Should we use GO in intermediate-risk AML patients? NO

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Disclosures of Lorenzo Brunetti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						X	
Abbvie						X	

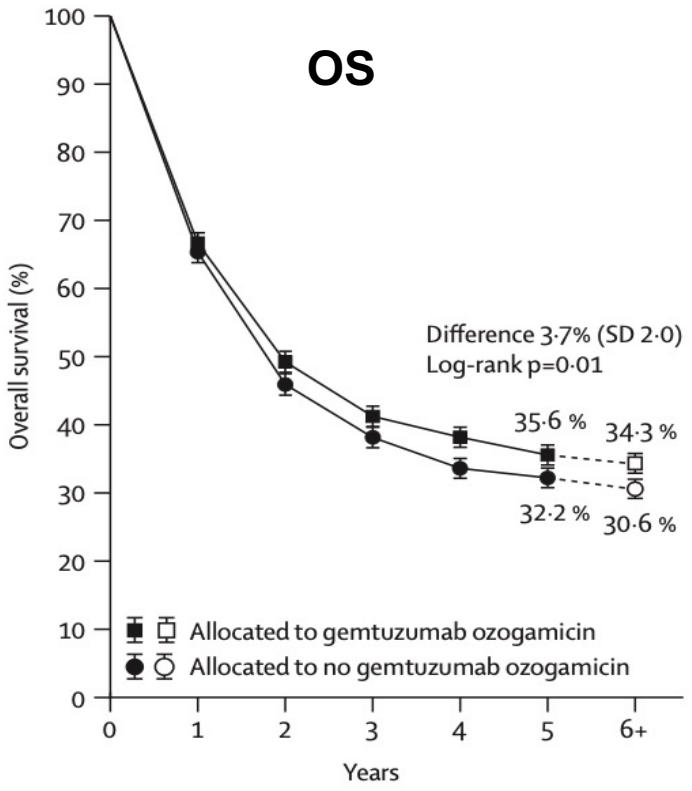
GO in AML: the Hills metanalysis

Five randomized controlled studies
~3000 individual patients
Different cohorts and GO doses

<u>3 mg/m^2 single dose</u>
MRC AML 15 (18-60y)
MRC AML 16 (unfit for HDAC ~50-80y)

<u>3 mg/m^2 fractionated</u>
ALFA-0701 (50-70y)*

<u>6 mg/m^2 dose</u>
SWOG 0106 (18-60y)
GOELAMS 2006 IR (18-60y)



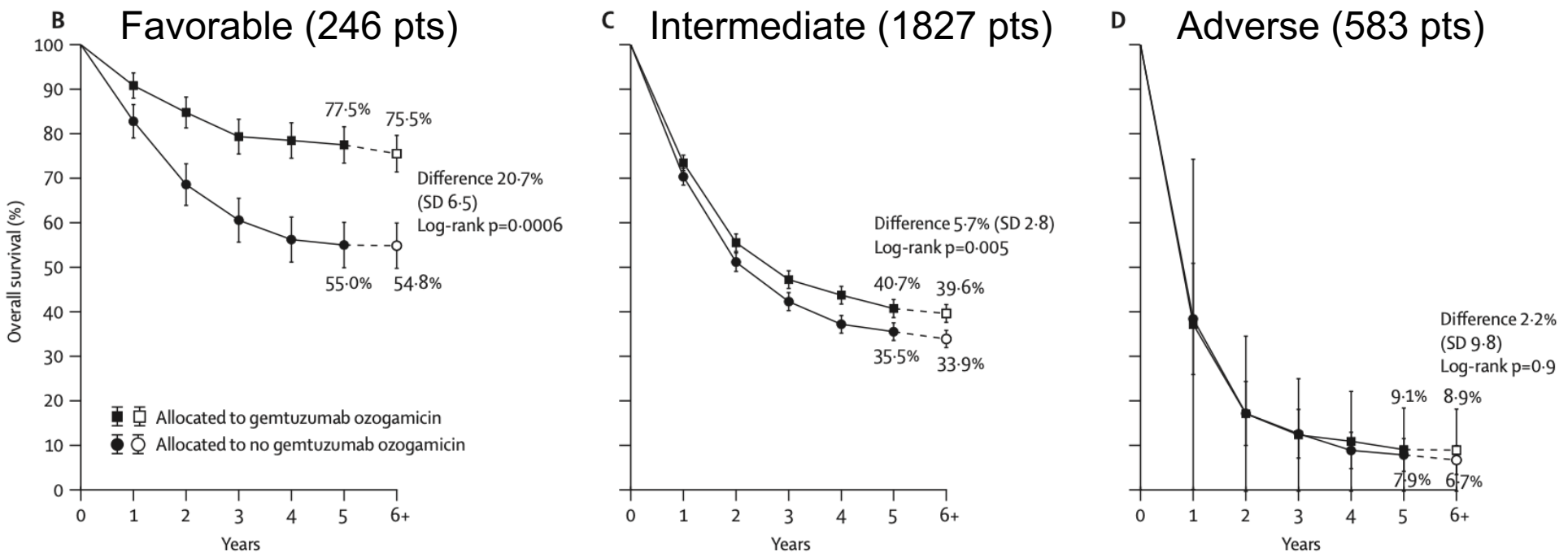
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	26·7 % SD 0·8	3·5 % SD 0·8
No gemtuzumab ozogamicin	29·5 % SD 0·9	5·2 % SD 1·0

*OS data not updated despite longer FU

Hills, et al. Lancet Oncol 2014

GO in AML: the Hills metanalysis

Overall survival



Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	22·4% SD 1·0	2·7% SD 0·9
No gemtuzumab ozogamicin	26·2% SD 1·1	4·9% SD 1·3

