Randomized Phase III Study of Standard Intensive Chemotherapy *versus* Intensive Chemotherapy with CPX-351 in Adult Patients with Newly Diagnosed AML and Intermediate- or Adverse Genetics

AMLSG 30-18

Protocol number:	AMLSG 30-18
Therapeutic Area:	Hematology/Oncology
Substance Identifier:	CPX-351(daunorubicin and cytarabine) Liposome for injection, "CPX-351"
EudraCT Number:	2018-002678-34
Included in clinicaltrials.gov Database:	Yes ☒ No ☐
Status:	Version 1.4
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Sponsor: Ulm University Hospital, Ulm, Germany;
represented by the Chairman of the Board

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1. SYNOPSIS

Title of Study	Randomized Phase III Study of Standard Intensive Chemotherapy *versus* Intensive Chemotherapy with CPX-351 in Adult Patients with Newly Diagnosed AML and Intermediate- or Adverse Genetics - AMLSG 30-18
Investigational Medicine Product	CPX-351 will be provided by JAZZ Pharmaceuticals
Reference Therapy Drugs	Daunorubicin and cytarabine are provided by the pharmacy of the participating centers
Therapeutic area	Hematology / Oncology
Indication	Newly diagnosed acute myeloid leukemia (AML)
Protocol Number	AMLSG 30-18
Coordinating Investigator	PD Dr. Peter Paschka
Background of the clinical study	AML is a genetically and clinically heterogeneous hematologic malignancy. Outcome is influenced by various factors, including patient features (e.g., age, comorbidities, performance status) and disease characteristics (e.g., genetics of leukemic cells). In patients considered suitable for intensive induction therapy, the combination of an anthracycline and cytarabine ("3+7") has remained the standard of care, followed by consolidation therapy with either chemotherapy (e.g., repetitive cycles of higher doses of cytarabine) or allogeneic HCT. In younger adult patients, overall responses are achieved in 70-80% of patients, with a 5-year overall survival (OS) rate of 40-45%; only about 40-60% of older patients achieve remission, and the vast majority will relapse, with about 10% surviving more than 5 years. In AML with features of poor prognosis, such as intermediate- or adverse-risk genetics, secondary AML evolving from an antecedent myeloid disorder, and in therapy-related AML the outcome remains poor after conventional intensive chemotherapy. Thus, there remains a great unmet medical need in adult AML patients. CPX-351 is an encapsulation in nano-scale liposomes of cytarabine and daunorubicin at a synergistic 5:1 molar ratio. A fixed molar ratio is maintained in human plasma for at least 24 hours after final dose, and drug exposure is maintained for 7 days. In leukemia-bearing mice it has been shown that there is selective uptake by leukemic compared to normal cells in bone marrow. Phase II studies suggested a beneficial effect of the agent in first-line treatment of secondary and therapy-related AML, and in the poor-risk stratum (by the European Prognostic Index [EPI]) of relapsed AML. A subsequent phase III trial randomized 309 patients age 60 to 75 years with high-risk AML, defined as AML with

