Tagraxofusp (SL-401) in Patients with Chronic Myelomonocytic Leukemia (CMML)

Study Product: Tagraxofusp (SL-401)

Protocol Number: STML-401-0314

IND Number: 114513

Issue Date: 30 September 2021

Sponsor:

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CONFIDENTIAL – PROPRIETARY INFORMATION

INVESTIGATOR PROTOCOL AGREEMENT

Tagraxofusp (SL-401) in Patients with Chronic Myelomonocytic Leukemia (CMML)

I hereby agree to:

- Conduct the study as outlined in this protocol with reference to national/local regulations and current International Council for Harmonisation (ICH) / Good Clinical Practice (GCP) guidelines.
- Discuss and agree upon any modification to the protocol with Stemline Therapeutics, Inc., or representatives hereof.
- Fully co-operate with monitoring and auditing and allow access to all documentation by authorized individuals representing Stemline Therapeutics, Inc., or Health authorities.

Protocol Version (Date): Amendment 9 (30 September 2021)

To be signed by Principal Investigator:

Print Name			
Signature		**Date**	
Institution			

To be signed by Stemline Therapeutics, Inc.:

Print Name			
Signature	[redacted]	**Date**	01 October 2021
Title			

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1 Protocol Overview

Tagraxofusp injection (Elzonris; formerly SL-401, DT388IL3), a CD123-directed cytotoxin, is a recombinant fusion protein comprised of human interleukin-3 (IL-3) and truncated diphtheria toxin (DT) that targets the alpha chain of the IL-3 receptor, or CD123 (Mani 2018). Tagraxofusp was granted breakthrough therapy designation for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN), a myeloid malignancy, in August 2016 and was approved by the United States (US) Food and Drug Administration (FDA) for the treatment of BPDCN in adults and pediatric patients, 2 years and older, in December 2018 (Jen 2020).

The current study, Study STML-401-0314 (Study 0314), was initially designed as a 2-stage, non-randomized, open-label, multicenter study of tagraxofusp in patients with subtypes of advanced, high risk myeloproliferative neoplasms. The candidate patients for the study were comprised of: patients with chronic myelomonocytic leukemia (CMML); patients with myelofibrosis (MF), which includes those diagnosed with primary myelofibrosis (PMF) and those who transformed to MF from polycythemia vera (post-PV MF) or essential thrombocythemia (post-ET MF); patients with chronic eosinophilic leukaemia; and patients with mastocytosis (includes cutaneous mastocytosis [CM], systemic mastocytosis [SM] (comprised of indolent systemic mastocytosis [ISM], smoldering systemic mastocytosis [SSM], systemic mastocytosis with associated haematological non-mast cell disease [SM-AHNMD], aggressive systemic mastocytosis [ASM] mast cell leukemia [MCL]), and mast cell sarcoma).

The primary objective of Stage 1 of this study, which is now complete, was to establish the maximum tolerated dose (MTD) or the maximum tested dose (MTeD) at which multiple dose limiting toxicities (DLTs) are not observed. In Stage 1, 9 patients (5 with CMML and 4 with MF) received tagraxofusp at doses of 7, 9, or 12 mcg/kg via intravenous infusion on Days 1-3 every 21 days for Cycles 1-4, every 28 days for Cycles 5-7, and every 42 days for Cycles 8 and beyond. No MTD was identified, and the MTeD was 12 mcg/kg (the recommended phase 2 dose). As Stage 1 is complete, details regarding conduct of this stage have been removed from the protocol.

Stage 2 intended to further characterize the safety profile of tagraxofusp, initially in the same 4 candidate patient populations and then subsequently only in populations treated in Stage 1 (CMML and MF). Preliminary assessment of clinical activity associated with tagraxofusp in patients with CMML or MF was also an objective of Stage 2. Enrollment in Stage 2 is closed. However, both CMML and MF patients who are already enrolled may continue study participation in Stage 2.

In the ongoing Stage 3a of this study, patients with CMML will receive tagraxofusp at the recommended phase 2 dose, 12 mcg/kg, on the same schedule as Stage 1.

As of July 2021, 36 patients have been enrolled, comprising 20 patients with CMML-1 and 16 with CMML-2; median age was 69 years (range 42–81), and 75% of patients were male. Twenty-three patients (64%) had either high- or intermediate-risk genetics based on CPSS,

GFM, MMM, or ELN risk stratification systems. Prior therapies included HMA in 16 patients (43%), allogeneic stem cell transplantation (allo-SCT) in 3 (8%), and other in 12 (32%); 7 patients (19%) were high-risk and treatment naive. Overall, 16 patients (44%) had baseline palpable splenomegaly; in 12 of these patients, spleen size was ≥5 cm below left costal margin. Overall, 4 of 36 (11%) patients achieved bone marrow morphological complete responses (BMCRs), 1 of whom was bridged to allo-SCT; all 4 patients had splenomegaly at baseline. It is noteworthy that 2 of the 4 BMCRs, were observed in patients with high-risk genetic features. Fifteen patients (42%) with baseline splenomegaly had spleen responses; 9 patients (60%) had a ≥50% reduction in spleen size, including 5 (42%) with splenomegaly of ≥5 cm at baseline.

Based on these preliminary results and increasing scientific and clinical knowledge on CMML, the protocol has been amended to add Stage 3A in patients with CMML. The Myelodysplastic Syndrome/ Myeloproliferative Neoplasm (MDS/MPN) 2015 criteria (Savona 2015) represent the current consensus criteria for evaluation of clinical benefit in patients with MDS/MPN, beyond those specified in the IWG response criteria for MDS (Cheson 2006), however, these criteria are not specific to CMML. Thus, in Stage 3A, the endpoints indicated in the MDS/MPN 2015 criteria will be individually evaluated to enable a prospective definition of a primary efficacy endpoint, specifically in CMML, that will provide the primary evidence of efficacy for regulatory decision-making. The hematology community has recognized that a lack of a stable disease (SD) category in the 2015 MDS/MPN IWG criteria creates considerable uncertainty in the categorization of patients on any CMML study. Therefore, a SD category, defined as those patients not belonging to any of the defined categories in the 2015 criteria, has been added as a response category.

Stage 3A will enroll 2 populations of patients with CMML, previously untreated patients who are not expected to benefit from HMAs (previously untreated patients; approximately 20 patients) and patients who are primary or secondary failures to first-line therapy (first-line failure patients; approximately 20 patients), as defined in the inclusion criteria for Stage 3A (Section 7.1.1). In addition, central analysis of CD123 expression will be performed by flow cytometry and immunohistochemistry to evaluate the presence of CD123 expressing cells and the relationship between CD123 expression and clinical response.