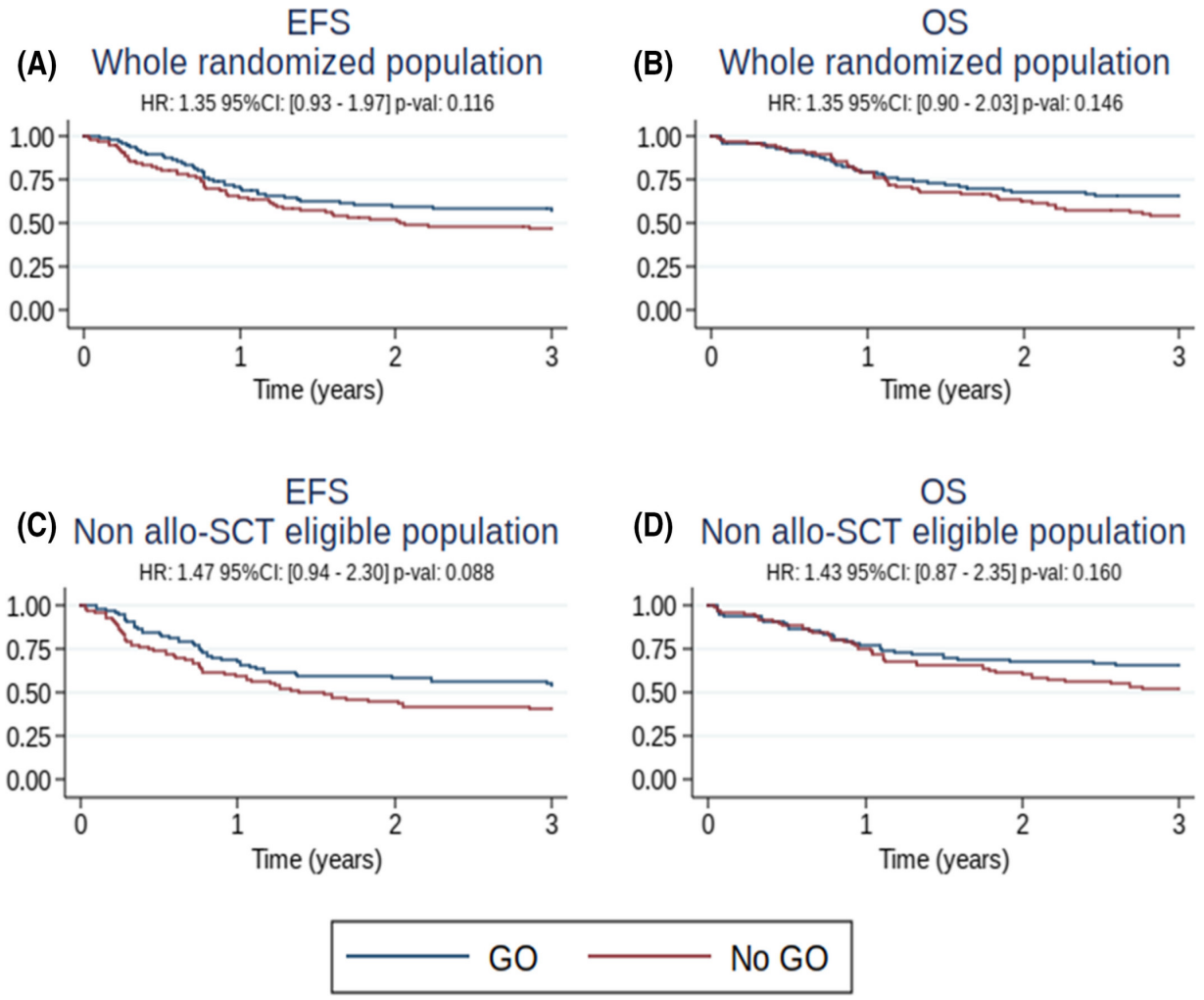
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	73·8% SD 4·6	2·4% SD 2·4
No gemtuzumab ozogamicin	76·7% SD 4·8	21·1% SD 10·5

Hills, et al. Lancet Oncol 2014

Any randomized study in intermediate cytogenetics?

GOELAMS/FILO AML 2006 IR (included in the Hills metanalysis)

- 236 patients randomized, primary endpoint EFS
- Intermediate-risk cytogenetics
- Age 18-60
- Treatment
  - Ind: 3+7 ± GO 6mg/m^2 d4
  - Cons: Intensive for non allo; non-intensive for allo
- 33% underwent allo
- <u>No difference in EFS nor OS</u>
- Early stop for safety signals (7 early deaths)



Bouvier, et al. Am J Hematol 2021

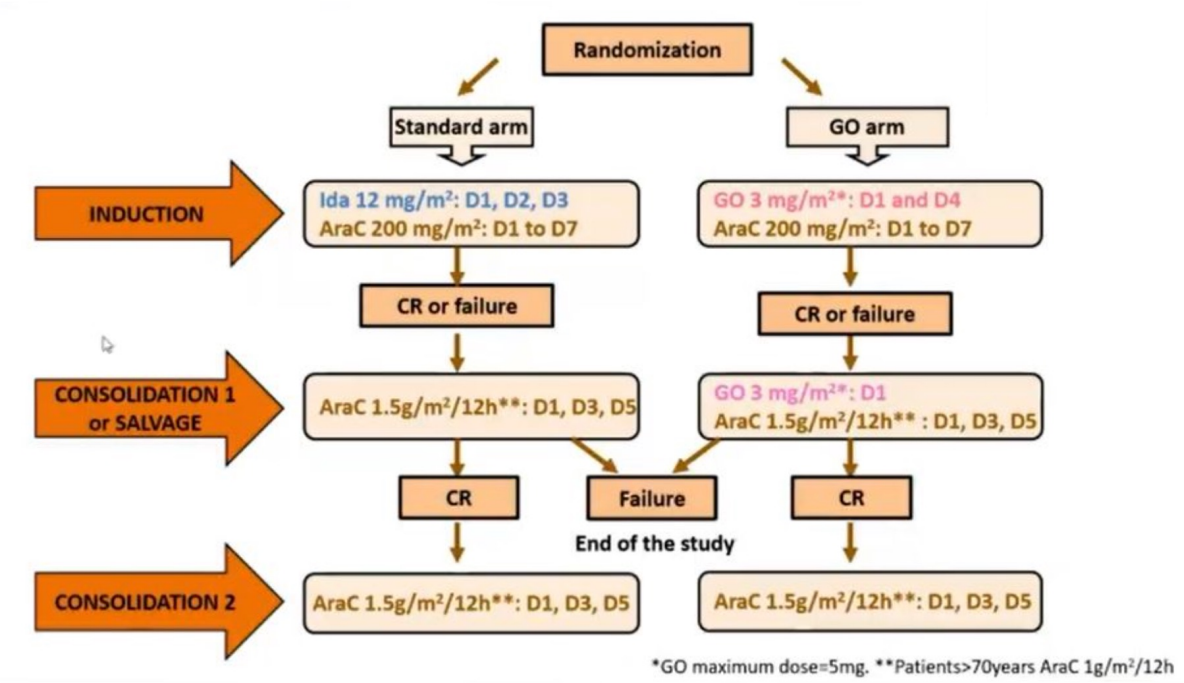
ALFA1401 – GO in intermediate cytogenetics* in older adults (60-80 y)

