# Frontline Induction Therapy in 2017

#### Alan K Burnett

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 44<sup>th</sup> anniversary of "3+7"

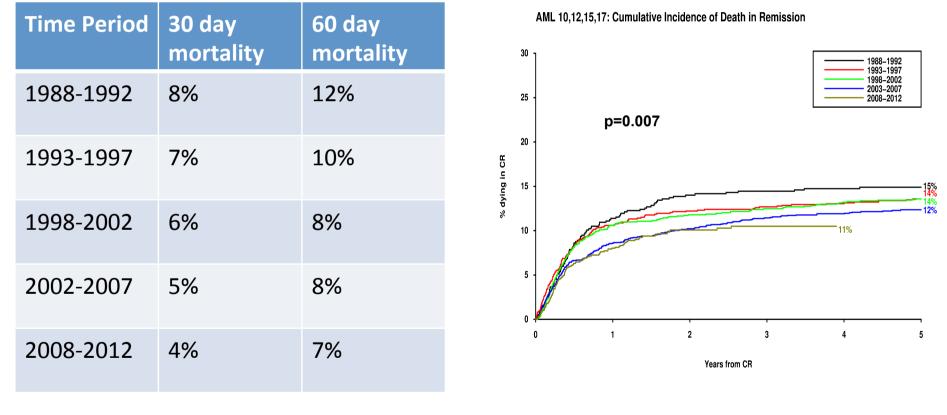
- DNR 45 mg/m<sup>2</sup>, D 1-3
- Ara-C 100 mg/m<sup>2</sup>, D 1-7

Yates JW et al, Cancer Chemother Rep 1973

## Changes in outcome with time: remission rates

Age (years)	Pre-198 0	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**



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%	
		р	=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<sup>2</sup> compared to DNR 30-50 mg/m<sup>2</sup>
  - superior CR rate in some studies<sup>1,2</sup> but not in others<sup>3</sup>
- Idarubicin 12-13 mg/m<sup>2</sup> compared to DNR 45-50 mg/ m<sup>2</sup>
  - superior CR rate and possibly longer OS<sup>4</sup>

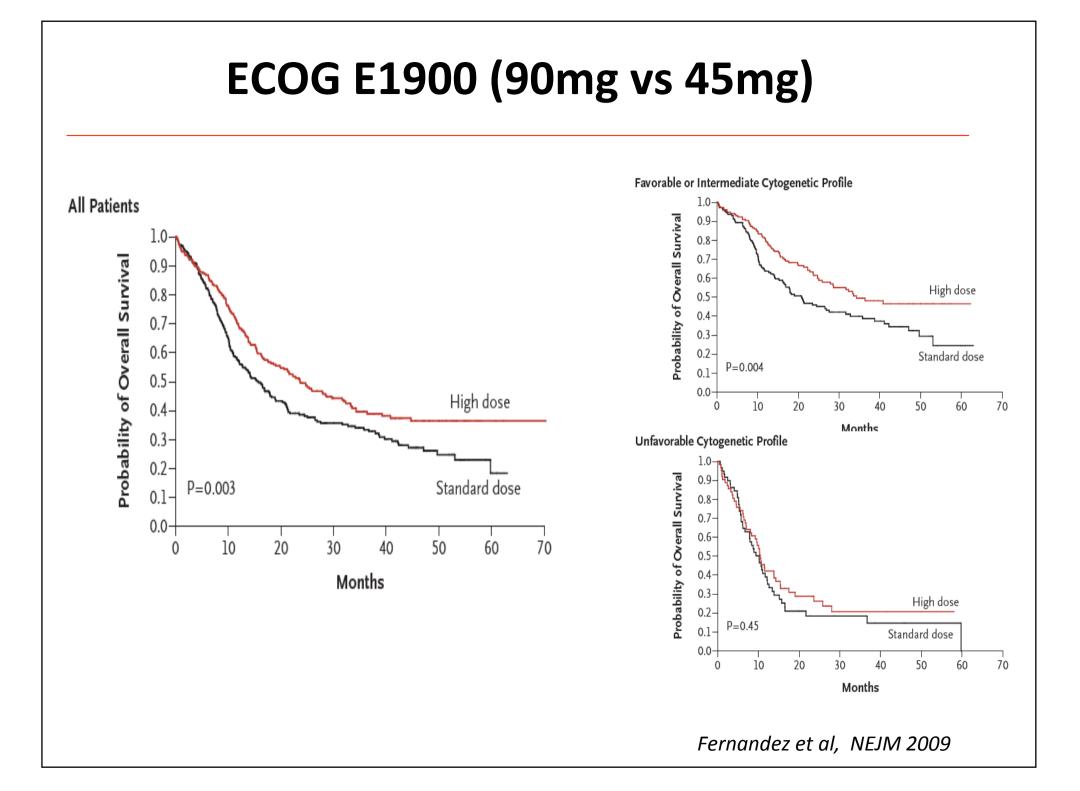
<sup>1</sup>Lowenberg et al, JCO 1998; <sup>2</sup>Arlin et al, Leukemia1990; <sup>3</sup>Mandelli et al, JCO 2009; <sup>4</sup>Berman et al, Cancer 1997

## **Daily Ara-C Dose?**

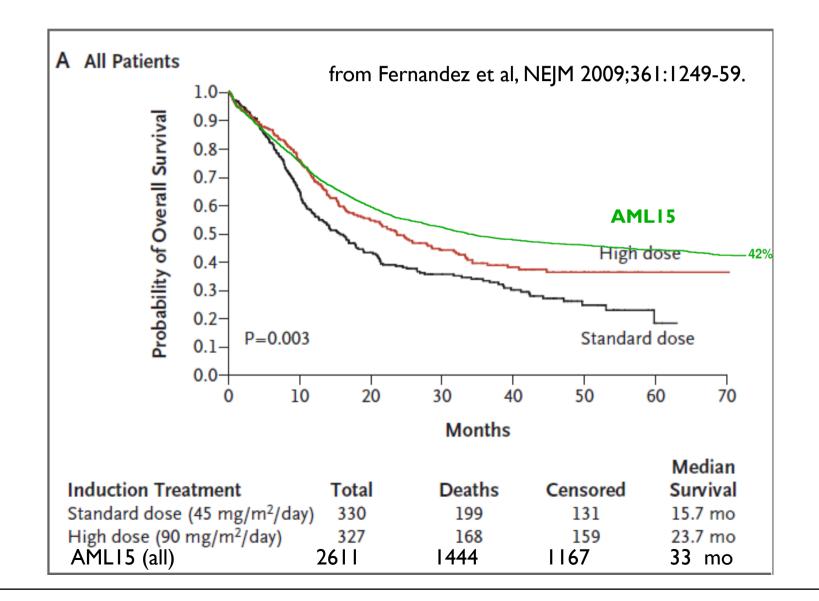
- A) 100mg/m<sup>2</sup>/day
- B) 200mg/m<sup>2</sup>/twice daily
- C)  $1.0g/m^2/day$
- D)  $3.0g/m^2/day$

