# Addition of the nuclear export inhibitor selinexor to standard intensive treatment for elderly patients with AML and high risk MDS

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**Article**

**Keywords:** AML, high-risk MDS, selinexor, clinical trial, XPO1 inhibitor, elderly

**Posted Date:** June 2nd, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-1690216/v1



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**Version of Record:** A version of this preprint was published at Leukemia on July 22nd, 2022. See the published version at https://doi.org/10.1038/s41375-022-01657-3.

# Abstract

Treatment results of AML in elderly patients are unsatisfactory. In an open label randomized phase II study, we investigated whether addition of the XPO1 inhibitor selinexor to intensive chemotherapy would improve outcome in this population. 102 AML patients > 65 years of age (median 69 (65–80)) were randomly assigned to standard chemotherapy (3 + 7) with or without oral selinexor 60 mg twice weekly (both arms $n = 51$), days 1–24. In the second cycle, cytarabine 1000 mg/m$^2$ twice daily, days 1–6 with or without selinexor was given. CR/CRi rates were significantly higher in the control arm than in the investigational arm (80% (95% C.I. 69–91%) vs. 59% (45–72%; p = 0.018), respectively). At 18 months, event-free survival was 45% for the control arm versus 26% for the investigational arm (Cox-p = 0.012) and overall survival 58% vs. 33%, respectively ($p = 0.009$). AML and infectious complications accounted for an increased death rate in the investigational arm. Irrespective of treatment, MRD status after two cycles appeared to be correlated with survival. We conclude that the addition of selinexor to standard chemotherapy does negatively affect the therapeutic outcome of elderly AML patients. (Netherlands Trial Registry number NL5748 (NTR5902), www.trialregister.nl).


# Introduction

The incidence of acute myeloid leukemia strongly increases with age. In the elderly patient group, the disease has a particularly poor prognosis due to poor tolerance to intensive chemotherapy and a higher occurrence of prognostically adverse cytogenetic and molecular abnormalities. In those who are unable to undergo intensive chemotherapy, treatment options are mostly palliative. Hypomethylating agents like azacitidine and decitabine, preferentially combined with the BCL-2 inhibitor venetoclax may however induce complete remissions that are rather durable in a small subset of patients.[1] In patients who are fit enough, intensive chemotherapy may be curative. Complete remissions are obtained in 60–70%, however at least half of these patients will sooner or later relapse. Improvements may be expected from new targeted compounds like IDH1/IDH2 inhibitors and FLT3 inhibitors, but the molecular abnormalities they target are only found in a subgroup of elderly patients. Studies with these compounds as adjunct to intensive chemotherapy are underway.[2,3] CPX-351, a liposome-encapsuled formulation of daunorubicine and cytarabine resulted in a modest improvement of outcome in patients with secondary AML and therapy-related AML, but mostly in patients who were eligible for allogeneic stem cell transplantation (alloSCT).[4] In general however, although alloSCT can be curative even in elderly patients and improved transplant strategies have resulted in a decrease in transplant related mortality, still relatively few patients qualify for this treatment modality.

Improvement of AML treatment results is therefore urgently needed. The HOVON/SAKK cooperative group therefore designed the HOVON 103 study with the aim to rapidly select potential promising compounds that would have a large impact on complete remission rates as adjuncts to intensive chemotherapy in a so-called Octopus design, where multiple drugs were added to the standard 3 + 7 backbone in randomized phase 2 substudies. With this design, around 100 patients per experimental arm would be needed.

Results of the addition of lenalidomide and tosedostat have recently been published.[5,6] Here, we report on the results of the investigational arm with selinexor. Selinexor is an XPO1 inhibitor. XPO1, also called exportin-1 or CRM1 is a nuclear exporter protein that is involved in the transport of several proteins and mRNA molecules from the nucleus to the cytoplasm. Among these are tumor suppressor proteins and ribosome subunits. Many tumor cell types show elevated expression of XPO1, thereby on the one hand reducing tumor suppressor protein availability in the nucleus where they e.g. normally act by keeping cell cycle progression in check, and on the other hand reducing biogenesis of mRNA molecules involved in cell cycle regulation or apoptosis induction. Inhibition of XPO1 would restore these processes, leading to reduced tumorigenesis.