- 214 patients aged 60-80
- *95% intermediate cytogenetics, 5% favorable

- GO replace IDA in induction 3mg/sqm (max 5mg) d1 and 4
- GO added to consolidation 1 3mg/sqm (max 5 mg) d1

- Randomization 2:1 GO vs standard arm

- Roughly 20% of patients allo-HSCT



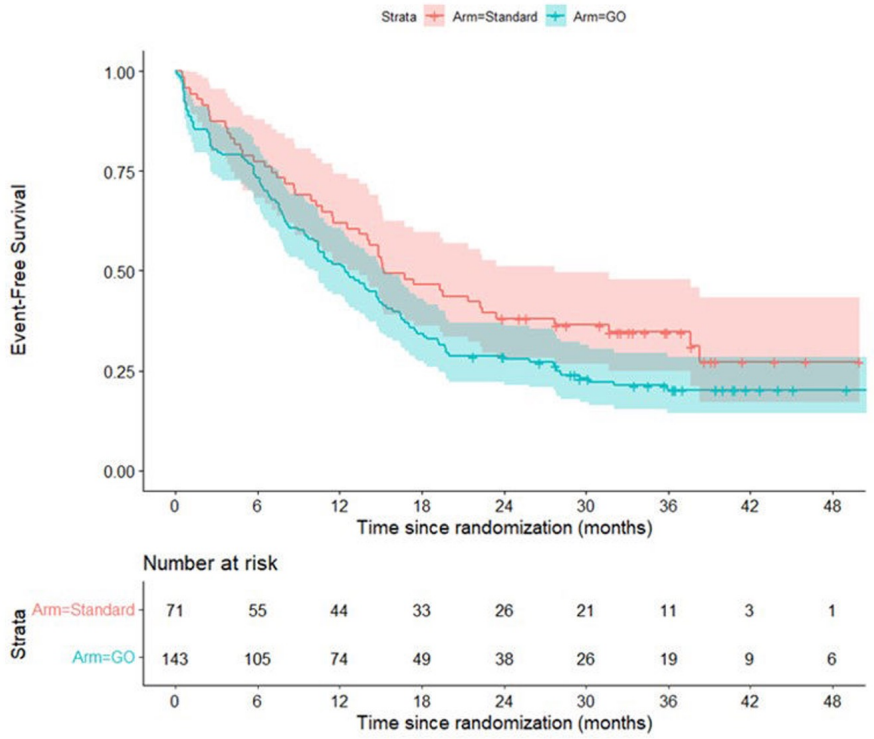
Lambert, et al. ASH 2021

ALFA1401 – MidoFrance 4

- CR/CRp/CRi 90% standard arm vs 82% GO arm
- Estimated 2-y EFS 38% standard arm vs 29% GO arm
- 60-day mortality 4% standard arm vs 10% GO arm
- Grade 3-5 bleeding 7% standard arm vs 29% GO arm
- SAE 34% standard arm vs 49% GO arm

Replacing IDA with GO resulted in lower efficacy and higher toxicity

EFS only, data on OS not available

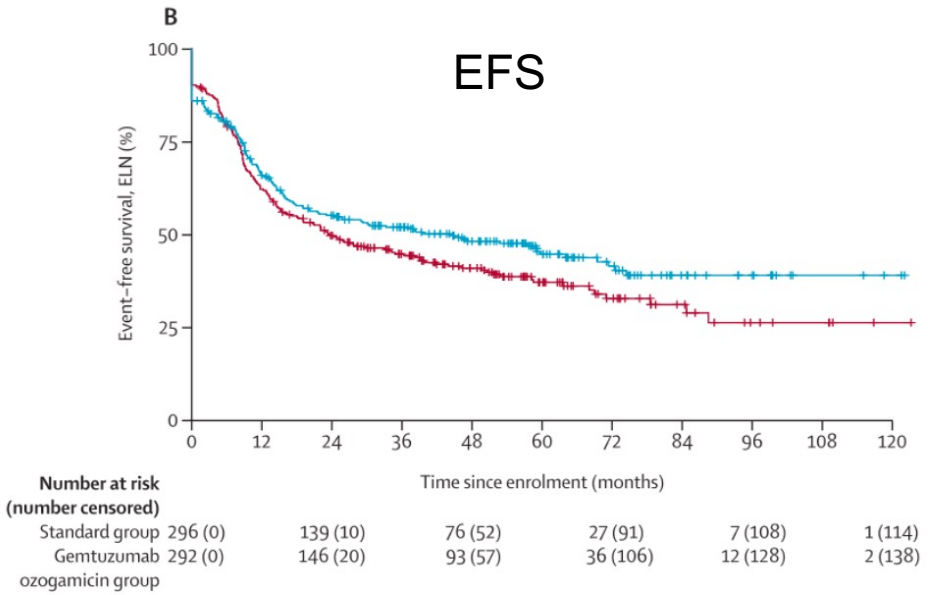


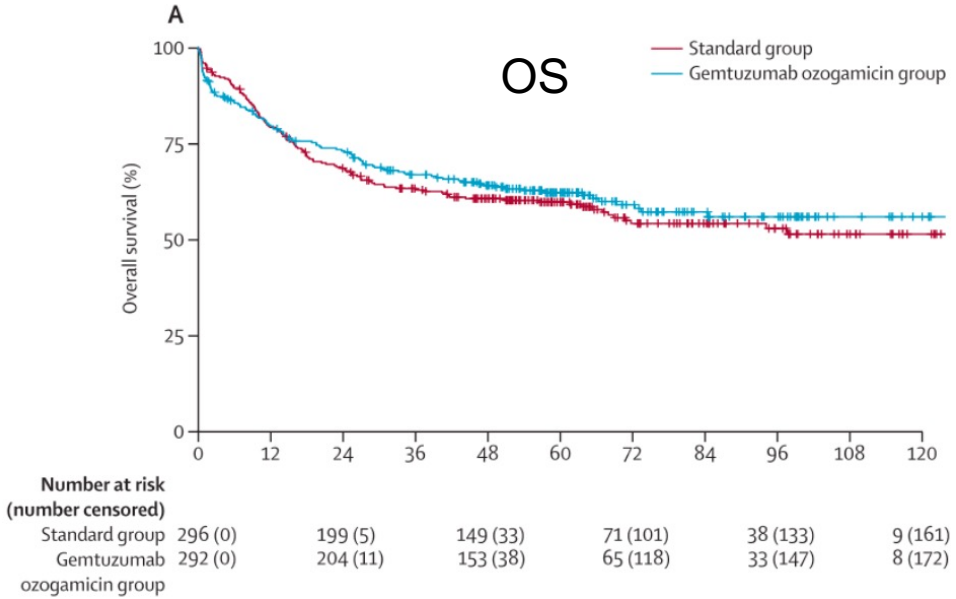
Lambert, et al. ASH 2021

RCT of GO in *NPM1*-mutated patients (AMLSG 09-09): no EFS nor OS benefit

- ICE + ATRA +/- GO (3mg/m2 d1 of inductions and consolidation 1)
- 588 randomized adult patients, no age limit (median 59 y), 18% FLT3-ITD, 91% ELN 2017 Favourable