## **Daunorubicin Dose**

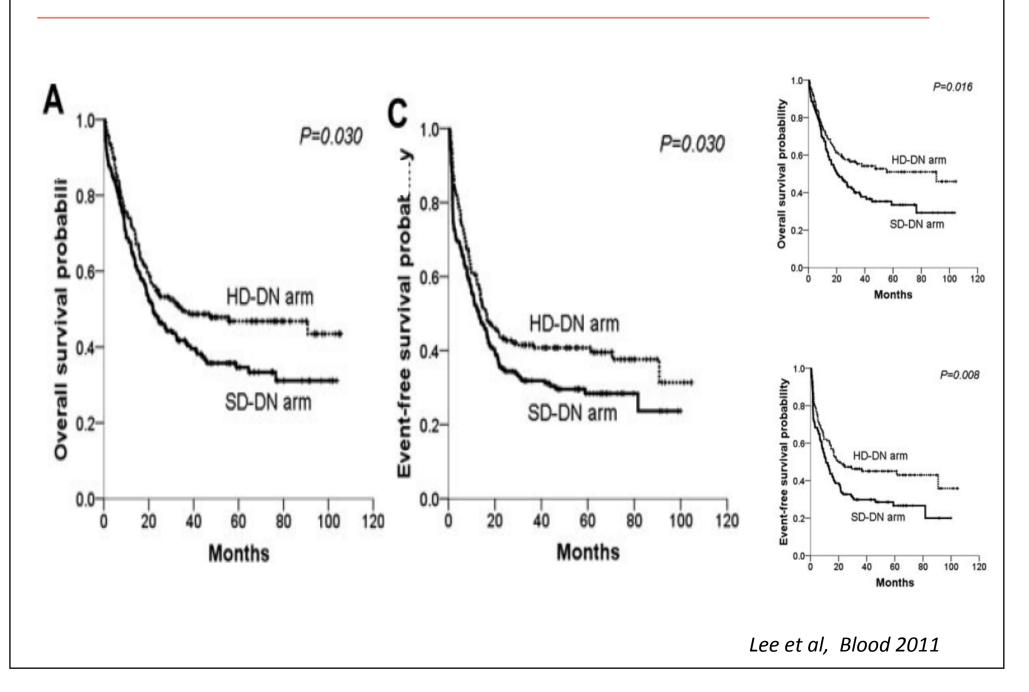
- A)  $45 \text{mg/m}^2$
- B) 60mg/m<sup>2</sup>
- C) 90mg/m<sup>2</sup>



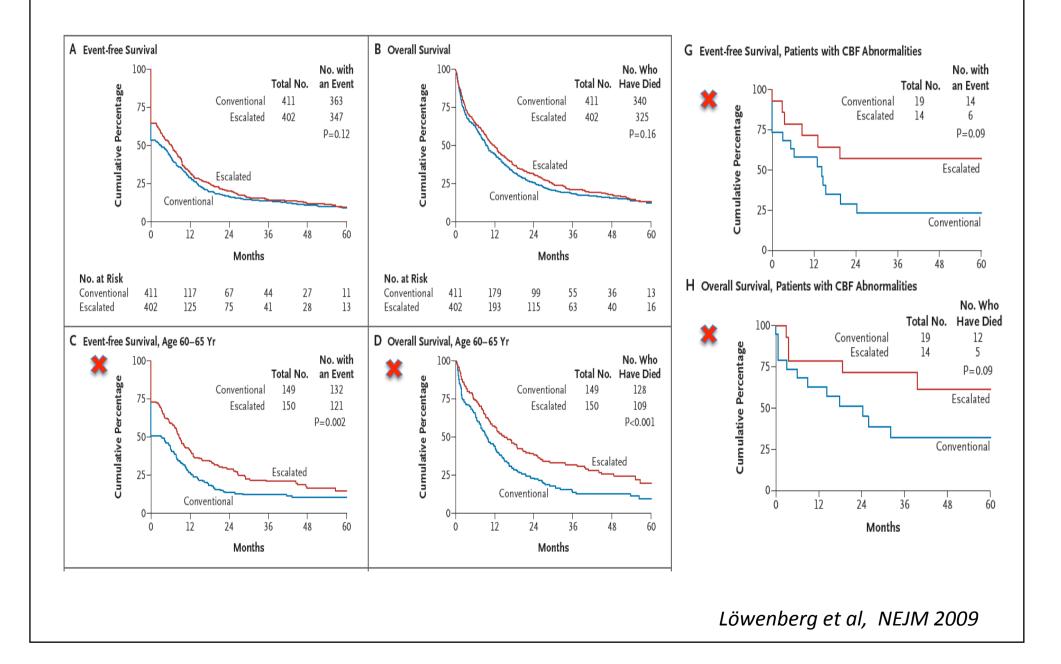
## DA 90mg vs 45mg in younger patients



## **Korean Study**



## **HOVON-SAKK-AMLSG STUDY**



## **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

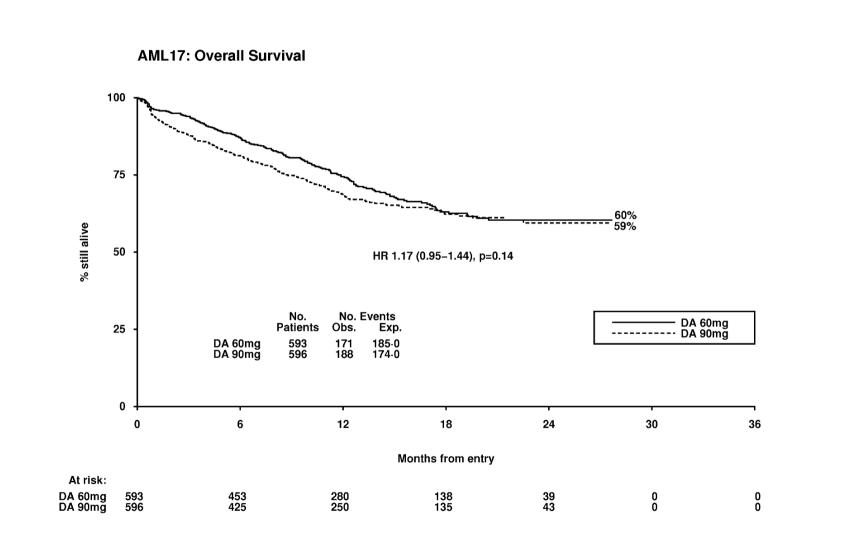
 Patel JP, Gonen M, Figueroa ME, et al. Prognostic relevance of integrated Genetic profiling in acute myeloid leukemia. *N.Engl J Med*. 2012; 366 (12): 1079-1089.

DNMT3A, NPM1, and MLL-PTD

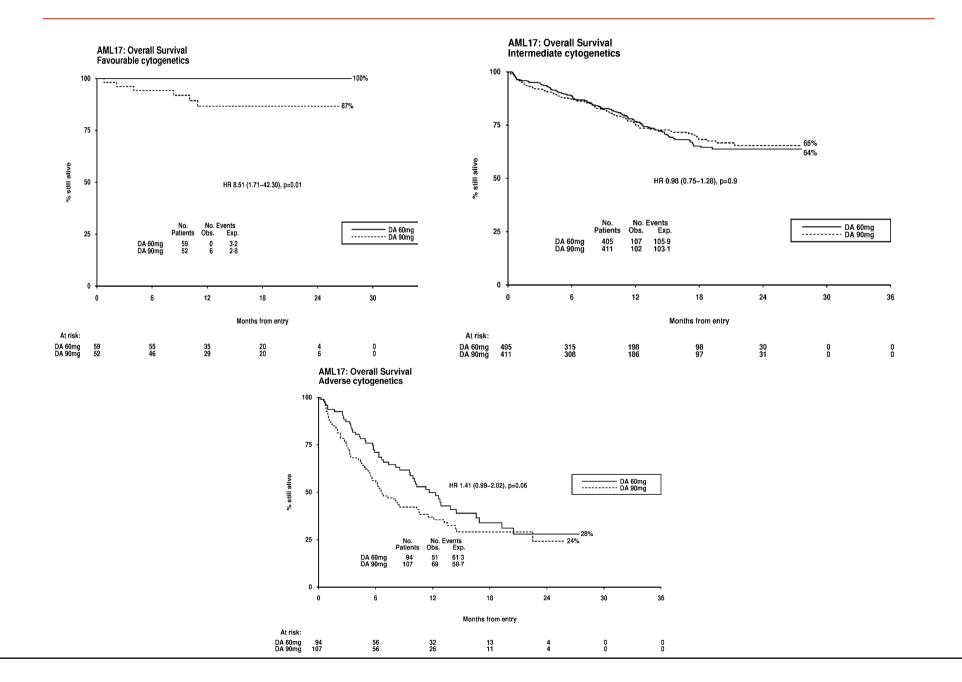
• Luskin MR, Lee J-W, Fernandez HF et al., Benefit of high dose daunorubicin in AML induction extends across cytogenetic and molecular groups: updated analysis of E1900 Blood 2016 Blood-2015-07-657403.

