These recent results demonstrated some advantage for patients treated with GO. In addition, induction mortality was not increased in these studies. Efficacy was observed, typically in patients with favorable risk, and sometimes in intermediate risk. The reason for this has not been elucidated. Molecular analyses concomitant with clinical outcome data will be needed to address this in the future.

Doses of GO and anthracyclines differed in these studies. From the recent studies, 3–6 mg/m^2 of GO for 1 day and 50–60 mg/m^2 of DNR for 3 days may be chosen. Ongoing and future studies may help to demonstrate the optimal dosage of these agents in combination chemotherapy including GO.

Low-dose AraC (LDAC, 20 mg, twice a day) was administered randomly with or without GO (5 mg) in 495 elderly patients with AML [91]. GO improved OR rate, but not OS, at 1 year. Improvement of OS in elderly AML remains a challenge for treatments, including GO.

GO for pediatric AML

Reports of results from pediatric patients treated with GO remain relatively limited. Twelve children with relapsed/refractory AML received GO (1.8–9 mg/m^2 at 2-week intervals for 1–2 doses) [92]. Five children responded to treatment with blast reduction, but no child achieved CR. One patient treated GO after HSCT developed reversible VOD.

Seventeen children with relapsed/refractory AML received GO (3 mg/m^2 on days 1, 4 and 7) plus AraC (100 mg/m^2 for 7 days) (GOCYT), and seven of these received GO-based consolidation [93]. The OR rate was 35 and 53 % after induction therapy and consolidation therapy with GO, respectively. VOD was not observed.

Thirty children with AML, who were refractory to re-induction at first relapse, received GO (7.5 mg/m^2 at 2-week intervals for 1–2 doses) [94]. The OR rate was 37 %, and 3-year OS was 27 %. Grade 3–4 bilirubinemia and transient transaminitis were observed in one and two cases, respectively.

Twenty-nine children with relapsed/refractory AML received GO (6, 7.5 or 9 mg/m^2 at 2-week intervals for two doses) [95]. In 13 (45 %) of them, GO was administered after HSCT. The OR rate was 97 %. Grade 3 or 4 bilirubinemia and transaminitis were observed in 7 and 21 %, respectively. VOD was observed in seven (26 %) patients, six of whom had received HSCT.

A group of 230 children with untreated AML were treated with high-dose (18 g/m^2) or low-dose (2 g/m^2) AraC, DNR and ETP (ADE; induction 1), followed by ADE with or without GO (ADE; induction 2) [96]. ADE plus GO was shown to be feasible. CR was achieved in 80 % after induction 1, and 94 % after induction 2. The 3-year EFS and OS were 63 and 71 %, respectively.

In the Children's Oncology Group (COG)-AAML00P2 trial, the maximum tolerated dose (MTD) of GO in combination with AraC and MIT, and with AraC and l-asparaginase was analyzed, and was concluded to be 3 and 2 mg/m^2, respectively [97].

A group of 350 children with previously untreated AML were enrolled to the COG-AAML03P1 [98]. GO (3 mg/m^2 on day 6 of the first course) was administrated with chemotherapy with DNR, AraC, and ETP. The CR rate was 83 % after the first course. The mortality rate after the first course was 1.5 %. The 3-year EFS and OS rates were 53 and 66 %, respectively.

The Nordic Society of Pediatric Hematology and Oncology (NOPHO)-AML 2004 trial estimated post-consolidation effect of GO (6 mg/m^2 at 3-week intervals for two doses) in children with AML. Of a total of 120 patients randomized, 59 received GO [99]. GO was well tolerated, but the relapse rate, median time to relapse, the 5-year EFS and OS were not different between the two groups.

Given these equivocal results, the efficacy of GO in children with AML remains uncertain.

In vitro efficacy of GO for APL

In our in vitro study, GO showed equivalent effects on ATRA and/or ATO-resistant APL cells unless they expressed P-gp [100]. The cell lines used in our study are NB4, ATRA-resistant NB4 (NB4/RA), P-gp-positive NB4 and NB4/RA (NB4/MDR and NB4/RA/MDR) and ATO-resistant NB4 (NB4/As). GO did not exhibit cross-resistance with ATRA- and ATO-resistance. GO is likely useful for induction therapy after resistance to these drugs has been acquired.

Relapsed and recurrent APL

While ATRA combined with chemotherapy has been the standard treatment for patients with APL, approximately 20 % undergo relapse [101–103]. Several salvage therapies, including Am80, ATO, and stem cell transplantation, have been introduced for the treatment of APL [104, 105]. GO was also administered to APL, and the successful use of this therapy has been reported for patients with newly diagnosed or relapsed APL [106–108].

Several ideas have been proposed to explain the efficacy of GO for APL [100, 109]. First, a large amount of CD33 is commonly expressed on the surface of APL cells. Second, the level of P-gp on the surface of APL cells is lower than that of AML. Third, APL cells are highly sensitive for free calicheamicin.