- **Early stopping at pre-planned interim analysis for futility (primary endpoint: EFS)**





Döhner, et al. Lancet Haematol 2023

Summary 1

- The Hills metanalysis found a significant 5% OS improvement in intermediate cytogenetics with GO
- The two prospective randomized studies in intermediate cytogenetics and the one on *NPM1*-mutated AML have all failed
- Toxicity is an issue

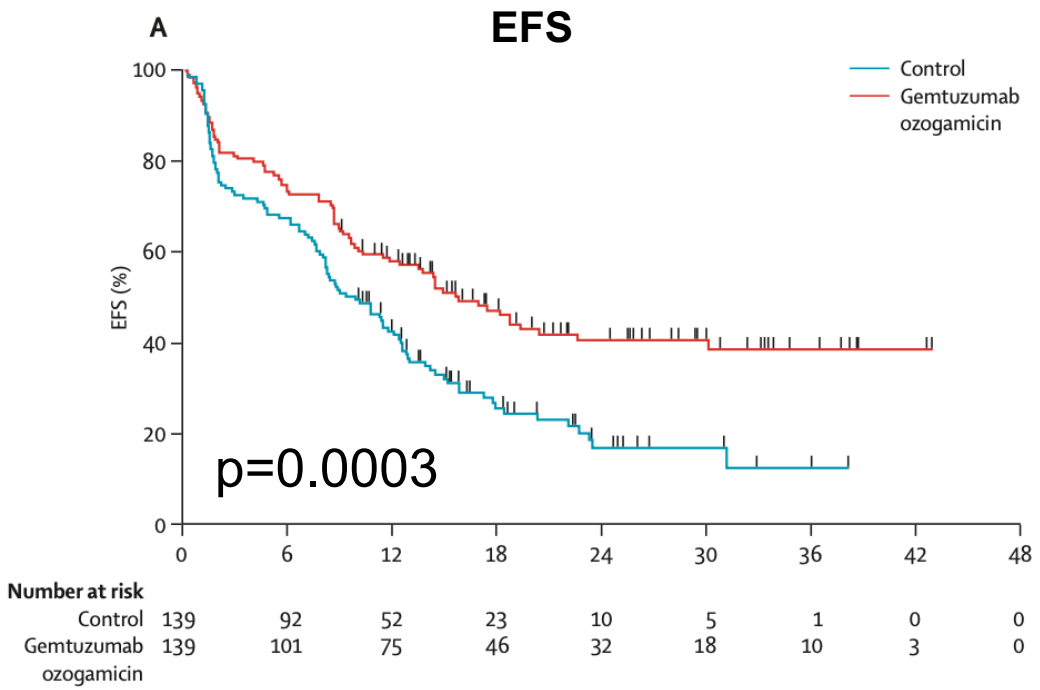
ALFA-0701 study

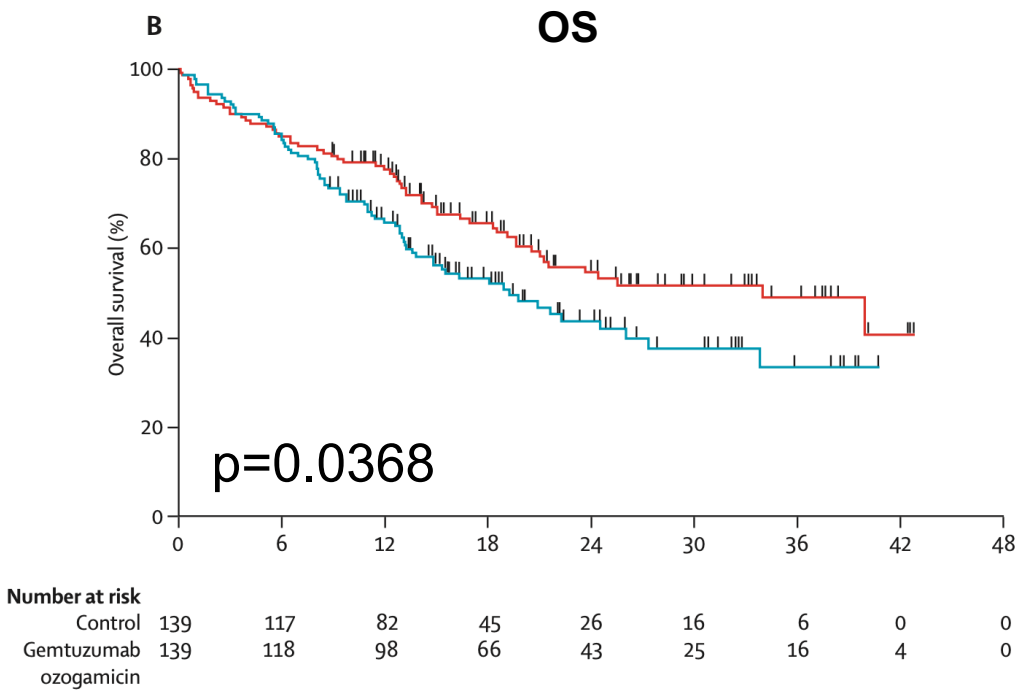
- 280 patients 50-70 y
- 66% intermediate cytogenetics
- Standard chemotherapy +/- GO

- Induction: GO 3 mg/sqm (cap 5 mg) d1, 4, 7
- Consolidation I: GO same dose d1
- Consolidation II: GO same dose d1