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

## AML17: 90mg/m<sup>2</sup> vs 60mg/m<sup>2</sup>: OS



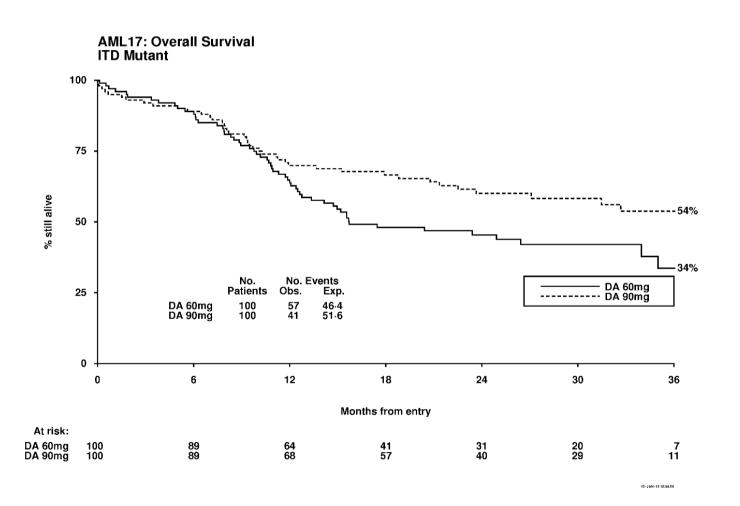
### AML17: 90mg/m<sup>2</sup> vs 60mg/m<sup>2</sup>: OS by Risk Group



#### AML17: 90mg/m<sup>2</sup> vs 60mg/m<sup>2</sup>: Stratified Analysis of survival

Stratum		Deaths/ DA90	Patients DA60	Stat (O–E)	istics Var.		& 95% CI 0 : DA60)	
otratam		DAGO	DAG	(0-2)	Tan.	(84.		
Age:								
Age 16-2		13/59	10/59	1.7	5.7	_		1.35 (0.60, 3.06)
Age 30-0		9/63	16/65	-3.7	6.2	—	+	0.55 (0.25. 1.20)
Age 40-4		40/119	28/119	7.4	17.0			1.55 (0.96, 2.49)
Age 50-5	59	71/196	60/194	8.9	32.6		+	1.31 (0.93, 1.85)
Age 60+		55/158	57/156	0.1	27.9	-	+	1.00 (0.69, 1.45)
	Subtotal:	188/595	171/593	14-3	89.4		₽	1.17 (0.95, 1.44 2P = 0·1; NS
	heterogeneity betwee trend between subgro			5				,
			5 61116					
Diagnos		110/200	407 700				L	
De Novo		142/502	137/501	5.3	69.7		₹.	1.08 (0.85. 1.36)
Seconda	ıry	24/58	30/59	5.4	13.3		<b>—</b>	1.50 (0.88, 2.57)
MDS		16/34	10/34	4.2	6.4		<u> </u>	1.91 (0.88. 4.14)
	Subtotal:	182/594	177/594	14-8	89.4		₽	1.18 (0.96, 1.45 2P = 0.1; NS
Test for h	heterogeneity betwee	en subgroups: Χ <sub>2</sub>	= 2·8; P = 0·2; N	3				
Cytogen	etics:							
Favourat	ble	6/51	0/59	3.2	1.5			8.51 (1.71, 42.30)
Intermed	liate	102/411	107/405	-1.1	52.2		+	0.98 (0.75, 1.28)
Adverse		69/107	51/94	10.3	29.8		┝╼─	1.41 (0.99, 2.02)
							1	
	Subtotal: heterogeneity betwee trend between subgro			12.4	83-5		₽	1.16 (0.94, 1.44 2P = 0·2; NS
Test for H Test for t FLT3 ITE	heterogeneity betwee trend between subgro	en subgroups: $\chi^2_2$	= 8·6; P = 0·01	12·4 17·8	<b>83-5</b> 65-3			2P = 0·2; NS
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Test for H Test for t FLT3 ITE ITD WT	heterogeneity betwee trend between subgro D:	en subgroups: Χ <sup>2</sup> <sub>2</sub> oups: Χ <sup>2</sup> = 0-4; Ρ 144/456	= 8·6; P = 0·01 = 0·5; NS 118/450	17-8	<del>65</del> ·3	$\subset$		2P = 0-2; NS 1.31 (1.03, 1.67) 0.74 (0.47, 1.17) 1.16 (0.94, 1.44
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Test for H Test for t FLT3 ITC ITD WT ITD Muta Test for H NPM1 M NPM1 W	heterogeneity between rrend between subgro D: ant Subtotal: heterogeneity between utation: /T utation:	en subgroups: X <sup>2</sup> <sub>2</sub> pups: X <sup>2</sup> = 0-4; P 144/456 32/99 <b>176/555</b> en subgroups: X <sup>2</sup> 132/380 40/163 <b>172/543</b>	= 8·6; P = 0·01 = 0·5; NS 118/450 41/99 159/549 = 4·7; P = 0·03 122/394 34/150 156/544	17·8 -5·5 12:3 11·4 3·1 14-5	65-3 18-1 <b>83-5</b> 63-3 18-5			2P = 0-2; NS 1.31 (1.03, 1.67) 0.74 (0.47, 1.17) 1.16 (0.94, 1.44 2P = 0-2; NS 1.20 (0.94, 1.53) 1.18 (0.75, 1.87)
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Test for H Test for t FLT3 ITC ITD WT ITD Muta Test for H NPM1 W NPM1 W NPM1 M Test for H ITD/NPM ITD WT, ITD WT, ITD Muta	heterogeneity betwee rend between subgro D: Subtotal: heterogeneity betwee utation: /T utant Subtotal: heterogeneity betwee f: NPM1 WT NPM1 Mutant ant, NPM1 Mutant ant, NPM1 Mutant Subtotal:	en subgroups: $\chi^2_2$ = 0-4; P 144/456 32/99 176/555 en subgroups: $\chi^2$ 132/380 40/163 172/543 en subgroups: $\chi^2$ 120/246 20/99 12/34 20/64 172/443	= 8·6; P = 0·01 = 0·5; NS 118/450 41/99 <b>159/549</b> = 4·7; P = 0·03 122/394 34/150 <b>156/544</b> = 0·0; P = 1·0; N: 101/350 14/95 21/44 20/55 <b>156/544</b>	17-8 -5·5 12-3 11-4 3·1 14-5 5 14-1 3·9 -2-8 -2·1 13-1	65·3 18·1 <b>83·5</b> 63·3 18·5 <b>81·7</b> 55·1 8·4 8·0 9·9	_		2P = 0-2; NS 1.31 (1.03, 1.67) 0.74 (0.47, 1.17) 1.16 (0.94, 1.44 2P = 0-2; NS 1.20 (0.94, 1.53) 1.18 (0.75, 1.87) 1.19 (0.96, 1.48 2P = 0-1; NS 1.59 (0.91, 1.68) 1.59 (0.91, 1.13) 0.70 (0.35, 1.40) 0.81 (0.43, 1.51)
Test for H Test for t FLT3 ITC ITD WT ITD Muta Test for H NPM1 W NPM1 W NPM1 M Test for H ITD/NPM ITD WT, ITD WT, ITD Muta	heterogeneity betwee trend between subgro D: subtotal: heterogeneity betwee utation: /T subtotal: heterogeneity betwee f: NPM1 WT NPM1 Mutant ant, NPM1 Mutant	en subgroups: $\chi^2_2$ = 0-4; P 144/456 32/99 176/555 en subgroups: $\chi^2$ 132/380 40/163 172/543 en subgroups: $\chi^2$ 120/246 20/99 12/34 20/64 172/443	= 8·6; P = 0·01 = 0·5; NS 118/450 41/99 <b>159/549</b> = 4·7; P = 0·03 122/394 34/150 <b>156/544</b> = 0·0; P = 1·0; N: 101/350 14/95 21/44 20/55 <b>156/544</b>	17-8 -5·5 12-3 11-4 3·1 14-5 5 14-1 3·9 -2-8 -2·1 13-1	65·3 18·1 <b>83·5</b> 63·3 18·5 <b>81·7</b> 55·1 8·4 8·0 9·9	_		2P = 0.2; NS 1.31 (1.03, 1.67) 0.74 (0.47, 1.17) 1.16 (0.94, 1.44 2P = 0.2; NS 1.20 (0.94, 1.53) 1.18 (0.75, 1.87) 1.19 (0.96, 1.48 2P = 0.1; NS 1.59 (0.81, 3.13) 0.70 (0.35, 1.40) 0.81 (0.43, 1.51) 1.18 (0.95, 1.46
Test for H Test for t FLT3 ITC ITD WT ITD Muta Test for H NPM1 W NPM1 W NPM1 M Test for H ITD/NPM ITD WT, ITD WT, ITD Muta	heterogeneity betwee rend between subgro D: Subtotal: heterogeneity betwee utation: /T utant Subtotal: heterogeneity betwee f: NPM1 WT NPM1 Mutant ant, NPM1 Mutant ant, NPM1 Mutant Subtotal:	en subgroups: $\chi^2_2$ = 0-4; P 144/456 32/99 176/555 en subgroups: $\chi^2$ 132/380 40/163 172/543 en subgroups: $\chi^2$ 120/246 20/99 12/34 20/64 172/443	= 8·6; P = 0·01 = 0·5; NS 118/450 41/99 <b>159/549</b> = 4·7; P = 0·03 122/394 34/150 <b>156/544</b> = 0·0; P = 1·0; N: 101/350 14/95 21/44 20/55 <b>156/544</b>	17-8 -5·5 12-3 11-4 3·1 14-5 5 14-1 3·9 -2-8 -2·1 13-1	65·3 18·1 <b>83·5</b> 63·3 18·5 <b>81·7</b> 55·1 8·4 8·0 9·9		↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓	2P = 0.2; NS 1.31 (1.03, 1.67) 0.74 (0.47, 1.17) 1.16 (0.94, 1.44 2P = 0.2; NS 1.20 (0.94, 1.53) 1.18 (0.75, 1.87) 1.19 (0.96, 1.48 2P = 0.1; NS 1.29 (0.99, 1.68) 1.59 (0.81, 3.13) 0.70 (0.35, 1.40) 0.81 (0.43, 1.51) 1.18 (0.95, 1.46