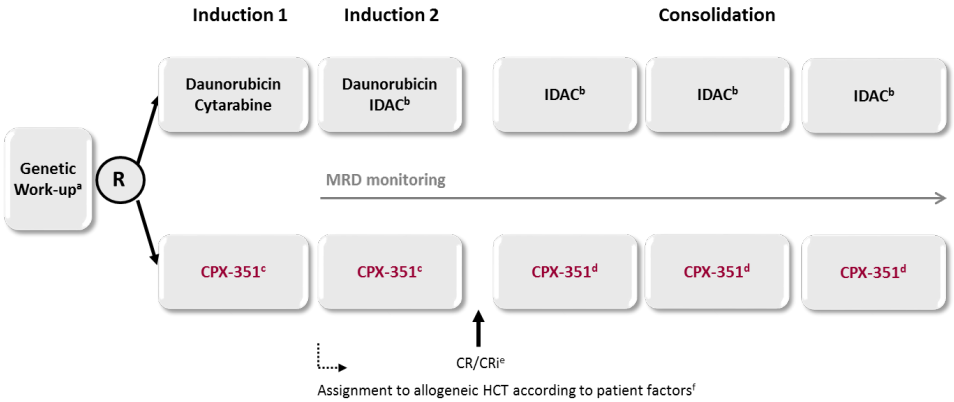
	myelodysplasia-related changes or therapy-related AML, to CPX-351 or "7+3". CPX-351 produced a higher response rate (CR/CRi, 47.7% *vs* 33.3%; P=.016), and longer OS (HR 0.69, P=.005 with medians of 9.6 *vs* 6 months and 2-year survival rates of 31% and 12%). The benefit in response rates and overall survival was seen in both age groups, i.e., patients 60-69 and 70-75 years of age. Of note, numerically more patients after CPX-351 received allogeneic transplant, and in an exploratory analysis, post-transplant OS was longer with CPX-351. Thus, CPX-351 may improve therapy of older AML patients with poor prognosis features. It may also have the potential to improve survival in younger adult AML patients with less favorable genetic and clinical disease characteristics
Study Objectives and Endpoints	**Primary Efficacy Objective** • To evaluate the impact of CPX-351 *vs* standard intensive chemotherapy on event-free survival (EFS) in adult patients with newly diagnosed AML and intermediate- or adverse genetics **Secondary Efficacy Objectives** • To evaluate the impact of CPX-351 *vs* standard intensive chemotherapy on overall survival (OS) • To evaluate the impact of CPX-351 *vs* standard intensive chemotherapy on response rate, relapse-free survival (RFS), and cumulative incidence of relapse (CIR) and death (CID) • To evaluate the impact of CPX-351 *vs* standard intensive chemotherapy on EFS, RFS, CIR/CID, and OS with patients censored at the time of allogeneic HCT • To assess safety and feasibility of CPX-351 *vs* standard intensive chemotherapy on incidence and intensity of adverse events (AEs) according to Common Terminology Criteria for Adverse Events (CTCAE) version v4.0) **Exploratory Objectives** • To evaluate the prognostic and predictive impact of cytogenetic and molecular genetic changes on response to therapy and survival endpoints • To evaluate the impact of minimal residual disease (MRD) assessment as a surrogate for EFS and OS • To evaluate the Quality of Life (Qol) with CPX-351 treatment *vs* standard intensive chemotherapy • To evaluate the use of resources with CPX-351 *vs* standard intensive chemotherapy **Primary Efficacy Endpoint**

	• Event-free survival (EFS) **Secondary Efficacy Endpoint** • Overall survival (OS) • Rate of objective responses (complete remission [CR], CR with incomplete hematologic recovery [CRi], CR without minimal residual disease [CR_{MRD}-]), relapse-free survival (RFS), cumulative incidence of relapse (CIR) and death (CID) • EFS, RFS, CIR/CID, and OS with patients censored at the time of allogeneic HCT • Incidence and intensity of adverse events (AEs) according to Common Terminology Criteria for Adverse Events (CTCAE) version v4.0) **Exploratory Endpoints** • Prognostic/predictive impact of AML-associated genetic changes • Prognostic/predictive impact of MRD monitoring • Comparison between treatment groups on QoL assessment • Comparison between treatment groups on resource utilization
Study Design	Randomized, phase III, open-label, multi-center trial in adult patients with newly diagnosed AML and intermediate- or adverse genetics as defined in the inclusion / exclusion criteria
Planned Study Period	Start of recruitment: Q1/2019 End of recruitment: Q2/2021 End of Follow-Up: Q2/2023
Planned Total Number of Study Centers and Patients	A total of 593 patients will be recruited at about 50 AMLSG sites in Germany and Austria.
Treatment plan	Patients will be randomized to either standard chemotherapy or therapy with CPX-351 (see Figure). All patients will receive two cycles of induction chemotherapy; patients not achieving CR/CRi after two cycles will be off protocol. Patients achieving CR/CRi will continue with consolidation treatment according to initial randomization, either with intermediate-dose cytarabine or with CPX-351. Based on the poor disease factors of patients entering the study, the majority of patients may be assigned to allogeneic HCT. Assignment to allogeneic HCT will be based on individual patient assessment and established risk scores (e.g., HCT-CI score). Response assessment will be performed after each cycle (standard arm: induction cycles between day 21 and 28, consolidation cycles between day 29 and 43; investigational arm: induction cycles between day 21 and

day 35, consolidation cycles between day 29 and 43). MRD analysis by MFC will be performed after one and two induction cycles, and after end of consolidation.