In preclinical studies, the drug appeared synergistic with anthracyclines and etoposide, and in phase 1 studies, selinexor showed promising single agent activity in several tumors, with an overall response rate of 14% in AML patients with, in general, relatively little adverse effects.[7,8] We therefore investigated the addition of selinexor to standard 3 + 7 chemotherapy in a randomized phase 2 study.

## Patients And Methods

# Patients

Previously untreated patients, 66 years of age or older, with a cytologically confirmed diagnosis of de novo or secondary AML (not acute promyelocytic leukemia or CML blast crisis) or with refractory anemia with excess of blasts and a Revised International Prognostic Scoring System (R-IPSS) score of higher than 4.5 and a WHO performance score of 2 or less were eligible for inclusion. Except for hydroxyurea for < 2 weeks, no other previous AML treatment was allowed. Exclusion criteria included clinically significant cardiovascular disease, including cerebrovascular accidents (< 6 months before randomization), myocardial infarction (< 6 months before randomization), unstable angina, New York Heart Association grade 2 or greater congestive heart failure, serious cardiac arrhythmia requiring medication and other standard general medical exclusions. The trial was approved by the institutional review boards of all participating institutions. The study was performed in accordance with the Declaration of Helsinki, and all patients provided written informed consent.

# 4.2. Risk classification

Based on the karyotype and molecular genotype of the leukemic cells, patients were classified into prognostic categories according slight modifications of the ELN 2010, as described previously.[6]

# 4.3. Study design and chemotherapy

Selinexor was provided free of charge by Karyopharm. The study was divided in two parts. The first part was planned to be a randomized dose selection safety run-in phase with oral selinexor 60 mg twice weekly, days 1–24 in cycle 1 and cycle 2, added to standard induction chemotherapy.

During the Phase II part, one interim analysis regarding efficacy was performed after enrollment of 100 patients (50 per arm) on the primary endpoint according to protocol. Patients were randomly assigned to remission induction regimens with or without selinexor. Cycle 1 consisted of daunorubicin at 60 mg/$m^2$ (3-hr infusion on days 1, 2 and 3) and cytarabine at a dose of 200 mg/$m^2$ (per continuous infusion on days 1–7) with or without oral selinexor at 60 mg twice weekly, days 1–24. Cycle 2 contained cytarabine 1000 mg/$m^2$ q 12 hrs via 6 hrs infusion from day 1–6 (12 doses) with or without selinexor at 60 mg twice weekly, days 1–24. Patients could be allotransplanted off protocol according to local policy. Measurable residual disease (MRD) analysis and detection was performed as previously described.[9]

# 4.4. Statistical analysis

The primary endpoint of the second part of the study was the rate of complete remission after induction treatment. A patient was considered to have a response if the best response to remission induction therapy (cycle 1 and/or 2) was a CR/CRi. Secondary endpoints were considered as exploratory and included: overall survival (OS), event free survival (EFS), disease free survival (DFS), the prognostic value of leukemic molecular markers and gene expression profiles and the prognostic value of minimal residual disease measurements following therapy. The definition of endpoints was according to the ELN 2017 recommendations.[10] A planned futility interim analysis was incorporated after 100 patients were randomized.

At final analysis, selinexor was considered not effective as addition to standard chemotherapy if no difference in CR/CRi rate in favor of selinexor was seen i.e. when the upper limit of the 80% confidence interval (CI) of the difference in CR rate would be less than 15%, which is the case if the observed difference in complete response rates was less than 2% in favor of the investigational arm. Otherwise, we would consider continuing as Phase III. Kaplan-Meier survival curves and Cox tests were used to compare the survival distributions between the treatment arms.

# Results

The study was activated in 2017 and closed after an interim efficacy analysis in 2019. Median FU of patients still alive is 19 months (range: <0.1–30). In total, 105 patients were registered and randomized. Three patients were subsequently excluded from analysis as they were later found to be non-eligible and one patient in the investigational arm went off-protocol before the drug was given, but was included in the final analysis of the study. The intention-to-treat analysis presented here therefore includes 51 patients eligible for the investigational arm and 51 patients in the control arm who received standard treatment. See CONSORT diagram shown in Fig. 1.

