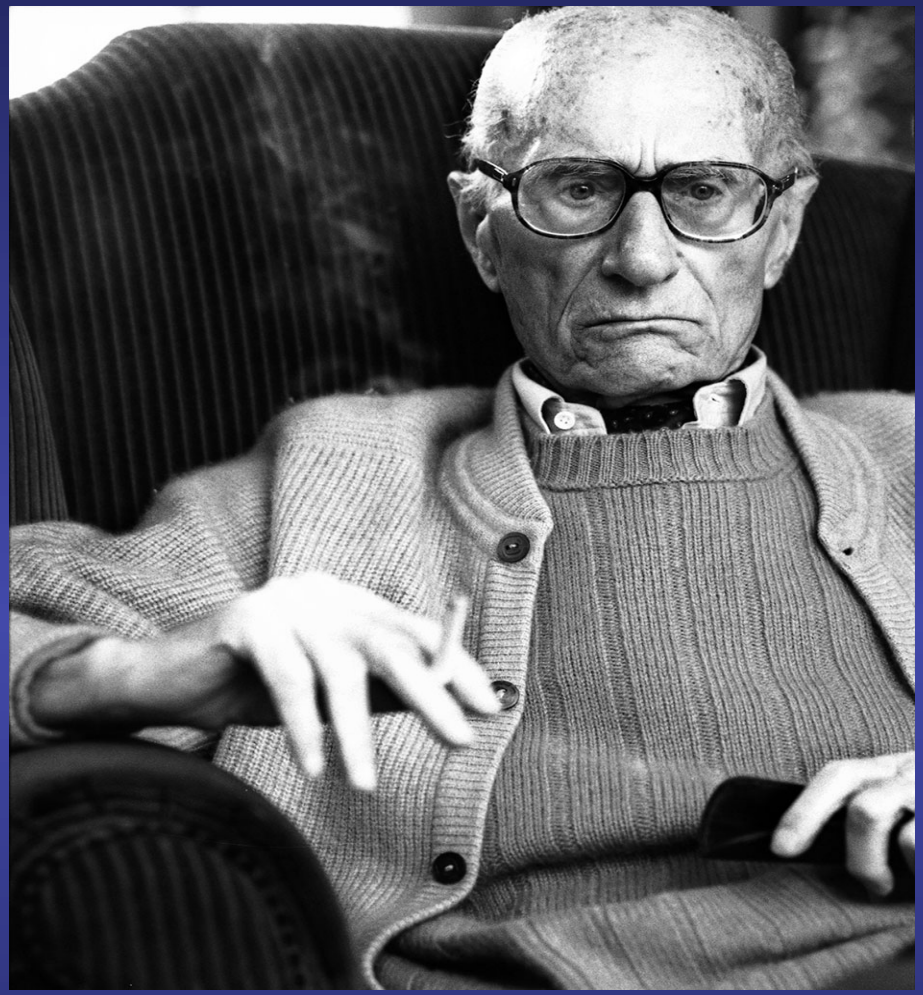
1ST CUNEO CITY IMMUNOTHERAPY CONFERENCE

17-18 Maggio 2018

PASSIVE IMMUNOTHERAPY ANTIBODY-DRUG CONJUGATES GEMTUZUMAB OZOGAMICIN

Dott. Filippo Gherlinzoni
Direttore Unità Operativa Complessa di Ematologia
Ospedale "Ca' Foncello" - Treviso

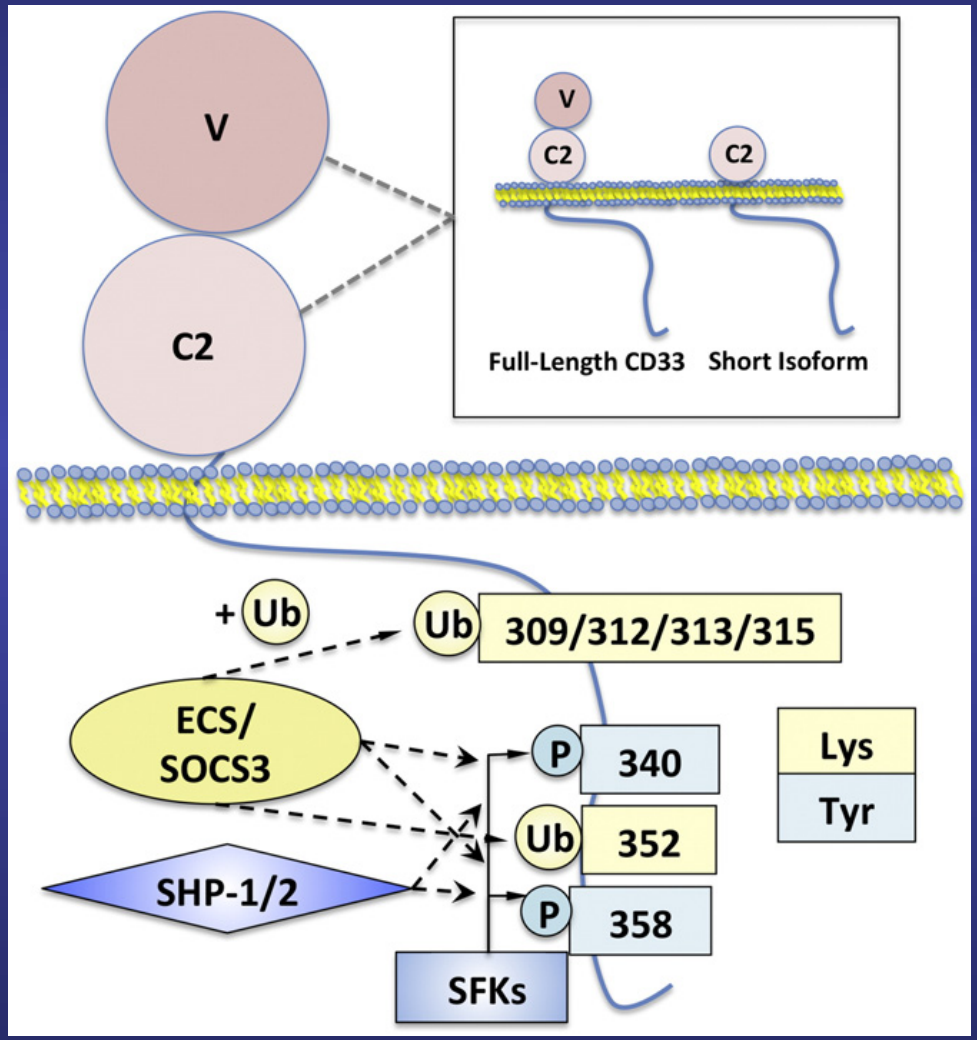


IL RIECCOLO

REVIEW

The past and future of CD33 as therapeutic target in acute myeloid leukemia

George S. Laszlo [a], Elihu H. Estey [a,b], Roland B. Walter [a,b,c,*]



Laszlo G.S. et al Blood Reviews 2014, 143-153

CD33

- ANTIGENE DI DIFFERENZIAZIONE MIELOIDE ESPRESSO SUI NORMALI PRECURSORI MIELOIDI MULTIPOTENTI, UNIPOTENTI GRANULOCITI E MONOCITI, MA NON SULLE CELLULE STAMINALI EMOPOIETICHE
- PUO' ANCHE ESSERE ESPRESSO SU ALCUNI SUBSET DI LINFOCITI B, T-ATTIVATI E CELLULE NK
- NON E' ESPRESSO AL DI FUORI DEL SISTEMA EMATOPOIETICO
- LA DENSITA' DI ESPRESSIONE DI SUPERFICIE E' MOLTO VARIABILE (1-20 X 10^3 MOLECOLE/CELLULA)

FUNZIONE PUTATIVA DI CD33

- ALCUNE EVIDENZE SPERIMENTALI SUGGERISCONO CHE LA MOLECOLA CD33 SIA COINVOLTA NELLA MODULAZIONE DELLE RISPOSTE INFIAMMATORIE E IMMUNI ATTRAVERSO UN EFFETTO INIBITORIO DI PATHWAYS DI SIGNALING CITOPLASMATICO TYROSINE-KINASE DRIVER

- STUDI IN VITRO HANNO DIMOSTRATO CHE CD33 SOPPRIME COSTITUTIVAMENTE LA PRODUZIONE DI CITOKINE PRO-INFIAMMATORIE COME IL-1β, TNF-α EIL-8 IN MANIERA DIPENDENTE DALL'ACIDO SIALICO E DA SOCS-3 (Sutherland D., Blood 2006; Orr S.J., Blood 2007; Lajaunias F., Eur J Immunol 2015)

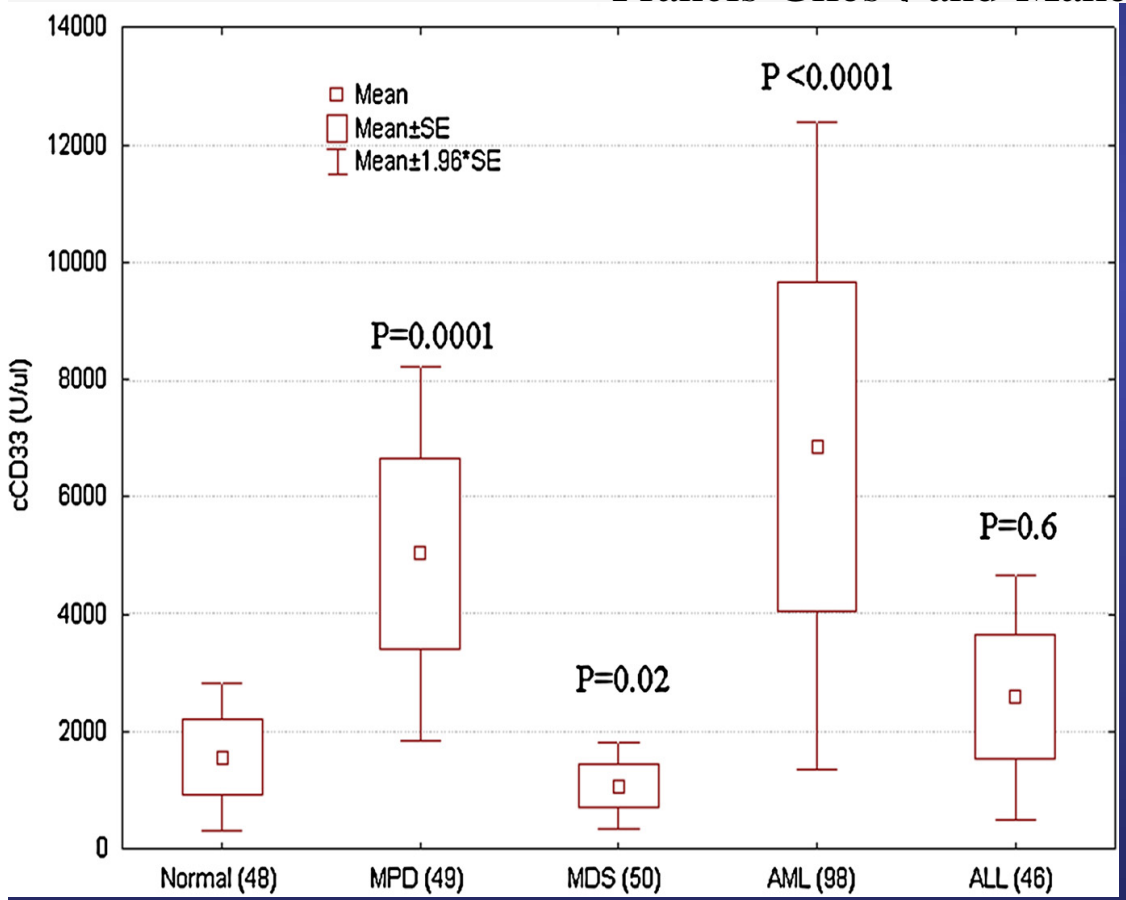
CD33

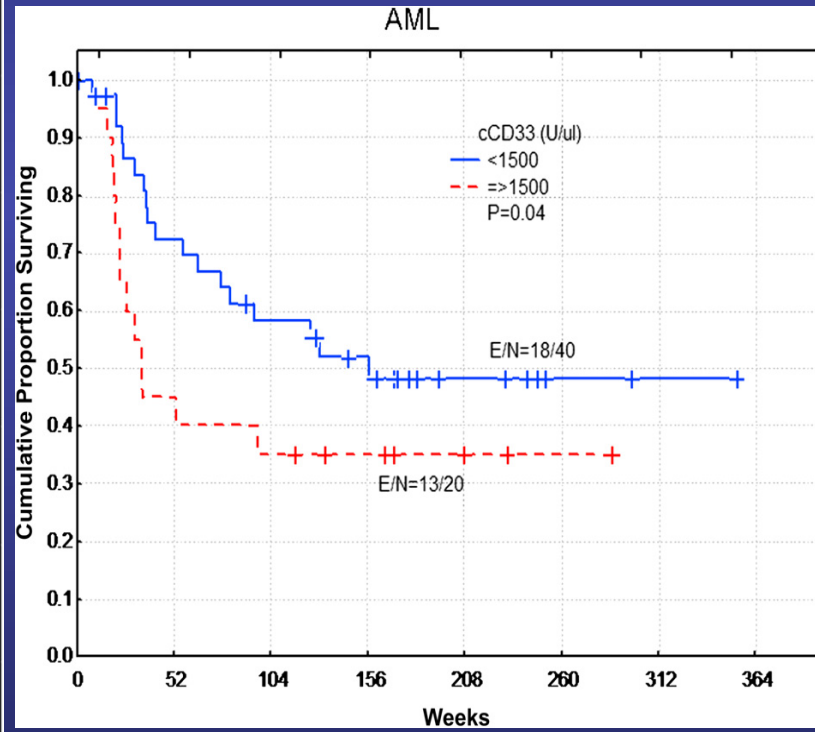
- CIRCA 85-90% DELLE AML SONO CD33-POSITIVE
- L'ESPRESSIONE DI CD33 E' PIU' ELEVATA E OMOGENEA NEI PROMIELOCITI LEUCEMICI
- ELEVATI LIVELLI DI CD33 SONO ASSOCIATI ALLA MUTAZIONE DI NPM1 E DI FLT3/ITD
- NEI PAZIENTI CON AML CD33 PUO' ANCHE ESSERE EVIDENZIATA IN CIRCOLO COME MOLECOLA SOLUBILE. NON E' CHIARO SE E IN CHE MISURA IL CD 33 SOLUBILE POSSA INTERFERIRE CON L'EFFICACIA TERAPEUTICA DEGLI ANTICORPI ANTI-CD33

CD33

Circulating CD33 and its clinical value in acute leukemia

Adam Abdool[a], Chen-Hsiung Yeh[a], Hagop Kantarjian[b], Susan O'Brien[b], JeanMarie Bruey[a], Francis Giles[c], and Maher Albitar[a]





Abdool A. et al Exp. Hematology 2010

Expression of surface antigens for potential antibody therapy in ALL.

Surface antigen	ALL subtype	Expression on >20% of LBC		Monoclonal antibody
		Thiel[a]	Raponi[4]	
CD19	B-precursor	95%	100%	Blinatumomab
	Mature B-ALL	94%	100%	
CD20	B-precursor	41%	22–30%	Rituximab
	Mature B-ALL	86%	100%	
CD22	B-precursor	60–85%	93–96%	Epratuzumab
	Mature B-ALL	69%	100%	
CD33	B-precursor	23%	17–26%	Gemtuzumab ozogamicin[b]
	T-precursor	40%		
	Ph+ ALL	9%		
CD52	B-precursor	79%		Alemtuzumab
	T-precursor	77%		

[a] Data from the German Multicentre Study Group for Adult ALL (GMALL) central Immunophenotyping, E. Thiel, S. Schwartz, Berlin, Germany (personal communication).

[b] Not available anymore.

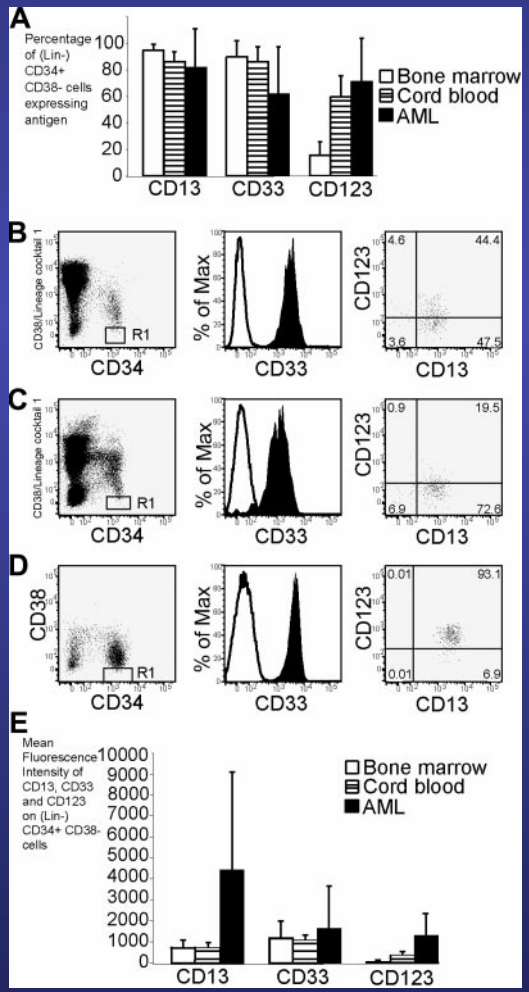
Hoelzer D. et al Blood Reviews 2012

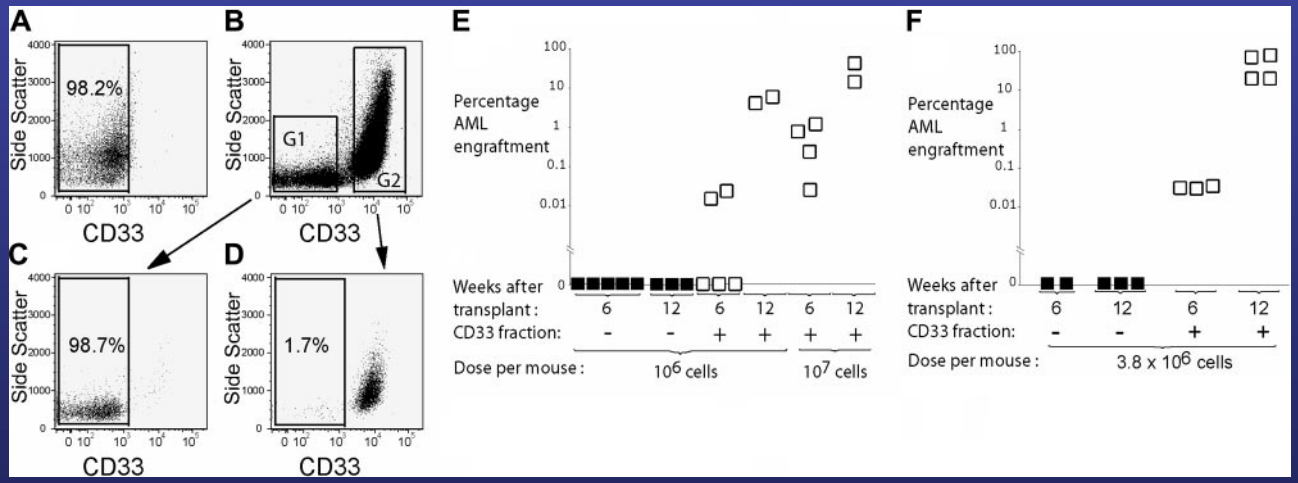
CD33 PUO' ESSERE ESPRESSA ANCHE A LIVELLO DELLE CELLULE STAMINALI LEUCEMICHE

Hematopoietic stem cells express multiple myeloid markers: implications for the origin and targeted therapy of acute myeloid leukemia

David C. Taussig, Daniel J. Pearce, Catherine Simpson, Ama Z. Rohatiner, T. Andrew Lister, Gavin Kelly, Jennifer L. Luongo, Gwenn-aël H. Danet-Desnoyers, and Dominique Bonnet

Human hematopoietic stem cells (HSCs) are generally regarded as being devoid of the markers expressed by differentiated blood cells, the lineage-specific antigens. However, recent work suggests that genes associated with the myeloid lineage are transcribed in mouse HSCs. Here, we explore whether myeloid genes are actually translated in human HSCs. We show that CD33, CD13, and CD123, well-established myeloid markers, are expressed on human long-term repopulating cells from cord blood and bone marrow. In addition, we demonstrate that nonobese diabetic/severe combined immunodeficiency (NOD/SCID) leukemia-initiating cells (SL-ICs) are restricted to the CD33$^+$ fraction in 11 of 12 acute myeloid leukemia (AML) samples studied, indicating that leukemic stem cells (LSCs) express this antigen. This study changes our view of HSCs and the process of differentiation. Furthermore, based on the phenotypic similarity of HSCs and LSCs, our data provide support for the hypothesis that AML derives from an HSC. Our findings also provide a challenge to contemporary attempts to improve the outcome of AML using myeloid antigen-targeted therapies, given the potential for HSC killing. (Blood. 2005; 106:4086-4092)





Taussig D.C. et al Blood 2005

UNCONJUGATED ANTIBODIES

MoAb	Characteristics	Clinical Results
LINTUZUMAB (SGN-33)	HUMANIZED IgG1	VERY MODEST ACTIVITY AS SINGLE AGENT. FAILED TO IMPROVE SURVIVAL WHEN ADDED TO CONVENTIONAL CHEMOTHERAPEUTICS
MAb 33.1/ B1 836858	FULLY HUMAN IgG1 ENGINEERED TO HAVE INCREASED ADCC	

