Gemtuzumab ozogamicin, Pediatric Clinical Data

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2022 ELN Risk Categorization for AML

- The ELN AML risk classification is based on data from intensively treated patients and may need modifications for less-intensive therapies
- Initial risk assignment may change during the treatment course based on MRD analyses

Risk Category	Genetic Abnormalities
Favorable	▪ t(8;21)(q22;q22.1)/RUNX1::RUNX1T1 ▪ inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11 ▪ Mutated NPM1 without FLT3 ITD ▪ bZIP in-frame mutated CEBPA
Intermediate	▪ Mutated NPM1 with FLT3 ITD ▪ Wild-type NPM1 with FLT3 ITD ▪ t(9;11)(p21.3;q23.3)/MLLT3::KMT2A ▪ Cytogenetic and/or molecular abnormalities not classified as favorable or adverse

Risk Category	Genetic Abnormalities
Adverse	▪ t(6;9)(p23;q34.1)/DEK::NUP214 ▪ t(v;11q23.3)/KMT2A-rearranged ▪ t(9;22)(q34.1;q11.2)/BCR::ABL1 ▪ t(8;16)(p11;p13)/KAT6A::CREBBP ▪ inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2,MECOM(EVI1) ▪ t(3q26.2;v)/MECOM(EVI1) rearranged ▪ -5 or del(5q); -7; -17/abn(17p) ▪ Complex karyotype, monosomal karyotype ▪ Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2 ▪ Mutated TP53

Döhner. Blood. 2022;140:1345.

ELN: Initial Genetic Workup in AML

Cytogenetics*	Additional Information
Screening for gene mutations (for diagnosis) ▪ FLT3,† IDH1, IDH2 (actionable targets) ▪ NPM1	Results within 3-5 days
▪ CEBPA,‡ DDX41, TP53, ASXL1, BOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2	Results within first treatment cycle
Screening for gene rearrangements§ ▪ PML::RARA, CBFB::MYH11, RUNX1::RUNX1T1, KMT2A::R, BCR::ABL1, other fusion genes (if available)	Results within 3-5 days
Other recommended genes to test at diagnosis ▪ ANKRD26, BCORL1, BRAF, CBL, CSF3R, DNMT3A, ETV6, GATA2, JAK2, KIT, KRAS, NRAS, NF1, PHF6, PPM1D, PTPN11, RAD21, SETBP1, TET2, WT1	Information can be used to monitor disease by NGS-based MRD analyses (except mutations consistent with premalignant clonal hematopoiesis)

*In case of no analyzable metaphases, FISH is an alternative method to detect genetic abnormalities such as *RUNX1::RUNX1T1, CBFB::MYH11, KMT2A::R*, and *MECOM::R*, or myelodysplasia-related chromosome abnormalities, eg, del(5q), del(7q), or del(17p).
†*FLT3* mutational screening should include the analysis of internal tandem duplications and tyrosine kinase domain mutations.
‡Report should specify type of mutation: only in-frame mutations affecting the basic leucine zipper region of CEBPA, regardless of whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcomes.
§Performed if rapid information is needed for recommendation of suitable therapy, if chromosome morphology is of poor quality, or if there is typical morphology but the suspected cytogenetic abnormality is not present.

Döhner. Blood. 2022;140:1345.

Clinical Assessment of Response to Therapy

- Clinically relevant events in AML
- Death
- Failure to achieve remission or relapse, which are generally associated with bone marrow failure and increased risk for bleeding/

Endpoint	Definition
EFS Event-free Survival	Time from date of randomization/diagnosis to the date of an event of induction failure, relapse, or death of any cause, whichever came first
DFS/RFS Disease-Free Survival Relapse-Free Survival	Time from date of response to death of any cause
OS Overall Survival	Time from date of randomization/diagnosis to death of any cause

Goals of Therapy for AML

- The goal of AML therapy is to achieve complete remission with no MRD following initial induction therapy[1]
- Survival among those who achieve complete remission is longer than those who do not, irrespective of the type of induction therapy used[1]
- The goal of consolidation and maintenance therapy is to prolong remission for as long as possible, preventing relapse[1]
- Choice of treatment depends on functional status of the patient, prognostic risk groups, and the molecular profile of the leukemia cells[1]
  - Historically, age has been one of the main criteria for determining treatment eligibility; however, the development of therapeutic agents with manageable safety profiles means there are wider choices of treatment for older patients[2]
  - Comprehensive assessment of eligibility for intensive therapy at diagnosis should be carried out to determine the best therapeutic option for the patient[2]

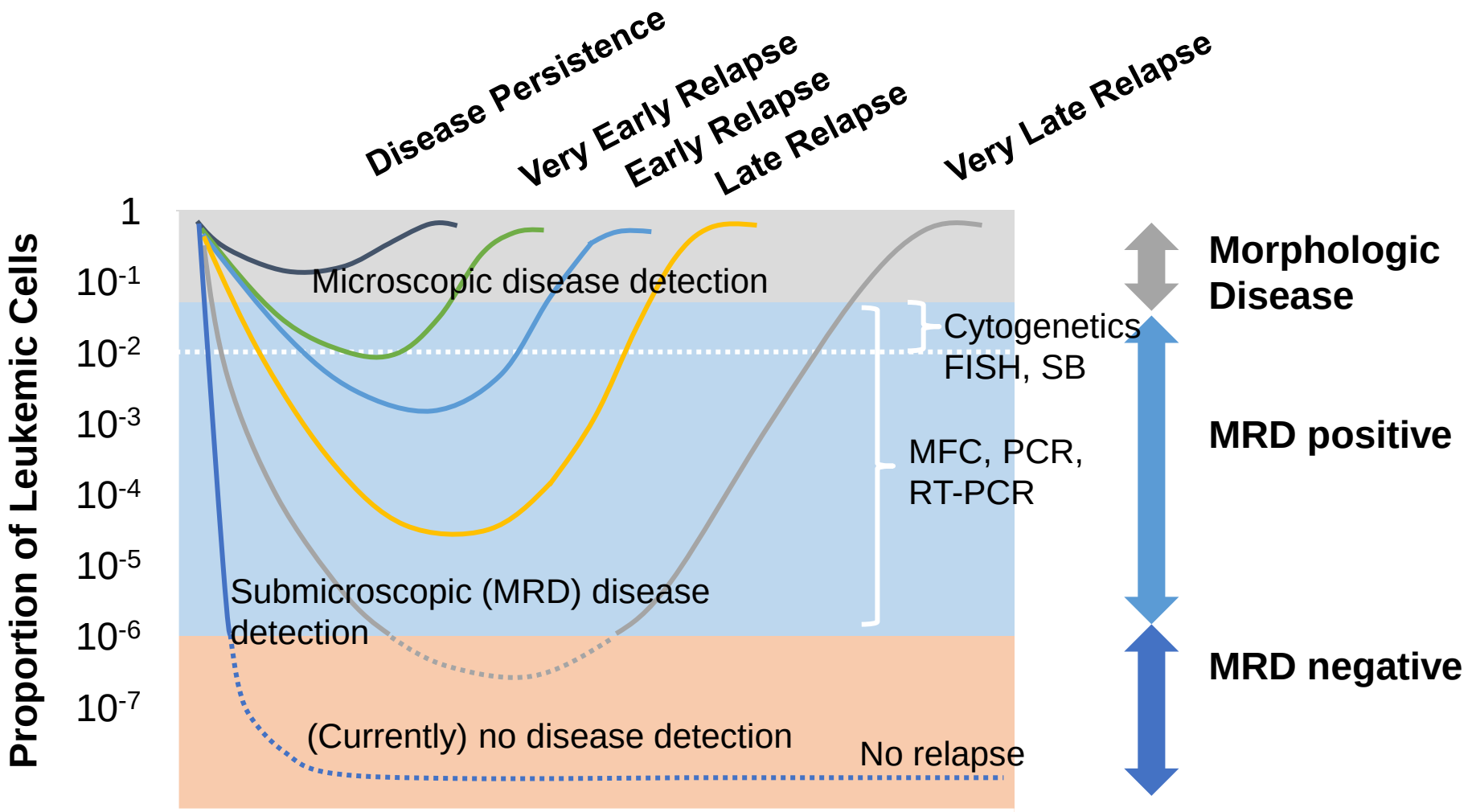
AML = acute myeloid leukemia; MRD = measurable residual disease

1. Vakit A, Mewawalla P. Acute Myeloid Leukemia 2023. Accessed May 2023 at: https://www.ncbi.nlm.nih.gov/books/NBK507875/

2. Venditti A et al. Expert Rev Hematol. 2023;16:181–90.

The Significance of Measurable Residual Disease (MRD)

<u>Definition:</u>
Residual leukemia not detected by morphology (< 5% blasts)



Buckley. Bone Marrow Transplant. 2013;48:630

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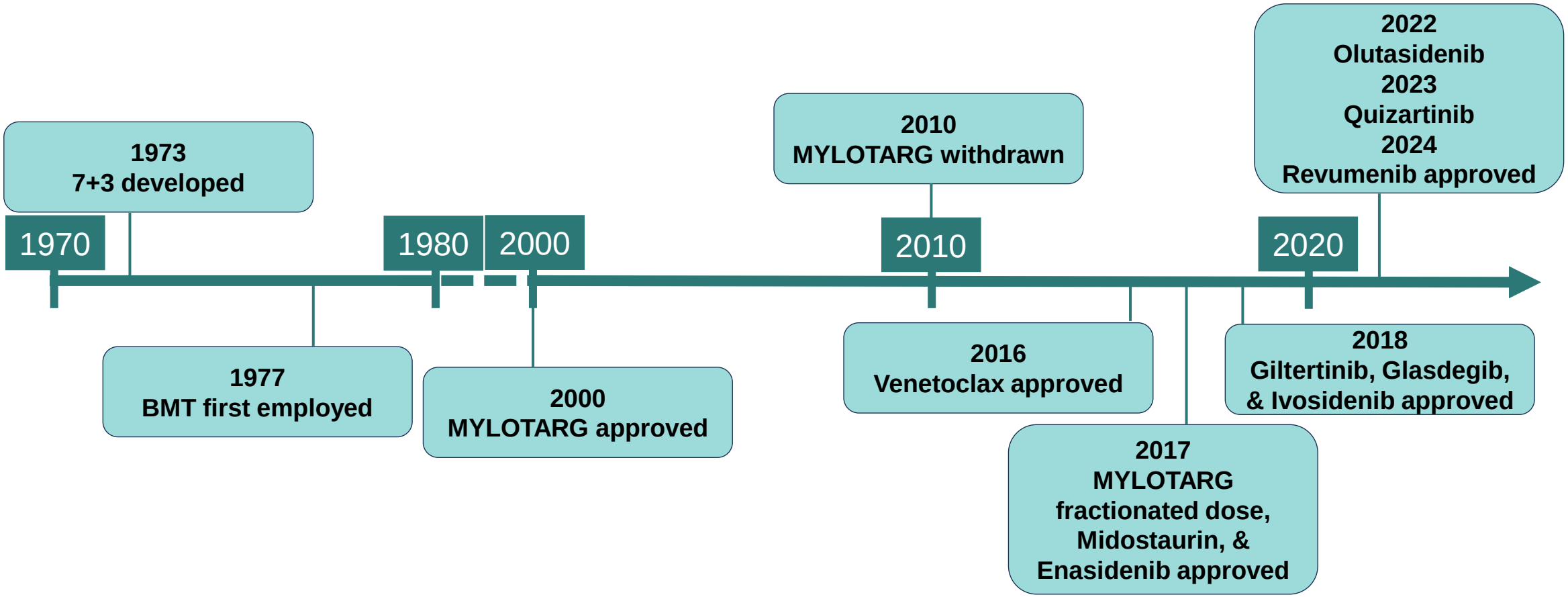
How MRD Can Guide AML Therapy

- Remission assessment (better than morphological CR)
  - Prognostic factor independent of clinical factors, cytogenetics, molecular analyses
  - Risk-adapted treatment approaches need validation
- Post remission monitoring (early relapse)
- Indicator of therapy failure/resistance
  - Presence of leukemia stem cells
  - Resistance to cytotoxic drugs
  - Selection of next therapy

AML Treatment Landscape Timeline



Targeting CD33

- CD33 is an adhesion protein expressed on the surface of myeloid blasts in approximately 90% of patients with AML. The Antibody drug congjugates (ADC) gemtuzumab ozogamicin connects a CD33 mAb to the toxic antibiotic calicheamicin via an acid-labile linker, which facilitates its release upon gemtuzumab internalization into CD33+ cell lysosomes.
- Gemtuzumab is currently FDA approved for adults with relapsed or de novo disease and for children with relapsed/refractory disease.
- FDA Approved for newly diagnosed pediatric CD33+ AML patients 1 month and older. (June 16, 2020)
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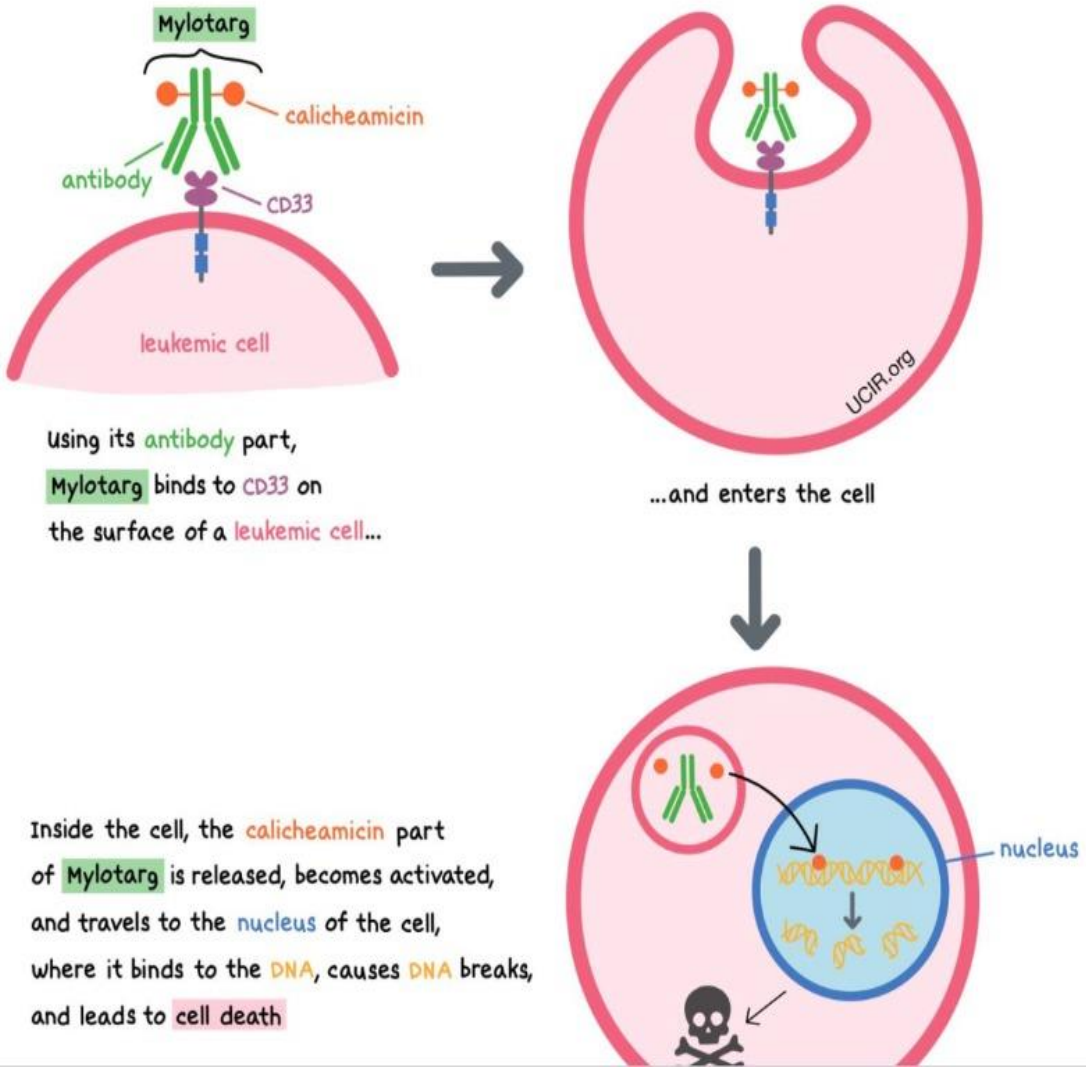
Mechanism of action gemtuzumab ozogamicin (GO)



- Gemtuzumab has been studied in children initially as a monotherapy then in combination with chemotherapy.
- Superior relapse-free survival with gemtuzumab added to chemotherapy was observed in some children with de novo AML treated in AAML0531.
- Based on these data, gemtuzumab is incorporated into frontline therapy for children, adolescents, and young adults with CD33 + AML in the most recent COG trial, AAML1831.

