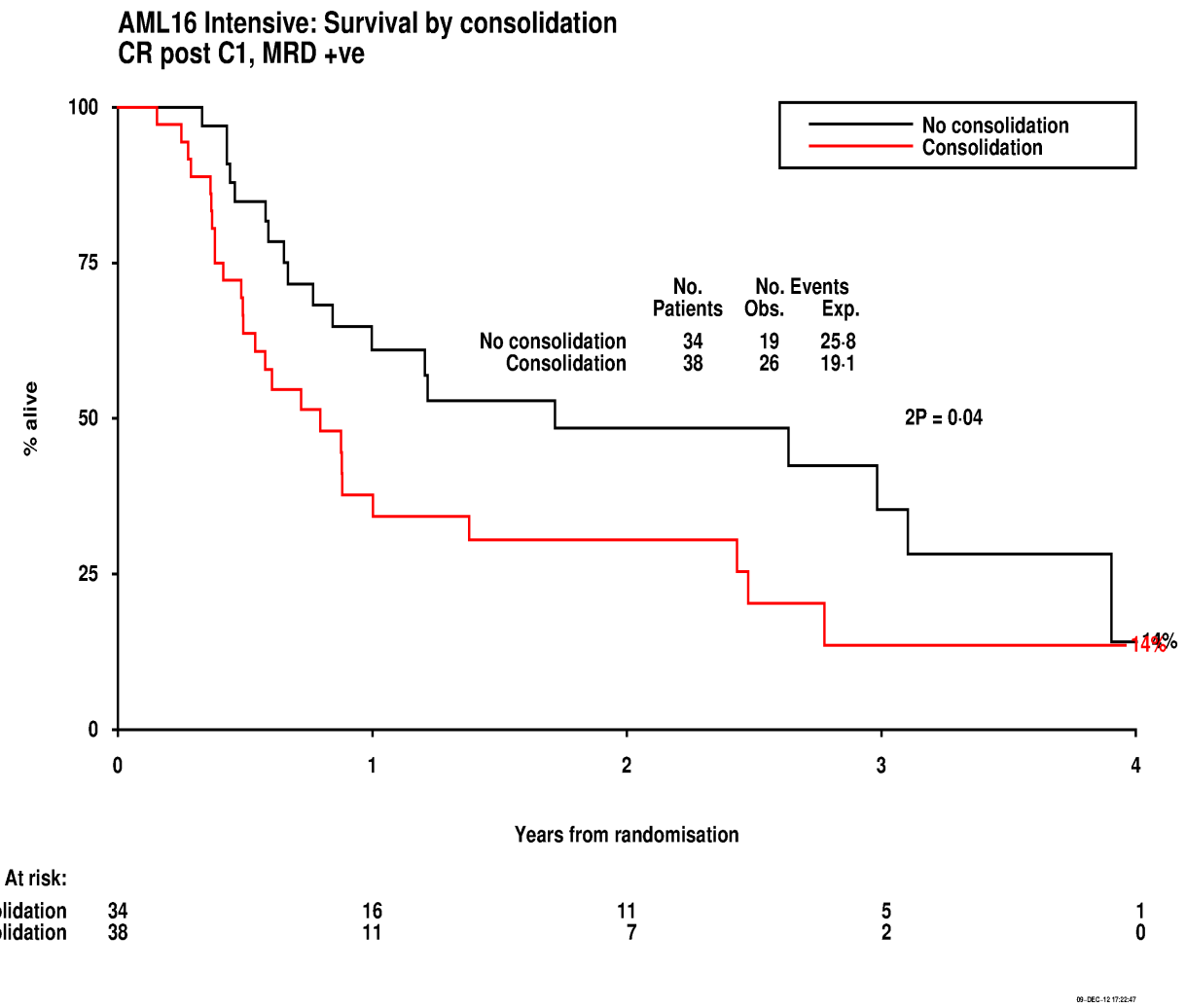
Implementation of MRD

- Specificity and sensitivity
- ? Does it tell us more than we already know.
- Is it prognostic or is it predictive?
- Is it treatment dependent?
- What are the indirect costs?
- “monitor vs no monitor”