2 Protocol Synopsis

Name of Finished Product:

Elzonris (tagraxofusp-erzs) Injection solution (1mg/ml) / Tagraxofusp for Injection lyophilized powder for solution (1 mg/vial)

Name of Active Ingredient:

Tagraxofusp (SL-401)

Study Title:

Tagraxofusp in Patients with Chronic Myelomonocytic Leukemia (CMML)

Study Number:

STML-401-0314

Study Phase:

2

Protocol Overview:

The current study was initially designed as a 2-stage, non-randomized, open-label, multicenter study of tagraxofusp in patients with subtypes of advanced, high risk myeloproliferative neoplasms. The candidate patients for the study were comprised of patients with CMML, MF, chronic eosinophilic leukemia, or mastocytosis.

The primary objective of Stage 1 of this study, which is now complete, was to establish the maximum tolerated dose (MTD) or the maximum tested dose (MTeD) at which multiple dose-limiting toxicities (DLTs) were not observed. In Stage 1, 9 patients (5 with CMML and 4 with MF) received tagraxofusp at doses of 7, 9, or 12 mcg/kg via intravenous (IV) infusion on Days 1-3 every 21 days for Cycles 1-4, every 28 days for Cycles 5-7, and every 42 days for Cycles 8 and beyond. No MTD was identified, and the MTeD was 12 mcg/kg (the recommended phase 2 dose). As Stage 1 is complete, details regarding conduct of this stage have been removed from the protocol.

Stage 2 intended to further characterize the safety profile of tagraxofusp, initially in the same 4 candidate patient populations and then subsequently only in populations treated in Stage 1, CMML and MF. Preliminary assessment of clinical activity associated with tagraxofusp in patients with CMML or MF was also an objective of Stage 2. As Stage 2 is complete, study details regarding the conduct of this stage have been removed.

Ongoing CMML and MF patients enrolled during Stage 2 will receive tagraxofusp at the recommended phase 2 dose, 12 mcg/kg, on the same schedule as Stage 1.

As of July 2021, 36 patients have been enrolled, comprising 20 patients with CMML-1 and 16 with CMML-2; median age was 69 years (range 42–81) and 75% were male. Twenty-three (64%) patients had either high-or intermediate-risk genetics based on CPSS, GFM, MMM, or ELN risk stratification systems. Prior therapies included HMA in 16 patients (43%), allogeneic stem cell transplantation (allo-SCT) in 3 (8%), and other in 12 (32%); 7 patients (19%) were high-risk and treatment naive. Overall, 16 patients (44%) had baseline palpable splenomegaly; in 12 of these patients, spleen size was ≥5 cm below left costal margin. Overall, 4 of 36 (11%) patients achieved bone marrow morphological complete responses (BMCRs), 1 of whom was bridged to allo-SCT; all 4 patients had splenomegaly at baseline. Notably, 2 of the 4 BMCRs were observed in patients with high-risk genetic features. Fifteen patients (42%) with baseline splenomegaly had spleen responses; 9 patients (60%) had a ≥50% reduction in spleen size, including 5 (42%) with splenomegaly of ≥5 cm at baseline.

Based on these preliminary results and increasing scientific and clinical knowledge on CMML, the protocol has been amended to add Stage 3A in patients with CMML. The Myelodysplastic Syndrome/ Myeloproliferative Neoplasm (MDS/MPN) 2015 criteria (Savona 2015) represent the current consensus criteria for evaluation of clinical benefit in patients with MDS/MPN, beyond those specified in the International Working Group (IWG) response criteria in MDS (Cheson 2006), however, these criteria are not specific to CMML. Thus, in Stage 3A, the endpoints indicated in the MDS/MPN 2015 criteria will be individually evaluated to enable a prospective definition of a primary efficacy endpoint, specifically in CMML, that will provide the primary evidence of efficacy for regulatory decision-making. The hematology community has recognized that a lack of a stable disease (SD) category in the 2015 MDS/MPN IWG criteria creates considerable uncertainty in the categorization of patients on any CMML study. Therefore, a SD category, defined as those patients not belonging to any of the defined

categories in the 2015 criteria, has been added as a response category.

Stage 3A will enroll 2 populations of patients with CMML, previously untreated patients who are not expected to benefit from HMAs (previously untreated patients; approximately 20 patients) and patients who are primary or secondary failures to first-line therapy (first-line failure patients; approximately 20 patients), as defined in the inclusion criteria for Stage 3A (Section 7.1.1). Enrollment in Stage 2 is closed; however, patients with CMML and MF who are already enrolled may continue study participation in Stage 2.

Objectives:

Stage 3A: Objectives of Stage 3a in patients with CMML are:

- To characterize the safety profile of tagraxofusp.
- To obtain preliminary evidence of response to tagraxofusp therapy as assessed by the MDS/MPN 2015 criteria (Savona 2015), with the addition of a stable disease category, and to obtain data relative to additional clinical parameters that may be used in determination of therapeutic benefit.

The MDS/MPN 2015 criteria (Savona 2015) represent the current consensus criteria for evaluation of clinical benefit in patients with CMML, beyond those specified in the IWG-MDS 2006 criteria. Thus, as an inherent component of the design of Stage 3A, responses to treatment are assessed using the MDS/MPN 2015 criteria.

The purpose of Stage 3A is to evaluate the clinical benefit derived from individual components, or variations thereof, of the MDS/MPN 2015 criteria that may allow for a prospective definition of a primary efficacy endpoint, that will provide the primary evidence of efficacy for regulatory decision-making in the planned confirmatory cohort (Stage 3B; to be added under the auspices of a separate amendment).

Study Population:

Stage 3A will include patients with CMML as follows:

- Patients with 2016 WHO-defined CMML, including those with
  - CMML-1 or CMML-2 who are refractory/resistant/intolerant to HMAs, or hydroxyurea (HU), or intensive chemotherapy; and
  - Treatment naïve CMML-1 or CMML-2 with molecular features associated with a poor prognosis.

Study Design:

This is a non-randomized, open-label, multicenter study divided into multiple stages.

Stage 3A (CMML):

Stage 3A is a 2-arm, non-randomized, open-label multicenter study stage in patients with CMML intended to identify clinically important responses that connote clinical benefit and potential endpoints to inform the design of a pivotal Stage 3B in patients with CMML (to be added under the auspices of a separate amendment), as well as gather data on the expression of CD123 on dendritic cells and monocytes in CMML. Additionally, monocyte subsets will be enumerated by flow cytometry.

In Stage 3A, patients will be administered tagraxofusp at a dose of 12 mcg/kg as a 15-minute IV infusion once daily on days 1 to 3 of a 21-day cycle (C1 to C4) and then on days 1 to 3 of a 28-day cycle (C5 and beyond). The dosing period may be extended for dose delays up to D10 of each cycle.

Study Centers:

The study will be conducted at approximately 30 study centers in North America and Europe.