In patients aged 18 – 60 years (with performance status 0-1) the initial dose of CPX-351 in induction will be 55 mg/m^2 daunorubicin/125 mg/m^2 cytarabine [125 U/m²] given in induction cycle 1 on days 1, 3, and 5; and in induction cycle 2 on days 1 and 3. The higher dose of CPX-351 in induction therapy will be evaluated based on the experience from ongoing pediatric phase I/II study (ClinicalTrials.gov NCT02642965), where CPX-351 is administered at a dose up to 59.4 mg/m² daunorubicin/135 mg/m² cytarabine [135 U/m^2]. A continuous safety assessment will be applied in younger patients. The feasibility of higher dose of CPX-351 will be evaluated after enrollment of 30 patients (18-60 years of age) based on hematologic toxicity (see Section 9.1). In case of excessive hematologic toxicity, the CPX-351 dose will be reduced by one level corresponding to the dose that has been proven effective and safe in the pivotal study performed in older patients aged 60 - 75 years (Lancet 2018).

Overall trial design:



[a] Exclusion: AML with favorable-risk genetics (according to 2017 ELN criteria); acute promyelocytic leukemia; AML with *BCR-ABL1*

[b] IDAC, intermediate-dose cytarabine; age-adjusted dose

[c] Patients 18-60 years: CPX-351 55 mg/m^2 daunorubicin / 125 mg/m^2 cytarabine [125 U/m²]; patients >60 yrs: CPX-351 44 mg/m^2 daunorubicin / 100 mg/m^2 cytarabine [100 U/m²]

[d] Patients 18-60 yeaars: CPX-351 35 mg/m^2 daunorubicin / 80 mg/m^2 cytarabine [80 U/m²]; patients >60 years: CPX-351 29 mg/m^2 daunorubicin / 65 mg/m^2 cytarabine] [65 U/m²]

[e] Patients not achieving CR or CRi after two cycles of chemotherapy will be off protocol

[f] Allogeneic hematopoietic cell transplantation (HCT) can be performed at any time point following one induction cycle

Dosages of chemotherapy – Standard arm

Induction Cycle 1

	Daunorubicin	60 mg/m^2 i.v.	d1-3
	Cytarabine	200 mg/m^2 cont. i.v.	d1-7
	Induction Cycle 2		
	Daunorubicin[a]	50 mg/m^2 i.v.	d1-3
	Intermediate-dose cytarabine[b]	1000 mg/m^2 q12h i.v.	d1-3
	Consolidation Cycles 1-3		
	Intermediate-dose cytarabine[c]	1500 mg/m^2 q12h i.v.	d1-3

[a] Daunorubicin only d1-2 in patients >60 years
[b] Intermediate-dose cytarabine only 500 mg/m^2 in patients >60 years
[c] Intermediate-dose cytarabine only 1000 mg/m^2 in patients >60 years

<u>Dosages of chemotherapy – Investigational arm</u>

Induction Cycle 1

Patients 18-60 years

CPX-351 — 55 mg/m^2 daunorubicin / 125 mg/m^2 cytarabine [125 U/m²] i.v. (90') d1,3,5

Patients >60 years

CPX-351 — 44 mg/m^2 daunorubicin / 100 mg/m^2 cytarabine [100 U/m²] i.v. (90') d1,3,5

Induction Cycle 2

Patients 18-60 years

CPX-351 — 55 mg/m^2 daunorubicin / 125 mg/m^2 cytarabine [125 U/m²] i.v. (90') d1,3

Patients >60 years

CPX-351 — 44 mg/m^2 daunorubicin / 100 mg/m^2 cytarabine [100 U/m²] i.v. (90') d1,3

Consolidation cycles 1-3

Patients 18-60 years

CPX-351 — 35 mg/m^2 daunorubicin / 80 mg/m^2 cytarabine [80 U/m²] i.v. (90') d1,3

Patients >60 years

CPX-351 — 29 mg/m^2 daunorubicin / 65 mg/m^2 cytarabine [65 U/m²] i.v. (90') d1,3

<u>Allogeneic hematopoietic cell transplantation (HCT)</u>:

Patients can be assigned to allogeneic HCT at any time during treatment following at least one cycle of induction therapy. Assignment is primarily based on established risk scores. The disease should preferably be in remission. Conditioning regimens can be selected according to institutional standards.