CLINICAL DEVELOPMENT ABANDONED

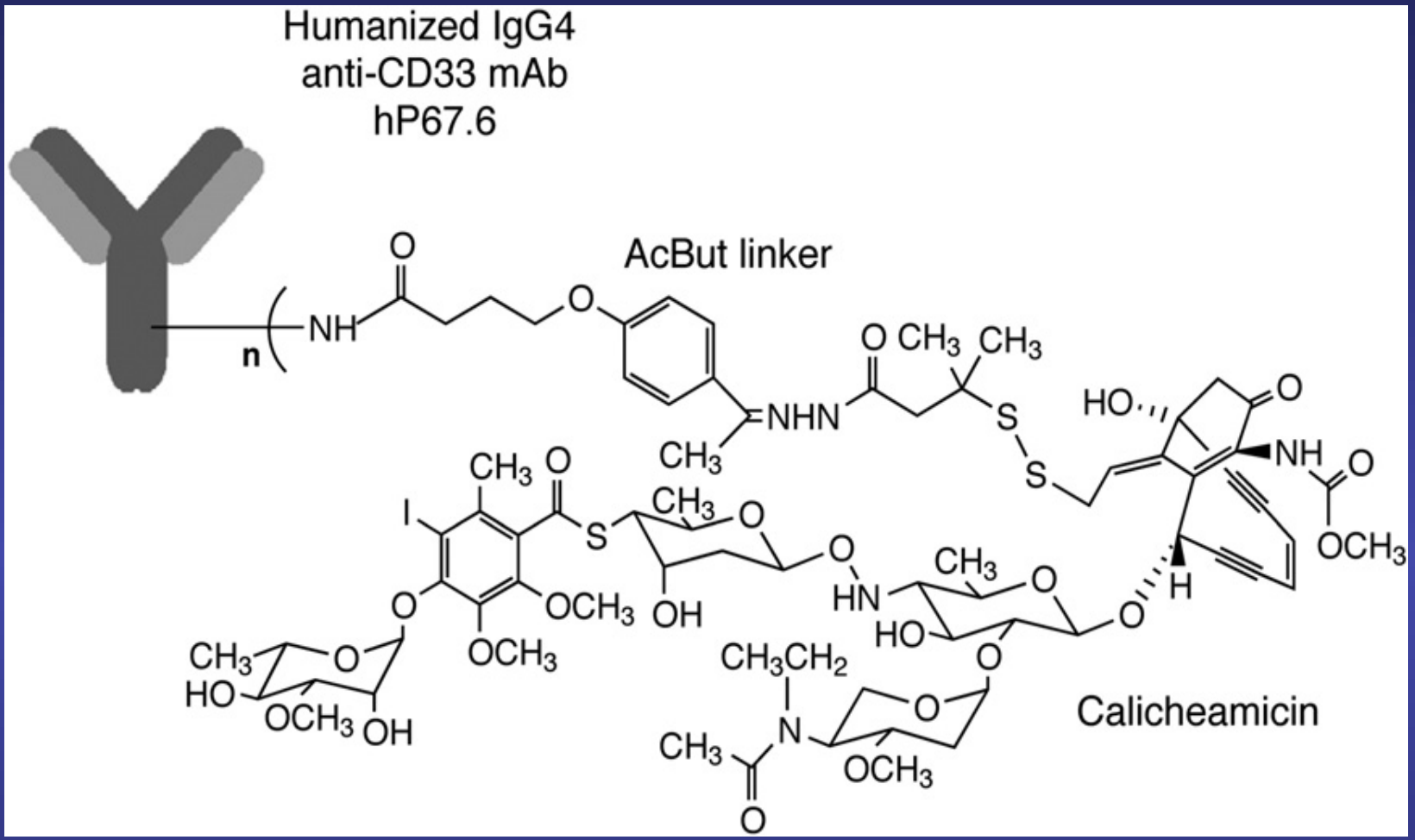
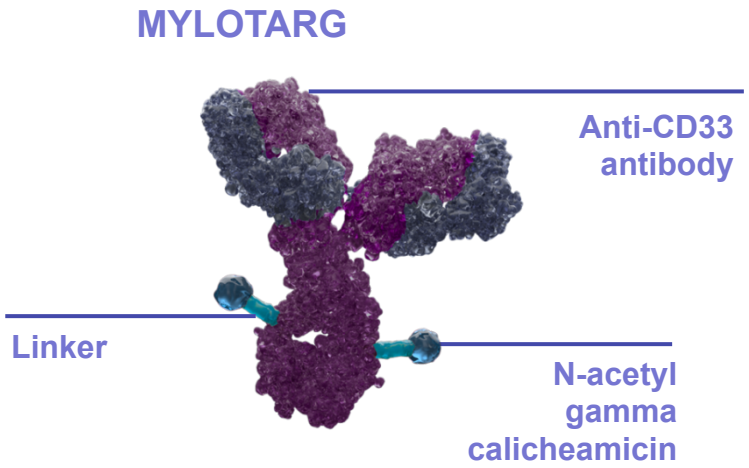
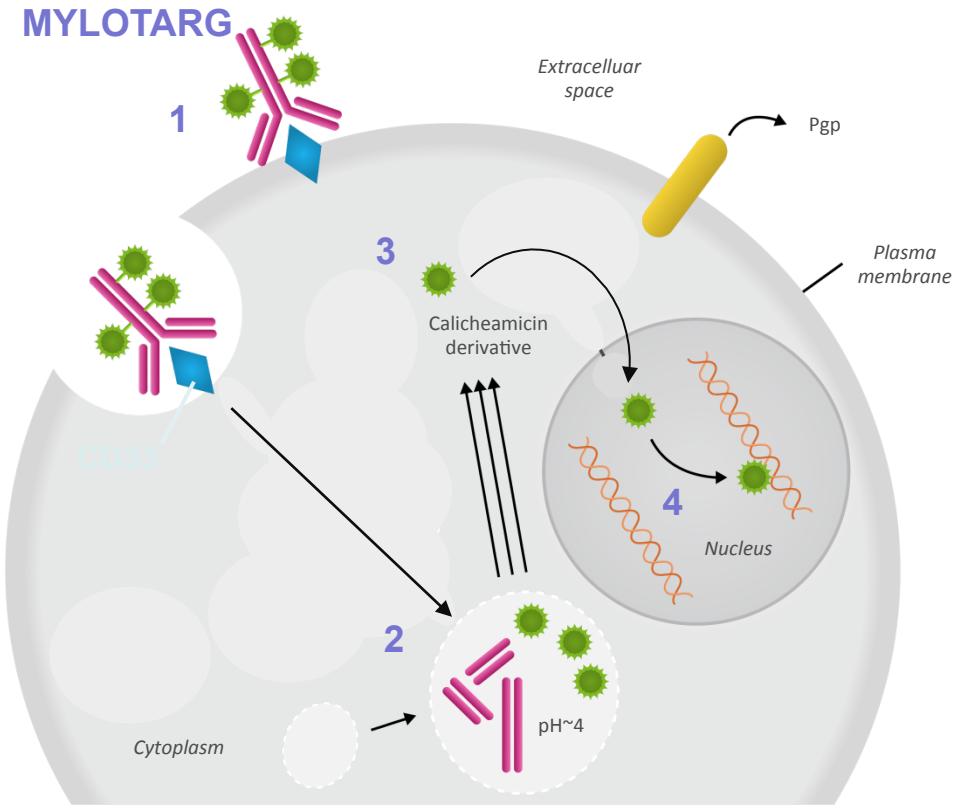


Fig. 2. Schematic structure of GO. The humanized IgG_4 CD33 antibody is conjugated to the calicheamicin-γ_1 derivative via a hybrid 4-(4′-acetylphenoxy)butanoic acid linker. GO has approximately 50% of the antibody loaded with 4–6 mol of the toxic moiety per mole of antibody; the remaining 50% of the antibody molecules are unconjugated.
Reprinted from *Current Opinion in Pharmacology* [165] with permission from Elsevier.

MYLOTARG: Mechanism of action





1. **MYLOTARG binds to CD33 antigens on leukaemic blasts**
2. **Once bound, the MYLOTARG/CD33 complex is internalised by receptor-mediated endocytosis**
3. **Calicheamicin is released from the antibody–drug complex and acts as a potent cytotoxic agent**
4. **Calicheamicin causes double-strand DNA breaks, causing the cell to undergo apoptosis**

ADC, antibody-drug conjugate; Pgp, P-glycoprotein

Ricart AD. *Clin Cancer* 2011;17:6417–6427

Efficacy and Safety of Gemtuzumab Ozogamicin in Patients With CD33-Positive Acute Myeloid Leukemia in First Relapse

By Eric L. Sievers, Richard A. Larson, Edward A. Stadtmauer, Elihu Estey, Bob Löwenberg, Hervé Dombret, Chatchada Karanes, Matthias Theobald, John M. Bennett, Matthew L. Sherman, Mark S. Berger, Catharine B. Eten, Michael R. Loken, Jacques J.M. van Dongen, Irwin D. Bernstein, and Frederick R. Appelbaum for the Mylotarg Study Group

Purpose: **Three open-label, multicenter trials were conducted to evaluate the efficacy and safety of single-agent Mylotarg (gemtuzumab ozogamicin; CMA-676; Wyeth Laboratories, Philadelphia, PA), an antibody-targeted chemotherapy agent, in patients with CD33-positive acute myeloid leukemia (AML) in untreated first relapse.**

Patients and Methods: **The study population comprised 142 patients with AML in first relapse with no history of an antecedent hematologic disorder and a median age of 61 years. All patients received Mylotarg as a 2-hour intravenous infusion, at a dose of 9 mg/m², at 2-week intervals for two doses. Patients were evaluated for remission, survival, and treatment-emergent adverse events.**

Results: **Thirty percent of patients treated with Mylotarg obtained remission as characterized by 5% or less blasts in the marrow, recovery of neutrophils to at least 1,500/μL, and RBC and platelet transfusion independence. Although patients treated with Mylotarg had relatively high incidences of myelosuppression, grade 3 or 4 hyperbilirubinemia (23%), and elevated hepatic transaminase levels (17%), the incidences of grade 3 or 4 mucositis (4%) and infections (28%) were relatively low. There was a low incidence of severe nausea and vomiting (11%) and no treatment-related cardiotoxicity, cerebellar toxicity, or alopecia. Many patients received Mylotarg on an outpatient basis (38% and 41% of patients for the first and second doses, respectively). Among the 142 patients, the median total duration of hospitalization was 24 days; 16% of patients required 7 days of hospitalization or less.**

Conclusion: **Administration of the antibody-targeted chemotherapy agent Mylotarg to patients with CD33-positive AML in first relapse induces complete remissions with what appears to be a favorable safety profile.**

J Clin Oncol 19:3244-3254.

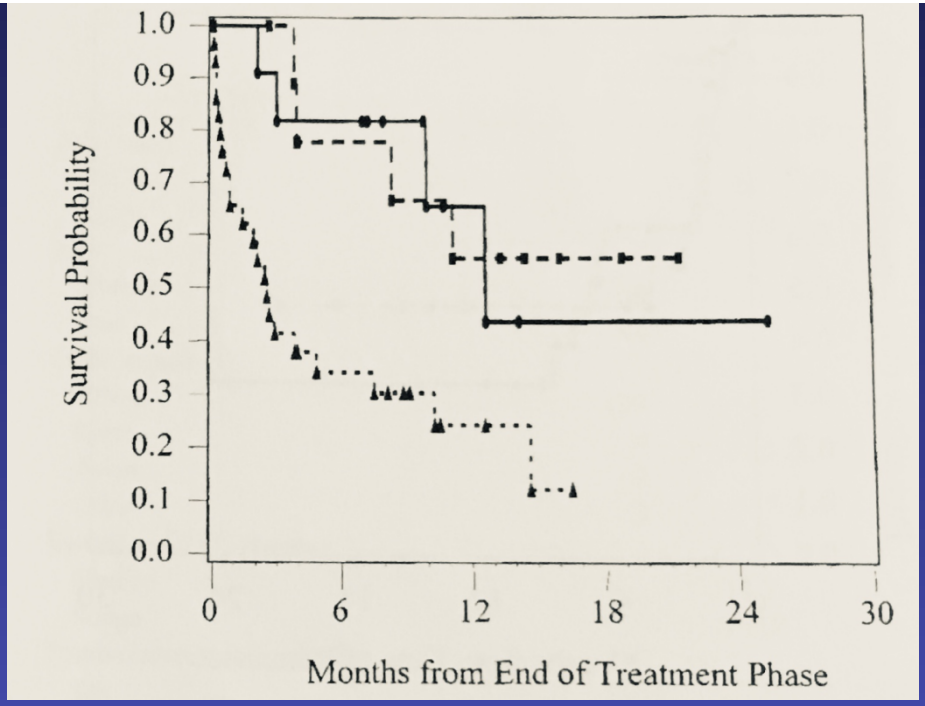
Characteristic	Patients (N = 142) No.	%
Age, years		
Median	61	
Range	22-84	
Sex		
Women	58	41
Men	84	59
Ethnic origin		
White	133	94
Black	4	3
Asian	2	1
Other	3	2
Duration of CR1, months		
Median	11.1	
Range	3-117	
Postremission therapy for CR1		
Yes	133	94
No	9	6
Cytogenetics at relapse		
Known	97	
Favorable-risk group	5	5
Intermediate-risk group	54	56
Poor-risk group	38	39
Unknown	45	

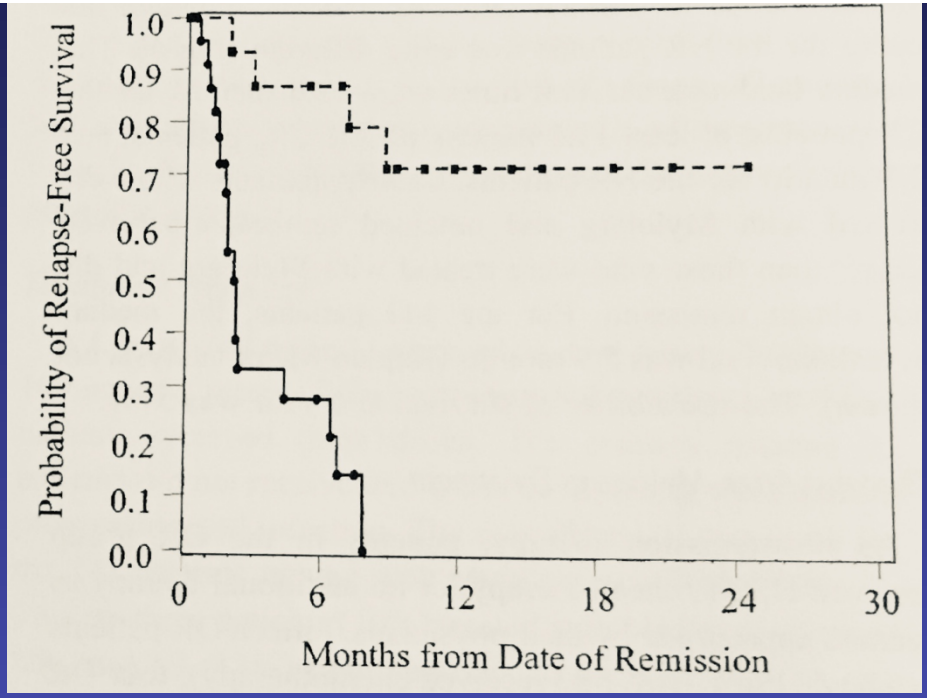
Risk Group	No.	OR Patients No.	OR Patients %	NR Patients No.	NR Patients %
Favorable	5	2	40	3	60
Intermediate	54	19	35	35	65
Poor	38	12	32	26	68
Unknown	45	9	20	36	80

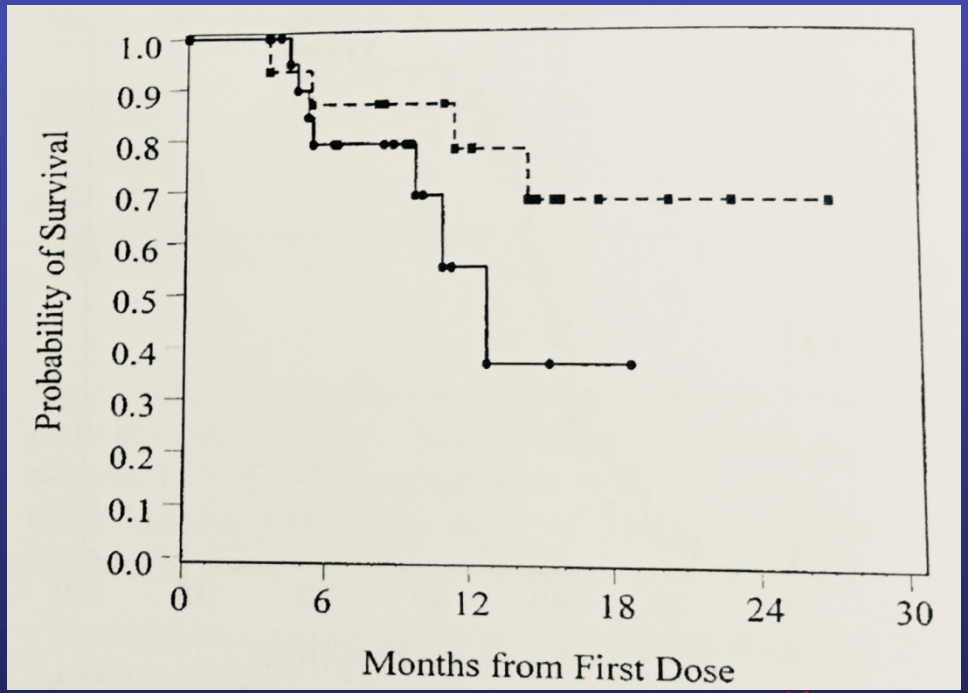
Type of Remission	No. of Patients (N = 142)	%	95% CI
CR	23	16	11-23
CR_p	19	13	8-20
OR*	42	30	22-38

*OR = CR + CR_p.

Sievers E.L. et al JCO 2001







Sievers E.L. et al JCO 2001

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Final Report of the Efficacy and Safety of Gemtuzumab Ozogamicin (Mylotarg) in Patients with CD33-Positive Acute Myeloid Leukemia in First Recurrence

BACKGROUND. In this study, the authors analyzed the efficacy and safety of gemtuzumab ozogamicin (GO) (Mylotarg®), an antibody-targeted chemotherapy for CD33-positive acute myeloid leukemia (AML).

METHODS. Patients with CD33-positive AML in first recurrence were entered in 3 open-label, single-arm, Phase II studies. Patients received monotherapy with GO 9 mg/m^2 as a 2-hour intravenous infusion in 2 doses separated by 2 weeks. Patients were evaluated for remission, survival, and treatment-emergent adverse events.

RESULTS. Two hundred seventy-seven patients (median age, 61 yrs) were treated with GO, and 71 patients (26%) achieved remission, which was defined as $\leq$ 5% blasts in the bone marrow without leukemic blasts in the peripheral blood, neutrophil recovery to $\geq$ 1500/μL, hemoglobin $\geq$ 9 g/dL, and independence from red blood cell and platelet transfusions. Complete remission (CR) with platelet recovery ($\geq$ 100,000/μL) or without full platelet recovery ($<$ 100,000/μL) (CRp) was observed in 35 patients (13%) and 36 patients (13%), respectively. The median recurrence-free survival was 6.4 months for patients who achieved CR and 4.5 months for patients who achieved CRp. Although expected incidences of Grade 3 or 4 neutropenia (98%) and thrombocytopenia (99%) were observed, the incidence of Grade 3 or 4 sepsis (17%) and pneumonia (8%) was relatively low. Grade 3 or 4 hyperbilirubinemia and hepatic aspartate aminotransferase and alanine aminotransferase elevations were reported in 29%, 18%, and 9% of patients, respectively; 0.9% of patients who did not undergo prior or subsequent hematopoietic stem cell transplantation developed hepatic venoocclusive disease after GO treatment.