Rationale for CD33 as a Target in AML

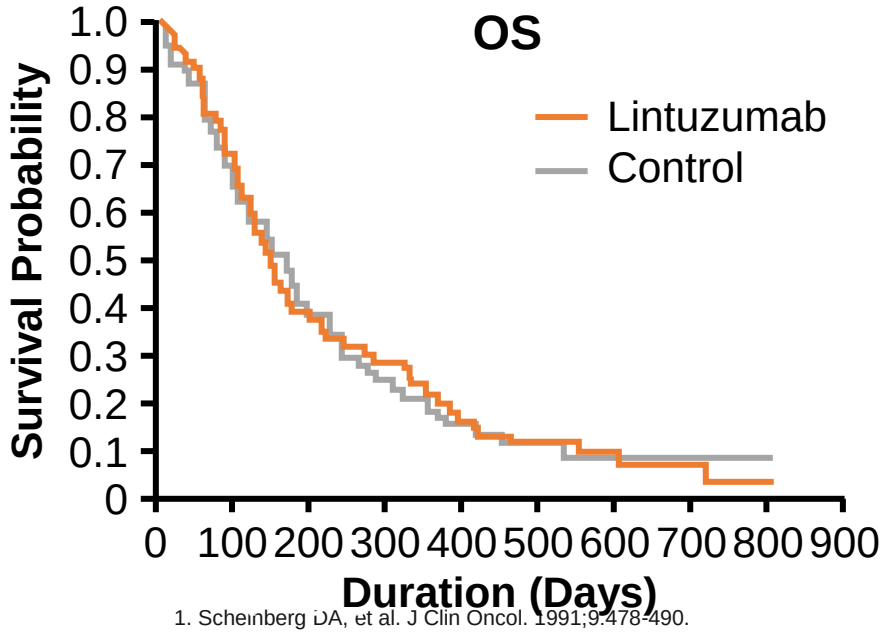
- CD33 broadly expressed in AML: 87% to 98% of cases[1,2]
- Function of CD33 poorly understood
  - Implicated in cell adhesion and activation
  - May function as an inhibitory receptor dampening immune response[3]
- CD33 internalized upon binding[4]
- In some myeloid leukemias, CD33 thought to be expressed on LSCs[5]

1. Ehninger A, et al. Blood Cancer J. 2014;4:e218. 2. Andrews RG, et al. J Exp Med. 1989:169:1721-1731. 3. Crocker PR, et al. Ann N Y Acad Sci. 2012;1253:102-111.
4. Walter RB, et al. J Leukoc Biol. 2008;83:200-211. 5. Walter RB, et al. Blood. 2012;119:6198-6208. 6. Crocker PR, et al. Nat Rev Immunol. 2007;7:255-266.

Early Attempt at Targeting CD33: Lintuzumab

- First drug to target CD33
  - Unconjugated anti-CD33 murine antibody that is rapidly internalized by bone marrow leukemia cells[1]
- Limited efficacy in clinical trials[1-3]
  - Phase I (N = 17): 4 CRs[2]
  - Phase III: addition of lintuzumab to MEC improved response rates, but not OS[3]
- Gemtuzumab ozogamicin developed as novel anti-CD33 conjugated antibody

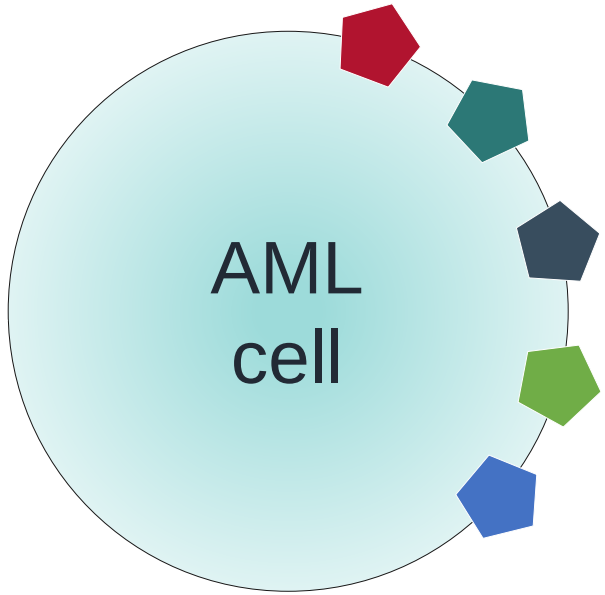
Response	Lintuzumab + Chemo (Test)		Chemo Alone (Control)	
	Pts, n	%	Pts, n	%
Pts, N	94	49	97	51
CR	27	29	22	23
CRp	7	7	5	5
ORR (CR + CRp)	34	36	27	28



1. Scheinberg DA, et al. J Clin Oncol. 1991;9:478-490.
2. Raza A, et al. Leuk Lymphoma. 2009;50:1336-1344.
3. Feldman EJ, et al. J Clin Oncol. 2005;23:4110-4116.

Target Antigens and Novel Antibodies in AML

Multiple antigen targets and agents



CD33
- ^{225}Ac-Lintuzumab (Actimab-A)
- Gemtuzumab ozogamicin (ADC)
- Vadastuximab talirine (SGN-CD33A ADC)
- IMGN779 (ADC)
- AMG 330 (BiTE; CD33/CD3)
- BVX001 (BiTE, CD33/CD7)

CD123
- SGN-CD123 (Halted)
- IMGN632
- XmAb 14045 (CD3/CD123)
- MGD006 (CD3/CD123)

CD45
- Iodine (^{131}I) Apamistamab (Iomab B)

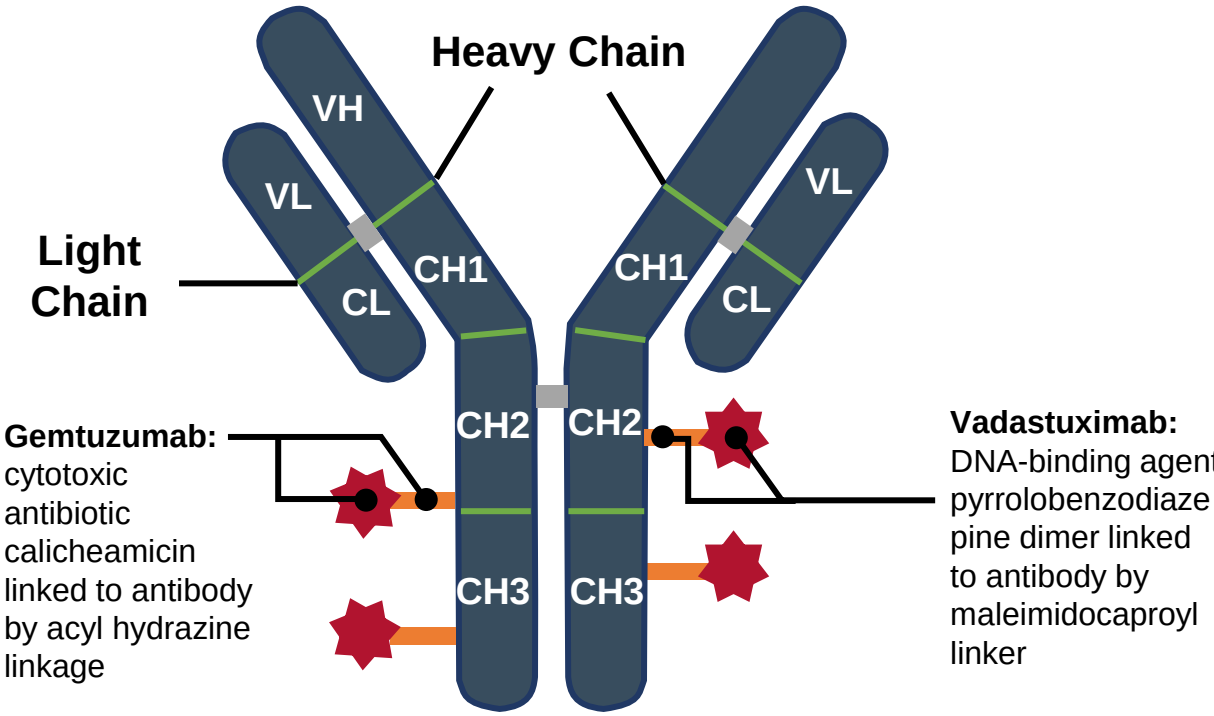
CD47
- Hu5F9-G4

CLL1
- MCCLA-1117 (BiTE)

Anti-CD33 ADCs in Development

- Vadastuximab talirine (SGN33A): humanized CD33 IgG1 antibody
  - **Further development halted due to safety concerns**
- IMGN779: humanized CD33 antibody conjugated via cleavable disulfide linker to indolino-benzodiazepine dimer[1]
  - Induces DNA alkylation/damage, G2/M arrest, and apoptosis
  - Phase I (N = 26): decreased peripheral blasts (median maximal reduction: 67%; range: 15% to 100%) in all 9 pts treated at higher doses[2]

Anti-CD33 Antibody
Vadastuximab vs
Gemtuzumab



Vadastuximab has more loading of the cytotoxic agent: ~ 2 pyrrolobenzodiazepine dimers per antibody whereas ~ 50% of the antibodies in clinical-grade gemtuzumab are conjugated to calicheamicin

1. Miller ML, et al. Mol Cancer Ther. 2016;15:1870-1878. 2. Cortes J, et al. ASH 2017. Abstract 1312.

Gemtuzumab Ozogamicin Mechanism of Action and Clinical Data in Newly Diagnosed Pediatric Patients

Clinical Trials Supporting GO Indications and Use

1

Newly diagnosed CD33-positive AML in **adults**[1]

Study ALFA-0701 *Combination regimen*

- Randomized, open-label Phase III study of adult patients with **newly diagnosed *de novo* AML**[2]

Study AML-19 *Single-Agent regimen*

- Multicenter, randomized, open-label Phase III study comparing GO to BSC for adult patients with **newly diagnosed AML**[3]

2

Newly diagnosed CD33-positive AML in **pediatric** patients 1 month and older[1]

Study AAML0531 *Combination regimen*

- Multicenter, randomized, open-label Phase III study comparing GO to standard chemotherapy for young patients with **newly diagnosed AML**[4]

3

Relapsed or refractory CD33-positive AML in **adults and in pediatric patients** 2 years and older[1]

Study MyloFrance-1 *Single-Agent regimen*

- Phase II, single-arm, open-label study in adult patients with **AML in first relapse**[5]

AML = acute myeloid leukemia; BSC = best supportive care; GO = gemtuzumab ozogamicin

1. MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021;
2. Lambert J et al. *Haematologica* 2018;doi:10.3324/haematol.2018.188888;
3. Amadori S et al. *J Clin Oncol* 2016;34:972–979;
4. Gamis A et al. *J Clin Oncol* 2014;32:3021–32;
5. Taksin A-L et al. *Leukemia* 2007;21:66–71.

Gemtuzumab Ozogamicin Use in Pediatric Patients

- The safety and effectiveness of GO in combination with standard chemotherapy have been established in pediatric patients 1 month and older with newly diagnosed *de novo* AML in a Phase III, randomized trial (AAML0531) with the following age groups:
  - Less than 27 days old (2 patients)
  - 28 days to less than 2 years old (94 patients)
  - 2 years to less than 12 years old (225 patients)
  - 12 years to less than 18 years old (175 patients)
  - 18 years or older (36 patients)
- The safety and effectiveness of GO with standard chemotherapy in pediatric patients less than 1 month of age with newly diagnosed *de novo* AML have not been established
- The safety and effectiveness of GO as a single agent in pediatric patients with newly diagnosed AML have not been established
- The safety and efficacy of GO as a single agent in the pediatric patients with relapsed or refractory AML is supported by a single-arm trial in 29 patients in the following age groups:
  - One month to less than two years old (1 patient)
  - Two years to less than 12 years old (13 patients)
  - 12 years to 18 years old (15 patients)
- A literature review included an additional 96 patients with ages ranging from 0.2 to 21 years. No differences in efficacy and safety were observed by age
- The safety and effectiveness of GO as a single agent in pediatric patients less than 2 years of age with relapsed or refractory AML have not been established

MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021.

TABLE 19.12 Therapy for newly diagnosed AML protocol.