# 2.1. Patients

Patient characteristics at diagnosis by treatment arm are shown in Table 1. Median age of the patients was 69 years in both arms with slightly more patients being > 70 years of age in the control arm. In the

investigational arm, the AML of 79% of patients classified as poor or very poor risk, whereas this was 59% in the control arm. Other major known risk factors were well-balanced over both arms.

## 2.2. Treatment, response and outcome

All 51 eligible patients in the standard arm and 50 of 51 patients in the investigational arm received the first treatment cycle. Ninety-three (92%) received full doses of daunorubicin according to the protocol and 100 (98%) received full doses of cytarabine in cycle 1. Twenty-six of 51 patients (51%) completed the full series of doses of selinexor according to protocol in cycle 1. The majority of the patients who did not receive the protocol-specified dosages of selinexor discontinued prematurely or received reduced dosages due to toxicity (specified below). Length of stay in the hospital was on average 2 days longer in the investigational arm than in the standard arm (mean 30 days compared to 28 days).

In cycle 2, cytarabine was administered at full dose in 35 of 38 patients (92%) in the control arm and in 30/35 (86%) of the investigational arm. Selinexor was given at full dose in 10 of 35 patients (29%), with 20/35 patients (57%) stopping early or interrupting treatment because of toxicity. Length of hospital stay for the second cycle was prolonged by 5 days in the investigational arm compared to the control arm (mean 35 days compared to 30 days). Sixteen patients (42%) in the control arm and 11 (31%) in the investigational arm proceeded to alloSCT.

CR/CRi rate on induction in the control arm was 80% (95%-CI: 69–91%) and 59% (95%-CI: 45–72%) in the investigational arm ($p = 0.018$). With a median follow-up time of patients still alive of 19 months, the overall survival in the control arm was significantly higher than in the investigational arm (Cox-$p = 0.009$, OS at 18 months 58% vs 33%, see Fig. 2a), as was event-free survival ($p = 0.01$; EFS at 18 months 45% versus 26%, see Fig. 2b) and disease-free survival ($p = 0.15$; DFS at 18 months 53 vs 39%, not shown). Also in the subgroup of patients with poor or very poor risk AML, results of the investigational arm were worse than those in the control arm (see Figure S1). Due to the limited number of patients, no separate survival analyses were done for the individual molecular subgroups.

Although early death rates within 30 days were comparable between both arms, the death rate within 60 days in the investigational arm exceeded that in the control arm (18% versus 8%). See Table 2 for an overview of these results.

## 2.3. Adverse events and hematological recovery

In Supplemental Tables 1 and 2, the number of AEs in cycles 1 and 2 by diagnosis category, common toxicity criteria (CTC) grade, and treatment arm of randomization are given. The frequencies of toxicities were higher in the investigational arm than in the control arm, with grade 3 nervous system AEs in 12 vs 2% in the first cycle, and, in the second cycle, grade 3–4 cardiac AEs in 11% vs 5%, grade 3–4 gastrointestinal AEs in 43% vs 26%, infectious AEs grade 3–4 in 57% vs 37% and metabolic and nutritional disorders AEs in 46% vs 29%. In the control arm, 19 patients (37%) of patients experienced at least 1 SAE, whereas this was 23 (45%) in the investigational arm, and of these SAEs, 7 in the control arm

and 14 in the investigational arm were life-threatening or resulted in death, the majority due to various infections.

After the first cycle, time to neutrophil recovery > 0.5 and 1.0 x $10^9$/L was delayed in the investigational arm (median 29 versus 25 days, p = 0.007; 37 versus 29 days, p < 0.001, respectively), whereas platelet recoveries were not significantly different (see Fig. 3a and 3b). After the second cycle no significant differences in hematological recovery times were noted between the arms. (See Suppl Figure S2).

## 2.3. Measurable residual disease (MRD)

In 45 patients (30 in the control arm and 15 in the investigational arm) MRD was assessed after the second cycle. MRD negativity rates were not different between the two arms. Overall, OS at 2 years was 75% for patients who became MRD-negative and 34% for MRD-positive patients. Disease-free survival at 2 years was 58% and 12%, respectively. Because of the limited numbers of patients, no p-values are given. (See Suppl Figure S3).