TOSSICITA' EPATICA G3-G4 DA MYLOTARG

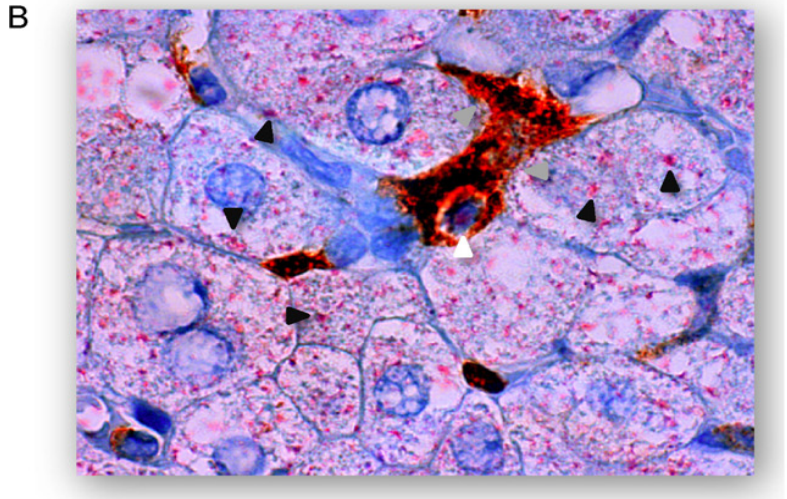
IPERBILIRUBINEMIA	29%
AUMENTO AST	18%
AUMENTO ALT	9%
VOD/SOS	5%, MA 17% NEI PAZIENTI SUCCESSIVAMENTE TRATTATI CON ALLOBMT

Larson R.A. et al Cancer 2005

GO-ASSOCIATED SINUSOIDAL OBSTRUCTIVE SYNDROME (SOS)

POSSIBILI MECCANISMI PATOGENETICI

- DANNO SULLE CELLULE ENDOTELIALI SINUSOIDALI EPATICHE DA PARTE DELLA CALICOMICINA UNA VOLTA STACCATASI DALL'ANTICORPO
- UPTAKE NON-SPECIFICO DEI COMPLESSI ANTICORPO-CALICOMICINA DA PARTE DELLE CELLULE DEL KUPFFER
- DEPLEZIONE DEL GLUTATIONE NELLE CELLULE ENDOTELIALI SINUSOIDALI



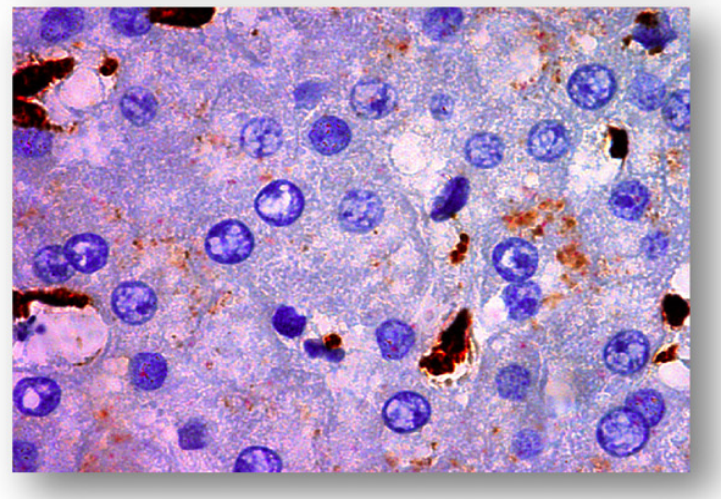


Fig. 1. Biochemical signs of hepatotoxicity after GO treatment and CD33 expression on Kupffer cells and hepatocytes. (A) Time course of ALAT concentrations showing a 5-fold increase less than two weeks after administration of the second GO dose. "GO" represents time of GO treatment and red arrowheads represent normal ALAT values (5-45 U/l). (B) Double immunohistochemical staining performed on stored formalin-fixed, paraffin-embedded liver tissue from a healthy individual. Double staining with CD33 (fast red precipitates; violet colored) and CD163 (DAB precipitates; brown colored) showing CD163 immunoreactivity limited to the constituent Kupffer cells (marked with grey arrowheads), which also express the myeloid lineage marker CD33 (marked with white arrowheads). Importantly, the staining shows that CD33 is highly expressed on hepatocytes (marked with black arrowheads) (Mayer's hematoxylin counterstain, original magnification $\times$100, oil). The figure is representative of several stainings of liver tissue from different healthy individuals. (C) An isotype-matched negative control antibody was used to evaluate non-specific binding of anti-CD33.

Maniecki M.B. et al Leuk Research 2011

MAGGIO 2000

- FDA-ACCELERATED APPROVAL OF MYLOTARG FOR THE TREATMENT OF PATIENTS WITH CD33+ AML IN FIRST RELAPSE WHO ARE ≥ 60-YRS OLD AND WHO ARE NOT CONSIDERED CANDIDATES FOR CYTOTOXIC CHEMOTHERAPY

- THE FIRST ANTIBODY-DRUG CONJUGATE APPROVED FOR CANCER THERAPY AND THE FIRST TARGETED AGENT IN NON-M3 AML SUBGROUP

A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia

Stephen H. Petersdorf,[1] Kenneth J. Kopecky,[1,2] Marilyn Slovak,[3] Cheryl Willman,[4] Thomas Nevill,[5] Joseph Brandwein,[6] Richard A. Larson,[7] Harry P. Erba,[8] Patrick J. Stiff,[9] Robert K. Stuart,[10] Roland B. Walter,[1] Martin S. Tallman,[11] Leif Stenke,[12] and Frederick R. Appelbaum[1]

Key Points

- The addition of gemtuzumab ozogamicin to induction or maintenance therapy failed to improve the complete response rate or overall survival in patients with acute myeloid leukemia.

This randomized phase 3 clinical trial evaluated the potential benefit of the addition of gemtuzumab ozogamicin (GO) to standard induction and postconsolidation therapy in patients with acute myeloid leukemia. Patients were randomly assigned to receive daunorubicin (45 mg/m^2 per day on days 1, 2, and 3), cytarabine (100 mg/m^2 per day by continuous infusion on days 1–7), and GO (6 mg/m^2 on day 4; DA+GO) vs standard induction therapy with daunorubicin (60 mg/m^2 per day on days 1, 2, and 3) and cytarabine alone (DA). Patients who achieved complete remission (CR) received 3 courses of high-dose cytarabine. Those remaining in CR after consolidation were randomly assigned to receive either no additional therapy or 3 doses of GO (5 mg/m^2 every 28 days). From August 2004 until August 2009, 637 patients were registered for induction. The CR rate was 69% for DA+GO and 70% for DA (P = .59). Among those who achieved a CR, the 5-year relapse-free survival rate was 43% in the DA+GO group and 42% in the DA group (P = .40). The 5-year overall survival rate was 46% in the DA+GO group and 50% in the DA group (P = .85). One hundred seventy-four patients in CR after consolidation underwent the postconsolidation randomization. Disease-free survival was not improved with postconsolidation GO (HR, 1.48; P = .97). In this study, the addition of GO to induction or postconsolidation therapy failed to show improvement in CR rate, disease-free survival, or overall survival. This trial is registered with www.clinicaltrials.gov as #NCT00085709. (*Blood*. 2013;121(24):4854-4860)

Petersdorf S.H. et al Blood 2013

	DA+GO (n = 295)		DA (n = 300)		
	Median	Min–Max	Median	Min–Max	P*
Age, years	47	18-60	48	18-60	.44
White blood cells, 10^9/L	10.7	0.5-545.0	12.5	0.2-243.5	.48
Peripheral blood blasts, % (n = 555)	34	0-99	27	0-99	.16
Neutrophils, % (n = 574)	9	0-97	10	0-72	.66
Absolute neutrophil count, 10^9/L (n = 574)	1.1	0-171.6	0.9	0-40.1	.32
Hemoglobin, g/dL (n = 583)	9.1	3.5-18.0	9.1	4.4-29.1	.81
Platelets, 10^9/L (n = 593)	53	2-7900	55	7-9300	.39
Bone marrow blasts, % (n = 584)	66	7-100	65	3-100	.72
	Patients	**%**	**Patients**	**%**	
Age, years					
<35	57	19%	56	19%	.92
≥35	238	81%	244	81%	
Sex					
Female	135	46%	147	49%	.46
Male	160	54%	153	51%	
French-American British classification					
M1	67	23%	58	20%	.76
M2	76	26%	68	24%	
M4	73	25%	71	25%	
M4eos	9	3%	10	3%	
M5	38	13%	47	16%	
M6	4	1%	9	3%	
M7	3	1%	3	1%	
M0	21	7%	23	8%	
Unknown	4	—	11	—	
Performance status					
0	117	40%	118	40%	.37
1	147	50%	136	46%	
2	22	7%	31	10%	
3	8	3%	13	4%	
Unknown	1	—	2	—	

*Two-sided *P* value from Wilcoxon test (continuous variables), Fisher's exact test (age group, sex), or Pearson's χ-square test (French-American British classification, performance status).

	DA+GO (n = 254)		DA (n = 242)		
	Patients	%	Patients	%	P*
Risk group					
Favorable	37	15	44	18	.47
Intermediate	137	54	132	55	
Unfavorable	62	24	55	23	
Indeterminate	18	7	11	5	
Normal	106	45	103	46	.85
CBF†	31	13	40	18	.20
inv(16)	17	7	23	10	.32
t(8;21)	14	6	17	8	.58
−7, 7q, −5 or −5q	29	12	22	10	.46
−7, 7q–	24	10	15	7	.19
−5, 5q–	14	6	14	6	1.00
+8	28	12	19	9	.28
11q23	11	5	13	6	.68
−17	9	4	6	3	.60
−18	6	3	5	2	1.00
t(9;11)	5	2	4	2	1.00
t(6;9)	4	2	2	1	.69
inv(3)	3	1	3	1	1.00
21q22	3	1	3	1	1.00
Marker/ring	17	7	9	4	.16
Complex‡	36	15	34	15	1.00
Other abnormality	79	34	74	33	.92

*Two-sided *P* value from Pearson's χ-square test (Risk group) or Fisher's exact test (normal or specific abnormalities, based on 234 DA+GO and 223 DA patients.

†Core binding factor.

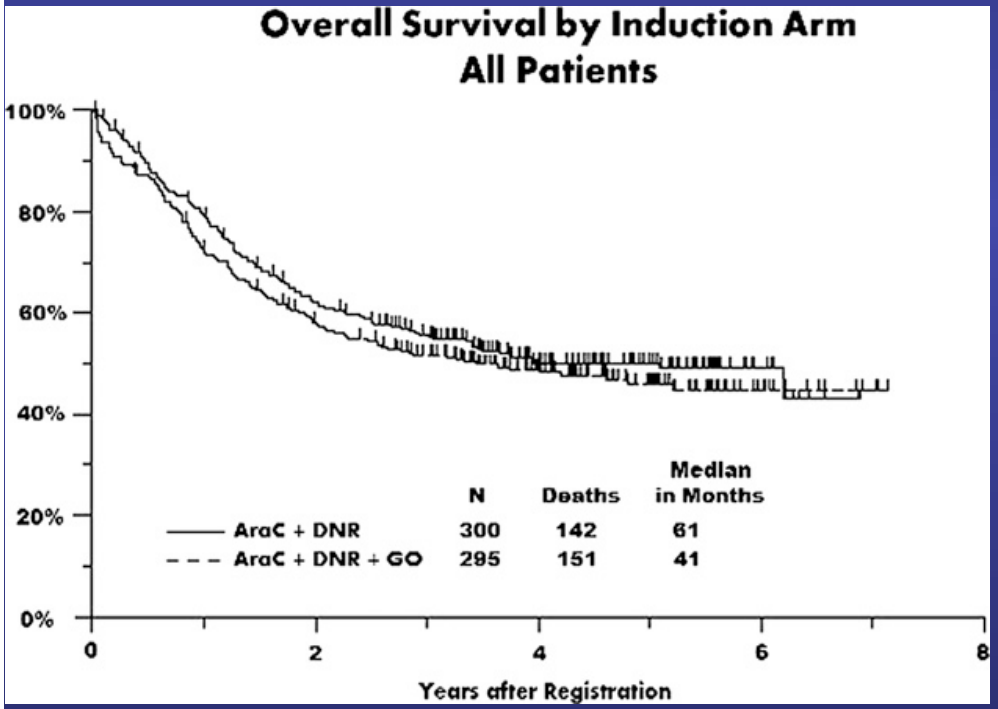
‡Three or more clonal cytogenetic abnormalities.

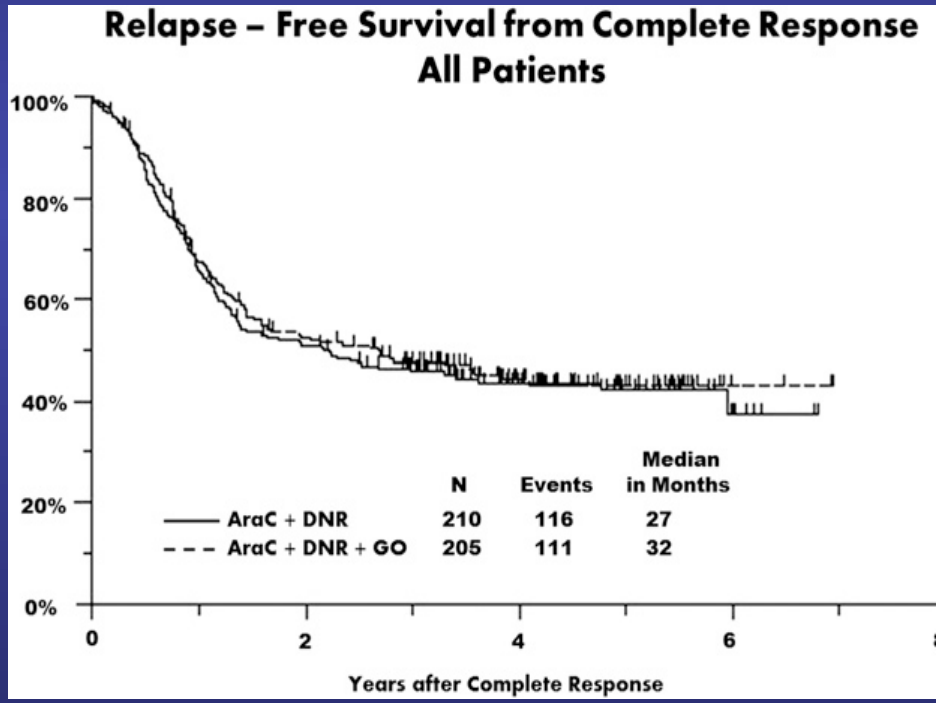
Petersdorf S.H. et al Blood 2013

Table 3. Treatment outcomes following induction chemotherapy of 595 adult patients with previously untreated AML, by treatment group

		CR		CR or Cri		Resistant disease		OS at 5 years		RFS at 5 years	
Group	**Patients**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
DA+GO	295	69	63-74	76	69-79	15	12-20	46	40-52	43	36-50
DA	300	70	64-75	74	69-79	20	16-25	50	44-56	42	35-49
*P**		.59		.36		.065		.85		.40	

*One-sided *P* value for superior outcome (higher CR rate, lower RD, HR<1) in DA+GO group, based on Fisher's exact test (CR, RD) or logrank test (OS, RFS).





Petersdorf S.H. et al Blood 2013

Table 6. Summary of induction toxicities among 586 adult patients with AML

	DA+GO (n = 292)		DA (n = 294)	
	Patients	**%**	**Patients**	**%**
Any fatal toxicity	16	5	4	1
Infection and/or febrile neutropenia	5		2	
Central nervous system hemorrhage	4		1	
Acute respiratory distress syndrome, dyspnea	3		0	
Lung hemorrhage	2		0	
Transfusion related acute lung injury with infection and central nervous system hemorrhage	1		0	
Liver dysfunction	1		0	
Other	0		1	
Any grade 4+ nonhematologic	61	21	36	12
Any grade 3+ nonhematologic	236	81	244	83

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2010

FDA DECIDE DI RITIRARE IL MYLOTARG DAL MERCATO

- **TREATMENT OF AML: RESURRECTION FOR GO?**

Gemtuzumab: Time to Bring Back on the Market?

Gemtuzumab Ozogamicin: Time to Resurrect?

Gemtuzumab ozogamicin in acute myeloid leukemia: a remarkable saga about an active drug

Gemtuzumab Ozogamicin in Children and Adolescents With De Novo Acute Myeloid Leukemia Improves Event-Free Survival by Reducing Relapse Risk: Results From the Randomized Phase III Children's Oncology Group Trial AAML0531

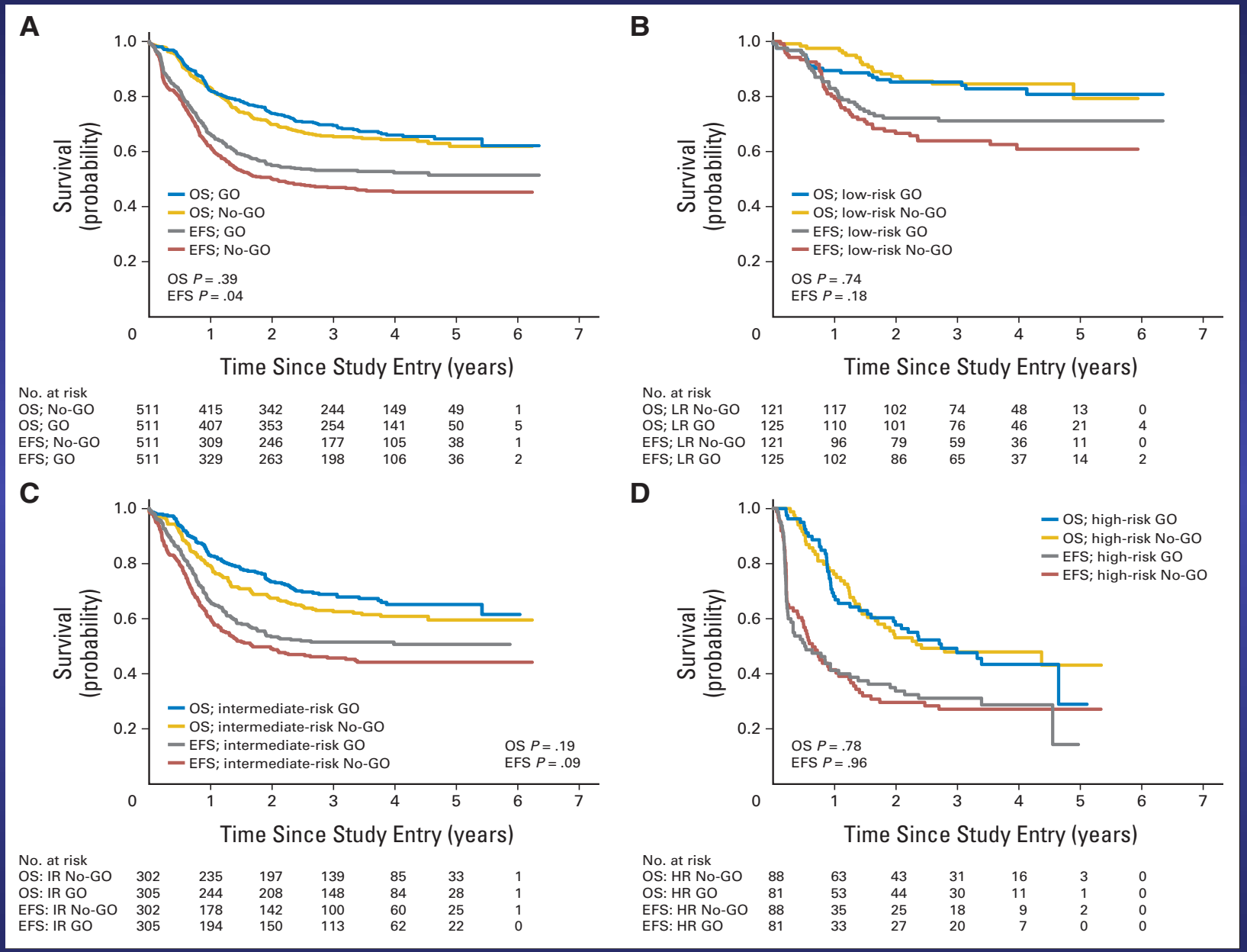
Alan S. Gamis, Todd A. Alonzo, Soheil Meshinchi, Lillian Sung, Robert B. Gerbing, Susana C. Raimondi, Betsy A. Hirsch, Samir B. Kahwash, Amy Heerema-McKenney, Laura Winter, Kathleen Glick, Stella M. Davies, Patti Byron, Franklin O. Smith, and Richard Aplenc

Table 1. COG AAML0531 Therapeutic Regimen

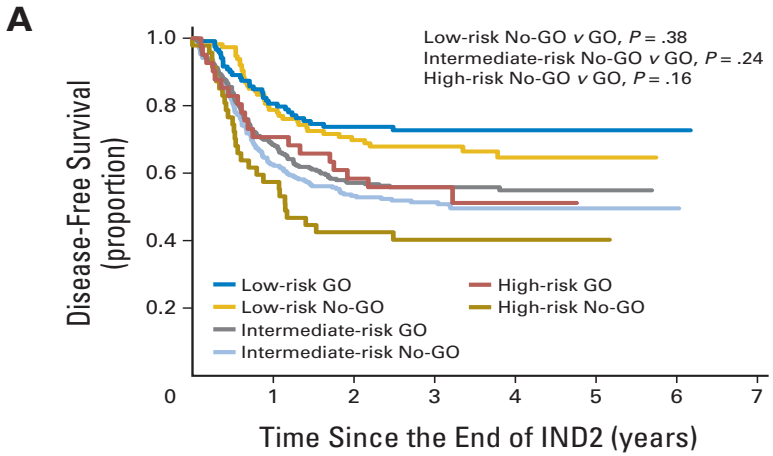
Course and Agent	Dose	Days
IND1		
Cytarabine	100 mg/m^2/dose twice per day IV	1 to 10
Daunomycin	50 mg/m^2/dose IV	1, 3, 5
Etoposide	100 mg/m^2/dose IV	1 to 5
Gemtuzumab, arm B only	3 mg/m^2/dose IV over 2 hours	6
IND2		
Cytarabine	100 mg/m^2/dose twice per day IV	1 to 8
Daunomycin	50 mg/m^2/dose IV	1, 3, 5
Etoposide	100 mg/m^2/dose IV	1 to 5
INT1		
Cytarabine	1,000 mg/m^2/dose twice per day IV	1 to 5
Etoposide	150 mg/m^2/dose IV	1 to 5
For patients not undergoing stem-cell transplantation		
INT2		
Mitoxantrone	12 mg/m^2/dose IV	3 to 6
Cytarabine	1,000 mg/m^2/dose twice per day IV	1 to 4
Gemtuzumab, arm B only	3 mg/m^2/dose IV over 2 hours	7
INT3		
Cytarabine	3,000 mg/m^2/dose twice per day IV	1, 2, 8, 9
Escherichia coli L-asparaginase	6,000 mg/m^2/dose IM	2, 9
For patients receiving matched family-donor stem-cell transplantation		
Busulfan, 16 total doses	Age and weight based	−9
< 10 kg or > 4 years old	0.8 mg/kg/dose once every 6 hours IV	
> 10 kg and < 4 years old	1 mg/kg/dose every 6 hours IV	
All patients	Adjusted AUC based on first dose	−8 to −6
Cyclophosphamide	50 mg/kg/dose IV once per day	−5 to −2

Abbreviations: AUC, area under the concentration-time curve; COG, Children's Oncology Group; IM, intramuscular; IND1, induction course; INT, intensification course; IV, intravenous.

