Treatment of therapy-related acute myeloid leukemia and acute myeloid leukemia with myelodysplasia-related changes: a comparative analysis of higher-dose intensive 7+3 induction chemotherapy *versus* liposomal cytarabine and daunorubicin

Dimitrios Kotsos,[1] Patrycja Gradowska,[1,2] Sjoerd J.F. Hermans,[1] Thomas Pabst,[3,4] Johan Maertens,[5] Markus Manz,[4,6] Dimitri A. Breems,[7] Bjorn T. Gjertsen,[8] Soren Lehmann,[9] Bart J. Biemond,[10] H. Berna Beverloo,[1] Peter J.M. Valk,[1] Jeroen J.W.M. Janssen,[11] Gert Ossenkoppele,[10] Bob Löwenberg,[1] Gerwin Huls,[12] Marc H.G.P. Raaijmakers[1] and Jurjen Versluis[1]

[1]Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands; [2]HOVON Foundation, Rotterdam, the Netherlands; [3]Department of Medical Oncology, University Hospital, Inselspital, Bern, Switzerland; [4]Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland; [5]University Hospital Gasthuisberg, Leuven, Belgium; [6]University Hospital Zurich, Zurich, Switzerland; [7]ZAS, Cadix Hospital, Antwerp, Belgium; [8]Haukeland University Hospital, University of Bergen, Bergen, Norway; [9]Karolinska University Hospital, Stockholm, Sweden; [10]Amsterdam UMC, Cancer Center Amsterdam, University of Amsterdam, Amsterdam, the Netherlands; [11]Radboud University Medical Center, Nijmegen, the Netherlands and [12]University Medical Center, University Groningen, Groningen, the Netherlands

Correspondence: J. Versluis
j.versluis.1@erasmusmc.nl

Received: October 16, 2025.
Accepted: March 11, 2026.
Early view: March 26, 2026.

https://doi.org/10.3324/haematol.2025.300065

©2026 Ferrata Storti Foundation
Published under a CC BY-NC license

Abstract

Therapy-related acute myeloid leukemia (t-AML) and acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) are associated with poor outcomes. The liposomal formulation of cytarabine and daunorubicin (CPX-351) improved complete remission (CR) and CR with incomplete hematologic recovery (CRi) rates and overall survival compared with 'standard' induction (7+3) chemotherapy in a phase III trial for patients aged 60-75 years. However, 7+3 dosing varies among trials and in clinical practice and it remains unknown whether CPX-351 is superior to 7+3 double-induction regimens including intermediate-dose cytarabine, as the one employed in the HOVON-SAKK-Nordic clinical trials. To address this question, we conducted a *post-hoc* analysis on t-AML/AML-MRC patients aged ≥60 years enrolled in three HOVON-SAKK-Nordic trials, defined a subset of patients who met the eligibility criteria of the CPX-351 trial and compared their outcomes with those of the CPX-351 arm using reconstructed survival data. CR/CRi rates were higher in the higher-intensity 7+3 cohort (67.8%) compared with the CPX-351 cohort (47.7%) with similar median overall survival in the two cohorts (10.1 months *vs*. 8.9 months, respectively, hazard ratio=0.99; 95% confidence interval: 0.78-1.26, *P*=0.95). Thirty-day mortality (4.4% for higher-intensity 7+3 *vs*. 5.9% for CPX-351) and adverse events, including febrile neutropenia (61% for higher-intensity 7+3 *vs*. 68% for CPX-351), were comparable. The data suggest that obligatory double-induction may achieve outcomes similar to CPX-351 in these patients and provide a strong rationale for ongoing clinical trials comparing these regimens.

Introduction

Acute myeloid leukemia (AML) is a biologically and clinically heterogeneous neoplasm characterized by proliferation of hematopoietic stem cells with a median age of 68 years at diagnosis.[1] AML disease ontogeny is clinically defined as *de novo*, secondary (s-AML) from antecedent hematologic disorders, such as myelodysplastic syndrome (MDS),

or myeloproliferative neoplasm (MPN), or therapy-related (t-AML) after previous exposure to chemotherapy or radiotherapy.[2,3] Recent classification systems have refined AML ontogeny by adding a genetic definition termed AML with MDS-related gene mutations.[2,3] The incidence of AML with MDS-related gene mutations or t-AML increases with age, and is associated with lower response rates to treatment and shorter overall survival (OS).[4-10]

For five decades, the conventional intensive remission induction chemotherapy regimen for AML has consisted of a combination of cytarabine and an anthracycline (7+3). Although targeted treatments such as FLT3 inhibitors have been efficacious when added to 7+3,[11,12] these mutations are less frequent in the subset of AML with myelodysplasia-related changes (AML-MRC) or t-AML. CPX-351, a liposomal formulation of cytarabine and daunorubicin, has been approved for patients with AML-MRC or t-AML.[13,14] In the pivotal randomized trial, CPX-351 prolonged median OS by 3.4 months compared to 7+3 induction chemotherapy and was associated with higher complete remission (CR) and CR with incomplete hematologic recovery (CRi) rates after induction (48% *vs*. 33%, respectively).[15]

Nevertheless, the 7+3 regimen is not administered uniformly across clinical practice, with differences in the cumulative doses and scheduling of cytarabine and anthracyclines between cooperative groups and geographical regions. For example, the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and the Swiss Group for Clinical Cancer Research (SAKK) clinical trial protocols use double-induction, including intermediate-dose cytarabine (IDAC) in the second cycle, in contrast to the control arm of the CPX-351 trial. These differences in intensity may partly explain the lower post-induction CR/CRi rates reported in the CPX-351 trial compared with those observed in the HOVON-SAKK-Nordic trials, in which CR/CRi rates for elderly patients were ~66%.[16]

The objective of our study was to evaluate key clinical features and treatment outcomes in older and intensively-treated patients with t-AML and AML-MRC. Moreover, given the lower dose of cytarabine in the control arm of the pivotal CPX-351 trial compared with the standard induction regimen of the HOVON-SAKK-Nordic trials, we retrospectively analyzed the response rates and OS of patients with AML-MRC and t-AML treated in HOVON-SAKK-Nordic protocols and compared them with patients treated with CPX-351 in the pivotal phase III trial.

Methods

Study population

Patients with newly diagnosed and previously untreated t-AML or AML-MRC aged 60 years and older who were treated between 2010 and 2017 with intensive chemotherapy in the HOVON-SAKK 102/30-09, 103/30-10 and 132/30-13 clinical trials were included.[16-18] Patients with high-risk MDS and a blast count between 10-19% were also included in these trials. s-AML was defined as having a documented diagnosis of prior MDS, chronic myelomonocytic leukemia or MPN >3 months prior to the diagnosis of AML. For t-AML, prior exposure to chemotherapy or radiotherapy for an unrelated disease was considered. *De novo* AML with MDS-related cytogenetics was defined according to the 2008 World Health Organization (WHO) criteria.[19] MDS-related gene mutations were defined as the presence of at least one mutation in *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR,* or *STAG2* genes.[20]

A total of 2,399 patients were enrolled in HOVON-SAKK 102/30-09, 103/30-10, and 132/30-13 clinical trials, of whom 1,223 were excluded because of age <60 years. After excluding patients with *de novo* AML without MDS-related cytogenetics, 428 patients were included in the final analysis and constituted the t-AML/AML-MRC cohort (Figure 1). This broader cohort was used to identify factors impacting OS in these older patients with t-AML and AML-MRC. Risk stratification in this cohort was performed according to the 2022 European LeukemiaNet (ELN2022) classification.[3]