- Primary endpoint: EFS
- Secondary endpoint: OS

Initial report of ALFA-0701: improved EFS and OS

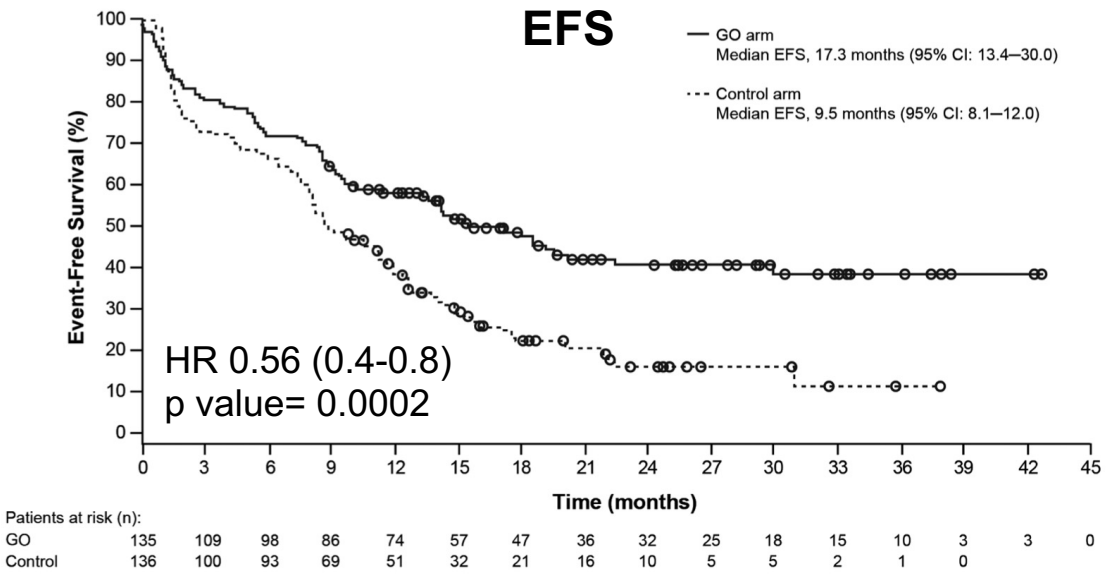


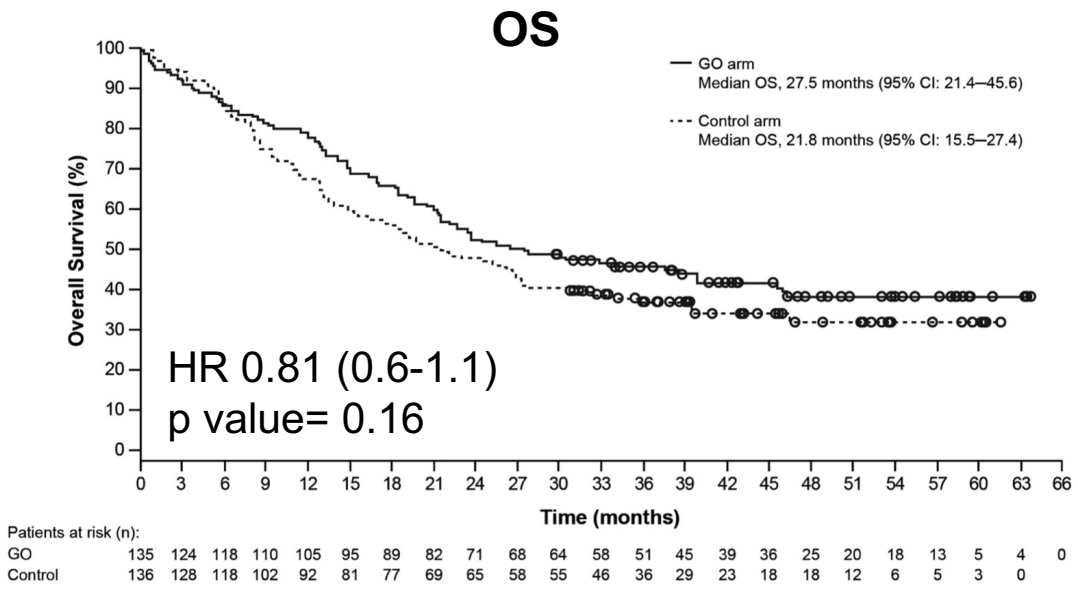


Median follow-up: 14.8 months

Castaigne, et al. Lancet 2012

Longer follow up of ALFA-0701 demonstrated no OS benefit





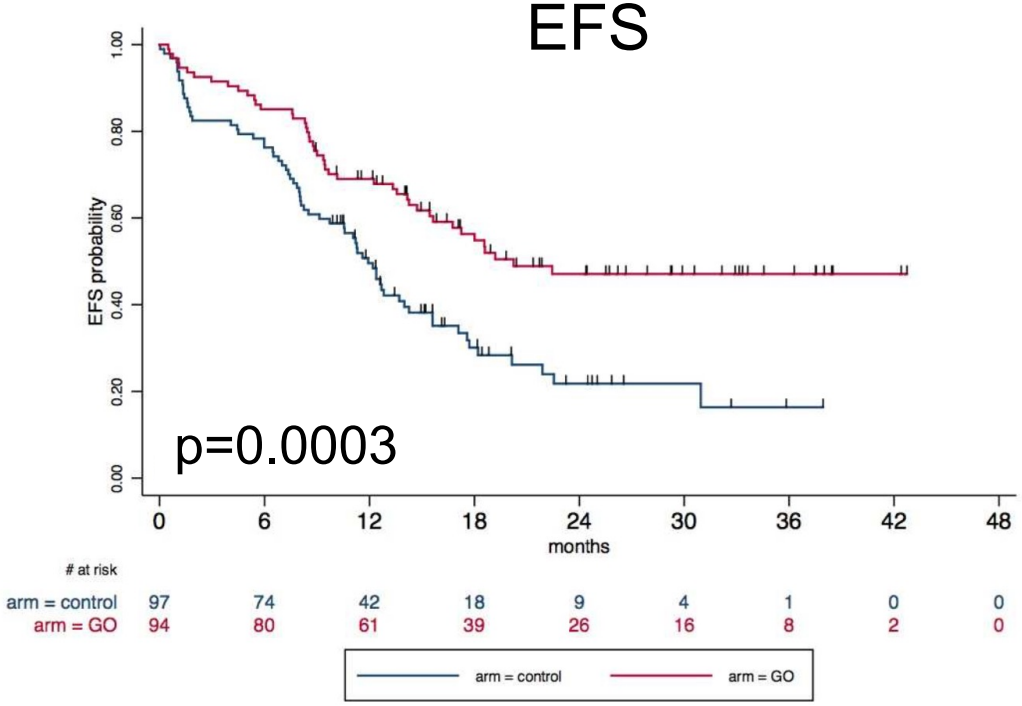
Median follow-up: 14.8 months

Median follow-up: >40 months

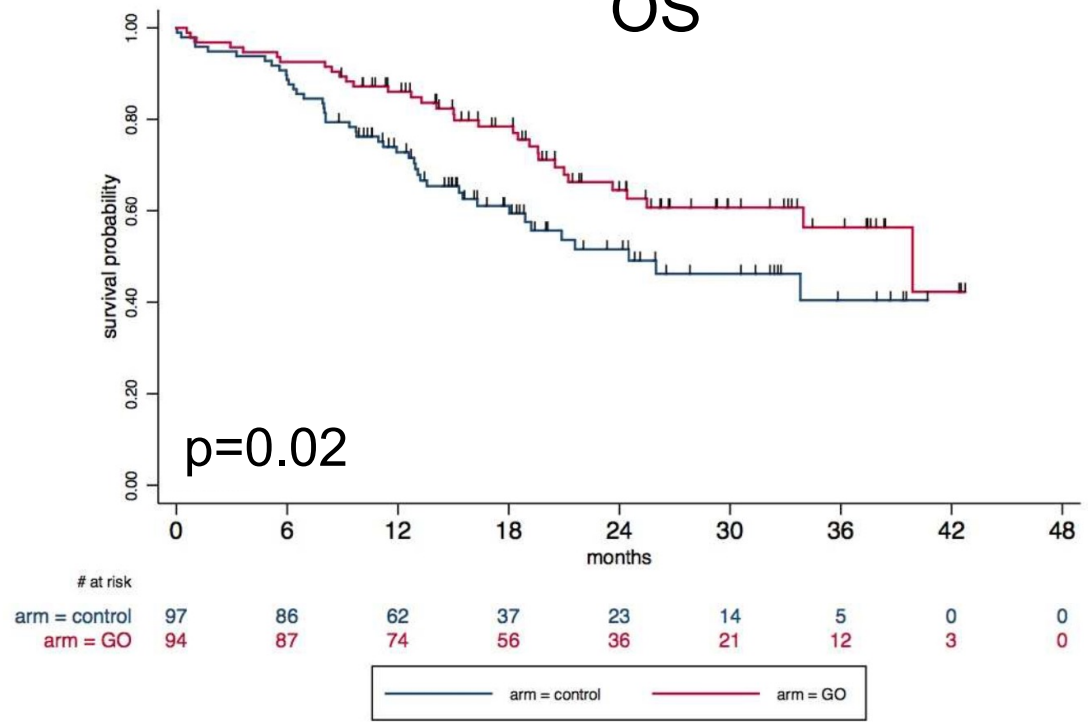
Lambert, et al. Haematologica 2019

ALFA-0701 subgroup analysis on fav/int cytogenetics

EFS



OS



Data on OS not updated with longer follow up in this subgroup

Castaigne, et al. Lancet 2012

Gained antileukemic effects at expense of toxicity (ALFA-0701)