Several investigators have reported the clinical efficacy of GO for patients of relapsed APL (Table 5). Lo-Coco et al. [107] reported that 14 of 16 patients with molecularly relapsed APL achieved molecular remission (MR) after GO monotherapy (6 mg/m^2 at 2-week intervals for three doses). Of 14 responders, seven (50 %) remained in sustained MR for a median of 15 months. GO was administered again in two patients with relapse, and both obtained a new MR.

We treated patients, who were in a third morphologic relapse with a considerable number of APL cells, by GO monotherapy (9 mg/m^2 on days 1 and 15). They developed prominent DIC after GO treatment [108]. Both patients achieved CR. One of the patients was treated with consolidation chemotherapy, but the other was not. Both patients had a considerably long remission period. GO may represent another treatment option if stem cell transplantation is not being considered in the near future. Treatment with GO may transiently increase the severity of DIC, as APL cells collapse rapidly.

Aribi et al. [109] reported the efficacy of a combination therapy consisting of ATO, ATRA, and GO in eight patients with APL in first recurrence. Patients were treated with ATO until CR, and then received the consolidation therapy including ATO, ATRA and GO (9 mg/m^2) once a month for 10 months. The second CR was longer than the first CR in 75 %. All patients achieved MR. There were no grade 3 or 4 non-hematological toxicities.

GO (3–6 mg/m^2 for two doses) was administered in three elderly patients with APL who had molecular relapse and were deemed unfit for intensive chemotherapy [110]. All of the patients achieved second MR, and did not relapse. The study suggested that low-dose GO is effective to treat MR in elderly APL patients.

In a Japanese post-marketing study of GO for APL, whose results were partially described in the previous section [76], remission duration of first CR and number of relapses influenced CR rates, but previous usage of ATO did not. Treatment-related adverse events (grade 3 or 4) in APL were similar to those seen in AML. GO may be more effective in APL compared to AML, and relatively safe in relapsed/refractory APL.

These reports show that GO is effective for APL patients with molecularly relapsed and advanced relapsed forms of the disease. These data also support the use of GO treatment for newly diagnosed APL.

Newly diagnosed APL

In the US study, 19 newly diagnosed patients with APL were treated with GO (9 mg/m^2) [106]. Patients received eight additional courses (once every 4–5 weeks) of GO and ATRA after CR was achieved. GO was shown to be feasible. CR and MR were achieved in 84 and 74 %, respectively. All patients tested during the study were PCR-negative 2–4 months from CR.

In another study, 19 untreated patients with high-risk APL were treated with GO (9 mg/m^2 on day 1) in addition to ATRA plus ATO as induction therapy [111]. Fifteen (79 %) out of 19 cases achieved CR, three cases relapsed. The authors suggested that GO was still effective for high-risk APL treated with ATRA and ATO.

In a third study, 82 newly diagnosed APL patients were treated with ATRA, ATO and GO [112]. The first cohort included 65 patients, who received ATRA followed by ATO. GO (9 mg/m^2 on day 1) was administered in high risk. The second cohort included 17 patients, who received ATRA and ATO simultaneously. GO (9 mg/m^2) was added on high risk or increase of WBC count above 30 $\times$ 10^9/L during induction. CR was achieved in 95 and 81 % cases with low-risk and high-risk APL, respectively; 3-year OS was 85 %. The addition of GO to ATRA plus ATO may represent a promising initial therapy for high-risk APL.

Larger clinical studies of GO for the treatment of relapsed/refractory APL are warranted to obtain clearer clinical evidence. The results may suggest how GO will be integrated into the management of APL. The Japan Adult Leukemia Study Group (JALSG) has also launched prospective studies for APL that include GO.

GO has introduced a new perspective into the treatment of AML. However, the second evaluation of this treatment did not yield positive results. Recent studies have shown the efficacy of GO in AML, with favorable risk in APL as well. Subsequent evaluations should focus on the efficacy of GO in core binding factor (CBF) leukemia and its mechanism of action, which may lead to the re-approval of GO.

Acknowledgments I am grateful to Drs. Toshio Kitamura and Hitoshi Kiyoi for the opportunity to present this review.

References

1. Tallman MS, Gillands DG, Rowe JM. Drug therapy for acute myeloid leukemia. Blood. 2005;106:1154–63.
2. Miyawaki S. Clinical studies of acute myeloid leukemia in the Japan Adult Leukemia Study Group. Int J Hematol. 2012;96:171–7.
3. Stein EM, Tallman MS. Remission induction in acute myeloid leukemia. Int J Hematol. 2012;96:164–70.
4. Kühnl A, Grimwade D. Molecular markers in acute myeloid leukaemia. Int J Hematol. 2012;96:153–63.
5. Naoe T, Kiyoi H. Gene mutations of acute myeloid leukemia in the genome era. Int J Hematol. 2013;97:165–74.
6. Freeman SD, Kelm S, Barber EK, Crocker PR. Characterization of CD33 as a new member of the sialoadesin family of cellular interaction molecules. Blood. 1995;85:2005–12.