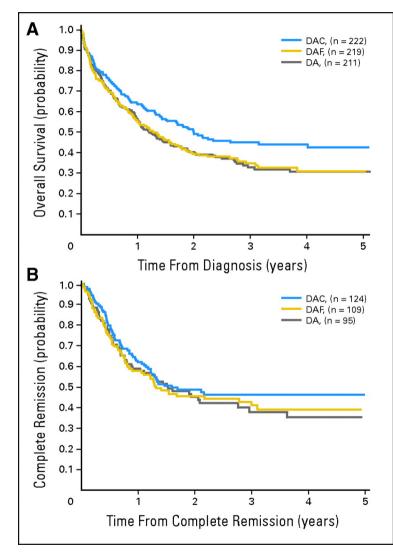
#### AML17 FLT3 Mutants: Dauno 90 vs. 60: Update



## Addition of a Third drug

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

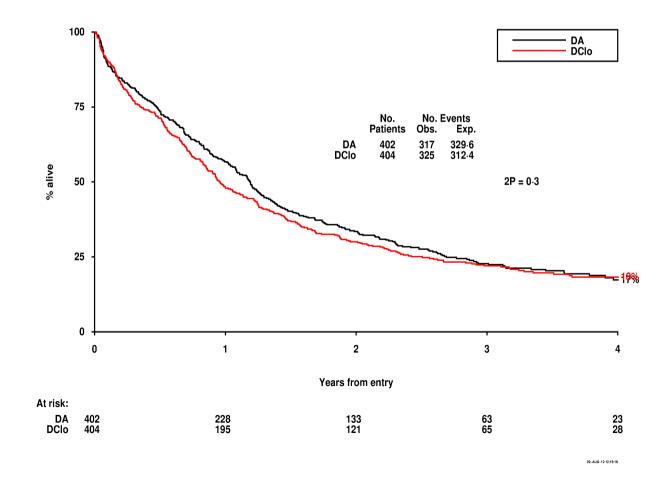
#### Addition of Cladrabine to DA: (A) overall and (B) leukemiafree survival.



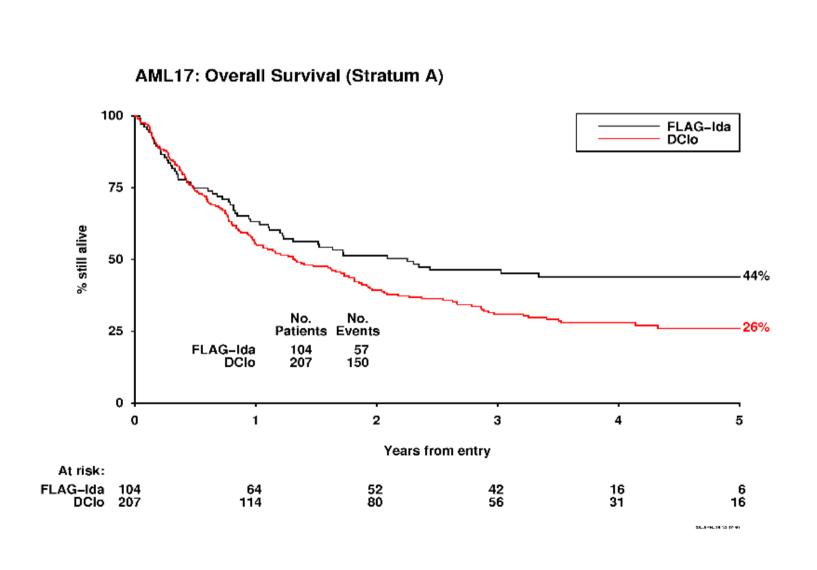
Holowiecki J et al. JCO 2012;30:2441-2448

