FRENCH INNOVATIVE
LEUKEMIA ORGANIZATION

CLINICAL STUDY PROTOCOL

TAGVEN

"Open label phase II study evaluating the efficacy and safety of the combination of tagraxofusp and venetoclax in treatment-naive blastic plasmacytoid dendritic cell neoplasm patients"

Sponsor :

FILO

CHU BRETONNEAU – Centre Henry Kaplan

Service d'hématologie et Thérapie Cellulaire

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RIPH1		
Decision of french authorization (CTIS)	*Authorised*	Authorization date : 26/05/2025

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PROTOCOL APPROVAL & SIGNATURE PAGE

FILO

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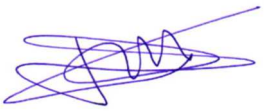

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Coordinating Investigator

AUTHORIZATION AND AMENDMENTS HISTORY

	AUTHORIZATION DATE	VERSION AND DATE OF PROTOCOL
INITIAL	26 MAY 2025	Version 1.3 du 15/05/2025
AMENDMENT 1		

Investigator Signature

I have read all the pages of this clinical study protocol for which FILO is the sponsor. I agree to conduct the study as outlined in the protocol. I confirm that I will conduct the study in accordance with ICH GCP guidelines. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

I understand that the FILO is the Data Controller for the clinical study, and as such will process my professional contact details (i.e: professional contact details, CV & education…) in order to be able to do business with me and to manage the study.

The objective of the process is scientific research, and the legal base is the legitim interest of FILO Group to perform medical research in Leukemia deseases. My data may be sent only to the sponsor and sponsor's sub contractors involved in the study (i.e: eCRF provider, data entry department) under responsibilities of Sponsor and signed Confidential agreement, and possibly to appropriate health care authorities under conditions guaranteeing data protection. My personal data will be process and stored within European Union and outside European Union as described in the protocol.

As per GCP, and per MR-001, FILO will keep such personal data for 25 years after the publication date of clinical study report related to this study. I understand that I can exercise my data protection rights* by contacting the Data Protection Officer of the FILO:

- by post mail: FILO "French Innovative Leukemia Organization" , Délégué à la Protection des Données (DPO) , CHRU Tours – Hôpital Bretonneau Bât B47 – 1er étage 2 Bd Tonnellé, 37044 TOURS Cedex 9 ;
- or by email: dpo@filo-leucemie.org

I understand that I can also contact the CNIL to file a complaint regarding the processing of my personal data.

I acknowledge that, as per the Good Clinical Practices (ICH E6), I cannot oppose that FILO processes my professional contact details as I agree to participate as an investigator to this clinical study.

(*) Right to be informed (transparency), right to know and inquire about what personal data we have collected about you and to get a copy of such data (access), right to request correction or deletion of such personal data, right to object, right to restrict the processing (limitation), right of data portability, right to know if an automated decision is made.

Principal investigator, printed name:	
Signature:	Date:

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ANSM	Agence Nationale de Sécurité du Médicament
AST	Aspartate aminotransferase (SGOT)
BST	Best Supportive Therapy
CPP	Comité de Protection des Personnes
CR	Complete Remission
CRi	CR with incomplete hematologic recovery
CRA	Clinical Research Assistant
CRP	C-reactive protein
e-CRF	Electronic-Case Report Form
CT	Chemotherapy
CTCAE	Common terminology criteria for adverse events
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELN	European Leukemia Net
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FILO	French Innovative Leukemia Organization
GCP	Good Clinical Practice
GCS-F	Granulocyte colony-stimulating factor
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HSCT	Hematopoietic Stem Cell Transplantation
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IP	Investigational Product
ITT	Intent To Treat
IB	Investigator Brochure
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver Function Tests
LVEF	Left Ventricular Ejection Fraction
MDS	Myelodysplastic syndrome
MRD	Minimal/Measurable Residual Disease
PD	Progressive Disease
ORR	Objective Response Rate
OS	Overall Survival

PFS	Progression-free survival
Po	Per Os
PR	Partial Response
PS	Performance Statut
RFS	Relapse Free Survival
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Adverse reaction
SD/NC	Stable Disease/No Change
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization

SYNOPSIS

Study code	**TAGVEN BPDCN trial**
Title	Open label phase II study evaluating the efficacy and safety of the combination of tagraxofusp and venetoclax in treatment-naive blastic plasmacytoid dendritic cell neoplasm (BPDCN) patients
Sponsor	FILO (French Innovative Leukemia Organization)
COORDINATING / PRINCIPAL INVESTIGATOR	**Coordinating Investigators:** Dr David Ghez Institut Gustave Roussy david.ghez@gustaveroussy.fr Pr Eric Deconinck CHRU Besançon edeconinck@chu-besancon.fr
Study population	Adult patients with a treatment naive BPDCN
Objectives	**Primary objective**: The primary objective is the **efficacy of the tagraxofusp + venetoclax combination** (TAGVEN) as measured by the rate of **composite complete remission (cCR),** defined as complete remission (CR) or complete remission with incomplete marrow recovery (Cri), according to the European Leukemia Net 2022 definitions for AML and adapted for BPDCN, see appendix 2) or complete response with minimal residual skin abnormality (CRc[clinical]) defined by a marked clearance of ≥ 75% of a patient's skin lesions from baseline (see appendix 2 and 5) and a complete metabolic response after 3 cycles of the combination of tagraxofusp and venetoclax in adult patients with a treatment-naive BPDCN. **Secondary objectives**: - Objective response rate (ORR) defined as cCR + partial response (PR) - Safety profile of the tagraxofusp and venetoclax combination - Incidence of Minimal Residual Disease (MRD)-Negative Responses measured by flow cytometry with a sensitivity of 0.1% - Progression-free Survival (PFS) - Relapse-free survival (RFS) - Duration of response (DOR) - Overall Survival (OS) - Number of patients bridged to allogeneic transplantation - Possible predictors of response with respect to cytogenetics and molecular status
Study design	Open label single arm multicenter phase II study
Sample size	31 evaluable patients (33 inclusions)
Statistical analysis for sample size calculation	TAGVEN study is an open label single arm phase II trial. The primary objective is to assess the rate of cCR after 3 TAGVEN cycles in patients with treatment naive BPDCN. cCR is defined as the proportion of participants who achieve a CR + CRi according to the European Leukemia Net 2022 definitions for AML and adapted for BPDCN + CRc (Appendix 2). The aim is to demonstrate that the rate of cCR after 3 TAGVEN cycles (P) is clearly above rate of 60%: P0. The intention is to check whether TAGVEN can bring this rate markedly above 60%. The following hypotheses will be considered:

	• H0 (null): a rate of cCR after 3 cycles of the tagraxofusp + venetoclax combination of 60% (P0) (not worth to pursue further investigation as it is the rate that can be reproducibly obtained with TAG alone or with standard chemotherapy); • H1 (alternative): a rate of cCR after 3 cycles of the tagraxofusp + venetoclax combination of 80% (P1) (warrants further investigation). The study was elaborated to test the following hypotheses: H0: P ≤ P0 versus H1: P ≥ P1 According to a Simon two-stage (Optimum) design with a one-sided 10% type I error (rare disease context) and power of 80%, **31 evaluable patients for the cCR status after 3 TAGVEN cycles** will need to be included: **Stage 1:** Safety and efficacy will be evaluated after inclusion of the **first 11 evaluable patients**: • A safety analysis will be performed on the clinical data of the first 11 evaluable patients. Study will be stopped if an excessive proportion of patients develop serious adverse events (see section 13.2 for details). • if 7 (63.6%) or less than 7 patients are identified with a cCR, the intervention could be declared uninteresting. No more additional patient will be included, and the study will be stopped. • if ≥ 8 (72.7%) patient is identified with a cCR, the study will proceed to enroll 20 additional patients (stage 2). **Stage 2:** If safety and efficacy criteria are met in the first 11 patients analysed in stage 1, the study will proceed to enroll 20 additional patients. Efficacy will be assessed on **31 evaluable patients**: • if ≤ 21 (67.7%) patients are identified with a complete response, the intervention will be declared inefficacious and the study will be declared negative for its primary objective, • if ≥ 22 (71.0%) patients are identified with a complete response, the intervention will be regarded as interesting for further evaluation and the study will be declared positive for its primary objective.
Length of study	Inclusion period: 36 months Treatment period: 24 months Follow up period: 12 months **Total study duration: 72 months** The date of study initiation is defined by the date of consent of the first patient registered into the eCRF. The end of study is defined by the last visit of the last enrolled patient. Patients will be followed thereafter for disease recurrence and survival.
Number of centers	FILO and ALFA centers: 34 centers
Target population	***INCLUSION CRITERIA*** 1. Patients with a confirmed BPDCN diagnosis according to WHO 2022 revised criteria and have not received previous treatment: patients with skin or lymph node lesions but no bone marrow involvement can be included 2. Age >18 years 3. Ability to understand the protocol and to sign an informed consent 4. Possibility of follow-up 5. ECOG < 3 6. Adequate renal function as demonstrated by a calculated creatinine clearance ≥ 60 mL/min by the Cockcroft-Gault formula.

7. Adequate cardiac function defined by LVEF >/= 50% by MUGA or ECHO and no clinically significant abnormalities on a 12-lead ECG
8. Albumin level ≥3,2g/dL
9. Adequate liver function as demonstrated by:
    - aspartate aminotransferase (AST) ≤ 2.5 × ULN*
    - alanine aminotransferase (ALT) ≤ 2.5 × ULN*
    - bilirubin ≤ 3.0 × ULN, unless due to Gilbert's syndrome*

** Unless considered due to leukemic organ involvement, in that cases values must be* ≤ 10 × ULN

10. Men, and women of childbearing potential must be using a highly effective method of contraception
11. Negative urine/blood pregnancy test within 1 week prior to the initiation of treatment (if applicable)
12. Patient covered by any social security system.

EXCLUSION CRITERIA

1. Participation to another clinical trial with any investigative drug within 30 days prior to study enrolment.
2. Previous treatment with venetoclax or tagraxofusp
3. Treatment of BPDCN with any prior chemotherapy or investigational agents, except hydroxyurea for less than 14 days at the time of inclusion
4. Concomitant immunosuppressive therapy –except for low-dose prednisone (≤10 mg/day)
5. Known allergy or sensitivity to tagraxofusp, venetoclax, and any of its components or excipients.
6. Pregnant or breastfeeding woman
7. Known positivity for hepatitis B or C infection except for those subjects with an undetectable viral load or subjects with serologic evidence of prior vaccination to HBV
8. Evidence of uncontrolled systemic infection requiring therapy (viral, bacterial, or fungal)
9. Subject has any history of clinically significant condition(s) that in the opinion of the investigator would adversely affect his/her participating in this study including, but not limited to:
    - Cardiovascular disease e.g., NYHA heart failure > class 2, uncontrolled angina, history of myocardial infarction, unstable angina, or stroke within 6 months prior to study entry, uncontrolled hypertension, or clinically significant arrythmias not controlled by medication.
    - Renal, pulmonary, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, or bleeding disorder independent of leukemia.
10. Subject with a history of other malignancies within the last three years prior to study entry, except for:
    - Adequately treated in situ carcinoma of the breast or cervix uteri
    - Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin
    - Prostate cancer without needs for specific therapy
    - Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.

	11. Malabsorption syndrome or other conditions that preclude enteral route of administration 12. Patient with hereditary fructose intolerance
Study treatment	This is an open label single arm study. All patients participating in the study will receive a maximum of 24 TAG + VEN combination cycles depending on the response observed after C3 (see below for details): • venetoclax 400mg/day orally after a ramp-up period of 3-days • tagraxofusp starting at the end of the venetoclax ramp-up period i.e. at day 4 for twelve 28-days cycles, TAG 12 μg/kg body weight administered as an intravenous infusion over 15 minutes, once daily, on days 1-3 of each 28 days-cycle 1- In patients in cCR after 3 TAGVEN cycles, TAGVEN will be continued until unacceptable side effects, progression or death, whichever comes first, <u>for a maximum of twenty-four 28-days cycles</u>, Per investigator's decision or patient's choice, in patients still in cCR after 12 TAGVEN cycles, either TAG or VEN may be discontinued for the remaining 12 cycles. Whenever feasible, allogeneic SCT will be systematically proposed to eligible patients reaching a cCR within or after the 3rd cycle. Additional TAGVEN cycles may be given pending the organization of the transplantation. 2- Patients in PR after the 3rd cycle will be considered to have failed the primary objective however 3 additional TAGVEN cycles (i.e. 6 cycles in total) may be administered per investigator's decision to try to reach cCR. Patients reaching a cCR after these 3 additional cycles will continue treatment according tho the protocol schedule, will be followed for secondary criteria e.g PFS, DOR and OS and may be considered for allogeneic SCT if eligible. Patients not reaching a cCR after these 3 additional cycles will exit the protocol and will be treated according to the local investigator's decision. 3- Patients in response < PR after the 3rd cycle will be considered as a protocol failure and will be treated according to the local investigator's decision. Triple prophylactic intrathecal chemotherapy (IT, methotrexate 15 mg, cytarabine 40 mg and depomedrol 40mg) will be systematically administered via lumbar puncture at each cycle until allogenic stem transplantation or for at east 8 injections. Monthly IT prophylaxis may the be administered according to local policyIn case of documented CNS involvement, IT (methotrexate 15 mg, cytarabine 40 mg and depomedrol 40mg) will be administered weekly until complete clearance of cerebrospinal fluid (CSF) tumor cells. After CSF sterilization, intrathecal injections will be administered once weekly for 1 months (4 injections) then monthly for at least 8 injections. Monthly IT prohylaxis may then be administered according to local policy.

Endpoints	**Primary endpoint** Proportion of participants who achieve a cCR (cCR (CR or Cri or CRc) after 3 TAGVEN cycles. **Secondary endpoints**: - Objective response rate (ORR) including cCR and partial remission (PR) after 3 TAGVEN cycles - Safety profile of the tagraxofusp and venetoclax combination - Proportion of patients with Minimal Residual Disease (MRD)-Negative responses measured by flow cytometry with a sensitivity of 0.1% - Progression-free Survival (PFS) defined as the time from start of treatment to first documentation of disease progression or death from any cause, whichever comes first. - Duration of response (DOR) defined as the time from first determination of response (cCR) until first documentation of progression or death, whichever comes first. - Overall Survival (OS) defined as the time from the enrolment until date of death from any cause. - Proportion of patients bridged to allogeneic stem cell transplantation - Possible predictors of response with respect to cytogenetics and mutational status. *All time-to-event variables: PFS, DOR and OS follow the updated FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics).*
Biological studies	Cells and nucleic acids (DNA, RNA) will be systematically banked at Pr Francine Garnache-Ottou's laboratory in Besançon. Besides centralized review of biological samples, further biological studies are planned: • Analysis of CD123 expression by flow cytometry and semi-quantitative quantification of CD123 antigenic sites (CELLQUANT CALIBRATOR ® Kit, Biocytex®) • Quantification of bcl-2 expression by flow cytometry • Functional assays measuring the cytotoxic activity of TAG and VEN on BPDCN blasts with regards to the level of CD123 and bcl-2 expression
Tumor evaluation	Response to treatment on bone marrow aspirate according to ELN 2022 definitions for AML and adapted for BPDCN, metabolic imaging (PET scanner) and cutaneous response (if applicable) using the SWAT score (>75% reduction in the score defined CRc, 50-71% reduction defined PR and <50% reduction defined failure).
Safety	Patient safety will be assessed based on clinical and laboratory evaluations, physical examinations, vital signs, and monitoring of adverse events (AEs). The investigators will grade AEs using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0, 27 november 2022, see appendix 5) Serious adverse events will be reported on the SAE form and sent to the FILO's PV department
Clinical study registry	Clinicaltrial.gov N°EU : 2024-511-003-42-00

1. ORGANISATION AND RESPONSIBILITIES

1.1. SPONSOR CONTACTS

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The FILO is a collaborative group working at developing clinical studies in the field of hematological malignancies. The AML committee launches clinical trials in AML after scientific discussions about research opportunities.

The FILO group has the necessary resources to conduct high-quality clinical trials with pharmacovigilance, electronic case report forms (e-CRFs), data quality control, coordination of monitoring tasks and data management, as well as storing patients pretreatment leukemic marrow and blood within a biobank (FILOthèque). A prerequisite for biobanking is the patient's informed consent. Pretreatment samples should include nucleic acids (DNA and RNA) and viable cells for further biology.