7. Lee MD, Dunne TS, Siegel MM, Chang CC, Morton GO, Borders DB. Calicheamicins, a novel family of antitumor antibiotics. 1: chemistry and partial structure of calicheamicin γ_1^I. J Am Chem Soc. 1987;109:3464–6.
8. Lee MD, Dunne TS, Chang CC, Ellestad GA, Siegel MM, Morton GO, McGahren WJ, Borders DB. Calicheamicins, a novel family of antitumor antibiotics. 2: chemistry and structure of calicheamicin γ_1^I. J Am Chem Soc. 1987;109:3466–8.
9. Zein N, Poncin M, Nilakantan R, Ellestad GA. Calicheamicin γ_1^I and DNA: molecular recognition process responsible for site-specificity. Science. 1989;244:697–9.
10. Hangeland JJ, De Voss JJ, Heath JA, Townsend CA. Specific abstraction of the 5′(S)- and 4′-deoxyribosyl hydrogen atoms from DNA by calicheamicin γ_1^I. J Am Chem Soc. 1992;114: 9200–2.
11. Tchilian EZ, Beverley PC, Young BD, Watt SM. Molecular cloning of two isoforms of the murine homolog of the myeloid CD33 antigen. Blood. 1994;83:3188–98.
12. Gao Z, McAlister VC, Williams GM. Repopulation of liver endothelium by bone-marrow-derived cells. Lancet. 2001;357:932–3.
13. Crocker PR. Siglecs: sialic-acid-binding immunoglobulin-like lectins in cell–cell interactions and signaling. Curr Opin Struct Biol. 2002;12:609–15.
14. Taylor VC, Buckley CD, Douglas M, Cody AJ, Simmons DL, Freeman SD. The myeloid-specific sialic acid-binding receptor, CD33, associates with the protein-tyrosine phosphatases, SHP-1 and SHP-2. Biol Chem. 1999;274:11505–12.
15. Andrews RG, Torok-Storb B, Bernstein ID. Myeloid-associated differentiation antigens on stem cells and their progeny identified by monoclonal antibodies. Blood. 1983;62:124–32.
16. Andrews RG, Takahashi M, Segal GM, Powell JS, Bernstein ID, Singer JW. The L4F3 antigen is expressed by unipotent and multipotent colony-forming cells but not by their precursors. Blood. 1986;68:1030–5.
17. Griffin JD, Linch D, Sabbath K, Larcom P, Schlossman SF. A monoclonal antibody reactive with normal and leukemic human myeloid progenitor cells. Leuk Res. 1984;8:521–34.
18. Robertson MJ, Soiffer RJ, Freedman AS, Rabinowe SL, Anderson KC, Ervin TJ, et al. Human bone marrow depleted of CD33-positive cells mediates delayed but durable reconstitution of hematopoiesis: clinical trial of MY9 monoclonal antibody-purged autografts for the treatment of acute myeloid leukemia. Blood. 1992;79:2229–36.
19. Wagner JE, Collins D, Fuller S, Schain LR, Berson AE, Almici C, et al. Isolation of small, primitive human hematopoietic stem cells: distribution of cell surface cytokine receptors and growth in SCID-Hu mice. Blood. 1995;86:512–23.
20. Dinndorf PA, Andrews RG, Benjamin D, Ridgway D, Wolff L, Bernstein ID. Expression of normal myeloid-associated antigens by acute leukemia cells. Blood. 1986;67:1048–53.
21. Scheinberg DA, Tanimoto M, McKenzie S, Strife A, Old LJ, Clarkson BD. Monoclonal antibody M195: a diagnostic marker for acute myelogenous leukemia. Leukemia. 1989;3:440–5.
22. Terstappen LW, Safford M, Konemann S, Loken MR, Zurlutter K, Buchner T, et al. Flow cytometric characterization of acute myeloid leukemia. Part II. Phenotypic heterogeneity at diagnosis. Leukemia. 1992;6:70–80.
23. Putti MC, Rondelli R, Cocito MG, Aricó M, Sainati L, Conter V, et al. Expression of myeloid markers lacks prognostic impact in children treated for acute lymphoblastic leukemia: Italian experience in AIEOP-ALL 88–91 studies. Blood. 1998;92:795–801.
24. Jilani I, Estey E, Huh Y, Joe Y, Manshouri T, Yared M, et al. Differences in CD33 intensity between various myeloid neoplasms. Am J Clin Path. 2002;118:560–6.