Course 1	ADE Ind1	Daunorubicin 50 mg/m^2 IV days 1, 3, and 5 with dexrazoxane 500 mg/m^2 give immediately prior to daunorubicin
		Cytarabine 100 mg/m^2 IV bolus every 12 h days 1–10 (20 doses)
		Etoposide 100 mg/m^2 IV (1 h infusion) days 1–5 Gemtuzumab ozogamicin (G0) 3 mg/m^2 IV (2 h infusion) on day 6 Premedicate with corticosteroids antihistamine and antipyretic IT cytarabine age-adjusted doses at time of diagnostic LP
Course 2	ADE Ind 2	Daunorubicin 50 mg/m^2 IV daily on days 1, 3, and 5 with dexrazoxane 500 mg/m^2 give immediately prior to daunorubicin
		Cytarabine 100 mg/m^2 IV bolus every 12 h on days 1–8 (16 doses)
		Etoposide 100 mg/m^2 IV daily (1 h infusion) days 1–5
		IT cytarabine age-adjusted dosing on day 1
Course 3[a]	AE Int1	Cytarabine 1000 mg/m^2 q12h IV days 1–5
		Etoposide 150 mg/m^2 IV daily (1 h infusion) days 1–5
Course 4[b]	MA Int2	Mitoxantrone 12 mg/m^2 IV daily (short infusion) days 3–6 with Dexrazoxane 400 mg/m^2 give immediately prior to mitoxantrone
		Cytarabine 1000 mg/m^2 12-hourly IV (2 h infusion) days 1–4 (8 doses)
		IT cytarabine age-adjusted dosing on day 1
Course 5	Capizzi Int3	Cytarabine 3000 mg/m^2 IV bid days 1,2 and 8,9
		Erwinia asparaginase 25,000 units/m^2 IV or IM on days 2 and 9 (6 h after start of cytarabine doses 4 and 8)

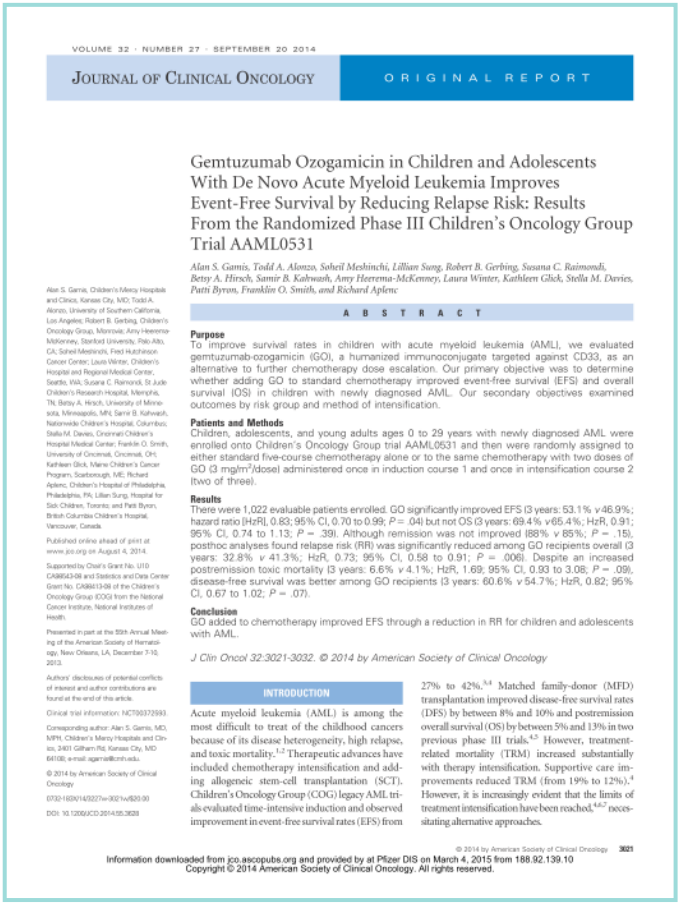
Gemtuzumab Ozogamicin in Children and Adolescents With De Novo Acute Myeloid Leukemia Improves Event-Free Survival by Reducing Relapse Risk: Results From the Randomized Phase III Children's Oncology Group Trial AAML0531

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32

COG Trial AAML0531

Objectives

To determine whether GO added to standard chemotherapy improved EFS and OS in children with newly diagnosed AML, and examine the outcomes by risk group and method of intensification



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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

ABSTRACT

Purpose
To improve survival rates in children with acute myeloid leukemia (AML), we evaluated gemtuzumab-ozogamicin (GO), a humanized immunoconjugate targeted against CD33, as an alternative to further chemotherapy dose escalation. Our primary objective was to determine whether adding GO to standard chemotherapy improved event-free survival (EFS) and overall survival (OS) in children with newly diagnosed AML. Our secondary objectives examined outcomes by risk group and method of intensification.

Patients and Methods
Children, adolescents, and young adults ages 0 to 29 years with newly diagnosed AML were enrolled onto Children's Oncology Group trial AAML0531 and then were randomly assigned to either standard five-course chemotherapy alone or to the same chemotherapy with two doses of GO (3 mg/m^2/dose) administered once in induction course 1 and once in intensification course 2 (two of three).

Results
There were 1,022 evaluable patients enrolled. GO significantly improved EFS (3 years: 53.1% *v* 46.9%; hazard ratio [HzR], 0.83; 95% CI, 0.70 to 0.99; $P = .04$) but not OS (3 years: 69.4% *v* 65.4%; HzR, 0.91; 95% CI, 0.74 to 1.13; $P = .39$). Although remission was not improved (88% *v* 85%; $P = .15$), posthoc analyses found relapse risk (RR) was significantly reduced among GO recipients overall (3 years: 32.8% *v* 41.3%; HzR, 0.73; 95% CI, 0.58 to 0.91; $P = .006$). Despite an increased postremission toxic mortality (3 years: 6.6% *v* 4.1%; HzR, 1.69; 95% CI, 0.93 to 3.08; $P = .09$), disease-free survival was better among GO recipients (3 years: 60.6% *v* 54.7%; HzR, 0.82; 95% CI, 0.67 to 1.02; $P = .07$).

Conclusion
GO added to chemotherapy improved EFS through a reduction in RR for children and adolescents with AML.

J Clin Oncol 32:3021-3032. © 2014 by American Society of Clinical Oncology

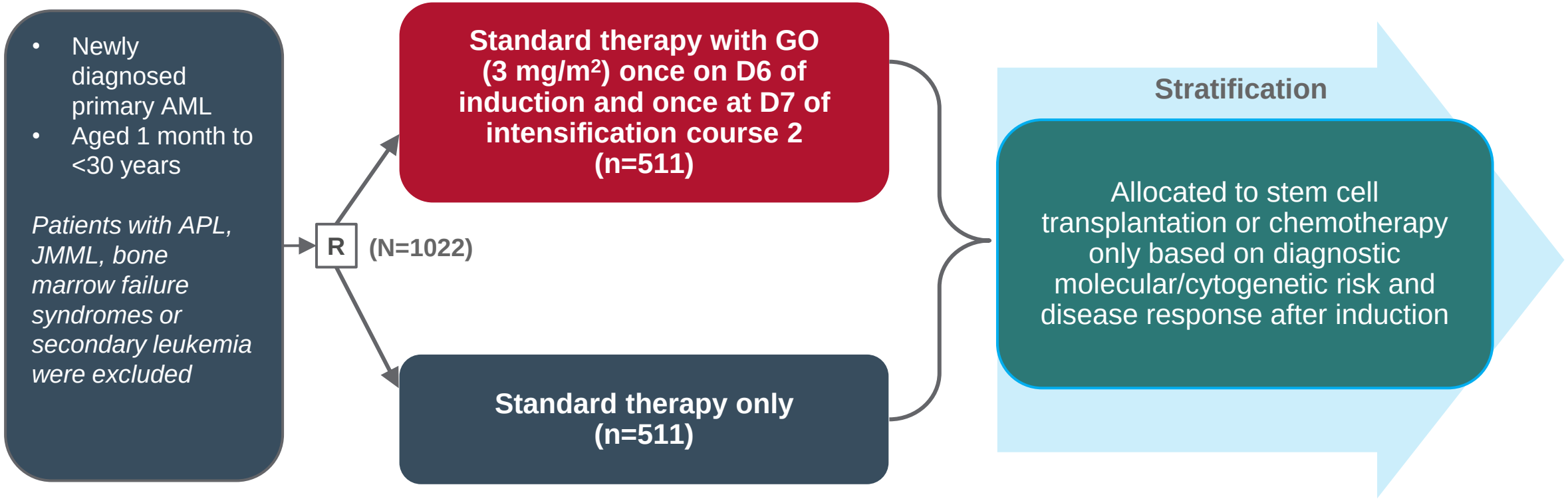
INTRODUCTION

Acute myeloid leukemia (AML) is among the most difficult to treat of the childhood cancers because of its disease heterogeneity, high relapse, and toxic mortality.[1,2] Therapeutic advances have included chemotherapy intensification and adding allogeneic stem-cell transplantation (SCT). Children's Oncology Group (COG) legacy AML trials evaluated time-intensive induction and observed improvement in event-free survival rates (EFS) from 27% to 42%.[3,4] Matched family-donor (MFD) transplantation improved disease-free survival rates (DFS) by between 8% and 10% and postremission overall survival (OS) by between 5% and 13% in two previous phase III trials.[4,5] However, treatment-related mortality (TRM) increased substantially with therapy intensification. Supportive care improvements reduced TRM (from 19% to 12%).[4] However, it is increasingly evident that the limits of treatment intensification have been reached,[4,6,7] necessitating alternative approaches.

AML = acute myeloid leukemia; EFS = event-free survival; GO = gemtuzumab ozogamicin; OS = overall survival

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Study Design



AML = acute myeloid leukemia; APL = acute promyelocytic leukemia; D = day; GO = gemtuzumab ozogamicin; JMML = juvenile myelomonocytic leukemia; R = randomized

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Therapeutic Regimen

- At enrollment, 1,022 patients were randomized to standard therapy alone (No-GO) or with GO (each dose 3 mg/m^2 administered once on Day 6 of IND1 and once on Day 7 of INT2)

Course and agent	Dose	Days
Induction course 1		
Cytarabine	100 mg/m^2/dose twice per day IV	1–10
Daunomycin	50 mg/m^2/dose IV	1, 3, 5
Etoposide	100 mg/m^2/dose IV	1–5
Gemtuzumab (first arm only)	3 mg/m^2/dose IV over 2 hours	6
Induction course 2		
Cytarabine	100 mg/m^2/dose twice per day IV	1–8
Daunomycin	50 mg/m^2/dose IV	1, 3, 5
Etoposide	100 mg/m^2/dose IV	1–5
Intensification course 1		
Cytarabine	1000 mg/m^2/dose twice per day IV	1–5
Etoposide	150 mg/m^2/dose IV	1–5

GO = gemtuzumab ozogamicin; IV = intravenous

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Therapeutic Regimen

- In both study arms, risk stratification determined allocation to SCT based on diagnostic molecular/cytogenetic risk criteria and disease response after the first induction

Course and agent	Dose	Days
For patients not undergoing stem cell transplantation		
Intensification course 2		
Mitoxantrone	12 mg/m^2/dose IV	3–6
Cytarabine	1000 mg/m^2/dose twice per day IV	1–4
Gemtuzumab (first arm only)	3 mg/m^2/dose IV over 2 hours	7
Intensification course 3		
Cytarabine	3000 mg/m^2/dose twice per day IV	1, 2, 8, 9
Escherichia coli L-asparaginase	6000 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 IV once per day	
All patients	Adjusted AUC based on first dose	-8 to -6
Cyclophosphamide	50 mg/kg/dose IV once per day	-5 to -2

AUC, area under the concentration-time curve; IM, intramuscular; IV, intravenous; SCT = stem cell transplant

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Demographic Characteristics (1/2)

- Patient characteristics were well balanced across study arms except that in patients treated with GO, *FLT3*-ITD HAR was more prevalent (P=0.09) and high-risk cytogenetics were less prevalent (P=0.03)

Characteristic	No GO Arm		GO Arm		All patients (N=1022)	
	n	%	n	%	n	%
Sex						
Male	264	51.7	244	47.7	508	49.7
Female	247	48.3	267	52.3	514	50.3
Age at diagnosis, years						
Median	9.5		9.9		9.7	
Range	0.003–29.8		0.02–29.4		0.003–29.8	
0–1 [0–730 days]	114	22.3	93	18.2	207	20.3
2–10	167	32.7	187	36.6	354	34.6
11–15	157	30.7	141	27.6	298	29.2
16–20	69	13.5	81	15.9	150	14.7
≥21	4	0.8	9	1.8	13	1.3

GO = gemtuzumab ozogamicin; HAR = high allelic ratio; ITD = internal tandem duplication

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Demographic Characteristics (2/2)

- Patient characteristics were well balanced across study arms except that in patients treated with GO, *FLT3*-ITD HAR was more prevalent (P=0.09) and high-risk cytogenetics were less prevalent (P=0.03)

Characteristic	No GO Arm		GO Arm		All patients (N=1022)	
	n	%	n	%	n	%
Race						
American Indian or Alaska Native	3	0.7	1	0.2	4	0.4
Asian	27	5.9	23	5.0	50	5.4
Native Hawaiian or other Pacific Islander	1	0.2	1	0.2	2	0.2
Black or African American	61	13.3	55	12.0	116	12.6
White	368	80.0	380	82.6	748	81.3
Unknown	51		51		102	
Ethnicity						
Hispanic or Latino	97	19.8	92	18.7	189	19.2
Not Hispanic or Latino	394	80.2	400	81.3	794	80.8
Unknown	20		19		39	

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GO = gemtuzumab ozogamicin; HAR = high allelic ratio; ITD = internal tandem duplication

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Baseline Leukemic Burdon

Characteristic	No GO Arm		GO Arm		All patients (N=1022)	
	n	%	n	%	Number	%
White blood cells, × 10^3/μL						
Median	24.3		23.6		24.0	
Range	0.2–526.0		0.4–827.2		0.2–827.2	
Patients with >100 × 10^3/μL	95	18.6	103	20.2	198	19.4
CNS disease classification at study entry						
CNS1	360	71.3	352	70.3	712	70.8
CNS2	99	19.6	98	19.6	197	19.6
CNS3	46	9.1	51	10.2	97	9.6
Unknown	6		10		16	
Extramedullary disease	74	14.5	66	12.9	140	13.7

CNS = central nervous system; GO = gemtuzumab ozogamicin

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Risk Factors and Stratification (1/2)

Characteristic	No GO Arm		GO Arm		All patients (N=1022)	
	n	%	n	%	n	%
Cytogenetics affecting risk classification						
t(8;21)*	69	13.5	68	13.3	137	13.4
Inv16, t(16:16)*	52	10.2	57	11.2	109	10.7
-7†	16	3.1	9	1.8	25	2.5
-5/5q†	10	2.0	4	0.8	14	1.4
Institution FLT3 results‡						
High FLT3-ITD allelic ratio (>0.4)†	25	7.7	38	11.7	63	9.7
End of IND1 response, bone marrow aspirate						
Complete remission	350	69.6	377	75.6	727	72.4**
Partial remission, 5–15% blasts	71	14.1	51	10.2	122	12.2
Persistent disease, >15% blasts†	61	12.1	53	10.6	114	11.4

*Low-risk factors (override response at end of IND1; high FLT3-ITD ratio override low-risk factors); †High-risk factors; ‡FLT3 totals and percentages derived from after study point when this was added to risk classification (n=324 in each arm); **P<0.05
IND1 = induction 1; GO = gemtuzumab ozogamicin

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Risk Factors and Stratification (2/2)

- Risk group assignment was balanced between treatment arms

Characteristic	No GO Arm		GO Arm		All patients (N=1022)	
	n	%	n	%	n	%
Risk group assignment*						
Low	121	23.7	125	24.5	246	24.1
Intermediate	302	59.1	305	59.7	607	59.4
High	88	17.2	81	15.9	169	16.5

*Risk group assignments are based on various factors, and some patients may have had more than one (e.g. persistent disease and – 7); numbers in rows are the total for each factor and therefore their total may exceed the number in the risk group assignment
GO = gemtuzumab ozogamicin

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Outcomes From Study Entry (1/2)