1.2. CENTER PARTICIPATION AND VOLUNTEERING

The objective is to complete recruitment to the trial as quickly as possible within an estimated time frame of 36 months.

The protocol will be proposed to around 30 centers belonging to the FILO and ALFA groups. Each center has to be declared as a participating center to the FILO and ALFA offices and identify a principal investigator for the center.

The principal investigator will be accountable for the coordination of the protocol, inclusion support and designation of sub-investigator(s).

Each investigator will have to send his/her curriculum vitae and participation statement to the FILO coordination center.

A total of 33 patients will be enrolled in the study to ensure the collection of 31 evaluable cases.

2. BACKGROUND

2.1. BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASMS

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive neoplasm of precursor plasmacytoid dendritic cells (PDC), representing 0.44% of hematologic malignancies and less than 1% of acute leukemias (Bueno, Haemaologica 2004). According to very recent epidemiological data from the SEER registry, the annual incidence of BPDCN is estimated to be 0.04 per 100.000 in the USA (Guru Murthy, Leuk Research 2018). BPDCN generally affects patients > 60 years, though there is another peak of incidence in patients younger than 20 years. Patients typically present with skin lesions, bone marrow infiltration and circulating cells. Neuromeningeal involvement may occur at diagnosis in 10% of the patients or during disease course (20-30% in relapsing patients). The diagnosis is usually established via skin or bone marrow biopsy analyses. Malignant cells display some characteristic morphologies. Immunophenotyping (either using immunohistochemistry or flow cytometry) demonstrating expression of CD56, CD123, TCL1 and CD303 is considered sufficient to confirm the diagnosis. An association between BPDCN and the development of acute myeloid leukemia (AML), most often of myelomonocytic lineage, has been reported (Khoury, Cancer 2002; Feuillard, Blood 2002; Petrella, Am J Clin Pathol 2005).

Chromosomal abnormalities occur in roughly 50% to 60% of patients with BPDCN; genomic imbalances are frequent, particularly partial or complete loss of chromosomes 9, 12, 13 and 17 affecting well-known tumour suppressor genes such as CDKN2A, CDKN1B, RB1 or TP53 (Jardin Leukemia 2009). Jardin et al reported 54% and 38% of TET2 and TP53 mutations in 13 cases of BDCN (Jardin, BJH 2011). Recent molecular analysis using next generation sequencing (NGS) has provided a better insight into the molecular anomalies in BPDCN. Mutations of NRAS, KRAS and ATM were found in 20-30% of cases and appeared mutually exclusive (Stenzinger, Oncotarget 2014). In the largest reported series (25 samples), mutations in 29 genes were observed, the most frequent of which being TET2 (36%), ASXL1 (32%), NRAS (20%), NPM1 (20%) and genes of the IKAROS family (20%) (Menezes, Leukemia 2013). Additional mutations, albeit with a lower frequency, in other genes such as DNMT3A, IDH1/2, SF3B1, U2AF1, EZH2 or ZRSR2 were also found. Interestingly, a notable proportion of genes mutated in BPDCN are involved in the DNA methylation, chromatin remodeling or splicing pathways, which are frequently mutated in myelodysplastic syndromes and secondary AML.

2.2. PROGNOSIS AND TREATMENT OF BPDCN

Because of the rarity of the disease, prospective clinical trials are lacking and there ais at present no standard of care (SOC) treatment has been established for patients with newly diagnosed (first-line) or refractory/relapsed (R/R) disease. Tagraxofusp is the only treatment approved by the FDA and EMA for the treatment of BPDCN, following the positive results of the STML-401-0114 study (Pemmaraju et al, 2019). Additional studies have confirmed the clinical efficacy of tragraxofusp in BPDCN (see §2.3) and tagraxofusp has EMA approval for 1L BPDCN and is reimbursed in several EU countries.

The wide diversity of empirical multi-agent chemotherapy regimens used to treat BPDCN patients highlights the lack of SOC therapy for patients with this disease, with treatments based on regimens used to treat patients with acute leukemias or lymphomas, and makes it very difficult to draw conclusions about individual therapy efficacy and, thus, opens a space for the development of novel targeted therapies for this aggressive disease (Laribi et al, 2016; Pagano

et al, 2016; Riaz et al, 2014). There is limited specific data in the safety of empirical chemotherapy regimens used to treat patients with BPDCN, but they are well known to be potentially very toxic, including causing prolonged bone marrow suppression and febrile neutropenia, to the extent that they carry a substantial risk of treatment-related death, estimated at 26% (Martín-Martín et al, 2015) and 17% (Pagano et al, 2013). ALL and AML-based induction regimens seem to be associated with the highest rate of complete remissions (CR) and best outcome (Reimer, BMT 2003; Pemmaraju, JCO 2012, Garnache, Blood Adv, 2019, Laribi, Blood Advances 2021) thus are now considered to be the best therapeutic options in fit patients.

Even with intensive regimens, the prognosis of BPDCN remains dismal. Though BPDCN may often respond to induction chemotherapy, durable responses are rare, and the median overall survival is usually < 1 year. Allogenic hematopoietic stem cell transplantation (SCT) may reduce the relapse rate and improve outcome. In a retrospective study from the European Group for Blood and Marrow Transplantation, allogeneic SCT could provide a durable control of the disease, with a 3-year cumulative incidence of relapse, disease-free survival, and overall survival of 32%, 33%, and 41%, respectively (Roos-Weil, Blood 2013). Expectedly, patients in CR were most likely to benefit from allo SCT. A French retrospective series of 89 patients demonstrated a 40% prolonged overall survival in allografted patients (Garnache, Blood Adv, 2019). The recent largest retrospective multicenter study on 398 patients confirms the benefit of allogeneic and question the place of autologous SCT in BPDCN (Laribi, Blood Advances 2021).

In patients older than 60, who represent most cases and are often ineligible to intensive chemotherapy and/or allogeneic SCT, the prognosis of BPDCN is extremely poor with a median time between diagnosis and death of 4.5 months (Guru Murthy, Leuk Research 2018). Azacitidine, which is approved alone or in combination with venetoclax in elderly AML patients considered unfit for intensive chemotherapy (DiNardo et al NEJM 2020) might be an option however there are only limited data in BPDCN. Azacitidine as monotherapy showed some clinical benefit in 5 older patients however responses rarely exceeded 6 months and 3 patients died from infections (Laribi, Eur J Haematol 2014, Khwadja, Leuk Lymphoma 2016, Chahine, Clin Lymphoma Myeloma & Leukemia 2020).

In conclusion, BPDCN remains an unmet medical need and newer therapeutic strategies are required to improve its prognosis in fit and unfit patients.

2.3. TAGRAXOFUSP IN THE TREATMENT OF BPDCN

The cell surface antigen CD123, the α-subunit of interleukin (IL)-3 receptor, is constantly overexpressed at the surface of tumoral cells (Muñoz et al, 2001). The BPDCN malignancy arises from proliferation of malignant plasmacytoid dendritic cells (pDCs) that ubiquitously express high levels of CD123, with a differential overexpression compared to normal cells. Tagraxofusp (ELZONRIS, formerly SL-401) is a novel protein comprised of recombinant human IL-3 genetically fused to a truncated diphtheria toxin protein, which targets the interleukin-3 receptor (IL-3R). The overexpression of IL-3R subunit alpha (IL3RA or CD123) is nearly constant in cases of BPDCN, making it a suitable candidate for tagraxofusp treatment.

Tagraxofusp is indicated as monotherapy for the first-line treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) and is the only authorized therapy for the treatment of this condition in the EU and US. The recommended dose is 12 µg/kg body weight tagraxofusp administered as an intravenous infusion over 15

minutes, once daily, on days 1-5 of a 21-day cycle. The dosing period may be extended for dose delays up to day 10 of the cycle. Treatment should be continued until disease progression or unacceptable toxicity.

A first small clinical study involving 11 patients with BPDCN yielded positive results (Frankel, Blood 2014). The results of a larger dose-finding confirmatory trial in 47 patients were published in 2019 (Pemmaraju, NEJM 2019). At the dose of 12 µg/kg, the objective response rate (ORR) was 90% in treatment naive patient Forty-five percent of first-line patients could proceed to allogeneic SCT. The rate of complete response plus clinical complete response was 72%. Survival rates at 18 and 24 months were 59% and 52%, respectively in this cohort. The ORR was 67% in previously treated patients and median overall survival was 8.5 months. These results have led to FDA approval of tagraxofusp in BPDCN. The first results of the STML-401-0114 phase 1/2 trial in 89 patients (65 first line and 19 R/R) who received a 12 µg/kg dose on days 1 to 5 of multiple 21-day cycles. Were presented at the 2021 ASH conference. Patients with known active or suspected central nervous system (CNS) leukaemia were not included in the study. The primary endpoint was the rate of complete response (CR), defined as complete resolution of the disease / clinical complete response (CRc), defined as CR with residual skin abnormality not indicative of active disease. The STML-401-0114 study confirmed the excellent results obtained with TAG, especially in first line patients (Pemmaraju, Blood 2021). Across all 65 previously traetmant-naive patients tagraxofusp resulted in a CR/CRc rate of 56.9% (95% confidence interval [CI]: 44.0, 69.2), including 13 patients in the confirmatory efficacy cohort where the CR/CRc rate was 53.8% (95% CI: 25.1, 80.8). A recent update of this trial with a median follow-up of 34 months has been published in 2022 (Pemmaraju JCO 2022). In first line patients the objective response rate was 75% and the CR + CRc rate was 57%. The median time to, and duration of, CR + CRc was 39 (range, 14-131) days and 24.9 months. Median OS was 15.8 months. Half the patients who achieved CR + CRc could be bridged to SCT (6 autologous and 13 allogeneic SCT). Median OS in the group was 38.4 months. Interestingly, four of 18 patients who achieved CR + CRc and were not transplanted had a response > 6 months, including two with responses lasting 27 and 52 months. In the 19 efficacy-evaluable R/R patients, the ORR was 58% including one CR and two CRc. Median OS was 8.2 months.Tolerance was satisfactory; most adverse events occurred during the first cycle. Eighteen patients who received 12 mcg/kg developed a CLS, which was non severe (grade 2) in 67% of patients and completely resolved. Myelosuppression was modest, reversible, and limited to the first or second treatment cycles. There was no cumulative hematologic toxicity with continued TAG treatment.

Preliminary results of a retrospective multicenter study of 22 patients (15 first line and 7 R/R) with BPDCN treated with tagraxofusp in the European Expanded Access Program have been presented at ASH in 2022 (Deconinck, Blood 2022). ORR was 87% in 1L and 57% in R/R pts. Allogeneic SCT was undertaken in 9 of 15 1L pts (60%; 6 CR, 3 PR) and in 2 of 7 R/R pts (29%; 1 CR, 1 PR). With a median follow-up of 9.5 months (range 1.0-25.0), median PFS was 7.8 months in first line and 4.3 months in R/R pts. Median OS was not reached in first line and was 8.6 months in R/R pts. In SCT pts, median OS was not reached both in first line and R/R pts.

Collectively, these results show that TAG monotherapy is associated with a high response rate and durable responses that allow many patients to proceed to SCT. In patients ineligible for SCT, TAG maintenance may be proposed to prolong disease control.

2.4. VENETOCLAX IN BPDCN

Preclinical data have shown that AML cells are sensitive to BCL-2 inhibition (Konopleva, Cancer 2006; Beurlet, Blood 2013; Pan, Cancer Discov 2014; Bogenberger, Leukemia 2014), prompting the launch of several clinical trials in AML and mydelodysplastic syndromes. Recently published and preliminary results of ongoing clinical trials in myeloid malignancies suggest that venetoclax, alone or in combination, is well tolerated (especially in older patients) and displays significant clinical activity (Konopleva, Cancer Discovery 2016; Di Nardo, Am J Hematol 2017; Di Nardo, Blood 2018). These results have led to the recent approval of venetoclax in combination with hypomethylating agents by the FDA and EMA in older patients with AML.

The clinical experience of venetoclax in BPDCN remains limited at present. Montero and colleagues have shown that BPDCN are sensitive to venetoclax in vitro and in vivo (Montero, Cancer Discov 2017). Venetoclax monotherapy in one patient with a relapsed refractory cutaneous BPDCN led to a complete response > 10 month (Grushchak, Medicine 2017). Agha and colleagues reported impressive efficacy of venetoclax monotherapy in one patient with refractory disease (Agha, NEJM 2018). We similarly treated with venetoclax alone a patient with a BPDCN that was refractory to 2 lines of induction therapy. The addition of venetoclax resulted in a complete remission that allowed proceeding to allogeneic SCT (Micol, NEJM 2019). An increasing number of reports seem to confirm the efficacy on venetoclax monotherapy even in heavily pretreated BPDCN patients (Beziat, Leuk Res 2019; Egger, J Drugs Dermatol 2021; Molina Castro, Cureus 2022, Schwede, Ann Hematology 2020). Collectively, these observations and preclinical experiments in vitro and in animal models strongly suggest that BPDCN cells are particularly sensitive to venetoclax.

2.5. RATIONALE FOR THE USE OF A TAGRAXOFUSP AND VENETOCLAX COMBINATION

Given the results described above, one may speculate that the association of venetoclax and tagraxofusp could display superior clinical activity than either drug alone and limit the emergence of resistant subclones. The most common side effects observed with tagraxofusp are capillary leak syndrome, hepatic dysfunction, and thrombocytopenia. Venetoclax is associated with neutropenia, thrombocytopenia, and tumor lysis syndrome. Because most side effects of the two drugs do not overlap and pharmacokinetics interactions are unlikely, it was anticipated that adding venetoclax to tagraxofusp should have an acceptable safety profile. Early data of a phase 1b trial combining tagraxofusp and azacitidine +/- venetoclax in 34 treatment-naive and relapsed/refractory CD123+ AML, including BDPDCN, have recently been presented at the 2021 ASH conference (Lane et al. Blood 2021). The adverse events observed were those expected with these molecules with no additional unexpected toxicities. Rather expectedly, the addition of venetoclax to tagraxofusp and azacitidine increased the risk of cytopenias. The results observed in BPDCN are interesting: 2 out of 3 patients who had relapsed after a prior tagraxofusp course reached another CR/CRi with the triplet combination and could proceeded to allogeneic SCT. In treatment naive non-BPDCN AML, which respond very poorly to tagraxofusp monotherapy, the triplet combination yielded an impressive 89% CR/CRi rate. Again, because of the trial design, it is difficult to determine whether the use of azacitidine with tagraxofusp and venetoclax had a positive impact on the response rate. It is worth mentioning that AML patients treated with

tagraxofusp + azacitidine responded poorly, which may indicate that venetoclax rather than azacitidine played a major role.

The goal of this phase II study is thus to investigate the efficacy and safety of the combination of tagraxofusp + venetoclax in patients with treatment naive BPDCN patients. We chose not to include azacitidine in the combination therapy, because the trial will include older patients (median age of BPDCN adult patients is 65-70 year), since:

a) the therapeutic efficacy of azacitidine alone is unclear at present in BPDCN and,

b) adding azacitidine would potentially increase toxicities (especially cytopenias).

Allogeneic SCT is currently the sole treatment that have demonstated a survival advantage in all published data and the delay to organize the procedure is usually 3 months. All patients responding within the first 3 cycles will be considered for allogeneic stem cell transplantation if they are eligible.

2.6. CNS PROPHYLAXIS AND TREATMENT

CNS is very frequently involved in BPDCN at diagnosis even if neurological symptoms are usually absent. In the most representative retrospective series, incidence of CNS involvement is about 30%, ranging from 10 to 100% and in current recommendations, a prophylactic intrathecal chemotherapy (IT) is mandatory in association with first line induction therapy. Even if venetoclax is known to cross hemato-cerebral barrier, systematic prophylactic IT will be associated to all TAGVEN cycles in this study and patients with a documented CNS involvement will receive a curative sequence of intrathecal chemotherapy concomitantly with the TAGVEN regimen.

3. OBJECTIVES OF THE STUDY

3.1. PRIMARY OBJECTIVE

The primary objective is the efficacy measured by the proportion of participants who achieve a composite complete remission (cCR) = complete remission [CR] or complete remission with incomplete marrow recovery [CRi] or complete response with minimal residual skin abnormality [CRc, clinical] defined by a marked clearance of ≥ 75% of a patient's skin lesions from baseline (see appendix 2 and 5) and a complete metabolic response after 3 cycles of the tagraxofusp + venetoclax combination.