25. Iwamoto S, Deguchi T, Ohta H, Kiyokawa N, Tsurusawa M, Yamada T, et al. Flow cytometric analysis of de novo acute lymphoblastic leukemia in childhood: report from the Japanese Pediatric Leukemia/Lymphoma Study Group. Int J Hematol. 2011;94:185–92.
26. Hernández-Caselles T, Martínez-Esparza M, Pérez-Oliva AB, Quintanilla-Cecconi AM, García-Alonso A, Alvarez-López DM, García-Peñarrubia P. A study of CD33 (SIGLEC-3) antigen expression and function on activated human T and NK cells: two isoforms of CD33 are generated by alternative splicing. J Leukoc Biol. 2006;79:46–58.
27. Sheinberg DA, Lovett D, Divgi CR, Graham MC, Berman E, Pentlow K, et al. A phase I trial of monoclonal antibody M195 in acute myelogenous leukemia: specific bone marrow targeting and internalization of radionuclide. J Clin Oncol. 1991;9:478–90.
28. Caron PC, Co MS, Bull MK, Avdalovic NM, Queen C, Scheinberg DA. Biological and immunological features of Humanized M195 (Anti-CD33) monoclonal antibodies. Cancer Res. 1992;52:6761–7.
29. Borthakur G, Rosenblum MG, Talpaz M, Daver N, Ravandi F, Faderl S, et al. Phase 1 study of an anti-CD33 immunotoxin, humanized monoclonal antibody M195 conjugated to recombinant gelonin (HUM-195/rGEL), in patients with advanced myeloid malignancies. Haematologica. 2013;98:217–21.
30. La Russa VF, Griffin JD, Kessler SW, Cutting MA, Knight RD, Blattler WA, et al. Effects of anti-CD33 blocked ricin immunotoxin on the capacity of CD34+ human marrow cells to establish in vitro hematopoiesis in long-term marrow cultures. Exp Hematol. 1992;20:442–8.
31. Appelbaum FR, Matthews DC, Eary JF, Badger CC, Kellogg M, Press OW, et al. The use of radiolabeled anti-CD33 antibody to augment marrow irradiation prior to marrow transplantation for acute myelogenous leukemia. Transplantation. 1992;54:829–33.
32. van der Velden VHJ, Boeckx N, Jedema I, te Marvelde JG, Hoogeveen PG, Boogaerts M, et al. High CD33-antigen loads in peripheral blood limit the efficacy of gemtuzumab ozogamicin (Mylotarg) treatment in acute myeloid leukemia patients. Leukemia. 2004;18:983–8.
33. Linenberger ML. CD33-directed therapy with gemtuzumab ozogamicin in acute myeloid leukemia: progress in understanding cytotoxicity and potential mechanisms of drug resistance. Leukemia. 2005;19:176–82.
34. Matsui H, Takeshita A, Naito K, Shinjo K, Shigeno K, Maekawa M, et al. Reduced effect of gemtuzumab ozogamicin (CMA-676) on P-glycoprotein and/or CD34-positive leukemia cells and its restoration by multidrug resistance modifiers. Leukemia. 2002;16:813–9.
35. Sievers EL, Larson RA, Stadtmauer EA, Estey E, Lowenberg B, Dombret H, Mylotarg Study Group, et al. Efficacy and safety of gemutuzumab ozogamicin in patients with CD33-positive acute myloid leukemia in first relapse. J Clin Oncol. 2001;19:3244–54.
36. Hamann PR, Hinman LM, Hollander I, Beyer CF, Lindh D, Holcomb R, et al. Gemtuzumab ozogamicin, a potent and selective anti-CD33 antibody-calicheamicin conjugate for treatment of acute myeloid leukemia. Bioconjug Chem. 2002;13:47–58.
37. McGrath MS, Rosenblum MG, Philips MR, Scheinberg DA. Immunotoxin resistance in multidrug resistant cells. Cancer Res. 2003;63:72–9.
38. Walter RB, Raden BW, Kamikura DM, Cooper JA, Bernstein ID. Influence of CD33 expression levels and ITIM-dependent internalization on gemtuzumab ozogamicin-induced cytotoxicity. Blood. 2005;105:1295–302.
39. Jedema I, Barge RM, van der Velden VH, Nijmeijer BA, van Dongen JJ, Willemze R, et al. Internalization and cell cycle-dependent killing of leukemic cells by Gemtuzumab Ozogamicin: rationale for efficacy in CD33-negative malignancies with endocytic capacity. Leukemia. 2004;18:316–25.