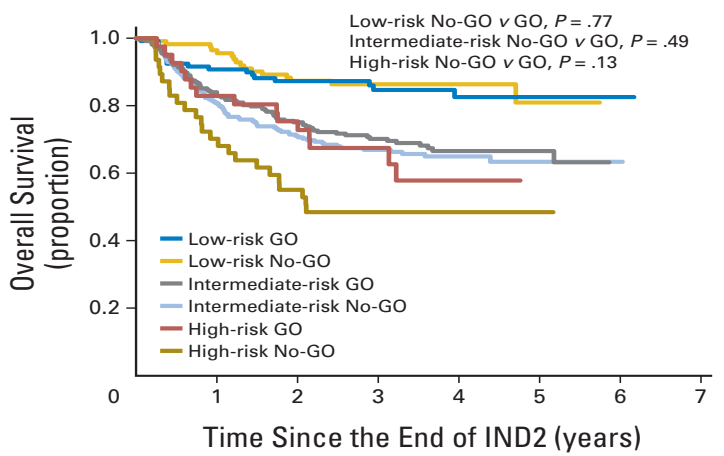
Gamis A. S. et al JCO 2014



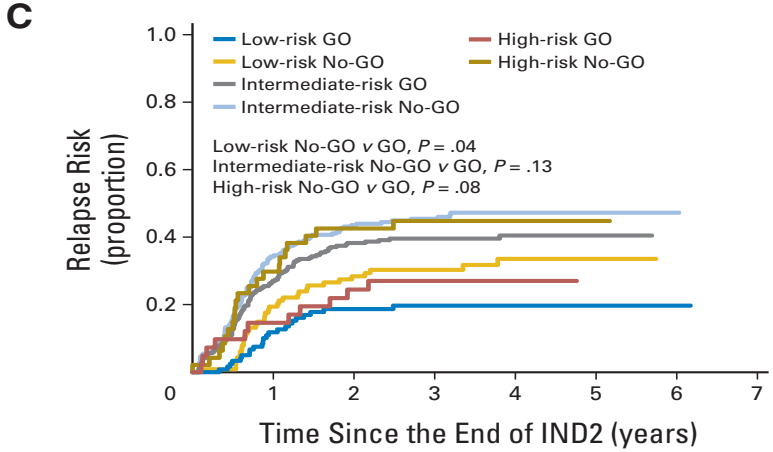
Gamis A. S. et al JCO 2014



No. at risk							
Low-risk No-GO	114	88	76	53	29	8	0
Low-risk GO	120	94	84	53	32	10	1
Intermediate-risk No-GO	257	156	127	93	50	22	1
Intermediate-risk GO	268	179	142	97	55	18	0
High-risk No-GO	47	27	20	13	4	1	0
High-risk GO	41	29	23	16	5	0	0



No. at risk							
Low-risk No-GO	114	107	94	64	39	10	0
Low-risk GO	120	106	97	62	39	15	2
Intermediate-risk No-GO	257	202	172	122	67	27	1
Intermediate-risk GO	268	220	186	122	69	22	0
High-risk No-GO	47	33	25	16	4	1	0
High-risk GO	41	34	29	19	6	0	0



No. at risk							
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Low-risk GO	120	94	84	53	32	10	1
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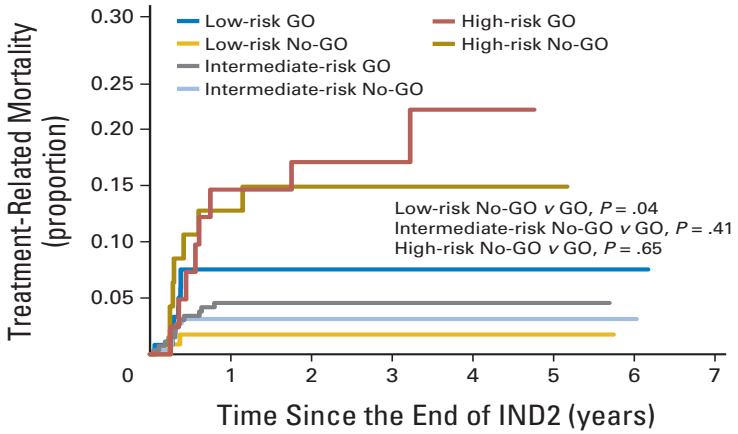

No. at risk							
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Low-risk GO	120	94	84	53	32	10	1
Intermediate-risk No-GO	257	156	127	93	50	22	1
Intermediate-risk GO	268	179	142	97	55	18	0
High-risk No-GO	47	27	20	13	4	1	0
High-risk GO	41	29	23	16	5	0	0

Gamis A. S. et al JCO 2014

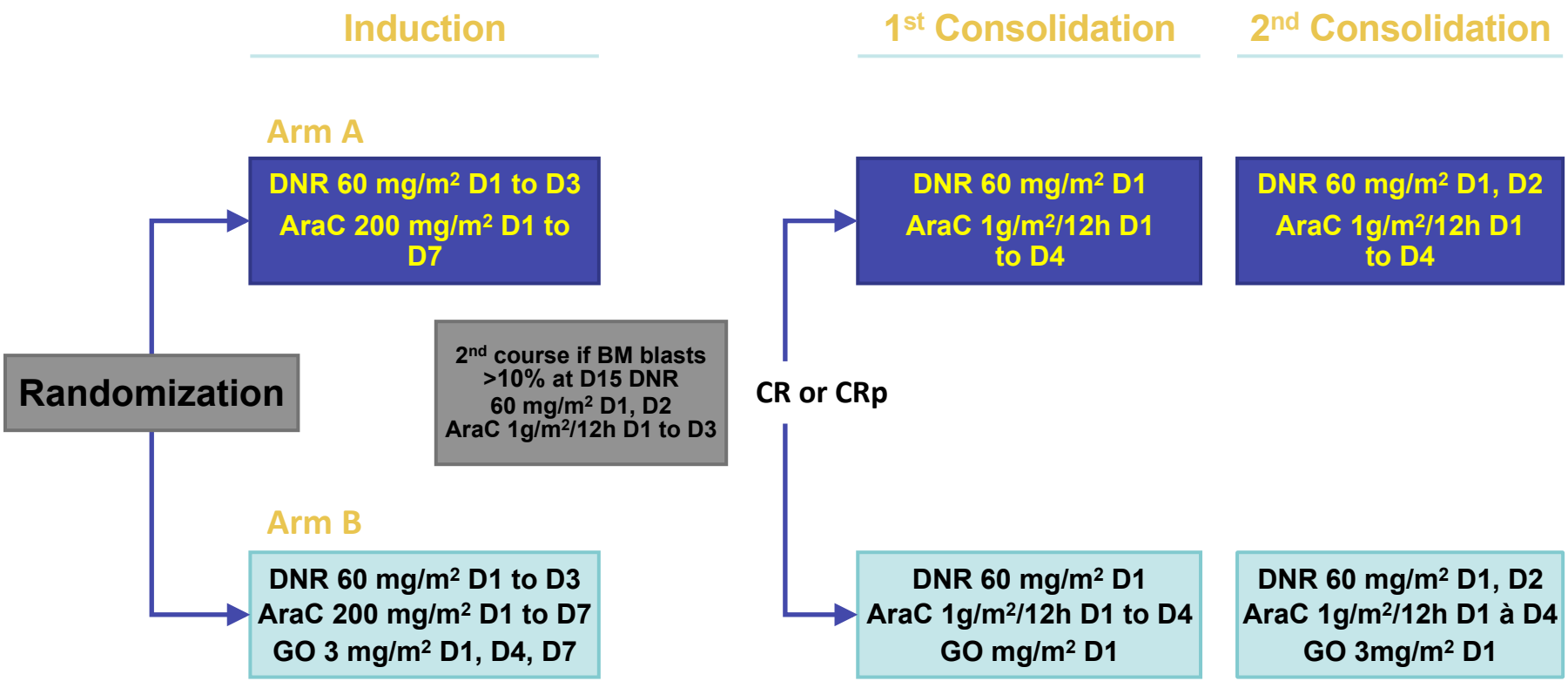
Study	n	Age, years	Characteristics	Dose of each administration of GO	Improved CR with GO	Improved RFS, EFS, DFS or OS with GO	Increased induction mortality	Increased hepatic toxicity
SWOG 0106[4]	637	18-60	DA+GO vs DA in induction and in maintenance	6 mg	No	No	Yes	No
MRC AML15[7]	1113	<60	Induction, consolidation, and maintenance, all with or without GO	3 mg	No	Yes: 1. Favorable cytogenetics 2. 70% of intermediate cytogenetics	No	No
ALFA 0701[9,10]	280	50-70	DA+GO vs DA in induction and in consolidation	3 mg	No	Yes: In favorable/ intermediate group	No	No
Groupe Ouest Est d'Etude des Leucémies Aiguës et Autres Maladies du Sang AML 2006 IR[10]	254	18-60	Induction with or without GO	6 mg	No	Yes: Improved EFS	No	Yes
National Cancer Research Institute AML16[8]	1115	51-84	Daunorubicin/ clofarabine induction, with or without GO	3 mg	No	Yes: In favorable/ intermediate group	No	No
Leukemia Research Fund AML14 and National Cancer Research Institute AML 16[11]	495	Older adults, for conventional chemotherapy	Low-dose cytarabine, with or without GO	3 mg	Yes	No	No	No

CR, complete remission; DA, daunorubicin/cytarabine; DFS, disease-free survival; EFS, event-free survival; FS, relapse-free survival.

Rowe J. M. et al Blood 2013

ALFA-0701: Study Design

- **Randomized Open-label Phase 3**



AraC, cytarabine; BM, bone marrow; CR, complete response; CRp, complete response with incomplete platelet recovery; D, day; DNR, daunorubicin; GO gemtuzumab ozogamicin (Mylotarg).

Figure adapted from Castaigne S, et al. Abstract Presented at the 56th ASH Annual Meeting and Exposition; December 6-9, 2014; San Francisco, CA.

ALFA-0701: Baseline Characteristics

	Control Group	GO Group	All Patients
Patients	139	139	278
Age in years, median (IQR)	61.7 (57.4-65.5)	62.8 (59.3-66.8)	62.2 (58.5-66.3)
Age ≥60	86 (62%)	100 (72%)	186 (67%)
Men	61 (44%)	77 (55%)	138 (50%)
ECOG performance status			
0	54 (39%)	50 (36%)	104 (37%)
1	65 (47%)	75 (54%)	140 (50%)
2	17 (12%)	13 (9%)	30 (11%)
3	1 (<1%)	1 (<1%)	2 (<1%)
Not available	2 (1%)	0	2 (<1%)
White Blood Cell Count ($x10^9$ per L; median, IQR)	5.0 (1.9-26.7)	6.9 (2.3-30.4)	5.9 (2.1-29.1)
Platelet count ($x10^9$ per L; median, IQR)	67.5 (36.3-125.5)	66.0 (36.5-118.5)	67.0 (36.0-122.0)
Percentage of CD33-expressing cells (median, IQR)	88% (57-96)	92% (67-97)	90% (63-97)

GO, gentuzumab ozogamicin; IQR, interquartile range.
Castaigne S et al. *Lancet*. 2012;379(9825):1508-1516.

ALFA-0701: Baseline Characteristics (cont'd)

	Control Group	GO Group	All Patients
Cytogenetics[a]			
Favorable	6 (4%)	3 (2%)	9 (3%)
Intermediate	91 (66%)	91 (66%)	182 (66%)
Unfavorable	30 (22%)	28 (20%)	58 (21%)
***NPM*1 status[a]**			
Mutated	48 (35%)	45 (32%)	93 (33%)
Wild type	90 (65%)	91 (65%)	181 (65%)
***FTL3*-ITD status[a]**			
Positive	27 (19)	22 (16%)	49 (18%)
Negative	111 (80%)	115 (83%)	226 (65%)
***CEBPA* status[a]**			
Mutated	8 (6%)	10 (7%)	18 (6%)
Wildtype	119 (86%)	110 (79%)	229 (82%)
Genotype[a]			
Favorable	24 (17%)	24 (17%)	48 (17%)
Unfavorable	101 (73%)	95 (68%)	196 (71%)

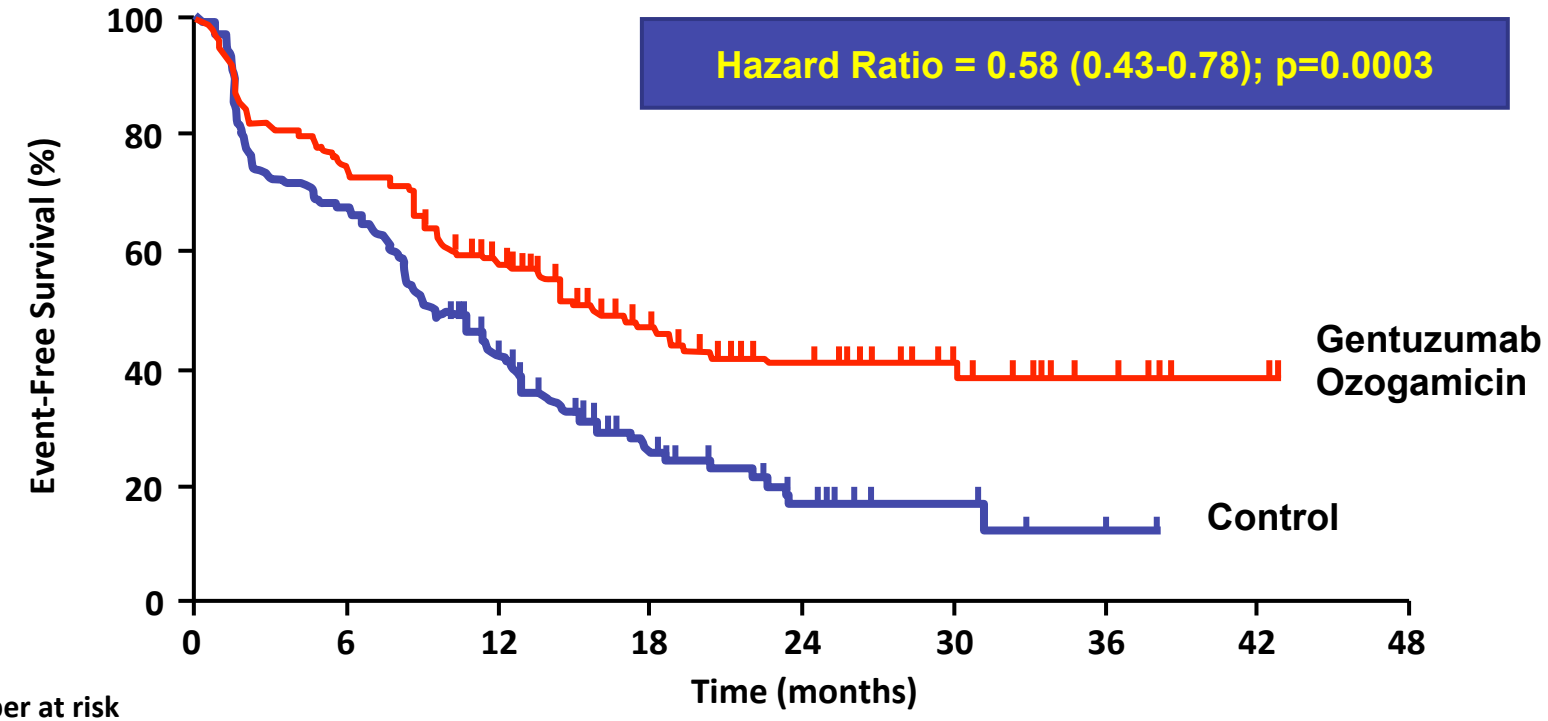
GO, gentuzumab ozogamicin .
a. Not shown: patients with information unavailable.
Castaigne S et al. *Lancet*. 2012;379(9825):1508-1516.

ALFA-0701: Outcomes

	Control Group	GO Group	Odds Ratio (95% CI)	*P* Value
All patients	139	139		
CR + CRp	104 (75%)	113 (81%)	1.46* (0.82-2.59)	0.25
CR	100 (72%)	102 (73%)		
CRp	4 (3%)	11 (8%)		
Induction courses				
1	104 (75%)	113 (81%)		
2	35 (25%)	25 (18%)		
Death before induction	1 (<1%)	0		
Death during induction	5 (4%)	9 (6%)		
Resistant disease (no CR or CRp)	29 (21%)	17 (12%)		

CI, confidence interval; CR, complete remission; CRp, complete remission with incomplete platelet recovery; GO, gemtuzumab ozogamicin).
Castaigne S et al. *Lancet*. 2012;379(9825):1508-1516.

ALFA-0701: Event-Free Survival



Number at risk

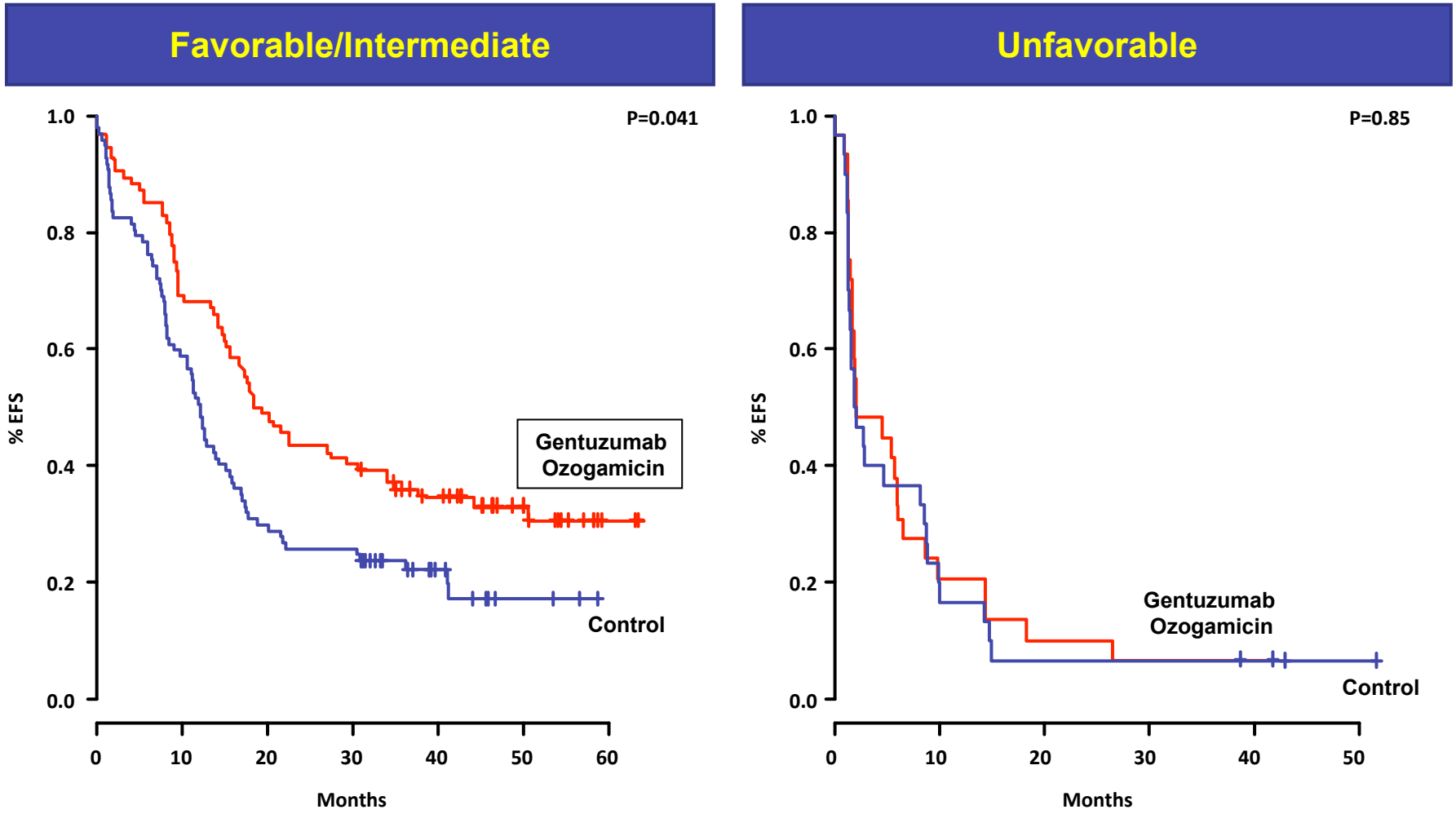
Control	139	92	52	23	10	5	1	0	0
Mylotarg	139	101	75	46	32	18	10	3	0

	Control Group (n=139)	GO Group (n=139)
Time (months; median, range)	9.7 (8.0-11.9)	15.6 (11.7-22.4)
Estimated rate at 2 years (95% CI)	17.1 % (10.8-27.1)	40.8 (32.8-50.8)

GO, gentuzumab ozogamicin.