3.2. SECONDARY OBJECTIVES

- Safety profile of the tagraxofusp and venetoclax combination
- Incidence of Minimal Residual Disease (MRD)-Negative Responses measured by flow cytometry with a sensitivity of 0.1%
- Objective Response Rate (ORR) after 3 TAGVEN cycles defined as the proportion of participants who achieve either a cCR or a partial remission (PR) according to the European Leukemia Net 2022 defintions adapted to BPDCN (appendix 2)
- Progression-free Survival (PFS)
- Relapse-free survival (RFS)
- Duration of response defined by cCR (DOR)

- Overall Survival (OS)
- Proportion of patients bridged to allogeneic stem cell transplantation after completion of at least 3 cycles of treatment.
- Possible predictors of response with respect to cytogenetics and mutational status

4. STUDY DESIGN

4.1. OVERALL DESIGN

This is a French wide multi-center non-randomized phase 2 study evaluating the efficacy and safety of the combination of tagraxofusp and venetoclax (TAGVEN) in treatment naive BPDCN patients.

A total of 33 patients will be enrolled in the study to ensure the recruitment of 31 evaluable patients.

An interim analysis will be planned after the first 11 inclusions and will be considered as the safety run of the study. If 7 (63.6%) or less than 7 patients are identified with a cCR or ≥ 4 patients must stop the treatment due to severe AEs, the intervention would be declared uninteresting, and no more additional patient will be included. The study will be stopped. We do not plan to explore lower doses or scheduels shifts.

4.2. STUDY DURATION

The accrual period is expected to last 36 months. The date of study initiation is defined by the date of consent of the first patient registered into the eCRF. The maximum treatment duration is twenty-four 28-days cycles.

All patients will receive at least 3 cycles of tagraxofusp with venetoclax (unless unacceptable toxicity). After the 3rd TAGVEN cycle, eligible patients may proceed to allogeneic hematopoietic stem cell transplantation. For patients not eligible for transplantation, a maximum of 12 cycles of tagraxofusp will be administered. Treatment with venetoclax will be administered until progression or unacceptable toxicity for a maximal duration of twenty-four 28-days cycles.

4.3. FOLLOW-UP

Patients will be followed until progression or death up to 12 months after the last administration of treatment. The total study duration is expected to be 72 months. The end of study is defined by the last visit last patient per protocol excluding the Long Term Follow Up.

For patients who discontinue study drugs for reasons other than disease progression, hematology and disease assessments data will be collected at 3 months intervals for 12 months after the last administration of treatment.

4.4. LONG TERM FOLLOW-UP

With patient consent, an observational study (RNIHS) for long term survival, and relapse, will be performed for a maximum of 5 additional years. Survival information and post treatment follow up (i.e., the date and cause of death, all post treatment cancer therapies including stem cell transplantation, regimens, dates of initiation and completion, etc.) will be collected every 6 months.

4.5. PREMATURE TERMINATION OF THE STUDY

The study will be prematurely terminated if one of the following conditions are met:

- the occurrence of serious unexpected side effects of treatment
- excessive treatment-related mortality
- relevant pertaining new information from other studies or publications
- excessive number of deviations from the study protocol
- any other fact which would change the risk-benefit analysis of this trial

4.6. END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to be 12 months after the end of experimental treatment of last patient. After the LPLV, the patient could enter in the observational phase during a maximum period of 5 additional years.

4.7. NUMBER OF SUBJECTS AND NUMBER OF CENTER

A total of 33 patients will be enrolled in the study to ensure that at least 31 patients could be analyzed. Approximately 30 French centers will participate to the study.

4.8. CONSTITUTION OF DSMB

The DSMB is composed of several members, independent of the sponsor and the investigators, the number of which is to be determined for each clinical study (a minimum of three members). The study DSMB should, whenever possible, include one or more clinicians and/or specialists in the pathology and/or therapeutics being studied, and a biostatistician when the study requires interim statistical analyses.
A data safety monitoring board (DSMB) will examine all Serious Adverse Events (SAE) and Serious Adverse Reactions (SAR) including Suspected Unexpected Serious Adverse Reaction (SUSAR) throughout the study.

The first DSMB will take place when the 11 first included patients will have reached 3 cycles for safety analysis.
Additionally, the DSMB will review the trial every year (DSUR is sent every year) or in case of an abnormal rate of SAE according to pharmacovigilance reporting. This independent committee will write a safety report to send it to the ethic committee (CPP) and health authorities (ANSM) after each DSMB.

The trial can be prematurely interrupted or terminated on the advice of the DSMB.

5. STUDY TREATMENT DESIGN

5.1. TREATMENT SCHEDULE

This is an open label multicenter non-randomized single arm study evaluating the efficacy and safety of tagraxofusp and venetoclax in patients with treatment naïve BPDCN. All patients participating in the study will receive (see section 8 for details):

- venetoclax 400mg/day orally after a pre-phase/ramp-up period of at least 3-days (maximum 28 days), VEN (daily administration) in combination with TAG twenty-four 28 days-cycles, the count of cycles (C1D1) starts on the day of the first TAG administration
- tagraxofusp starting at the end of the venetoclax ramp-up period i.e. at day 4 to 28 for twenty-four 28-days cycles, TAG 12 µg/kg body weight administered as an intravenous infusion over 15 minutes, once daily, on days 1-3 of each 28 days-cycle, C1D1 is the day of the first TAG administration

5.2. TREATMENT SCHEDULE ACCORDING TO RESPONSE

The primary objective of the trial is the rate of cCR after 3 cycles of the TAGVEN combination. Following the post C3 evaluation, treatment will follow these rules:

1- In patients in cCR after 3 TAGVEN cycles, TAGVEN will be continued until unacceptable side effects, progression or death, whichever comes first, for a maximum of twenty-four 28-days cycles, per investigator's decision or patient's choice, in patients still in cCR after 12 TAGVEN cycles, either TAG or VEN may be discontinued for the remaining 12 cycles. Whenever feasible, allogeneic SCT will be systematically proposed to eligible patients reaching a cCR within or after the 3rd cycle. Additional TAGVEN cycles are allowed if necessary to facilitate the transplant procedure organization.

2- Patients in PR after the 3rd cycle will be considered to have failed the primary objective however 3 additional TAGVEN cycles (i.e. 6 cycles in total) may be administered per investigator's decision to try to reach cCR. Patients reaching a cCR after these 3 additional cycles will continue treatment according tho the protocol schedule, will be followed for secondary criteria e.g PFS, FOR and OS. They may be considered for allogeneic SCT if eligible. Patients not reaching a cCR after these 3 additional cycles will exit the protocol and will be treated according to the local investigator's decision.

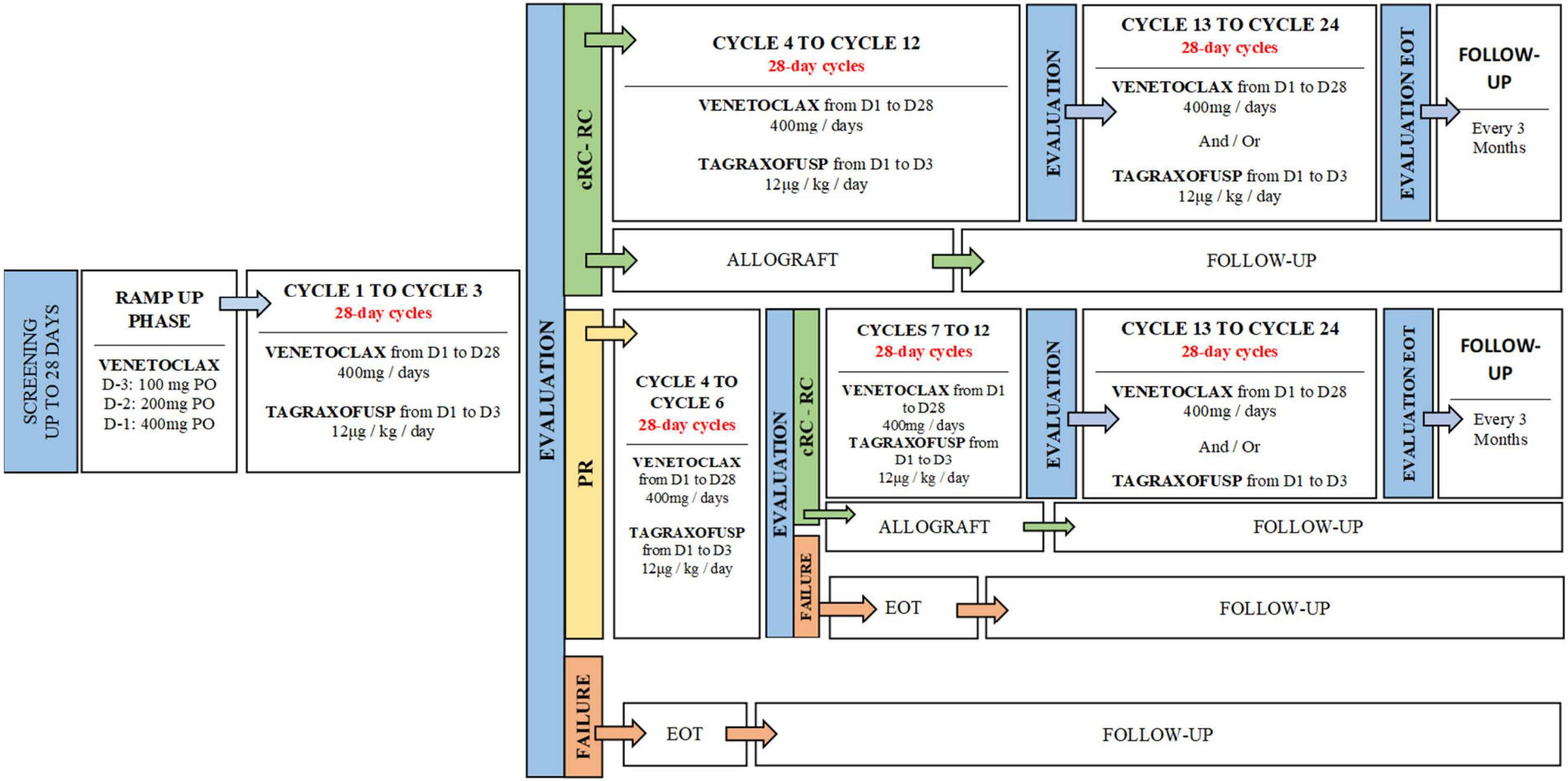
3- Patients in response < PR after the 3rd cycle will be considered as a protocol failure and will be treated according to the local investigator's decision.

5.3. CNS PROPHYLAXIS/TREATMENT

Triple prophylactic intrathecal chemotherapy (IT, methotrexate 15 mg, cytarabine 40 mg and depomedrol 40mg) will be systematically administered via lumbar puncture on screening ortreatment cycles avoindind the ramp-up phase. According to the National Comprehensive Cancer Network (NCCN) recommendations, triple prophylactic IT will be systematically administered at each cycle until allogeneic stem transplantation or for at least 8 injections. Monthly IT prohylaxis may then be administered according to local policy.

In case of documented CNS involvement, triple IT (methotrexate 15 mg, cytarabine 40 mg and depomedrol 40mg) will be administered twice weekly until complete clearance of cerebrospinal fluid (CSF) tumor cells. After CSF sterilization, intrathecal injections will be administered once weekly for 1 month (4 injections) then monthly for at least 8 injections. Monthly IT prohylaxis may then be administered according to local policy

5.4. STUDY DESIGN



See § 5.2: patients in PR after C3 may be given another 3 cycles of TAGVEN per investigator's decision and continue TAGVEN if they reach a cCR after these cycles. In patients still in cCR under TAGVEN after 12 cycles, the investigator may choose to discontinue either TAG or VEN up to cycle 24.

- **PATIENT REGISTRATION AND INCLUSION:**

Only patients with treatment naive BPDCN will be included in the study.

Registration will be done directly by entering patient's data in the eCRF before any initiation of treatment.

After validation of all inclusion criteria in the CRF, the inclusion number will be automatically assigned and sent by email to coordinator, head of project, and CRA monitor.

6. STUDY POPULATION

6.1. INCLUSION CRITERIA

1. Patients with a confirmed BPDCN diagnosis according to WHO 2022 revised criteria and naive of treatment ; patients with skin or lymph node lesions but no bone marrow involvement can be included
2. Age ≥18 years
3. Ability to understand the protocol and to sign an informed consent
4. Possibility of follow-up
5. ECOG < 3
6. Adequate renal function as demonstrated by a calculated creatinine clearance ≥ 60 mL/min by the Cockcroft-Gault formula.
7. Albumin level ≥3,2g/dL (albumin infusions are not permitted to enable eligibility)
8. Adequate cardiac function defined by LVEF >/= 50% by MUGA or ECHO and no clinically significant abnormalities on a 12-lead ECG
9. Adequate liver function as demonstrated by:
    a. aspartate aminotransferase (AST) ≤ 2.5 × ULN*
    b. alanine aminotransferase (ALT) ≤ 2.5 × ULN*
    c. bilirubin ≤ 3.0 × ULN, unless due to Gilbert's syndrome*

* *Unless considered due to leukemic organ involvement, in that cases values must be* ≤ 10 × ULN

10. Men, and women of childbearing potential (any fertile woman, following menarche and until becoming post-menopausal unless permanently sterile) must be using a highly effective method of contraception (approved contraceptives or intrauterine devices) during the study and for 1 week after the last tagraxofusp or venetoclax dose
11. Negative urine/blood pregnancy test within 1 week prior to the initiation of treatment (if applicable)
12. Patient covered by any social security system.

6.2. EXCLUSION CRITERIA

1. Participation to another clinical trial with any investigative drug, chemotherapy, wide-field radiation, or biologic therapy within 30 days prior to study enrolment.

2. Previous treatment with venetoclax or tagraxofusp for any malignancies or conditions
3. Treatment of BPDCN with any prior chemotherapy or investigational agents, except hydroxyurea for less than 14 days at the time of inclusion
4. Concomitant immunosuppressive therapy except for low-dose prednisone (≤10 mg/day)
5. Known allergy or sensitivity to tagraxofusp, venetoclax, and any of its components or excipients
6. Pregnant or breastfeeding women
7. Known positivity for hepatitis B or C infection except for those subjects with an undetectable viral load or subjects with serologic evidence of prior vaccination to HBV
8. Evidence of uncontrolled systemic infection requiring therapy (viral, bacterial, or fungal)
9. Subject has any history of clinically significant condition(s) that in the opinion of the investigator would adversely affect his/her participating in this study including, but not limited to:
    - Cardiovascular disease e.g. NYHA heart failure > class 2, uncontrolled angina, history of myocardial infarction, unstable angina or stroke within 6 months prior to study entry, uncontrolled hypertension, or clinically significant arrythmias not controlled by medication
    - Renal, pulmonary, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, or bleeding disorder independent of leukemia
10. Subject with a history of other malignancies prior to study entry, except for:
    a. Adequately treated in situ carcinoma of the breast or cervix uteri
    b. Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin
    c. Prostate cancer without needs for specific therapy
    d. Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
11. Malabsorption syndrome or other conditions that preclude enteral route of administration
12. Patient with hereditary fructose intolerance

7. SCHEDULE OF ASSESSMENTS

7.1. FLOW-CHART

	Inclusion phase	VEN prephase	Treatment Period													PEOT / EOT	Follow-up	Long Term Follow Up
	Screening[a]	D-3 D-2 D-1	C1D1	C1D28	C2D1	C2D28	C3D1C3D1	C3D28	Day 1 (C4 to C6)	C6D28	Day 1 (C7 to C12	End of C12	Day 1 (C13 to C18)	C18D28	Day 1 (C19 to C24)	No later than end of C24	**Every 12 weeks for 1 year**	**Observational study**
Informed consent	X																	
Inclusion /exclusion criteria	X																	
Demo data/ Medical history/ Cancer history	X																	
Patient status																	X	X
Safety assessments																		
Physical examination	X	X	X		X		X		X		X		X		X	X	X	
Vital signs/Weight[b]	X	X	X		X		X		X		X		X		X	X	X	
ECOG status	X	X	X		X		X		X		X		X		X	X	X	
12-lead standard ECG	X																	
Echocardiography	X																	
Adverse events[b]	X		X		X		X		X				X		X	X		
Concomitant treatment[b]	X		X		X		X		X				X		X	X		
Biological assessments																		
Hematology[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry	X[d]	X	X[d*]		X[d*]		X[d*]		X[d*]		X[d*]		X[d*]		X[d*]	X[d**]	X[d**]	
Coagulation[e]	X	X	X		X		X		X		X		X		X	X	X	
HIV, HCV, HBV	X																	
βHCG if applicable	X[f]		X		X		X		X		X		X		X			