- At the end of IND2, neither CR (P=0.15) nor Refractory Disease(RD) (P=0.12) were significantly different between arms
- RD significantly decreased among low risk (P=0.03) and intermediate risk (P=0.04) GO patients recipients; no LR patient in the GO cohort experienced RD
- Overall mortality during induction was similar between treatment arms

Group	n	CR* (%)	P†	RD* (%)	P†	EM* (%)	P†
All patients No GO GO	 511 511	 85.1 88.3	0.15	 12.6 9.5	0.12	 2.2 2.3	**0.98**
Low risk No GO GO	 121 125	 95.0 97.6	0.33	 4.2 0.0	0.03	 0.8 2.4	**0.62**
Intermediate risk No GO GO	 302 305	 87.4 92.7	0.03	 9.2 4.8	0.04	 3.4 2.4	**0.48**
High risk No GO GO	 88 81	 61.0 55.4	0.48	 39.0 43.2	0.59	 0.0 1.4	**0.49**

*CR, RD, and EM are cumulative incidences from study entry to end of IND2; †P-values are one of: Gray's P-value for TRM, RR analyses, or log-rank P-values for DFS or OS analyses
CR = complete remission; DFS = disease-free survival; EM = early mortality; GO = gemtuzumab ozogamicin; IND2 = induction 2; LR = low risk; OS = overall survival; RD = refractory disease; RR = relapse rate; TRM = treatment-related mortality

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Outcomes From Study Entry (2/2)

- EFS was significantly (P=0.04) improved in GO-treated patients recipients from study entry; GO did not improve OS
  - Only the low-risk and intermediate-risk groups had numerically improved EFS with GO
  - There was no difference in EFS or OS in the high-risk patients from study entry

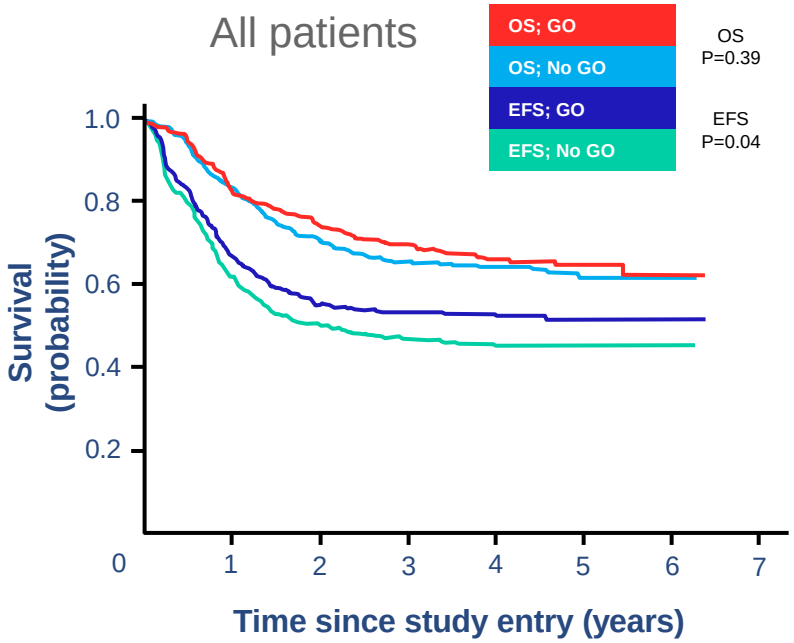
Group	n	3-year EFS	EFS HR (95% CI)	P*	3-year OS	OS HR (95% CI]	P*
All patients No GO GO	 511 511	 46.9 53.1	 1 0.83 (0.70–0.99)	0.04	 65.4 69.4	 1 0.91 (0.74–1.13)	0.39
Low-risk No GO GO	 121 125	 64.0 71.4	 1 0.74 (0.48–1.15)	0.18	 84.6 85.4	 1 1.11 (0.60–2.06)	0.74
Intermediate No GO GO	 302 305	 45.8 51.4	 1 0.82 (0.66–1.03)	0.09	 62.6 68.7	 1 0.83 (0.64–1.09)	0.19
High-risk No GO GO	 88 81	 27.2 31.2	 1 1.01 (0.70–1.45)	0.96	 48.0 47.7	 1 1.06 (0.70–1.62)	0.78

*P-values are log-rank P-values for OS analyses
CI = confidence interval; DFS = disease-free survival; EFS = event-free survival; GO = gemtuzumab ozogamicin; HR = hazard ratio; OS = overall survival; RR = relapse rate; TRM = treatment-related mortality

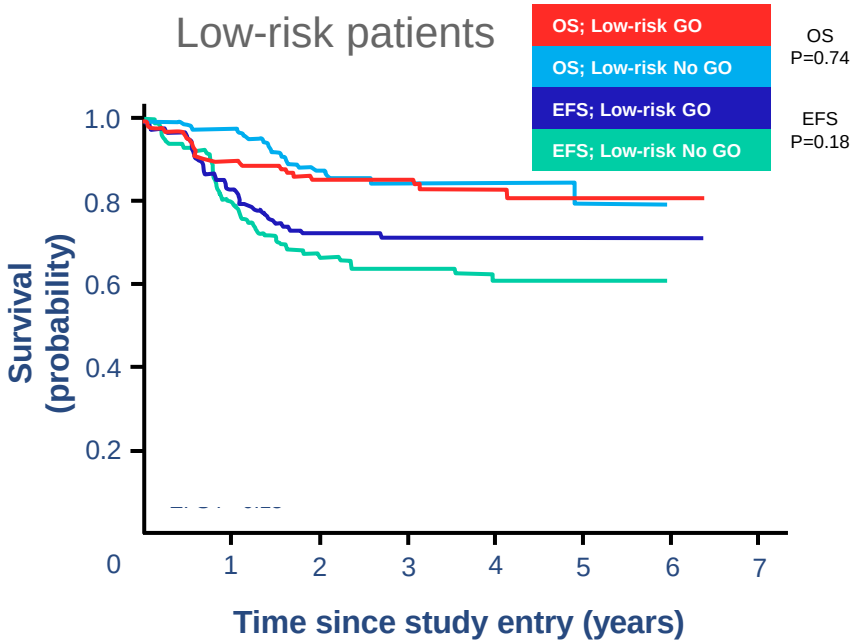
Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- OS and EFS (1/2)

- EFS was significantly improved (P=0.04) in the overall and low risk groups in GO vs. No GO patients
- OS was not significantly improved with GO vs No GO



No. at risk							
OS; No GO	511	415	342	244	149	49	1
OS; GO	511	407	353	254	141	50	5
EFS; No GO	511	309	246	177	105	38	1
EFS; GO	511	329	263	198	106	36	2



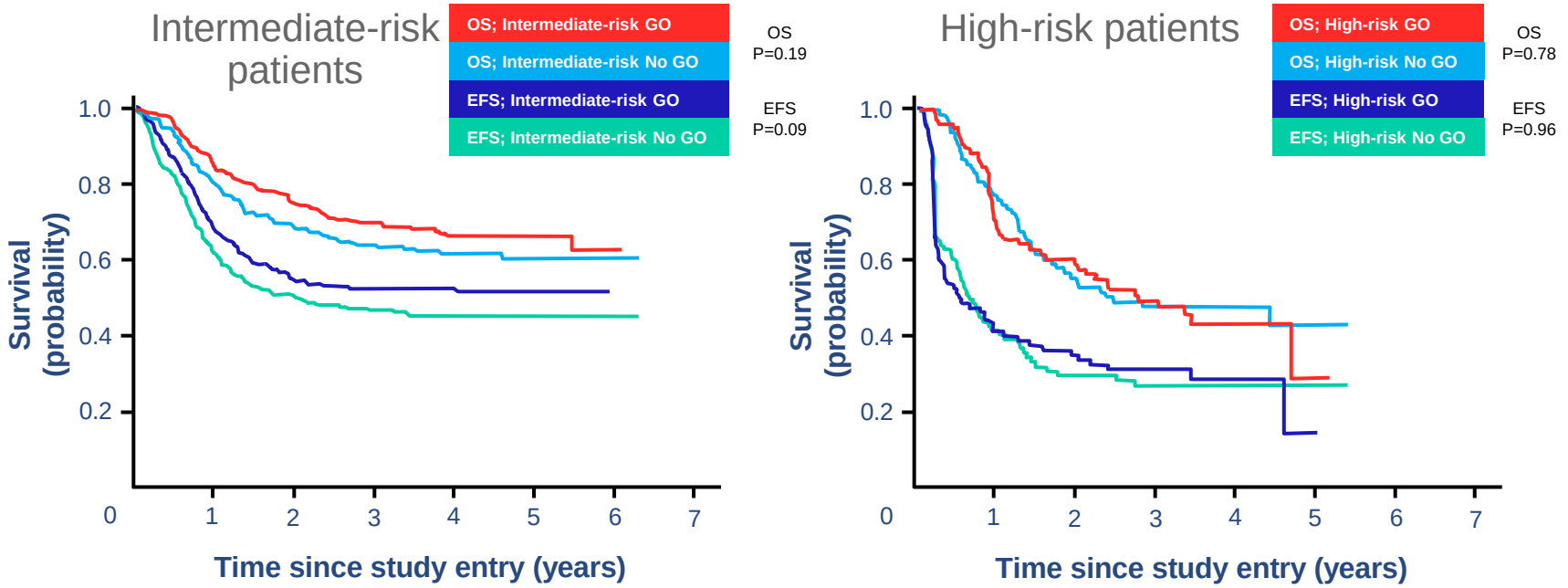
No. at risk							
OS; LR No GO	121	117	102	74	48	13	0
OS; LR GO	125	110	101	76	46	21	4
EFS; LR No GO	121	96	79	59	36	11	0
EFS; LR GO	125	102	86	65	37	14	2

EFS = event-free survival; GO = gemtuzumab ozogamicin; OS = overall survival

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- OS and EFS (2/2)

- EFS was numerically improved in the intermediate risk groups with GO vs. No GO
- OS was not significantly improved with GO vs No GO



No. at risk							
OS; IR No GO	302	235	197	139	85	33	1
OS; IR GO	305	244	208	148	84	28	1
EFS; IR No GO	302	178	142	100	60	25	1
EFS; IR GO	305	194	150	113	62	22	0

No. at risk							
OS; HR No GO	88	63	43	31	16	3	0
OS; HR GO	81	53	44	30	11	1	0
EFS; HR No GO	88	35	25	18	9	2	0
EFS; HR GO	81	33	27	20	7	0	0

EFS = event-free survival; GO = gemtuzumab ozogamicin; HR = high-risk; OS = overall survival

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Outcomes From Study Entry

- Three-year TRM rates were numerically greater with GO vs. No GO across all groups, with significantly improvement observed in the low-risk group (P=0.04)
- Exploratory analyses showed that there was significant (P=0.0006) decrease in (Relapse Rate) RR in overall patients treated with GO, with similar improvements in each risk group

Group	n	3-year TRM	TRM HR (95% CI)	P*	3-year RR	RR HR (95% CI)	P*
All patients No GO GO	 418 429	 4.1 6.6	 1.69 (0.93–3.08)	0.08	 41.3 32.8	0.73 (0.58–0.91)	0.006
Low-risk No GO GO	 114 120	1.8 7.5	 4.39 (0.95–20.4)	0.04	 30.3 19.7	 0.58 (0.34–0.97)	 0.04
Intermediate No GO GO	 257 268	 3.1 4.6	 1.45 (0.60–3.57)	0.41	 45.5 39.6	 0.81 (0.63–1.06)	 0.13
High-risk No GO GO	 47 41	 14.9 17.1	 1.27 (0.46–3.48)	0.65	 44.8 27.0	 0.53 (0.25–1.09)	 0.08

*P-values are Gray's P-value for TRM and RR analyses
CI = confidence interval; DFS = disease-free survival; GO = gemtuzumab ozogamicin;
HR = hazard ratio; OS = overall survival; RR = relapse rate; TRM = treatment-related mortality

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Outcomes From End of Induction Course 2

- At the end of induction 2, DFS was improved overall among patients treated with GO vs. No GO, with similar numerical improvements seen in each risk group
- Three-year OS rate was numerically improved with GO vs. No GO across all groups

Group	n	3-year DFS	DFS HR (95% CI)	P*	3-year OS*	OS HR (95% CI)	P
All patients No GO GO	 418 429	 54.7 60.6	 0.82 (0.67–1.02)	0.07	 70.1 74.0	 0.88 (0.68–1.13)	0.32
Low-risk No GO GO	 114 120	 67.9 72.8	 0.81 (0.51–1.30)	0.38	 86.4 84.7	 1.11 (0.56–2.17)	0.77
Intermediate No GO GO	 257 268	 51.4 55.9	 0.86 (0.67–1.11)	0.24	 66.9 70.2	 0.90 (0.67–1.22)	0.49
High-risk No GO GO	 47 41	 40.3 55.9	 0.66 (0.37–1.18)	0.16	 48.5 67.5	 0.61 (0.32–1.16)	0.13

*P-values are log-rank P-values for DFS or OS analyses
CI = confidence interval; DFS = disease-free survival; GO = gemtuzumab ozogamicin; HR = hazard ratio; OS = overall survival; RR = relapse rate; TRM = treatment-related mortality

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Toxicity (1/2)

- Rates of life-threatening SOS were similar across treatment arms
  - During IND1, 1 SOS event was reported in the No GO arm
  - A total of 5 SOS events were reported during SCT
    - No GO: 2/76 patients
    - GO: 3/82 patients
- There were similar rates of SOS of any degree
  - No GO arm: 14/511 patients
  - GO arm: 18/511 patients
- Hematologic toxicity was similar between treatment arms, including median time to neutrophil recovery
  - Post hoc analysis to examine factors contributing to TRM differences found a higher proportion of GO patients during INT2 with prolonged (>59 days) neutrophil recovery times (12.0% vs. 6.3%; P=0.01)

GO = gemtuzumab ozogamicin; IND1 = induction 1; INT2 = intensification course 2; NS = not significant; SCT = stem cell transplant; SOS = sinusoidal obstruction syndrome; TRM = treatment-related mortality

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Toxicity (1/2)

- Therapy reduction occurred in similar proportions of patients in both treatment arms
- Death in remission was numerically higher among GO vs. No GO patients (4.2% vs. 2.6%, respectively; P=0.21)
- Cumulative TRM from enrollment until last follow-up without relapse or induction failure was higher in GO vs. No GO recipients (8.6% ± 2.5% vs. 5.9% ± 2.1%, respectively; P=0.09)
  - Day 100 TRM rates for MFD and alternative-donor SCT patients were 1.8% (n=2) and 10.9% (n=5)
  - TRM rates beyond Day 100 were equivalent across treatment arms

.