To enable a comparison with the CPX-351 phase III trial, the inclusion and exclusion criteria of the CPX-351 phase III trial[14] were applied to patients in the three HOVON-SAKK-Nordic trials to obtain a similar 7+3 cohort (HOVON 7+3 cohort) (Figure 1). Patients with high-risk MDS with increased blast counts were included per eligibility criteria. Patients were excluded if they were aged >75 years, had a prior diagnosis of MPN, or if central nervous system (CNS) AML was present at diagnosis. Other clinical inclusion and exclusion criteria were similar across HOVON-SAKK-Nordic trials and the CPX-351 trial. Additionally, only patients assigned to the control arms of the three HOVON-SAKK-Nordic clinical trials were considered for comparison. FLT3 inhibitors were not used in the HOVON-SAKK-Nordic clinical trials as part of protocol treatment. Similar to the CPX-351 trial, responses in the HOVON-SAKK-Nordic trials were defined using the Revised International Working Group Criteria[21] and cytogenetic risk was stratified according to the National Comprehensive Cancer Network (NCCN) classification.[22] The original HOVON-SAKK-Nordic trials were approved by the institutional review boards and ethics committees of all participating centers and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Induction protocols

Patients aged ≥60 years enrolled in the HOVON-SAKK 102/30-09, 103/30-10, and 132/30-13 trials received double-induction chemotherapy per protocol, consisting of cytarabine at 200 mg/m^2/day for 7 days and an anthracycline for 3 days (either daunorubicin 60 mg/m^2/day or idarubicin at 12 mg/m^2/day) in the first cycle. The second cycle in HO102/30-09 consisted of IDAC with 1,000 mg/m^2

twice daily for 6 days and amsacrine 120 mg/m^2 for 3 days, whereas HO103/30-10 and HO132/30-13 used IDAC only in the control arm (1,000 mg/m^2 cytarabine twice daily for 6 days).[16-18] Patients in the experimental arm of the pivotal trial received CPX-351 with 100 mg/m^2 of cytarabine and 44 mg/m^2 of daunorubicin for 3 days and refractory patients received a second induction cycle with the same dose for 2 days. Patients assigned to the control arm received one induction cycle with cytarabine at 100 mg/m^2/day for 7 days, combined with daunorubicin at 60 mg/m^2 for 3 days. A second cycle consisting of cytarabine at 100 mg/m^2/day for 5 days with daunorubicin at 60 mg/m^2 for 2 days was given to patients with refractory disease.[14]

Statistical analysis

The primary endpoint was OS, and secondary endpoints included CR/CRi rates within two induction cycles, frequency of adverse events, early mortality rates, time to hematologic recovery, and duration of hospital stay. These endpoints were compared between the selected HOVON 7+3 cohort and the CPX-351 trial patients in the experimental arm. OS was defined as the time from randomization to death

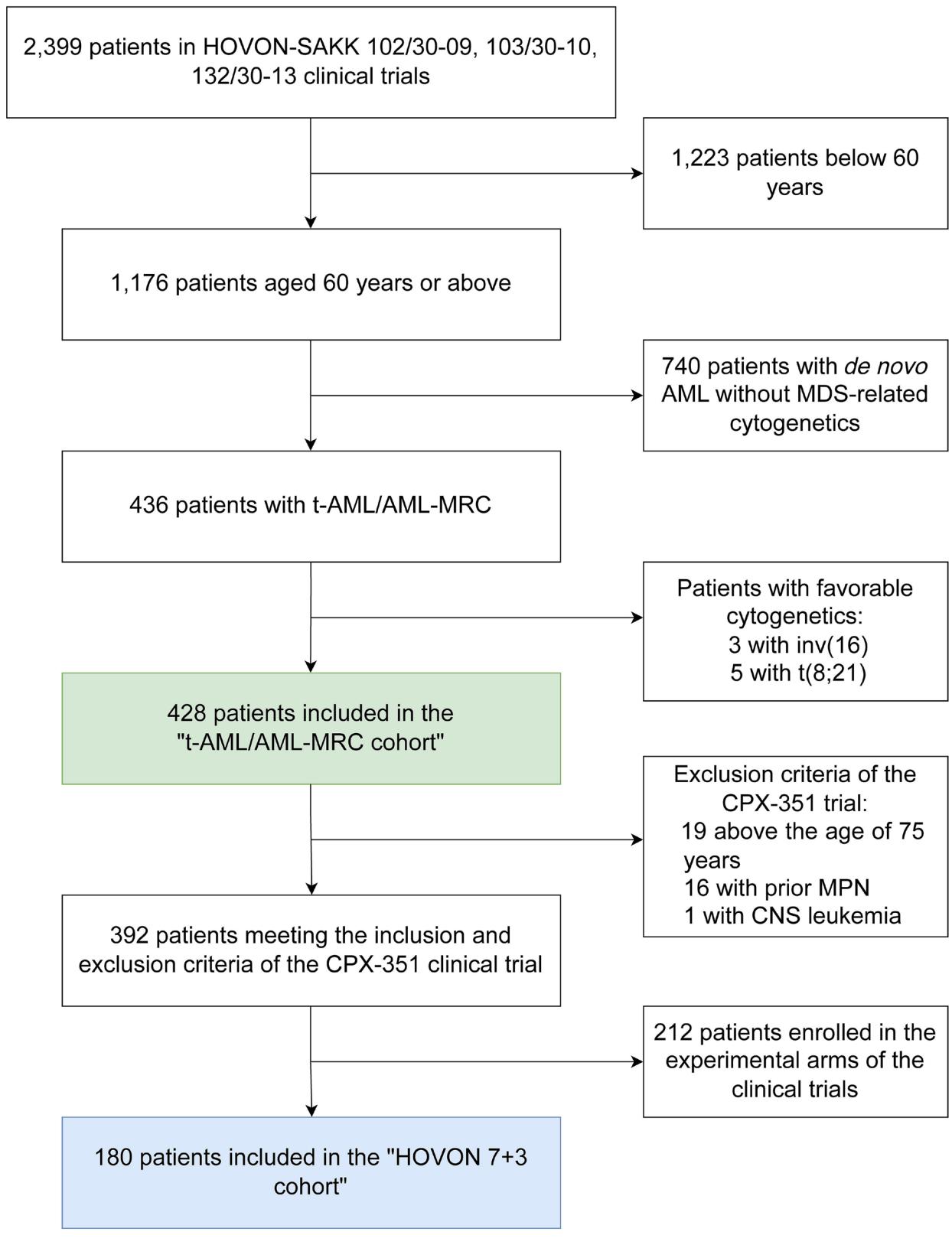


Figure 1. Flow diagram of the selection of patients in the two cohorts of this study. HOVON-SAKK: Dutch-Belgian Hemato-Oncology Cooperative Group and the Swiss Group for Clinical Cancer Research; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; t-AML: therapy-related acute myeloid leukemia; AML-MRC: acute myeloid leukemia with myelodysplasia-related changes; CPX-351: liposomal formulation of cytarabine and daunorubicin; MPN: myeloproliferative neoplasm; CNS: central nervous system; 7+3: 7 days of cytarabine and 3 days of an anthracycline.

from any cause. Continuous variables were described using the mean and standard deviation (SD) or the median and the interquartile range (IQR), in the case of not normally distributed data. Continuous data were compared using the Student *t* test or Mann-Whitney U test, in case of not normally distributed data. Categorical variables were summarized using counts and percentages and were compared using the χ^2 test, or the Fisher exact test, when required. Survival curves were estimated using the Kaplan-Meier method and the log-rank test was applied for comparison. The reverse Kaplan-Meier method was used to calculate the median follow-up. Survival estimates of the CPX-351 arm were regenerated using the number of patients at risk and the number of censored patients at each timepoint from the original publication.[15]

A multivariable Cox proportional hazards regression model was developed for the t-AML/AML-MRC cohort using a backward stepwise approach involving variables with a Cox *P* value <0.1 in univariable analysis. To account for the inherent heterogeneity of the three different HOVON-SAKK-Nordic trials, trial and treatment arm ("standard" or "experimental") were added in the multivariable model as stratifying factors. Allogeneic hematopoietic cell transplantation (allo-HCT) was considered as a time-varying variable.