- Permanent discontinuation of GO and/or chemotherapy
  - 31% GO arm
  - 7% control arm
- Persistent thrombocytopenia
  - 20% GO arm
  - 2% control arm

Lambert, et al. Haematologica 2019

Hemorrage is a major concern (ALFA-0701)

	GO (n=131)	Control (n=137)
All grades	118 (90)	107 (78)
Grade 3	23 (18)	12 (9)
Grade 4-5	7 (5)	1 (1)

Lambert et al Haematologica 2019

MRC AML15 and AML16 trials

- Intensive chemotherapy +/- GO
- AML15 ~1100 patients fit for high-dose ARA-C (~18-60y)
- AML16 ~1100 patients fit for chemo but unfit for high-dose ARA-C (~50-80y)

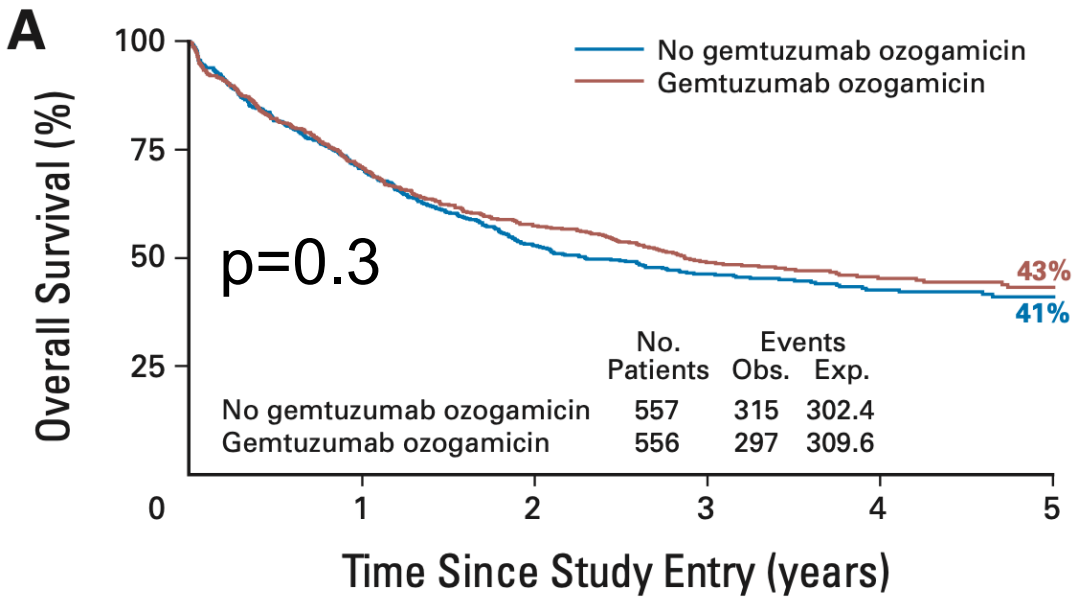
- In both studies GO 3 mg/sqm day 1 of first induction only

- Cytogenetics available for about 50% of patients in AML15 and the majority of patients in AML16