Inclusion Criteria:

Patients meeting all of the following criteria may be considered for enrollment:

1. The patient is ≥ 18 years old.
2. The patient has a life expectancy of > 6 months.
3. The patient has an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2.
4. The patient has adequate baseline organ function, including cardiac, renal, and hepatic function:
   - Left ventricular ejection fraction (LVEF) ≥ institutional lower limit of normal as measured by multigated acquisition scan (MUGA) or 2-dimensional (2-D) echocardiogram (ECHO) within 28 days prior to start of therapy and no clinically significant abnormalities on a 12-lead electrocardiogram (ECG).
   - Serum creatinine ≤ 1.5 mg/dL.
   - Serum albumin ≥ 3.2 g/dL (or ≥ 32 g/L) in the absence of receipt of IV albumin within the previous 72 hours.
   - Bilirubin ≤ 1.5 mg/dL.
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 times the upper limit of normal (ULN).
   - Creatine phosphokinase (CPK) ≤ 2.5 times the ULN.
   - Absolute neutrophil count (ANC) ≥ 0.5×109/L.
5. If a woman of child-bearing potential (WOCBP), the patient has a negative serum or urine pregnancy test within 1 week prior to tagraxofusp treatment (intervals shorter than 1 week are acceptable, if required by institutional guidelines).
6. The patient (either male or female) agrees to use acceptable contraceptive methods for the duration of time in the study, and to continue to use acceptable contraceptive methods for 1 week after the last tagraxofusp infusion.
7. The patient has signed informed consent prior to initiation of any study-specific procedures or treatment.
8. The patient is able to adhere to the study visit schedule and other protocol requirements, including follow-up for response assessments.
9. Patient has a 2016 WHO-defined diagnosis of CMML (persistent monocytosis ≥ 1×10^9/L for at least 3 months, with other causes excluded, and monocytes ≥ 10% of WBC in peripheral blood, no criteria and no previous history of chronic myeloid leukemia (CML), essential thrombocythemia (ET), polycythemia vera (PV), and acute promyelocytic leukemia; if eosinophilic, neither PDGFRA, PDGFRB, FGFR1 rearrangements nor PCM1-JAK2 translocation; < 20% blasts in peripheral blood and bone marrow aspirate; > 1 following criteria: dysplasia in > 1 myeloid lineage, acquired clonal cytogenetic or molecular abnormality in hematopoietic cells).
10. Patient has 2016 WHO-defined CMML-1 (2-4% blasts in peripheral blood and/or 5-9% blasts in bone marrow) and CMML-2 (5-19% blasts in peripheral blood and/or 10-19% blasts in bone marrow, and/or presence of Auer rods) (Arber 2016).
11. Patient is refractory/resistant/intolerant, as defined for the purposes of this study (in the absence of a standard definition for CMML) below, to HMAs, or HU, or intensive chemotherapy, including:
    - **Resistance/intolerance to HU** is defined as:
      - Uncontrolled myeloproliferation (platelets >400 x 10^9/L **and** WBC >10 x 10^9/L after 3 months of at least 2 g/day of HU); **or**
      - Myelosuppression at a clinically relevant dose; **or**
      - Presence of unacceptable HU-related non-hematological toxicities, such as mucocutaneous

manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU.

- **Conventional definition for HMA failure** is defined for the purposes of this study (in the absence of a standard definition for CMML) as:
  - Disease progression following at least 4 to 6 cycles of 5-azacitidine or decitabine; or
  - Relapse after achieving response; or
  - Intolerance to 5-azacitidine or decitabine at the prescribed dose.

OR

- Patient is classified as high-risk based on the presence of morphological features, as described by the 2016 WHO prognostic system (Arber 2016), and the clinical and molecular features described in molecularly-integrated prognostic systems, such as the Group Français des Myélodysplasies (GFM), Mayo Molecular Model (MMM), and the CMML-specific prognostic model (CPSS-Mol) (Woo 2020) and thus is not expected to benefit from HMAs.

12. Patient is ineligible for an immediate allo-SCT.

Investigational Product, Dose, and Mode of Administration:

Tagraxofusp Injection is a biologic fusion protein comprised of recombinant human interleukin-3 (IL-3) genetically fused to truncated diphtheria toxin (DT) protein. Tagraxofusp targets the IL-3 receptor (IL-3R), which is overexpressed on the cancer stem cells (CSC) and bulk of various leukemias and hematopoietic malignancies relative to normal hematopoietic stem cells and other hematopoietic cells.

Tagraxofusp is prepared in liquid or lyophilized formulations; study sites may be provided with either of the following:

- Tagraxofusp Injection is a preservative-free, sterile, clear, colorless solution supplied in single-dose glass vials containing 1 mL of sterile tagraxofusp solution (1 mg/vial) that should be stored in a freezer between -25°C and -15°C (-13°F and 5°F).
- Tagraxofusp for Injection (lyophilized powder), 1.0 mg is supplied in single-use, sterile, 2 mL glass vials packaged in labeled, single-vial cartons (study drug) and should be stored between 2°C and 8°C (36°F – 46°F).

Patients will receive 12 mcg/kg of tagraxofusp by IV infusion once daily for 3 consecutive days (or 3 doses over a period not to exceed 10 days if postponement is required to allow for toxicity resolution) of a cycle in the absence of progressive disease (PD) or other withdrawal criteria.

A treatment cycle is 21 days in C1-4 and 28 days in C5 and beyond.

The total per-patient dose is calculated based on patient body weight in kg at baseline (C1D1). This dose will be recalculated if there is a 10% or greater change from baseline in body weight.

The first cycle 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 ambulatory care setting that is equipped for intensive monitoring of patients with hematopoietic malignancies undergoing treatment, per the Investigator's discretion, institutional guidelines and capabilities. Patients will be monitored for at least 1 hour (or longer at the Investigator's discretion) following the administration of each infusion of tagraxofusp in Cycle 2 and beyond.

Patients with evidence of ongoing disease control during treatment (without evidence of clinically significant PD or intolerable toxicity) may receive repeated cycles of tagraxofusp even if an overall response, in the judgment of the Investigator, is not attained.

Patients will receive the following pre-medications 60 minutes (±15 minutes) before each tagraxofusp infusion:

- Acetaminophen 650 mg by mouth (PO) (or equivalent dose of paracetamol)
- Diphenhydramine 50 mg IV (or an equivalent dose of another H_1-histamine antagonist)
- Methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid)
- Famotidine 20 mg IV (or an equivalent dosage of another H_2-histamine antagonist)

During the dosing period for each cycle, individual tagraxofusp infusions may be delayed to allow for toxicity resolution, as detailed in Protocol Section 8.2.3.

Concomitant Medications:

Recommended Medications Per Institutional Guidelines/Practices:

The following types of prophylactic therapies/regimens may be administered, if indicated per institutional guidelines/practices or warranted for clinical management:

- Antibacterial: ciprofloxacin, levofloxacin, or an equivalent antibiotic.
- Antifungal: fluconazole, voriconazole, or an equivalent antifungal.
- Antiviral: acyclovir, valacyclovir, or an equivalent antiviral.

Allowed Medications/Therapies:

All patients may receive supportive care measures as clinically indicated, including prophylactic antibiotics, antihistamines, antiemetics, albumin, fluids (hydration), and supportive measures. Patients may receive growth factor support and/or blood product transfusions as per the discretion of their physician.