Results were considered statistically significant when the two-sided *P* value was <0.05 and confidence intervals (CI) were computed with 95% coverage. Statistical analyses were performed using R version 4.2.2 or higher.

Results

Characteristics and outcomes of all t-AML and AML-MRC patients

In the t-AML/AML-MRC cohort, the median age of patients was 66 years (IQR, 63-70) and 272 (63.6%) were male. The most frequent disease subtype was *de novo* AML with MDS-related cytogenetics (N=232, 54.2%), followed by s-AML with antecedent hematologic disorders (N=136, 31.8%), and t-AML (N=60, 14.0%) (*Online Supplementary Table S1*). Next-generation sequencing information was available for 327 patients; *TP53* was the most frequently mutated gene (N=128, 39.1%) (Figure 2). MDS-related

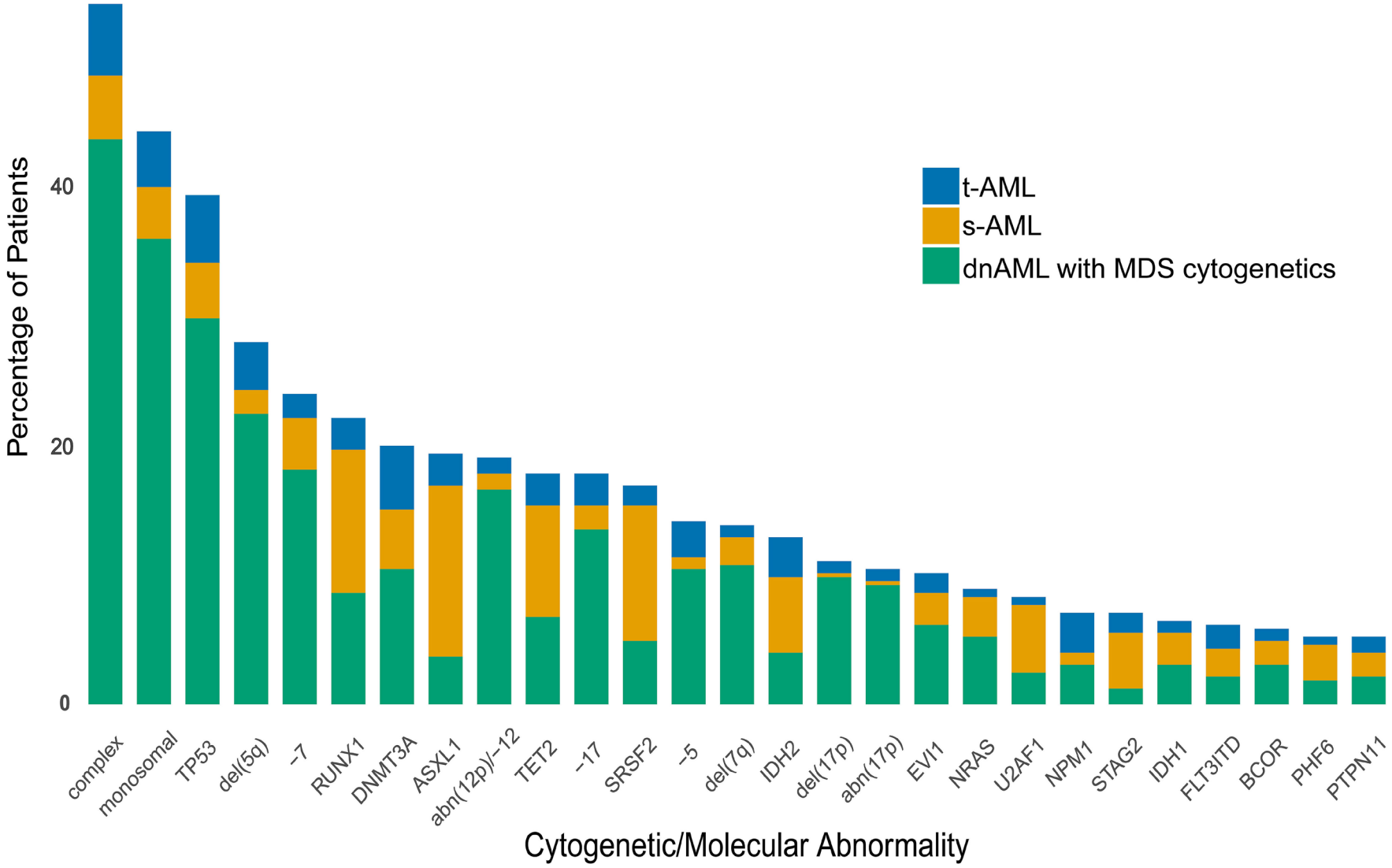


Figure 2. Driver events found in 327 out of 428 patients with newly diagnosed therapy-related acute myeloid leukemia or acute myeloid leukemia with myelodysplasia-related changes. Each bar represents a driver lesion, including gene mutations and chromosomal abnormalities. t-AML: therapy-related acute myeloid leukemia; s-AML: secondary acute myeloid leukemia; dnAML: *de novo* acute myeloid leukemia; MDS: myelodysplastic syndrome.

gene mutations were found in 45.0% (N=147) of patients, with *RUNX1* (N=72, 22.0%), *ASXL1* (N=63, 19.3%), and *SRSF2* (N=55, 16.8%) being the most frequent. Consequently, the majority of patients were assigned to the ELN2022 adverse-risk subgroup (87.8%). A total of 223 (52%) patients obtained CR/CRi after the first induction cycle, and this number increased to 276 (64%) after two induction cycles. The median follow-up was 68.0 months (IQR, 54.8-88.4). OS was poor in the entire t-AML/AML-MRC cohort, with a median of 8.9 months (95% CI: 8.0-10.1). *TP53* mutation, adverse-risk cytogenetics, higher baseline WHO score, and white blood cell count were associated with worse OS after adjustment for covariates and stratification for trial and treatment arm (*Online Supplementary Tables S2* and *S3*). Focusing on patients who obtained CR/CRi, allo-HCT recipients had significantly better OS compared with patients who did not receive allo-HCT as consolidation treatment (hazard ratio [HR] = 0.64; 95% CI: 0.46-0.89, *P*=0.008) (*Online Supplementary Table S4*).

Higher-intensity 7+3 induction *versus* CPX-351

Patients' characteristics

A total of 180 t-AML/AML-MRC patients were identified who fulfilled the key eligibility criteria of the CPX-351 trial,[14] excluding patients aged >75 years, patients with prior MPN or CNS leukemia, and patients assigned to the experimental treatment arms (HOVON 7+3 cohort) (Figure 1). These HOVON 7+3 patients were compared with patients enrolled in the CPX-351 arm of the phase III trial (Table 1). HOVON 7+3 patients were significantly younger than CPX-351 trial patients (mean age 66.1 *vs.* 67.8 years, *P*<0.001) and more

Table 1. Demographic and baseline characteristics of the HOVON 7+3 cohort and the CPX-351 arm of the phase III clinical trial of the liposomal drug.