## DA vs D-Clofarabine OS (n=806)

AML16 Intensive: Survival by DA/DClo randomisation

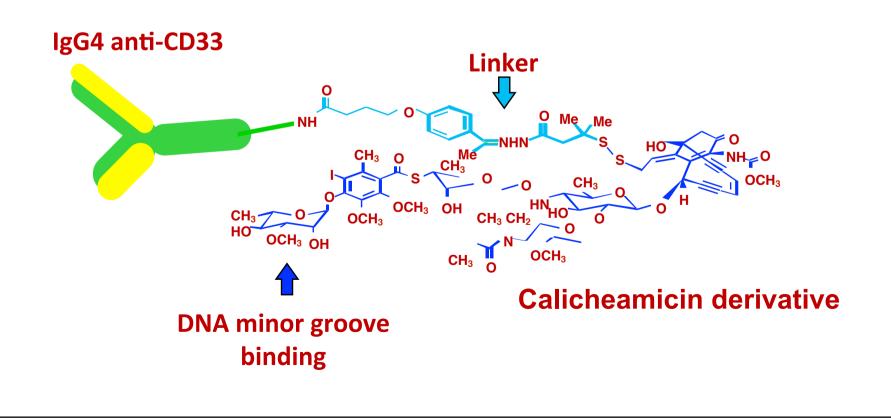


## **DClo vs FLAG-Ida for high risk**



## Mylotarg<sup>®</sup> (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/m <sup>2</sup> d1	ADE,DA, FLAG-Ida	1099	50 (15-71)	All
NCRI AML16	5 mg/m- ui	DA, DClo	1115	67 (51-84)	All
SWOG-0106	$G m g / m^2 d A$	DA (3+7)	595	47 (18-60)	All
GOELAMS AML2006/IR	6 mg/m <sup>2</sup> d4	DA (3+7)	238	50.5 (18-60)	Inter
ALFA-0701	3 mg/m <sup>2</sup> d1,4,7	DA (3+7)	278	62 (50-70)	Inter/Adv

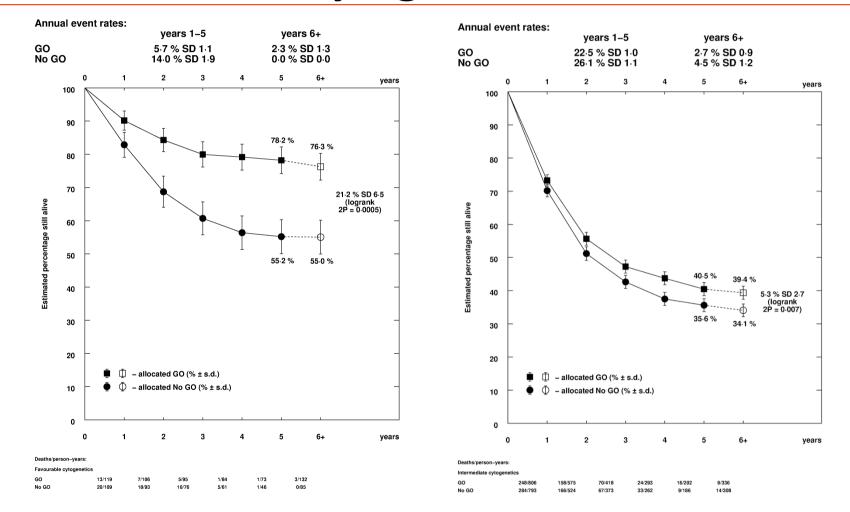
Hills RK et al. Lancet Oncol.

## **Results: Survival post remission**

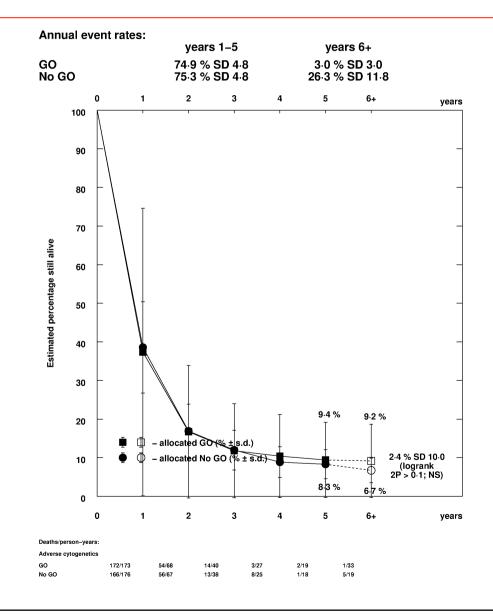
#### Meta-Analysis of Trials of GO in induction Survival from remission

Trial	Events/ GO	Patients No GO	Sta (O–E)	tistics Var.	H.R. & 95% (GO : No (		
3mg/m2 single dose:							
MRC AML15	244/474	277/484	-21·2	130.1	-	0.85 (0.72, 1.01)	
NCRI AML16	284/396	289/376	-27.4	141.7	-	0.82 (0.70, 0.97)	
Subtotal:	528/870	566/860	-48.6	271.8	♦	0.84 (0.74, 0.94) 2P = 0⋅003	
Test for heterogeneity b	etween trials	$\chi^2_1 = 0.1; P$	= 0·8; NS	6			
3mg/m2 fractionated:							
ALFA 0701	35/113	42/104	-9.4	18.6		0.61 (0.38, 0.95)	
Subtotal:	35/113	42/104	<b>-9</b> ·4	18.6		0.61 (0.38, 0.95) 2P = 0⋅03	
6mg/m2 dose:							
GOELAMS AML2006 IR	33/109	39/102	-4·0	18.0		0.80 (0.50, 1.27)	
SWOG 0106	94/222	91/222	2.2	46.2		1.05 (0.79, 1.40)	
Subtotal:	127/331	130/324	-1·8	64-2		0.97 (0.76, 1.24) 2P = 0⋅8; NS	
Test for heterogeneity between trials: $\chi_1^2 = 1.0$ ; P = 0.3; NS							
Total:	690/1314	738/1288	-59.8	354.6	$\Phi$	0.84 (0.76, 0.94)	
Test for heterogeneity (5 Test for heterogeneity b				0.0		1.5 2.0 No GO better 001	

## **Overall Survival: Favourable, Intermediate Cytogenetics**



### **Overall Survival: Adverse**

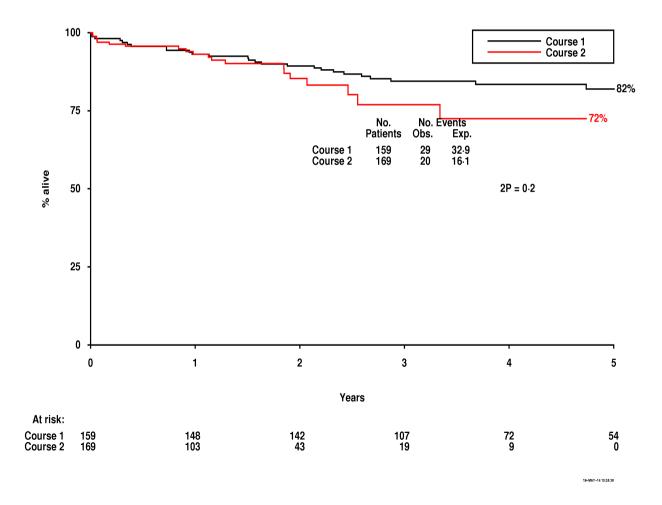


## **CBF Subset: Results of regression analysis**

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?