Albumin 25 g IV daily should be administered if serum albumin is < 3.0 g/dL during days when treatment is withheld or in the immediate post-treatment period. (Refer to Appendix Section 18.3 for albumin administration requirements in the setting of elements of capillary leak syndrome (CLS).)

Corticosteroid therapy is permitted and is governed by parameters detailed in Section 12.3 (Prohibited Medications/Therapies).

Granulocyte-colony stimulating factor (G-CSF) is permitted only for the treatment of febrile neutropenia. Following a febrile neutropenic event, G-CSF prophylaxis may be considered if there is evidence of response and the Investigator determines that ongoing tagraxofusp treatment is associated with a potentially favorable risk-benefit profile (such a determination should be made in consultation with the Medical Monitor).

Prohibited Medications/Therapies:

Prior to discontinuation of tagraxofusp, patients may not receive the following anticancer/ antimyeloproliferative agents: JAK inhibitors (ruxolitinib, fedratinib, and others), interferon-α, thalidomide, lenalidomide, cytotoxic chemotherapy agents (including 2-chlorodeoxyadenosine and other purine analogs), hypomethylating agents (5-aza, decitabine and others), tyrosine kinase inhibitors (including those which inhibit the BCR-ABL kinase such as imatinib), hydroxyurea (HU), and investigational anti-cancer agents.

Patients may not receive additional disease-modifying or cytoreductive agents such as danazol or anagrelide. Patients may not receive erythroid- or platelet-stimulating growth factors.

Hydroxyurea is prohibited during study participation except for cycle 1; short-term treatment with HU beyond cycle 1 with approval of the Medical Monitor is permitted.

Ongoing corticosteroid therapy at doses of > 20 mg/day prednisone (or equivalent) for > 7 days is not permitted; however transient increases in corticosteroid doses in the setting of infections or other “stress” settings are allowed.

Assessments:

Assessments for safety, efficacy, and biological/correlative effects will be performed according to the schedules outlined in Section 9 (Stage 2) and Section 10 (Stage 3A).

Safety Assessments:

Safety will be assessed throughout the duration of the study; safety assessments will include physical examinations, vital sign measurements, clinical laboratory evaluations, and adverse event (AE) reporting. Blood samples for immunogenicity assessments will be collected.

Efficacy Assessments:

Efficacy assessments will include bone marrow (aspirate and biopsy), peripheral blood (complete blood count [CBC] and differential with percent monocytes, neutrophils, neutrophil precursors, immature myeloid cells, and blasts), hepatosplenomegaly by MRI or CT, other extramedullary disease (e.g., cutaneous disease, disease-related

serous effusions), symptom score analysis by the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS), cytogenetic burden, molecular response, reduced dependence on transfusion, reduced risk of infection, and survival status. Refer to Appendix Section 18.1 for detailed response criteria established for CMML.

Biological/Target/Correlative Studies:

Plasmacytoid dendritic cells (pDCs) and CD123 expression will be assessed centrally on all bone marrow and peripheral blood samples by flow cytometry and immunohistochemistry prior to the start of and during treatment. Additionally, various monocyte subsets will be monitored in CMML.

Exploratory assessments for CMML patients will include peripheral blood for the evaluation of cytokine IL-10, $CD14^{+}/CD16^{-}$, CYTOF (Mass cytometry), and next generation sequencing (NGS) at selected sites prior to the start of and during treatment.

Immunogenicity Studies:

Blood samples will be collected for the detection of tagraxofusp reactive antibodies.

Statistical Methods:

Analyses will be performed on all patients that received any quantity of tagraxofusp (i.e., all treated patients). The baseline value for a given variable is defined as the last measurement for the variable prior to the first infusion of tagraxofusp. Day 1 for each individual patient is defined as the date the patient receives their first infusion of tagraxofusp.

Safety assessments include DLTs, AEs, serious adverse events (SAEs), physical examinations, vital sign measurements, ECGs, clinical laboratory evaluations, and reasons for treatment discontinuation due to toxicity.

Treatment-emergent AEs through 30 days after the last tagraxofusp infusion will be summarized by Medical Dictionary for Regulatory Activities (MedDRA™) Version 13.1 (or higher) System Organ Class and preferred term. The incidences and percentages of patients experiencing each AE preferred term will be summarized with descriptive statistics. AEs will also be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03 (or higher), grade and by causality (relationship to study drug). DLTs, Grade 3-4 AEs, SAEs, and AEs resulting in dose modification or treatment discontinuation will also be summarized by preferred term.

Laboratory results will be classified according to NCI CTCAE, Version 4.03. Laboratory results not corresponding to an NCI CTCAE term will not be graded. Incidences of laboratory abnormalities will be summarized with descriptive statistics.

Vital signs, physical examination results, and ECGs will be summarized with descriptive statistics.

Efficacy assessments include objective response rate (ORR), complete response (CR) rate, specific components of the response criteria for each indication, duration of response (DOR), progression-free survival (PFS), and overall survival (OS). All efficacy outcomes will be presented by subgroups defined by disease. Data from Stage 2 will be analyzed with descriptive statistical methods to provide estimates of rates of response. Stage 3A data will be analyzed with descriptive and correlation methods, with results intended to assist in the design of the confirmatory Stage 3B. Bayesian methods may also be used to determine likely values of response parameters, with Stage 2 results providing prior information for calculation of credible intervals based on Stage 3A data. Complete details of efficacy analyses will be provided in the Statistical Analysis Plan (SAP).

3 Abbreviations and Definitions

Abbreviation	Definition
2-D	2-Dimensional
AE	Adverse Event
ALL	Acute Lymphoid Leukemia
allo-SCT	Allogeneic Stem Cell Transplantation
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
BP	Blood Pressure
BPDCN	Blastic Plasmacytoid Dendritic Cell Neoplasm
BUN	Blood Urea Nitrogen
C	Cycle
CBC	Complete Blood Count
CEL	Chronic Eosinophilic Leukemia
CFR	Code of Federal Regulations
CI	Clinical Improvement
CLS	Capillary Leak Syndrome
CML	Chronic Myeloid Leukemia
CMML	Chronic Myelomonocytic Leukemia
CNL	Chronic Neutrophilic Leukemia
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CR	Complete Response / Remission
CSC	Cancer Stem Cell
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
DSRC	Data Safety Review Committee
DT	Diphtheria Toxin

Abbreviation	Definition
DT388IL3	Diphtheria Toxin Interleukin-3 Fusion Protein
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EHA	European Hematology Association
ELISA	Enzyme-linked Immunosorbent Assay
ELN	European LeukemiaNet
EMA	European Medicines Agency
EMH	Extramedullary Hematopoiesis
ET	Essential Thrombocythemia
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony Stimulating Factor
GM-CSF	Granulocyte Macrophage-colony Stimulating Factor
GVHD	Graft Versus Host Disease
Hb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HMA	Hypomethylating agent
HSC	Hematopoietic Stem Cell
HU	Hydroxyurea
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IL-3	Interleukin-3
IL-3R	Interleukin-3 Receptor
IL-3Rα	Alpha Subunit of the Human Interleukin-3 Receptor
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
IWG	International Working Group
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research

