# Gemtuzumab ozogamicin

Subjects: Biochemistry & Molecular Biology | Oncology

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Gemtuzumab ozogamicin (GO) is a humanized anti-CD33 monoclonal antibody conjugated to calicheamicin, a cytotoxic antitumor antibiotic. GO is indicated for the treatment of newly-diagnosed or relapsed/refractory CD33-positive acute myeloid leukemia (AML).

acute myeloid leukemia | gemtuzumab ozogamicin | biomarkers | CD33 | FLT3 | therapy

## 1. Introduction

Gemtuzumab ozogamicin (GO, Mylotarg®) is a humanized monoclonal antibody conjugated to cytotoxic compound called calicheamicin. The two molecules are covalently linked via a butanoic acid linker which is hydrolized in the acidic environment of the lysosome. GO is directed against the cluster of differentiation 33 (CD33) which represents a hallmark of myeloid leukemic blasts, widely expressed in AML patients. Previous studies have shown that it was expressed on leukemic blasts in about 90% of AML patients[1][2]. Several clinical studies have highlighted the clinical benefit of GO on patient outcome (**Table 1**). GO stands for the first antibody drug conjugate approved by the Food and Drug Administration (FDA).

**Table 1.** Overview of the main clinical trials evaluating GO efficacy.

| Phase | Patient Population | Median Age of Patients in Years (Range) | Evaluable Patients | GO Dosing | Treatment Plan | Outcomes | Ref. |
|---|---|---|---|---|---|---|---|
| I | Relapsed/refractory AML patients | 54 (24–73) | 40 | Escalating doses, 0.25 to 9 mg/m$^2$ | Single arm trial, GO administered as single agent | ORR: 8/40 patients (20%) | Sievers 1999 [3] |
| II | AML patients in first relapse | 61 (22–84) | 142 | 9 mg/m$^2$, 2 doses recommended (max. 3 | Single arm trial, GO administered as single agent | ORR: 42/142 patients (30%), CR | Sievers 2001 [4] |

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|---|---|---|---|---|---|---|---|
| | | | | doses), with at least 14 days between 2 doses | | rate: 16%, CRp rate: 13% | |
| II | De novo AML in first relapse | 64 (22–80) | 57 | Fractionated doses: 3 mg/m$^2$ on days 1, 4 and 7 of the first course | Single arm trial, GO administered as single agent in induction, followed by cytarabine-based consolidation | ORR: 19/57 (33%), CR rate: 15/57 (26%), CRp: 4/57 (7%) | Taksin 2007 [5] |
| I/II | De novo AML in first relapse | 60 (40–70) | 20 | Fractionated doses: 3 mg/m$^2$ on days 1, 4 and 7 of the first course | Single arm trial, GO combined with DA (DA dosing finding) | ORR: 13/20 patients (65%), CR rate: 11/20 patients (55%), CRp rate: 2/20 patients (10%) | Farhat 2012 [6] |
| III | De novo/secondary AML | 50 (15–71) | 1113 | 3 mg/m$^2$ on day 1 of course 1 +/− on day 1 of the course 3 | Randomization at induction and at consolidation. Induction regimen (DA or ADE or FLAG-Ida) +/− GO. Consolidation regimen (MACE or MidAC or high-dose cytarabine) +/− GO | GO- vs. no GO-arm: CR, 82% vs. 83%, OR: 1.04, 95% CI: 0.76–1.42, $p$ = 0.8; 5-year OS, 43% vs. 41%, HR: 0.92, 95% CI: 0.79–1.08, $p$ = 0.3; 5-year RFS: 39% vs. 35%, HR: 0.87, 95% CI: 0.73–1.02, $p$ = 0.09 | Burnett 2011 [7] |
| III | De novo AML | 47 (18–60) | 595 | 6 mg/m$^2$ on day 4; additional 3 doses of GO, | Randomized trial, GO plus modified DA (daunorubicin, 45 mg/m$^2$/d, day 1 to day 3; | DA + GO vs. DA alone: ORR: 76% vs. 74%, $p$ = | Petersdorf 2013 [8] |

