Addition of the nuclear export inhibitor selinexor to standard intensive treatment for elderly patients with acute myeloid leukemia and high risk myelodysplastic syndrome
Janssen, J. J. W. M.; Loewenberg, B.; Manz, M.; Biemond, B. J.; Westerweel, P. E.; Klein, S. K.; Fehr, M.; Sinnige, H. A. M.; Efthymiou, A.; Legdeur, M. C. J. C.

Published in:
Leukemia

DOI:
10.1038/s41375-022-01657-3

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Janssen, J. J. W. M., Loewenberg, B., Manz, M., Biemond, B. J., Westerweel, P. E., Klein, S. K., Fehr, M., Sinnige, H. A. M., Efthymiou, A., Legdeur, M. C. J. C., Pabst, T., Gregor, M., van der Poel, M. W. M., Deeren, D., Tick, L. W., Jongen-Lavrencic, M., van Obbergh, F., Boersma, R. S., de Weerdt, O., ... Ossenkoppele, G. J. (2022). Addition of the nuclear export inhibitor selinexor to standard intensive treatment for elderly patients with acute myeloid leukemia and high risk myelodysplastic syndrome. Leukemia, 36, 2189-2195. Advance online publication. https://doi.org/10.1038/s41375-022-01657-3

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Addition of the nuclear export inhibitor selinexor to standard intensive treatment for elderly patients with acute myeloid leukemia and high risk myelodysplastic syndrome

J. J. W. M. Janssen1, B. Löwenberg2, M. Manz3,4, B. J. Biemond5, P. E. Westerweel6, S. K. Klein7, M. Fehr8, H. A. M. Sinnige9, A. Ethfyomiou10, M. C. J. C. Legdeur11, T. Pabst6,12, M. Gregor4,13, M. W. M. van der Poel14, D. Deeren15, L. W. Tick16, M. Jongen-Lavrencic17, F. van Obbergh17, R. S. Boersma18, O. de Weerdt19, Y. Chalandon20, D. Heim21, O. Spertini2,22, G. van Sluis23, C. Graux24, G. Stüssi25, Y. van Norden26 and G. J. Ossenkoppele1

© The Author(s), under exclusive licence to Springer Nature Limited 2022

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/m² 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 NLS748 (NTR5902), www.trialregister.nl).

Leukemia; https://doi.org/10.1038/s41375-022-01657-3

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 liposomally encapsulated formulation of daunorubicin 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 drug was given, but was included in the 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.

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.

**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].

**Study design and chemotherapy**

Selinexor was provided free of charge by Karyopharm. The study was initially planned to start with a randomized dose selection safety run-in phase with either standard chemotherapy only or oral selinexor added to standard induction chemotherapy. The starting dose of selinexor of 60 mg twice weekly, days 1–24 was meant to be increased depending on the occurrence of dose-limiting toxicities. Shortly after the start of the study however, based on external data, the Data and Safety Monitoring Board advised to keep the selinexor dose at 60 mg and to not escalate further. Therefore, all patients in the investigational arm of the study received the same selinexor dose as above. Cycle 1 consisted of daunorubicin at 60 mg/m² (3 h infusion on days 1, 2 and 3) and cytarabine at a dose of 200 mg/m² (per continuous infusion on days 1–7) with or without oral selinexor. Cycle 2 contained cytarabine 1000 mg/m² q 12 h via 6 h infusion from day 1–6 (12 doses) with or without selinexor at the same dose as in Cycle 1. Patients could be allotransplanted off protocol according to local policy.

One interim analysis regarding efficacy was performed after enrollment of 100 patients (50 per arm) on the primary endpoint according to protocol after which the DSMB advised to close the study.

Measurable residual disease (MRD) analysis and detection was performed by immunophenotyping at the central AmsterdamUMC lab as described previously [9]. The MRD percentage was defined as the percentage of leukemia-associated immunophenotype-positive (LAIP) cells within the white blood cell compartment An MRD percentage ≤ 0.1% was considered negative, > 0.1% as MRD positive. The maximal sensitivity of the MRD detection was 0.01% (i.e., 1 × 10⁻⁹).

**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.

**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.

**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 Fig. 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.

**Adverse events and hematological recovery**
In Supplemental Tables 3, 4, 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 × 10⁹/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, b). After the second cycle no significant differences in hematological recovery times were noted between the arms. (See Suppl Fig. S2).