	Inclusion phase	VEN prephase	Treatment Period													PEOT / EOT	Follo w-up	Long Term Follow Up
	Screening[a]	D-3 D-2 D-1	C1D1	C1D28	C2D1	C2D28	C3D1	C3D28	Day 1 (C4 to C6)	C6D28	Day 1 (C7 to C12	End of C12	Day 1 (C13 to C18)	C18D28	Day 1 (C19 to C24)	No later than end of C24	**Every 12 weeks for 1 year**	**Observatio nal study**
Disease evaluation at end of cycle or begining of subsequent cycle																		
Bone Marrow Aspirate[g]	X			X		X		X		X		X		X		X		
Disease assessment	X			X		X		X		X		X		X		X	X	X
Cytogenetics[g]	X			X		X		X		X		X		X		X		
Molecular Biology (NGS) / MRD analysis	X			X[h]		X[h]		X[h]		X[h]		X[h]		X[h]		X[h]		
Lumbar puncture[i]	X[i]		X[i]		X[i]		X[i]		X[i]		X[i]		X[i]		X[i]			
Metabolic imaging (FDG Pet Scanner)[j]	X		X[j]		X[j]			X										
SWAT Score	X		X[k]	X		X		X				X		X		X		
Centralized assessments																		
Blood/marrow banking (besançon lab)	X			X		X		X				X				X		
Centralized review (Besançon lab) Complete phenotype diagnosis LpDC	X																	
MRD analysis of BM with flow cytometry (Besançon lab)				X		X		X				X				X		
Treatment administration																		
Venetoclax		X[l]	X	X	X	X	X	X	X	X	X	X	X[n]	X[n]	X[n]			
Tagraxofusp			X[m]		X		X		X				X[n]		X[n]			

Footnotes:

a. Within 28 days of C1D1
b. Vital signs, weight, AE and concomitant medications should be monitored daily during TAG infusions.
c. Complete Blood Count includes hemoglobin, white blood cell (WBC) count, absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils) and platelet count. In the event of neutropenia (absolute neutrophil count [ANC] < 0.750x109/L) or thrombocytopenia (platelets of less than 50x109/L), these assessments will be conducted as frequently as the

investigator feels necessary. *During the venetoclax prephase/ramp up period: complete blood count should be monitored at least twice a day. Additional monitoring may be scheduled at the discretion of investigators.*

d. Serum chemistry should be performed daily during the VEN prephase and all TAG infusion. Clinical chemistry includes sodium, potassium, chloride, bicarbonate, calcium, uric acid, total protein, albumin, lactate dehydrogenase (LDH), fasting glucose, creatinine, creatinine clearance (using Cockroft and Gault formula), CRP, total and indirect bilirubin, , ALAT, ASAT, alkaline phosphatase and,GGT. In the event of ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted as frequently as the investigator feels it necessary and until toxicity resolves to ≤ Grade 2. *During the venetoclax prephase/ramp up period: blood chemistry including serum creatinin, sodium, potassium, chloride, bicarbonate, calcemia, phosphoremia, LDH should be monitored at least twice a day. Additional monitoring may be scheduled at the discretion of investigators.*

d*. Serum chemistry should be performed daily during the VEN prephase and all TAG infusion. Clinical chemistry includes sodium, potassium, chloride, bicarbonate, calcium, uric acid, total protein, albumin, lactate dehydrogenase (LDH), fasting glucose, creatinine, creatinine clearance (using Cockroft and Gault formula), total and indirect bilirubin, , ALAT, ASAT, alkaline phosphatase and,GGT.

d**.Serum chemistry should be performed daily during the VEN prephase and all TAG infusion. Clinical chemistry includes sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, creatinine, creatinine clearance (using Cockroft and Gault formula), total and indirect bilirubin, ALAT, ASAT, alkaline phosphatase and GGT.

e. Coagulation profile includes prothrombin time (PT), which will also be reported as international normalized ratio (INR). + TCA+ fibrinogen. *During the venetoclax prephase/ramp up period coagulation test should be monitored at least twice daily. Additional monitoring may be scheduled at the discretion of investigators.*

f. βHCG testing will be realized at screening in women with childbearing potential and repeated on day 1 of each subsequent cycle, until all study drugs are permanently withdrawn.

g. Bone marrow disease evaluation should be performed at the end of cycle 1, 2 and 3. Thereafter, bone marrow aspirate will be performed at the investigator's discretion but at least twice per year after the beginning of treatment and at the end of treatment.

h. Molecular biology using high-level sequencing enables local analysis of residual disease from C1D28 until the end of the study.

i. A 1st lumbar puncture should be performed on screening or cycle 1 avoiding the venetoclax ramp up phase. Triple prophylactic intrathecal chemotherapy (IT, methotrexate 15 mg, cytarabine 40 mg and depomedrol 40 mg) will be systematically administered at each cycle until allogeneic stem transplantation or for a maximum of 8 injections. In case of documented CNS involvement, triple IT will be administered twice weekly until complete clearance of cerebrospinal fluid (CSF) tumor cells. After CSF sterilization, intrathecal injections will be administered once weekly for 1 months (4 injections) then monthly for at least 8 injections.A PET scanner should be performed at screening and the end of cycle 3.

j. An optional PET scanner can be realized at the end of cycle 1 or 2 at the investigator's discretion

k. If not done at screening

l. VEN dosing according to the pre-phase/ramp-up schedule

m. TAG will be started at the earliest on day 4 of the initiation of venetoclax and no later than day 28. C1D1 will be defined by the first day of the first TAG infusion following the VEN prephase.

n. Per investigator's decision or patient's choice, in patients still in cCR after 12 TAGVEN cycles, either TAG or VEN may be discontinued for the remaining 12 cycles.

7.2. SCREENING

All patients must provide a written informed consent prior to any study-specific examination or procedure. Duration of screening period (from written informed consent to first day of induction phase) is 28 days maximum. Only patients who fulfill all inclusion criteria and none of the exclusion criteria may be enrolled in the study.

7.2.1 Clinical screening assessments

- Medical history including demographics, previous and current diseases, medications, and transfusions
- ECOG performance status (PS) (appendix 1)
- Physical examination, including weight, height, vital signs, cardiopulmonary examination and evaluation of lymph nodes, liver and spleen involvement.
- Evaluation of skin involvement using the SWAT score (appendix 5) if applicable

7.2.2 Standard biological screening assessments

- Complete Blood Count with hemoglobin, WBC count with differentials, platelets, and numeration of circulating blasts
- Serum electrolytes (sodium, potassium, chloride, bicarbonate, calcium, uric acid)
- Total protein, albumin, LDH, glucose, serum creatinine, creatinine clearance (using Cockroft and Gault formula), CRP
- Liver function tests (LFTs): total and indirect bilirubin, AST, ALT, alkaline phosphatase, GGT
- Coagulation: TCA; fibrinogen; prothrombin time (PT), INR
- Beta-HCG (if applicable)
- HIV, HBV (Ag Hbs, anti-Hbs and Hbc Abs), HCV serologies
- Bone marrow aspiration with cytochemistry, cytogenetics and flow cytometry (for diagnosis and assessment of measurable residual disease) according to ELN 2022 recommendations
- Standard AML molecular biology NGS (NPM1, FLT3, CEBPA, DNMT3A, IDH1, IDH2, RUNX1, ASXL1, TP53, N/KRAS, ZRSR2, SRSF2, IZKF1 mutations) will be performed in each center according to local procedures and ELN 2022 recommendations.
- Lumbar puncture for CSF examination and first intrathecal chemotherapy dose can be done during the screening phase or the first cycle, at investigator's discretion.

7.2.3 Standard radiological screening assessments

- A metabolic imaging (PET scanner) to assess extramedullary involvement will be systematically realized at baseline.

7.2.4 Cardiologic screening assessment

- An echocardiography (or MUGA) scan will be performed before the initiation of treatment.
- 12-lead ECG

7.2.5 Centralized biological assessments at screening

A sample of bone marrow (3 mL on EDTA) and 35 mL of peripheral blood (4 tubes 7 mL EDTA vacutainer and 1 dry tube 7 mL) will be shipped to Pr Francine Garnache-Ottou's reference laboratory in Besançon for centralized review.

Besides centralized review, cells and nucleic acids (DNA, RNA) will be systematically banked at the reference laboratory in Besançon. Further biological studies are planned:

- Analysis of CD123 expression by flow cytometry and semi-quantitative quantification of CD123 antigenic sites (CELLQUANT CALIBRATOR ® Kit, Biocytex®)
- Quantification of bcl-2 expression by flow cytometry
- Functional assays measuring the cytotoxic activity of TAG and VEN on BPDCN blasts with regards to the level of CD123 and bcl-2 expression

7.3. EVALUATIONS DURING THE TREATMENT PERIOD

7.3.1 Standard evaluations

These evaluations should be performed at the beginning of each treatment cycle. Other biological assessments may be performed at the investigator's discretion.

7.3.1.1. Clinical evaluation

- ECOG performance status (PS) (appendix 1)
- Physical examination including weight, vital signs (to be performed twice daily during the venetoclax prephase and first tagraxofusp cycle)
- Extramedullary localizations (clinical and relevant morphology assessments, no dedicated imaging required) including evaluation of skin involvement using the SWAT score if applicable.

7.3.1.2. Standard biological evaluation

- Complete Blood Count (CBC) before treatment with hemoglobin, WBC count with differentials, platelets, and numeration of circulating blasts. CBC is mandatory for C1D1. For D1 of cycles 2, 3, 4, 7 and 13, CBC must only be performed if D28 of cycles 1, 2, 3, 6 and 12 respectively has not been performed the previous day.
- Serum electrolytes (sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, Uric acid)
- total protein, Albumin, LDH, glucose, serum creatinine, creatinine clearance (using Cockroft and Gault formula)
- Liver function tests (LFTs): total and indirect bilirubin, AST, ALT, alkaline phosphatase, GGT
- Coagulation: TCA, fibrinogen, prothrombin time (PT), INR
- Virology tests will be performed as clinically necessary

- Beta-HCG on day 1 of each cycle in women with childbearing potential until all study drugs are permanently withdrawn

NB: because of the potential risk of TLS during the venetoclax prephase/ramp-up period, complete blood count; coagulation; blood chemistry including serum creatinin, sodium, potassium, chloride, bicarbonate, calcemia, phosphoremia and LDH should be monitored at least twice a day. Additional monitoring may be scheduled at the investigator's discretion.

7.3.2 Disease evaluation

7.3.2.1 Bone marrow evaluations

A bone marrow aspiration to assess disease response as per IWG criteria will be performed at end of cycle 1, end of cycle 2 and cycle 3 (± 3 days). Thereafter, bone marrow aspirate will be performed at the investigator's discretion, ideally every 3 months, but at least every 6 months until 2 years after the beginning of treatment (i.e. at C6, C12; C18 and C24).

7.3.2.2 MRD analysis

Additionnal bone marrow samples must be obtained for cytogenetics, molecular biology and MRD assessment according to study flow chart at the end each first 3 cycles, end of cycle 12 and 24 or EOT. MRD will be performed in each center according to local procedures by molecular biology NGS (NPM1, FLT3, CEBPA, DNMT3A, IDH1, IDH2, RUNX1, ASXL1, TP53, N/KRAS, ZRSR2, SRSF2, IZKF1 mutations, TCRg and IGH translocation). In addition, MRD will be measured on bone marrow samples in the central laboratory in Besançon using multicolour flow cytometry with a specific combination of markers: CD4+, CD56+, CD123+, MPO, BDCA-2, BDCA-4, cTCL1, nTCF4, TcER1, NG2, IRF8, BadLamp.

7.3.2.3 Metabolic Imaging

A PET-scanner will be performed at screening and at the end of cycle 3. Optionnal PET- scanner could also be realized at the end of cycle 1 or 2 at the investigator's discretion.

7.4. END OF TREATMENT/PREMATURE END OF TREATMENT EVALUATION

7.4.1 Clinical evaluation

- ECOG performance status (PS)
- Physical examination including weight, vital signs
- Extramedullary localizations (clinical and relevant morphology assessments, no dedicated imaging or procedure required)

7.4.2 Standard biological assessment

- Complete Blood Count with hemoglobin, WBC count with differentials, platelets, and numeration of circulating blasts
- Serum electrolytes (sodium, potassium, chloride, bicarbonate)

- Total protein, Albumin, serum creatinine, creatinine clearance (using Cockroft and Gault formula)
- Liver function tests (LFTs): total and indirect bilirubin, AST, ALT, alkaline phosphatase, GGT
- Coagulation : TCA, fibrinogen, prothrombin time (PT), INR

7.4.3 Disease evaluation

A bone marrow aspirate with centralized MRD analysis will be systematically realized at the end of treatment, cytogenetics, molecular biology (NGS) could be realized in each center at the investigator's discretion.

7.5. FOLLOW-UP

Patients will be followed until progression or death up to 12 months after the last administration of treatment. For patients who discontinue study drugs for reasons other than disease progression, hematology and disease assessments data will be collected every 3 months.

7.6. LONG TERM FOLLOW-UP

An observational study (RNIHS) for long term survival, and relapse, will be performed for a maximum of 5 additional years. Survival information and post treatment follow up (i.e., the date and cause of death, all post treatment cancer therapies including stem cell transplantation, regimens, dates of initiation and completion, etc.) will be collected every 6 months.

8. STUDY TREATMENT

8.1. VENETOCLAX ADMINISTRATION AND SCHEDULE

To avoid the risk of concomitant tumor lysis syndrome (TLS) and capillary leak syndrome (CLS), a prephase/rump up period with venetoclax alone will be initiated. Treatment with venetoclax will be introduced over a 3-days period using a progressive increase of daily dosage according to the ramp-up dose schedule described in table 1.

Table 1 : Venetoclax dosing during ramp up period

Day -3		100 mg daily
Day -2		200mg daily
Day -1 and beyond		400 mg daily

Tagraxofusp injection will begin at the end of the ramp-up dose schedule (see below), at the earliest on day 4 of the initiation of venetoclax and no later than day 28.

Following the prephase/ramp-up period, patients will receive continuous treatment with Venetoclax 400 mg orally once daily in 28 days cycles.

The maximum total duration of treatment with venetoclax is twenty-four 28-days cycles in combination with TAG. The possibility to continue the treatment until progression after 24 cycles in case of ineligibility for the stem cell transplant as per treatment guidelines will be offered to patients still benefitting from the treatment.

8.2. TAGRAXOFUSP ADMINISTRATION AND SCHEDULE

A cycle of tagraxofusp is 28 days. The first injection of tagraxofusp will start after completion of the venetoclax prephase ramp-up period, in the absence of TLS or any grade 3-4 unresolved adverse event, hence on day 4 after the beginning of venetoclax prephase at the earliest, and no later than day 28. The day of the first injection of tagraxofusp will be considered the first day of the first study cycle (C1D1).

All patients will be hospitalized before the initiation of treatment.

From C1 to C24, patients will receive tagraxofusp 12 µg/kg/day for 3 consecutive days (day 1 to day 3) as a 15-minute IV infusion via syringe pump "piggybacked" into an established IV line of 0.9% normal saline. In cases where doses are held, all 3 doses should be delivered within a period of 10 consecutive days. If all 3 doses cannot be delivered in these 10 consecutive days, they should be skipped.

The dose of tagraxofusp will be dependent upon the patient's baseline (i.e. day of first infusion in C1) body weight in kg. This dose will be recalculated if there is a ≥ 10% change in body weight from baseline after a cycle has been completed.

Dose preparation and administration directions are outlined in the accompanying pharmacy manual for tagraxofusp.

C1 of tagraxofusp must be administered in the inpatient setting, with hospitalization beginning the day of the first infusion of tagraxofusp (or a prior day) and ending approximately 24 hours after the last infusion of tagraxofusp. Subsequent cycles of tagraxofusp can be administered in the inpatient setting or in a suitable outpatient ambulatoy care setting equipped for intensive monitoring of patients with hematopoietic malignancies undergoing treatment. Patients will be monitored for at least 4 hours following the administration of each infusion of tagraxofusp.