# Discussion

In this randomized phase II clinical study we evaluated the addition of the XPO1 inhibitor selinexor in newly diagnosed elderly AML patients who were deemed fit enough for intensive chemotherapy, as part of the HOVON 103 study where several promising investigational agents are successively examined in combination with an intensive chemotherapy backbone. The results of the current study are disappointing, with comparatively reduced overall and disease-free survival for the investigational selinexor treatment arm. This seems to have mainly been caused by a lower CR/CRi rate, increased toxicities and infection rates in relation to the addition of selinexor, and may in part also relate to the higher proportion of patients with a high or very high disease risk that were randomized to the experimental arm, although results seem equally poor in this category of patients.

Our choice for selinexor was based on positive results of preclinical studies and of a clinical phase I dose-escalation study with single agent selinexor in 95 relapsed/refractory AML patients, which showed an objective response rate of 14% with 31% of patients obtaining at least a 50% reduction in blast counts.[8,11] Recently, in a randomized phase II study in 118 selinexor (single agent) treated relapsed/refractory AML patients, an overall response rate of 14% was obtained, compared to 9% in the control arm treated with either best supportive care alone, (BSC), BSC plus low-dose cytarabine or BSC plus a hypomethylating agent.[12]

The drug was also evaluated in combinations with daunorubicine/cytarabine, cladribine/cytarabine, FLAG-IDA and high dose cytarabine/mitoxantrone, and with decitabine in a 10 days regimen, in small (n = 14–40) phase I studies, mostly with relapsed or refractory, elderly AML patients.[13–17] Although some signals of additive activity of selinexor were suggested, these studies showed increased toxicity of the combination with, amongst others, many electrolyte disturbances consisting of hyponatremia,

hypophosphatemia, hyperglycemia and anorexia, nausea and vomiting. This limited dosing of selinexor to 60 mg twice weekly.

The results of our study are especially unsatisfactory, as the drug has been shown to be effective in other hematological malignancies, like relapsed/refractory diffuse large-cell B-cell lymphoma, and in combination with dexamethasone and bortezomib in relapsed multiple myeloma, where it was recently approved by the FDA. In the first study however, selinexor was given as a single drug, whereas co-treatment with dexamethasone and bortezomib proved to be tolerable for the majority of patients in the latter study.[18,19] Nevertheless, cytopenias and gastrointestinal adverse effects were common in both studies and, like in our study, infectious adverse events were more frequent in the selinexor containing arm of the myeloma study. Moreover, gastro-intestinal adverse effects were common in these studies, corresponding with our experience. Apparently, any added toxicity on top of that caused by the 3 + 7 regimen is poorly tolerated by this relatively old age group.

As the nausea and vomiting of selinexor are presumably related to its central nervous system penetration, a next generation XPO1 inhibitor, KPT-8602, eltanexor, was developed. Brain barrier crossing is reduced with this compound which enables daily and higher dosing and, in high risk myelodysplastic syndromes, induced a total disease control rate of 60%.[20] Studies in AML with this compound are in progress.[21]

Still, efforts to enhance antileukemic activity of standard intensive chemotherapy by the addition of novel agents have proven to be challenging. Apparently, patients of older age have a limited margin to tolerate toxicities added to those of the intensive chemotherapy itself. With new and targeted treatments appearing on the horizon, like the BCL2 inhibitor venetoclax or the IDH1/2 inhibitors ivosidenib and enasidenib, these agents still need to be assessed for their tolerability in combination with intensive chemotherapy in fit elderly patients. Clearly, venetoclax addition to azacitidine resulted in delayed neutrophil and platelet recovery, and this likely also applies to the combination of venetoclax with intensive chemotherapy regimens.[22] Nevertheless, as venetoclax resistance may be related to increased MCL1 expression, selinexor, or its newer derivative, which reduces MCL1 through inhibition of its mRNA transport into the cytoplasm, may be rational drugs to combine with venetoclax.[23]

Although the overall result of the study is negative, our data suggest the importance of MRD status after two cycles of chemotherapy, regardless of treatment arm. Patients who were MRD negative at that timepoint had superior survival compared to the MRD positive patients. While we and others have previously shown the prognostic value of the MRD status in younger age groups, only two studies have reported on its role in elderly AML patients, with matching conclusions.[5,9,24–25]

# Conclusions

In this prospective randomized phase II study, the addition of selinexor to the current 3 + 7 standard of chemotherapy resulted in reduced treatment outcome, mainly as the consequence of lower anti-leukemic

activity and more infection-related deaths. Regardless of treatment arm, MRD status after two cycles of chemotherapy appears strongly correlated with outcome.