GO = gemtuzumab ozogamicin; MFD = matched family donor; SCT = stem cell transplant;
SOS = sinusoidal obstruction syndrome; TRM = treatment-related mortality

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Trial AAML0531- Conclusion

- This was the largest randomized pediatric *de novo* AML trial to date
- After the addition of GO, EFS was improved (P=0.04) and relapse was significantly reduced (P=0.0006)
- TRM increased with addition of GO, despite a lack of difference in overall toxicity between treatment arms
  - Increased TRM was limited to the low-risk cohort and occurred in individuals with a markedly delayed recovery of neutrophils in the final two (of five) courses
    - Recent reports showed no benefit with a fifth course of therapy
    - COG no longer includes the final course of chemotherapy, which may lessen this risk in future GO trials
- There were no differences in the incidence of SOS events, most likely due to the 3 mg/m^2 GO dose selection and timing

AML = acute myeloid leukemia; COG = Children's Oncology Group; EFS = event-free survival; GO = gemtuzumab ozogamicin; LR = low-risk; SOS = sinusoidal obstruction syndrome; TRM = treatment-related mortality

Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

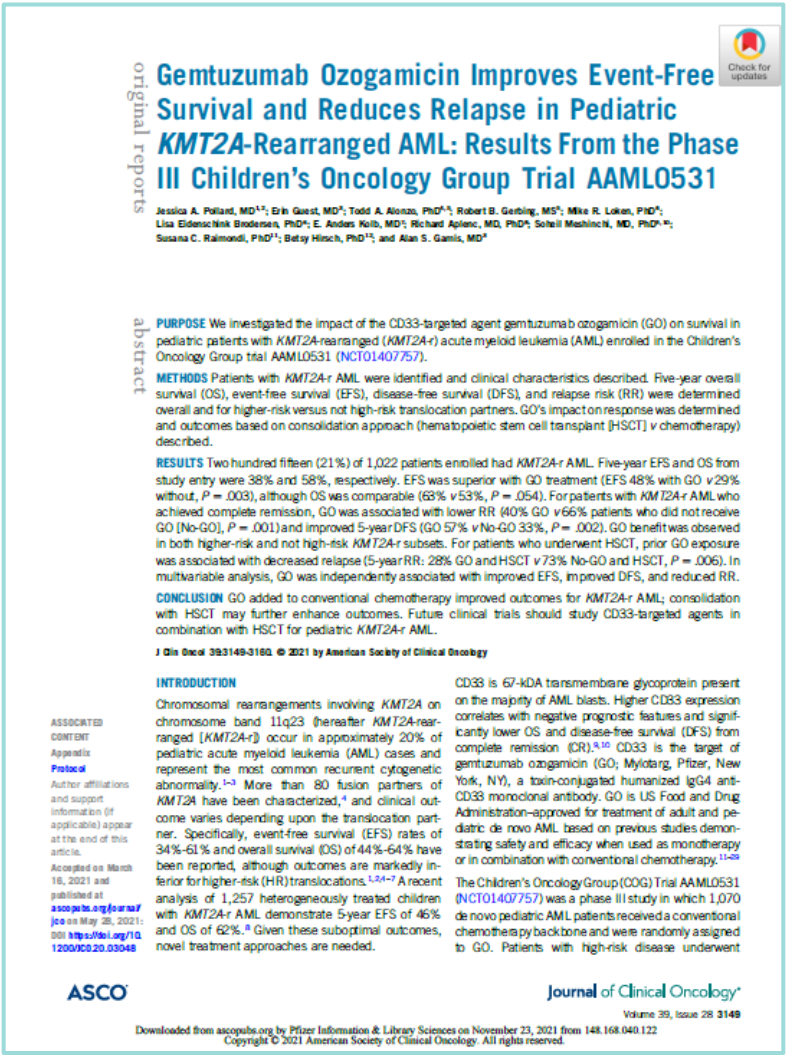
Gemtuzumab Ozogamicin Improves Event-Free Survival and Reduces Relapse in Pediatric KMT2A-rearranged AML: Results From the Phase III Children's Oncology Group Trial AAML0531

Pollard JA et al. *J Clin Oncol* 2021;39:3149–60

COG Phase III Trial (AAML0531) in *KMT2A-rearranged* AML

Objectives

- To evaluate whether GO in combination with standard chemotherapy provided therapeutic benefit versus standard chemotherapy alone in pediatric patients with *KMT2A*-rearranged (*KMT2A-r*) de novo AML, both overall and for those with higher-risk vs. not high-risk translocation partners



original reports abstract

Gemtuzumab Ozogamicin Improves Event-Free Survival and Reduces Relapse in Pediatric *KMT2A*-Rearranged AML: Results From the Phase III Children's Oncology Group Trial AAML0531

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PURPOSE We investigated the impact of the CD33-targeted agent gemtuzumab ozogamicin (GO) on survival in pediatric patients with *KMT2A*-rearranged (*KMT2A-r*) acute myeloid leukemia (AML) enrolled in the Children's Oncology Group trial AAML0531 (NCT01407757).

METHODS Patients with *KMT2A-r* AML were identified and clinical characteristics described. Five-year overall survival (OS), event-free survival (EFS), disease-free survival (DFS), and relapse risk (RR) were determined overall and for higher-risk versus not high-risk translocation partners. GO's impact on response was determined and outcomes based on consolidation approach (hematopoietic stem cell transplant [HSCT] *v* chemotherapy) described.

RESULTS Two hundred fifteen (21%) of 1,022 patients enrolled had *KMT2A-r* AML. Five-year EFS and OS from study entry were 38% and 58%, respectively. EFS was superior with GO treatment (EFS 48% with GO *v* 29% without, $P = .003$), although OS was comparable (63% *v* 53%, $P = .054$). For patients with *KMT2A-r* AML who achieved complete remission, GO was associated with lower RR (40% GO *v* 66% patients who did not receive GO [No-GO], $P = .001$) and improved 5-year DFS (GO 57% *v* No-GO 33%, $P = .002$). GO benefit was observed in both higher-risk and not high-risk *KMT2A-r* subsets. For patients who underwent HSCT, prior GO exposure was associated with decreased relapse (5-year RR: 28% GO and HSCT *v* 73% No-GO and HSCT, $P = .006$). In multivariable analysis, GO was independently associated with improved EFS, improved DFS, and reduced RR.

CONCLUSION GO added to conventional chemotherapy improved outcomes for *KMT2A-r* AML; consolidation with HSCT may further enhance outcomes. Future clinical trials should study CD33-targeted agents in combination with HSCT for pediatric *KMT2A-r* AML.

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INTRODUCTION

Chromosomal rearrangements involving *KMT2A* on chromosome band 11q23 (hereafter *KMT2A*-rearranged [*KMT2A-r*]) occur in approximately 20% of pediatric acute myeloid leukemia (AML) cases and represent the most common recurrent cytogenetic abnormality.[1-3] More than 80 fusion partners of *KMT2A* have been characterized,[4] and clinical outcome varies depending upon the translocation partner. Specifically, event-free survival (EFS) rates of 34%-61% and overall survival (OS) of 44%-64% have been reported, although outcomes are markedly inferior for higher-risk (HR) translocations.[1,2,4-7] A recent analysis of 1,257 heterogeneously treated children with *KMT2A-r* AML demonstrate 5-year EFS of 46% and OS of 62%.[8] Given these suboptimal outcomes, novel treatment approaches are needed.

CD33 is 67-kDA transmembrane glycoprotein present on the majority of AML blasts. Higher CD33 expression correlates with negative prognostic features and significantly lower OS and disease-free survival (DFS) from complete remission (CR).[9,10] CD33 is the target of gemtuzumab ozogamicin (GO; Mylotarg, Pfizer, New York, NY), a toxin-conjugated humanized IgG4 anti-CD33 monoclonal antibody. GO is US Food and Drug Administration–approved for treatment of adult and pediatric de novo AML based on previous studies demonstrating safety and efficacy when used as monotherapy or in combination with conventional chemotherapy.[11-29]

The Children's Oncology Group (COG) Trial AAML0531 (NCT01407757) was a phase III study in which 1,070 de novo pediatric AML patients received a conventional chemotherapy backbone and were randomly assigned to GO. Patients with high-risk disease underwent

ASSOCIATED CONTENT
Appendix
Protocol
Author affiliations and support information (if applicable) appear at the end of this article.
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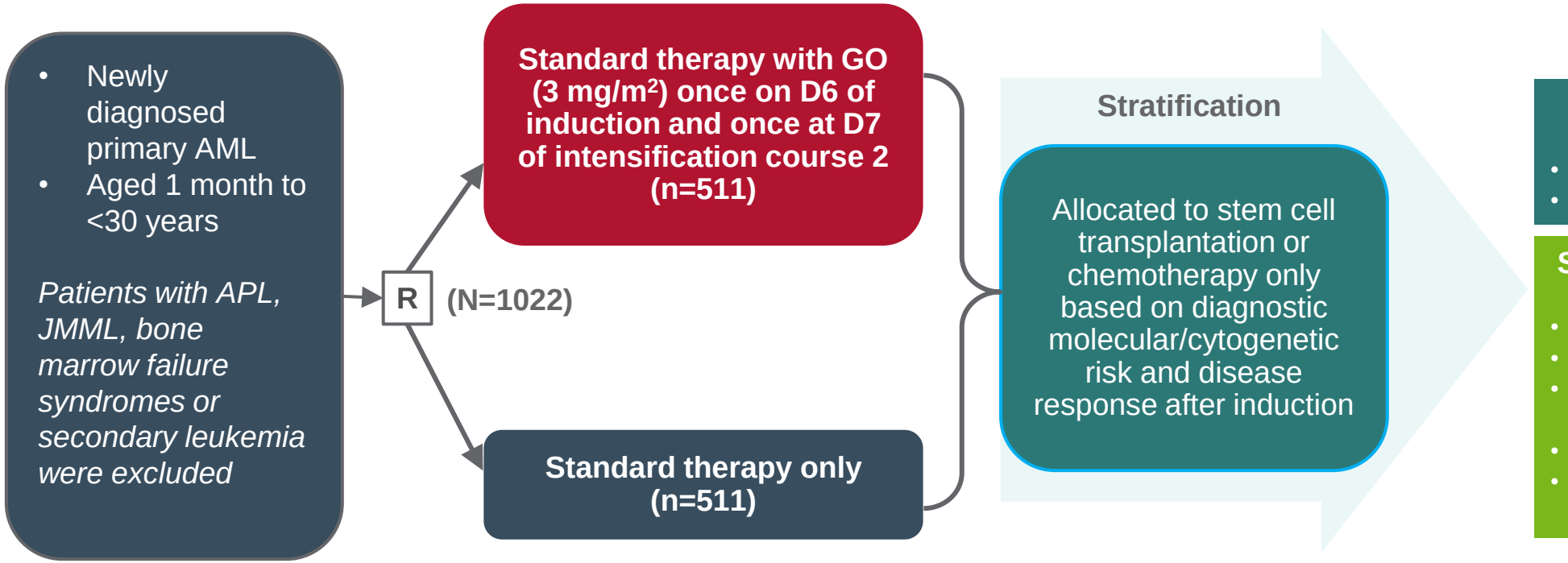
AML = acute myeloid leukemia; DFS = disease-free survival; EFS = event-free survival; HSCT = hematopoietic stem cell transplantation; GO = gemtuzumab ozogamicin; OS = overall survival; RR = relapse risk.

Pollard JA et al. *J Clin Oncol* 2021;39:3149–60.

COG Phase III Trial (AAML0531) in *KMT2A-rearranged* AML

Study Design[1]



Primary endpoints[2]

- **OS**
- **EFS**

Secondary endpoints[2]

- **Remission rates**
- **Postinduction DFS,**
- **EFS and OS censoring SCT patients**
- **TRM**
- **OS and EFS by risk group**

- Among patients included in the trial, 988 had evaluable cytogenetic data and were assessed for KMT2A status

	GO	No-GO
KMT2A-r	108	107
KMT2A-WT	384	389

AML = acute myeloid leukemia; APL = acute promyelocytic leukemia; COG = Children's Oncology Group; DFS = disease-free survival; EFS = event-free survival; GO = gemtuzumab ozogamicin; HSCT = hematopoietic stem cell transplantation; IV = intravenous; JMML = juvenile myelomonocytic leukemia; *KMT2A*-r = rearranged *KMT2A*; *KMT2A*-WT = wild type *KMT2A;* No-GO = did not receive GO; OS = overall survival; R = randomized; RR = relapse risk; TRM = treatment-related mortality.

1. Pollard JA et al. *J Clin Oncol* 2021;39:3149–60;
2. Gamis AS et al. *J Clin Oncol* 2014;32:3021–32.

COG Phase III Trial (AAML0531) in *KMT2A*-rearranged AML

Clinical Characteristics by KMT2A Cytogenetic Classification

- Clinical characteristics were similar across treatment arms and for HR vs. NHR *KMT2A*-r AML

Characteristic	KMT2A-r: No-GO vs. GO			HR KMT2A-r: No-GO vs. GO			NHR KMT2A-r: No-GO vs. GO		
	No-GO (n=107)	GO (n=108)	P	No-GO (n=33)	GO (n=37)	P	No-GO (n=56)	GO (n=51)	P
Age, median (range), years	2.03 (0.003–18.7)	3.3 (0.02–18.3)	0.287	1.3 (0.003–18.7)	3.7 (0.09–1.82)	0.711	2.3 (0.18–18.1)	4.3 (0.14–18.3)	0.097
Male, n (%)	59 (55)	48 (44)	0.117	19 (58)	15 (41)	0.155	33 (59)	22 (43)	0.103
WBC count, median (range), x 10^3/µl	24.2 (0.5–526)	29.8 (0.4–610)	0.790	25.6 (0.5–519)	43.7 (0.8–263.1)	0.455	21.95 (0.9–526)	12.7 (0.4–610)	0.566
CNS-positive, n (%)	8 (7)	6 (6)	0.568	2 (6)	2 (5)	1.000	5 (9)	3 (6)	0.718
Non-CNS EMD, n (%)	25 (23)	28 (26)	0.663	10 (30)	17 (46)	0.180	13 (23)	8 (16)	0.328
FLT3/ITD, n (%)	4 (4)	1 (1)	0.192	1 (3)	1 (3)	1.000	2 (4)	0 (0)	0.495
CEPBA, n (%)	0 (0)	0 (0)	-	0 (0)	0 (0)	-	0 (0)	0 (0)	-
NPM1, n (%)	0 (0)	0 (1)	-	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Cytogenetic complexity									
0	-	-	-	-	-	-	-	-	-
1–2	82 (77)	77 (73)	0.498	28 (85)	27 (73)	0.227	41 (73)	38 (75)	0.879
≥3	24 (23)	28 (27)	0.498	5 (15)	10 (27)	0.227	15 (27)	13 (25)	0.879
CR at Induction 1	68 (64)	82 (77)	**0.035**	20 (61)	23 (64)	0.779	35 (63)	42 (82)	**0.022**
MRD at Induction 1	18 (22)	17 (20)	0.755	6 (22)	7 (25)	0.809	7 (18)	7 (18)	0.958
HSCT received	11 (10)	19 (18)	0.122	6 (18)	3 (8)	0.290	4 (7)	11 (22)	**0.032**

AML = acute myeloid leukemia; CNS = central nervous system; COG = Children's Oncology Group; CR = complete remission; EMD = extramedullary disease; GO = gemtuzumab ozogamicin; ITD = internal tandem duplication; *KMT2A*-r = rearranged *KMT2A*; *KMT2A*-WT = wild type *KMT2A*; MRD = minimal residual disease; No-GO = did not receive GO; WBC = white blood cell.