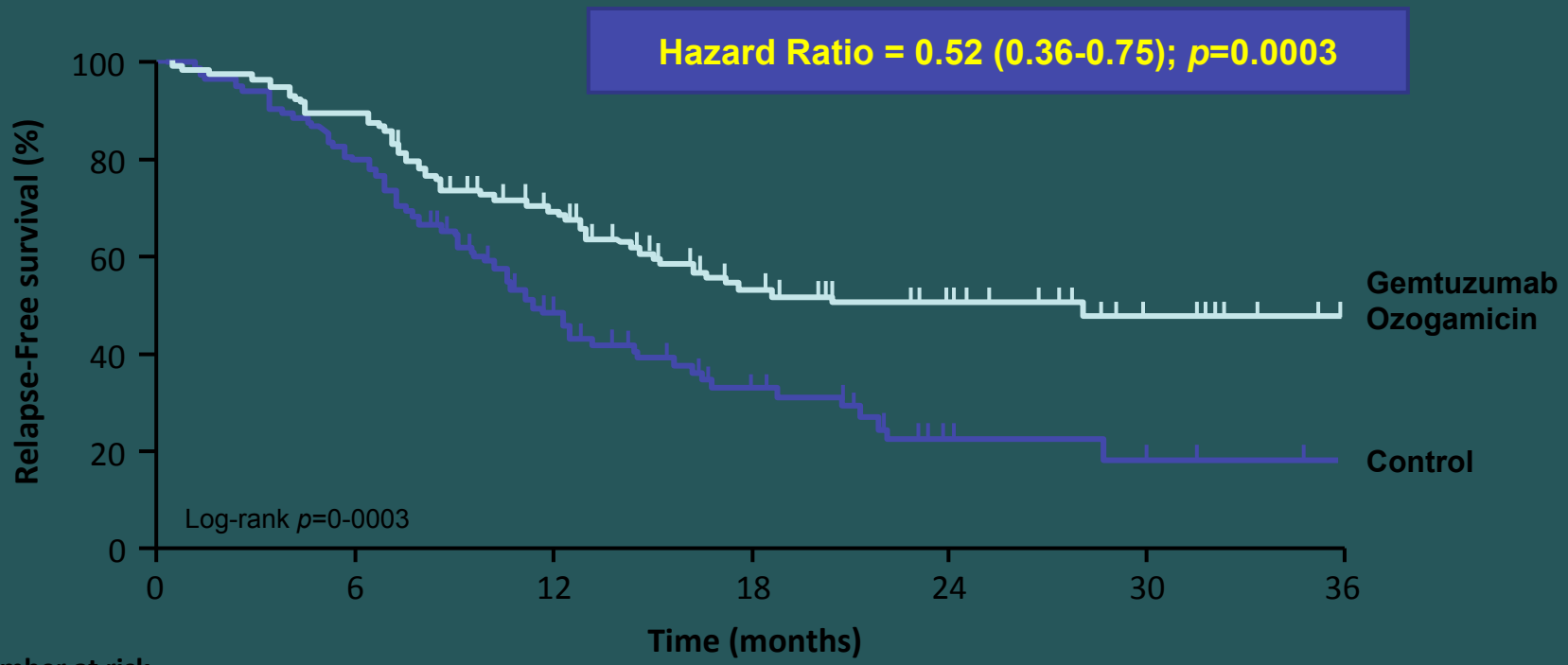
Castaigne S et al. *Lancet*. 2012;379(9825):1508-1516.

ALFA-0701: Event-Free Survival by Cytogenetic Status (Final Analyses)



Castaigne S, et al. Abstract Presented at the 56th ASH Annual Meeting and Exposition; December 6-9, 2014; San Francisco, CA.

ALFA-0701: Relapse-Free Survival



Number at risk

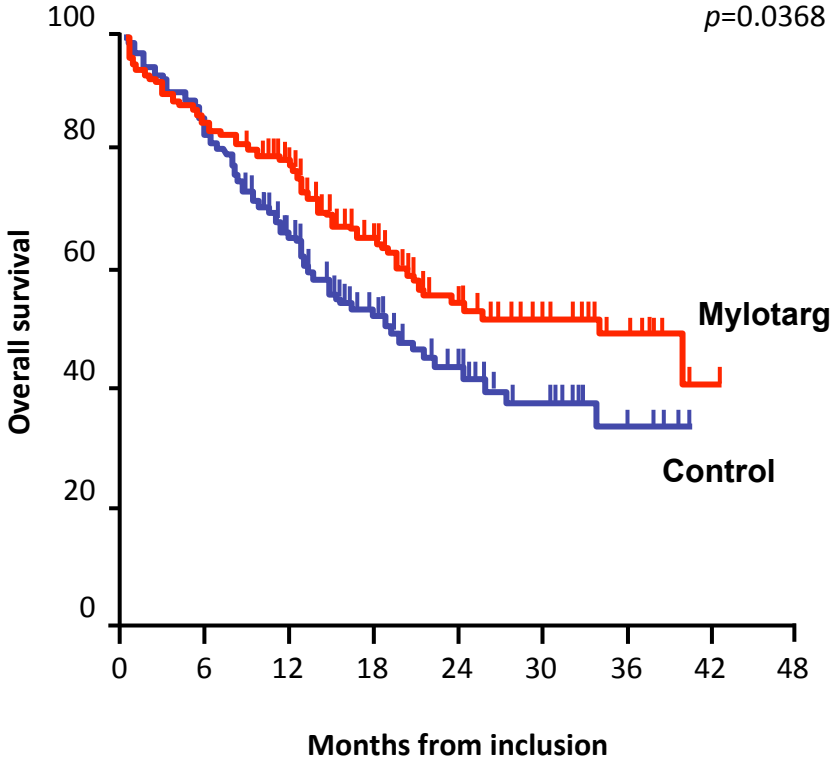
Control	104	83	39	19	6	3	1
Mylotarg	113	101	68	41	29	16	8

	Control Group (n=139)	Mylotarg Group (n=139)
Time (months; median, range)	11.4 (9.9 – 14.5)	28.1 (15.0-NR)
Estimated rate at 2 years (95% CI)	22.7% (14.5-35.7)	50.3% (41.0-61.6)

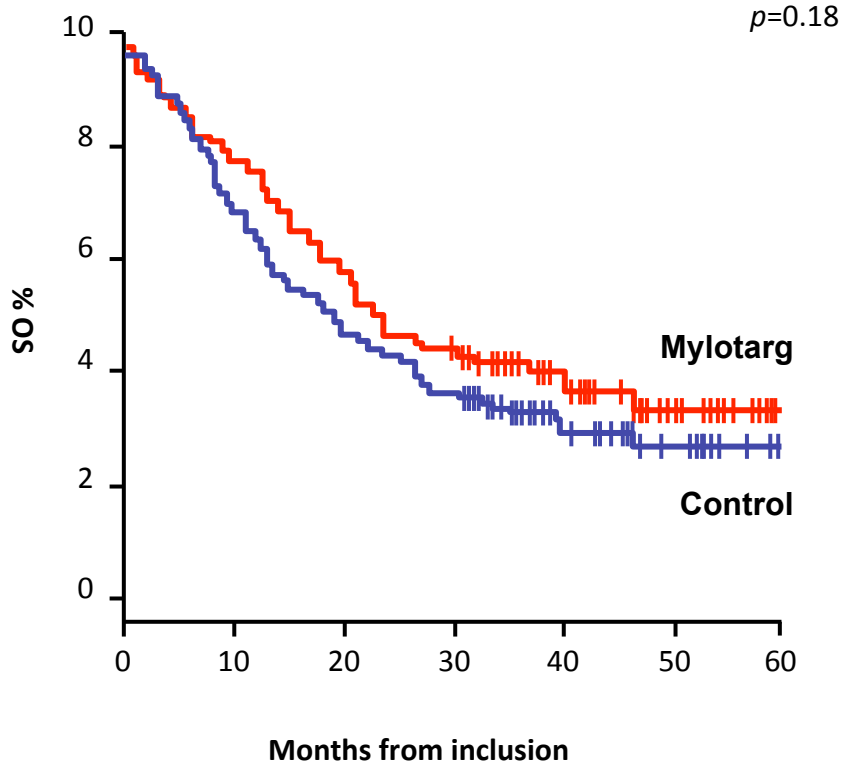
Castaigne S et al. Lancet. 2012;379(9825):1508-1516.

ALFA-0701: Overall Survival

Primary Analyses[1]



Long-term Analyses[2]



GO, gentuzumab ozogamicin.

1. Castaigne S et al. *Lancet*. 2012;379(9825):1508-1516.
2. Castaigne S, et al. Abstract Presented at the 56th ASH Annual Meeting and Exposition; December 6-9, 2014; San Francisco, CA.

ALFA-0701: Hematologic Toxicity

Duration of Treatment-induced Cytopenia (Median Days)

	Control Group (n=139)	GO Group (n=139)	Point Difference* (95% CI)	*P* Value
Neutropenia (<0.5x10^9 cells per L)				
After induction	22 (18-27)	22 (20-26)	-0.4 (-2.6 to -1.8)	0.68
After first consolidation	10 (8-15)	13 (10-18)	-2.9 (-5.4 to -0.6)	0.0017
After second consolidation	13 (10-16)	15 (12-20)	-3.7 (-6.2 to -1.4)	0.0021
Thrombocytopenia (<50 x 10^9 cells per L)				
After induction	21 (18-25)	25 (20-30)	-3.3 (-5.8 to -0.8)	0.0006
After first consolidation	9 (6-13)	17 (11-27)	-9.5 (-16.4 to -2.8)	<0.0001
After second consolidation	13 (9-20)	24 (15-35)	-9.5 (-13.5 to -5.4)	<0.0001
Persistent Thrombocytopenia (<50 x10^9 cells per L)				
By day 45 after induction	0/139	4/139 (3%)	0 (0 to 0.9)	0.125
By day 45 after first consolidation	2/98 (2%)	9/99 (9%)	0.2(0.1 to 0.9)	0.05825
By day 45 after second consolidation	2/90 (2%)	9/85 (11%)	0.2 (0.1 to 0.8)	0.02895

Data are median (interquartile range [IQR]) or n/N (%) unless otherwise indicated.
*All values mean difference except for persistent thrombocytopenia, which reflects relative risk.
GO, gemtuzumab ozogamicin (Mylotarg).
Castaigne S et al. *Lancet*. 2012;379(9825):1508-1516.

ALFA-0701: Non-Hematologic Toxicity

	Control Group (n=139)	GO Group (n=139)	Relative Risk (95% CI)	*P* Value
Induction death	5/139 (4%)	9/139 (6%)	0.56 (0.20–1.54)	0.41
Transfer to intensive-care unit	17/139 (12%)	20/139 (14%)	0.85 (0.47–1.54)	0.72
Treatment-related death during CR or CRp	8/104* (8%)	2/113 (2%)	4.35 (1·.07–17.84)	0.051
Grade 3 and 4 AEs				
Hemorrhage	4/139 (3%)	12/139 (9%)	0.33 (0.12–0.95)	0.068
Cardiac	9/139 (6%)	11/139 (8%)	0.82 (0.36–1.87)	0.82
Liver	9/139 (6%)	18/139 (13%)	0.50 (0.24–1.05)	0.10
Skin or mucosa	25/139 (18%)	32/139 (23%)	0.11 (0.03–0.42)	0.37
Gastrointestinal	14/139 (10%)	22/139 (16%)	0.64 (0.34–1.18)	0.21
Pulmonary	16/139 (12%)	16/139 (12%)	1.00 (0.53–1.90)	1.00
Grade 3 and 4 Infections				
During induction	50/131 (38%)	59/129 (46%)	0.83 (0.62–1.11)	0.26
During first consolidation	38/95 (40%)	48/97 (49%)	0.80 (0.59–1.11)	0.19
During second consolidation	38/82 (46%)	38/81 (47%)	0.99 (0.71–1.37)	0.99

Data are n/N (%) unless otherwise indicated.
AE, adverse event; CR, complete remission; CRp, complete remission with incomplete platelet recovery.
*Includes 5 deaths after stem cell transplants.
Castaigne S et al. *Lancet*. 2012;379(9825):1508-1516.

ALFA-0701: Conclusions

- Fractionated doses of gemtuzumab ozogamicin added to standard chemotherapy improved clinical outcomes in patients aged 50–70 years with *de novo* AML
  - Significantly improved EFS (primary endpoint) in patients with favorable or intermediate cytogenetics
  - Improvement in OS in treatment arm containing fractionated dosing of gemtuzumab ozogamicin suggested in primary analysis, but OS not statistically significant at final, long-term analysis
- 3-3-3 gemtuzumab ozogamicin regimen associated with an acceptable safety profile and allowed delivery of high cumulative dose of gemtuzumab ozogamicin without excess toxicity
  - Hematologic toxicity, particularly persistent thrombocytopenia, more common in gemtuzumab ozogamicin-containing treatment arm than in the control arm
  - Gemtuzumab ozogamicin use not associated with an increase in the risk of death from toxicity or in the incidence of any grade 3 or 4 AE

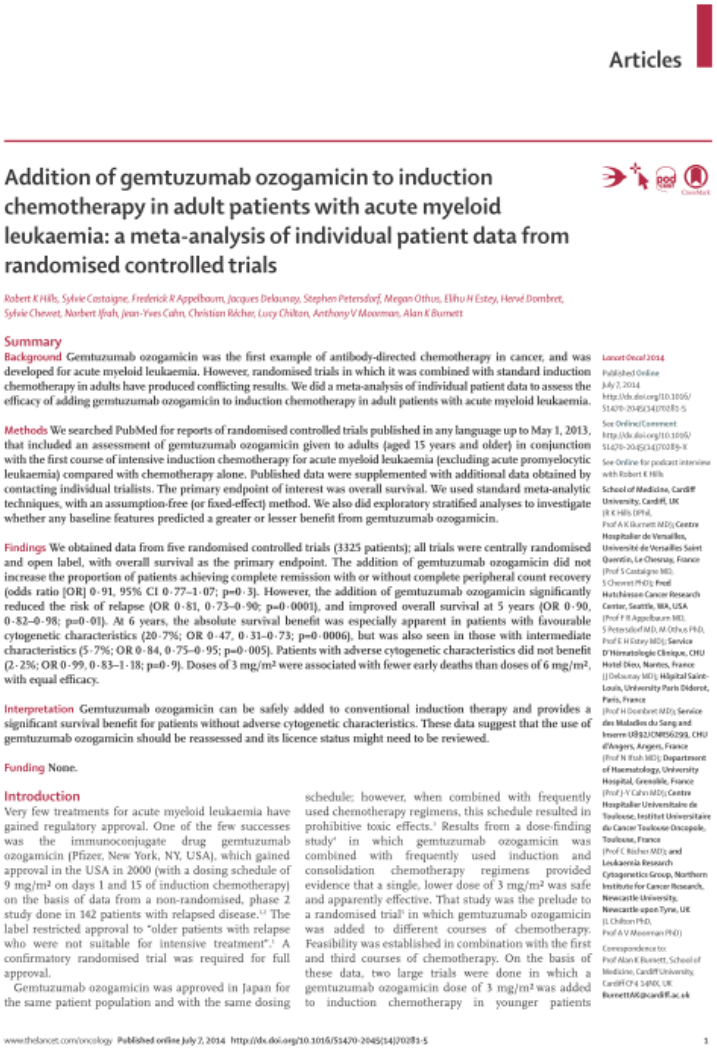
AML, acute myeloid leukemia; EFS, event-free survival; OS, overall survival.

Castaigne S et al. Lancet. 2012;379(9825):1508-1516.
Castaigne S, et al. Abstract Presented at the 56th ASH Annual Meeting and Exposition; December 6-9, 2014; San Francisco, CA.

Hills et al. (2014) Meta-Analysis

Objective

- **Meta-Analysis of individual patient data from 5 trials in adults in which gemtuzumab ozogamicin was given in combination with standard induction chemotherapy**
  - **Does gemtuzumab ozogamicin provide overall benefit with acceptable early mortality?**
  - **What is the optimum dose and dosing schedule?**



Articles

Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials

Robert K Hills, Sylvie Castaigne, Frederick R Appelbaum, Jacques Delaunay, Stephen Petersdorf, Megan Othus, Elihu H Estey, Hervé Dombret, Sylvie Chevret, Norbert Ifrah, Jean-Yves Cahn, Christian Récher, Lucy Chilton, Anthony V Moorman, Alan K Burnett

Summary

Background Gemtuzumab ozogamicin was the first example of antibody-directed chemotherapy in cancer, and was developed for acute myeloid leukaemia. However, randomised trials in which it was combined with standard induction chemotherapy in adults have produced conflicting results. We did a meta-analysis of individual patient data to assess the efficacy of adding gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia.

Methods We searched PubMed for reports of randomised controlled trials published in any language up to May 1, 2013, that included an assessment of gemtuzumab ozogamicin given to adults (aged 15 years and older) in conjunction with the first course of intensive induction chemotherapy for acute myeloid leukaemia (excluding acute promyelocytic leukaemia) compared with chemotherapy alone. Published data were supplemented with additional data obtained by contacting individual trialists. The primary endpoint of interest was overall survival. We used standard meta-analytic techniques, with an assumption-free (or fixed-effect) method. We also did exploratory stratified analyses to investigate whether any baseline features predicted a greater or lesser benefit from gemtuzumab ozogamicin.

Findings We obtained data from five randomised controlled trials (3325 patients); all trials were centrally randomised and open label, with overall survival as the primary endpoint. The addition of gemtuzumab ozogamicin did not increase the proportion of patients achieving complete remission with or without complete peripheral count recovery (odds ratio [OR] 0·91, 95% CI 0·77–1·07; p=0·3). However, the addition of gemtuzumab ozogamicin significantly reduced the risk of relapse (OR 0·81, 0·73–0·90; p=0·0001), and improved overall survival at 5 years (OR 0·90, 0·82–0·98; p=0·01). At 6 years, the absolute survival benefit was especially apparent in patients with favourable cytogenetic characteristics (20·7%; OR 0·47, 0·31–0·73; p=0·0006), but was also seen in those with intermediate characteristics (5·7%; OR 0·84, 0·75–0·95; p=0·005). Patients with adverse cytogenetic characteristics did not benefit (2·2%; OR 0·99, 0·83–1·18; p=0·9). Doses of 3 mg/m² were associated with fewer early deaths than doses of 6 mg/m², with equal efficacy.

Interpretation Gemtuzumab ozogamicin can be safely added to conventional induction therapy and provides a significant survival benefit for patients without adverse cytogenetic characteristics. These data suggest that the use of gemtuzumab ozogamicin should be reassessed and its licence status might need to be reviewed.

Funding None.

Introduction

Very few treatments for acute myeloid leukaemia have gained regulatory approval. One of the few successes was the immunoconjugate drug gemtuzumab ozogamicin (Pfizer, New York, NY, USA), which gained approval in the USA in 2000 (with a dosing schedule of 9 mg/m² on days 1 and 15 of induction chemotherapy) on the basis of data from a non-randomised, phase 2 study done in 142 patients with relapsed disease.[1,2] The label restricted approval to "older patients with relapse who were not suitable for intensive treatment".[3] A confirmatory randomised trial was required for full approval.

Gemtuzumab ozogamicin was approved in Japan for the same patient population and with the same dosing schedule; however, when combined with frequently used chemotherapy regimens, this schedule resulted in prohibitive toxic effects.[3] Results from a dose-finding study[4] in which gemtuzumab ozogamicin was combined with frequently used induction and consolidation chemotherapy regimens provided evidence that a single, lower dose of 3 mg/m² was safe and apparently effective. That study was the prelude to a randomised trial[5] in which gemtuzumab ozogamicin was added to different courses of chemotherapy. Feasibility was established in combination with the first and third courses of chemotherapy. On the basis of these data, two large trials were done in which a gemtuzumab ozogamicin dose of 3 mg/m² was added to induction chemotherapy in younger patients

Lancet Oncol 2014
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See Online for podcast interview with Robert K Hills

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Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

Hills Meta-Analysis: Study Design and Selection of Datasets

- Data from 3,325 patients
  - Enrolled in 1 of 5 randomized controlled trials of GO given with a first course of intensive induction chemotherapy vs. intensive induction chemotherapy alone
- All patients ≥15 years old with newly diagnosed AML (*de novo* or secondary) or high-risk myelodysplastic syndrome
- Trials involving less intensive induction regimens (not administered to induce complete remission) and/or patients with acute promyelocytic leukemia were excluded
- Relevant randomized controlled trials published up to May 1, 2013 were identified by a PubMed search using search terms "randomized" and "gemtuzumab"
- Individual trialists were also contacted to confirm identification of all relevant studies and collect individual patient data

Hills RK, et al. *Lancet Oncol*. 2014;15:986-996.

Hills Meta-Analysis: Outcomes

- Primary endpoint: overall survival
- Secondary endpoints:
  - Complete remission with or without complete peripheral count recovery
  - 30-day mortality
  - Relapse-Free survival
  - Relapse risk
  - Death in complete remission
  - Survival from complete remission
  - Survival censored at stem-cell transplantation
- Endpoints defined in accordance with revised International Working Group criteria, except that peripheral count recovery not required for complete remission

Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

Hills Meta-Analysis: Studies Included

Trial	No. Patients	Eligibility Criteria	Median Age in Years (Range)	Chemotherapy	Dose and Schedule of GO	Median Follow-up for Survival
ALFA-0701 (Castaigne et al, 2012)	278	*de novo* AML; aged 50-70 years	62 (50-70)	DA (3+7)	3 mg/m² on days 1, 4, and 7 of chemotherapy, up to 5 mg per dose	24.1 months (IQR 15.7-32.8)
MRC AML15 (Burnett et al, 2011)	1,099	AML, either *de novo* or secondary; mostly aged <60 years	50 (15-71)	DA (3+10, then 3+8), ADE (3+10+5, then 3+8+5), or FLAG-Ida	3 mg/m² on day 1 of chemotherapy	86.0 months (IQR 76.6-99.4)
NCRI AML16 (Burnett et al, 2012)	1,115	AML, either *de novo* or secondary, or high-risk MDS; mostly aged ≥60 years	67 (51-84)	DA (3+10, then 3+8) or daunorubicin (days 1, 3, and 5) plus clofarabine (days 1-5)	3 mg/m² on day 1 of chemotherapy	45.5 months (IQR 34.3-57.6)
SWOG S0106 (Petersdorf et al, 2013)	595	*de novo* AML; aged 18-60 years	47 (18-60)	DA (3+7) plus G-CSF or GM-CSF	6 mg/m² on day 4 of chemotherapy	55.2 months (IQR 46.0-66.3)
GOELAMS AML 2006 IR (Delaunay et al, 2011)	238	*de novo* AML, aged 18-60 years	50.5 (18-60)	DA (3+7)	6 mg/m² on day 4 of chemotherapy	39.3 months (IQR 29.1-44.4)

GO = gemtuzumab ozogamicin; AML = acute myelocytic leukemia; DA = daunorubicin plus cytarabine; ADE = daunorubicin, cytarabine, and etoposide; FLAG-Ida = fludarabine, cytarabine, G-CSF, and idarubicin; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IQR = interquartile range; IR = immediate release; MDS = myelodysplastic syndrome; MRC = Medical Research Council; NCRI = National Cancer Research Institute; SWOG = Southwest Oncology Group.