Variable	HOVON 7+3	CPX-351	*P*
N of patients	180	153	-
Age, years, mean (SD)	66.1 (4.1)	67.8 (4.2)	<0.001
Age group 60-69 years, N (%) ≥70 years, N (%)	180 139 (77.2) 41 (22.8)	153 96 (62.7) 57 (37.3)	0.005
Sex Male, N (%)	180 108 (60.0)	153 94 (61.4)	0.82
WHO PS 0-1, N (%) 2, N (%)	177 167 (94.4) 10 (5.6)	153 138 (90.2) 15 (9.8)	0.21
AML subtype t-AML, N (%) s-AML, N (%) s-AML with antecedent MDS, N (%) Without prior HMA, N (%) With prior HMA, N (%) s-AML with antecedent CMML, N (%) dnAML with MDS cytogenetics, N (%)	180 30 (16.7) 46 (25.6) 45 (25.0) 45 (25.0) 0 (0.0) 1 (0.6) 104 (57.7)	153 30 (19.6) 82 (53.6) 71 (46.4) 21 (13.7) 50 (32.7) 11 (7.2) 41 (26.8)	<0.001
WBC count <20 × 10^9/L, N (%) ≥20 × 10^9/L, N (%)	179 161 (89.9) 18 (10.1)	153 131 (85.6) 22 (14.4)	0.24
NCCN risk group Favorable/intermediate, N (%) Adverse, N (%)	176 57 (32.4) 119 (67.6)	143 71 (49.7) 72 (50.3)	0.002
FLT3 mutation Absent, N (%) Present, N (%)	140 129 (92.1) 11 (7.9)	138 116 (84.1) 22 (15.9)	0.04
Prior anthracycline exposure, N (%)	6 (3.3)	6 (3.9)	0.78
Allo-HCT Yes, N (%)	180 67 (37.2)	153 53 (34.6)	0.65

HOVON: Dutch-Belgian Hemato-Oncology Cooperative Group; 7+3: 7 days of cytarabine and 3 days of an anthracycline; CPX-351: liposomal formulation of cytarabine and daunorubicin; SD: standard deviation; WHO PS: World Health Organization performance status; AML: acute myeloid leukemia; t-AML: therapy-related acute myeloid leukemia; s-AML: secondary acute myeloid leukemia; MDS: myelodysplastic syndrome; HMA: hypomethylating agents; CMML: chronic myelomonocytic leukemia; dnAML: *de novo* acute myeloid leukemia; WBC count: white blood cell count; NCCN: National Comprehensive Cancer Network; allo-HCT: allogeneic hematopoietic cell transplantation.

frequently classified as having *de novo* AML with MDS cytogenetics (57.7% *vs*. 26.8% for the CPX-351 arm), whereas s-AML was mostly found in the CPX-351 cohort (53.6% *vs*. 25.6% for the HOVON 7+3 cohort). Adverse cytogenetic risk according to NCCN criteria was more frequent in the HOVON 7+3 cohort than in the CPX-351 cohort (67.6% *vs*. 50.3%, respectively).

Induction treatment efficacy

A total of 130/180 (72.2%) patients in the HOVON 7+3 cohort received two cycles of 7+3 induction chemotherapy, which was a higher percentage than in the CPX-351 arm (48/153, 31.4%) and the control 7+3 arm (51/156, 32.7%). First, we compared CR/CRi rates after one induction cycle between the two cohorts. After the first induction cycle, the CR/CRi rate was 54.4% (98/180) in the HOVON 7+3 cohort, compared with 37.9% (58/153) in the CPX-351 cohort and 21.7% (34/156) in the 7+3 arm of the CPX-351 study. After the second cycle with IDAC, remission rates further increased, with 122/180 patients (67.8%) in the HOVON 7+3 cohort achieving CR/CRi and 111/180 (61.7%) achieving CR. In contrast, there were lower rates in the CPX-351 arm and the 7+3 arm of the CPX-351 study (CR/CRi 73/153, 47.7% and CR 57/153, 37.3% for the CPX-351 arm, CR/CRi 52/156,

Table 2. Best response rates after induction of the HOVON 7+3 cohort and the CPX-351 arm of the phase III clinical trial of the liposomal drug.

Response	HOVON 7+3	CPX-351	*P*
N of patients	180	153	
CR/CRi, N (%)	122 (67.8)	73 (47.7)	<0.001
CR, N (%)	111 (61.7)	57 (37.3)	<0.001
Age group			
N in 60-69-year age group	139	96	
CR/CRi, N (%)	98 (70.5)	48 (50.0)	0.002
CR, N (%)	90 (64.7)	38 (39.6)	<0.001
N in ≥70-year age group	41	57	
CR/CRi, N (%)	24 (58.5)	25 (43.9)	0.22
CR, N (%)	21 (51.2)	19 (33.3)	0.10
AML subtype			
N with t-AML	30	30	
CR/CRi, N (%)	20 (66.7)	14 (46.7)	0.19
CR, N (%)	19 (63.3)	11 (36.7)	0.07
N with s-AML	46	82	
s-AML with antecedent MDS (no prior HMA)	45	21	
CR/CRi, N (%)	31 (68.9)	14 (66.7)	1.00
CR, N (%)	25 (55.6)	12 (57.1)	1.00
s-AML with antecedent MDS (with prior HMA)	0	50	
CR/CRi, N (%)	0 (0.00)	18 (36.0)	-
CR, N (%)	0 (0.00)	13 (26.0)	-
s-AML with antecedent CMML	1	11	
CR/CRi, N (%)	1 (100.0)	4 (36.4)	0.42
CR, N (%)	1 (100.0)	2 (18.2)	0.25
N with dnAML with MDS cytogenetics	104	41	
CR/CRi, N (%)	70 (67.3)	23 (56.1)	0.25
CR, N (%)	66 (63.5)	19 (46.3)	0.06
Cytogenetic risk at screening by NCCN			
N with favorable/intermediate risk	57	71	
CR/CRi, N (%)	47 (82.5)	39 (54.9)	0.001
CR, N (%)	42 (73.7)	30 (42.3)	<0.001
N with adverse risk	119	72	
CR/CRi, N (%)	72 (60.5)	31 (43.1)	0.02
CR, N (%)	66 (55.5)	25 (34.7)	0.007
FLT3 mutation status			
N with *FLT3* mutation	11	22	
CR/CRi, N (%)	7 (63.6)	15 (68.2)	1.00
CR, N (%)	6 (54.5)	12 (54.5)	1.00

HOVON: Dutch-Belgian Hemato-Oncology Cooperative Group; 7+3: 7 days of cytarabine and 3 days of an anthracycline; CPX-351: liposomal formulation of cytarabine and daunorubicin; CR: complete remission; CRi: complete remission with incomplete hematologic recovery; AML: acute myeloid leukemia; t-AML: therapy-related acute myeloid leukemia; s-AML: secondary acute myeloid leukemia; MDS: myelodysplastic syndrome; HMA: hypomethylating agents; CMML: chronic myelomonocytic leukemia; dnAML: *de novo* acute myeloid leukemia; NCCN: National Comprehensive Cancer Network.

33.3% and CR 40/156, 25.6% for the 7+3 arm) (Table 2). Higher remission rates were consistently observed in the HOVON 7+3 cohort across the cytogenetic groups per NCCN and age groups, whereas remission rates were similar in treatment-naïve s-AML patients (Table 2).

