Randomized phase III GnG study on two schedules of gemtuzumab ozogamicin as adjunct to intensive induction therapy and double-blinded intensive post-remission therapy with or without glasdegib in patients with newly diagnosed acute myeloid leukemia

The presented study is a randomized phase III trial with measurable residual disease (MRD) after induction therapy and event-free survival as co-primary endpoints. Patients were upfront randomized 1:1 into one of two induction schedules; gemtuzumab ozogamicin (GO) administered to intensive induction therapy on days 1, 4 and 7 (GO-147) *versus* GO administered once on day 1 (GO-1), as well as to glasdegib *versus* placebo adjunct to consolidation therapy followed by glasdegib 6-month maintenance therapy *versus* physician's choice.[1] All patients entering the maintenance phase were offered the opportunity to switch to oral azacitidine. The approvals of venetoclax (Venclyxto®) in unfit older patients with acute myeloid leukemia (AML) and oral azacitidine (Onureg®) as maintenance therapy in 2021 hampered recruitment considerably. Therefore, the study was closed on May 5, 2022. Based on descriptive analysis for the randomization of GO-147 *versus* GO-1, the numerical value of MRD negativity after induction therapy was higher in the GO-147 arm with 75% (9/12) compared to 45.5% (5/11) in the GO-1 arm. This higher rate of MRD negativity after induction therapy also translated into a numerically better median event-free survival (EFS) (296 *vs.* 206 days).

GO was re-approved for use in newly diagnosed AML patients by the Food and Drug Administration in 2017 and by the European Medicines Agency in 2018, after it had been withdrawn from the market in June 2010 by the marketing pharmaceutical company. In the pivotal ALFA 0701 study leading to re-approval of GO, patients in the GO arm had significantly improved median EFS (19.6 *vs.* 11.9 months; *P*=0.00018) and OS (34 *vs.* 19.2 months; *P*=0.046).[2] Although the difference in OS was not statistically significant when updated data were analyzed,[3] the trend to a longer OS observed in the GO arm of ALFA-0701 is consistent with the results found in a meta-analysis of individual patient data that showed a significant improvement in OS in patients treated with GO.[4] Glasdegib 100 mg daily in a phase II study in older patients not fit for intensive chemotherapy in combination with low-dose cytarabine resulted in a significantly higher CR rate and better OS as compared to low-dose cytarabine alone.[5] Interestingly, the beneficial effect of glasdegib on OS was not restricted to patients achieving a CR, supporting a leukemic stem cell targeting effect of glasedib.[5]

Patients included in our study had newly diagnosed CD33-positive AML, were age 18 or older, and had Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less. The originally planned age at inclusion was ≥60 years, however, due to unsatisfactory recruitment the age limit for inclusion was lowered to age ≥18 years via an amendment on September 28, 2021 after 9 months of recruitment. Survival endpoints were defined as recommended by the European LeukemiaNet.[6] MRD negativity was defined as the absence of leukemic cells at the end of the induction therapy assessed by flow cytometry with a sensitivity of 10^{-4} to 10^{-5}.

The total planned sample size was 252. Patient recruitment was terminated after the inclusion of 30 patients. Of these, 26 patients were randomized to treatment, of those one never received treatment due to cardiac comorbidity and was excluded from analyses.

From the 25 patients included in the analysis only 13 patients received consolidation therapy within the trial. Therefore, efficacy was only evaluated for the first comparison, i.e., GO-1 *versus* GO-147. The remaining 12 patients either failed to obtain complete remission (CR) (N=7) or were censored due to early study termination (N=5).

Overall, median age at diagnosis was 64 years, 76% were male and 52% had ECOG 1 at inclusion. Secondary or therapy-related AML was present in 16% of patients. Other baseline characteristics can be found in *Online Supplementary Table S1*.

The CR and complete remission with incomplete hematological recovery (CRi) rate was 54.5% (N=6) in the GO-1 arm and 83.3% (N=10) in the GO-147 arm (*P*=0.134, rate difference 28.8%, 95% confidence interval [CI]: 7.4-65). Table 1 summarizes the response to induction therapy according to therapy arm. Regarding MRD responses, there were no significant differences observable among patients achieving a CR or CRi between induction regimens. Overall MRD negativity achievement was 45.5% in the GO-1 arm and 75% in the GO-147 arm (*P*=0.147; rate difference 29.5%, 95% CI: 8.7-67.8). Patients treated in the GO-1 arm showed a median EFS of 206 days (95% CI: 28-206), and in the GO-147 arm

Table 1. Response to induction therapy.