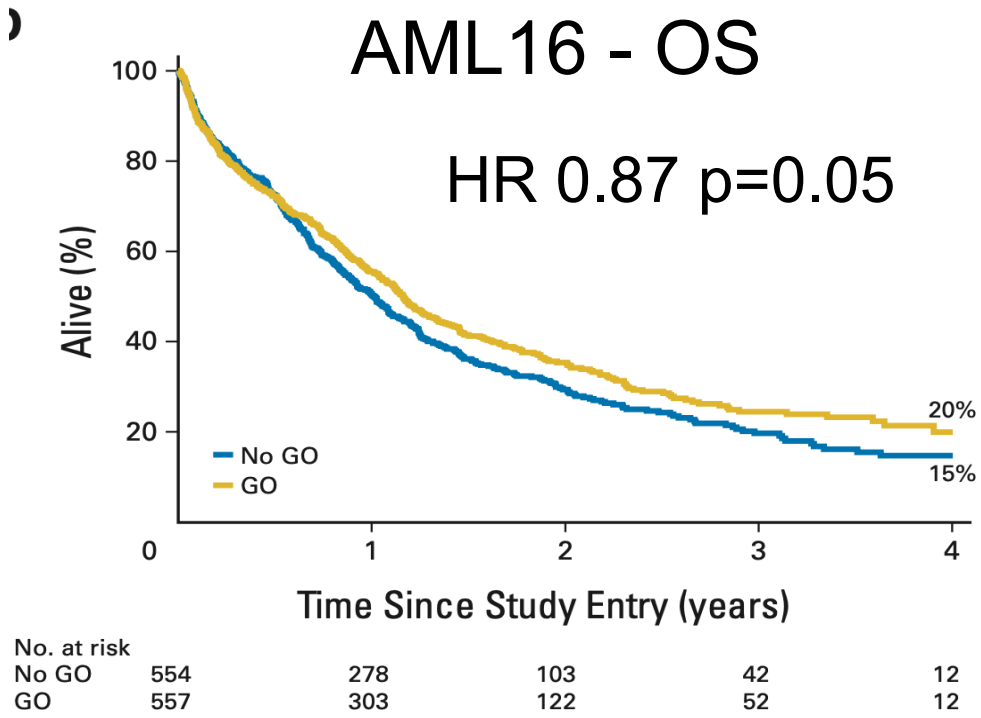
- Transplant in CR1 in <20% of patients in AML15, 8% in AML16

OS benefit (small) only in AML16 in the whole cohort

AML15 - OS



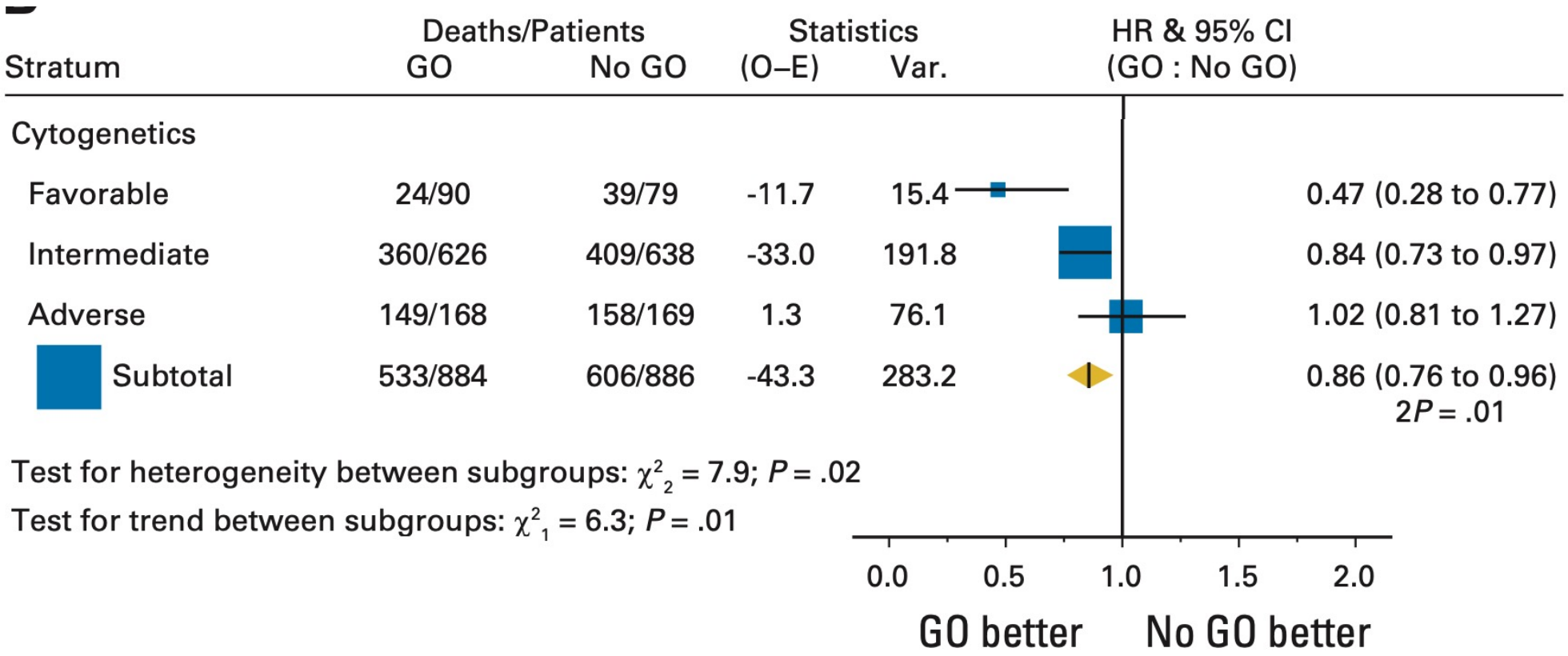
AML16 - OS



Burnett et al JCO 2011

Burnett et al JCO 2012

Metanalysis of AML15 and AML16 suggests improved OS for intermediate cytogenetics*



*Single dose in induction only!

Burnett et al JCO 2012

Summary 2

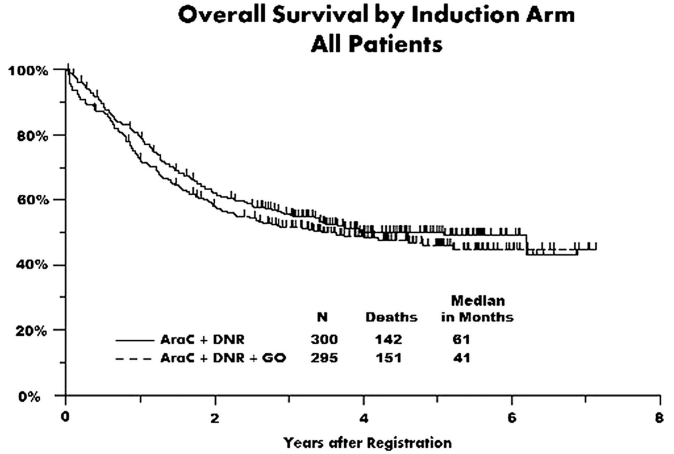
- There are insufficient evidences for the use of fractionated GO in patients with intermediate cytogenetics