Abbreviation	Definition
	and Treatment
JAK	Janus Kinase
JAKi	JAK inhibitor
JMML	Juvenile Myelomonocytic Leukemia
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MCL	Mast Cell Lymphoma
MDS	Myelodysplastic Syndrome
MedDRA™	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MPD	Myeloproliferative Disorder
MPN	Myeloproliferative Neoplasm
MPN-SAF TSS	Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score
MPN-U	Myeloproliferative Neoplasm, Unclassifiable
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MTeD	Maximum Tested Dose
MUGA	Multigated Acquisition Scan
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PB	Peripheral Blood
PD	Progressive Disease
pDC	Plasmacytoid Dendritic Cell
PDGFRα	Platelet-derived Growth Factor Receptor-alpha
PDGFRβ	Platelet-derived Growth Factor Receptor-beta
pET	Post-essential Thrombocythemia
PFS	Progression-free Survival
PK	Pharmacokinetics
PMF	Primary Myelofibrosis
PR	Partial Response / Remission
pRBC	Packed Red Blood Cell
PS	Performance status
PT	Prothrombin Time

Abbreviation	Definition
PV	Polycythemia Vera
R/R	Relapsed/Refractory
RBC	Red Blood Cell
RS	Ring Sideroblasts
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SM	Systemic Mastocytosis
SM-AHNMD	Systemic Mastocytosis with Associated Haematological Non-Mast Cell Disease
SSM	Smoldering Systemic Mastocytosis
TEAE	Treatment-emergent Adverse Event
TLS	Tumor Lysis Syndrome
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

4 Background Information

4.1 Myeloproliferative Neoplasms and Myelodysplastic Syndrome/Myeloproliferative Neoplasms

In 2008, World Health Organization (WHO)-appointed experts replaced the historical term 'myeloproliferative disorders' (MPD) with the term 'myeloproliferative neoplasm' (MPN) in alignment with the enhanced knowledge about the molecular biology of these diseases. The 2016 edition of the WHO-classification recognizes MPNs to comprise of several subtypes: chronic myeloid leukemia (CML), polycythaemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF) and several 'atypical' subtypes, which include chronic neutrophilic leukaemia (CNL), chronic eosinophilic leukemia, not otherwise specified (CEL), and myeloproliferative neoplasm, unclassifiable (MPN-U). The various MPN subtypes have traditionally been distinguished from one another by clinicopathological features and, in some cases, the disease-defining genetic aberrations. In clinical practice, since most patients present with neutrophilia, it is important to establish the presence or absence of *BCR-ABL1* rearrangement, which defines CML.

The *BCR-ABL1*-negative MPNs are a group of clonal myeloid malignancies characterized by excessive accumulation of one or more myeloid cell lineages and an inherent ability to transform to acute myeloid leukemia (AML). In tandem with the 2016 WHO edition, revised diagnostic criteria for the various subtypes were also developed to enable better diagnostic work-up and help distinguish MPN from secondary/reactive erythrocytosis or thrombocytosis in challenging cases.

An important tenet of the 2016 WHO-classification is that in myelodysplastic syndrome (MDS)/MPN, the dysplastic and proliferative features must be present at the time of initial diagnosis, with the sole exception of MDS/MPN with ring sideroblasts (RS) and thrombocytosis. Patients with other subtypes, including chronic myelomonocytic leukemia (CMML), may present in earlier phases in which the full disease phenotype has not fully developed. Indeed, a recent publication has proposed broadening the category of CMML to encompass variants in which monocytosis develops after a prior diagnosis of a myeloid malignancy, a category which is not included in the 2016 WHO classification (Valent 2019). The MDS/MPN subtypes are typically identified by the type of myeloid subset that predominates in the peripheral blood (PB). For example, CMML and juvenile myelomonocytic leukemia (JMML) are characterized by a unique expansion of peripheral blood monocytes, while atypical CML is associated with highly dysplastic granulocyte predominance. Multiparameter flow cytometry helps to characterize patients with CMML who have a specific expansion of 'classical' monocytes ($CD14^{hi}/CD16^{neg}$), albeit with varying degrees of differentiation and proliferation which, in turn, result in the remarkable clinical heterogeneity, in contrast to the genetic landscape, which is relatively homogeneous with four well defined mutations (*ASXL1, NRAS, RUNX1*, and *SETBP1)* which exert a prognostic impact on the patients. Patients with MDS/MPNs often present with

neutrophilia and have clinical features consistent with features of ineffective hematopoiesis (anemia, infections, bleeding), constitutional symptoms and splenomegaly associated with myeloproliferation.

A recent study (Zhang 2019) suggests that once CML, JMML, and the JAK2/MPL/CALR-associated MPNs are excluded, many of the chronic myeloid malignancies appear to share genetic and epigenetic features and it is possible that they should be considered collectively for risk stratification, treatment, and clinical studies.

4.1.1 Chronic Myelomonocytic Leukemia

The annual incidence of CMML is estimated at 1,100 cases per year in the United States (US), with a median age of 70 years and a male predominance. The diagnosis of CMML is based upon laboratory, morphological and clinical parameters. Recurrent somatic mutations are noted in > 90% of the patients and clonal cytogenetic abnormalities in > 30%. A cardinal feature of CMML is the PB monocytosis (> 1×10^9/L), with monocytes accounting for > 10% of white blood cells (WBC). Clinical presentation includes dysplastic features such as cytopenias and excess of blasts, or proliferative features such as high WBC count (≥ 13×10^9/L) and splenomegaly; rarely skin and lymph node infiltration and serous membrane effusions can occur.

CMML is divided by the 2016 WHO diagnostic criteria into three groups based upon blast percentage:

- CMML-0 with < 2% blasts in PB and < 5% blasts in the bone marrow,
- CMML-1 with 2% to 4% blasts in PB and/or 5% to 9% blasts in bone marrow and
- CMML-2 with 5% to 19% blasts in PB and/or 10% to 19% in bone marrow, and/or presence of Auer rods.

The so-called ‘proliferative type’ CMML (leukocyte count ≥ 13×10^9/L) and ‘dysplastic type’ CMML (< 13×10^9/L) are distinguished solely by leukocyte count; however, mutational patterns may help to distinguish between the two types. For example, mutations involving the JAK2/RAS/MAPK signaling pathways tend to be more common in patients with the ‘proliferative type’ CMML.