**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**
With a median age at diagnosis of around 70 years, AML is primarily a disease of the elderly. Although tolerance to intensive induction regimens diminishes with age, large registry data show that a majority of patients up to the age of 79 years old can tolerate intensive chemotherapy with over half of them attaining CR [11]. However, as survival in elderly AML patients is clearly below 30% at two years, better treatments are urgently needed. We therefore 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. This chemotherapy regimen includes a relatively high cytarabine dose of 1000 mg/m² for 6 days as a second induction cycle, which has been the standard of care since many years in subsequent HOVON/SAKK AML trials for patients 60 years and above and it has remained so for the ongoing major

![Consort diagram](https://example.com/consort-diagram.png)

*Fig. 1 Consort diagram. Distribution of patients over both treatment arms and number of patients going off-protocol shown in the boxes below.*
Table 1. Baseline patient characteristics.

|                  | Control arm (n = 51) | Selinexor 60 mg (n = 51) | Total |
|------------------|----------------------|-------------------------|-------|
| **Sex**          |                      |                         |       |
| M                | 28 (55%)             | 38 (75%)                | 66 (65%) |
| F                | 23 (45%)             | 13 (25%)                | 36 (35%) |
| **Age groups**   |                      |                         |       |
| ≤ 70 years       | 31 (61%)             | 34 (67%)                | 65 (64%) |
| > 70 years       | 20 (39%)             | 17 (33%)                | 37 (36%) |
| **Age (years)**  |                      |                         |       |
| Mean; SD         | 69.9; 2.9            | 69.7; 3.5               | 69.8; 3.2 |
| Median; range    | 69; 65–78            | 69; 65–80               | 69; 65–80 |
| **WHO performance** |                    |                         |       |
| 0                | 21 (41%)             | 27 (53%)                | 48 (47%) |
| 1                | 28 (55%)             | 23 (45%)                | 51 (50%) |
| 2                | 2 (4%)               | 1 (2%)                  | 3 (3%)  |
| **Diagnosis**    |                      |                         |       |
| MDS (RAEB)       | 3 (6%)               | 10 (20%)                | 13 (13%) |
| AML              | 48 (94%)             | 41 (80%)                | 89 (87%) |
| **Prior HM**     |                      |                         |       |
| No               | 49 (96%)             | 47 (92%)                | 96 (94%) |
| Yes              | 2 (4%)               | 3 (6%)                  | 5 (6%)  |
| **AML risk group (acc. to HOVON 103 protocol)** | | | |
| Good             | 3 (6%)               | 3 (6%)                  | 6 (6%)  |
| Intermediate     | 18 (35%)             | 8 (16%)                 | 26 (25%) |
| Poor             | 24 (47%)             | 29 (57%)                | 53 (52%) |
| Very poor        | 6 (12%)              | 11 (22%)                | 17 (17%) |
| **IPSS-R risk score (if RAEB)** | | | |
| 5.0              | 2                    | 1                       | 3       |
| 5.5              | 0                    | 2                       | 2       |
| 6.0              | 0                    | 1                       | 1       |
| 7.5              | 0                    | 2                       | 2       |
| 8.0              | 0                    | 1                       | 1       |
| unknown          | 1                    | 3                       | 4       |
| **WBC at diagnosis [×10^9/L]** | | | |
| Mean (SD)        | 20.0 (35.5)          | 15.8 (40.8)             | 17.9 (38.1) |
| Median           | 2.20                 | 3.45                    | 3.20 |
| Range            | 0.60–121             | 0.60–245                | 0.60–245 |
| **Blasts in BM [%]** | | | |
| Mean (SD)        | 43.5 (25.8)          | 41.5 (27.4)             | 42.5 (26.5) |
| Median           | 31                   | 31                      | 34 |
| Range            | 4–96                 | 2–99                    | 2–99 |
| **NPM1 mutation** |                     |                         |       |
| Neg              | 20 (39%)             | 22 (43%)                | 42 (41%) |
| Pos              | 6 (12%)              | 5 (10%)                 | 11 (11%) |
| NA               | 25 (49%)             | 24 (47%)                | 49 (48%) |
| **FLT3 ITD**     |                      |                         |       |
| Neg              | 26 (51%)             | 27 (53%)                | 53 (52%) |
| Pos              | 4 (8%)               | 2 (4%)                  | 6 (6%)  |
| NA               | 21 (41%)             | 22 (47%)                | 43 (42%) |