# Declarations

**Funding:** Dutch Cancer Foundation for financial support; Karyopharm for financial support and delivery of drug for free.

**Study design, data analysis, preparation of publication:** The study was designed by the Leukemia Working Group of the HOVON/SAKK Cooperative Groups, the HOVON Data Center was responsible for the central data and trial management and YvN performed the analysis of the data. The decision to publish was made by the cooperative group. JJWMJ and subsequently BL, YvN and GO produced the first version of the manuscript, which was circulated for comments to the other authors.

**Author Contributions:** writing—original draft preparation, JJWMJ, GO, BL and YvN**.** All authors have read, commented on and agreed to the published version of the manuscript.

**Acknowledgments:** The Authors thank the local and central data managers as well as the HOVON Data center Trial team and Karyopharm for free drug supply.

**Conflicts of Interest:**

**JJWMJ:** Research support: Novartis, BMS. President, Apps for Care and Science, nonprofit foundation supported by Abbvie, Alexion, Amgen, Astellas, BMS, Daiichi-Sankyo, Janssen-Cilag, Olympus, Incyte, Sanofi Genzyme, Servier, Jazz, Takeda. Honoraria: Abbvie, Novartis, Pfizer, Incyte.

**BL**: Advisory role with honoraria for AbbVie, Astellas, Bristol Myers Squibb/Celgene, Catamaran Bio, Celgene, AvenCell/GeMoaB, Frame Pharmaceuticals, Gilead, Kronos Bio, Oxford Biomedica, Servier, holding stocks of Frame Pharmaceuticals,

**YC**: consulting fees from MSD, Novartis, Incyte, BMS, Pfizer, Abbvie, Roche, Jazz, Gilead, Amgen, Astra-Zeneca Servier, Travel support from MSD, Roche, Gilead, Amgen, Incyte, Abbvie, Janssen, Astra-Zeneca, Jazz.

**GJO**: Research support: Novartis, J&J, Celgene, Becton Dickinson, Consultancy: J&J, Sunesis, Celgene, Roche, Advisory board: Novartis, Pfizer, BMS, J&J, Sunesis, Celgene, Agios, Amgen, Astellas, Roche, Jazz Pharmaceuticals, Merus.

**Others**: None declared.

The funders had no role in the design of the study, nor in the collection, analyses, or interpretation of data, nor in the writing of the manuscript, or in the decision to publish the results.

**Data availability statement:** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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# Tables

Table 1-2 are available in the Supplementary Files section.