Cytogenetic abnormalities include trisomy 8, monosomy 7, del(7q) and rearrangements with a 12p breakpoint; however, del(5q) is almost never found. As previously mentioned, PB monocytosis with monocytes accounting for > 10% of WBCs is the hallmark of CMML. Morphologically, these monocytes demonstrate an abnormal appearance with bizarre nuclei and cytoplasmic granules. In some patients, blood cells identified as monocytes are later recognized to be dysplastic and immature granulocytes endowed with immunosuppressive properties, i.e. so-called para- myeloid cells. Islands of $CD123^{high}$ cells have been commonly described in the bone marrow of patients with CMML (Niyongere 2019). Using a multiparameter flow cytometry assay, an excess of $CD123^+$ mononucleated cells that are lineage-negative, $CD45^+$, $CD11c^-$, $CD33^-$, $HLA\text{-}DR^+$, $BDCA\text{-}2^+$, $BDCA\text{-}4^+$ in the bone marrow of 32/159 (20%) patients were

detected in a recent study and characterized as plasmacytoid dendritic cells (pDCs) (Lucas 2019). Furthermore, an excess of pDCs correlates with regulatory T cell accumulation and an increased risk of acute leukemia transformation. These results demonstrate the FLT3-independent accumulation of clonal pDCs in the bone marrow of CMML patients with mutations affecting the RAS pathway, which is associated with a higher risk of progressive disease (PD).

Multiple prognostic scoring systems, based on monocyte counts, genetic lesions, clinical features and risk to transform to AML have been proposed and validated (Itzykson 2018). As illustration, Itzykson et al proposed a prognostic score based on *ASXL1* mutations, age, hemoglobin, WBC, and platelet counts that defined three prognostic groups with varied overall survival (OS) (Itzykson 2013).

Splenomegaly is a major source of morbidity in approximately 30%-50% of patients with CMML and is associated with abdominal discomfort, left subcostal pain and early satiety, as well as serious risk of splenic rupture and splenectomy sequelae (Padron 2014, Pophali 2018). The effectiveness of splenectomy in alleviating many of the symptoms of CMML was demonstrated in a study of patients with CMML where splenectomy was medically necessary. In this study, 85% of patients who underwent a splenectomy achieved durable resolution of symptoms. However, splenectomy was also associated with perioperative morbidity and mortality rates of 43% and 13%, respectively (Pophali 2018).

The management of patients with CMML is often a challenge with a small subset of patients having an indolent course with median survival in excess of 10 years, whilst others progress rapidly to AML. Allogeneic stem cell transplantation (allo-SCT) remains the only treatment modality associated with long term remissions and long-term OS benefit (10-year OS rate of 40%). Factors associated with favorable outcomes appear to be CMML risk group (CMML-0 vs. CMML-1 vs. CMML-2), pre-transplant hematocrit, cytogenetic risk category, co-morbidity index, and age (Germing 2004). Splenomegaly at the time of allo-SCT was reported to be associated with poorer OS post-transplant (Park 2013).

At present, there are no satisfactory non-transplant treatment options, and the only US FDA-approved therapies are two hypomethylating agents (HMAs), azacitidine and decitabine. While these agents may transiently improve cytopenias in patient with CMML with dysplastic features, treatment outcomes are less favorable in patients with CMML with proliferative features (Padron 2014, Padron 2016, Pardanani 2019). Azacitidine was approved in 2004 for the treatment of patients with several MDS subtypes, including CMML. In the pivotal study, the objective response rate (ORR) for the entire MDS population (N=89) was 16% and in the 2 supportive studies (N=72 and N=48) was 14% and 19%, respectively. The ORR for the CMML subpopulation (n=19; approximately 8-9% of enrolled MDS patients) ranged between 11% and 20%. Decitabine was approved in 2006 for the treatment of patients with all MDS subtypes, including CMML. In the pivotal study, the ORR for the entire MDS population (N=89) was 17% and in the 2 supportive studies (N=66 and N=98) was 26% and 24%, respectively. The ORR for the CMML subpopulation (n=28; approximately 10-11% of enrolled MDS patients) ranged

between 17% and 27% across the three studies. In a 2010 update to the original package insert, results from an additional single-arm clinical study were included and were consistent with results of the controlled study (16% ORR in 99 patients, including 11 patients with CMML). It is of interest that European Medicines Agency (EMA) approved azacitidine, but not decitabine, for the treatment of non-proliferative (dysplastic) CMML only, in 2008.

Cytoreductive agents such as hydroxyurea (HU) or cytarabine can reduce leukocytosis and, very rarely, splenomegaly in CMML with proliferative features, but usually worsen cytopenias and have modest impact on disease-associated symptoms (Padron 2014). Subsequent to the HMA approvals in MDS, additional clinical studies of these agents in CMML have demonstrated ORR centered at approximately 30-40% (range ~25% to 75%) upon initial exposure to HMAs, but responses were generally not sustained (Alfonso 2017, Moyo 2017, Patnaik 2016, Padron 2014, Coston 2019), with complete response (CR) rates of approximately 15%, and median OS of 12 to 37 months (see Table 8 in Appendix Section 18.1) (Patnaik 2016). Clinical studies with a variety of cytotoxic drugs and targeted therapies have generally been disappointing and therapy was associated with significant toxicities (Patnaik 2016).

Given these results, there is a need for additional therapies for patients with CMML, and especially those who have been previously treated with or are not expected to derive benefit from treatment with an HMA. Moreover, it has been recommended that *"every CMML patient be considered for clinical trials irrespective of risk stratification or treatment history because of limited prospective clinical data and the disease's aggressive natural history."* (Padron 2014).

Historically (including in the current study), given CMML's original classification as an MDS, clinical studies enrolling CMML patients had responses measured via the International Working Group (IWG) response criteria for MDS. However, it was subsequently observed that approximately 50% of patients with CMML predominantly present with myeloproliferative, rather than myelodysplastic features (Loghavi 2018).

An international consortium of thought leaders recommended new response criteria to measure treatment response in MDS/MPN, including CMML, to capture measures of clinical benefit relating to CMML with proliferative features (Savona 2015) (see Table 8 in Appendix18.1 for full response criteria). These revisions were justified by the authors, who indicated that "*the molecular and clinical heterogeneity and absence of uniform response criteria by which to assess meaningful therapeutic benefit make developing and comparing new therapies a challenge. Novel agents that target biological features important in MDS/MPN are in development; testing the effectiveness of these agents requires a harmonized assessment approach designed specifically for MDS/MPN"*.

One publication reports a retrospective validation of the revised criteria by outcome analysis of 79 patients with CMML. In this analysis, response status between the IWG 2006 criteria and newer MDS/MPN criteria was concordant in 86% of cases, and both sets of response criteria led to similar predictive power for OS. Notably, the more stringent definition of progression by the

MDS/MPN criteria was described by the authors as 'relevant', as 6 patients who had PD per the IWG 2006 criteria at first assessment finally achieved response, whereas no patients with progression per overlap-MDS/MPN achieved response (Duchmann 2017).