Pollard JA et al. *J Clin Oncol* 2021;39:3149–60.

COG Phase III Trial (AAML0531) in *KMT2A*-rearranged AML

Impact of GO on Clinical Outcomes in KMT2A-r AML(1/3)

- Patients with *KMT2A*-r AML treated with GO had improved outcomes vs. those who did not receive GO
  - At EOI1, patients with *KMT2A*-r AML receiving GO had higher rates of morphologic CR vs. those who did not receive GO (77% vs. 64%; P=0.035), but MRD rates were comparable
  - Patients with *KMT2A*-r AML derived clinically significant, long-term benefits with GO treatment (**Table**)

5-year Outcome	KMT2A-r: No-GO vs. GO			HR* KMT2A-r: No-GO vs. GO (n=70)			NHR† KMT2A-r: No-GO vs. GO (n=107)		
	No-GO n (%) [95% CI]	GO n (%) [95% CI]	P	No-GO n (%) [95% CI]	GO n (%) [95% CI]	P	No-GO n (%) [95% CI]	GO n (%) [95% CI]	P
EFS	107 (29) [20–38]	108 (48) [38–57]	**0.003**	33 (6) [1–18]	37 (27) [14–41]	**0.013**	56 (42) [29–55]	51 (66) [51–77]	**0.017**
OS	107 (53) [43–62]	108 (63) [53–72]	0.054	33 (36) [21–52]	37 (49) [32–65]	0.139	56 (67) [53–78]	51 (76) [61–85]	0.244
DFS‡	68 (33) [22–44]	82 (57) [46–67]	**0.002**	20 (10) [2–27]	23 (29) [12–49]	**0.053**	35 (50) [32–65]	42 (75) [59–86]	**0.025**
RR‡	68 (66) [53–76]	82 (40) [29–51]	**0.001**	20 (90) [60–98]	23 (66) [42–83]	**0.027**	35 (47) [29–63]	42 (22) [11–36]	**0.026**
TRM‡	68 (2) [0.1–7]	82 (2) [0.5–8]	0.609	20 (0) [0–0]	23 (4) [0.3–19]	0.355	35 (3) [0.2–13]	42 (2) [0.2–11]	0.884

*HR *KMT2A* translocation partners were defined as 6q27, 10p11.2, 10p12, 4q21.3, and 19p13.3 based on previously published data;
†The NHR cohort included the remaining *KMT2A*-r cases but excluded other partners (defined as a NHR translocation with fewer than five cases) as their rarity precluded analysis of the impact of the fusion partner on prognosis, and the unknown partners, given the unclear origin of the fusion partner; ‡from end of induction 1 for patients in CR.

AML = acute myeloid leukemia; COG = Children's Oncology Group; DFS = disease-free survival; EFS = event-free survival; EOI1 = end of Induction 1; GO = gemtuzumab ozogamicin; HR = higher risk; *KMT2A*-r = rearranged *KMT2A*; *KMT2A*-WT = wild type *KMT2A*; NHR = not high-risk; No-GO = did not receive GO; OS = overall survival; RR = relapse risk; TRM = treatment-related mortality.

Pollard JA et al. *J Clin Oncol* 2021;39:3149–60.

TABLE A5. Outcomes by Treatment Arm for Patients With *KMT2A*-r AML in CD33 Expression Q1-Q2[10]

	CD33 Q1-Q2: No GO		CD33 Q1-Q2: GO		
	n = 26		n = 25		
Additional Clinical Outcome	**No.**	**% (95% CI)**	**No.**	**% (95% CI)**	***P***
5-Year EFS from study entry	26	28 (13 to 46)	25	68 (46 to 83)	**.011**
5-Year OS from study entry	26	50 (30 to 67)	25	80 (58 to 91)	**.032**
5-Year DFS from end induction I (patients in CR)	19	32 (13 to 52)	18	83 (57 to 94)	**.002**
5-Year RR from end induction I (patients in CR)	19	68 (41 to 85)	18	11 (2 to 30)	**.001**
5-Year TRM from end induction I (patients in CR)	19	0 (0 to 0)	18	6 (0.3 to 23)	.305

	KMT2A-WT *v KMT2A*-r					No-GO: *KMT2A*-WT *v KMT2A*-r					GO: *KMT2A*-WT *v KMT2A*-r				
	KMT2A WT		*KMT2A*-r			*KMT2A* WT		*KMT2A*-r			*KMT2A* WT		*KMT2A*-r		
Clinical Response	**No.**	**% (95% CI)**	**No.**	**% (95% CI)**	***P***	**No.**	**% (95% CI)**	**No.**	**% (95% CI)**	***P***	**No.**	**% ± 2 SE%**	**No.**	**% ± 2 SE%**	***P***
5-Year EFS from study entry	773	51 (48 to 55)	215	38 (32 to 45)	**< .001**	389	50 (45 to 55)	107	29 (20 to 38)	**< .001**	384	53 (48 to 58)	108	48 (38 to 57)	.325
5-Year OS from study entry	773	66 (62 to 69)	215	58 (51 to 65)	**.020**	389	66 (61 to 70)	107	53 (43 to 62)	**.004**	384	66 (61 to 71)	108	63 (53 to 72)	.643
5-Year DFS from end induction I (patients in CR)	555	58 (54 to 62)	150	46 (38 to 54)	**.004**	272	56 (50 to 62)	68	33 (22 to 44)	**< .001**	283	60 (54 to 65)	82	57 (46 to 67)	.673
5-Year RR from end induction I (patients in CR)	555	36 (32 to 40)	150	52 (43 to 60)	**< .001**	272	40 (34 to 46)	68	66 (53 to 76)	**< .001**	283	33 (27 to 38)	82	40 (29 to 51)	.196
5-Year TRM from end induction I (patients in CR)	555	6 (4 to 8)	150	2 (0.6 to 5)	.068	272	4 (2 to 6)	68	2 (0.1 to 7)	.363	283	8 (5 to 11)	82	2 (0.5 to 8)	.100

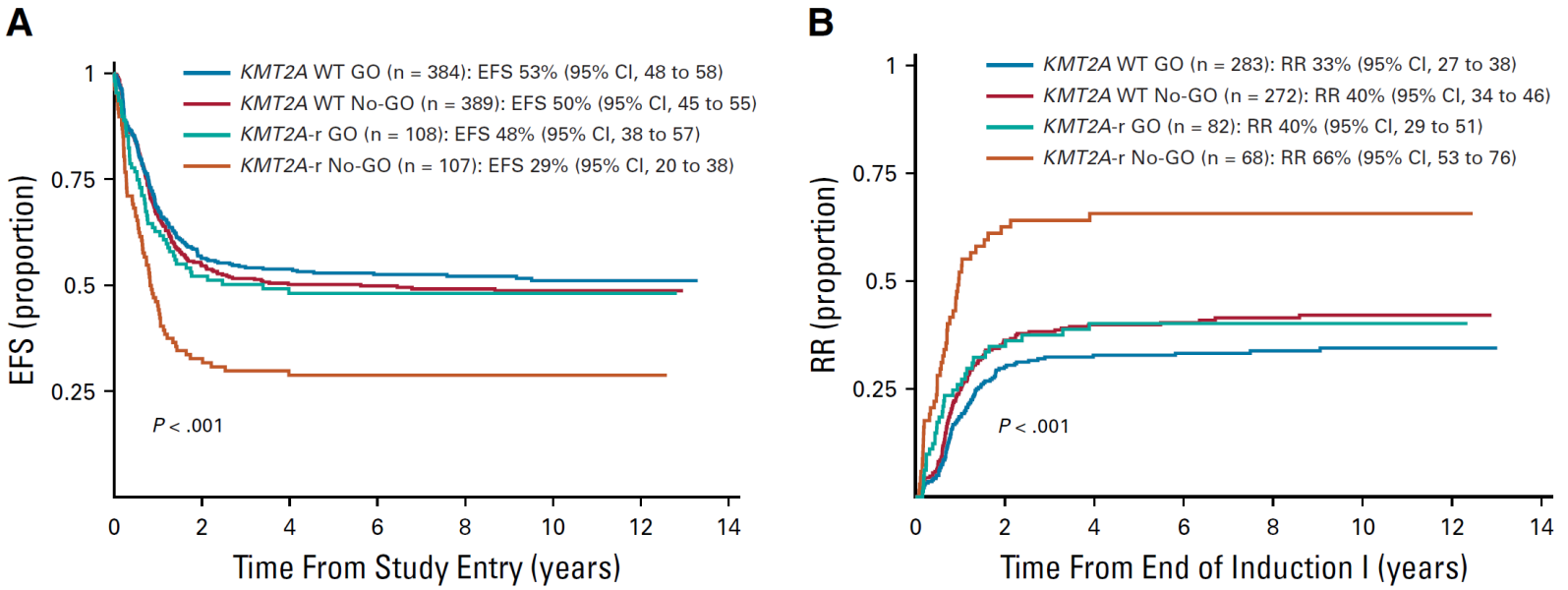
NOTE. Bold indicates statistical significance.

Abbreviations: CR, complete remission; DFS, disease-free survival; EFS, event-free survival; GO, gemtuzumab ozogamicin; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; *KMT2A*-r, *KMT2A*-rearranged; MRD, minimal measurable residual disease; OS, overall survival; RR, relapse risk; TRM, treatment-related mortality; WT, wild-type.

COG Phase III Trial (AAML0531) in *KMT2A*-rearranged AML

Impact of GO on Clinical Outcomes in KMT2A-r AML(2/3)

- Patients with *KMT2A*-r AML receiving GO had similar clinical outcomes as those with *KMT2A*-WT AML regardless of GO exposure



No. at risk:

Group	0	1	2	3	4	5	6	7	8	9	10	11	12	13
KMT2A WT GO	384	254	207	186	173	163	155	138	123	109	78	39	17	2
KMT2A WT No-GO	389	252	203	187	172	164	148	132	121	108	80	32	15	0
KMT2A-r GO	108	66	54	51	46	44	40	37	36	30	20	11	5	0
KMT2A-r No-GO	107	47	34	31	28	27	24	23	23	21	18	11	4	0

No. at risk:

Group	0	1	2	3	4	5	6	7	8	9	10	11	12	13
KMT2A WT GO	283	209	173	153	142	136	124	113	101	91	63	34	14	1
KMT2A WT No-GO	272	188	156	146	135	126	111	98	90	82	58	26	13	0
KMT2A-r GO	82	57	48	46	42	40	36	33	32	26	18	10	4	0
KMT2A-r No-GO	68	31	24	23	21	20	17	17	16	14	14	7	3	0

AML = acute myeloid leukemia; COG = Children's Oncology Group; EFS = event-free survival; GO = gemtuzumab ozogamicin; *KMT2A*-r = rearranged *KMT2A*; *KMT2A*-WT = wild type *KMT2A*; No-GO = did not receive GO; RR = relapse risk.

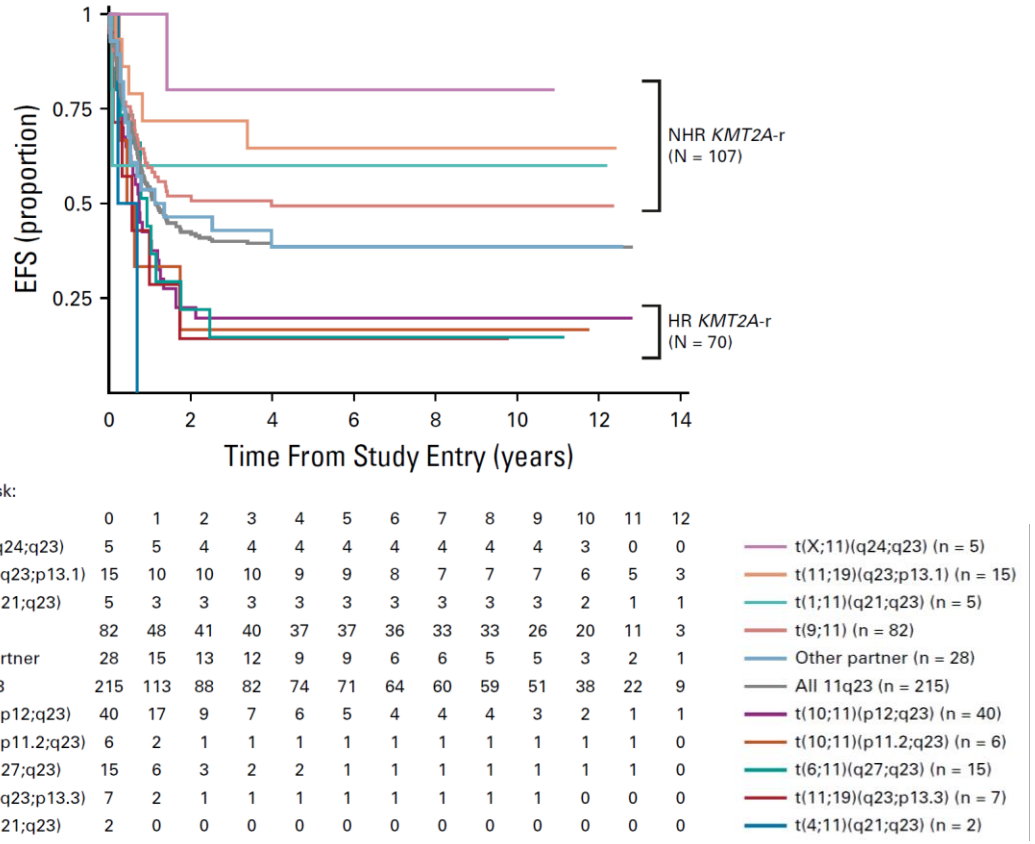
Pollard JA et al. *J Clin Oncol* 2021;39:3149–60.

COG Phase III Trial (AAML0531) in *KMT2A*-rearranged AML

Impact of GO on Clinical Outcomes in KMT2A-r AML(3/3)

- For *KMT2A*-r disease, most clinical outcomes for the HR cohort were inferior vs. the NHR cohort (**Table; Figure**)
- Treatment with GO improved outcomes vs. No-GO in both HR and NHR cohorts

5-year Outcome, n (%) [95% CI]	HR* GO (n=37)	NHR† GO (n=51)	P	HR* No-GO (n=33)	NHR† No-GO (n=56)	P
EFS	37 (27) [14–41]	51 (66) [51–77]	**0.001**	33 (6) [1–18]	56 (42) [29–55]	**0.001**
OS	37 (49) [32–65]	51 (76) [61–85]	**0.023**	33 (36) [21–52]	56 (67) [53–78]	**0.013**
DFS‡	23 (29) [12–49]	42 (75) [59–86]	**0.001**	20 (10) [2–27]	35 (50) [32–65]	**0.003**
RR‡	23 (66) [42–83]	42 (22) [11–36]	**0.001**	20 (90) [60–98]	35 (47) [29–63]	**0.002**
TRM‡	23 (4) [0.3–19]	42 (2) [0.2–11]	0.686	20 (0) [0–0]	35 (3) [0.2–13]	0.443



*HR *KMT2A* translocation partners were defined as 6q27, 10p11.2, 10p12, 4q21.3, and 19p13.3 based on previously published data; †The NHR cohort included the remaining *KMT2A*-r cases but excluded other partners (defined as a NHR translocation with fewer than five cases) as their rarity precluded analysis of the impact of the fusion partner on prognosis, and the unknown partners, given the unclear origin of the fusion partner; ‡from end of induction 1 for patients in CR.
AML = acute myeloid leukemia; COG = Children's Oncology Group; CR = complete remission; DFS = disease-free survival; EFS = event-free survival; GO = gemtuzumab ozogamicin; HR = higher risk; *KMT2A*-r = rearranged *KMT2A*; *KMT2A*-WT = wild type *KMT2A*; NHR = not high-risk; No-GO = did not receive GO; OS = overall survival; RR = relapse risk; TRM = treatment-related mortality.