Hills RK, et al. *Lancet Oncol*. 2014;15:986-996.

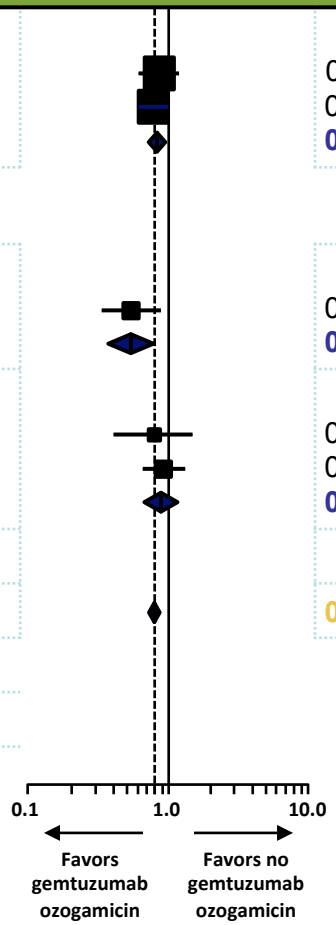
Hills Meta-Analysis: Patient Characteristics

- Ages ranged from 15 to 84 years (median 58 years)
- Of 3,325 participants
  - 1,842 (55%) were male
  - 2927 (88%) had *de novo* disease
  - 285 (9%) had secondary disease
  - 113 (3%) had high-risk myelodysplastic syndrome
- NPM1 mutation data available for 1,370 (41%) patients, of whom 398 (29%) had NPM1 mutation
- Data for FLT3 internal tandem duplications available for 1,802 (54%) patients, of whom 354 (20%) had FLT3 internal tandem duplication mutations

Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

Hills Meta-Analysis: Effect of Gemtuzumab Ozogamicin on Relapse

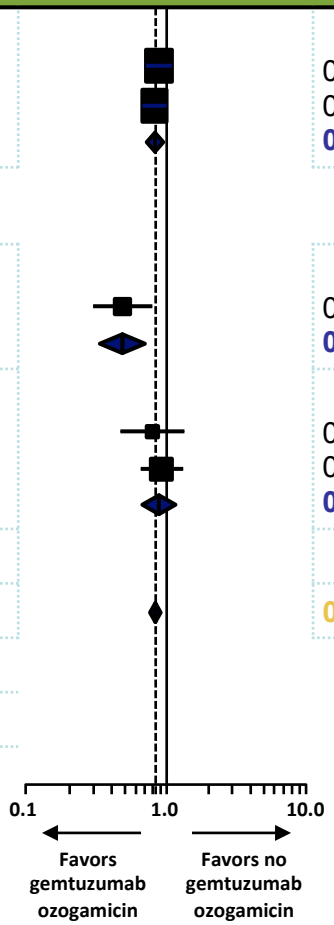
	Events/Patients		o-e	Variance	*OR (CI*)*	p value
	Gemtuzumab ozogamicin group	No gemtuzumab ozogamicin group				
3mg.m^2 single dose						
MRC AML15	213/466	237/478	-15.5	112.3	0.87 (0.68-1.11)	
NCRI AML16	272/396	286/376	-32.7	137.8	0.79 (0.63-0.98)	
Subtotal	**485/862**	**523/854**	**-48.2**	**250.2**	**0.85 (0.73-0.93)**	**0.002**
Test for heterogeneity between trials χ^2=0.6; p=0.4						
3mg.m^2 fractionated						
ALFA-0701	49/113	61/104	-15.7	26.2	0.55 (0.33-0.91)	
Subtotal	**49/113**	**61/104**	**-15.7**	**26.2**	**0.55 (0.33-0.91)**	**0.002**
6mg.m^3 dose						
GOELAMS AML2006 IR	31/109	36/102	-4.3	16.7	0.77 (0.41-1.46)	
SWOG 0106	94/222	101/222	-3.7	46.7	0.92 (0.63-1.35)	
Subtotal	**125/331**	**137/324**	**-8.0**	**63.4**	**0.88 (0.69-1.13)**	**0.3**
Test for heterogeneity between trials χ^2=0.4; p=0.5						
Total	**659/1306**	**721/1282**	**-71.9**	**339.8**	**0.81 (0.73-0.90)**	**0.0001**
Test for heterogeneity (five trials) χ^2=5.4; p=0.2						
Test for heterogeneity between subtotals χ^2=4.4; p=0.1						



Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

Hills Meta-Analysis: Effect of Gemtuzumab Ozogamicin on Relapse-Free Survival

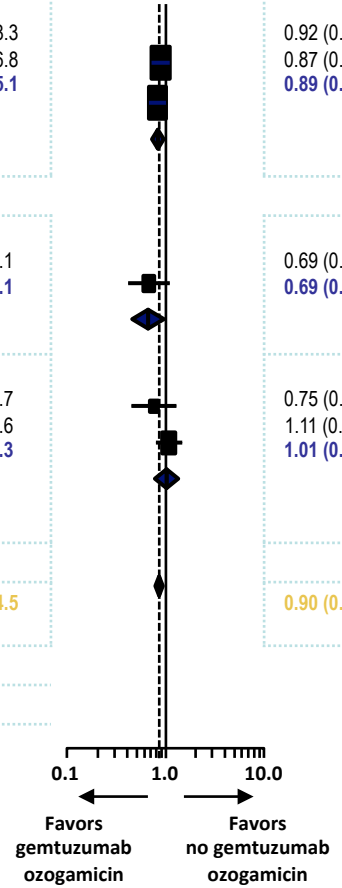
	Events/Patients		o-e	Variance	*OR (CI*)*	p value
	Gemtuzumab ozogamicin group	No gemtuzumab ozogamicin group				
3mg.m^2 single dose						
MRC AML15	282/466	314/478	-20.8	148.8	0.87 (0.70-1.07)	
NCRI AML16	625/396	321/376	-27.2	158.5	0.84 (0.69-1.03)	
Subtotal	**607/862**	**635/854**	**-48.0**	**308.2**	**0.86 (0.77-0.96)**	**0.006**
Test for heterogeneity between trials χ^2=0.1; p=0.8						
3mg.m^2 fractionated						
ALFA-0701	51/113	69/104	-19.1	28.7	0.51 (0.32-0.83)	
Subtotal	**51/113**	**69/104**	**-19.1**	**28.7**	**0.51 (0.36-0.74)**	**0.0004**
6mg.m^3 dose						
GOELAMS AML2006 IR	43/109	48/102	-4.9	22.7	0.81 (0.47-1.39)	
SWOG 0106	118/222	122/222	-2.5	59.9	0.96 (0.69-1.34)	
Subtotal	**161/331**	**170/324**	**-7.4**	**82.6**	**0.91 (0.74-1.14)**	**0.4**
Test for heterogeneity between trials χ^2=0.5; p=0.5						
Total	**819/1306**	**874/1282**	**-74.4**	**419.5**	**0.84 (0.76-0.92)**	**0.0003**
Test for heterogeneity (five trials) χ^2=8.2; p=0.08						
Test for heterogeneity between subtotals χ^2=7.7; p=0.02						

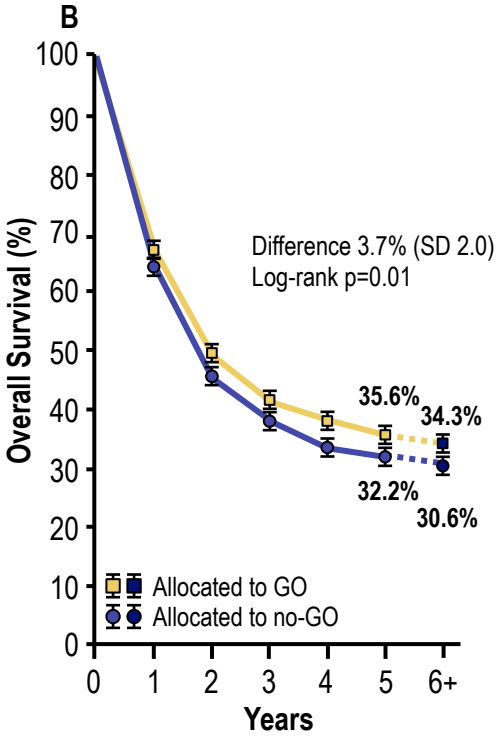


Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

Hills Meta-Analysis: Effect of Gemtuzumab Ozogamicin on Overall Survival

	Events/Patients		o-e	Var	OR (CI*)	p value
	Gemtuzumab ozogamicin group	No gemtuzumab ozogamicin group				
3mg.m² single dose						
MRC AML15	326/548	348/551	-14.7	168.3	0.92 (0.75-1.12)	
NCRI AML16	447/559	466/554	-31.1	226.8	0.87 (0.73-1.03)	
Subtotal	**773/1107**	**814/1105**	**-45.7**	**395.1**	**0.89 (0.81-0.98)**	**0.02**
Test for heterogeneity between trials χ^2=0.2; p=0.6						
3mg.m² fractionated						
ALFA-0701	59/139	72/139	-11.8	32.1	0.69 (0.44-1.09)	
Subtotal	**59/139**	**72/139**	**-11.8**	**32.1**	**0.69 (0.49-0.98)**	**0.04**
6mg.m³ dose						
GOELAMS AML2006 IR	41/119	54/119	-7.0	23.7	0.75 (0.44-1.27)	
SWOG 0106	151/295	144/300	8.0	73.6	1.11 (0.83-1.50)	
Subtotal	**192/414**	**198/419**	**1.0**	**97.3**	**1.01 (0.83-1.23)**	**0.9**
Test for heterogeneity between trials χ^2=2.9; p=0.09						
Total	**1024/1660**	**1084/1663**	**-56.6**	**524.5**	**0.90 (0.82-0.98)**	**0.01**
Test for heterogeneity (five trials) χ^2=6.7; p=0.2						
Test for heterogeneity between subtotals χ^2=3.6; p=0.2						



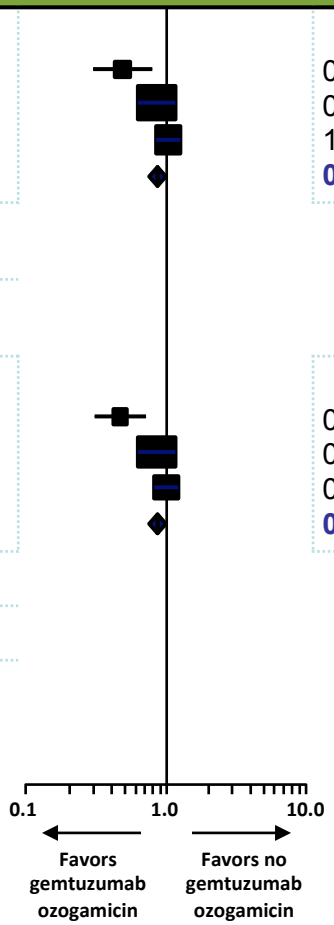


Annual Event Rates	Years 1-5	Years 6+
GO	26.7% SD 0.8	3.5% SD 0.8
No-GO	29.5% SD 0.9	5.2% SD 1.0

Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

Hills Meta-Analysis: Overall Survival by Cytogenetic Status

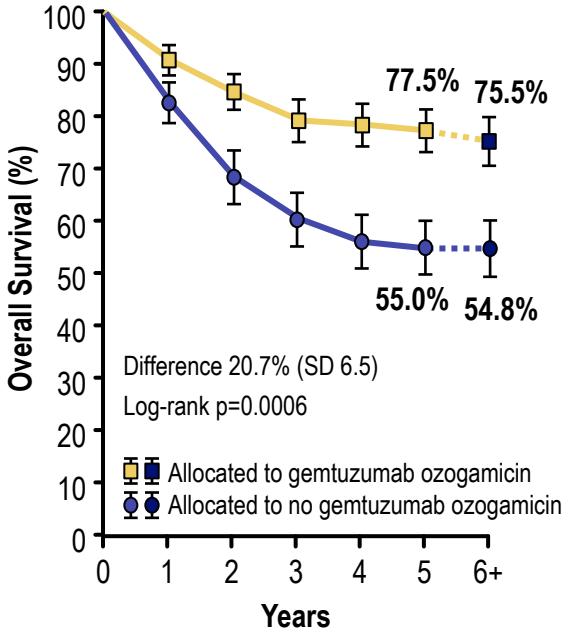
	Events/Patients					
	Gemtuzumab ozogamicin group	No gemtuzumab ozogamicin group	o-e	Variance	*OR (CI*)*	p value
Original coding						
Favourable	32/125	54/126	-14.3	20.5	0.50 (0.32-0.77)	
Intermediate	549/962	596/964	-44.2	284.4	0.86 (0.76-0.96)	
Adverse	223/261	227/256	3.1	110.6	1.03 (0.85-1.24)	
Subtotal	**804/1348**	**877/1346**	**-55.4**	**415.5**	**0.88 (0.79-0.96)**	**0.007**
Test for heterogeneity between subgroups χ^2=9.6; p=0.008						
Test for trend between subgroups χ^2=7.8; p=0.005						
Revised MRC coding[12]						
Favourable	30/122	54/124	-15.5	20.6	0.47 (0.31-0.73)	
Intermediate	506/911	559/916	-45.3	264.6	0.84 (0.75-0.95)	
Adverse	260/299	258/284	1.2	127.6	0.99 (0.83-1.18)	
Subtotal	**796/1332**	**871/1324**	**-61.9**	**412.8**	**0.86 (0.78-0.95)**	**0.002**
Test for heterogeneity between subgroups χ^2=10.1; p=0.006						
Test for trend between subgroups χ^2=7.7; p=0.006						



Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

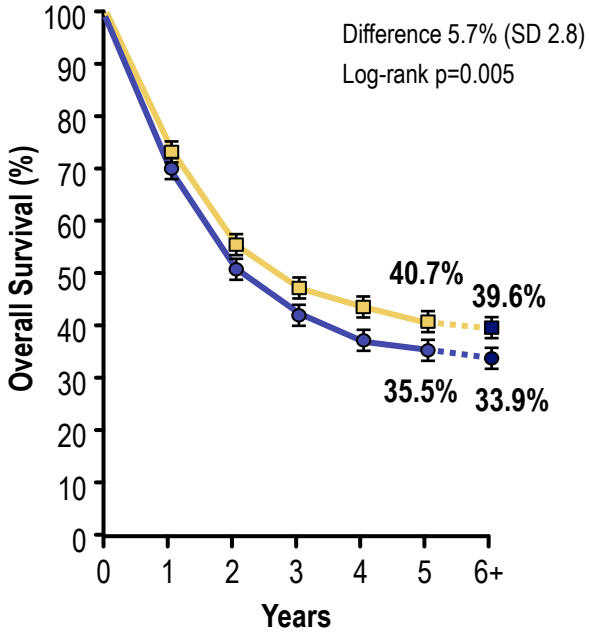
Hills Meta-Analysis: Overall Survival by Cytogenetic Status

Favorable



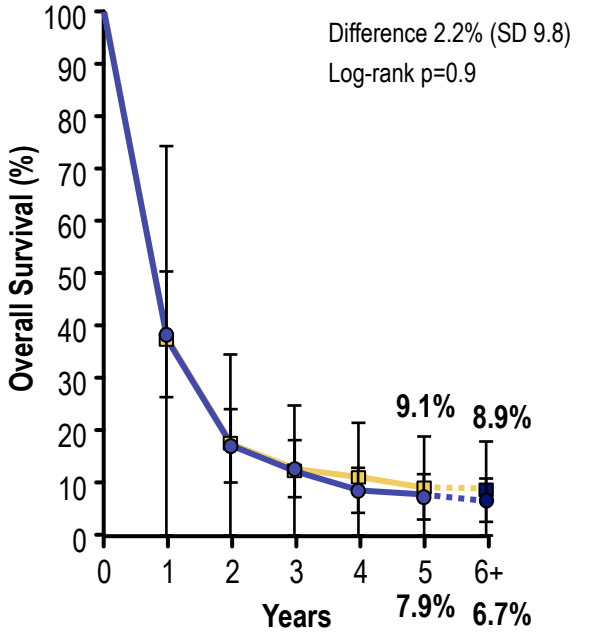
Annual Event Rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	5.8% SD 1.1	2.3% SD 1.3
No-gemtuzumab ozogamicin	14.1% SD 1.9	0.0% SD 0.0

Intermediate



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

Adverse



Annual Event Rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	73.8% SD 4.6	2.4% SD 0.8
No-gemtuzumab ozogamicin	76.7% SD 4.8	21.1% SD 10.5

Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

Hills Meta-Analysis: No Effect on 30-Day Mortality, Death in Complete Remission, or Survival after Remission

- Nonsignificant increase in 30-day mortality with gemtuzumab ozogamicin
- 30-day mortality was significantly greater for patients given gemtuzumab ozogamicin at 6 mg/m^2 than for those given 3 mg/m^2 (heterogeneity P = .03)
- No significant difference between treatment groups with respect to deaths while in complete remission
- None of the trial results suggested that patient deaths while in remission were increased among those receiving gemtuzumab ozogamicin
- Reduction of relapse with addition of gemtuzumab ozogamicin led to significantly improved survival after achieving remission

Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

Conclusions

- GO can be added safely to conventional induction therapy and significantly improves overall survival
  - 10% reduction in risk of death (*P* = .01)
  - 16% reduction in risk of relapse (*P* = .0003)
- 30-day mortality
  - Lower with 3 mg/m^2 vs. 6 mg/m^2
  - When SWOG S0106 excluded, GO not associated with increased 30-day mortality for remaining patients
- Cytogenetics showed significant interaction with treatment
  - Survival benefit strongest in those with favorable cytogenetic characteristics
  - Survival benefit also evident in those with intermediate characteristics
  - Patients with adverse cytogenetic characteristics did not benefit

Hills RK, et al. *Lancet Oncol.* 2014;15:986-996.

AML-19

Objective

- Sequential Phase 2-3 design
  - Phase 2: determine which of 2 schedules of low-dose GO induction monotherapy was more promising to continue phase III comparison with BSC in the study population
  - Phase 3: to compare GO to BSC in untreated AML in older patients unfit for intensive chemotherapy

- Accrued June 2004 through Dec 2006
- Phase 2 results published 2012 in *Br J Haematol*[1]
- Phase 3 results published 2016 in *JCO*

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Gemtuzumab Ozogamicin Versus Best Supportive Care in Older Patients With Newly Diagnosed Acute Myeloid Leukemia Unsuitable for Intensive Chemotherapy: Results of the Randomized Phase III EORTC-GIMEMA AML-19 Trial

Sergio Amadori, Stefan Suciu, Dominik Selleslag, Franco Aversa, Gianluca Gaidano, Maurizio Musso, Luciana Annino, Adriano Venditti, Maria Teresa Voso, Carla Mazzone, Domenico Magro, Paolo De Fabritiis, Petra Muus, Giuliana Alimena, Marco Mancini, Anne Hagemeijer, Francesca Paolini, Marco Vignetti, Paola Fazi, Liv Meert, Safàa Mahmoud Ramadan, Roel Willemze, Theo de Witte, and Frédéric Baron

A B S T R A C T

Purpose
To compare single-agent gemtuzumab ozogamicin (GO) with best supportive care (BSC) including hydroxyurea as first-line therapy in older patients with acute myeloid leukemia unsuitable for intensive chemotherapy.

Patients and Methods
In this trial, patients at least 61 years old were centrally randomized (1:1) to receive either a single induction course of GO (6 mg/m^2 on day 1 and 3 mg/m^2 on day 8) or BSC. Patients who did not progress after GO induction could receive up to eight monthly infusions of the immunoconjugate at 2 mg/m^2. Randomization was stratified by age, WHO performance score, CD33 expression status, and center. The primary end point was overall survival (OS) by intention-to-treat analysis.

Results
A total of 237 patients were randomly assigned (118 to GO and 119 to BSC). The median OS was 4.9 months (95% CI, 4.2 to 6.8 months) in the GO group and 3.6 months (95% CI, 2.6 to 4.2 months) in the BSC group (hazard ratio, 0.69; 95% CI, 0.53 to 0.90; $P = .005$); the 1-year OS rate was 24.3% with GO and 9.7% with BSC. The OS benefit with GO was consistent across most subgroups, and was especially apparent in patients with high CD33 expression status, in those with favorable/intermediate cytogenetic risk profile, and in women. Overall, complete remission (CR [complete remission] + CRi [CR with incomplete recovery of peripheral blood counts]) occurred in 30 of 111 (27%) GO recipients. The rates of serious adverse events (AEs) were similar in the two groups, and no excess mortality from AEs was observed with GO.