40. Zhao B, Konno S, Wu JM, Oronsky AL. Modulation of nicotinamide adenine dinucleotide and poly(adenosine diphosphoribose) metabolism by calicheamicin gamma 1 in human HL-60 cells. Cancer Lett. 1990;50:141–7.
41. Nicolaou KC, Pitsinos EN, Theodorakis EA, Saimoto H, Wrasidlo W. Synthetic calicheamicin mimics with novel initiation mechanisms: DNA cleavage, cytotoxicity, and apoptosis. Chem Biol. 1994;1:57–66.
42. Lode HN, Reisfeld RA, Handgretinger R, Nicolaou KC, Gaedicke G, Wrasidlo W. Targeted therapy with a novel enediyene antibiotic calicheamicin ϑ_1 effectively suppresses growth and dissemination of liver metastases in a syngeneic model of murine neuroblastoma. Cancer Res. 1998;58:2925–8.
43. Naito K, Takeshita A, Shigeno K, Nakamura S, Fujisawa S, Shinjo K, et al. Calicheamicin-conjugated humanized anti-CD33 monoclonal antibody (gemtuzumab zogamicin, CMA-676) shows cytocidal effect on CD33-positive leukemia cell lines, but is inactive on P-glycoprotein-expressing sublines. Leukemia. 2000;14:1436–43.
44. Matsui H, Takeshita A, Naito K, Shinjo K, Shigeno K, Maekawa M, et al. Reduced effect of gemtuzumab ozogamicin (CMA-676) on P-glycoprotein and/or CD34-positive leukemia cells and its restoration by multidrug resistance modifiers. Leukemia. 2002;16:810–9.
45. Amico D, Barbui AM, Erba E, Rambaldi A, Introna M, Golay J. Differential response of human acute myeloid leukemia cells to gemtuzumab ozogamicin in vitro: role of Chk1 and Chk2 phosphorylation and caspase 3. Blood. 2003;101:4589–97.
46. Kartner N, Evernden-Porelle D, Bradley G, Ling V. Detection of P-glycoprotein in multidrug-resistant cell lines by monoclonal antibodies. Nature. 1985;316:820–3.
47. Gottesman MM, Pastan I, Ambudkar SV. P-glycoprotein and multidrug resistance. Curr Opin Genet Dev. 1996;6:610–7.
48. Walter RB, Raden BW, Hong TC, Flowers DA, Bernstein ID, Linenberger ML. Multidrug resistance protein attenuates gemtuzumab ozogamicin-induced cytotoxicity in acute myeloid leukemia cells. Blood. 2004;102:1466–73.
49. Linenberger ML, Hong T, Flowers D, Sievers EL, Gooley TA, Bennett JM, et al. Multidrug-resistance phenotype and clinical responses to gemtuzumab ozogamicin. Blood. 2001;98:988–94.
50. Baba M, Nakanishi O, Sato W, Saito A, Miyama Y, Yano O, et al. Relationship between multidrug resistant gene expression and multidrug resistant-reversing effect of MS-209 in various tumor cells. Cancer Chemother Pharmacol. 1995;36:361–7.
51. Friche E, Jensen PB, Nissen NI. Comparison of cyclosporin A and SDZ PSC833 as multidrug-resistance modulators in a daunorubicin-resistant Ehrlich ascites tumor. Cancer Chemother Pharmacol. 1992;30:235–7.
52. Matsumoto T, Jimi S, Hara S, Takamatsu Y, Suzumiya J, Tamura K. Importance of inducible multidrug resistance 1 expression in HL-60 cells resistant to gemtuzumab ozogamicin. Leuk Lymphoma. 2012;53:1399–405.
53. Takeshita A, Yamakage N, Shinjo K, Ono T, Hirano I, Nakamura S, et al. CMC-544 (inotuzumab ozogamicin), an anti-CD22 immuno-conjugate of calicheamicin, alters the levels of target molecules of malignant B-cells. Leukemia. 2009;23:1329–36.
54. Takeshita A, Shinjo K, Yamakage N, Ono T, Hirano I, Matsui H, et al. CMC-544 (inotuzumab ozogamicin) shows less effect on multidrug resistant cells: analyses in cell lines and cells from patients with B-cell chronic lymphocytic leukaemia and lymphoma. Br J Haematol. 2009;146:34–43.
55. Apostolidou E, Cortes J, Tsimberidou A, Estey E, Kantarjian H, Giles FJ. Pilot study of gemtuzumab ozogamicin, liposomal daunorubicin, cytarabine and cyclosporine regimen in patients with refractory acute myelogenous leukemia. Leuk Res. 2003;27:887–91.