| Phase | Patient Population | Median Age of Patients in Years (Range) | Evaluable Patients | GO Dosing | Treatment Plan | Outcomes | Ref. |
|---|---|---|---|---|---|---|---|
| | | | | 5 mg/m$^2$ for patients in CR after consolidation | cytarabine, 100 mg/m$^2$/d, day 1 to day 7) vs. standard DA (daunorubicin, 60 mg/m$^2$/d, day 1 to day 3; cytarabine, 100 mg/m$^2$/d, day 1 to day 7) | 0.36; CR rate: 69% vs. 70%, $p$ = 0.59; 5-year RFS: 43% vs. 42%, $p$ = 0.40; 5-year OS: 46% vs. 50%, $p$ = 0.85 | |
| III | De novo/secondary AML and high-risk MDS | 67 (51–84) | 1115 | 3 mg/m$^2$ on day 1 of the first course | Randomized trial: DA or daunorubicin/clofarabine +/− GO | GO- vs. no GO-arm: ORR: 70% vs. 68%, OR: 0.88, 95% CI: 0.68–1.13, $p$ = 0.3; 3-year OS: 25% vs. 20%; HR: 0.87, 95% CI: 0.76–1.00, $p$ = 0.05; 3-year RFS: 21% vs. 16%, HR: 0.84, 95%CI: 0.71–0.99, $p$ = 0.04 | Burnett 2012 [9] |
| III | De novo AML patients with intermediate cytogenetic risk | 50 (18–60) | 238 | 6 mg/m$^2$ on day 4 of the induction and on day 4 of the first consolidation course | Randomized trial: intensive induction regimen (DA) +/− GO, consolidation (MidAC) +/− GO, +/− HSCT | GO- vs. no-GO-arm: CR rate: 91.6% vs. 86.5%, $p$ = NS; 3-year OS: 53% vs. 46%, $p$ = NS; 3-year EFS: 51% vs. 33%, $p$ = NS. In non HSCT recipients, GO vs. no GO-arm: 3- | Delaunay 2011 [10] |

| Phase | Patient Population | Median Age of Patients in Years (Range) | Evaluable Patients | GO Dosing | Treatment Plan | Outcomes | Ref. |
|---|---|---|---|---|---|---|---|
| | | | | | | year EFS: 53.7% vs. 27%, $p$ = 0.0308 | |
| III | De novo AML | 62 (50–70) | 271 | 3 mg/m$^2$ on days 1, 4, and 7 of induction and on day 1 of each of the subsequent two consolidation courses | Randomized trial: DA +/− GO | GO- vs. no-GO-arm: ORR: 81.5% vs. 73.5% ($p$ = 0.15) (CR: 70.4% vs. 69.9%; CRp:11.1% vs. 3.7%); median EFS: 13.6 months vs. 8.5 months, HR: 0.66, 95% CI: 0.49–0.89, $p$ = 0.006; median OS: 27.5 months vs. 21.8 months, HR: 0.81, 95% CI: 0.60–1.09, $p$ = 0.16 | Castaigne 2012, Lambert 2019 [11] [12] |
| III | De novo or secondary AML and high-risk MDS | 50 (0–81) | 788 | 3 mg/m$^2$ vs. 6 mg/m$^2$ on day 1 of induction | Randomized trial: GO 3 vs. 6 mg/m$^2$ + combined with ADE vs. DA | GO 3 mg/m$^2$ vs. 6 mg/m$^2$: ORR: 89% vs. 86%, HR: 1.34, 95%CI:0.88–2.04, $p$ = 0.17; (CR rate 82% vs. 76%, OR: 1.46, 95%CI: 1.04–2.06, $p$ = 0.03); 4-year OS: 50% vs. 47%, HR: | Burnett 2016 [13] |

| Phase | Patient Population | Median Age of Patients in Years (Range) | Evaluable Patients | GO Dosing | Treatment Plan | Outcomes | Ref. |
|---|---|---|---|---|---|---|---|
| | | | | | | 1.10, 95% CI: 0.90–1.34, $p$ = 0.3; 4-year RFS: 44% vs. 38%, HR: 1.11, 95% CI: 0.91–1.35, $p$ = 0.3 | |
| III | De novo/secondary AML | 67 (60–75) | 472 | 3 mg/m$^2$ for 2 doses, on days 1 and 15 of induction, 3 mg/m$^2$ on the first day of consolidation | Randomized trial: intensive chemotherapy (MICE induction) +/− GO | GO vs. no-GO-arm: ORR: 45% vs. 49%; OR: 0.86, 95% CI, 0.6–1.23, $p$ = 0.46; OS: HR: 1.20, 95% CI: 0.99–1.45, $p$ = 0.07; RFS: HR: 1.08, 95% CI: 0.81–1.44, $p$ = 0.61 | Amadori 2013 [14] |
| III | De novo/secondary AML unfit for intensive chemotherapy | 77 (62–88) | 237 | 6 mg/m$^2$ on day 1 and 3 mg/m$^2$ on day 8, +/−2 mg/m$^2$/month for up to 8 doses | Randomized trial: GO alone vs. BSC | GO- vs. BSC-arm: median OS: 4.9 months vs. 3.6 months, HR: [20]0.69, 95% CI: 0.53–0.90, $p$ = 0.005 | Amadori 2016 [15] |
| I [21][22] | Relapsed/refractory AML patients | 12 (1–16) | 29 | Escalating doses, 6 to 9 mg/m$^2$ | Single arm trial, GO administered as single agent | ORR: 8/29 patients (28%); CR rate: 14%; CRp rate: 14%) | Arceci et al. 2005 [16] |

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# 3. Mechanism of Action

After binding to the CD33 antigen, the GO-CD33 complex is rapidly internalized[23]. In the cytoplasm, the complex is routed in the lysosome. Under the acidic environment of the lysosome, the butanoic acid linker is hydrolyzed, releasing the toxic moiety of the GO. The calicheamicin derivative is reduced by the glutathione into a highly reactive species which induces simple- and double-stranded DNA breaks, leading to DNA-damage and cell death[24].