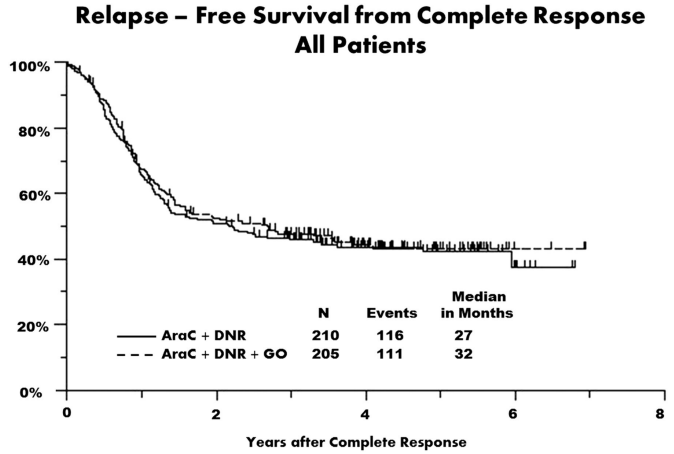
- More solid data with GO single dose in induction (AML15 and AML16)
  - OS benefit
  - No safety issues

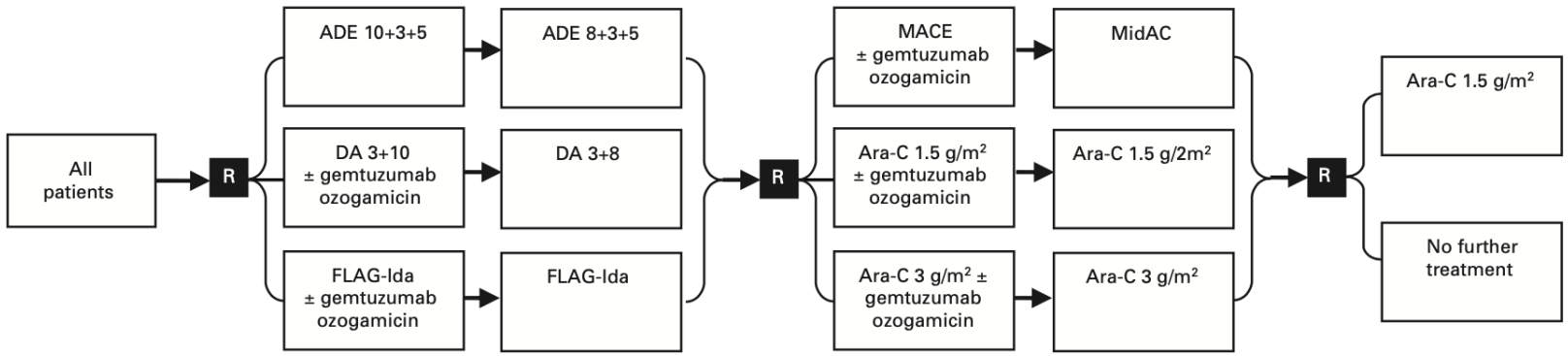
- Availability of updated OS data in the fav/int cytogenetics

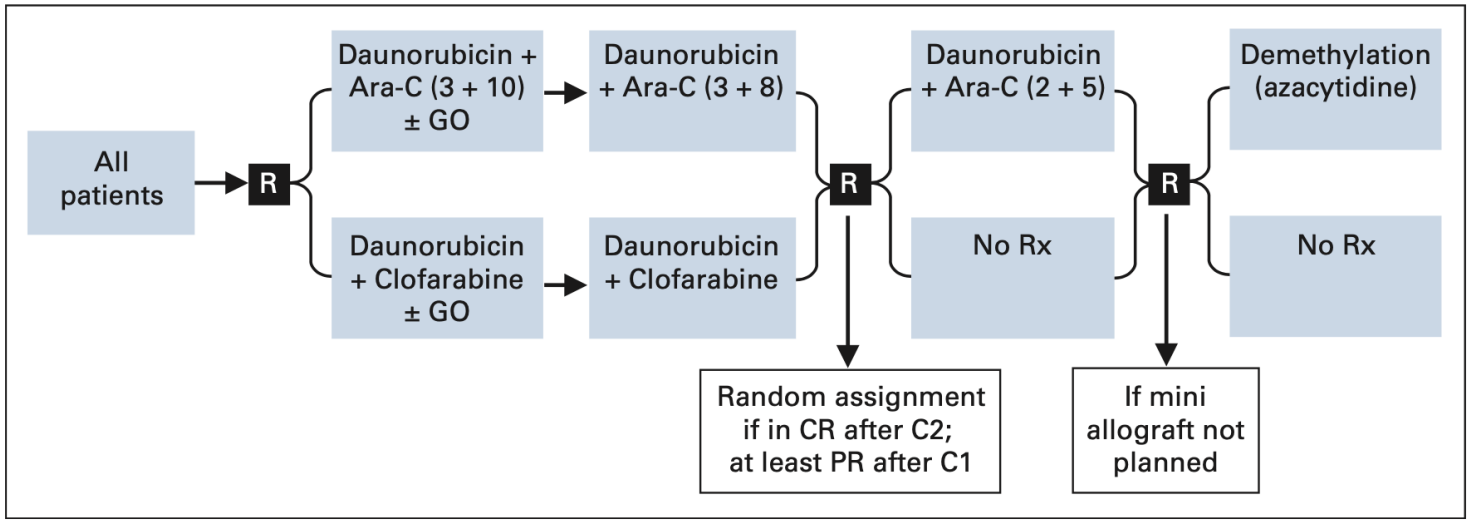
SWOG S0106 (included in the Hills metaanalysis)

- 637 pt randomized, 595 treated, primary endpoint CR rate
- Age: 18-60
- Treatment:
  - 7+3 (60 mg/sqm) vs 7+3 (45 mg/sqm) + GO 6 mg/sqm d4
  - Consolidation: HiDAC 3 cycles
- No difference in CR rate, RFS, OS
- Early termination for increased early death in the GO arm






All patients
R
ADE 10+3+5
ADE 8+3+5
DA 3+10 ± gemtuzumab ozogamicin
DA 3+8
FLAG-Ida ± gemtuzumab ozogamicin
FLAG-Ida
R
MACE ± gemtuzumab ozogamicin
MidAC
Ara-C 1.5 g/m² ± gemtuzumab ozogamicin
Ara-C 1.5 g/2m²
Ara-C 3 g/m² ± gemtuzumab ozogamicin
Ara-C 3 g/m²
R
Ara-C 1.5 g/m²
No further treatment


All patients
R
Daunorubicin + Ara-C (3 + 10) ± GO
Daunorubicin + Ara-C (3 + 8)
Daunorubicin + Clofarabine ± GO
Daunorubicin + Clofarabine
R
Daunorubicin + Ara-C (2 + 5)
No Rx
R
Demethylation (azacytidine)
No Rx
Random assignment if in CR after C2; at least PR after C1
If mini allograft not planned