The median follow-up was 67.3 months (IQR, 54.8-90.3) in the HOVON 7+3 cohort and 60.9 months (IQR, 60.1-63.0) in the CPX-351 cohort. After regenerating and superimposing the CPX-351 survival curve onto the HOVON 7+3 survival curve, OS was not significantly different with a median OS of 8.9 months (95% CI: 7.1-11.9) in the CPX-351 cohort *versus* 10.1 months (95% CI: 9.1-13.4) in the HOVON 7+3 cohort (HR=0.99; 95% CI: 0.78-1.26, *P*=0.95) (Figure 3). Since the CPX-351 trial included patients with prior exposure to hypomethylating agents, we then focused on the subset of patients who had not received prior hypomethylating agents. CPX-351 and HOVON 7+3 cohorts were again associated with similar OS (HR=0.84; 95% CI: 0.63-1.11, *P*=0.22) (Figure 4A). Similarly, no significant difference in OS was observed across the two age groups, 60-69 and 70-75 years (Figure 4B, C), as well as within t-AML, s-AML, and *de novo* AML with MDS cytogenetics subtypes (*Online Supplementary Figures S1-S3).*

Allo-HCT in CR/CRi was applied comparably in the HOVON 7+3 and CPX-351 cohorts (66/122, 54.1% *vs*. 41/73, 56.2%, *P*=0.88) (*Online Supplementary Figure S4A*). Within this selected subgroup of CR/CRi patients who proceeded to allo-HCT, OS was significantly longer for patients who received CPX-351 as induction therapy compared with HOVON 7+3 (median OS: not reached *vs*. 14.4 months, respectively, *P*=0.007) (*Online Supplementary Figure S4B*).

Since *TP53* was the dominant mutation in the HOVON 7+3 cohort (*Online Supplementary Figure S5*), we specifically analyzed outcomes of this subset of patients. This revealed that the CR/CRi rate was 56.9% in the HOVON 7+3 cohort, with a median OS of 8.0 months (95% CI: 5.8-9.6). In a separate analysis of *TP53*-mutated patients of the CPX-351 trial, a CR/CRi rate of 33.3% was observed with a median OS of 5.0 months (95% CI: 2.7-7.6).[23] In patients with MDS-related gene mutations without mutated *TP53*, HOVON 7+3 patients had a median OS of 15.8 months (95% CI: 10.6-30.8). In comparison, the CPX-351 pivotal trial reported a median OS of 9.7 months (95% CI: 6.2-13.7) for the corresponding subgroup.[24]

Induction treatment toxicity

Early mortality rates in the CPX-351 and HOVON 7+3 cohorts were comparable, with a 30-day mortality of 5.9% for the CPX-351 cohort *versus* 4.4% for the HOVON 7+3 cohort, and a 60-day mortality of 13.7% for the CPX-351 cohort *versus* 11.7% for the HOVON 7+3 cohort. The duration of hospital stay was comparable for both the initial and second cycles of induction (cycle 1: 28 days for the CPX-351 cohort *vs*. 29 days for the HOVON 7+3 cohort; cycle 2: 28 days for the CPX-351 cohort *vs*. 28 days for the HOVON 7+3 cohort).[25] For patients who reached CR/CRi, the median time until neutrophil recovery (≥500/μL) or platelet recovery (≥50,000/μL) was longer for CPX-351 patients compared with HOVON 7+3 patients (neutrophil recovery cycle 1: 35 *vs*. 26 days, cycle 2: 35 *vs*. 25; respectively, platelet recovery cycle 1: 37 *vs*. 25 days and cycle 2: 35 *vs*. 33 days, respectively). The most common grade 3 to 5 adverse events were observed similarly in the CPX-351 and HOVON 7+3 cohorts (febrile neutropenia: 68% *vs*. 61%, respectively; pneumonia: 20%

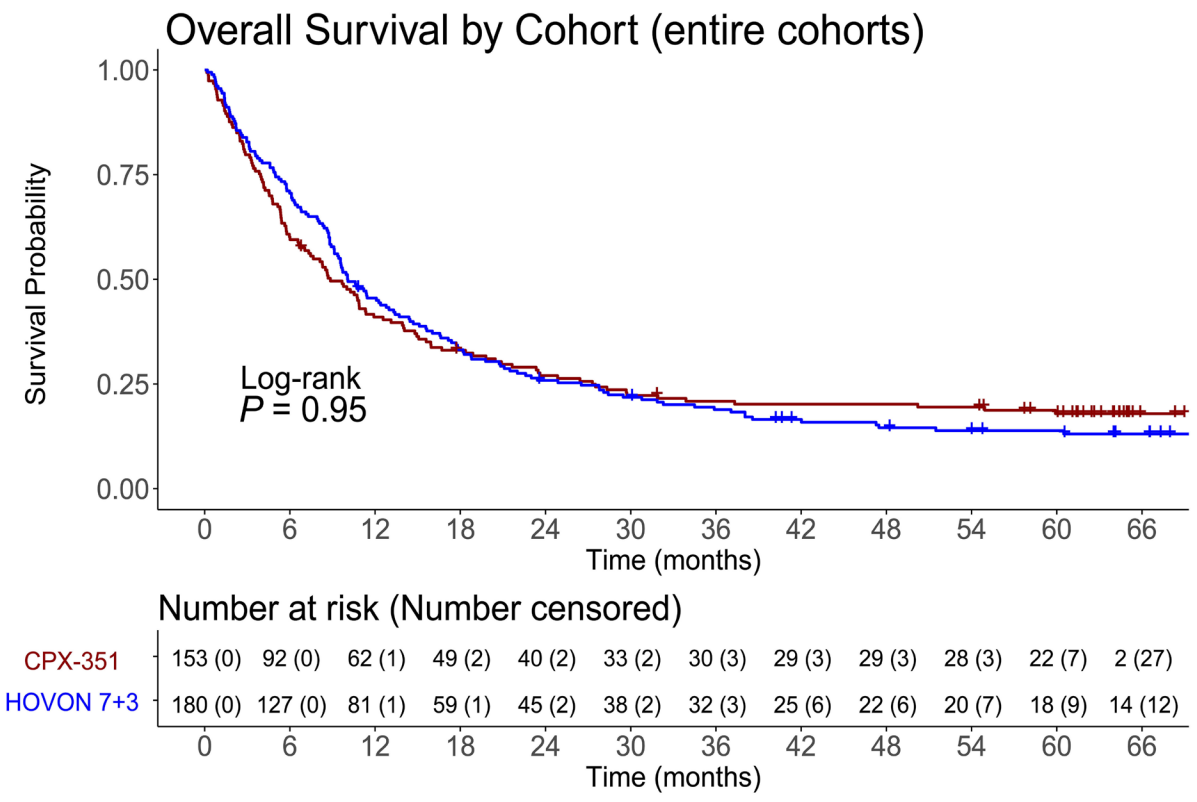


Figure 3. Overall survival of the entire CPX-351 arm of the phase III clinical trial *versus* the selected HOVON 7+3 cohort. CPX-351: liposomal formulation of cytarabine and daunorubicin; 7+3: 7 days of cytarabine and 3 days of an anthracycline.