Pollard JA et al. *J Clin Oncol* 2021;39:3149–60.

COG Phase III Trial (AAML0531) in *KMT2A*-rearranged AML

Additional Key Takeaways

- In the subset of patients with *KMT2A-r* who proceeded to HSCT (n=30), prior treatment with GO was associated with a lower 5-year relapse rate
  - RR was reduced with GO compared with No-GO (28% [95% CI, 10–50] vs. 73% [95% CI, 32–91]; P=0.006)
  - These results suggest that combination of GO and HSCT may improve outcomes for pediatric patients with *KMT2A-r* AML; however, further prospective studies are needed to explore the additive benefit of GO and HSCT
- In a subset of patients with evaluable CD33 expression (n=168), the intensity of CD33 expression was shown to impact GO response, though even patients with lower CD33 expression derived clinical benefit from the addition of GO

AML = acute myeloid leukemia; GO = gemtuzumab ozogamicin; HSCT = hematopoietic stem cell transplantation; No-GO = did not receive GO; RR = relapse risk

Pollard JA et al. *J Clin Oncol* 2021;39:3149–60.

COG Phase III Trial (AAML0531) in *KMT2A*-rearranged AML

Conclusion

- Pediatric patients with *KMT2A*-r AML treated with GO experienced statistically significant improvements in EFS and DFS by reducing RR without increasing TRM in both HR and NHR cohorts
- Patients with *KMT2A*-r disease receiving treatment with GO had similar clinical outcomes as patients with *KMT2A*-WT AML with or without GO treatment, supporting the use of GO in all patients with *KMT2A*-r AML treated with a COG backbone of therapy
- Consolidation with HSCT led to additive improvements in outcomes, indicating that GO may impact post-HSCT prognosis

AML = acute myeloid leukemia; COG = Children's Oncology Group; DFS = disease-free survival; EFS = event-free survival; GO = gemtuzumab ozogamicin; HR = higher risk; *KMT2A*-r = rearranged *KMT2A*; *KMT2A*-WT = wild type *KMT2A*; NHR = not high-risk; RR = relapse risk; TRM = treatment-related mortality.

Pollard JA et al. *J Clin Oncol* 2021;39:3149–60.

WARNING: HEPATOTOXICITY

Hepatotoxicity, including severe or fatal hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), has been reported in association with the use of MYLOTARG as a single agent, and as part of a combination chemotherapy regimen. Monitor frequently for signs and symptoms of VOD after treatment with MYLOTARG.

MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021.

Important Safety Information (1/3)

- **Hepatotoxicity, Including Veno-occlusive Liver Disease (VOD):**

An increased risk of VOD was observed in patients with moderate/severe hepatic impairment and patients who received MYLOTARG either before or after HSCT.

Assess ALT, AST, total bilirubin, and alkaline phosphatase prior to each dose of MYLOTARG.

After treatment with MYLOTARG, monitor frequently for signs and symptoms of VOD: elevations in ALT, AST, total bilirubin, hepatomegaly (which may be painful), rapid weight gain, and ascites.

Monitoring only total bilirubin may not identify all patients at risk of VOD. For patients who develop abnormal liver tests, more frequent monitoring of liver tests and clinical signs and symptoms of hepatotoxicity is recommended.

For patients who proceed to HSCT, monitor liver tests frequently during the post-HSCT period, as appropriate.

Manage signs or symptoms of hepatic toxicity by dose interruption or discontinuation of MYLOTARG.

In patients who experience VOD, discontinue MYLOTARG and treat according to standard medical practice.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HSCT = hematopoietic stem cell transplant; VOD = veno-occlusive disease

MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021.

Infusion-Related Reactions (Including Anaphylaxis):

- Life-threatening or fatal infusion-related reactions can occur during or within 24 hours following infusion of MYLOTARG.
- Fever, chills, hypotension, tachycardia, hypoxia, and respiratory failure.
- Premedicate prior to MYLOTARG infusion.
- Monitor vital signs frequently during infusion.
- Interrupt infusion immediately for patients who develop evidence of infusion reaction, especially dyspnea, bronchospasm, or hypotension.
- Monitor patients during and for at least 1 hour after the end of the infusion or until signs and symptoms completely resolve.
- Discontinue use of MYLOTARG in patients who develop signs or symptoms of anaphylaxis, including severe respiratory symptoms or clinically significant hypotension.

Important Safety Information (2/3)

- **Hemorrhage:** MYLOTARG is myelosuppressive and can cause fatal or life-threatening hemorrhage due to prolonged thrombocytopenia.
- Assess blood counts prior to each dose of MYLOTARG and monitor blood counts frequently after treatment.
- Monitor patients for signs and symptoms of bleeding during treatment with MYLOTARG.

- **QT Interval Prolongation:** QT interval prolongation has been observed in patients treated with other drugs containing calicheamicin. When administering MYLOTARG to patients who have a history of or predisposition for QTc prolongation, who are taking medicinal products that are known to prolong QT interval, and in patients with electrolyte disturbances, obtain **electrocardiograms** and electrolytes prior to the start of treatment and as needed during administration.

- **Adverse Cytogenetics:** In subgroup analyses in ALFA-0701, the addition of MYLOTARG to standard combination chemotherapy did not improve event-free survival in the subgroup of patients having adverse-risk cytogenetics. For patients being treated with MYLOTARG in combination with daunorubicin and cytarabine for newly diagnosed de novo AML, when cytogenetics testing results become available consider whether the potential benefit of continuing treatment with MYLOTARG outweighs the risks for the individual patient.
- **Embryo-Fetal Toxicity:** MYLOTARG can cause embryo-fetal harm.

QTc = corrected QT interval

MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021.

Important Safety Information (3/3)

- **Adverse Reactions:** The most common adverse reactions (greater than 15%) were hemorrhage, infection, fever, nausea, vomiting, constipation, headache, increased AST, increased ALT, rash, mucositis, febrile neutropenia, and decreased appetite.
- **Contraindications:** Hypersensitivity to MYLOTARG or any of its components. Reactions have included anaphylaxis

ALT = alanine aminotransferase; AST = aspartate aminotransferase

MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021.

Premedication

Premedication and Special Considerations

Premedication

- **Pediatric patients 1 month and older:** Premedicate with acetaminophen 15 mg/kg (maximum of 650 mg), diphenhydramine 1 mg/kg (maximum of 50 mg) 1 hour prior to MYLOTARG dosing, and 1 mg/kg methylprednisolone orally or intravenously within 30 minutes prior to infusion of MYLOTARG; additional doses of acetaminophen and diphenhydramine may be administered every 4 hours after the initial pretreatment dose
- Repeat with the same dose of methylprednisolone or an equivalent corticosteroid for any sign of an infusion reaction, such as fever, chills, hypotension, or dyspnea during the infusion or within 4 hours afterwards

Special Considerations

- Use appropriate measures to prevent tumor lysis syndrome
- For patients with hyperleukocytosis (leukocyte count greater than or equal to 30.000/ µL), cytoreduction is recommended prior to administration of MYLOTARG

MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021.

Recommended Dosage

Combination or Single Agent Regimen

Recommended Dosage for Newly Diagnosed *De Novo* AML – Combination Regimen: Pediatric Patients (Age ≥1 Month)

Recommended Dose in Pediatric Patients 1 Month and Older
MYLOTARG 3 mg/m^2 for patients with BSA ≥0.6 m^2
MYLOTARG 0.1 mg/kg for patients with BSA <0.6 m^2

- For Induction 1, MYLOTARG is given once in combination with standard chemotherapy
- No MYLOTARG is given in the second induction cycle
- No MYLOTARG is given in the first or third intensification cycles
- For Intensification 2, MYLOTARG is given once in combination with standard chemotherapy
- Consider the risks and potential benefits before giving MYLOTARG during Intensification 2

AML = acute myeloid leukemia; BSA = body surface area

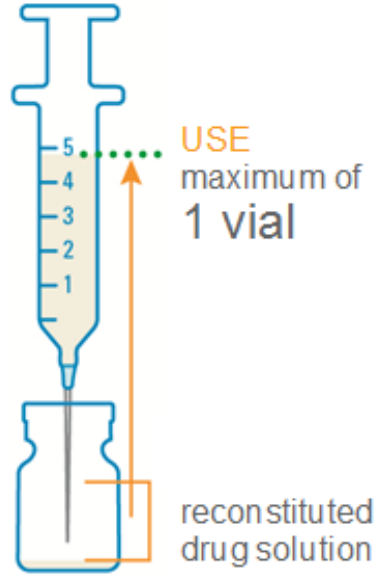
MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021.

Recommended Dosage for Newly Diagnosed *De Novo* CD33-positive AML – Combination Regimen

Clarification on Maximum Dose

To prepare a dose, draw up the required dose volume from a reconstituted vial (1 mg/mL).[1] The vial has an extractable volume of 4.5 mL (4.5 mg) however excess volume is present in the vial[2]

For the combination regimen in this population, each dose should not exceed 1 vial, regardless of BSA[1]



Concentration after reconstitution is 1 mg/mL[1]

AML = acute myeloid leukemia; BSA = body surface area

1. MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021;

2. US DHHS/FDA/CDER/CBER. Silver Springs, MD. 2015. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389069.pdf. Accessed on December 16, 2021.

Recommended Dosage

Relapsed/Refractory CD33-positive AML
(Single-Agent Regimen)

Recommended Dosage for Relapsed/Refractory AML – Single-Agent Regimen: Adults and Pediatric Patients (Age ≥2 Years)

Single Course
MYLOTARG 3 mg/m^2 (up to one 4.5 mg vial): Days 1, 4, and 7

- Treatment in the relapsed or refractory setting consists of a single course of MYLOTARG
- **COG AAML00P2 trial (dose escalation with chemo):** MTD 3 mg/m^2 with cytarabine + mitoxantrone in relapsed pediatric AM
- **FM study group:** 1–4 cycles 2.5–10 mg/m^2 GO with/without chemotherapy, HSCT bridging

AML = acute myeloid leukemia

MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021.

Multicenter Study > Br J Haematol. 2022 Jul;198(2):373-381. doi: 10.1111/bjh.18203.
Epub 2022 Apr 19.

Single-dose (4.5 mg/m²) gemtuzumab ozogamicin in combination with fludarabine, cytarabine and anthracycline as reinduction therapy in relapsed or refractory paediatric acute myeloid leukaemia

Chloé Dhunputh [1], Marion Strullu [2], Arnaud Petit [3], Maria Merched [4], Marlène Pasquet [5], Saba Azarnoush [2], Guy Leverger [3], Stéphane Ducassou [1]

Affiliations + expand

PMID: 35438187 DOI: 10.1111/bjh.18203

Clinical Trial > Pediatr Blood Cancer. 2020 Jun;67(6):e28305. doi: 10.1002/pbc.28305.
Epub 2020 Apr 19.

Association of fludarabin, cytarabine, and fractioned gemtuzumab followed by hematopoietic stem cell transplantation for first-line refractory acute myeloid leukemia in children: A single-center experience

Mathilde Penel-Page [1 2], Adriana Plesa [3], Sandrine Girard [4], Alice Marceau-Renaut [5], Cécile Renard [1], Yves Bertrand [1 2]

Affiliations + expand

PMID: 32307866 DOI: 10.1002/pbc.28305

Abstract

Context: Acute myeloid leukemia (AML) is a rare disease in children, with only 50% to 60% event-free survival. Among patients with AML, 10% do not respond to first-line chemotherapy. There is no recommendation concerning second-line treatments. Gemtuzumab ozogamicin (GO) is a monoclonal antibody targeting CD33, linked to calicheamicin. We report the efficacy and tolerance of a salvage regimen of fludarabin, cytarabine, and GO (FLA-GO) in patients refractory to first-line treatment.

Methods: Eight patients (median age 14.5 years), who had more than 2% minimal residual disease (MRD) by flow cytometry (MRD flow), received gemtuzumab 3 mg/m^2 on days 1, 4, 7, associated with cytarabine 2000 mg/m^2 and fludarabin 30 mg/m^2 on days 1 to 5.

Gemtuzumab ozogamicin in children with relapsed or refractory acute myeloid leukemia: a report by Berlin-Frankfurt-Münster study group

Naghmeh Niktoreh,[1*] Beate Lerius,[1*] Martin Zimmermann,[2] Bernd Gruhn,[3] Gabriele Escherich,[4] Jean-Pierre Bourquin,[5] Michael Dworzak,[6] Lucie Sramkova,[7] Claudia Rossig,[8] Ursula Creutzig,[2] Dirk Reinhardt[1] and Mareike Rasche[1]

[1]Department of Pediatric Hematology and Oncology, University Hospital Essen, Germany; [2]Department of Pediatric Hematology and Oncology, Hannover Medical School, Germany; [3]Department of Pediatrics, Jena University Hospital, Germany; [4]Department of Pediatric Hematology and Oncology, Eppendorf University Hospital, Hamburg, Germany; [5]Division of Pediatric Hematology/Oncology, University Children's Hospital Zurich, Switzerland; [6]St. Anna Children's Hospital and Children's Cancer Research Institute, Department of Pediatrics, Medical University of Vienna, Austria; [7]Department of Pediatric Hematology and Oncology, 2nd Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic and [8]University Children's Hospital Münster, Pediatric Hematology and Oncology, Germany

**NN and BL contributed equally to this work as first authors.*

ABSTRACT

Despite intensified salvage treatments, children with relapsed/refractory acute myeloid leukemia (AML) have poor survival. We evaluated gemtuzumab ozogamicin (CD33-targeted drug) used on a compassionate basis in patients diagnosed from 1995 until 2014 within Acute Myeloid Leukemia Berlin-Frankfurt-Münster studies, and identified 76 patients (<18 years) with highly-advanced and pre-treated AML [refractory *de novo* acute myeloid leukemia (n=10), *de novo* AML refractory to relapse (1st early: n=41; 1st late: n=10; 2nd or more: n=10), and secondary AML (n=5)]. At doses of 2.5-10 mg/m^2, gemtuzumab ozogamicin was administered in 1-4 cycles as single agent (47%), combined with cytarabine (47%), or others (6%). Most common