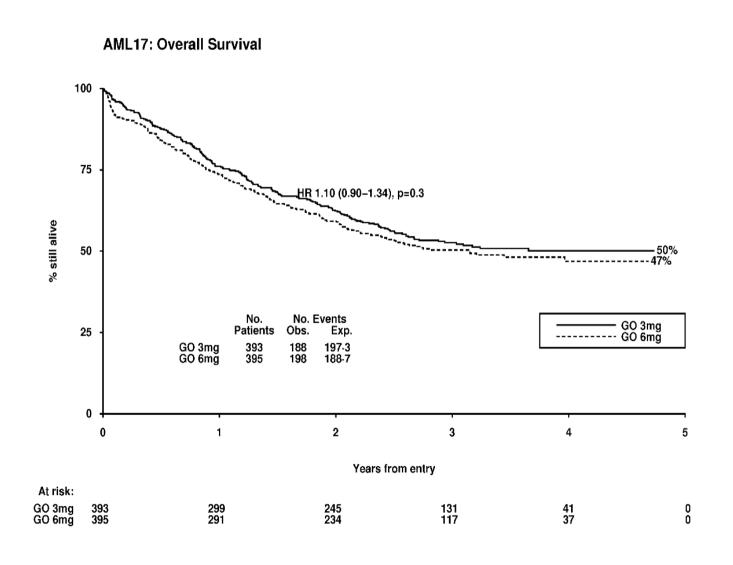
AML15,17: CBF – Survival by intended course for GO



## **Mylotarg: Remaining Issues**

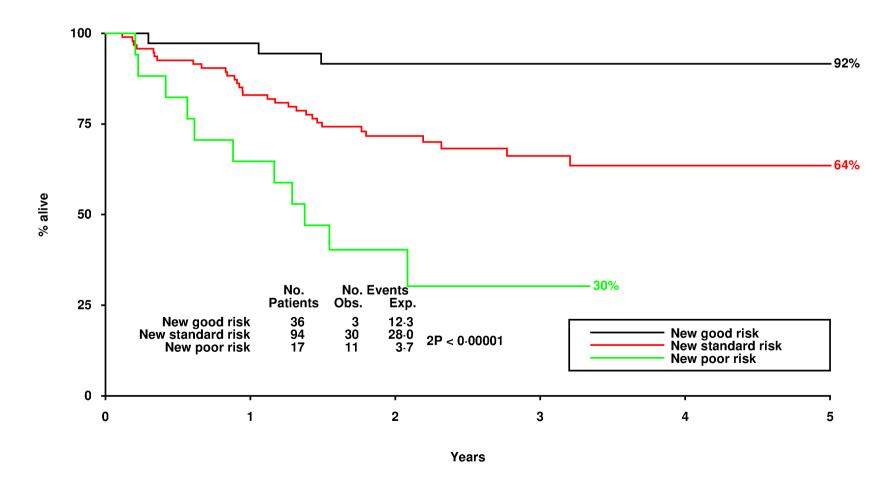
- Optimum dose
- Schedule
- Use in consolidation
- Use in APL
- Availability/ approval

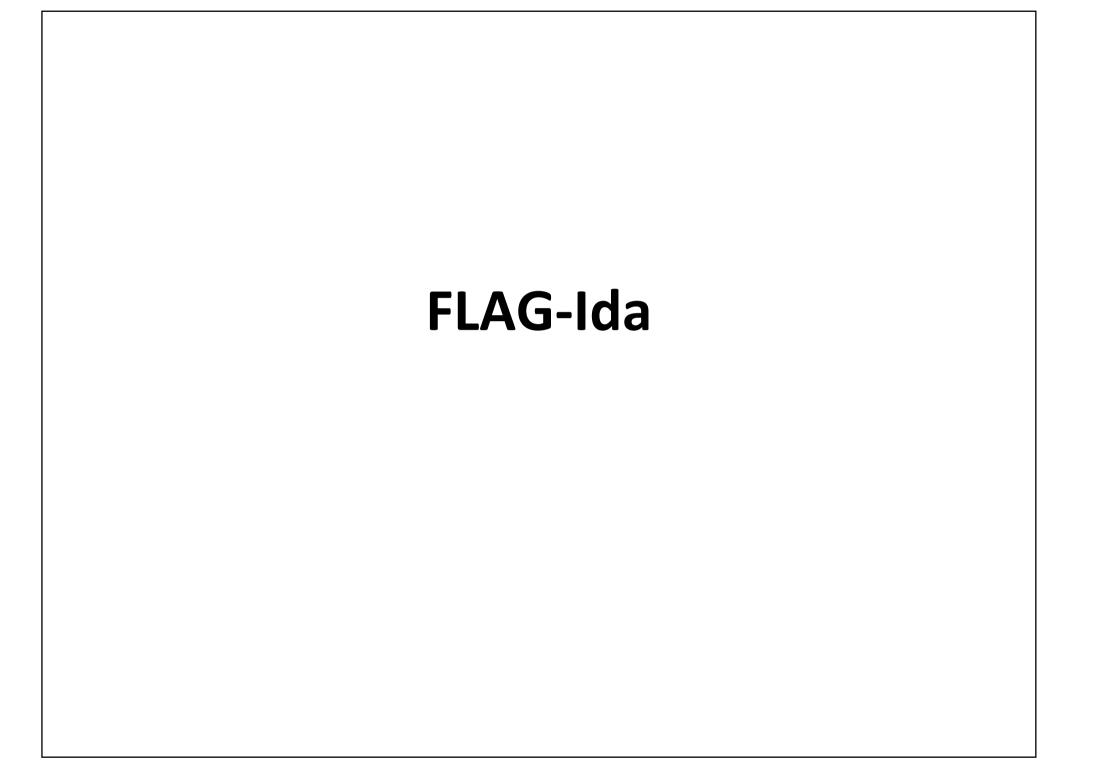
## AML17: GO 6mg vs 3mg (n=788)



### **Role for Transplant? The Mylotarg Impact**

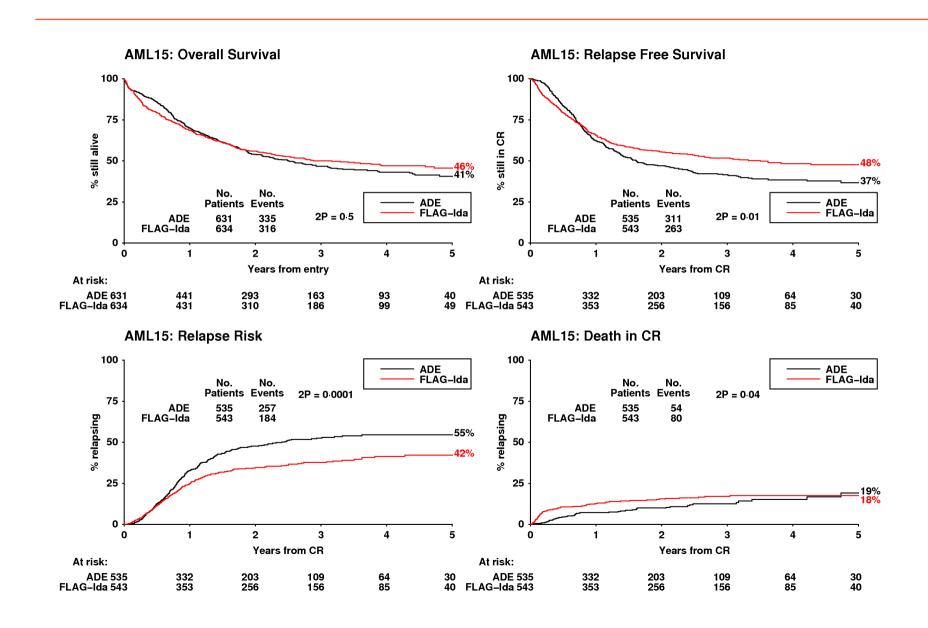
MRC AML 15 adults: Survival from CR (Mylotarg age<45)





AML 15 Patients <60 yrs: Remission Rates				
DA vs	ADE	ADE vs FLAG-Ida		DA(90)
78	82	81	84	71
63	69	67	77	59
81	84	83	<b>92</b>	83
	<b>DA vs</b> 78 63	DA vs       ADE         78       82         63       69	Rates         DA vs ADE       ADE vs F         78       82       81         63       69       67	Rates         DA vs ADE       ADE vs FLAG-Ida         78       82       81       84         63       69       67       77