56. Tsimberidou A, Estey E, Cortes J, Thomas D, Faderl S, Verstovsek S, et al. Gemtuzumab, fludarabine, cytarabine, and cyclosporine in patients with newly diagnosed acute myelogenous leukemia or high-risk myelodysplastic syndromes. Cancer. 2003;97:1481–7.
57. Tsimberidou A, Cortes J, Thomas D, Garcia-Manero G, Verstovsek S, Faderl S, et al. Gemtuzumab ozogamicin, fludarabine, cytarabine and cyclosporine combination regimen in patients with CD33 + primary resistant or relapsed acute myeloid leukemia. Leuk Res. 2003;27:893–7.
58. Legrand O, Zittoun R, Marie J-P. Role of MRP1 in multidrug resistance in acute myeloid leukemia. Leukemia. 1999;13:578–84.
59. Cianfriglia M, Mallano A, Ascione A, Dupuis ML. Multidrug transporter proteins and cellular factors involved in free and mAb linked calicheamicin-gamma1 (gentuzumab ozogamicin, GO) resistance and in the selection of GO resistant variants of the HL60 AML cell line. Int J Oncol. 2010;36:1513–20.
60. Moore J, Seiter K, Kolitz J, Stock W, Giles F, Kalaycio M, et al. A Phase II study of Bcl-2 antisense (oblimersen sodium) combined with gemtuzumab ozogamicin in older patients with acute myeloid leukemia in first relapse. Leuk Res. 2006;30:777–83.
61. Walter RB, Raden BW, Cronk MR, Bernstein ID, Appelbaum FR, Banker DE. The peripheral benzodiazepine receptor ligand PK11195 overcomes different resistance mechanisms to sensitize AML cells to gemtuzumab ozogamicin. Blood. 2004;103:4276–84.
62. Haag P, Viktorsson K, Lindberg ML, Kanter L, Lewensohn R, Stenke L. Deficient activation of Bak and Bax confers resistance to gemtuzumab ozogamicin-induced apoptotic cell death in AML. Exp Hematol. 2009;37:755–66.
63. Rosen DB, Harrington KH, Cordeiro JA, Leung LY, Putta S, Lacayo N, et al. AKT signaling as a novel factor associated with in vitro resistance of human AML to gemtuzumab ozogamicin. PLoS ONE. 2013;8:e53518. doi:10.1371.
64. van der Velden VH, te Marvelde JG, Hoogeveen PG, Bernstein ID, Houtsmuller AB, Berger MS, van Dongen JJ. Targeting of the CD33-calicheamicin immunoconjugate Mylotarg (CMA-676) in acute myeloid leukemia: in vivo and in vitro saturation and internalization by leukemic and normal myeloid cells. Blood. 2001;97:3197–204.
65. Kell WJ, Burnett AK, Chopra R, Yin JA, Clark RE, Rohatiner A, et al. A feasibility study of simultaneous administration of gemtuzumab ozogamicin with intensive chemotherapy in induction and consolidation in younger patients with acute myeloid leukemia. Blood. 2003;102:4277–83.
66. ten Cate B, Samplonius DF, Bijma T, de Leij LF, Helfrich W, Bremer E. The histone deacetylase inhibitor valproic acid potently augments gemtuzumab ozogamicin-induced apoptosis in acute myeloid leukemic cells. Leukemia. 2007;21:248–52.
67. Sievers EL, Larson RA, Stadtmauer EA, Estey E, Löwenberg B, Dombret H, et al. Mylotarg Study Group. Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. J Clin Oncol. 2001;19:3244–54.
68. Bross PF, Beitz J, Chen G, Chen XH, Duffy E, Kieffer L, et al. Approval summary: gemtuzumab ozogamicin in relapsed acute myeloid leukemia. Clin Cancer Res. 2001;7:1490–6.
69. Larson RA, Boogaerts M, Estey E, Karanes C, Stadtmauer EA, Sievers EL, Mylotarg Study Group, et al. Antibody-targeted chemotherapy of older patients with acute myeloid leukemia in first relapse using Mylotarg (gemtuzumab ozogamicin). Leukemia. 2002;16:1627–36.
70. Leopold LH, Berger MS, Cheng SC, Cortes-Franco JE, Giles FJ, Estey EH, et al. Comparative efficacy and safety of gemtuzumab ozogamicin monotherapy and high-dose cytarabine combination