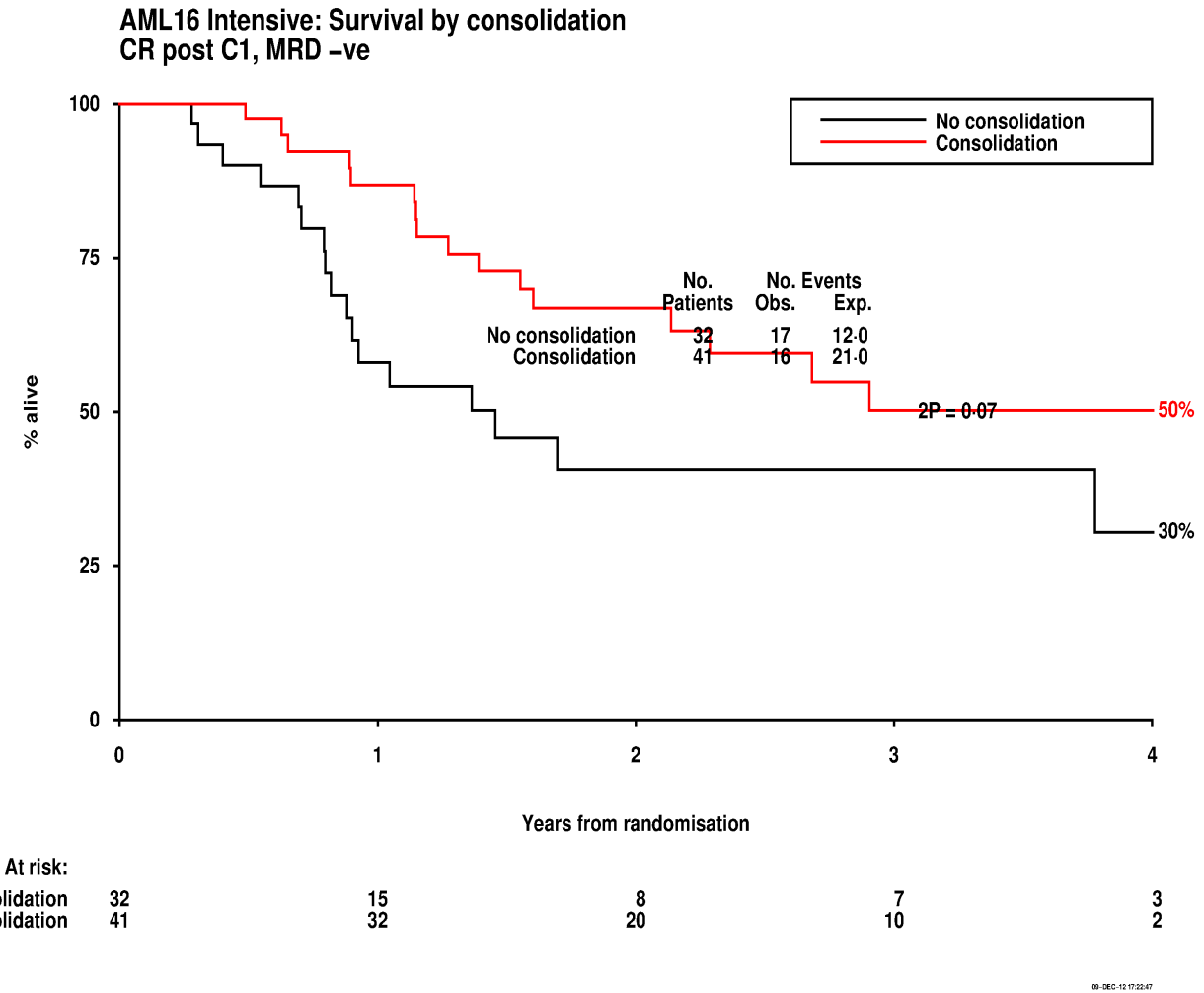
MRD: Cumulative Incidence of Relapse



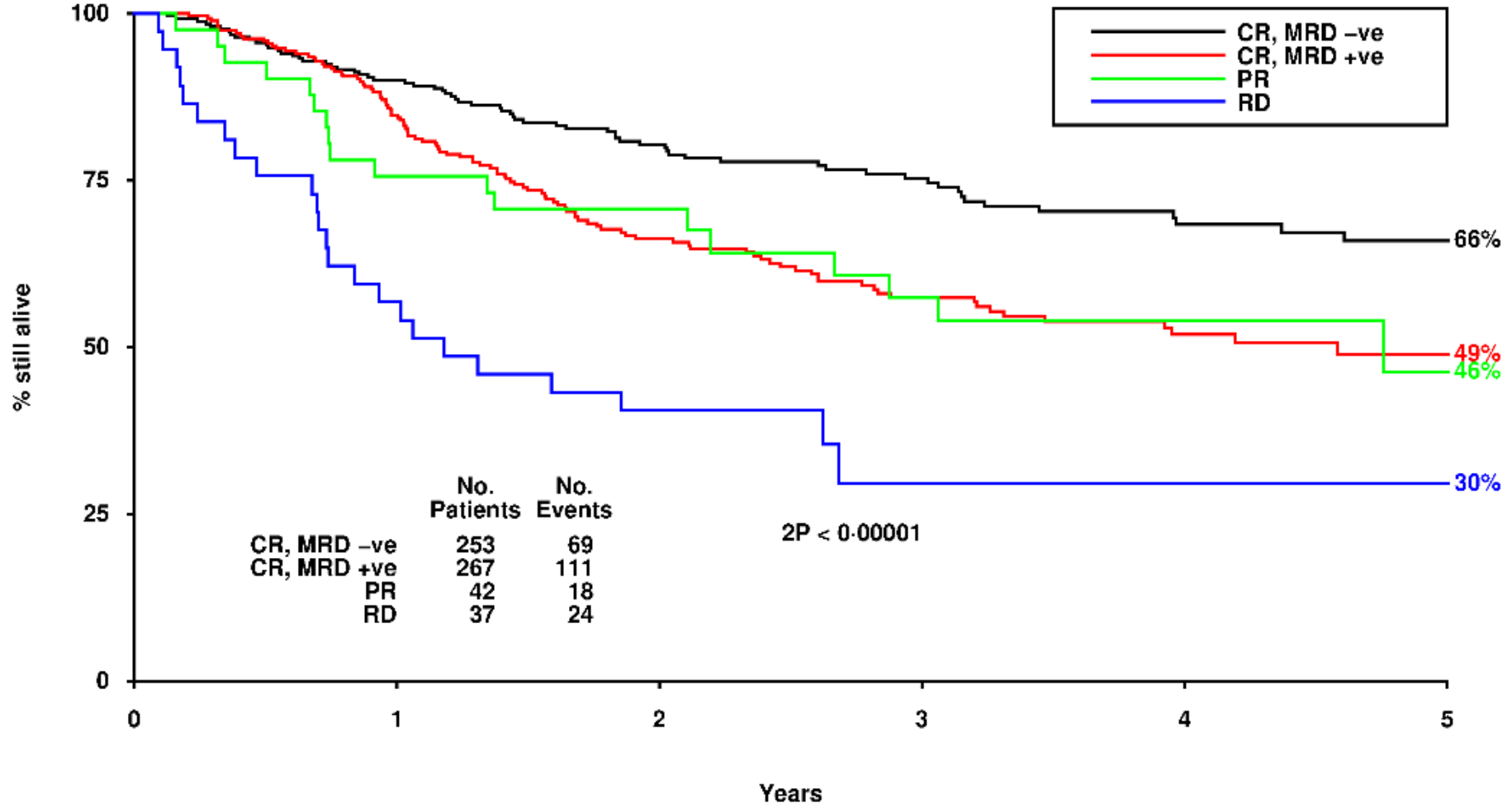
Addition of Consolidation in MRD +ve



Addition of Consolidation in MRD-ve