The possibility to continue the treatment until progression after 24 cycles in case of ineligibility for the stem cell transplant as per treatment guidelines will be offered to patients still benefitting from the treatment.

8.3. TAGRAXOFUSP PREMEDICATION:

Patients will receive the following premedications 60 minutes before each tagraxofusp infusion:

- paracetamol 1000 mg PO
- dexchlorphéniramine 50 mg (or equivalent dose of another H1-histamine antagonist (e.g.hydroxyzine 50 mg)
- Ranitidine 50 mg IV (or equivalent dose of another H2-histamine antagonist)
- Methylprednisolone 1mg/kg IV (or an equivalent dose of another corticosteroid)

8.4. PROPHYLAXIS AND MANAGEMENT OF THE TUMOR LYSIS SYNDROME (TLS)

Patients with acute leukemias are at risk of TLS, especially in those with elevated leukocyte count, circulating blasts, high burden of leukemia involvement in bone marrow, elevated pretreatment LDH levels, renal dysfunction, and dehydration. Venetoclax (and to a lesser extent tagraxofusp) has been associated with TLS in CLL and AML. Prophylactic reductions of potassium, calcium, creatinine, inorganic phosphorus, or uric acid above normal range are recommended prior to beginning study treatment and continue based on the ongoing risk of TLS. Below are the minimum requirements for TLS prophylaxis and management for subjects enrolled into the study. Additional measures should be considered, including increased laboratory tests. All other prophylaxis and monitoring and reducing venetoclax starting dose procedures for TLS will be implemented according to institutional guidelines:

- All subjects will be hospitalized on or before the initiation of the prephase/ramp-up period of VEN and remain in the hospital for at least for 24 hours after reaching the final dose of TAG.
- All patients should have white blood cell count $<25\times 10^9$ /l prior to initiation of venetoclax and cytoreduction prior to treatment may be required.
- All patients should be adequately hydrated and receive anti-hyperuricaemic agents prior to initiation of first dose of venetoclax and during dose-titration phase. Administration of uric acid reducing agent, adequate oral and intravenous hydration while monitoring the fluid status of the subject prior to and during the ramp up of venetoclax will be based on institutional guidelines.
- TLS chemistry tests to be drawn (calcium, inorganic phosphorus, potassium, uric acid, and creatinine) on the first day of venetoclax dosing and each day of a new dose at 0 (within 4 hours prior to dosing) and 6 – 8 hours post dose.
- Additional laboratory assessments may be performed, per investigator discretion, post-dose during ramp up and up to 48 hours after reaching final dose if clinically indicated.
- Abnormal chemistry tests should be corrected promptly.
- If a subject meets criteria for clinically significant laboratory or clinical TLS grade >2, venetoclax should be withheld until resolution.
- Monitor blood counts frequently through resolution of cytopenias. Dose modification and interruptions for cytopenias are dependent on remission status.

8.5. PROPHYLAXIS OR TREATMENT OF CNS LOCALIZATIONS

Triple intrathecal chemotherapy (IT, methotrexate 15 mg, cytarabine 40 mg and Depomedrol 40mg) will be systematically administered via lumbar puncture during screening phase and treatment cycles avoiding the ramp-up phase. According to the NCCN recommendations, triple prophylactic intrathecal chemotherapy (IT, methotrexate 15 mg, cytarabine 40 mg and depomedrol 40mg) will be systematically administered via lumbar puncture at each cycle until allogeneic stem transplantation or for at least of 8 injections. Monthly IT prohylaxis may then be administeredaccording to local policy.

In case of documented CNS involvement, IT (methotrexate 15 mg, cytarabine 40 mg and depomedrol 40mg) will be administered twice weekly until complete clearance of cerebrospinal fluid (CSF) tumor cells. After CSF sterilization,

intrathecal injections will be administered once weekly for 1 months (4 injections) then monthly for at least 8 injections. Monthly IT prohylaxis may then be administered according to local policy.

8.6. INFECTION PROPHYLAXIS

HSV/VZV prophylaxis will be systematically administered using valaciclovir 500 mg twice a day from day 1 until the end of treatment (thereafter at the investigator's discretion).

Pneumocystis jiroveci prophylaxis will be administered using trimethoprim 160 mg/sulfamethoxazole 800 mg (Bactrim Forte ®) one tablet 3 times a week or trimethoprim 80 mg/sulfamethoxazole 400 mg (Bactrim ®) one tablet daily, from day 1 (start of treatment) until the CD4-positive lymphocyte count remains > 0.2 10^9/L. In case of intolerance or allergy to Bactrim, it may be replaced by atovaquone 750 mg twice a day orally. Prohylaxis of fungal infections may used per investgator's decision. Azoles, all of which are CYP3A inhibitors, are widely used in this setting. As venetoclax is predominantly metabolized by CYP3A, co-administration with antifungal agents which are strong or moderate CYP3A inhibitors are expected to increase venetoclax exposure. Dose reductions of venetoclax may be required. When feasible, administration of such a medication should be planned prior to beginning ramp up or beginning of a cycle to prevent dose reductions during a treatment cycle.

8.7. VENETOCLAX DOSE MODIFICATION

8.7.1 Venetoclax dose reduction for hematologic toxicity

Myelosuppression with cytopenias and their complications are extremely frequent in acute leukemias. Patients with neutropenia or thrombocytopenia because of their disease i.e. who have not achieved remission do not require treatment interruptions for myelosuppression. The management of hematologic toxicities attributed to venetoclax is described in table 2.

Venetoclax will be held for in patients reaching CR, Cri or having morphologically leukemia free bone marrow (MLFS) in case of grade 4 neutropenia or grade 4 thrombocytopenia lasting ≥ 7 days. During the first occurrence, venetoclax will be resumed at the same dose upon resolution to grade 1 or 2. For subsequent occurrences, venetoclax will be resumed at the same dose upon resolution to grade 1 or 2 but treatment duration will be reduced by 7 days for each of the subsequent cycles e.g. 21 days instead of 28 days, 14 days instead of 21 days, etc…

8.7.2 Venetoclax dose reduction for non-hematologic toxicity

For non-hematological toxicities ≥ Grade 3 suspected to be related to venetoclax, interrupt venetoclax if not resolved with supportive care. Upon resolution to grade 1 or baseline level, resume venetoclax at the same dose (see table 2).

Table 2: Venetoclax dose modifications guidelines

Adverse Reaction	Occurrence	Dosage Modification
Haematologic Adverse Reactions		
Grade 4 neutropenia (ANC < 500/microlitre) with or without fever or infection; or grade 4	Occurrence prior to achieving remission[a]	In most instances, do not interrupt venetoclax in combination with tagraxofusp due to cytopenias prior to achieving remission

thrombocytopenia (platelet count <25 x 10^3/ microlitre)	First occurrence after achieving remission and lasting at least 7 days	Delay subsequent cycle of venetoclax in combination with tagraxofusp granulocytecolony stimulating factor (G-CSF) if clinically indicated for neutropenia. Upon resolution to grade 1 or 2, resume venetoclax at the same dose in combination with tagaxofusp.
	Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	Delay subsequent cycle of venetoclax in combination with tagraxofusp and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia. Upon resolution to grade 1 or 2, resume venetoclax at the same dose in combination with tagraxofusp, and reduce venetoclax duration by 7 days during each of the subsequent cycles, such as 21 days instead of 28 days.
Non-Haematologic Adverse Reactions		
Grade 3 or 4 non-hematologic toxicities	Any occurrence	Interrupt venetoclax if not resolved with supportive care. Upon resolution to grade 1 or baseline level, resume venetoclax at the same dose.

NB: Should venetoclax be withheld for more than 28 days or in the case of unacceptable toxicity attributable to venetoclax, venetoclax will be discontinued. Patients may continue to receive tagraxofusp as a single agent for a maximum of 24 cycles.

8.7.3 Dose modifications for use with CYP3A inhibitors

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure (i.e., Cmax and AUC) and may increase the risk for TLS at initiation and during the dose titration phase and for other toxicities (see section 10.4).

In all patients, if a CYP3A inhibitor must be used, follow the recommendations for managing drugdrug interactions summarized in Table 3. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted.

The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor (see sections 10.4 and Appendix 5).

Table 3: Management of potential venetoclax interactions with CYP3A inhibitors

Inhibitor	Phase	Venetoclax Dose
Strong CYP3A inhibitor	Initiation and dose titration phase	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg or less.
	Steady daily dose (After dose-titration phase)	Reduce the venetoclax dose to 100 mg or less (or by at least 75% if already modified for other reasons)

Moderate CYP3A inhibitor	All	Reduce the venetoclax dose by at least 50%

8.8. TAGRAXOFUSP ADAPTATION AND INTERRUPTION

8.8.1 Adaptation for non-hematologic toxicities

Most common adverse reactions (incidence ≥ 30%) observed with tagraxofusp are capillary leak syndrome, nausea, fatigue, pyrexia, peripheral edema, and weight increase. Most common laboratory abnormalities (incidence ≥ 50%) are decreases in albumin, platelets, hemoglobin, calcium, and sodium, and increases in glucose, ALT and AST.

During the dosing period for each cycle, individual tagraxofusp infusions may be delayed allowing for toxicity resolution. If all 3 doses are unable to be delivered within 10 consecutive days, they should be skipped. Generally, doses of tagraxofusp will be held for toxicity and then resumed at the same dose following resolution of the event. These guidelines (see table 4) should be followed in the case of the following adverse reaction. In the case of other non-hematological grade ≥ 3 toxicities without resolution to Grade ≤1 or baseline by Day 21 of cycle, delay the start subsequent cycle by up to 14 days (i.e., up to 35 days since the first dose in the previous cycle).

`Table 4 : Tagraxofusp dosage modifications guidelines

Parameter	Severity Criteria	Dosage Modification
Serum albumin	Serum albumin < 3.5 g/dL or reduced ≥ 0.5 g/dL from value measured prior to initiation of the current cycle	See CLS Management Guidelines (Table 5)
Body weight	Body weight increase ≥ 1.5 kg over pretreatment weight on prior treatment day	See CLS Management Guidelines (Table 5)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	ALT or AST increase > 5 times the upper limit of normal	Withhold tagraxofusp until transaminase elevations are ≤ 2.5 times the upper limit of normal.
Serum creatinine	Serum creatinine > 1.8 mg/dL (159 micromol/L) or creatinine clearance < 60 mL/minute	Withhold tagraxofusp until serum creatinine resolves to ≤ 1.8 mg/dL (159 micromol/L) or creatinine clearance ≥ 60 mL/minute.
Systolic blood pressure	Systolic blood pressure ≥ 160 mmHg or ≤ 80 mmHg	Withhold tagraxofusp until systolic blood pressure is < 160 mmHg or > 80 mmHg.
Heart rate	Heart rate ≥ 130 bpm or ≤ 40 bpm	Withhold tagraxofusp until heart rate is < 130 bpm or > 40 bpm.
Body temperature	Body temperature ≥ 38°C	Withhold untiltagraxofuspuntil body temperature is < 38°C.
Hypersensitivity reactions	Mild or moderate	Withhold tagraxofusp until resolution of any mild or moderate hypersensitivity reaction. Resume tagraxofusp at the same infusion rate.
	Severe or life-threatening	Discontinue tagraxofusp permanently.

Tagraxofusp has been associated with capillary leak syndrome, hypersensitivity reactions and hepatotoxicity. Guidelines for the management of these adverse reactions are described more specifically in the paragraphs below.

NB: Should tagraxofusp be discontinued for toxicities, patients may continue to receive venetoclax as a single agent for a maximum of 24 cycles.

8.8.2 Management of the Capillary Leak Syndrome (CLS)

Capillary leak syndrome (CLS), including life-threatening and fatal cases, has been reported among patients treated with tagraxofusp. In patients receiving tagraxofusp in clinical trials, the overall incidence of CLS was 53% (65/122), including Grade 1 or 2 in 43% (52/122) of patients, Grade 3 in 7% (8/122) of patients, Grade 4 in 1% (1/122) of patients, and four fatalities (3%) The median time to onset was 4 days (range - 1 to 46 days), and all but 5 patients experienced an event in Cycle 1.

Before initiating therapy with tagraxofusp (i.e. before the first dose of the cycle 1), ensure that the patient has adequate cardiac function and serum albumin is greater than or equal to 3.2 g/dL. If the patient has an albumin level ≤ 4 g/dL, consider systematic prophylactic albumin infusion before beginning tagraxofusp.

For subsequent tagraxofusp cycles, monitor serum albumin levels prior to the initiation of each dose of tagraxofusp and as indicated clinically thereafter. Albumin must be > 3.5 g/dL or < 0.5 g/dL change from previous cycle prior to the first infusion of the cycle. Assess patients for other signs or symptoms of CLS, including weight gain, new onset or worsening edema, including pulmonary edema, hypotension or hemodynamic instability.

Table 5: CLS management guidelines

Time of Presentation	CLS Sign/Symptom	Recommended Action	Tagraxofusp Dosing Management
Prior to 1st dose of TAG in cycle1	Serum albumin < 3.2 g/dL	Administer 25g intravenous albumin (q12h or more frequently as practical) until serum albumin is ≥ 3.5 g/dL.	
During TAG dosing	Serum albumin < 3.5 g/dL	Administer 25g intravenous albumin (q12h or more frequently as practical) until serum albumin is ≥ 3.5 g/dL AND not more than 0.5 g/dL lower than the value measured prior to dosing initiation of the current cycle.	Interrupt TAG dosing until the relevant CLS sign/symptom has resolved[1].
	Serum albumin reduced by ≥ 0.5 g/dL from the albumin value measured prior to tagraxofusp dosing initiation of the current cycle		
	A predose body weight that is increased by ≥ 1.5 kg over the previous day's predose weight	Administer 25g intravenous albumin (q12h or more frequently as practical), and manage fluid status as indicated clinically (e.g., generally with intravenous fluids and vasopressors if hypotensive and with diuretics if normotensive or hypertensive), until body weight increase has resolved (i.e., the increase is no longer ≥ 1.5 kg greater than the previous day's predose weight).	
	Edema, fluid overload and/or hypotension	Administer 25g intravenous albumin (q12h, or more frequently as practical) until serum albumin is ≥ 3.5 g/dL. Administer 1 mg/kg of methylprednisolone (or an equivalent) per day, until resolution of CLS sign/symptom or as indicated clinically. Aggressive management of fluid status and hypotension if present, which could include intravenous fluids and/or diuretics or other blood pressure management, until resolution of CLS or as clinically indicated.	Interrupt TAG dosing until the relevant CLS sign/symptom has resolved[1].

[1] If tagraxofusp dose is held:

- Tagraxofusp administration may resume in the same cycle if all CLS signs/symptoms have resolved and the patient did not require measures to treat hemodynamic instability
- Tagraxofusp administration should be held for the remainder of the cycle if CLS signs/symptoms have not resolved or the patient required measures to treat hemodynamic instability (e.g., required administration of intravenous fluids and/or vasopressors to treat hypotension) (even if resolved), and
- Tagraxofusp administration may only resume in the next cycle if all CLS signs/symptoms have resolved, and the patient is hemodynamically stable.

8.8.3 Management of hypersensitivity reactions

Tagraxofusp can cause severe hypersensitivity reactions. In patients receiving tagraxofusp in clinical trials, hypersensitivity reactions were reported in 43% (53/122) of patients treated with tagraxofusp and were Grade ≥ 3 in 7% (9/122). Manifestations of hypersensitivity reported in ≥ 5% of patients include rash, pruritus, and stomatitis. Monitor patients for hypersensitivity reactions during treatment with tagraxofusp. Interrupt tagraxofusp infusion and provide supportive care as needed if a hypersensitivity reaction should occur (see table 4).

8.8.4 Management of hepatotoxicity

Treatment with tagraxofusp was associated with elevations in liver enzymes. In patients receiving tagraxofusp in clinical trials, elevations in ALT occurred in 79% (96/122) and elevations in AST occurred in 76% (93/122). Grade 3 ALT elevations were reported in 26% (32/122) of patients. Grade 3 AST elevations were reported in 30% (36/122) and Grade 4 AST elevations were reported in 3% (4/122) of patients. Elevated liver enzymes occurred in the majority of patients in Cycle 1 and were reversible following dose interruption.