*Exclusive of previous MDS

Table 1. continued

|                  | Control arm (n = 51) | Selinexor 60 mg (n = 51) | Total |
|------------------|----------------------|-------------------------|-------|
| **FLT3 TKD835**  |                      |                         |       |
| Neg              | 11 (22%)             | 14 (27%)                | 25 (25%) |
| Pos              | 2 (4%)               | 1 (2%)                  | 3 (3%)  |
| NA               | 38 (75%)             | 36 (71%)                | 58 (73%) |
| **CEBPA DM**     |                      |                         |       |
| Neg              | 27 (53%)             | 26 (51%)                | 53 (52%) |
| Pos              | 0                    | 1 (2%)                  | 1 (1%)  |
| NA               | 24 (47%)             | 24 (47%)                | 48 (47%) |
| **FLT3/ITD × NPM1 mutation** | | | |
| Pos × Pos        | 2 (4%)               | 1 (2%)                  | 3 (3%)  |
| Pos × neg        | 2 (4%)               | 1 (2%)                  | 3 (3%)  |
| Neg × Pos        | 4 (8%)               | 3 (6%)                  | 7 (7%)  |
| Neg × Neg        | 18 (35%)             | 20 (39%)                | 38 (37%) |
| NA               | 25 (49%)             | 26 (51%)                | 51 (50%) |

HOVON 150 and 156 studies. The 30- and 60-day mortality rates, 4 and 8% in the standard arm of the current study, compare favorably with those from other collaborative groups using lower cytarabine dosages, or with fewer administrations. Of note, for the older age category that was enrolled in this study, 1000 mg/m² cytarabine dosages, or with fewer administrations. Of note, for the older age category that was enrolled in this study, 1000 mg/m² cytarabine days 1–6, is single agent treatment in the second cycle.

Nevertheless, 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, 12]. 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 [13].

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 [14, 15]. 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 [16, 17]. 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, gastrointestinal 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

![Fig. 2 Overall survival and event-free survival.](image)

**Table 2.** Treatment outcome of patients randomized to standard chemotherapy with or without selinexor.

|                  | Control treatment | Selinexor 60 mg | HR (95% C.I.) | p    |
|------------------|-------------------|----------------|---------------|------|
| Complete remission/CRi | 80%               | 59%            | 0.018         |      |
| 95% C.I. (%)     | 69–91             | (45–72)        |               |      |
| CR/CRi (after cycle I) | 71%               | 46%            |               |      |
| Death within 30 days | 4%                | 6%             |               |      |
| Death within 60 days | 8%                | 18%            |               |      |
| OS at 18 months  | 58                | 33             | 2.10 (1.21–3.65) | 0.009|
| EFS at 18 months | 45                | 26             | 1.91 (1.15–3.16) | 0.01 |
| DFS at 18 months | 53                | 39             | 1.59 (0.85–2.98) | 0.15 |

HR: Hazard ratio, CI: Confidence interval, CR: Complete remission, CRi: Complete remission with incomplete hematologic recovery, OS: Overall survival, EFS: Event-free survival, DFS: Disease-free survival.

![Fig. 3 Hematological recovery after cycle 1.](image)
poorly tolerated by this relatively old age group, even though these patients were relatively fit in view of the restrictive inclusion criteria.

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% [18]. Studies in AML with this compound are in progress [19].

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 [20]. 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 [21].

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, 22, 23].

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.

Study design, data analysis, preparation of publication

The study was designed by the Leukemia Working Group of the HOVON/SACK 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. JWWJM and subsequently BL, YvN and GO produced the first version of the manuscript, which was circulated for comments to the other authors.