therapy in patients with acute myeloid leukemia in first relapse. Clin Adv Hematol Oncol. 2003;1:220–5.
71. Piccaluga PP, Martinelli G, Rondoni M, Malagola M, Gaitani S, Isidori A, et al. Gemtuzumab ozogamicin for relapsed and refractory acute myeloid leukemia and myeloid sarcomas. Leuk Lymphoma 2004;45:1971–5.
72. Larson RA, Sievers EL, Stadtmauer EA, Löwenberg B, Estey EH, Dombret H, et al. Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. Cancer. 2005;104:1442–52.
73. Taksin AL, Legrand O, Raffoux E, de Revel T, Thomas X, Contentin N, et al. High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: a prospective study of the alfa group. Leukemia. 2007;21:66–71.
74. Amadori S, Suciu S, Stasi R, Willemze R, Mandelli F, Selleslag D, et al. Gemtuzumab ozogamicin (Mylotarg) as single-agent treatment for frail patients 61 years of age and older with acute myeloid leukemia: final results of AML-15B, a phase 2 study of the European Organisation for Research and Treatment of Cancer and Gruppo Italiano Malattie Ematologiche dell'Adulto Leukemia Groups. Leukemia. 2005;19:1768–73.
75. Kobayashi Y, Tobinai K, Takeshita A, Naito K, Asai O, Dobashi N, et al. Phase I/II study of humanized anti-CD33 antibody conjugated with calicheamicin, gemtuzumab ozogamicin, in relapsed or refractory acute myeloid leukemia: final results of Japanese multicenter cooperative study. Int J Hematol. 2009;89:460–9.
76. Takeshita A, Ono T, Kojima Y, Kyo T, Asou N, Suzushima H, et al. Efficacy of gemtuzumab ozogamicin (GO) monotherapy on relapsed/refractory acute promyelocytic leukemia (APL). Blood. 2011;118:Abst. #1532.
77. Cortes J, Tsimberidou AM, Alvarez R, Thomas D, Beran M, Kantarjian H, et al. Mylotarg combined with topotecan and cytarabine in patients with refractory acute myelogenous leukemia. Cancer Chemother Pharmacol. 2002;50:497–500.
78. Alvarado Y, Tsimberidou A, Kantarjian H, Cortes J, Garcia-Manero G, Faderl S, et al. Pilot study of Mylotarg, idarubicin and cytarabine combination regimen in patients with primary resistant or relapsed acute myeloid leukemia. Cancer Chemother Pharmacol. 2003;51:87–90.
79. Piccaluga PP, Martinelli G, Rondoni M, Malagola M, Gaitani S, Visani G, Baccarani M. First experience with gemtuzumab ozogamicin plus cytarabine as continuous infusion for elderly acute myeloid leukaemia patients. Leuk Res. 2004;28:987–90.
80. Chevallier P, Roland V, Mahé B, Juge-Morineau N, Dubruille V, Guillaume T, et al. Administration of mylotarg 4 days after beginning of a chemotherapy including intermediate-dose a-racytin and mitoxantrone (MIDAM regimen) produces a high rate of complete hematologic remission in patients with CD33+ primary resistant or relapsed acute myeloid leukemia. Leuk Res. 2005;29:1003–7.
81. Stone RM, Moser B, Sanford B, Schulman P, Kolitz JE, Allen S, et al. Cancer and Leukemia Group B. High dose cytarabine plus gemtuzumab ozogamicin for patients with relapsed or refractory acute myeloid leukemia: cancer and Leukemia Group B study 19902. Leuk Res. 2011;35:329–33.
82. Estey EH, Thall PF, Giles FJ, Wang XM, Cortes JE, Beran M, et al. Gemtuzumab ozogamicin with or without interleukin 11 in patients 65 years of age or older with untreated acute myeloid leukemia and high-risk myelodysplastic syndrome: comparison with idarubicin plus continuous-infusion, high-dose cytosine arabinoside. Blood. 2002;99:4343–9.
83. De Angelo DJ, Stone RM, Durrant S, Liu D, Baccarani M, Schiffer CA, et al., Mylotarg Study Group. Gemtuzumab Ozogamicin (Mylotarg®) in combination with induction chemotherapy for the treatment of patients with de novo acute myeloid leukemia: two age-specific phase 2 trials. Blood. 2003;102:100a, Abstr. #341.
84. Amadori S, Suciu S, Willemze R, Mandelli F, Selleslag D, Stauder R, et al. EORTC leukemia group; GIMEMA leukemia group. Sequential administration of gemtuzumab ozogamicin and conventional chemotherapy as first line therapy in elderly patients with acute myeloid leukemia: a phase II study (AML-15) of the EORTC and GIMEMA leukemia groups. Haematologica. 2004;89:950–6.
85. Fianchi L, Pagano L, Leoni F, Storti S, Voso MT, Valentini CG, et al. Gemtuzumab ozogamicin, cytosine arabinoside, G-CSF combination (G-AraMy) in the treatment of elderly patients with poor-prognosis acute myeloid leukemia. Ann Oncol. 2008;19:128–34.
86. Petersdorf S, Kopecky K, Stuart RK, Larson RA, Nevill TJ, Stenke L, et al. Preliminary results of Southwest Oncology Group Study S0106: an international intergroup phase 3 randomized trial comparing the addition of gemtuzumab ozogamicin to standard induction therapy versus standard induction therapy followed by a second randomization to post-consolidation gemtuzumab ozogamicin versus no additional therapy for previously untreated acute myeloid leukemia. Blood. 2009;114:Abstr.#790.
87. Delaunay J, Recher C, Pigneux A, Witz F, Vey N, Blanchet O, et al. Addition of Gemtuzumab ozogamycin to chemotherapy improves event-free survival but not overall survival of aml patients with intermediate cytogenetics not eligible for allogeneic transplantation. Results of the GOELAMS AML 2006 IR Study. Blood. 2011;118:Abstr.#79.
88. Burnett AK, Hills RK, Milligan D, Kjeldsen L, Kell J, Russell NH, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. J Clin Oncol. 2011;29:369–77.
89. Burnett AK, Russell NH, Hills RK, Kell J, Freeman S, Kjeldsen L, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. J Clin Oncol. 2012;30:3924–31.
90. Castaigne S, Pautas C, Terré C, Raffoux E, Bordessoule D, Bastie JN, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet. 2012;379:1508–16.
91. Burnett AK, Hills RK, Hunter AE, Milligan D, Kell WJ, Wheatley K. et al; UK National Cancer Research Institute AML Working Group. The addition of gemtuzumab ozogamicin to low-dose Ara-C improves remission rate but does not significantly prolong survival in older patients with acute myeloid leukaemia: results from the LRF AML14 and NCRI AML16 pick-a-winner comparison. Leukemia. 2013;27:75–81.
92. Reinhardt D, Diekamp S, Fleischhack G, Corbacioglu C, Jürgens H, Dworzak M, et al. Gemtuzumab ozogamicin (Mylotarg) in children with refractory or relapsed acute myeloid leukemia. Onkologie. 2004;27:269–72.
93. Brethon B, Yakouben K, Oudot C, Boutard P, Bruno B, Jérome C, et al. Efficacy of fractionated gemtuzumab ozogamicin combined with cytarabine in advanced childhood myeloid leukaemia. Br J Haematol. 2008;143:541–7.
94. Zwaan CM, Reinhardt D, Zimmerman M, Hasle H, Stary J, Stark B, et al. Salvage treatment for children with refractory first or second relapse of acute myeloid leukaemia with gemtuzumab ozogamicin: results of a phase II study. Br J Haematol. 2010;148:768–76.
95. Arceci RJ, Sande J, Lange B, Shannon K, Franklin J, Hutchinson R, et al. Safety and efficacy of gemtuzumab ozogamicin in