The 2018 European Hematology Association/European LeukemiaNet (EHA/ELN) expert panel for CMML recommends PB and bone marrow aspirate (cytology) assessment as mandatory; bone marrow biopsy is considered useful for the diagnosis as it allows the assessment of cellularity, description of stroma, of fibrosis, and detects the rare association of mast cells (in patients with concomitant systemic mastocytosis [SM] and CMML). Suggested immunohistochemistry and flow cytometry immunophenotyping include CD34 and the monocytic markers CD68, CD163, CD14, and CD16. $CD14^{+}/CD16^{-}$ monocytes are considered 'classical' and are proposed as biomarkers to monitor response to therapy. Cytogenetic analysis and the assessment of 4 genes -*ASXL1, NRAS, RUNX1*, and *SETBP1* were considered mandatory. The panel also recommends that while the MDS/MPN 2015 criteria require additional validation in CMML, it is preferable to use the IWG 2006 criteria for monitoring response to treatment. For patients with splenomegaly, the panel recommended an imaging technique (ultrasound, computed tomography [CT] or magnetic resonance imaging [MRI]) rather than physical examination alone. Symptom burden has not been studied specifically in CMML and the use of Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) as an initial tool for symptom assessment is reasonable.

4.2 Targeting Cancer Stem Cells

Cancer stem cells (CSCs) possess the capacity to self-renew in addition to generating the heterogeneous cancer cells that comprise the tumor (Jordan 2006). CSCs are defined by the ability to divide and give rise to a new stem cell (self-renewal), the ability to give rise to the differentiated cells of an organ, and the genetic constraints on expansion of the cell population. Though challenging, useful CSC models have now been developed in myeloid malignancies. Recent studies propose how CSCs can be identified, and these, in turn, have helped garner a greater biological understanding and develop novel treatments that have the potential to destroy these quiescent chemoresistant cells. The notion of how CSCs adapt as a response to therapeutic pressures, cross-talks with the tumor microenvironment and drive interactions with the cancer ecosystem, which includes immune cells, fibroblasts and other extracellular components, is now recognized (Prager 2019). Taken collectively, CSCs significantly contribute to tumor heterogeneity, metastasis and resistance (Desai 2019). As illustration, canonical cell surface markers and functional approaches such as the reactive oxygen species production helped identify how BCL-2 inhibition is critical in diverse myeloid malignancies (Konopleva 2006, Lagadinou 2013). Recent work has also identified how $CD123^{+}/CD47^{+}$ leukemia stem cells (LSCs) are correlated with AML cell sensitivities and how CD123 may serve as a biomarker for chemoresistance (Yan 2019, Arai 2019). Furthermore, xenograft models of high-risk MDS demonstrate how autologous CD123 chimeric antigen receptor T cells may be useful as therapeutic options on the basis of CD123 expression on LSCs, making them a suitable cancer

target in these patients (Stevens 2019). In this context overexpression of CD123 has been observed in several other myeloid cell lines, including those derived from patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) and CMML (Frankel 2014; Economides 2019, Lucas 2019).

4.3 IL-3 Receptor (IL-3Rα) Overexpression in Hematologic Malignancies

The alpha subunit of the human interleukin-3 receptor (IL-3 α receptor = IL-3Rα, also called multi-colony stimulating factor) is a type I transmembrane glycoprotein belonging to the cytokine receptor superfamily; all the members of this superfamily are characterized by a conserved region homologous to the fibronectin type III domain. The IL-3R is a heterodimer of α (CD123) and β chains (the β chain is shared by interleukin-3 (IL-3), IL-5, and granulocyte macrophage-colony stimulating factor [GM-CSF] receptors). The receptor, found on pluripotent progenitor cells, induces tyrosine phosphorylation within the cell and promotes proliferation and differentiation within the hematopoietic cell lines.

IL-3R is overexpressed on myeloid leukemic blasts and CSCs relative to normal hematopoietic stem cells (Jordan 2000; Jordan 2006; Tehranchi 2010). $CD34^{+}/38^{-}$ CSCs strongly express IL-3R, whereas IL-3R is virtually undetectable on normal $CD34^{+}/38^{-}$ hematopoietic stem cells (HSCs) (Jordan 2000; Jordan 2006). The differential expression of IL-3R between malignant and normal stem cells provides a potential opportunity for a therapeutic window in which to target CSCs with an IL-3R-targeted therapy (e.g., tagraxofusp), while minimizing toxicity to normal bone marrow including normal HSCs.

In addition to AML, IL-3R has also been shown to be differentially expressed on other hematological cancers, including blastic plasmacytoid dendritic cell neoplasm (BPDCN), MDS, CML, acute lymphoid leukemia (ALL), hairy cell leukemia, Hodgkin's disease, and certain aggressive non-Hodgkin's lymphomas (e.g., follicular cell, mantle cell, and Burkitt's lymphomas) (Tehranchi 2010; Aldinucci 2005; Munoz 2001; Aldinucci 2002; Black 2003; Frolova 2010). Moreover, IL-3R is also overexpressed on CSCs of multiple hematologic malignancies, including CML, MDS, and T-cell ALL (Jordan 2006; Florian 2006; Lhermitte 2006).

A higher percentage of IL-3R-expressing CSCs within a patient's tumor relates to poor outcome (Vergez 2011). In particular, AML patients with IL-3R-expressing CSCs that comprise ≥ 3.5% of their entire leukemia have a worse prognosis than patients with IL-3R-expressing CSCs that comprise < 3.5% of their entire leukemia (van Rhenen 2005). Interestingly, IL-3R-rich pDCs have been found to be increased in the bone marrow of patients with CMML (Lucas 2019).

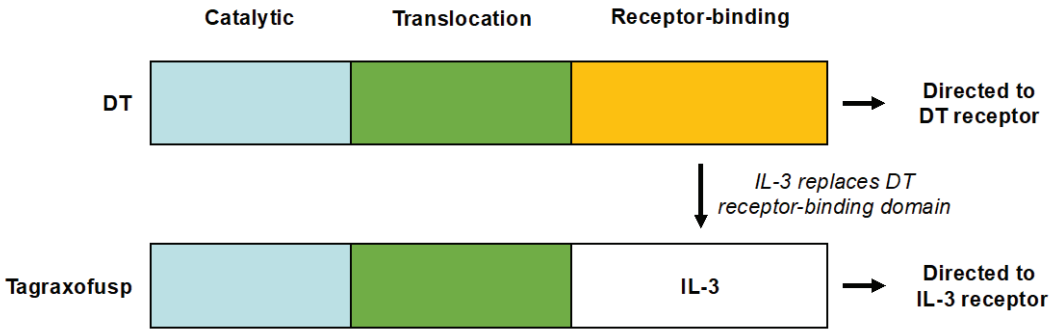
4.4 Tagraxofusp

Tagraxofusp (Elzonris; formerly known as SL-401, DT388IL3), a CD123-directed cytotoxin, is a recombinant fusion protein comprised of human IL-3 and truncated diphtheria toxin (DT) that targets the IL-3R. Tagraxofusp was granted breakthrough therapy designation for the treatment

of BPDCN in August 2016 and was approved by the US FDA for the treatment of BPDCN in adults and pediatric patients, 2 years and older, in December 2018.