Conclusion
First-line monotherapy with low-dose GO, as compared with BSC, significantly improved OS in older patients with acute myeloid leukemia who were ineligible for intensive chemotherapy. No unexpected AEs were identified and toxicity was manageable.

J Clin Oncol 34. © 2016 by American Society of Clinical Oncology

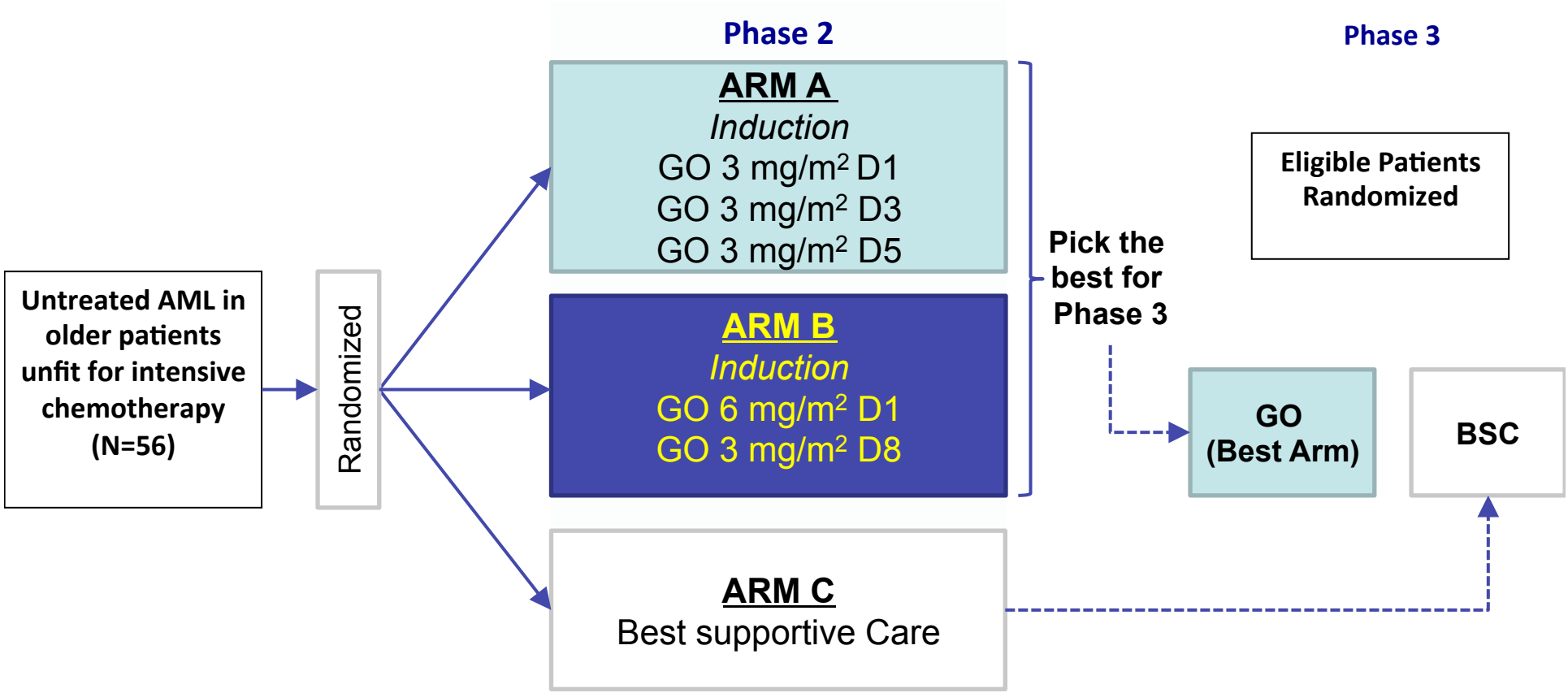
INTRODUCTION

Treatment of acute myeloid leukemia (AML) in older patients remains challenging. In this age group, the benefit associated with intensive chemotherapy is marginal and the chance for cure continues to be less than 10%.[1,2] Several host- and disease-related factors contribute to poor outcome in elderly patients with AML, including medical comorbidities, physical frailty, and increased incidence of poor-risk biologic features (eg, adverse cytogenetics, expression of multidrug resistance proteins, or prior myelodysplasia).[3] As a result, most elderly patients, in particular those over the age of 75 years and those with significant comorbidities, are not considered suitable for an intensive treatment approach. These patients are treated with best supportive care (BSC) including hydroxyurea or low-dose cytarabine, but outcomes remain dismal.[4] There is therefore an unmet medical need in this patient population for safer and more effective therapies.

BSC, best supportive care; GO gemtuzumab ozogamicin; OS, overall survival

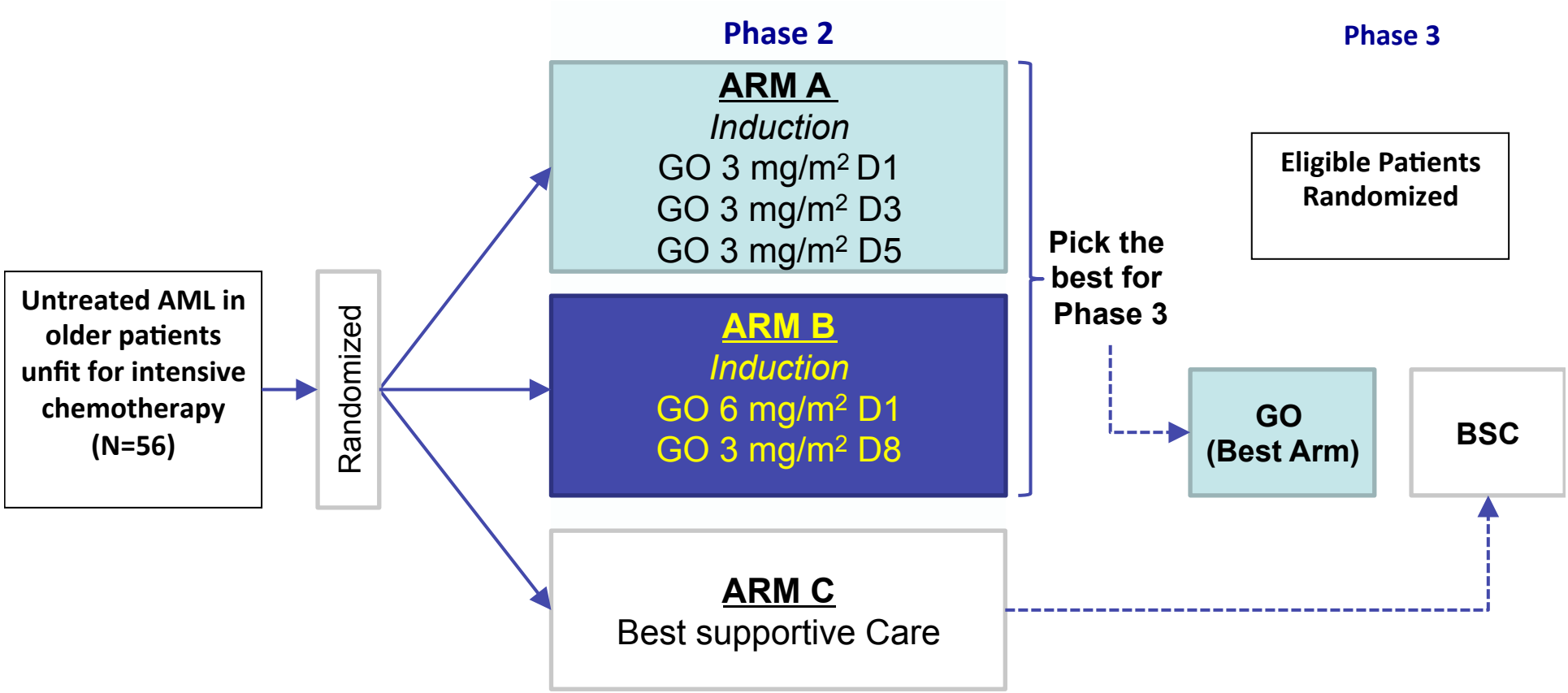
1. Amadori S, et al. *Br J Haematol*. 2010;149(3):376-82.
2. Amadori S, Suciu S, Selleslag D et al. *J Clin Oncol.* 2016 Jan 25. pii: JCO640060. [Epub ahead of print]

AML-19: Overall Study Design



AML, acute myeloid leukemia; BSC, best supportive care; D, day; GO, gemtuzumab ozogamicin.
Amadori S, et al. *Br J Haematol*. 2010;149(3):376-82.

AML-19: Overall Study Design



AML, acute myeloid leukemia; BSC, best supportive care; D, day; GO, gemtuzumab ozogamicin.
Amadori S, et al. *Br J Haematol*. 2010;149(3):376-82.

AML-19: Eligibility Criteria

Inclusion

- **Previously untreated patients**
- ***de novo* or secondary AML**
- **Not considered candidates for intensive chemotherapy**
  - **All >75 years**
  - **61-75 years with a WHO PS >2 or unwilling to receive intensive chemotherapy**

Exclusion

- **Acute promyelocytic leukemia**
- **Central nervous system leukemia**
- **Blast crisis of CML or AML**
- **Concomitant malignant disease**
- **Severe cardiac or pulmonary dysfunction**
- **Active uncontrolled infection**
- **HIV positivity**

AML, acute myeloid leukemia; CML, chronic myeloid leukemia; PS, performance status; WHO, World Health Organization.

Amadori S, et al. *Br J Haematol.* 2010;149(3):376-82.

AML-019: Summary of Clinical Response by Treatment Arm, Phase 2

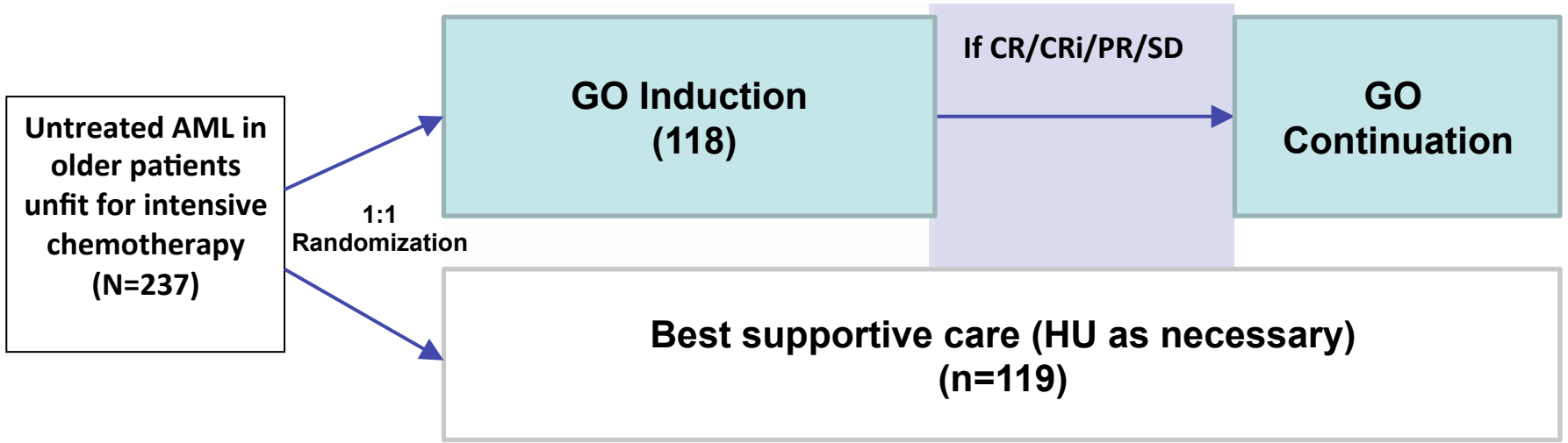
Response		Treatment Arm	
	All Patients (n=56)	A [D1,3,5] (n=29)	B [D1, 8] (n=27)
	N (%)	N(%)	N (%)
CR	11 (20)	6 (21)	5 (18)
CRp	1 (2)	0	1 (4)
PR	1 (2)	1 (3)	0
SD	15 (26)	4 (14)	11 (41)
PD	19 (34)	12 (41)	7 (26)
DnP	28 (50)	11 (38)	17 (63%)
Death (≤6 weeks)	7 (12)	4 (14)	3 (11)
Un-assessable	2 (4)	2 (7)	0

Arm B: Highest Rate of DnP; Met the Statistical Criteria to be Selected as the Preferred Regimen for Phase III Comparison with Best Supportive Care

CR, complete remission; CRp, complete remission without platelet recovery; DnP, disease non-progression; PR, partial remission; SD, stable disease; PD, progressive disease.

Amadori S, et al. *Br J Haematol*. 2010;149(3):376-82.

AML-019: Phase 3 Study Design

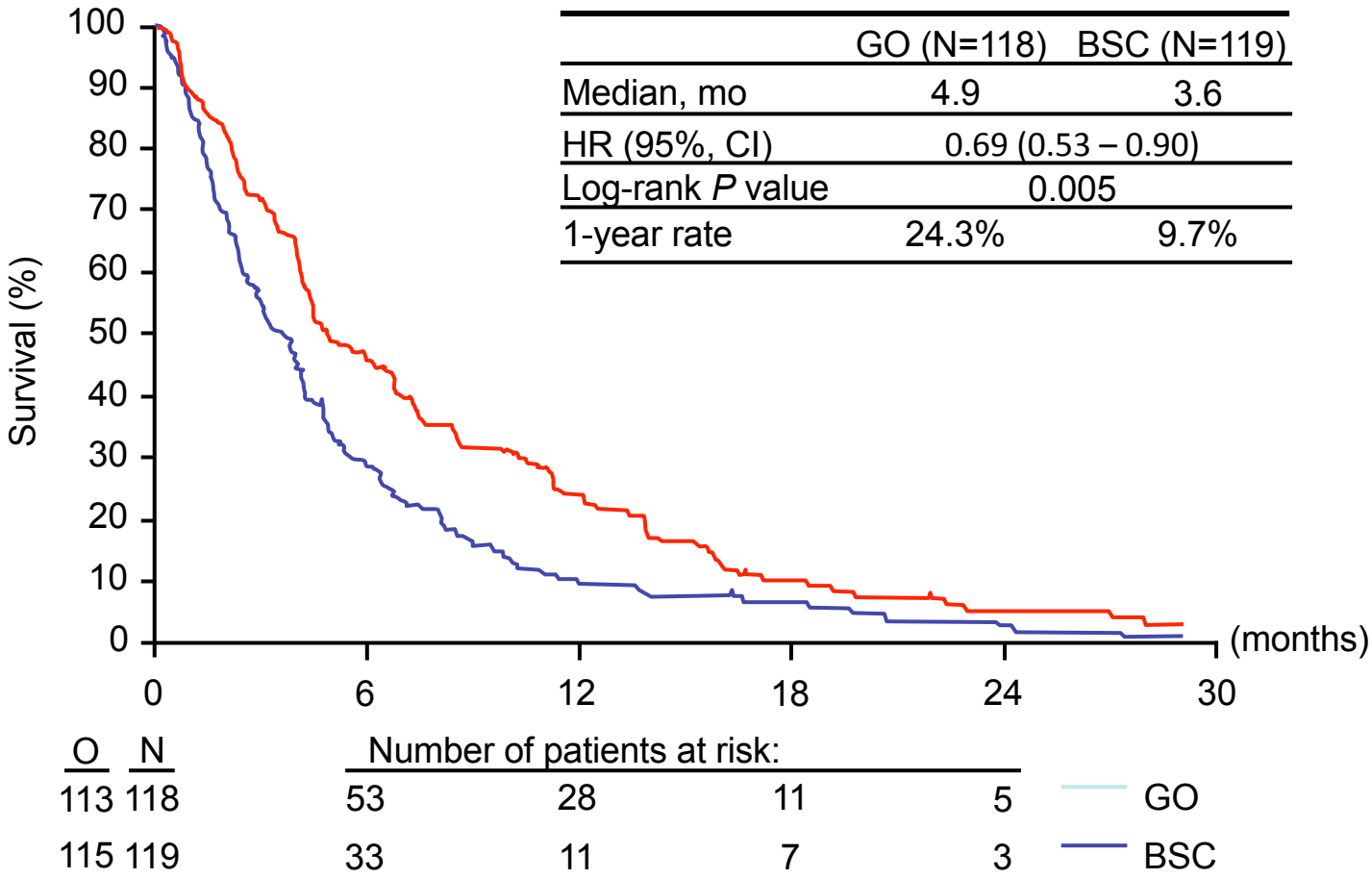


GO Schedules	
Induction	6 mg/m^2 day 1 + 3 mg/m^2 day 8
Continuation	2 mg/m^2 monthly (max 8)

AML, acute myeloid leukemia; BSC, best supportive care; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; GO gemtuzumab ozogamicin (Mylotarg); HU, hydroxyurea; PR, partial response; SD, stable disease

Amadori S, Suciu S, Selleslag D et al. *J Clin Oncol.* 2016 Jan 25. pii: JCO640060. [Epub ahead of print]

AML-019: Overall Survival



	GO (N=118)	BSC (N=119)
Median, mo	4.9	3.6
HR (95%, CI)	0.69 (0.53 – 0.90)	
Log-rank *P* value	0.005	
1-year rate	24.3%	9.7%

BSC, best supportive care; GO, gemtuzumab ozogamicin; N, number of patients; O, observed number of events

Amadori S, Suciu S, Selleslag D et al. *J Clin Oncol.* 2016 Jan 25. pii: JCO640060. [Epub ahead of print]

Overall Survival by Patient Subgroup

	Deaths/Patients				
	GO	BSC	HR	95% CI	Interaction Test
Sex					
Male	57/57	71/73	0.90	0.63 – 1.28	*P* = .05
Female	56/61	44/46	0.53	0.35 – 0.79	
CD33 expression					
<20%	9/10	13/14	1.52	0.65 – 3.58	*P* = .05
20-80%	58/58	58/58	0.75	0.52 – 1.09	
>80%	44/48	44/47	0.49	0.32 – 0.76	
Cytogenetic Risk					
Favorable/Intermediate	54/59	45/45	0.55	0.37 – 0.82	*P* = .08
Adverse	33/33	29/32	1.11	0.67 – 1.83	
Unknown	26/26	41/42	0.85	0.52 – 1.40	

Selected subgroups only

BSC, best supportive care; CI, confidence interval; GO, gemtuzumab ozogamicin ’ HR, hazard ratio

Amadori S, Suciu S, Selleslag D et al. *J Clin Oncol.* 2016 Jan 25. pii: JCO640060. [Epub ahead of print]

AML-19: Response to Gemtuzumab Ozogamicin

Response, % (n=111)	Induction Response	Best Response at Any Time
CR + CRi	24.3	27.0
CR	8.1	15.3
CRi	16.2	11.7
PR	6.3	5.4
SD	39.6	38.7
Progressive Disease	14.4	
Induction Death	7.2	
Not Evaluable	8.1	

CR, complete remission; CRi, complete remission with incomplete platelet recovery; PR, partial response; SD, stable disease.

Amadori S, Suciu S, Selleslag D et al. *J Clin Oncol.* 2016 Jan 25. pii: JCO640060. [Epub ahead of print]

AML-19: Adverse Events on Study

AEs, % (Safety Population)	GO (N=111)	BSC (N=114)
All-grade AEs	87.3	90.4
Grade ≥3 AEs	61.2	67.5
Deaths Due to AEs	17.1	20.2
30-day Mortality, %	11	13.5
60-day Mortality, %	17.8	30.4

AE, adverse, event; BSC, best supportive care; d, day; GO gemtuzumab ozogamicin .

Amadori S, Suciu S, Selleslag D et al. *J Clin Oncol.* 2016 Jan 25. pii: JCO640060. [Epub ahead of print]

AML-19: Non-Hematologic Toxicity

Maximal Grade ≥3 Adverse Events (AEs) Occurring in >5% of Patients

AEs, % (Safety Population)	GO (N=111)	BSC (N=114)
Infection	35.1	34.3
Febrile neutropenia	18.0	23.7
Bleeding	12.6	12.3
Fatigue	11.7	21.0
Liver	7.2	6.1
Cardiac	6.3	14.0
Metabolic	3.6	6.1
Renal	3.6	4.4

AE, adverse events; BSC, best supportive care; GO gemtuzumab ozogamicin .