pediatric patients with advanced CD33+ acute myeloid leukemia. Blood. 2005;106:1183–8.
96. Rubnitz JE, Inaba H, Dahl G, Ribeiro RC, Bowman WP, Taub J, et al. Minimal residual disease-directed therapy for childhood acute myeloid leukaemia: results of the AML02 multicentre trial. Lancet Oncol. 2010;11:543–52.
97. Aplenc R, Alonzo TA, Gerbing RB, Lange BJ, Hurwitz CA, Wells RJ, et al. Safety and efficacy of gemtuzumab ozogamicin in combination with chemotherapy for pediatric acute myeloid leukemia: a report from the Children's Oncology Group. J Clin Oncol. 2008;26:2390–3295.
98. Cooper TM, Franklin J, Gerbing RB, Alonzo TA, Hurwitz C, Raimondi SC, et al. AAML03P1, a pilot study of the safety of gemtuzumab ozogamicin in combination with chemotherapy for newly diagnosed childhood acute myeloid leukemia: a report from the Children's Oncology Group. Cancer. 2012;118:761–9.
99. Hasle H, Abrahamsson J, Forestier E, Ha SY, Heldrup J, Jahnukainen K, et al. Nordic Society of Paediatric Haematology and Oncology (NOPHO). Gemtuzumab ozogamicin as postconsolidation therapy does not prevent relapse in children with AML: results from NOPHO-AML 2004. Blood. 2012;120:978–84.
100. Takeshita A, Shinjo K, Naito K, Matsui H, Sahara N, Shigeno K, et al. Efficacy of gemtuzumab ozogamicin on ATRA- and arsenic-resistant acute promyelocytic leukemia (APL) cells. Leukemia. 2005;19:1306–11.
101. Asou N, Adachi K, Tamura U, Kanamaru A, Kageyama S, Hiraoka A, et al. Analysis of prognostic factorsin newly diagnosed patients with acute promyelocytic leukemia: the APL92 study of the Japan Adult Leukemia Study Group (JALSG). Cancer Chemother Pharmacol. 2001;48(Suppl 1):S65–71.
102. Ohno R, Asou N, Ohnishi K. Treatment of acute promyelocytic leukemia: strategy toward further increase of cure rate. Leukemia. 2003;17:1454–63.
103. Douer D. New advances in the treatment of acute promyelocytic leukemia. Int J Hematol. 2002;76(Suppl 2):179–87.
104. Tobita T, Takeshita A, Kitamura K, Ohnishi K, Yanagi M, Hiraoka A, et al. Treatment with a new synthetic retinoid, Am80, of acute promyelocytic leukemia relapsed from complete remission induced by all-trans retinoic acid. Blood. 1997;90:967–73.
105. Soignet SL, Maslak P, Wang ZG, Jhanwar S, Calleja E, Dardashti LJ, et al. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. N Engl J Med. 1998;339:1341–8.
106. Estey EH, Giles FJ, Beran M, O'Brien S, Pierce SA, Faderl SH, et al. Experience with gemtuzumab ozogamycin ("Mylotarg") and all-*trans* retinoic acid in untreated acute promyelocytic leukemia. Blood. 2002;99:4222–4.
107. Lo Coco F, Cimino G, Breccia M, Noguera NI, Diverio D, Finolezzi E, et al. Gemtuzumab ozogamicin (Mylotarg) as a single agent for molecularly relapsed acute promyelocytic leukemia. Blood. 2004;104:1995–9.
108. Takeshita A, Shinjo K, Naito K, Matsui H, Sahara N, Shigeno K, et al. Two patients with all-trans retinoic acid-resistant acute promyelocytic leukemia treated successfully with gemtuzumab ozogamicin as a single agent. Int J Hematol. 2005;82:445–8.
109. Aribi A, Kantarjian HM, Estey EH, Koller CA, Thomas DA, Kornblau SM, et al. Combination therapy with arsenic trioxide, all-trans retinoic acid, and gemtuzumab ozogamicin in recurrent acute promyelocytic leukemia. Cancer. 2007;109:1355–9.
110. Breccia M, Cimino G, Diverio D, Gentilini F, Mandelli F, Lo Coco F. Sustained molecular remission after low dose gemtuzumab-ozogamicin in elderly patients with advanced acute promyelocytic leukemia. Haematologica. 2007;92:1273–4.
111. Estey EH, Garcia-Manero G, Ferrajoli A, Faderl S, Verstovsek S, Jones D, Kantarjian H. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. Blood. 2006;107:3469–73.
112. Ravandi F, Estey E, Jones D, Faderl S, O'Brien S, Fiorentino J, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide and gemtuzumab ozogamicin. J Clin Oncol. 2009;27:504–10.