Inclusion Criteria	1. Patients with newly diagnosed AML and intermediate- or adverse-risk genetics (according to 2017 ELN criteria), including AML with myelodysplasia-related changes (AML-MRC) and therapy-related AML according to the World Health Organization (WHO)classification 2. Age ≥ 18 years, no upper age limit 3. Patient considered eligible for intensive chemotherapy 4. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 at screening 5. Genetic assessment in AMLSG central laboratory 6. Adequate renal function as evidenced by serum creatinine ≤ 2.0 × ULN or creatinine clearance >40 mL/min based on the Cockcroft-Gault glomerular filtration rate (GFR) 7. Adequate hepatic function as evidenced by: ○ Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) unless considered due to Gilbert's disease, or leukemic involvement following approval by the Coordinating investigator or Trial Coordinator ○ Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) ≤ 3.0 × ULN, unless considered due to leukemic involvement following approval by the Coordinating Investigator or Trial Coordinator 8. No prior chemotherapy for AML except hydroxyurea for up to 7 days during the diagnostic screening phase for the control of peripheral leukemic blasts in patients with leukocytosis (e.g., white blood cell [WBC] counts >30x10^9/L); prior treatment of myelodysplastic syndrome with hypomethylating agents is allowed 9. Non-pregnant and non-nursing women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within a sensitivity of at least 25 mIU/mL within 72 hours prior to registration ("Women of childbearing potential" is defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 consecutive months) 10. Female patients of reproductive age must agree to avoid getting pregnant while on therapy and for 3 months after the last dose of CPX-351 11. Women of child-bearing potential must either commit to continued abstinence from heterosexual intercourse or begin one acceptable method of birth control (IUD, tubal ligation, or partner's vasectomy). Hormonal contraception is an inadequate method of

	birth control 12. Men must use a latex condom during any sexual contact with women of childbearing potential, even if they have undergone a successful vasectomy and must agree to avoid to father a child (while on therapy and for 3 months after the last dose of CPX-351) 13. Able to understand and willing to sign an informed consent form (ICF)

Exclusion Criteria	1. AML with favorable-risk genetics according to 2017 ELN criteria 2. Acute promyelocytic leukemia (APL) with t(15;17)(q22;q12); *PML-RARA*; or one of the other pathognomonic variant chromosomal translocations/ fusion genes 3. AML with *BCR-ABL1* 4. Prior treatment of an antecedent hematologic disorder with intensive chemotherapy or bone marrow transplant with a curative intent 5. Significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association (NYHA) class III or IV congestive heart failure; myocardial infarction, unstable angina and/or stroke; or left ventricular ejection fraction (LVEF) <50% by ultrasound obtained within 28 days prior to the start of study treatment 6. Severe obstructive or restrictive ventilation disorder 7. Uncontrolled infection 8. Clinical symptoms suggestive of active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid (CSF) during screening is only required, if there is a clinical suspicion of CNS involvement by leukemia during screening 9. Known history of positive test for hepatitis B surface Antigen (HBSAg) or hepatitis C antibody or history of positive test for Human Immunodeficiency Virus (HIV) 10. Patients with a “currently active” second malignancy. Patients are not considered to have a currently active malignancy, if they have completed therapy and are considered by their physician to be at < 30% risk of relapse within one year. However, subjects with the following history/concurrent conditions are allowed: o Basal or squamous cell carcinoma of the skin o Carcinoma in situ of the cervix o Carcinoma in situ of the breast o Incidental histologic finding of prostate cancer 11. Severe neurological or psychiatric disorder interfering with ability to give an informed consent 12. No consent for registration, storage and processing of the individual disease characteristics and course as well as information of the family physician about study participation 13. No consent for biobanking of patient’s biological specimens

	14. Current participation in any other interventional clinical study within 30 days before the first administration of the investigational product or at any time during the study 15. Patients with prior cumulative anthracycline exposure of greater than 368 mg/m^2 daunorubicin (or equivalent) 16. Hypersensitivity to cytarabine, daunorubicin or liposomal products 17. History of Wilson's disease or other copper-metabolism disorder
Statistical planning	The calculation for the primary endpoint sample size in this study is based on pooled data from previous AMLSG trials, where younger (18-60 years; ClinicalTrials.gov Identifier NCT00151242) and older (>60 years; ClinicalTrials.gov Identifier NCT00151255) AML patients were intensively treated. Among 1,192 genetically well characterized patients from these AMLSG trials, 768 patients could be assigned to the intermediate- (n=402) or adverse-risk (n=367) group, and pooled data from these 768 patients served as basis for the sample size calculation. The estimated EFS at 2 years in this cohort (n=768) was 21.7%. To detect an increase in EFS at 2 years of about 10% by treatment in the investigational arm (CPX-351), which will correspond to a hazard ratio of 0.75 (Power: 80%), it will require 553 evaluable patients. Considering a drop-out rate of 10%, a total of 593 patients need to be recruited into the trial over 2 years with a 1-year follow-up period after inclusion of the last patient. Based on these assumptions the estimated duration of the entire trial will be 3 years.