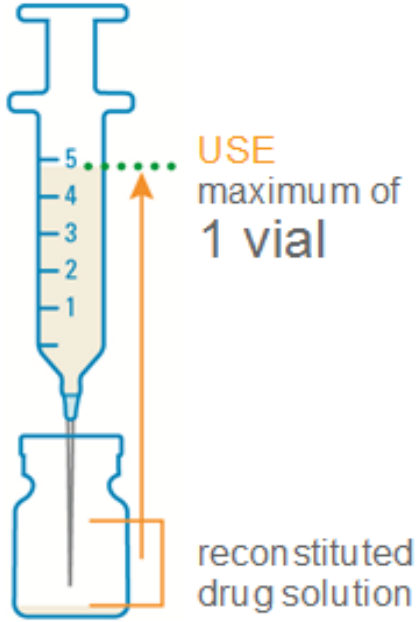
Hematologic and Nonhematologic Toxicities	Recommended Action
For patients receiving MYLOTARG in combination therapy	
Persistent thrombocytopenia	• Adults: If platelet count does not recover to greater than or equal to 100 Gi/L within 14 days following the planned start date of the consolidation cycle (14 days after hematologic recovery following previous cycle), discontinue MYLOTARG (do not administer MYLOTARG in the consolidation cycles). • Pediatrics: Patients should have a platelet count of 75 Gi/L before the next cycle (induction or intensification).
Persistent neutropenia	• Adults: If neutrophil count does not recover to greater than 0.5 Gi/L within 14 days following the planned start date of the consolidation cycle (14 days after hematologic recovery following previous cycle), discontinue MYLOTARG (do not administer MYLOTARG in the consolidation cycles). • Pediatrics: Patients should have a neutrophil count of 1 Gi/L before the next cycle (induction or intensification).
For all patients receiving MYLOTARG (Monotherapy or in Combination)	
VOD	• Discontinue MYLOTARG [see Warnings and Precautions (5.1)].
Total bilirubin greater than 2 × ULN, or AST and/or ALT greater than 2.5 × ULN	• Delay treatment with MYLOTARG until recovery of total bilirubin to less than or equal to 2 × ULN and AST and ALT to less than or equal to 2.5 × ULN prior to each dose. • Omit scheduled dose if delayed more than 2 days between sequential infusions.
Infusion-related reactions	• Interrupt the infusion and institute appropriate medical management. • Administer acetaminophen, diphenhydramine and/or methylprednisolone, if needed [see Dosage and Administration (2.1)] • Provide supportive care measures as needed. • For mild, moderate or severe infusion-related reactions, once symptoms resolve, consider resuming the infusion at no more than half the rate at which the reaction occurred. Repeat the procedure above in the event of recurrence of symptoms. • Permanently discontinue MYLOTARG upon occurrence of a severe infusion reaction or for any life-threatening infusion reaction [see

Recommended Dosage for Relapsed/Refractory CD33-positive AML – Single-Agent Regimen

Clarification on Maximum Dose

To prepare a dose, draw up the required dose volume from a reconstituted vial (1 mg/mL)[1]. The vial has an extractable volume of 4.5 mL (4.5 mg) however excess volume is present in the vial[2]

To the extent possible, this excess volume may be drawn out to accommodate doses from 4.5 mg to 5 mg (vial fill amount). However, for use as a single-agent regimen in the relapsed or refractory setting, each dose should not exceed 1 vial, regardless of BSA[1]



Concentration after reconstitution is 1 mg/mL[1]

AML = acute myeloid leukemia; BSA = body surface area

1. MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021;

2. US DHHS/FDA/CDER/CBER. Silver Springs, MD. 2015. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389069.pdf. Accessed on December 16, 2021.

Dose Modifications

MYLOTARG™ (gemtuzumab ozogamicin) Dose Modifications for Toxicities

Hematologic and Non-hematologic Toxicities	Recommended Action
For patients receiving MYLOTARG in combination therapy	
Persistent thrombocytopenia	• Adults: If platelet count does not recover to greater than or equal to 100 Gi/L within 14 days following the planned start date of the consolidation cycle (14 days after hematologic recovery following previous cycle), discontinue MYLOTARG (do not administer MYLOTARG in the consolidation cycles). • Pediatrics: Patients should have a platelet count of 75 Gi/L before the next cycle (induction or intensification).
Persistent neutropenia	• Adults: If neutrophil count does not recover to greater than 0.5 Gi/L within 14 days following the planned start date of the consolidation cycle (14 days after hematologic recovery following previous cycle), discontinue MYLOTARG (do not administer MYLOTARG in the consolidation cycles). • Pediatrics: Patients should have a neutrophil count of 1 Gi/L before the next cycle (induction or intensification).
For all patients receiving MYLOTARG (monotherapy or in combination)	
VOD	• Discontinue MYLOTARG
Total bilirubin greater than 2 × ULN, or AST and/or ALT greater than 2.5 × ULN	• Delay treatment with MYLOTARG until recovery of total bilirubin to less than or equal to 2 × ULN and AST and ALT to less than or equal to 2.5 × ULN prior to each dose. • Omit scheduled dose if delayed more than 2 days between sequential infusions.
Infusion-related reactions	• Interrupt the infusion and institute appropriate medical management. • Administer acetaminophen, diphenhydramine and/or methylprednisolone, if needed. • Provide supportive care measures as needed. • For mild, moderate or severe infusion-related reactions, once symptoms resolve, consider resuming the infusion at no more than half the rate at which the reaction occurred. Repeat the procedure above in the event of recurrence of symptoms. • Permanently discontinue MYLOTARG upon occurrence of a severe infusion reaction or for any life-threatening infusion reaction.
Other severe or life-threatening non-hematologic toxicities	• Delay treatment with MYLOTARG until recovery to a severity of no more than mild. • Omit scheduled dose if delayed more than 2 days between sequential infusions.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal;
VOD = veno-occlusive disease

MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021.

Posology: Reconstitution, Dilution, and Administration

Additional Information

Reconstitution: Instructions

Use appropriate aseptic technique for the reconstitution and dilution procedures. Protect the reconstituted and diluted MYLOTARG solution from light.[1]

- MYLOTARG is a cytotoxic drug. Follow applicable special handling and disposal procedures.[2]
- Calculate the dose (mg) and number of vials of MYLOTARG required.[1]
- Prior to reconstitution, allow drug product vials to reach room temperature (up to 30°C) for approximately 5 minutes.[1]
- Reconstitute each vial with 5 mL of Sterile Water for Injection, USP to obtain a concentration of 1 mg/mL of MYLOTARG that delivers 4.5 mL (4.5 mg).[1]
- Gently swirl the vial to aid dissolution. DO NOT SHAKE.[1]
- Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution may contain small white to off-white, opaque to translucent, and amorphous to fiber-like particles.[1]
- MYLOTARG contains no bacteriostatic preservatives.[1]
- If the reconstituted solution cannot be used immediately, it may be stored in the original vial for up to 16 hours in a refrigerator (2 to 8°C; 36 to 46°F) or up to 3 hours at room temperature (up to 30°C). **PROTECT FROM LIGHT. DO NOT FREEZE.**[1]

USP = United States Pharmacopeia

1. MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021

2. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html. Accessed on December 16, 2021.

Reconstitution: Fill Amount and Extractable Volume

ADD
5 mL
Sterile Water for Injection, USP

5 mg
gemtuzumab ozogamicin powder
(fill amount)

To reconstitute, add 5 mL of Sterile Water for Injection, USP to the vial containing 5 mg of gemtuzumab ozogamicin powder[1]

Gently swirl to dissolve; DO NOT SHAKE

Protect solution from light

Do NOT freeze solution

Final concentration of the reconstituted drug solution is 1 mg/mL[1]

Calculate volume needed based on the required dose

Use a syringe to withdraw volume from vial based on the dose calculated for the patient[1]

The amount of gemtuzumab ozogamicin in the vial is 5 mg. When reconstituted with 5 mL of Sterile Water for Injection, USP, the concentration in the vial is 1 mg/mL.[1] The vial and carton labeling (4.5 mg) reflects a regulatory determination of extractable volume after reconstitution[2]

USP = United States Pharmacopeia

1. MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021;

2. US DHHS/FDA/CDER/CBER. Silver Springs, MD. 2015. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389069.pdf. Accessed on December 16, 2021.

Dilution: Instructions

Use appropriate aseptic technique for the reconstitution and dilution procedures. Protect the reconstituted and diluted MYLOTARG solution from light.

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to patient body surface area. Withdraw this amount from the vial(s) using a syringe. PROTECT FROM LIGHT. Discard any unused reconstituted solution left in the vial
- **Doses must be mixed to a concentration between 0.075 mg/mL to 0.234 mg/mL according to the following instructions:**
  - Doses less than 3.9 mg must be prepared for administration by syringe. Add the reconstituted MYLOTARG solution to a syringe with 0.9% Sodium Chloride Injection to a final concentration between 0.075 mg/mL to 0.234 mg/mL. PROTECT FROM LIGHT.
  - Doses greater than or equal to 3.9 mg are to be diluted in a syringe or a polyvinyl chloride (PVC) with di(2-ethylhexyl)phthalate (DEHP), non-PVC polyolefin, or ethylene vinyl acetate intravenous infusion bag in an appropriate volume of 0.9% Sodium Chloride Injection to ensure a final concentration between 0.075 mg/mL to 0.234 mg/mL. PROTECT FROM LIGHT.
  - Gently invert the infusion container to mix the diluted solution. DO NOT SHAKE.
  - Following dilution with 0.9% Sodium Chloride Injection, MYLOTARG solution should be infused immediately. If not used immediately, the diluted solution may be stored up to 18 hours in a refrigerator (2°C to 8°C; 36°F to 46°F) and for up to 6 hours at room temperature (up to 30°C). The allowed time at room temperature (up to 30°C) includes the time required for preparation of the diluted solution, equilibration, if needed, and the 2 hours needed to administer to the patient. PROTECT FROM LIGHT and DO NOT FREEZE.

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Dilution: Infusion Container Based on Dose

- Doses must be mixed to a concentration between 0.075 mg/mL to 0.234 mg/mL according to the following instructions:[1]
  - Doses less than 3.9 mg must be prepared for administration by syringe. Add the reconstituted MYLOTARG solution to a syringe with 0.9% Sodium Chloride Injection to a final concentration between 0.075 mg/mL to 0.234 mg/mL
  - Doses greater than or equal to 3.9 mg are to be diluted in a syringe or a polyvinyl chloride (PVC) with di(2-ethylhexyl)phthalate (DEHP), non-PVC polyolefin, or ethylene vinyl acetate intravenous infusion bag in an appropriate volume of 0.9% Sodium Chloride Injection to ensure a final concentration between 0.075 mg/mL to 0.234 mg/mL
- Examples of appropriate infusion containers based on dose are summarized in the table below[2]

Dose of Mylotarg Based on BSA	Infusion Container
0.3 mg up to 0.45 mg	4 mL in a syringe
0.45 mg up to 0.75 mg	6 mL in a syringe
0.75 mg up to 1.89 mg	10 mL in a syringe
1.89 mg up to 3.9 mg	25 mL in a syringe
3.9 mg up to 11.7 mg	50 mL IV bag
11.7 mg up to 21.6 mg	100 mL IV bag

1. MYLOTARG™ (gemtuzumab ozogamicin) package insert. Pfizer; New York, NY. 2021;

BSA = body surface area; IV = intravenous

2. Pfizer Data on File

Storage Guidelines

Storage Times and Conditions for Reconstituted and Diluted MYLOTARG Solution		
Time Intervals		
After Reconstitution	After Dilution	Administration
Use immediately If the reconstituted solution (in sterile water) cannot be used immediately, it may be stored in the original vial for up to 16 hours in a refrigerator (2°C to 8°C; 36°F to 46°F) or up to 3 hours at room temperature (up to 30°C).	Use immediately If not used immediately, the diluted solution (using 0.9% sodium chloride) may be stored up to 18 hours in a refrigerator (2°C to 8°C; 36°F to 46°F) and for up to 6 hours at room temperature (up to 30°C). The allowed time at room temperature (up to 30°C) includes the time required for preparation of the diluted solution, equilibration, if needed, and the 2 hours needed to administer to the patient. After dilution, protect from light and do not freeze.	2-hour infusion The infusion must be completed prior to the end of the allowed 6-hour storage of the diluted solution at room temperature (up to 30 °C).

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Administration: Instructions

- Use an in-line 0.2 micron PES filter for infusion of MYLOTARG.
- Protect the intravenous bag from light using a light-blocking cover during infusion. The infusion line does not need to be protected from light.
- Infuse the diluted solution over 2 hours using an infusion set made of polyvinyl chloride (PVC) with DEHP, PVC non-DEHP, polyethylene, or polyurethane. The infusion must be completed prior to the end of the allowed 6-hour storage of the diluted solution at room temperature (up to 30°C).
- Do not mix MYLOTARG with, or administer as an infusion with, other medicinal products.

PES = polyethersulfone

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آماده‌سازی داروی Gemtuzumab (Mylotarg)

- دوز را به میلی‌گرم محاسبه کرده و تعداد ویال‌های مورد نیاز را تعیین کنید.
- اجازه دهید ویال‌ها حدود ۵ دقیقه در دمای محیط قرار بگیرند.
- هر ویال را با ۵ میلی‌لیتر آب استریل تزریقی برای تهیه غلظت ۱ میلی‌گرم در میلی‌لیتر مجدداً حل کنید.
- ویال را تکان ندهید؛ به آرامی ویال را بچرخانید تا کمک به حل شدن دارو شود.
- محلول آماده شده را از نظر وجود ذرات معلق و تغییر رنگ بررسی کنید.
- محلول آماده شده ممکن است حاوی ذرات کوچک سفید تا زرد کم‌رنگ، کدر تا شفاف و آمورف یا شبیه فیبر باشد.

- **Premedication درکودکان و نوجوانان**
- یک ساعت قبل از درمان، با استامینوفن و دیفن هیدرامین پیش‌درمانی کنید، سپس ۳۰ دقیقه قبل با متیل‌پردنیزولون.
- استامینوفن ۱۵ میلی‌گرم به ازای هر کیلوگرم وزن بدن (تا حداکثر ۶۵۰ میلی‌گرم در هر دوز) خوراکی (PO)
- دیفن هیدرامین ۱ میلی‌گرم به ازای هر کیلوگرم وزن بدن (تا حداکثر ۵۰ میلی‌گرم در هر دوز) خوراکی (PO) یا وریدی (IV) **و**
- متیل‌پردنیزولون ۱ میلی‌گرم به ازای هر کیلوگرم وزن بدن، خوراکی یا وریدی (PO/IV)
- دوزهای اضافی استامینوفن و دیفن هیدرامین می‌توانند هر ۴ ساعت پس از دوز پیش‌درمانی اولیه داده شوند.
- در صورت بروز هر علامت واکنش به تزریق (مانند تب، لرز، افت فشار خون یا تنگی نفس) در حین تزریق یا تا ۴ ساعت پس از آن، دوز متیل‌پردنیزولون یا کورتیکواستروئید معادل به همان مقدار تکرار شود.


MYLOTARG
for Injection
4.5 mg/vial
MYLOTARG
for Injection
4.5 mg/vial
For Intravenous Infusion Only
Reconstitution and dilution required
No Preservatives
One Single-Dose Vial. Discard unused portion.
Rx only

Thank You