Monitor alanine aminotransferase (ALT) and aspartate aminotransferase (AST) prior to each infusion with tagraxofusp. Withhold tagraxofusp temporarily if the transaminases rise to greater than 5 times the upper limit of normal and resume treatment upon normalization or when resolved (see table 4).

8.8.5 Adaptation for hematologic toxicities

Tagraxofusp in not associated with myelosuppression hence no dose adaptation should be required. Myelosuppression with cytopenias and their complications are extremely frequent in acute leukemias. Patients with neutropenia or thrombocytopenia because of their disease do not require treatment interruptions for myelosuppression.

8.8.6 Adaptation for tumor lysis syndrome

As opposed to venetoclax, tagraxofusp has rarely been associated with TLS. Refer to §9.5 for prophylaxis and management of TLS. Should a subject meet criterion for clinically significant laboratory or clinical TLS thought to be related to tagraxofusp administration, tagraxofusp should be withheld until resolution.

8.9. ALLOGENEIC STEM CELL TRANSPLANTATION

In all eligible patient who reach a cCR or better after 3 cycles of treatment, allogeneic stem cell transplantation will be systematically considered. Study treatment may be continued until patients proceed to transplantation.

9. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

9.1. PERMITTED MEDICATIONS

All patients may receive supportive care measures as clinically indicated, including prophylactic antibiotics, antihistamines, antiemetics, albumin, fluids (hydration), and supportive measures. All concomitant medications taken during the study will be recorded in the eCRF with indication and dates of administration. Subjects with high tumor burden should be monitored closely and prophylactic measures, including allopurinol, may be instituted per institutional standards.

9.2. PROHIBITED OR RESTRICTED MEDICATIONS

Patients should not receive other anticancer therapy (cytotoxic, biologic, or immunotherapy) or radiotherapy while on treatment in this study. Hormone therapy may be allowed after discussion with the medical monitor, but other anticancer therapy should not be administered until permanent treatment discontinuation of the study drugs has occurred.

The use of the following concomitant medications is prohibited during venetoclax ramp-up phase and cautionary thereafter (see Appendix 5 for examples):

- Strong and moderate CYP3A inhibitors

If subject requires use of these medications at the cohort designated dose, use with caution and reduce the venetoclax dose by 50% for moderate inhibitors and at least 75% for strong inhibitors during co-administration (see table3). After discontinuation of CYP3A inhibitor, wait for 2 to 3 days before venetoclax dose is increased back to the initial maintenance/target dose.

- Strong and moderate CYP3A inducers

Concomitant use of venetoclax with strong or moderate CYP3A inducers should be avoided. Alternative treatments with a lesser inductive effect on CYP3A should be considered. If subject requires use of these medications, use with caution and contact medical monitor for guidance.

Concomitant medications that fall into the categories below could potentially lead to adverse reaction(s) and should be considered cautionary (except where noted). If a potential study patient is taking any of the medications in the categories described below, the investigator will assess and document the use of medications known or suspected to fall in the following medication categories:

- Warfarin, Azythromycin, Bile acid sequestrants, and Gastric acid reducing agents,
- P-gp substrates.
- BCRP substrates.
- OATP1B1/1B3 substrates.
- P-gp inhibitors.
- BCRP inhibitors.

A sample list of excluded medications and cautionary medications that fall into the categories within this section can be found in Appendix 4. It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, please refer to the appropriate product label.

9.3. OTHER SUPPORTIVE TREATMENTS

Transfusions of red blood cells and platelets may be administered at the investigator's discretion. Rhu-GCSF is allowed in the event of grade 4 neutropenia.

Erythropoietin or erythropoiesis stimulating agents may be administered if hemoglobin falls below 10 g/dL, at the investigator's discretion.

9.4. CONTRACEPTION RECOMMENDATIONS

Female patients of childbearing potential (any fertile woman, following menarche and until becoming post-menopausal unless permanently sterile) must practice highly effective methods of contraception (approved contraceptives or intrauterine devices in association with barrier measures).

Women of childbearing potential and male partners of such women should take necessary precautions to avoid pregnancy while receiving tagraxofusp and/or venetoclax, during 90 days after the last dose. In case of pregnancy during the conduct of the study, the patient must discontinue the study drugs.

Male patients must be abstinent, vasectomized, or agree to the use of barrier contraception in combination with other methods. Venetoclax may compromise male fertility, and before starting treatment, counselling on sperm storage may be considered in some male patients.

9.5. PROHIBITED FOOD

Use of the following foods is prohibited during the study and for at least 3 days prior to initiation of venetoclax treatment:

- Grapefruit
- Grapefruit juice
- Grapefruit-containing products
- Seville oranges (including marmalade containing Seville oranges)
- Star fruit

9.6. PACKAGING, LABELING, STORAGE AND TEMPERATURE EXCURSION OF VENETOCLAX

Venetoclax will be supplied by AbbVie as tablets in bottles or blisters. Venetoclax tablets will be packaged to accommodate the study design. Each packaged unit of venetoclax will be labeled to comply with local regulatory requirements. Labels must remain affixed to the packaged unit.

Venetoclax drug must be maintained under adequate security and stored as specified on the clinical label. The investigational product is for investigational use only and is to be used only within the context of this study.

Any temperature excursion must be reported to AbbVie immediately. Study medication should be quarantined and not dispensed until AbbVie deems the medication as acceptable for use.

10. TREATMENT DISCONTINUATION / STUDY WITHDRAWAL

10.1. TREATMENT DISCONTINUATION

A subject's study treatment should be discontinued:

- In the absence of response defined as a response < cCR after 3 cycles of tagraxofusp plus venetoclax
- In case of confirmed disease progression on therapy
- In case of unacceptable toxicity
- per patient's decision

- Upon the investigator's or sponsor's decision
- If patient becomes eligible for allogeneic stem cell transplantation
- Completion of protocol-defined follow-up
- Death

In case of early study treatment discontinuation, the patient will continue the follow–up visits planned in the protocol, for toxicity, disease progression and survival.

The reason and date for discontinuation will be collected for all patients.

10.2. STUDY WITHDRAWAL

Subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Withdrawal of consent for study participation
- Sponsor terminates the study.

Before a subject is considered lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal.

The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study treatment assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study, assessments outlined in the End-of-Study Visit should be obtained.

11. SAFETY AND PHARMACOVIGILANCE INSTRUCTIONS

11.1. DESCRIPTION OF PARAMETERS FOR ASSESSING SAFETY AND DEFINITIONS

All adverse events are to be reported to the sponsor by the investigators. A DSMB is established to review the safety data collected during the study.

Definitions and classifications

Adverse Event (AE)

'Adverse event' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

Notes:

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not the event is considered causally related to the use of the product or to the research.

Baseline conditions (existing prior to study treatment initiation) that worsen during the study, should be reported as AE.

Adverse Reaction

There is a reasonable possibility of establishing a causal relationship between the adverse event and the investigational medicinal product (IMP) based on an analysis of available evidence

Serious Adverse Event (SAE)

Any adverse event that at any dose requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, is life-threatening or results in death.

Some medical events may jeopardize the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events, hereinafter referred to as 'important medical events', should also be considered as 'serious' in accordance with the definition.

Notes:

- Results in death: death is not an event but should be reported as the outcome of an adverse event (fatal).
- Is life threatening: The AE must be an immediate threat for life; this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires unforeseen inpatient hospitalization or hospitalization prolongation: Planned hospitalizations for study drug administration or for concomitant condition are not SAE.

Adverse Events of Special Interest (AESIs)

Adverse Events of Special Interest are serious or non-serious events of scientific or medical concern related to a specific product for which ongoing monitoring and rapid communication by investigators is warranted.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction of which the nature, severity or outcome is not consistent with the reference safety information (RSI).

Unexpected Events

All unexpected events that might materially influence the benefit-risk assessment of the medicinal product or that would lead to changes in the administration of a medicinal product or in overall conduct of a clinical trial. This concerns all unexpected events which affect the benefit-risk balance of the clinical trial but are not suspected unexpected serious adverse reaction.

Examples of such unexpected events include an increase in the rate of occurrence of expected serious adverse reactions which may be clinically important, a significant hazard to the patient population, such as lack of efficacy of a medicinal product, or a major safety finding from a newly completed animal study (such as carcinogenicity).

Serious breaches

A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

Examples of serious breaches can be found in Appendix I of the document via the internet link: https://www.ema.europa.eu/documents/template-form/appendix-iii-b-information-besubmitted-notification-serious-breach-guideline-notification-serious/2014-clinical-trialprotocol_en.docx.

Severity

Severity of AE will be graded according to CTCAE v5.0, November 27, 2017 (appendix 4).

Adverse events not included in the classification system will be graded according to a 5-grade system:

- *Class 1, mild:* discomfort reported but no disturbance or normal everyday activity
- *Class 2, moderate:* discomfort sufficiently notable to reduce the number of normal everyday activities or to have an influence upon them
- *Class 3, severe:* inability to work or carry out normal everyday activities
- *Class 4, life-threatening:* urgent intervention indicated
- *Class 5, death.*

Medication error

A medication error is an unintended failure in the drug treatment process that leads to or has the potential to lead to a serious adverse event.

Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the clinical trial protocol.

Abuse

Abuse corresponds to the persistent or sporadic, intentional, and voluntary excessive use of a psychoactive medicinal product, which is accompanied with sought harmful physical or psychological effects.

Overdose

Overdose refers to the accidental administration of a quantity of a study drug given per administration or cumulatively, which is above the maximum recommended dose according to the clinical trial protocol.

Auxiliary medicinal product

Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess endpoints in a clinical trial).

11.2. INVESTIGATOR'S RESPONSIBILITIES

11.2.1 Reporting of adverse events and other situations to the sponsor

The investigator assesses each adverse event including abnormal values or tests results occurring in a person taking part in the clinical trial and monitor for seriousness. Medication errors, use not consistent with the protocol, misuse and abuse are also adverse events.

All adverse events (serious and non serious) occurring after informed consent must be reported in the electronic case report form (eCRF) until 30 days after the last administration of IMP, except clinical AE grade 1 and hematologic AE grade 1 and 2.

The investigator must notify the sponsor, **without undue delay but no later than within 24 hours of awareness of its occurrence**:

- all SAE
- AESIs identified by Stemline Therapeutics listed below, only when the event meets seriousness criteria and is, at least, possibly related to tagraxofusp:
    - Capillary Leak Syndrome
    - Hepatotoxicity
    - Choroid Plexus Lesions
    - Hypersensitivity Reactions
    - Delayed engraftment or graft failure reported after allogeneic stem cell transplantation in patients previously treated with tagraxofusp
- pregnancy (even if not associated with a SAE),
- pregnancy in partners enrolled in the study (effect of IMP on sperm is unknown),
- medication errors, use not consistent with the protocol, misuse and abuse (even if not associated with a SAE),
- suspected transmission of an infectious agent,

in a written report signed by the investigator using the SAE form and the special situation form (for reporting medication errors, use not consistent with the protocol, misuse and abuse associated with SAE). If no SAE is associated with medication errors, use not consistent with the protocol, misuse and abuse, only the special situation form should be completed.

The investigator must send the form(s) to the sponsor's Vigilance division:

by email to **safety@fordrugconsulting.fr**

or if not possible by email,

by fax at **01 47 46 18 48**

SAEs are to be reported from informed consent and until 30 days after the last administration of the IMP, all applicable sections of the SAE form must be completed in order to provide a clinically thorough report.

The investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the SAE and not the individual signs/symptoms. The investigator must assess and record in the SAE form, the relationship of each SAE to the IMP, or to other cause.

Follow-up information is sent to the sponsor using a new SAE form stating that this is a follow-up to the previously reported SAE, without undue delay but no later than within 24 hours of learning of its occurrence. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event. Investigator must monitor the pregnant woman throughout her pregnancy and until the pregnancy is terminated and must notify the sponsor with the outcome of the pregnancy. Outcomes of pregnancy as miscarriage, pregnancy termination, fetal death, birth defect, etc. fall within the definition of a SAE. A specific informed consent for the pregnancy follow-up, is available for the study and will be presented for the participant and the participant's partner.

Any SAEs experienced after the end of the period of SAE reporting (30 days after last IMP administration) should only be reported to the sponsor if the investigator suspects a causal relationship to the study treatment or procedure imposed by the protocol.

Reminder: These serious adverse events, as all adverse events, are also to be recorded in the "adverse event" section of the case report form.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

11.2.2 Serious adverse events that do not require the investigator to immediately notify the sponsor

Disease relapse should not be recorded as an adverse event or serious adverse event. Deaths because of disease progression are not considered SAE but must be collected on the appropriate eCRF form. The site should continue to follow all subjects for survival and collect information around the death on the appropriate eCRF form until the end of the trial. Instead, signs and symptoms of clinical sequelae resulting from lack of efficacy will be reported if they fulfill the serious adverse event definition.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: hospitalizations that were planned before the signing of the informed consent form, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

- A standard procedure for protocol therapy administration will not be reported as a serious adverse event. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a serious adverse event.
- The administration of blood or platelet transfusion for disease management under study. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Prolonged hospitalization for technical, practical, or social reasons in the absence of an adverse event.

11.3. OBLIGATIONS OF THE SPONSOR

The sponsor continuously assesses the safety of the trial and then, of the IMP.

The sponsor assesses causal relationship of the serious adverse events with the IMP, specific medical procedure added by the research and with other possible treatments. When an adverse event considered to be 'reasonably related' to the study drug, it is classified as an adverse reaction.

The sponsor assesses the expected or unexpected nature of the adverse reactions according to the RSI.

When a serious adverse event meets the definition of a serious adverse reaction that is unexpected, it will be classified as a SUSAR.

11.3.1 SUSAR reporting to the competent authorities

The sponsor must report any SUSAR associated or not to a special situation occurring in this clinical trial, to the European Medicines Agency (EMA) through the Eudravigilance clinical trial module (EVCTM) within the regulatory deadlines:

- For initial reports :
  - In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than 7 days after the sponsor became aware of the reaction. If the initial notification of a SUSAR resulting in death or life-threatening for the participant is incomplete (for example if the sponsor has not provided all the information in a period of seven days), the sponsor has an additional period of 8 days to submit a completed report based on initial information.
  - In the case of non-fatal or non-life-threatening SUSARs, not later than 15 days after the sponsor became aware of the reaction.

- For significant new information on an already reported SUSAR (follow-up reports):
  - In case if a SUSAR which was initially considered to be non-fatal or non-life threatening but which turns out to be fatal or life-threatening, the follow-up information will be submitted as soon as possible and, in any event, not later than 7 days after the sponsor became aware of the follow-up information reaction being fatal or life-threatening.

- Not later than 15 days after the sponsor became aware of the follow-up information.

11.3.2 Development safety update reports (DSURs)

The sponsor shall submit once a year throughout the clinical trial, an annual safety report (Development Safety Update Report - DSUR) to the EMA through the CTIS, within 60 days from the data lock point (DLP).

At the DLP, the sponsor must draw up the DSUR which includes:

- a line listing of suspected serious adverse reactions that occurred during the period covered by the report,
- a cumulative summary tabulation of serious adverse events that have occurred since the start of the research,
- an analysis of this information in regard of the safety of the research subjects.

11.3.3 Reporting of Serious breaches, unexpected events affecting the benefit-risk balance and urgent safety measures

Serious breaches

The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

Unexpected events

The sponsor shall notify the unexpected events which affect the benefit-risk balance of the clinical trial (other than SUSARs), to the EMA through the CTIS. This notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

Urgent safety measures

When an unexpected event or serious breach is likely to seriously affect the benefit-risk balance of the clinical trial, the sponsor and the investigator shall take appropriate urgent safety measures to protect the patients. Urgent safety measures must be notified to the EMA through the CTIS without undue delay but not later than 7 days from the date the measures have been taken. In case of clinical trial interruption, it must be notified without undue delay but not later than 15 days.

11.3.4 Reporting to the investigators by the sponsor

The sponsor informs all the investigators concerned of any data that could have an unfavorable impact on the safety of the people who are involved in the research.

11.3.5 Reporting to the IMP manufacturers

The sponsor will report safety events in accordance with the agreements entered into between the sponsor and the IMP drug manufacturers, in this case Stemline Therapeutics, Inc. and AbbVie, Inc.