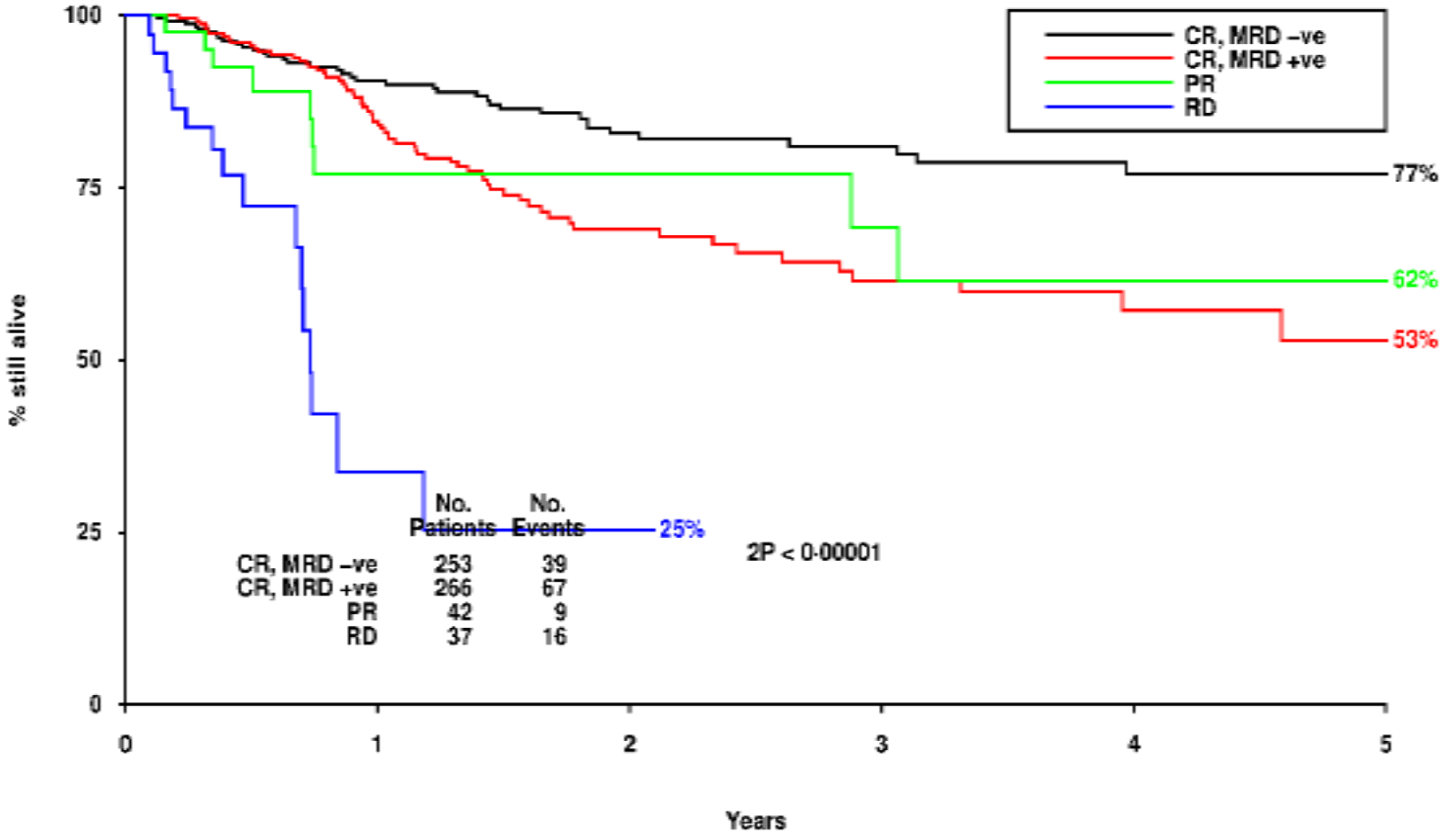


OS: Standard Risk (N=699)



Freeman S. et al

OS Standard Risk Censored at SCT



Freeman S. et al

Conclusions

- There is better than “3+7” available
- Daunorubicin 60mg dose is optimal for most
- Addition of mylotarg; cladrabine; and/or FLAG-Ida may be superior
- The efficacy of induction determines OS when intensive therapy use.
- MRD status may clarify post induction choices