DATA AVAILABILITY

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

REFERENCES

1. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020;383:617–29.
2. A Study of Gilteritinib Versus Midostaurin in Combination With Induction and Consolidation Therapy Followed by One-year Maintenance in Patients With Newly Diagnosed Acute Myeloid Leukemia or Myelodysplastic Syndromes With Excess Blasts-2 With FLT3 Mutations Eligible for Intensive Chemotherapy - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04027309 (accessed 5 Mar 2022).
3. A Study of Ivosidenib or Enasidenib in Combination With Induction Therapy and Consolidation Therapy, Followed by Maintenance Therapy in Patients With Newly Diagnosed Acute Myeloid Leukemia or Myelodysplastic Syndrome EB2, With an IDH1 or IDH2 Mutation, Respectively, Eligible for Intensive Chemotherapy - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03839771 (accessed 5 Mar 2022).
4. Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, et al. CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia. J Clin Oncol. 2018;36:2684–92.
5. Löwenberg B, Pabst T, Maertens J, Gradowiska P, Biemond BJ, Sertpini O, et al. Addition of lenalidomide to intensive treatment in younger and middle-aged adults with newly diagnosed AML: the HOVON-SAKK-132 trial. Blood Adv. 2021;5:1110–21.
6. Janssen J, Löwenberg B, Manz M, Bargetzi M, Biemond B, Borne P, et al. Inferior Outcome of Addition of the Aminopeptidase Inhibitor Tosedostat to Standard Intensive Treatment for Elderly Patients with AML and High Risk MDs. Cancers 2021;13. https://doi.org/10.3390/cancers13040672.
7. Ranganathan P, Kashyap T, Yu X, Meng X, Lai Y-H, McNeil B, et al. XPO1 Inhibition using Selinexor Synergizes with Chemotherapy in Acute Myeloid Leukemia by Targeting DNA Repair and Restoring Topoisomerase IIa to the Nucleus. Clin Cancer Res. 2016;22:6142–52.
8. Garzon R, Savona M, Baz R, Andreeff M, Gabrail N, Gutierrez M, et al. A phase 1 clinical trial of single-agent selinexor in acute myeloid leukemia. Blood. 2017;129:1365–74.
9. Terwijn M, van Putten WJL, Kelder A, van der Velden VH, Brooimans RA, Pabst T, et al. High prognostic impact of flow cytometric minimal residual disease detection in acute myeloid leukemia: data from the HOVON/SAKK AML 42A study. J Clin Oncol. 2013;31:3889–97.
10. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129:424–47.
11. Juliusson G. Older patients with acute myeloid leukemia benefit from intensive chemotherapy: an update from the Swedish Acute Leukemia Registry. Clin Lymphoma Myeloma Leuk. 2011;11:554–9.
12. Etchin J, Montero J, Berezovsky A, Le BT, Kentsis A, Christie AL, et al. Activity of a selective inhibitor of nuclear export, selinexor (KPT-330), against AML-initiating cells engrafed into immunosuppressed NSG mice. Leukemia. 2016;30:190–9.
13. Sweet K, Bhattacharjee R, Dohner H, Donnellen W, Frankfurter O, Heuser M, et al. A 2:1 randomized, open-label, phase II study of selinexor vs. physician’s choice in older patients with relapsed or refractory acute myeloid leukemia. Leuk Lymphoma. 2021;62:3192–203.
14. Sweet K, Komrki J, Padron E, Cubitt CL, Turner JG, Zhou J, et al. Phase I Clinical Trial of Selinexor in Combination with Daunorubicin and Cytarabine in Previously Untreated Poor-Risk Acute Myeloid Leukemia. Clin Cancer Res. 2020;26:54–60.
15. Bhattacharjee R, Zhao Q, Mims AS, Vasu S, Bebeboni GR, Larkin K, et al. Selinexor in combination with decitabine in patients with acute myeloid leukemia: results from a phase 1 study. Leuk Lymphoma. 2020;61:387–96.
16. Kalakonda N, Maerevoet M, Cavalllo F, Follows G, Goy A, Vermaat JS, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. Lancet Haematol. 2020;7:e511–e522.
17. Grocki S, Simonova M, Spicka I, Pour L, Kriachok I, Gavriatopoulou M, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet. 2020;396:1563–73.
18. Lee S, Mohan S, Knupp J, Chamoun K, Bai X, Ma X, et al. Updated overall survival of eltanexor for the treatment of patients with hypomethylating agent refractory myelodysplastic syndrome. J Clin Oncol. 2021;39:e19037–e19037.
19. Study of the Safety, Tolerability and Efficacy of KPT-8602 in Participants With Relapsed/Refractory Cancer Indications. https://clinicaltrials.gov/ct2/show/NCT02649790 (accessed 6 Mar 2022).
20. Chua CC, Roberts AW, Reynolds J, Fong CY, Ting SB, Salmon JM, et al. Chemotherapy and Venetoclax in Elderly Acute Myeloid Leukemia Trial (CAVEAT): A Phase Ib Dose-Escalation Study of Venetoclax Combined With Modified Intensive Chemotherapy. J Clin Oncol. 2020;38:3506–17.
21. Luedtke DA, Su Y, Liu S, Edwards H, Wang Y, Lin H, et al. Inhibition of XPO1 enhances cell death induced by ABT-199 in acute myeloid leukaemia via Mcl-1. J Cell Mol Med. 2018;22:6099–111.
22. Freeman SD, Virgo P, Couzens S, Grimwade D, Russell N, Hills RK, et al. Prognostic relevance of treatment response measured by flow cytometric residual disease detection in older patients with acute myeloid leukaemia. J Clin Oncol. 2013;31:4123–31.
23. Veltri L, Rezvani K, Oran B, Mehta R, Rondon G, Kebriaei P, et al. Allotransplants for Patients 65 Years or Older with High-Risk Acute Myeloid Leukemia. Blood Marrow Transplant. 2019;25:505–14.
ACKNOWLEDGEMENTS
The Authors thank the local and central data managers as well as the HOVON Data center Trial team and Karyopharm for free drug supply.

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.

FUNDING
Dutch Cancer Foundation for financial support; Karyopharm for financial support and delivery of drug for free.

CONFLICT 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.

ADDITIONAL INFORMATION
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41375-022-01657-3.

Correspondence and requests for materials should be addressed to J. J. W. M. Janssen.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.