11.4 REPORTING TEMPERATURE EXCURSIONS AND SHIPPING ISSUES OF TAGRAXOFUSP

If a temperature excursion occurred during shipping, email the data along with a completed Temperature Out of Range (TOR) form (see in a separate document-Pharmacy Manuel) so that the excursion information can be evaluated to make a determination regarding continued use of the study drug. For temperature excursions that occur during

storage at your site, email the freezer temperature logs with the completed TOR form to Stemline and FILO. Send all TOR forms and temperature data to TE@stemline.com and FILO to secretariat@filo-leucemie.org. Do not use the product until directed to do so by Stemline.

11.5 CLINICAL PRODUCT COMPLAINTS OF TAGRAXOFUSP

A Clinical Product Complaint (CPC) is a report of a potential quality issue with CTM identified by clinical site personnel during receipt, storage or dose preparation. Examples can include but are not limited to cracked or broken vials, crushed or damaged cartons, incorrect or mutilated labels, or nonconforming product appearance. Report potential quality issues with CTM in a Stemline clinical study using the form (see in a separate document – Pharmacy Manuel) . The form should be completed by the clinical site personnel and sent to Stemline for assessment and further action, as needed.

A CPC form should not be completed for accidental mishandling of the CTM at the clinical site level (e.g. temperature excursions, damage caused by dropping the CTM etc.).

Quarantine any CTM impacted by the CPC, as applicable and physically quarantine at the site until a written disposition is provided by Stemline. Do not dispose CTM without the express consent of Stemline.The CPC form should be sent to: ProductComplaints@stemline.com and FILO to secretariat@filo-leucemie.org

12. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

12.1. STUDY ENDPOINTS

12.1.1 Primary Endpoints:

The primary objective is the efficacy measured by the proportion of participants who achieve a composite a cCR (CR or CRi according to the European Leukemia Net 2022 definitions), or complete response with minimal residual skin abnormality (CRc) evaluated according to ELN 2022 definitions for AML and adapted for BPDCN (see appendix 2 and 5) and a complete metabolic response after 3 TAG+VEN cycles.

12.1.2 Secondary Endpoints:

Safety endpoints

The following secondary safety endpoints will be evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE v5.0)

1. The incidence, timing, and severity of treatment-emergent AEs (TEAE)
2. The incidence of AEs describe below:
    a. CLS
    b. TLS
    c. Grade 3-4 Hematologic toxicity in cycle 2 and 3 and further cycles
3. The incidence, severity, timing, and causation of TEAEs leading to study drug discontinuation

Efficacy endpoints

- Incidence of Minimal Residual Disease (MRD)-Negative Responses measured by flow cytometry with a sensitivity of 0.1%
- Objective response rate (ORR) including cCR + PR
- Progression-free Survival (PFS), defined as the time from start of treatment to disease progression or death from any cause, whichever comes first. PFS will be estimated using the Kaplan-Meier method in the ITT Population. PFS censoring rule will follow FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2015) and Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics Guidance for Industry (see appendices A-D, https://www.fda.gov/media/116860/download) and defined as the time from start of treatment to first documentation of disease progression or death from any cause, whichever comes first .
- Overall Survival (OS), defined as the period from the study entry to death from any cause. Patients who have not died until the time of the analysis will be censored at their last contact date. Survival curve will be estimated by the Kaplan Meier method and analyzed in a same way described previously. Cause-specific mortality curves will be displayed in a competing risks framework. Treatment by covariates interactions will be tested by the Gail and Simon test (Biometrics 1985). Such analyses will be exploratory.

  Duration of response (DOR), defined as the time from first determination of response to the date of progression or death, whichever comes first. Death due to unrelated causes are censored. Survival free of relapse or progression will be estimated by the Kaplan Meier method and analyzed in a same way described previously.
- Proportion of patients bridged to allogeneic stem cell transplantation after completion of at least 3 cycles of treatment.
- Possible predictors of response with respect to cytogenetics and mutational status
- Proportion of patients with Minimal Residual Disease (MRD)-Negative Responses measured by flow cytometry with a sensitivity of 0.1%

12.2. STATISTICAL METHODS AND ANALYSIS

The TAGVEN study is an open label single arm phase II trial. The primary objective is to assess the rate of cCR after 3 cycles of the tagraxofusp + venetoclax combination in patients with treatment naive BPDCN.

cCR is defined as the proportion of participants who achieve a complete CR + CRi + CRc according to ELN 2022 definitions for AML and adapted for BPDCN (appendix 2).

The aim is to demonstrate that the rate of cCR after 3 cycles of the tagraxofusp + venetoclax combination (P) is clearly above a low rate of 60%: P0, which would be not satisfactory. The intention is to check whether tagraxofusp + venetoclax combination can bring this rate markedly above this low rate of 60%.

The following hypotheses will be considered:

- H0 (null): a rate of cCR after 3 cycles of the tagraxofusp + venetoclax combination of 60% (P0) (not worth to pursue any further investigation as it is the rate that can be reproducibly obtained with TAG alone or with standard chemotherapy);
- H1 (alternative): a rate of cCR after 3 cycles of the tagraxofusp + venetoclax combination of 80% (P1) (warrants further investigation).

In terms of statistic, the study was elaborated to test the following hypotheses: H0: $P \leq P0$ versus H1: $P \geq P1$

According to a Simon two-stage (Optimum) design with a one-sided 10% type I error (rare disease context) and power of 80%, **31 evaluable patients for the cCR status after 3 cycles** of the tagraxofusp + venetoclax combination will need to be included in the study to test the previous hypotheses.

Stage 1:

Safety and efficacy will be evaluated after inclusion of the **first 11 evaluable patients**:

- if 7 (63.6) or less than 7 patients are identified with a cCR, the intervention will be declared inefficacious No more additional patient will be included, and the study will be stopped.
- if ≥ 8 (72.7%) patient is identified with a complete response, 20 additional patients will be included for stage 2.

A **safety analysis** will be performed on the safety clinical data of the first 11 evaluable patients. Study will be stopped if an excessive proportion of patients develop serious adverse events, defined as:

- hematological toxicity (leukopenia, febrile neutropenia, anemia, thrombocytopenia) grade 3 or above in >60% of patients (excluding during cycle 1).

- tumor lysis syndrome grade 3 or above in >10% of patients.

- capillary leak syndrome associated with tagraxofusp grade 3 or above in >30% of patients.

- hypersensitivity reaction to tagraxofusp grade 3 or above in > 30% of patients.

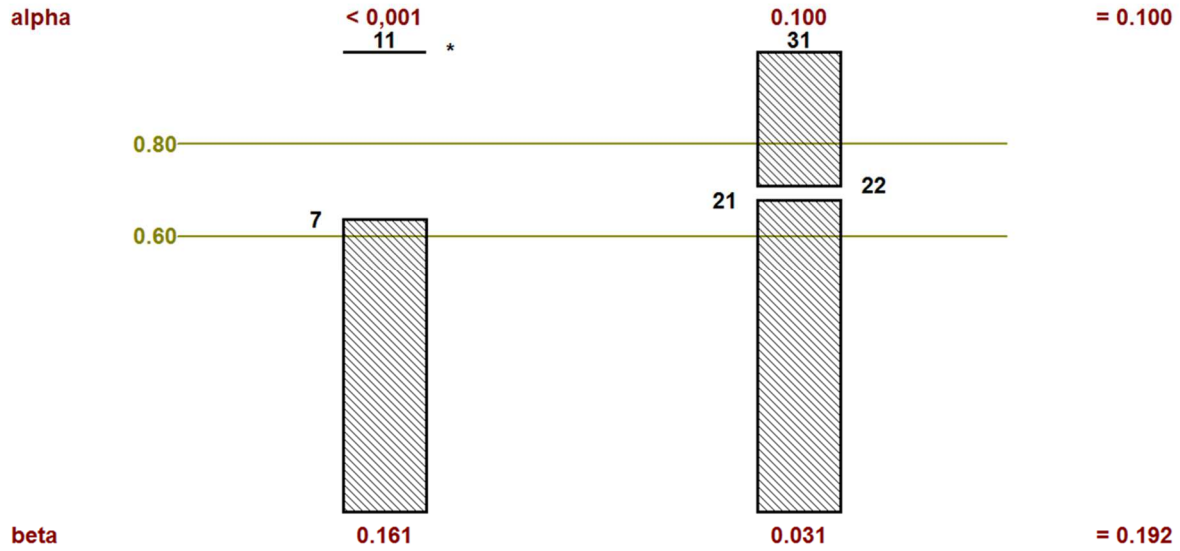
- elevation of transaminases grade 3 or above in > 50% of patients.

Stage 2:

After recruitment of **31 evaluable patients**:

- if ≤ 21 (67.7%) patients are identified with a complete response, the intervention will be declared uninteresting and the study will be declared negative for its primary objective,
- if ≥ 22 (71.0%) patients are identified with a complete response, the intervention will be regarded as interesting for further evaluation and the study will be declared positive for its primary objective.

Figure: Statistic plan



By considering a 5% rate of patient not evaluable or drop out it will be necessary to include **a total of 33 patients.**

The primary analysis will be on modified intention-to-treat (mITT) population, i.e. including all evaluable patients for the primary objective regardless of their eligibility who have received at least 3 cycles of the tagraxofusp + venetoclax combination.

Confirmative analyses will be conducted firstly in the ITT population (not assessable patients and patients with drop out considered as a failure) and secondly, in the Per Protocol population defined as patients with no major deviations from the protocol.

Analyses of safety will be conducted in all patients who have received at least one dose of treatment.

13. ETHICS AND REGULATORY CONSIDERATIONS

13.1. GOOD CLINICAL PRACTICE

This study will be conducted according in full compliance with the study protocol, international Good Clinical Practice standards (guideline for Good Clinical Practice ICH E6 (R2)), and regulations concerning clinical studies (regulation EU n°536/2014 of the European parliament and of council of 16 April 2014 on clinical trials on medicinal products for human use).

13.2. INFORMED CONSENT

The Investigator, or official co-investigator, is responsible for collection of written informed consent from each patient participating in the study, after a clear explanation of study objectives, design, methods, potential benefits, and hazards. In addition, each patient must have read and understood the Patient Information Leaflet written in French.

Investigators must specify to patients that they are completely free to accept or refuse their participation and to withdraw from the study at any time and for whatever reason, without any prejudice on the quality-of-care patients have the right to expect.

Patient Information Leaflet must be initialed, and the Informed Consent Form dated and signed off by both the patient and the Investigator (or Co-investigator) in duplicate. One copy is kept by the patient and the original by the investigator.

In case of new data that could significantly alter the potential risks of the study or the consent of the patients, the Patient Information Leaflet will be reviewed and updated accordingly. All patients, including those already on study treatment, must be provided with these new data and give their consent to pursue the study.

13.3. PATIENT CONFIDENTIALITY

Investigators must ensure that patients anonymity is guaranteed, and their identity is not disclosed to non-authorized persons. Patients name must not be visible on e-CRFs nor other documents transferred to the sponsor. Patient's identification must be coded. Investigators should keep a comprehensive list of patients identifications, with their name, code and address. This document (and others without patient's anonymity, such as Informed Consent Form) must not be collected or copied by the sponsor and must be kept by investigators with high confidentiality.

A case report form number will be assigned during pre-inclusion of the patient. The first letter of the last name, first letter of the first name and the month and year if birth will be the only identity information reported in the case report form and which will make it possible later to associate the case report form with the concerned patient.

13.4. ETHICS COMMITTEES

The sponsor is responsible for submitting the clinical research project to approbation by the Ethic Committee (CPP) in the investigational center where the Coordinator regularly works, and to Health Authorities.

Approbation of the CPP and authorization of the ANSM must be obtained before study initiation.

13.5. INSURANCE

The sponsor states having taken out an insurance policy covering, according to clauses in the policy and within the limit of sums determined the pecuniary consequences of their civil liability as resulting from application of Article L.209-7 of the French Public Health Code. This policy covers in particular investigators as well as all of their co-workers and assistants carrying out clinical trials in accordance with current law. Taking out of such a policy by the sponsor does not deprive the sponsor of rights of recourse against the above-mentioned individuals should they commit any errors.

13.6. DATA PROTECTION

The personal data processing incurred by this clinical trial is covered by a declaration of conformity to MR-001 (Méthodologie de Référence 1), submitted by the FILO to the French Data Protection Agency, the CNIL. FILO is the controller of the personal data collected during the clinical trial. The objective of the process is scientific research,

and the legal base legitim interest of FILO Group. The legitim interest of FILO is to perform medical research in Leukemia diseases.

Encoded medical data may be sent only to the sponsor, sponsor's sub-contractors involved in the study (i.e: eCRF provider, data entry department) and Hospital as Investigator sites under responsibilities of Sponsor and signed Confidential agreement, and possibly to appropriate health care authorities under conditions guaranteeing data protection.

Personal data will be processed and transferred within European Union but also outside EU, in member countries of the European Environment Agency (EEA) and/or in countries considered adequate for their compliance with the GDPR, and in Country where laws about keeping information are less strict than in the EU, but Sponsor will make his best efforts so that the recipients respect the EU GDPR and ensure that technical and organisational measures are in place at recipient to protect your personal data.

The sponsor and government authorities may request direct access to medical records to check procedures and/or data from the clinical trial, without violating confidentiality and within limits permitted by laws and regulations.

13.7. PROTOCOL AMENDMENTS

Any significant modification of the clinical study must be approved by the CPP and ANSM.

No modification of the trial can therefore be implemented prior to these authorizations, unless changes are necessary to prevent immediate hazards that would threat study patients, or changes pertaining only to administrative/logistic aspects (e.g. change of CRA, of telephone number, etc…).

14. STUDY DOCUMENTATION AND ARCHIVING

14.1. INVESTIGATOR STUDY FILES

Investigators should record properly and precisely medical and study data to fully document the course of the study and allow further data verification. These documents should be filed into 2 separate categories: (1) Study Investigator Binder and (2) Patient's Source Documents.

Investigator Binder will contain the last approved version of the protocol and amendments, one specimen of the e-CRF, CPP approbation and ANSM authorization for the initial protocol and all subsequent amendments, one specimen of the Patient Information Leaflet and Informed Consent Form, Drug Movement Forms, local study team, mailing, etc…

Source Documents should include patient's medical chart, nurse notes, cyto-pathology reports, surgery reports, imaging reports and other special examination reports, examination appointments, laboratory results, ECG, signed Informed Consent Forms, correspondence with consulting physicians.

Investigators should allow CRAs to have free access to all patients' Source Documents, necessary for verification of e-CRF data.

Upon request, investigators will provide the sponsor with any necessary encoded data for study documentation. This is particularly important when transcription errors are suspected. In case of specific problems, or Health Authority requests, it is mandatory to have access to all study data, with preservation of patient's confidentiality.

Source Documents and e-CRFs should be archived for at least 25 years after the publication date of the clinical study report according to REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

If the Investigator wishes to transfer study files, the sponsor must be previously informed.

14.2. CASE REPORT FORM

A case report form will be created for each patient on the centralized Webtrial© database.

The structure of the e-CRF will be created by the coordinating investigator with the project manager and the datamanager. All is controlled by an administrator of the Platform.

Webtrial© is a solution developed by Quanticsoft and used by several French platforms, including the FILO group for online completion of e-CRFs of protocolized patients. The web server is a Linux-progiciel exploited under Debian GNU/Linux behind a first firewall and the database server is PostGresSQL. Internet connectivity uses Transfix towards WorldCom-MCI/UUnet and is doubled by a second Transfix line on HSRP routers. The database server is located on a non-public network, visible by the Web served and separated by a second firewall. Transmissions are encrypted by a standard 128bits SSL certificate valid for HTTPS. Maintenance is performed on a 24/24 7/7 basis, with safeguarded daily copies of the database.

The structure of the e-CRFs follows that of each study, with a series of "visits" (ex: inclusion, treatment schedules, follow-up, biological investigations). Each visit contains "forms" in which are created the relevant "items". These various tools are created at wish, to best fit the study and, mostly, collection of the information necessary for assessment of the study and statistical analysis. Each form is encrypted and saved at completion on the central database. There is no need to install any specific software and no information is stored on users computers. The administrator in charge of creating the e-CRF with the coordinating investigators also maintains the list of investigational sites and opens access to the relevant investigators and namely operators (ex: study coordinators, clinicians, biologists, monitors). Everyone registered receives a personal login and password.