Response	GO 1 N=12	GO 147 N=13
CR/Cri, N (%) MRD$^-$ MRD$^+$	6 (54.5) 5 1	10 (83.4) 8 2
Death during induction, N (%)	1 (9.1)	1 (8.3)
Refractory disease, N (%)	4 (36.4)	1 (8.3)
Missing, N (%)	1	1

GO: gemtuzumab ozogamicin; GO-1: GO administered once on day 1; GO-147: GO administered to intensive induction therapy on days 1, 4 and 7; CR: complete remission; Cri: complete remission with incomplete hematological recovery; MRD: measurable residual disease.

of 296 days (95% CI: 35-not calculable; *P*=0.155) (*Online Supplementary Figure S1*). Relapse-free survival was also in favor of GO-147 with a median of 260 days *versus* 176 days in the GO-1 arm (*P*=0.411) (*Online Supplementary Figure S2*). Concerning toxicity during the induction phase, 96% (24/25) of patients overall experienced at least one or more adverse events (AE). Toxicity rates were numerically higher in the GO-147 arm with a percentage of serious adverse events (SAE) of 61.5% (8/13) compared to 41.7% (5/12) in the GO-1 arm. Most frequent SAE during induction therapy were cytopenias and fever in neutropenia. During the observation periods of the consolidation and maintenance phase, rates of serious AE excluding cytopenia were 14% (1/7) in the control arm and 67% (4/6) in the glasdegib arm. Half of the patients treated with glasdegib maintenance (N=5) experienced dysgeusia and one third of the patients experienced muscle cramps as previously described.[2,4]

The development of clinical studies sponsored by academic centers is fraught with multifaceted challenges. Securing adequate funding, maintaining scientific and ethical standards in study design, and addressing participant recruitment and retention are formidable tasks made more complex by our constrained staffing levels. In addition to that, excessive regulatory hurdles in conducting highly complex clinical studies sponsored by academic institutions often delay the activation of well-designed trials. Not seldom, at the time point when studies are ready to be initiated, more attractive therapeutic approaches are available. During the planning and conduct of this study the approval of venetoclax for patients deemed unfit for intensive chemotherapy revolutionized the therapy of AML of those patients, and the therapy proposed in this trial ceased to be recommendable.[7] Venetoclax and azacitidine are increasingly used in patients above the age of 65 years.[8] Firstly, due to concerns about such patients' ability to tolerate intensive chemotherapy regimens and secondly the limited response to intensive induction and consolidation regimens.[9] Venetoclax as adjunct to low-dose hypomethylating agents showed significant improvements in remission rates and OS compared to placebo.[10,11] Success of such new therapeutic approaches with non-intensive regimens affected patient recruitment in our study negatively. Particularly during the COVID-19 pandemic, approaches that facilitate outpatient therapies were preferred.[7] Furthermore, recent retrospective data analysis suggested in the same direction that azacitidine and venetoclax treatment may be equally effective to intensive chemotherapy and is associated with significantly lower infectious complications and shorter stays in hospital.[12]

Aiming to avoid a too early study termination the attempt was made to improve the feasibility of the trial by two consecutive amendments that reduced the patient age to 18 years. However, recruitment of the trial did not improve significantly. As a result, the study was halted, with this decision finally being supported by the previously published data concerning the broad toxicity spectrum of GO, especially in older patients.[13,14] Indeed, according to the final results from the AMLSG 0909 study, the older population has obviously no benefit from the addition of GO on day 1 in any of the response or survival endpoints, whereas the rates of CR/CRi, EFS and cumulative incidence of relapse were similar between the standard and the GO arm.[14] Moreover, the 30- and 60-day mortality rates were higher in the GO arm. Nonetheless, in our study, the initial hypothesis that treatment during induction therapy with GO-147 results in a higher rate of MRD negativity compared to GO-1 was at least numerically supported, and the question is still remaining whether GO administered on days 1, 4 and 7 as applied in the ALFA 0701 trial[3] is in fact better as compared to GO administered only once as conducted in several other trials.[4,13] In agreement with the findings of the AMLSG 0909 publication,[13] we found an important amount of toxicity in both therapy arms, which was not unexpectedly higher in the GO-147 arm. Therefore, if GO therapy should be pursued during induction therapy, it should preferably be administered to a young and fit population of patients. These findings are also supported by a recent publication in which 852 older patients with AML or high-risk MDS were randomized to receive GO on day 1 (GO1) or GO on days 1 and 4 (GO2). Results showed greater reduction in MRD and improved survival in older adults with non-adverse risk genetics by GO2. This benefit from GO2 was dependent on allogeneic transplantation to translate the better leukemia clearance into improved survival.[15]

According to previous publications, patients harboring mutations in the *NPM1* gene respond favorably to intensive induction with the "7+3" regimen plus GO, with CR rates around 85% and 5-year OS around 40-50%.[14] However, impressive responses have also been observed with azacitidine and venetoclax. In the VIALE-A phase III study the overall response rate was 93% and the 2-year OS was 75% for patients (N=27) harboring a *NPM1* mutation.[11] The response data suggest that the less intensive combination of azacitidine and venetoclax may potentially rival inten-

sive chemotherapy in clinical outcomes for patients with *NPM1*-mutated AML. However, it's crucial to acknowledge the limitations of these observations, given the absence of randomized trials. The open question is whether there are indications to start gemtuzumab ozogamicine during induction therapy in newly diagnosed AML or if it is time to let it go?

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Contributions

RFS developed the concept and designed the study. SJ provided study materials. All authors collected and assembled data, analyzed and interpreted data, wrote the manuscript, and gave their final approval of the manuscript.

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Data-sharing statement

The datasets used and/or analyzed during the current study are available from the last author on reasonable request.

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