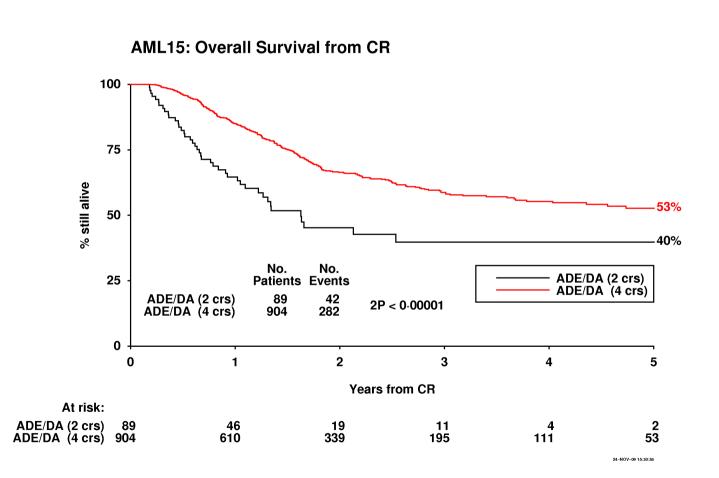
### **ADE vs FLAG-Ida**



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

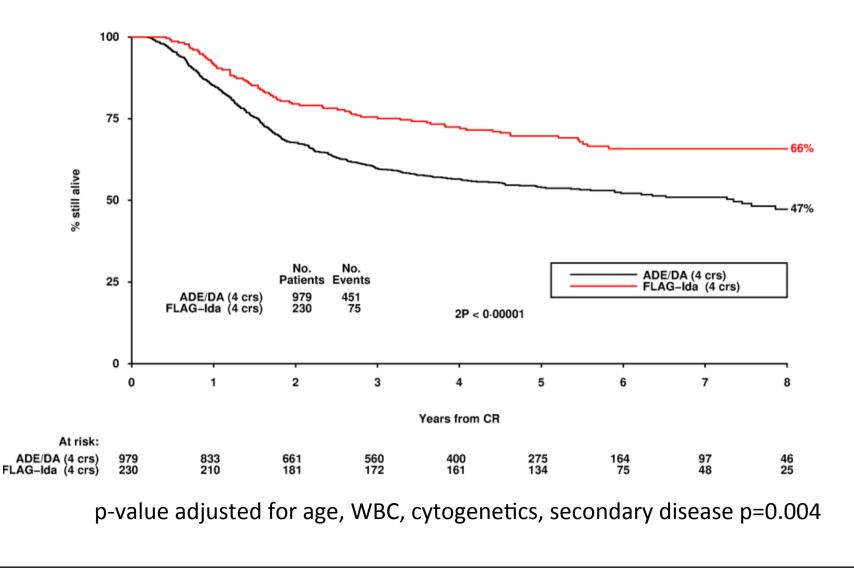
AML15: Overall Survival from CR % still alive 58% 53% No. No. FLAG-Ida (2 crs) ADE/DA (4 crs) Patients Events FLAG-Ida (2 crs) 2P = 0.5 ADE/DA (4 crs) Years from CR At risk: <sup>-</sup>LAG–Ida (2 crs) 54 ADE/DA (4 crs) 904 24-NOV-09 15:30:38