# Figures

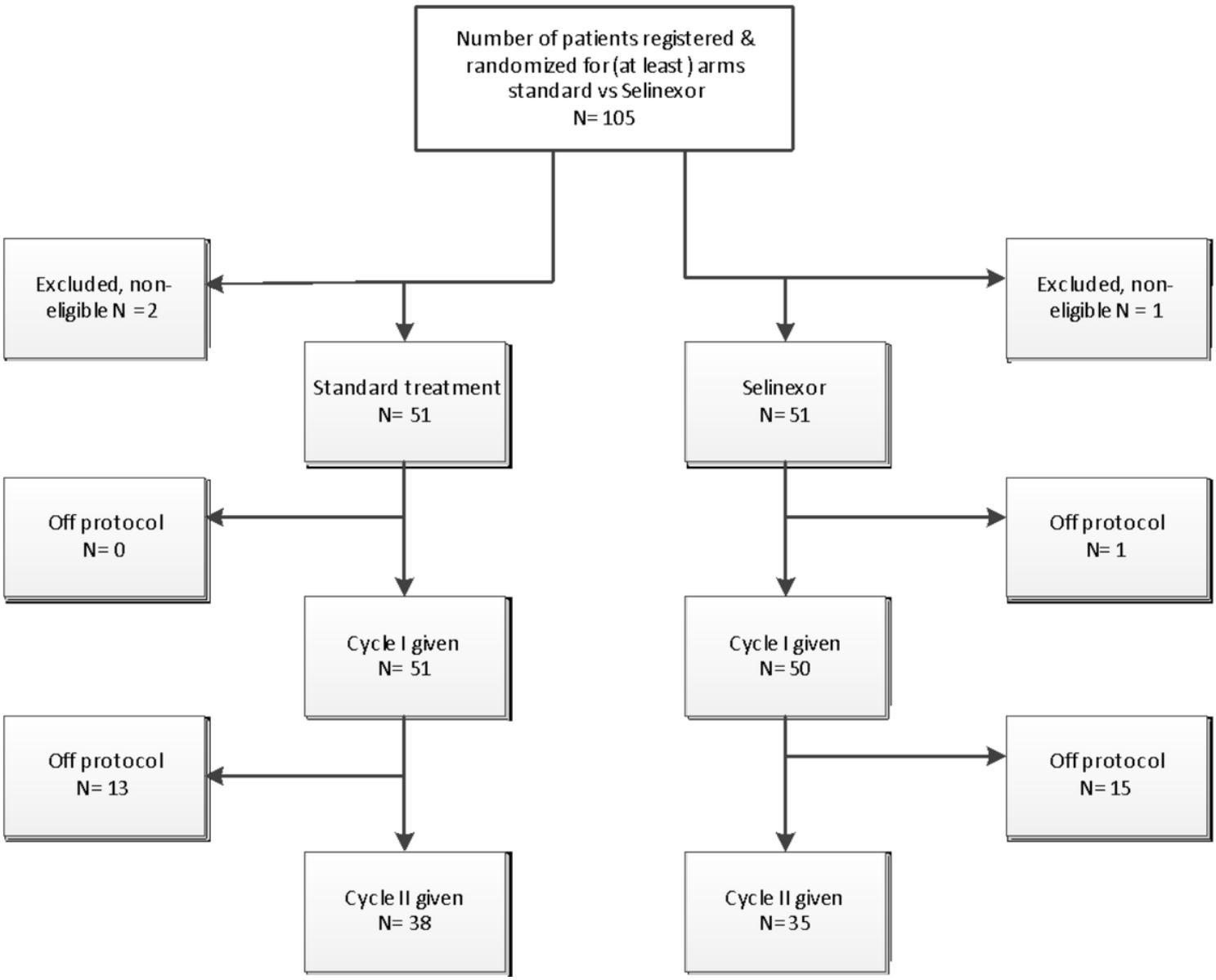


**Figure 1**

Consort diagram of the study

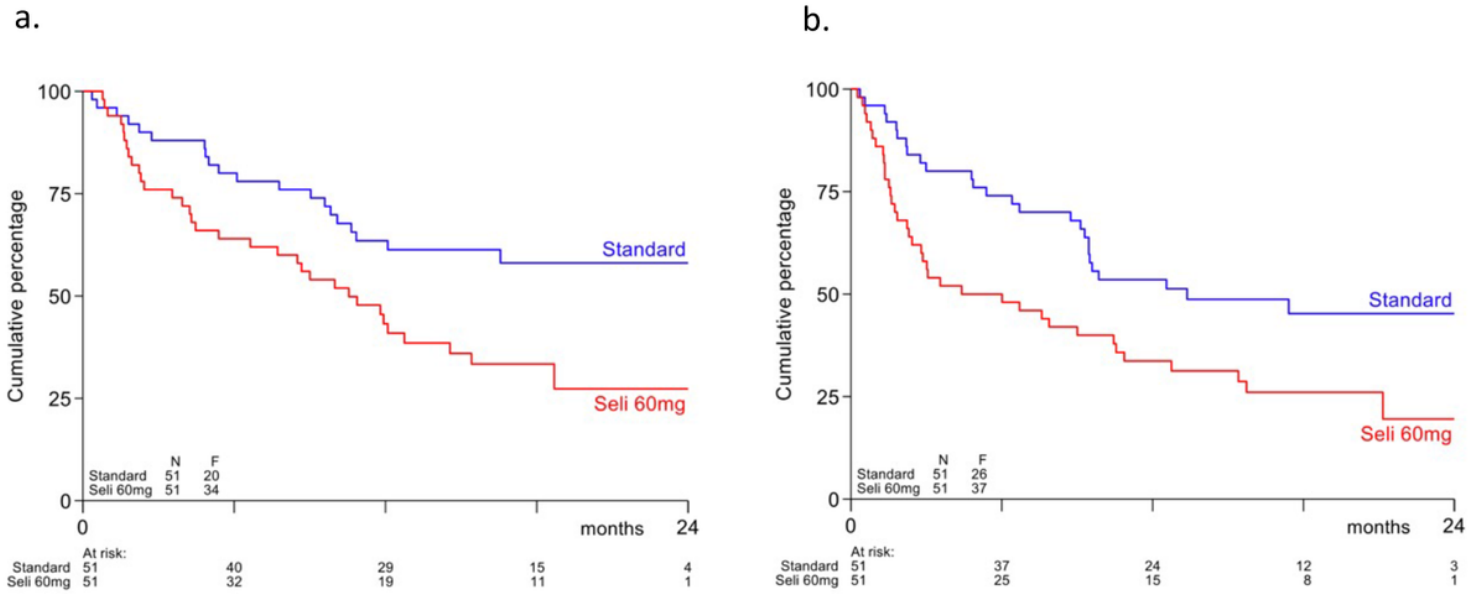


**Figure 2**

(a) Overall survival (b) Event-free survival.

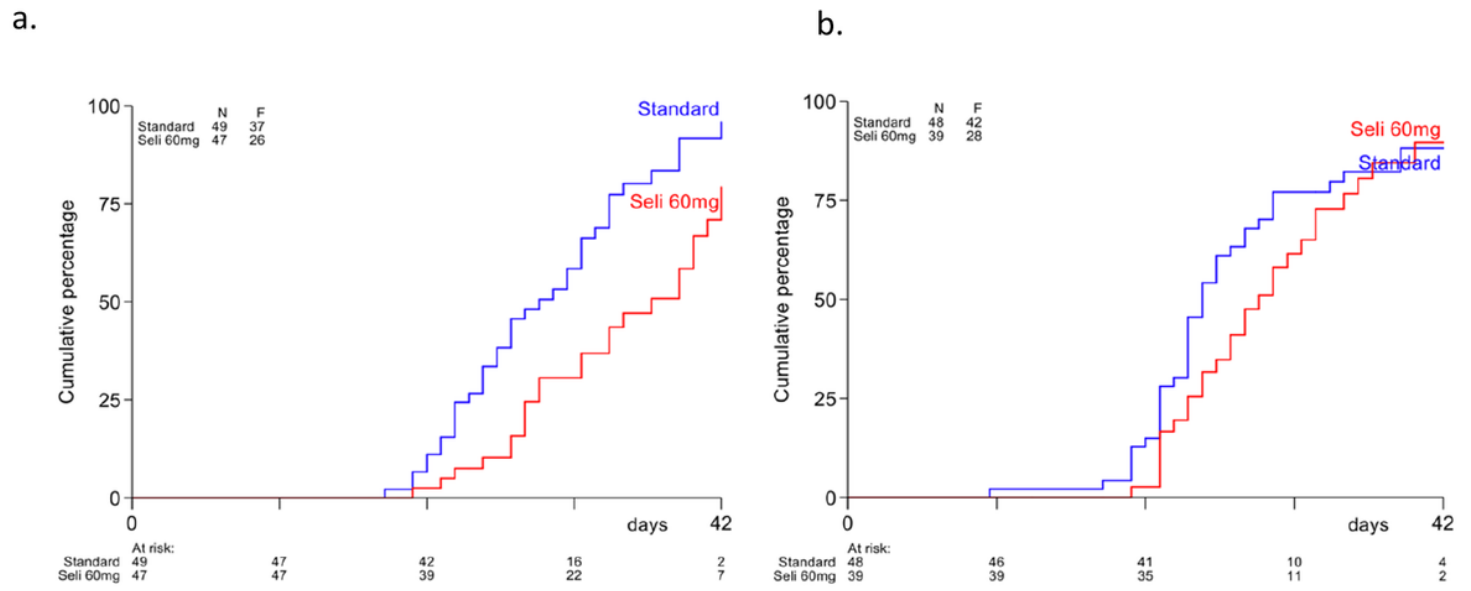


**Figure 3**

(a) Recovery time to ANC > 1.0 x $10^9$/L (b) Recovery time to platelets > 50 x $10^9$/L, both after cycle 1.

# Supplementary Files

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- FigureS3.pdf
- TableS1.xlsx
- TableS2.xlsx
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