The password must be changed upon reception and is valid for 6 months. Three mistakes in typing the password will block access to the e-CRF. The rights for entering data or only seeing them are defined during the creation of the e-CRF for each item. Globally, users can read and write data for their own site. Only the administator can remove patients from the trial after a demand by a user. Each entry is visibly traced with identity, date and time. The coordinating investigators can read information from all sites. Monitoring is visibly traced. Clinical research assistants who perform monitoring are only allowed to view data, and either validate or invalidate the information. In the latter case, a quiery is posted so that the wrong value can be modified by the authorized person. After this modification, the research assistant can change the status of the item and validate it. Validated data cannot be modified.

Both statisticians, coordinating investigators, project manager and the administrator can perform extractions of the database.

Data will be extracted from the on-line e-CRF for statistical analysis.

14.3. STUDY FOLLOW-UP AND MONITORING

The CRA appointed by the sponsor will contact investigators and will regularly visit them. She/he will be authorized to check study data upon request (e-CRF and other relevant document).

The CRA is responsible for regularly checking e-CRFs along study, ensuring that the protocol is respected, and that complete, precise, and consistent data are entered in the e-CRF. Investigators, or any person appointed by the investigators, should cooperate with CRAs, to help resolve any issue detected during study visits.

14.4. AUDITS AND INSPECTIONS

In case of audit or inspection, investigators must provide representatives mandated for the audit or Health Authority inspectors with the study Source Documents they demand. e-CRF data verification should be performed by direct comparison with Source Documents.

14.5. PUBLICATION OF STUDY RESULTS

The results of the clinical trial will be published after complete data collection and evaluation. Partial or preliminary results can be published beforehand. Publication is to be initiated by the study coordinators.

All study data and publication are property of the FILO.

The first author will be the writer of the paper. The last author will be one of the principal investigators (NB: the principal investigator can be the writer).

The author is to consider any physician as co-author who has contributed at least 10% of the evaluable patients to the study. The sequence of authorship is not to be in accordance with the number of contributed patients but with the author's implication in the study. Nevertheless, the first author's center should be considered to put a second name among the authorship, in accordance with the number of contributed patients.

Any publication in the form of published paper, lecture, poster must basically be approved by the FILO within one month after proposal. All refusals must be justified, in a written document. Such publication should generally not occur before the publication of the study group. Inquiries from the press and public concerning study results may only be answered by the study coordinator.

15. REFERENCES

Döhner H, 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.

Bueno C, Almeida J, Lucio P, et al. Incidence and characteristics of CD4 (1)/HLA DR^{hi} dendritic cell malignancies. Haematologica. 2004; 89(1):58-69.

Guru Murthy GS, et al. Epidemiology and survival of blastic plasmacytoid dendritic cell neoplasm. Leuk Res. 2018; 73:21-23.

Khoury JD, et al. CD56 (1) TdT (1) blastic naturalkiller cell tumor of the skin: A primitive systemic malignancy related to myelomonocytic leukemia. Cancer 2002; 94:2401–2408.

Feuillard J, et al. Clinical and biologic features of CD4 (1) CD56 (1) malignancies. Blood 2002; 99:1556–1563.

Petrella T, et al. Blastic NK-cell lymphomas (agranular CD41CD561 hematodermic neoplasms): A review. Am J Clin Pathol 2005; 123:662–675

Jardin et al. recurrent genomic aberrations combined with deletions of various tumour suppressor genes may deregulate the G1/S transition in CD4+CD56+ haematodermic neoplasms and contribute to the aggressiveness of the disease. Leukemia. 2009; 23:698-707.

Jardin F, Ruminy P, Parmentier F, Troussard X, Vaida I, Stamatoullas A et al. TET2 and TP53 mutations are frequently observed in blastic plasmacytoid dendritic cell neoplasm. Br J Haematol 2011; 153: 413–416.

Stenzinger, et al. Targeted ultra-deep sequencing reveals recurrent and mutually exclusive mutations of cancer genes in blastic plasmacytoid dendritic cell neoplasm. Oncotarget. 2014 Aug 15; 5(15):6404-13.

Menezes et al. Exome sequencing reveals novel and recurrent mutations with clinical impact in blastic plasmacytoid dendritic cell neoplasm. Leukemia. 2014; 28(4):823-9.

Roos-Weil, et al. Stem cell transplantation can provide durable disease control in blastic plasmacytoid dendritic cell neoplasm: a retrospective study from the European Group for Blood and Marrow Transplantation. Blood. 2013; 121(3):440-6.

Reimer P, et al. What is CD4+CD56+ malignancy and how should it be treated? Bone MarrowTransplant. 2003; 32(7):637-646.

Pemmaraju N, et al. Analysis of outcomes of patients (pts) with blastic plasmacytoid dendritic cell neoplasm (BPDCN) [abstract]. J Clin Oncol. 2012; 30. Abstract 6578

Garnache-Ottou et al. How should we diagnose and treat blastic plasmacytoid dendritic cell neoplasm patients? Blood Adv. 2019 Dec 23; 3(24):4238-4251Laribi K, et al. Blastic plasmacytoid dendritic cell neoplasms: results of an international survey on 398 adult patients. Blood Adv. 2020 Oct 13; 4(19):4838-4848

Frankel AE, Woo JH, Ahn C, et al. Activity of SL-401, a targeted therapy directed to interleukin-3 receptor, in blastic plasmacytoid dendritic cell neoplasm patients. Blood 2014; 124:385-92.

Pemmaraju N, et al. Tagraxofusp in Blastic Plasmacytoid Dendritic-Cell Neoplasm. N Engl J Med. 2019; 380(17):1628-1637.

Pemmaraju N, et al Tagraxofusp, an Anti-CD123 Therapy, in Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm: Subanalyses of a Pivotal Trial by Age and Baseline Disease Involvement. Blood (2021) 138 (Supplement 1): 874.

Pemmaraju N, et al. Long-Term Benefits of Tagraxofusp for Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm. J Clin Oncol. 2022 Sep 10; 40(26):3032-3036.

Deconinck E, et al. Preliminary Results from an Observational Multicenter Study of Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm Treated with Tagraxofusp in the European Expanded Access Program. Blood (2022) 140 (Supplement 1): 8115–8116.

Konopleva M, et al. Mechanisms of apoptosis sensitivity and resistance to the BH3 mimetic ABT-737 in acute myeloid leukemia. Cancer Cell. 2006; 10(5):375-388.

Beurlet S, et al. BCL-2 inhibition with ABT-737 prolongs survival in an NRAS/BCL-2 mouse model of AML by targeting primitive LSK and progenitor cells. Blood. 2013; 122(16):2864-2876

Pan R, et al. Selective BCL-2 inhibition by ABT-199 causes on-target cell death in acute myeloid leukemia.Cancer Discov. 2014; 4(3):362-75.

Bogenberger J, et al. BCL-2 family proteins as 5-Azacitidine-sensitizing targets and determinants of response in myeloid malignancies. Leukemia. 2014; 28(8):1657-65.

Konopleva, et al. Efficacy and Biological Correlates of Response in a Phase II Study of Venetoclax Monotherapy in Patients with Acute Myelogenous Leukemia. Cancer Discov. 2016; 6:1106-1117.

DiNardo CD, et al. Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemia and related myeloid malignancies. Am. J. Hematol. 2017; 93:401–407.

DiNardo CD, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2018 Oct 25. pii: blood-2018-08-868752.

Montero J, et al. Blastic plasmacytoid dendritic cell neoplasm is dependent on BCL2 and sensitive to venetoclax. Cancer Discov. 2017; 7(2):156-164.

Grushchak S, et al.Novel treatment of blastic plasmacytoid dendritic cell neoplasm: A case report. Medicine (Baltimore). 2017 Dec; 96(51):e9452

Agha ME, Monaghan SA, Swerdlow SH. Venetoclax in a Patient with a Blastic Plasmacytoid Dendritic-Cell Neoplasm. N Engl J Med. 2018; 379(15):1479-1481.

Micol JB, Pilorge S, Ghez D. More on Blastic Plasmacytoid Dendritic-Cell Neoplasms. N Engl J Med 2019; 380:695-697.

Egger A, et al. A Case of Cutaneous Blastic Plasmacytoid Dendritic Cell Neoplasm Treated With a Bcl-2 Inhibitor. J Drugs Dermatol 2021 May 1; 20(5):550-551.

Molina Castro et al. Blastic Plasmacytoid Dendritic Cell Neoplasm with Central Nervous System Involvement: A Case Report. Cureus 2022 Apr 6; 14(4):e23888.

Schwede M, et al Venetoclax monotherapy for cutaneous blastic plasmacytoid dendritic cell neoplasm. Annals of Hematology 2020; 99:2973–2975

Beziat G, et al. Venetoclax to treat relapsed blastic plasmacytoid dendritic cell neoplasm: A case-report and review of literature. Leuk Res 2019 Oct; 85:106199.

DiNardo CD, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020 Aug 13; 383 (7):617-629

Blastic plasmacytoid dendritic cell neoplasm: the first report of two cases treated by 5-azacitidine. Laribi K, et al. Blastic plasmacytoid dendritic cell neoplasm: the first report of two cases treated by 5-azacitidine. Eur J Haematol. 2014 Jul; 93 (1):81-5.

Khwaja R, et al. Azacitidine in the treatment of blastic plasmacytoid dendritic cell neoplasm: a report of 3 cases. Leuk Lymphoma. 2016 Nov; 57 (11):2720-2

Chahine C, et al. Bortezomib, Lenalidomide, and Dexamethasone in Elderly Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm. Clin Lymphoma Myeloma Leuk 2020 Dec; 20 (12):e986-e989.

Lane A, et al. Safety and Efficacy of Combining Tagraxofusp (SL-401) with Azacitidine or Azacitidine and Venetoclax in a Phase 1b Study for CD123 Positive AML, MDS, or BPDCN. Blood 2021. Volume 138, Supplement 1, 23; Page 2346

16. APPENDICES

Appendix 1. ECOG performance status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

Appendix 2. Tumor Response for BPDCN

Tumor Response Criteria for BPDCN

Response	Location	Criteria
Complete Response (CR)	Marrow	• Normalization of blast percentage (≤5%)
	Peripheral Blood	• Normalization of neutrophil count (≥1,000/μL) and platelet count (≥100,000/μL) • Absence of leukemic blasts
	Skin	• 100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline
	Nodal Masses	• Regression to normal size on CT
	Spleen, Liver	• Not palpable, nodules disappeared
CR with incomplete blood count recovery (CRi)	Marrow	• Normalization of blast percentage (≤5%)
	Peripheral Blood	• Incomplete recovery of neutrophil and/or platelet count • Absence of leukemic blasts
	Skin	• 100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline
	Nodal Masses	• Regression to normal size on CT
	Spleen, Liver	• Not palpable, nodules disappeared
CR [clinical] with minimal residual skin abnormality (CRc)	Marrow	• Normalization of blast percentage (≤5%)
	Peripheral Blood	• Normalization of neutrophil count (≥1,000/μL) and platelet count (≥100,000/μL) • Absence of leukemic blasts
	Skin	• Marked clearance of all skin lesions from baseline; residual hyperpigmentation or abnormality with BPDCN identified on biopsy (or no biopsy performed)
	Nodal Masses	• Regression to normal size on CT
	Spleen, Liver	• Not palpable, nodules disappeared
Partial Response (PR)	Marrow	• Decrease by ≥50% in blast percentage to 5 − 25%
	Peripheral Blood	• Normalization of neutrophil count (≥1,000/μL) and platelet count (≥100,000/μL)
	Skin	• 50% − <100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline
	Nodal Masses	• ≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes
	Spleen, Liver	• ≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen
Stable Disease (SD)		• Failure to achieve at least a PR, but no evidence of progression for at least 8 weeks
Relapse after CR/CRi/CRc	Marrow	• Blast percentage >5% (if no peripheral blasts, then confirmation aspirate required ≥1 week later)
	Peripheral Blood	• Presence of leukemic blasts
	Skin	• Increase in skin score greater than the sum of nadir plus 50% baseline score
	Nodal Masses	• Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase from nadir in SPD of more than one node, or ≥50% increase from nadir in longest diameter of a previously identified node >1 cm in short axis
	Spleen, Liver	• >50% increase from nadir in the SPD of any previous lesions

Supplement to: Pemmaraju N, Lane AA, Sweet KL, et al. Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. N Engl J Med 2019;380:1628-37. DOI: 10.1056/NEJMoa1815105

Tumor Response Criteria for BPDCN (continued)

Relapse after PR	Marrow	• Blast percentage ≥25% (if no peripheral blasts, then confirmation aspirate required ≥1 week later)
	Skin	• Increase in skin score greater than the sum of nadir plus 50% baseline score
	Nodal Masses	• Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase from nadir in SPD of more than one node, or ≥50% increase from nadir in longest diameter of a previously identified node >1 cm in short axis
	Spleen, Liver	• >50% increase from nadir in the SPD of any previous lesions
Progressive Disease (PD)	Marrow	• ≥50% increase in blasts from baseline (and blast percentage >5%)
	Peripheral Blood	One or more of the following: • ≥50% decrease from peak remission levels in platelets or granulocytes; • Reduction in hemoglobin concentration by at least 2 g/dL; • Transfusion dependence
	Skin[a]	One or more of the following: • ≥25% increase in skin disease from baseline[a] • Any new tumors in patients without tumors at baseline
	Nodal Masses	• Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase from nadir in SPD of more than one node, or ≥50% increase from nadir in longest diameter of a previously identified node >1 cm in short axis
	Spleen, Liver	• >50% increase from nadir in the SPD of any previous lesions

Source: Cheson BD, Pfistner B, Juweid ME, et al. The International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-586.
Abbreviations: CT, computed tomography; SPD, sum of the product of the diameters.

Supplement to: Pemmaraju N, Lane AA, Sweet KL, et al. Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. N Engl J Med 2019;380:1628-37. DOI: 10.1056/NEJMoa1815105

Appendix 3. NCIC CTC grading scale

Severity of AEs will be graded according to NCIC common toxicity criteria (CTCAE v5.0, November 27, 2017, available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix 4. Sample List of Excluded and Cautionary Medication

Excluded
Anticancer therapies including chemotherapy, radiotherapy, or other investigational therapy, including targeted small molecule agents: Excluded 5 half-lives prior to first dose and throughout Venetoclax administration **Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic intent:** Excluded 30 days prior to first dose and throughout Venetoclax administration
Excluded during ramp-up phase and Cautionary at the Cohort Designated Dose:
Strong CYP3A inducers - avasimibe,carbamazepine, enzalutamine, mitotane, phenytoin, rifampin, St. John's wort **Moderate CYP3A inducers -** bosentan, efavirenz, etravirine, modafinil, nafcillin Exclude during ramp-up phase and consider alternative medications. If subject requires use of these medications at the cohort designated dose, use with caution and contact AbbVie medical monitor for guidance. **Strong CYP3A inhibitors -** boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, paritaprevir/ritonavir combinations, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole **Moderate CYP3A inhibitors -** amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib*, cyclosporine*, darunavir/ritonavir, diltiazem1, erythromycin, fluconazole, fosamprenavir, imatinib*, isavuconazole, tofisopam, verapamil Exclude during ramp-up phase and consider alternative medications. If subject requires use of these medications at the cohort designated dose, use with caution and reduce the Venetoclax dose by 50% for moderate inhibitors and at least 75% for strong inhibitors during co-administration. After discontinuation of CYP3A inhibitor, wait for 2 to 3 days before Venetoclax dose is increased back to the initial maintenance/target dose.
Cautionary
Warfarin** **P-gp substrates** Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus*, fexofenadine, lapatinib*, loperamide, maraviroc, nilotinib*, ranolazine, saxagliptin, sirolimus*, sitagliptin, talinolol, tolvaptan, topotecan* **BCRP substrates** Methotrexate*, mitoxantrone*, irrinotecan*, lapatinib*, rosuvastatin, sulfasalazine, topotecan* **OATP1B1/1B3 substrates** Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan **P-gp inhibitors** Amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, quinidine, ronalzine, ticagrelor **BCRP inhibitors** Geftinib*

Note that this is not an exhaustive list. For an updated list, see the following link:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

In addition to the medications listed in this table, subjects receiving Venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruits.

* These are anticancer agents; consult contact medical monitor before use.

** Closely monitor the international normalized ratio (INR).

Appendix 5. mSWAT score

Modified Severity Weighted Assessment Tool (mSWAT) scoring system

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch	Plaque	Tumor
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		×1	×2	×4
Subtotal lesion BSA × weighting factor				

mSWAT score equals summation of each column line. Abbreviations: BSA, body surface area. Patch: any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present. Plaque: Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present. Tumor: Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.