Amadori S, Suciu S, Selleslag D et al. *J Clin Oncol.* 2016 Jan 25. pii: JCO640060. [Epub ahead of print]

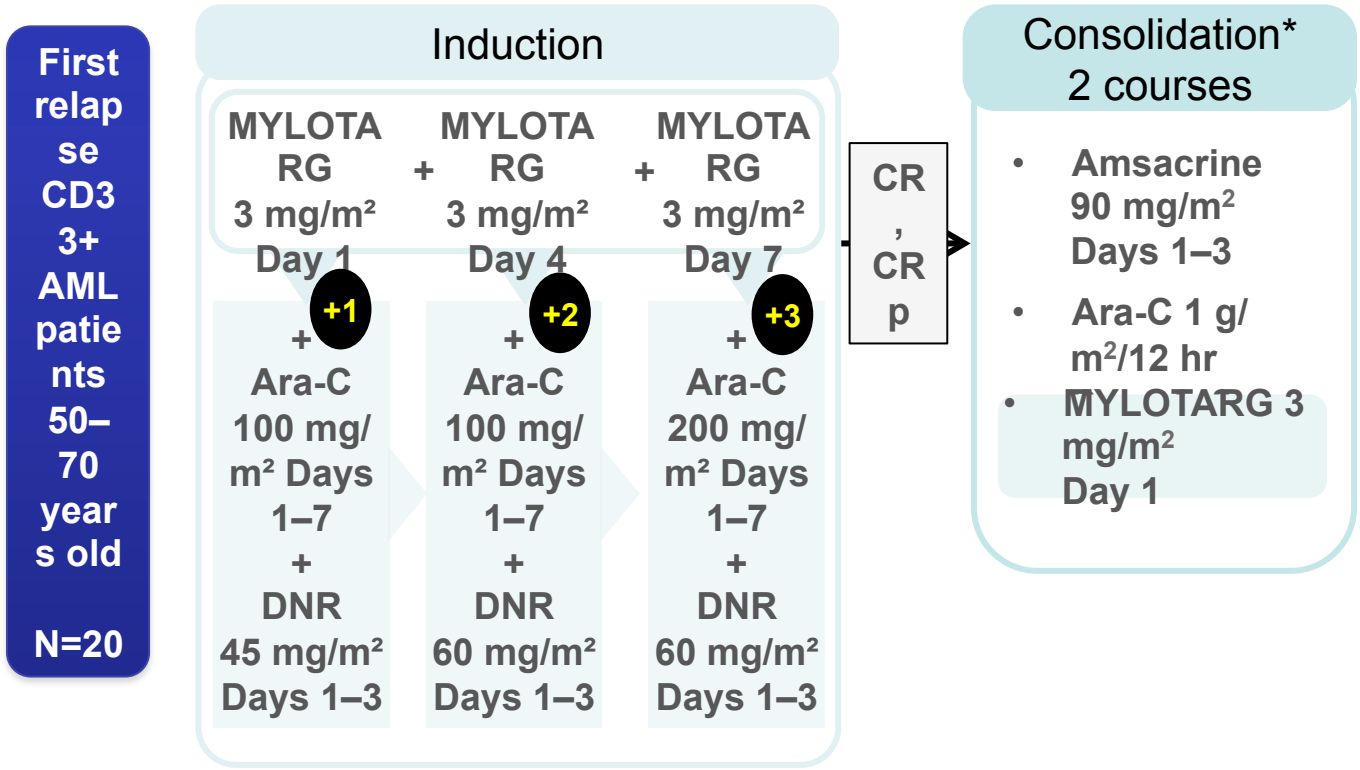
AML-19: Conclusions

- In older patients with newly diagnosed AML unsuitable for intensive chemotherapy, GO significantly improved OS compared with BSC
- Subgroup analyses revealed interactions between baseline CD33 expression, sex, and cytogenetic profile and treatment effect for OS
  - GO significantly improved OS compared with BSC
    - In patients with >80% CD33-positive blasts
    - In women
    - In patients with favorable/intermediate cytogenetic risk profiles
- No apparent increase in toxicity
  - Incidence of adverse events similar in both arms
  - Deaths due to AEs less common with gemtuzumab ozogamicin
- Further development of GO in this area of high unmet medical need is warranted

AE, adverse event; BSC, supportive care; GO, gemtuzumab ozogamicin; OS, overall survival

Amadori S, Suciu S, Selleslag D et al. *J Clin Oncol.* 2016 Jan 25. pii: JCO640060. [Epub ahead of print]

MyloFrance-2: Phase I/II study of fractionated doses of MYLOTARG with escalated doses of DNR and Ara-C as first AML salvage



- Primary objective
  - Determine optimal DNR and Ara-C doses to be combined with fractionated dosing of MYLOTARG
- Secondary objectives
  - Remission rate
  - RFS
  - OS

MyloFrance-2: Key eligibility criteria

Inclusion criteria

- 50–70 years old
- CD33+ AML in first relapse
- ECOG PS ≤2
- Serum creatinine ≤2.0 mg/dl
- ALT and AST levels <2× ULN

Exclusion criteria

- APL
- Secondary AML

MyloFrance-2: Baseline characteristics

Characteristics	N or %
Number of patients, n	20
Median age (range), years	60 (50–70)
Median duration of CR1 (range), months	10 (6–42)
Cytogenetics	
Evaluable, n	19
Favourable, n	2
Intermediate risk, n	15
Poor risk, n	2

MyloFrance-2: Overall results by dose level

	Dose level 1	Dose level 2	Dose level 3	
N	4	4	4	8
Responder	2	2	4	6
CR	2	1	4	4
CRp	-	-		2
PR	-	1		-
Failure	2	1		1
Early death	-	1		1
Grade 3/4 fever	2	1	1	0
Grade 3/4 infection	1	3	3	4
Grade 3/4 liver toxicity	-	1	-	1
DLT	0	1	0	

Overall, the third dose level was considered as tolerable, with only 1 DLT observed at dose level 2

MyloFrance-2: Overall results

Main efficacy outcomes	N=20
CR/CRp, n (%)	13 (65.0)
Median CR duration	12 months
Median OS	15 months

Main safety outcomes	N=20
Median duration of neutropenia <500/µl	30 days
Median duration of thrombocytopenia <50,000/µl	32 days
Early deaths, n (%)	2 (10.0)
Grade 3/4 fever, n (%)	5 (25.0)
Grade 3/4 infection, n (%)	11 (55.0)
Grade 3/4 liver toxicity, n (%)	2 (10.0)

No episodes of VOD

MyloFrance-2: Conclusions

MF-2: MYLOTARG (3 mg/m^2/Days 1, 4, 7) in combination with DNR
(60mg/m^2/d Days 1–3) and AraC (200 mg/m^2/d Days 1–7)

Time to recovery of neutrophils and platelets was longer than previously reported

Good hepatic tolerance was observed, NO VOD (4 patients with HSCT)

The results of the trial suggest that this combination is associated with **acceptable toxicity**

SETTEMBRE 2017

- FDA RE-APPROVAL OF GO FOR THE TREATMENT OF NEWLY-DIAGNOSED CD33+ AML IN ADULTS AND FOR THE TREATMENT OF RELAPSED OR REFRACTORY CD33+ AML IN ADULTS AND IN PEDIATRIC PATIENTS > 2 YRS. GO MAY BE USED IN COMBINATION WITH DAUNORUBICIN AND CYTARABINE FOR ADULTS WITH NEWLY-DIAGNOSED AML, OR AS A STAND-ALONE TREATMENT FOR CERTAIN ADULT AND PEDIATRIC PATIENTS

- LE DOSI DI MYLOTARG DA UTILIZZARE SONO QUELLE DEGLI STUDY ALFA0701 E DELL'AML-19

- WARNING PER LA TOSSICITA' EPATICA

CORE BINDING FACTOR (CBF)-LEUKEMIAS

- I BLASTI CON t(8;21) NELLA MAGGIOR PARTE DEI CASI NON ESPRIMONO LA Pgp (OVVERO IL PRODOTTO DEL GENE MDR1), PROBABILMENTE PER UNA SELETTIVA REPRESSIONE DEL PROMOTER DI MDR-1 DA PARTE DI AML1-ETO. DIVERSI STUDI HANNO DIMOSTRATO COME LA ESTRUSIONE DI GO DA PARTE DI Pgp POSSA CONDIZIONARE LA RISPOSTA AL MYLOTARG

- LE LEUKEMIA-INIZIATING CELLS DELLE CBF AML, A DIFFERENZA DI ALTRI TIPI DI AML, ORIGINEREBBERO DA PRECURSORI MIELOIDI EARLY-COMMITTED PIUTTOSTO CHE DA HSCs PIU' IMMATURE E QUINDI SAREBBERO PIU' SENSIBILI AL MYLOTARG A CAUSA DELLA PIU' ELEVATA ESPRESSIONE DI CD33

Clinical and experimental efficacy of gemtuzumab ozogamicin in core binding factor acute myeloid leukemia

Michele Gottardi,[1] Federico Mosna,[1]
Sergio de Angeli,[2]
Cristina Papayannidis,[3] Anna Candoni,[4]
Marino Clavio,[5] Cristina Tecchio,[6]
Andrea Piccin,[7]
Marta Campo dell'Orto,[8]
Fabio Benedetti,[6] Giovanni Martinelli,[3]
Filippo Gherlinzoni[1]

COMPARAZIONE RETROSPETTIVA DI 25 PAZIENTI CON CBF AML TRATTATI IN INDUZIONE CON FLAI5 VS 12 PAZIENTI CON CBF AML TRATTATI CON FLAI5+MYLOTARG 3 mg/m^2 IL GIORNO 6

↓

CONSOLIDAMENTO CON 2-3CICLI DI ARA-C AD ALTE DOSI

↓

I PAZIENTI CON MUTAZIONE TKD^{816} ALLA DIAGNOSI O IN CASO DI PERSISTENZA DEL TRASCRITTO MOLECOLARE AL TERMINE DEL CONSOLIDAMENTO

↓

ALLOGENICO O AUTOLOGO

Gottardi M. et al Hematology Reports 2017

	FLAI5	My-FLAI5	P
Median age	41.3 (18-66)	46.3 (29-67)	0.2602
Sex	12 M + 13 F	6 M + 6 F	0.909
Secondary acute myeloid leukemia	0	0	NA
Hepatomegaly	4	2	1.0
Splenomegaly	3	2	1.0
Sarcoma	0	1	1.0
Hemoglobin gr/dL	8.4 (4.2-11)	8.5 (5-13.6)	0.9100
White blood cells $\times 10^3$/ L	19.0 (1.6-95)	18.7 (4.5-45.5)	0.9706
N $\times 10^3$/ L	1.86 (0.33-6.35)	2.58 (0.45-11.36)	0.3680
Mo $\times 10^3$/ L	0.95 (0.01-2.56)	0.58 (0.01-2.68)	0.1330
Ly $\times 10^3$/ L	2.67 (0.50-6.80)	2.86 (0.60-7.73)	0.8016
Blasts $\times 10^3$/ L	10.9 (0.01-65.55)	11.6 (0.22-32.0)	0.9074
Platelets $\times 10^3$/ L	60.66 (8-255)	73.72 (6-531)	0.7150
Elevated LDH	18	10	0.638
DIC	2	2	0.305
Acute renal failure	0	1	0.314
t(8;21)/inv(16)	13/12	8/4	0.491
FLT3-ITD	3	2	1.0
NPM1 mutated	0	0	NA
KIT TKD ^{816} mutated	1	1	1.0
Packed BM (>80%)	12	5	0.717
Additional cytogenetic abnormalities	None: 14 pts; 1: 7 pts; 2: 3 pts; 3: 1 pts	None: 4; 1: 5 pts; 2: 1 pts; 3: 2 pts	0.387

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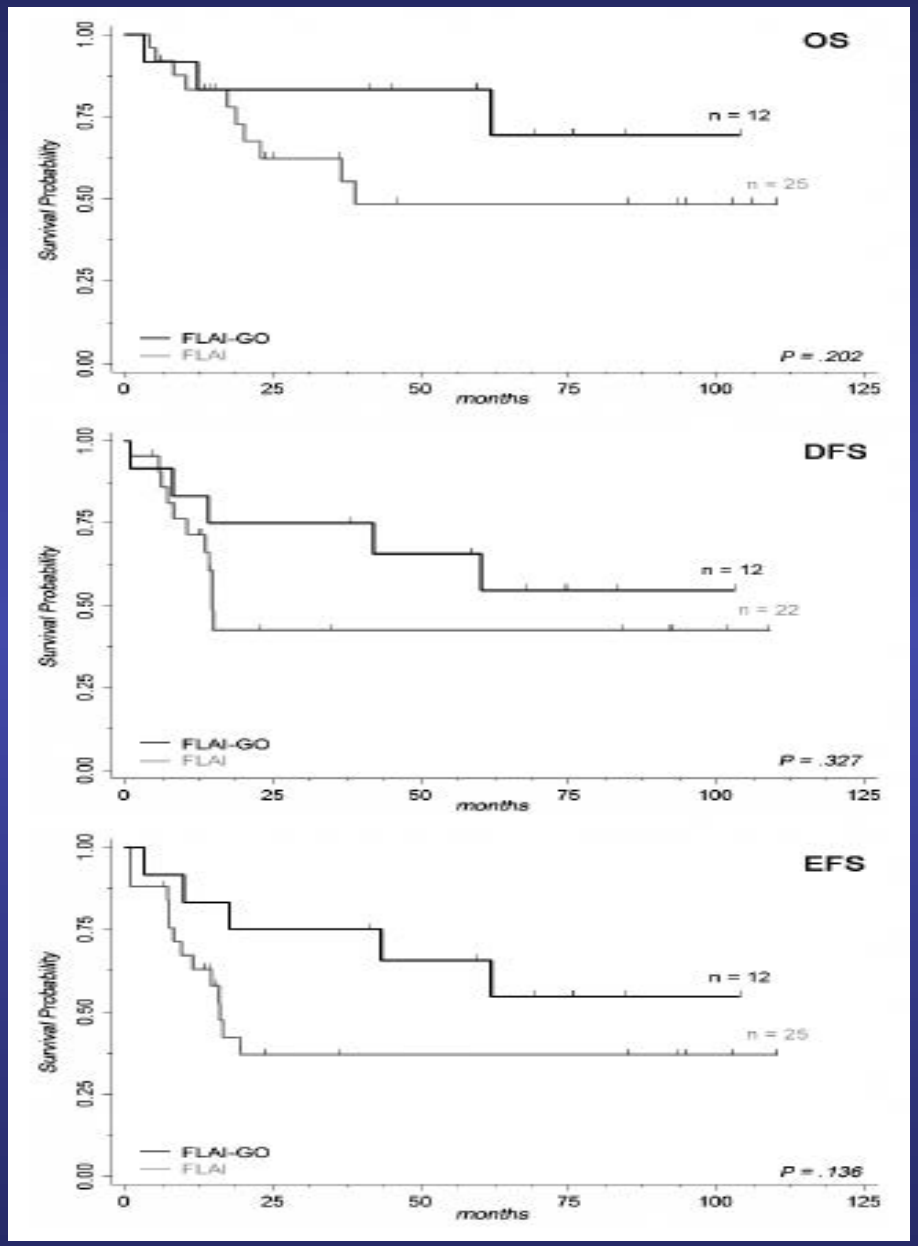
RISULTATI

	FLAI5	My-FLAI5
RC DOPO INDUZIONE	22/25 (88%)	12/12 (100%)
RICADUTE Follow up 69.2 mesi	11/22 (50%)	3/12 (25%)

- NESSUNA MORTE TOSSICA
- TUTTI I PAZIENTI HANNO COMPLETATO LA PREVISTA SCHEDULA DI TRATTAMENTO

Gottardi M. et al Hematology Reports 2017



Gottardi M. et al Hematology Reports 2017

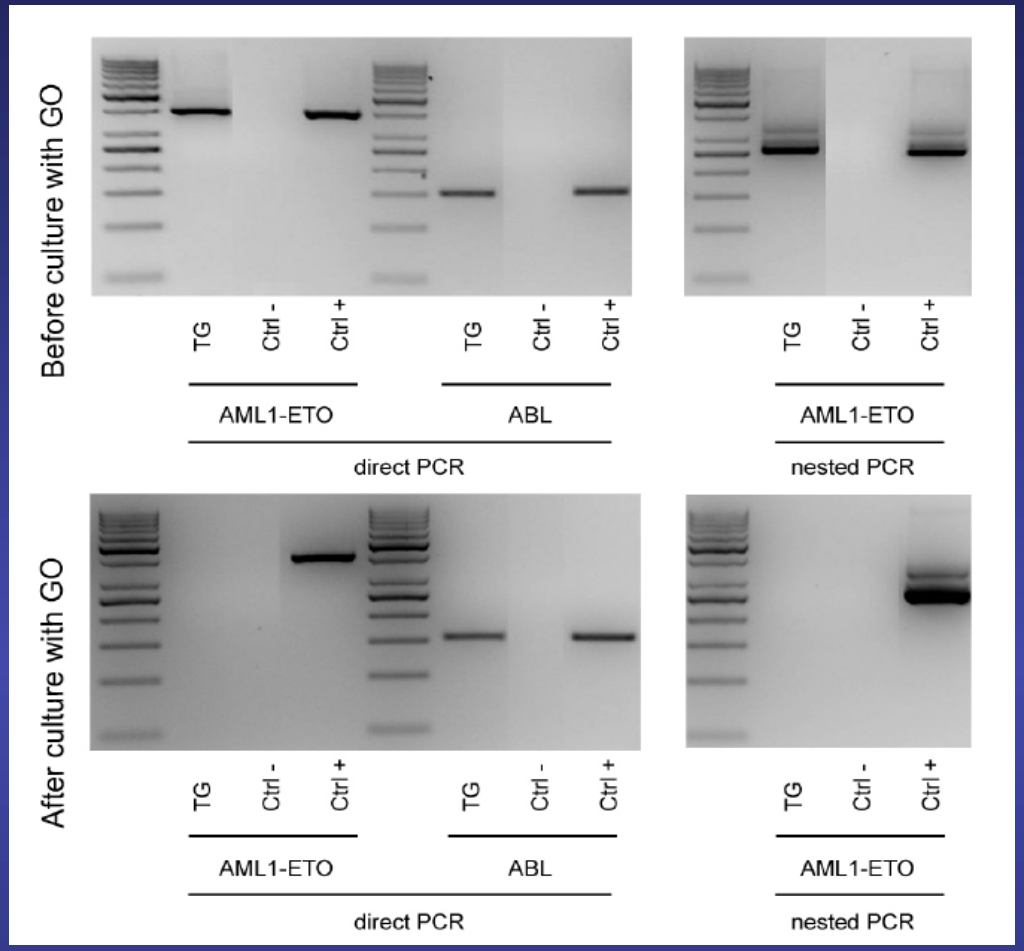
PBSC PURGING WITH MYLOTARG?

Autologous Stem Cell Transplantation with PCR-Negative Graft Would Be Associated with a Favorable Outcome in Core-Binding Factor Acute Myeloid Leukemia

Hideki Nakasone,[1] Koji Izutsu,[1] Satoshi Wakita,[2] Hiroki Yamaguchi,[2] Michiko Muramatsu-Kida,[1] Kensuke Usuki[1]

Although core-binding factor acute myeloid leukemia (CBF-AML) is generally considered to be a low-risk form of AML, the survival rate is still 50% to 60%. To evaluate the effectiveness of autologous stem cell transplantation (ASCT) with a PCR-negative graft we analyzed a series of consecutive CBF-AML patients. Between 1997 and 2006, 18 patients aged <60 years were referred under a diagnosis of CBF-AML. Peripheral blood stem cells (PBSC) were collected after a second or further course of postremission therapy. When >2.0 × 10^6/kg CD34-positive cells with minimal residual disease (MRD) undetectable by nested polymerase chain reaction (PCR) had been collected, ASCT was performed with busulfan, etoposide, and cytarabine combined with granulocyte colony-stimulating factor. Event-free survival (EFS) and complications of ASCT were then assessed. Fourteen of the 18 patients received ASCT. The median observation period was 4.4 years. The 5-year EFS was 93% for ASCT patients, despite the presence of adverse factors. In 8 of 10 patients who had detectable MRD in the bone marrow before ASCT, MRD became undetectable after ASCT. Neutrophils recovered promptly within 2 weeks, but platelets recovered relatively slowly. Half of the patients suffered from varicella zoster virus infection. Although 1 case of myelodysplastic syndrome occurred, there was no case of relapse. ASCT with a PCR-negative graft was associated with excellent EFS. For patients with CBF-AML, especially with adverse factors or remnant MRD in the bone marrow, this strategy is the treatment of choice.

Nakasone H. et al Biol Blood Marrow Transplant 2008



GO PUO' FUNZIONARE COME PURGING IN VITRO (O ANCHE IN VIVO PRIMA DELLA RACCOLTA DELLE PBSC NEI PAZIENTI MRD-POSITIVI), SENZA MENOMARE IL POTENZIALE CLONOGENICO DELLE CELLULE CD34+/CD38-

Gottardi M. et al Hematology Reports 2017

CONCLUSIONI

- DOPO CIRCA 25 ANNI DI UN PERCORSO TRAVAGLIATO DI STUDI PRE-CLINICI E CLINICI, MYLOTARG HA TROVATO LA SUA APPROVAZIONE DEFINITIVA NELLE AML CD33+, ALLA DIAGNOSI O CON MALATTIA RICADUTA/REFRATTARIA, NEI PAZIENTI PEDIATRICI, ADULTI O ANZIANI, IN COMBINAZIONE O SINGLE-AGENT

- IL PROFILO DI TOSSICITA' E' ASSOLUTAMENTE ACCETTABILE CON DOSI RIDOTTE E FRAZIONATE

- EFFICACE SOPRATTUTTO NEI PAZIENTI A RISCHIO BASSO O INTERMEDIO, E PARTICOLARMENTE NELLE CBF-LEUKEMIAS

- MECCANISMI DI RESISTENZA
- PURGING IN VITRO O IN VIVO?

SVILUPPI FUTURI

- **NUOVI AGENTI CHE ABBIANO COME TARGET CD33**

VADASTUXIMAB TALARINE (SGN-33A)

ANTICORPO LINTUZUMAB CONIUGATO A 2 MOLECOLE DI UN DIMERO PIRROLOBENZODIAZEPINICO
RISULTATI MOLTO PROMETTENTI IN ASSOCIAZIONE AD IPOMETILANTI, MA ELEVATA TOSSICITA'

RADIOIMMUNOTERAPIA CON ^{225}Ac-LINTUZUMAB

- **NUOVI AGENTI CHE ABBIANO COME TARGET ALTRE MOLECOLE DIVERSE DAL CD33 → CD123**

- **SL-401 = ANTICORPO+TOSSINA DIFTERICA**