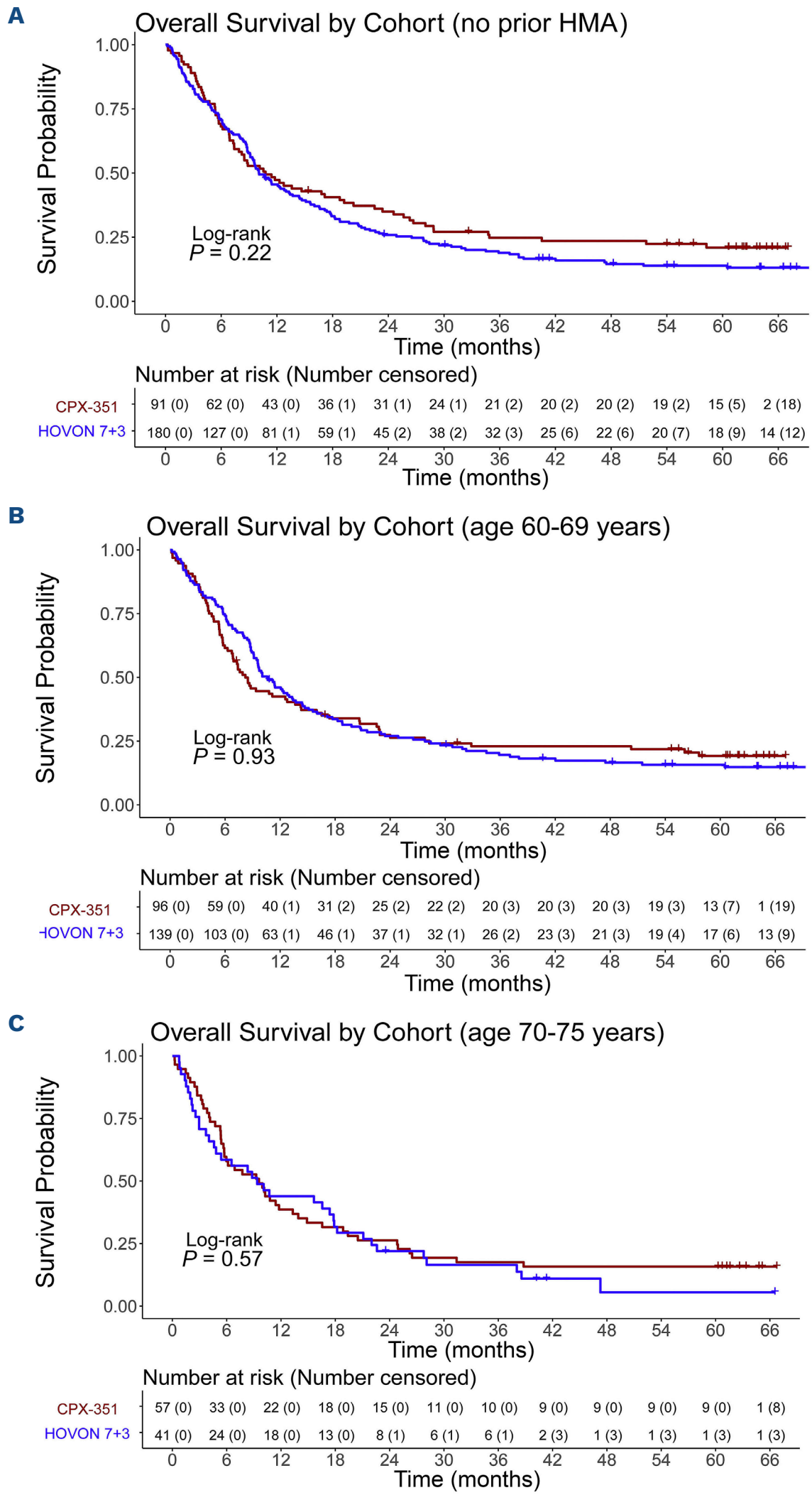


Figure 4. Overall survival in subgroups of the CPX-351 arm of the phase III clinical trial *versus* the selected HOVON 7+3 cohort. (A) Overall survival of the patients without prior exposure to hypomethylating agents of the CPX-351 arm of the phase III clinical trial *versus* the selected HOVON 7+3 cohort (all patients were treatment-naïve). (B) Overall survival of the 60-69-year age group of the CPX-351 arm of the phase III clinical trial *versus* the 60-69-year age group of the selected HOVON 7+3 cohort. (C) Overall survival of the 70-75-year age group of the CPX-351 arm of the phase III clinical trial *versus* the 70-75-year age group of the selected HOVON 7+3 cohort. HMA: hypomethylating agents; CPX-351: liposomal formulation of cytarabine and daunorubicin; 7+3: 7 days of cytarabine and 3 days of an anthracycline.

vs. 23%, respectively), while hypoxia was more frequent in the CPX-351 cohort (13% *vs*. 3%, respectively).

Discussion

Outcomes of patients with t-AML and AML-MRC remain poor despite recent advancements in the induction treatment paradigm for AML. CPX-351 has demonstrated improved OS compared with 7+3 in the population of patients aged 60-75 years, but CR/CRi rates were relatively low, particularly for patients enrolled in the control 7+3 arm of the pivotal trial.[14] The obligatory double-induction 7+3 regimen used within the HOVON-SAKK-Nordic trials included IDAC in the second cycle, prompting a comparison between patients with t-AML or AML-MRC aged 60-75 years treated in these trials and patients enrolled in the CPX-351 pivotal trial. These trials had similar key eligibility criteria and used similar response definitions. We observed higher CR/CRi rates for HOVON-SAKK-Nordic patients, while OS was similar in the HOVON 7+3 and CPX-351 cohorts. Additionally, the rate of allo-HCT, early mortality and toxicity were similar in the two cohorts. These data indicate that induction regimens incorporating IDAC, as used within HOVON-SAKK-Nordic trials, might benefit these patients and highlight the need for further investigation into the comparative efficacy of CPX-351 and an obligatory double-induction regimen; indeed, a randomized clinical trial on this aspect is currently underway (NCT03897127).

The optimal dosing of 7+3 has been extensively studied in the last decades.[26-28] The obligatory double-induction regimen used in recent HOVON-SAKK-Nordic trials differs from the 7+3 regimen used in the control arm of the CPX-351 trial with double doses of cytarabine (200 mg/m^2/day *vs*. 100 mg/m^2/day, respectively) in the first cycle. However, these doses are generally considered clinically equivalent.[29] More importantly, all eligible HOVON-SAKK-Nordic patients were scheduled for a second IDAC induction cycle with 2,000 mg/m^2/day of cytarabine, whereas the CPX-351 trial protocol only scheduled a second cycle of 5+2, including 100 mg/m^2/day cytarabine, for refractory patients. In these selected trial populations, the CR/CRi rates after the first cycle and within two cycles were consistently higher in the HOVON 7+3 cohort than in the 7+3 arm used in the CPX-351 trial. Cytarabine dosing for patients with AML has been previously studied in randomized clinical trials. A previous HOVON-SAKK trial showed that intensification of cytarabine dosing beyond intermediate levels did not provide any therapeutic benefit and instead led to increased toxicity.[30] Similarly, Röllig *et al*. reported higher CR rates after induction with intermediate-dose cytarabine for 4 days combined with mitoxantrone compared with 100 mg/m^2/day cytarabine for 7 days and daunorubicin, while early mortality was similar.[31] In addition, double-induction with 7+3-like regimens in elderly patients has been associated with estimated CR/CRi rates of 65-70% confirming the results observed in this selected t-AML and AML-MRC population.[16,32,33] Building on these observations and our findings, the control arm of the pivotal CPX-351 trial has been compared with real-world IDAC in a propensity score analysis, in which significantly higher CR rates and longer OS were observed with IDAC, highlighting the benefit of higher doses of cytarabine during induction and consolidation for these high-risk AML patients.[34]