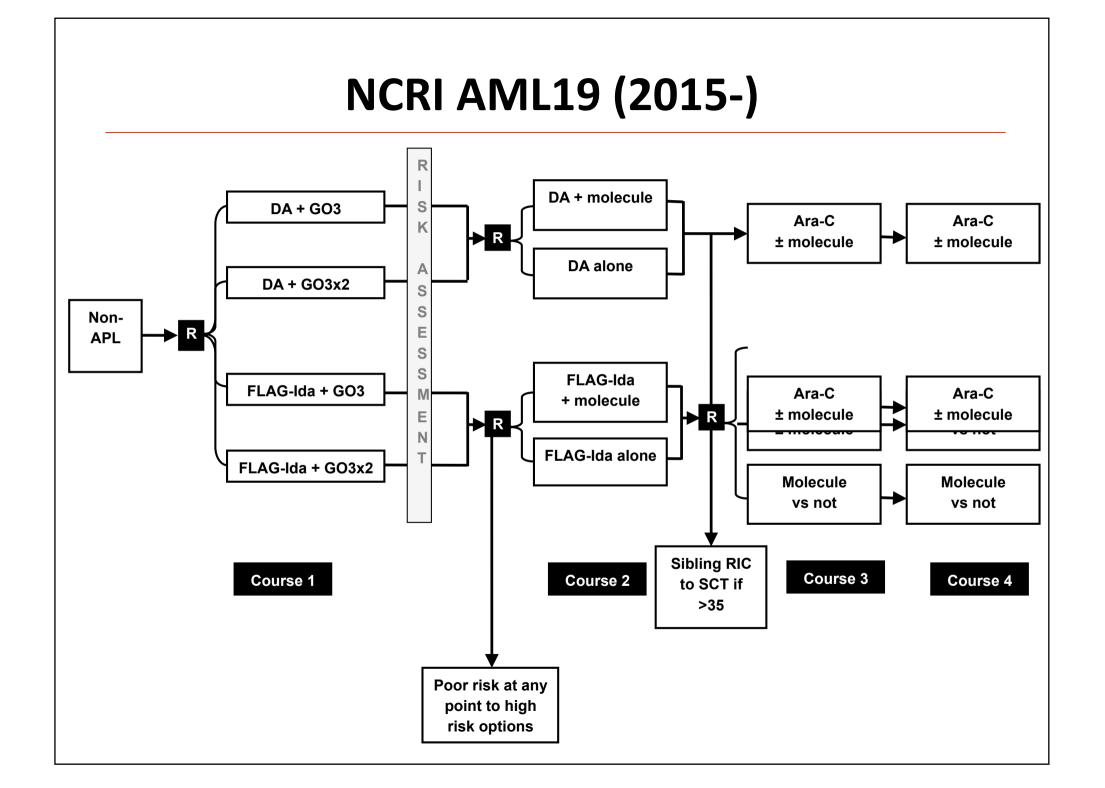
## 2 or 4 courses? ADE/DA



#### ADE/DA vs FLAG-Ida – 4 courses

AML15: Overall Survival from CR



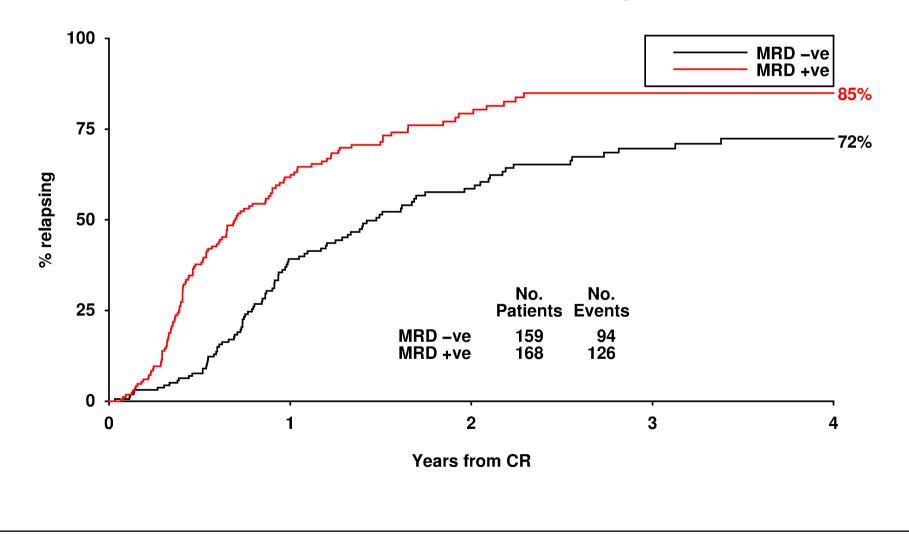


## **Implementation of MRD**

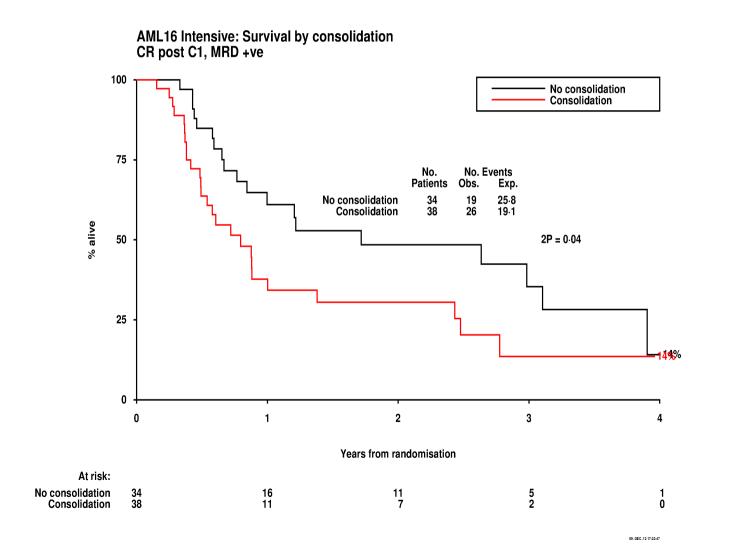
- Specificity and sensitivity
- ? Does it tell us more than we already know.
- Is it prognostic or is it predictive?
- Is it treatment dependent?
- What are the indirect costs?
- "monitor vs no monitor"

## **MRD: Cumulative Incidence of Relapse**

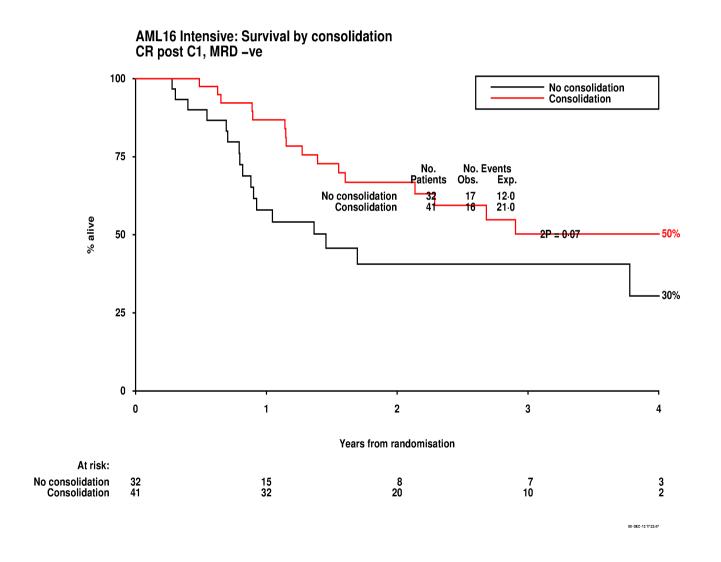
AML16 Intensive: Cumulative Incidence of Relapse

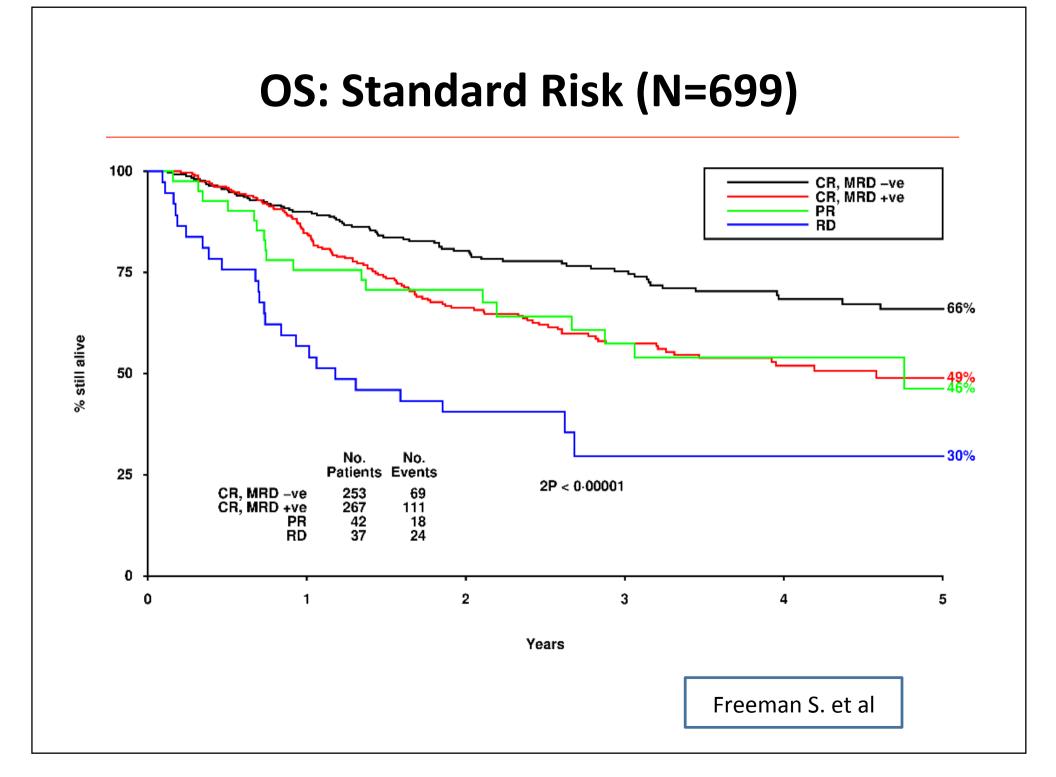


## Addition of Consolidation in MRD +ve

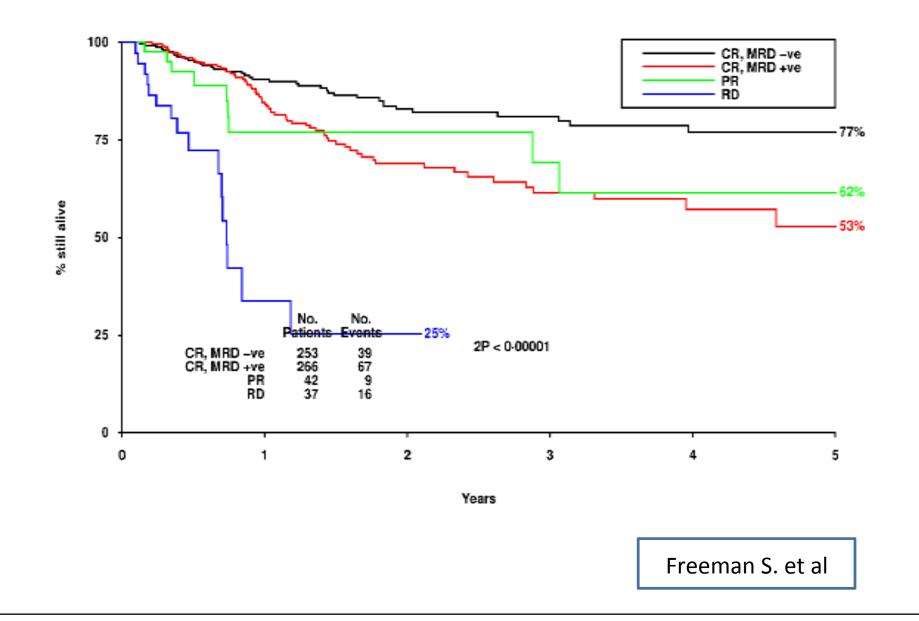


#### Addition of Consolidation in MRD-ve





## **OS Standard Risk Censored at SCT**



## 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