| Phase | Patient Population | Median Age of Patients in Years (Range) | Evaluable Patients | GO Dosing | Treatment Plan | Outcomes | Ref. |
|---|---|---|---|---|---|---|---|
| II | [11][27] Refractory de novo AML or newly diagnosed secondary AML | 11.5 (0.8–19.8) | [28] 45 | 2 to 3 mg/m$^2$ | [25] [26] Non randomized multi-arm trial, GO + cytarabine + mitoxantrone (arm A) vs. GO+ cytarabine+ L-asparaginase (arm B) | Arm A vs. arm B: ORR: 55% vs. 40%, $p$ = NS; 1-year EFS: 55% vs. 21.8%, $p$ = NS; 1-year OS: 64.6% vs. 45.0% $p$ = [29] [30] NS | Aplenc 2008 [17] |
| II | Newly diagnosed de novo AML | 9.5 (0.07–21.6) | 340 | 3 mg/m$^2$ on day 6 of course 1 and day 7 of course 4 [32] | Single arm trial, GO combined with intensive chemotherapy | CR rate: 83.1%; 3-year OS: 66%; 3-year EFS: 53% [31] | Cooper 2012 [18] |
| III | Newly diagnosed de novo AML | 9.7 (0–29) | 1022 | 3 mg/m$^2$ on day 6 of induction course 1, and on day 7 of intensification course 2 | Randomized trial, GO +/− standard chemotherapy | GO- vs. no-GO arm: CR rate: 88.3% vs. 85.1, $p$ = 0.15; 3-year EFS: 53.1% vs. 46.9%, HR: 0.83, 95% CI: 0.70–0.99, $p$ = 0.04; 3-year OS: 69.4% vs. 65.4%; HR: 0.91, 95% CI: 0.74–1.13, $p$ = 0.39 | Gamis 2014 [19] |

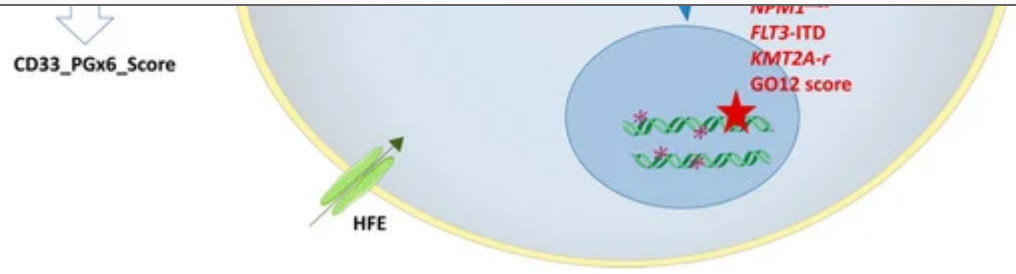


**Figure 1.** Gemtuzumab ozogamicin (GO) mechanism of action and biomarkers of response. SOCS3: Suppressor Of Cytokine Signaling 3; *ABCB1:* ATP-binding cassette subfamily B member 1 gene; *NPM1$^{mut}$:* Nucleophosmin 1 gene mutation; *FLT3*-ITD: FMS-Like Tyrosine Kinase 3 Internal Tandem Duplication; *KMT2A-r:* Lysine Methyltransferase 2A rearrangement.

COG: Children's Oncology Group; MDS: myelodysplastic syndrome; CR: Complete Remission; CRp: all criteria for CR without the full recovery of platelets count; ORR: overall response rate (CR+CRp); DA: daunorubicin plus cytarabine; DAE: cytarabine, daunorubicin, and etoposide; FLAG-Ida: fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; MACE: amsacrine, cytarabine and etoposide; MidAC: mitoxantrone and cytarabine; MICE: mitoxantrone, cytarabine, and etoposide; BSC: best supportive care, HSCT: hematopoietic stem cell transplantation; NA: Not available; NS: not significant.

# 4.Conclusions

Given its high expression on AML blasts, CD33 antigen represents an attractive target in AML. Different clinical trials have confirmed the anti-leukemic activity of GO in CD33-positive AML cells and have shown improved outcome in AML patients. Over the past years, flow cytometry, cytogenetics, and molecular approaches, including sequencing technologies, MRD monitoring, and genotyping studies of *CD33* and *ABCB1* SNPs have offered a comprehensive analysis of promising biomarkers for GO response. Collectively, these improvements have helped to refine the subset of patients that may benefit from GO and improve patient management. Increasing knowledge of the molecular alterations in AML paves the way to new combinatory regimens that may enhance GO efficacy. Hence, ongoing trials are evaluating the feasibility and the efficacy of combining GO to FLT3-ITD inhibitors (NCT03900949, NCT04385290, NCT04293562) and Bcl-2 inhibitors (NCT04070768, NCT04070768).

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