There is heterogeneity of response rates documented by real-world CPX-351 studies. Some of these studies show CR/CRi rates of 60-70%,[35,36] whereas others report CR/CRi rates of 47-53% in high-risk t-AML and AML-MRC patients.[37,38] Additionally, therapy-related morbidity and mortality is a major concern in the elderly AML subgroup. The HOVON 7+3 and CPX-351 cohorts were comparable regarding 30-day and 60-day mortality, duration of hospitalization per induction cycle, and most frequent adverse events (febrile neutropenia and pneumonia), while days to hematologic recovery were shorter with the higher-intensity 7+3 regimen. Real-world studies identified similar rates of toxicity,[35,37-39] although gastrointestinal events are reported to be less frequent and of lower grade in the CPX-351 setting.[40] Although OS was similar in the two cohorts in our study, the potential for lower gastrointestinal toxicity with CPX-351 observed in real-world reports may be considered when selecting therapy, particularly in patients at higher risk of treatment-related morbidity. These observations from real-world use of CPX-351 again warrant a follow-up trial comparing CPX-351 with higher doses of cytarabine (NCT03897127).

Overall, the survival of elderly patients with t-AML/AML-MRC remains poor with a median OS of less than 12 months, highlighting the significant unmet medical need in the management of these patients. In our t-AML/AML-MRC cohort, adverse cytogenetic risk and *TP53* mutations were present at a high incidence and associated with worse OS, in accordance with the findings of previous studies.[9,14,41] This confirms the known challenges of treating t-AML and AML-MRC in patients with *TP53* mutations, a subgroup with a dismal prognosis and resistance to chemotherapy-based therapies.[42-44] A *post-hoc* analysis of the phase III trial showed that CPX-351 also did not substantially improve the short OS associated with *TP53*-mutated AML.[23] Recent studies indicate that the benefit of CPX-351 over standard chemotherapy is driven by the improved OS of patients with MDS-related gene mutations, while those harboring high-risk cytogenetics or *TP53* alterations derive limited benefit.[24,45] The HOVON 7+3 cohort of patients with MDS-related gene mutations appeared to have relatively favorable survival, although a formal comparison to the CPX-351 cohort with MDS-related gene mutations was not possible.[24]

Allo-HCT remains the ultimate path to cure for these high-risk patients. In our total cohort, allo-HCT was asso-

ciated with a 36% reduction in risk of death compared with non-transplanted patients with CR/CRi after induction. In the subset of patients with a CR/CRi who received allo-HCT, patients given CPX-351 induction had a better post-transplant OS compared with those treated with HOVON 7+3. Favorable OS rates have also been previously observed in real-world CPX-351 studies that reported a high rate of allo-HCT.[35,36,38,46] Ultimately, allo-HCT remains the cornerstone of curative treatment for t-AML and AML-MRC. Thus, the primary objective of intensive induction therapy is to achieve a (deep) CR with minimal toxicity, especially in older patients, allowing them to proceed to transplantation.

Our study has some limitations. Patients in the HOVON 7+3 cohort were treatment-naïve, while the CPX-351 trial also enrolled patients with prior exposure to hypomethylating agents. However, a subgroup analysis did not show a significant survival difference when the subset of CPX-351 trial patients who had no prior exposure to hypomethylating agents was compared with the HOVON 7+3 cohort. Secondly, the actual data of the CPX-351 trial were not available in order to perform a propensity score matched analysis or multivariable analysis given the inherent differences in baseline characteristics. Although we cannot fully adjust for potential confounders and this is a comparison across trials, we were able to stratify by clinically relevant subgroups (age groups, AML subtype). Moreover, both cohorts consisted of patients enrolled in clinical trials and were selected using similar strict inclusion and exclusion criteria. Therefore, the cohorts were likely comparable with regards to frailty and comorbidities, as shown by the similar WHO performance scores and age. Additionally, the trials were conducted during the same time period (HOVON-SAKK-Nordic trials 2010-2017 and the CPX-351 trial 2012-2014), minimizing potential confounding by treatment trends in different decades. Despite harmonizing key predictors, these results should be interpreted with caution since residual differences in baseline disease biology and ontogeny, and variations in response evaluation timing may have lowered the CR/CRi rates in the CPX-351 arm. Additionally, details of salvage treatment in the CPX-351 trial are not available which might explain why OS is similar, despite different first CR/CRi rates between the CPX-351 arm and the HOVON 7+3 cohort.

In conclusion, in older patients with t-AML or AML-MRC, OS with CPX-351 induction treatment was not significantly different from that with the obligatory double-induction treatment that included a second cycle with IDAC. These results were similarly observed in different subgroups, whereas CR/CRi rates were higher with the HOVON 7+3 regimen. Toxicity analysis also indicated comparable outcomes, with fewer days to hematologic recovery with the HOVON 7+3 regimen. Further randomized studies, including the ongoing trial (NCT03897127), are needed to clarify whether CPX-351 achieves better outcomes than the more intensive 7+3 regimen, and to identify possible molecular features or populations of patients who might benefit from CPX-351. Importantly, allo-HCT remains the most effective curative strategy for these patients, and should be offered to as many t-AML/AML-MRC patients as possible.

Disclosures

No conflicts of interest to disclose.

Contributions

DK performed the formal analysis, curated data, was responsible for visualization, wrote the first draft of the manuscript and contributed to the manuscript review and editing. PG contributed to data curation and manuscript review and editing. SJFH, TP, JM, MM, DAB, BTG, SL, BJB, HBB, PJMV, JJWMJ, GO, and BL contributed to manuscript review and editing. GH contributed to writing the original draft and manuscript review and editing. MHGPR contributed to conceptualization, writing the original draft, and manuscript review and editing. JV supervised the study, contributed to conceptualization, data curation, visualization, writing the original draft, and manuscript review and editing. All authors approved the final version of the manuscript.

Funding

For this scientific work DK was supported by the Onassis Foundation – Scholarship ID: F ZS 026-1/2022-2023 and the Bodossaki Foundation. The publication of this article was supported by the Onassis Foundation Scholars' Association.

Data-sharing statement

These data are from clinical trials in which patients could be traceable based on clinical data. Upon request, de-identified data are available.

References

1. DiNardo CD, Erba HP, Freeman SD, Wei AH. Acute myeloid leukaemia. Lancet. 2023;401(10393):2073-2086.
2. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
3. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377.
4. McNerney ME, Godley LA, Le Beau MM. Therapy-related myeloid neoplasms: when genetics and environment collide. Nat Rev Cancer. 2017;17(9):513-527.
5. Østgård LSG, Medeiros BC, Sengeløv H, et al. Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: a national population-based cohort study. J

Clin Oncol. 2015;33(31):3641-3649.
6. Hulegårdh E, Nilsson C, Lazarevic V, et al. Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: a report from the Swedish Acute Leukemia Registry. Am J Hematol. 2015;90(3):208-214.
7. Kayser S, Döhner K, Krauter J, et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood. 2011;117(7):2137-2145.
8. Samra B, Richard-Carpentier G, Kadia TM, et al. Characteristics and outcomes of patients with therapy-related acute myeloid leukemia with normal karyotype. Blood Cancer J. 2020;10(5):47.
9. Versluis J, Metzner M, Wang A, et al. Risk stratification in older intensively treated patients with AML. J Clin Oncol. 2024;42(34):4084-4094.
10. Tsai XCH, Sun KJ, Lo MY, et al. Poor prognostic implications of myelodysplasia-related mutations in both older and younger patients with de novo AML. Blood Cancer J. 2023;13(1):4.
11. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454-464.
12. Erba HP, Montesinos P, Kim HJ, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023;401(10388):1571-1583.
13. Lancet JE, Cortes JE, Hogge DE, et al. Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/daunorubicin, vs cytarabine/daunorubicin in older adults with untreated AML. Blood. 2014;123(21):3239-3246.
14. Lancet JE, Uy GL, Cortes JE, 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(26):2684-2692.
15. Lancet JE, Uy GL, Newell LF, et al. CPX-351 versus 7+3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial. Lancet Haematol. 2021;8(7):e481-e491.
16. Ossenkoppele GJ, Breems DA, Stuessi G, et al. Lenalidomide added to standard intensive treatment for older patients with AML and high-risk MDS. Leukemia. 2020;34(7):1751-1759.
17. Löwenberg B, Pabst T, Maertens J, 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(4):1110-1121.
18. Löwenberg B, Pabst T, Maertens J, et al. Therapeutic value of clofarabine in younger and middle-aged (18-65 years) adults with newly diagnosed AML. Blood. 2017;129(12):1636-1645.
19. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114(5):937-951.
20. Lindsley RC, Mar BG, Mazzola E, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. Blood. 2015;125(9):1367-1376.
21. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol. 2003;21(24):4642-4649.
22. O'Donnell MR, Abboud CN, Altman J, et al. NCCN clinical practice guidelines acute myeloid leukemia. J Natl Compr Canc Netw. 2012;10(8):984-1021.
23. Cortes JE, Lin TL, Asubonteng K, Faderl S, Lancet JE, Prebet T. Efficacy and safety of CPX-351 versus 7 + 3 chemotherapy by European LeukemiaNet 2017 risk subgroups in older adults with newly diagnosed, high-risk/secondary AML: post hoc analysis of a randomized, phase 3 trial. J Hematol Oncol. 2022;15(1):155.
24. Shimony S, Murdock HM, Keating JH, et al. CPX-351 selectively benefits patients with AML and myelodysplasia-related mutations in the pivotal randomized trial. Blood Adv. 2026;10(8):2854-2864.
25. Villa KF, Ryan RJ, Chiarella M, Louie AC. Healthcare resource utilization in a phase 3 study of CPX-351 in patients with newly diagnosed high-risk/secondary acute myeloid leukemia. J Med Econ. 2020;23(7):714-720.
26. Stone RM. Consolidation chemotherapy for adults with AML in first remission: is there a best choice? J Clin Oncol. 2013;31(17):2067-2069.
27. McCurdy SR, Luger SM. Dose intensity for induction in acute myeloid leukemia: what, when, and for whom? Haematologica. 2021;106(10):2544-2554.
28. Kantarjian HM, Kadia TM, DiNardo CD, Welch MA, Ravandi F. Acute myeloid leukemia - treatment and research outlook in 2021, and the MD Anderson approach. Cancer. 2021;127(8):1186-1207.
29. Dillman RO, Davis RB, Green MR, et al. A comparative study of two different doses of cytarabine for acute myeloid leukemia: a phase III trial of Cancer and Leukemia Group B. Blood. 1991;78(10):2520-2526.
30. Löwenberg B, Pabst T, Vellenga E, et al. Cytarabine dose for acute myeloid leukemia. N Engl J Med. 2011;364(11):1027-1036.
31. Röllig C, Kramer M, Gabrecht M, et al. Intermediate-dose cytarabine plus mitoxantrone versus standard-dose cytarabine plus daunorubicin for acute myeloid leukemia in elderly patients. Ann Oncol. 2018;29(4):973-978.
32. Kahl C, Krahl R, Becker C, et al. Long-term follow-up of the AML97 study for patients aged 60 years and above with acute myeloid leukaemia: a study of the East German Haematology and Oncology Study Group (OSHO). J Cancer Res Clin Oncol. 2016;142(1):305-315.
33. Schaich M, Parmentier S, Kramer M, et al. High-dose cytarabine consolidation with or without additional amsacrine and mitoxantrone in acute myeloid leukemia: results of the prospective randomized AML2003 trial. J Clin Oncol. 2013;31(17):2094-2102.
34. Abé C, Keto J, Lilja M, et al. Cytarabine dose intensification improves survival in older patients with secondary/high-risk acute myeloid leukemia in matched real-world versus clinical trial data. Leuk Lymphoma. 2024;65(10):1493-1501.
35. Chiche E, Rahme R, Bertoli S, et al. Real-life experience with CPX-351 and impact on the outcome of high-risk AML patients: A multicentric French cohort. Blood Adv. 2021;5(1):176-184.
36. Guolo F, Fianchi L, Minetto P, et al. CPX-351 treatment in secondary acute myeloblastic leukemia is effective and improves the feasibility of allogeneic stem cell transplantation: results of the Italian compassionate use program. Blood Cancer J. 2020;10(10):96.
37. Mehta P, Campbell V, Maddox J, et al. CREST-UK: real-world effectiveness, safety and outpatient delivery of CPX-351 for first-line treatment of newly diagnosed therapy-related AML and AML with myelodysplasia-related changes in the UK. Br J Haematol. 2024;205(4):1326-1336.

38. Rautenberg C, Stölzel F, Röllig C, et al. Real-world experience of CPX-351 as first-line treatment for patients with acute myeloid leukemia. Blood Cancer J. 2021;11(10):164.
39. Matthews AH, Perl AE, Luger SM, et al. Real-world effectiveness of CPX-351 vs venetoclax and azacitidine in acute myeloid leukemia. Blood Adv. 2022;6(13):3997-4005.
40. Lemoli RM, Montesinos P, Jain A. Real-world experience with CPX-351 in high-risk acute myeloid leukemia. Crit Rev Oncol Hematol. 2023;185:103984.
41. Martínez-Cuadrón D, Megías-Vericat JE, Gil C, et al. Outcomes after intensive chemotherapy for secondary and myeloid-related changes acute myeloid leukemia patients aged 60 to 75 years old: a retrospective analysis from the PETHEMA registry. Haematologica. 2024;109(1):115-128.
42. Stengel A, Kern W, Haferlach T, Meggendorfer M, Fasan A, Haferlach C. The impact of TP53 mutations and TP53 deletions on survival varies between AML, ALL, MDS and CLL: an analysis of 3307 cases. Leukemia. 2017;31(3):705-711.
43. Daver NG, Iqbal S, Renard C, et al. Treatment outcomes for newly diagnosed, treatment-naïve TP53-mutated acute myeloid leukemia: a systematic review and meta-analysis. J Hematol Oncol. 2023;16(1):19.
44. Versluis J, Coleman Lindsley R. Transplant for TP53-mutated MDS and AML: because we can or because we should? Hematology Am Soc Hematol Educ Program. 2022;2022(1):522-527.
45. Othman J, Wilhelm-Benartzi C, Dillon R, et al. A randomized comparison of CPX-351 and FLAG-Ida in adverse karyotype AML and high-risk MDS: the UK NCRI AML19 trial. Blood Adv. 2023;7(16):4539-4549.
46. Klingler F, Alsdorf WH, Ghandili S, et al. Retrospective analysis of three induction chemotherapy regimens in acute myeloid leukemia including CPX-351, cytarabine/daunorubicin with and without the addition of cladribine. Leuk Lymphoma. 2022;63(11):2645-2651.