Tagraxofusp is a 524-amino acid recombinant fusion protein expressed in *Escherichia coli* from a hybrid gene composed of the deoxyribonucleic acid (DNA) sequence of a truncated DT payload genetically fused to the DNA sequence of human IL-3 (Figure 1). The tagraxofusp protein consists of an N-terminal methionine, followed by the first 388 amino acids of DT comprising the catalytic and translocation domains. This truncated DT fragment is joined at the C-terminus through a 2-amino acid linker to the full amino acid sequence for human IL-3. The protein is engineered such that the IL-3 domain replaces the native receptor-binding domain of DT and is thereby able to target tagraxofusp to cells that express CD123.

Figure 1: Schematic of Tagraxofusp Construction



Abbreviations: DT=diphtheria toxin; IL-3=interleukin-3

The IL-3 domain of tagraxofusp binds to cell surface IL-3R and triggers receptor-mediated endocytosis of tagraxofusp into endosomes (Gesner 1988, Rapoport 1996). In the acidic environment of the early endosomes and lysosomes, the DT domain of tagraxofusp undergoes nicking in the loop between the catalytic and translocation domains by cellular proteases such as trypsin and furin (Drazin 1971, Tsuneoka 1993, Gordon 1995). The DT translocation domain undergoes a conformational change, during which its hydrophobic helices insert into the endosomal membrane to form a pore, facilitating the passage of the DT catalytic domain into the cytosol (Boquet 1976, Donovan 1981, Kagan 1981) in a process aided by multiple host cell cytosolic proteins (Ratts 2003, Ratts 2005). Upon exposure to the reducing environment of the cytosol, the DT catalytic domain dissociates from the DT translocation and IL-3 domains (Collier 1971). In the cytosol, the DT catalytic domain of tagraxofusp catalyzes the transfer of adenosine diphosphate-ribose from nicotinamide adenine dinucleotide to a diphthamide residue on EF-2 (Honjo 1968), leading to irreversible inhibition of protein synthesis and ultimately apoptosis (Kochi 1993).

Tagraxofusp drug product is prepared as liquid or lyophilized formulations. The study site may be provided with either of the following:

- Tagraxofusp Injection is a preservative-free, sterile, clear, colorless solution supplied in single-dose glass vials containing 1 mL of sterile tagraxofusp solution (1 mg/vial) that should be stored in a freezer between -25°C and -15°C (-13°F and 5°F).
- Tagraxofusp for Injection (lyophilized powder), 1.0 mg is supplied in single-use, sterile, 2 mL glass vials packaged in labeled, single-vial cartons (study drug) and should be stored between 2°C and 8°C (36°F – 46°F).

Overall, tagraxofusp was generally well-tolerated in the clinical development program, and no evidence of cumulative toxicity with tagraxofusp has been seen. The most common treatment-emergent adverse events (TEAEs) with tagraxofusp include liver transaminase elevations; manifestations of capillary leak syndrome (CLS), including hypoalbuminemia, edema, and weight increases; hematologic abnormalities, primarily thrombocytopenia and anemia; nausea and other gastrointestinal symptoms; and constitutional symptoms.

Refer to the Investigator's Brochure for complete information on tagraxofusp.

4.5 Rationale for the Current Study

Certain subtypes of MPNs and MDS/MPNs represent clonal proliferations arising from malignant myeloid stem cells with propensity to overexpress IL-3R, rendering them potentially susceptible to tagraxofusp. MPNs are associated with considerable morbidity and mortality, and risk of transformation to AML. The substantial IL-3R expression on mast cells and eosinophils suggests that tagraxofusp may have the potential to diminish tumor bulk in addition to relevant underlying stem cell populations. The visible presence of pDC nodular infiltrates in the bone marrow of a subset of CMML patients suggests a potential role of supporting dendritic cells within some of these neoplasia; preclinical data from other myeloid malignancies has indicated that targeting of these IL-3R expressing supporting cell populations may augment tagraxofusp antineoplastic effects observed against malignancies characterized by IL-3R expression (Chauhan 2014).

CD123 expression has been detected on CMML blasts, CMML monocytes, and LSCs in both MPNs and CMML (Shen 2015, Krishnan 2018). In one study of 20 CMML patient samples, CD123 was found to be expressed at higher levels on blasts and monocytes compared to lymphocytes, which showed low to no expression (Krishnan 2018). Moreover, CD123 expression on both blasts and monocytes was higher in CMML-1 and CMML-2 patients relative to CMML-0 patients (Krishnan 2018). Another study assessing 118 CMML bone marrow samples by a validated multi-color flow cytometry immunophenotyping assay found that CD34+ blasts exhibited increased expression of CD123 in 64% of CMML patients compared to 3% of control patients (Shen 2015).

CD123 is also expressed on neoplastic pDCs in the tumor microenvironment of CMML (Facchetti 2016, Lucas 2019, Vermi 2004, Brunetti 2017, Ji 2014, Naresh 2010, Vermi 2011). These pDCs have been shown to share mutations with, and belong to, the malignant CMML clone (Lucas 2019). In particular, pDCs have been shown to share RAS pathway mutations with

the CMML clone, which are associated with poor prognosis including a significant increase in the cumulative risk of AML transformation (Lucas 2019). Notably, RAS pathway mutations are associated with a higher fraction of pDCs in the bone marrow (> 5%) of patients with CMML and clinically manifest as proliferative disease (Lucas 2019, Ricci 2010). Consistent with these findings, pDCs have been identified in the spleen of some patients with CMML, and it has been suggested that pDCs could serve as a therapeutic target in patients with CMML (Lucas 2019, Pophali 2018).

Initially in this study, patients with CMML and MF as well as mastocytosis, or advanced symptomatic CEL were eligible for enrollment. The primary objective of Stage 1 was to establish the MTD or the MTeD at which multiple DLTs were not observed. In Stage 2, further characterization of the safety and initial assessment of clinical activity at the recommended phase 2 dose were intended in patients with MF and CMML.

In Stage 1, 9 patients (5 with CMML and 4 with MF) received tagraxofusp at doses of 7, 9, or 12 mcg/kg via IV infusion on days 1-3 every 21 days for Cycles 1-4, every 28 days for Cycles 5-7, and every 42 days for Cycles 8 and beyond. In Stage 2, patients with CMML and MF received tagraxofusp at the recommended phase 2 dose, 12 mcg/kg, on the same schedule as Stage 1.

As of July 2021, 36 patients have been enrolled, comprising 20 patients with CMML-1 and 16 with CMML-2; median age was 69 years (range 42–81), and 75% of patients were male. Twenty-three patients (64%) had either high- or intermediate-risk genetics based on CPSS, GFM, MMM, or ELN risk stratification systems. Prior therapies included HMA in 16 patients (43%), allogeneic stem cell transplantation (allo-SCT) in 3 (8%), and other in 12 (32%); 7 patients (19%) were high-risk and treatment naive. Overall, 16 patients (44%) had baseline palpable splenomegaly; in 12 of these patients, spleen size was ≥5 cm below left costal margin. Overall, 4 of 36 (11%) patients achieved bone marrow morphological complete responses (BMCRs), 1 of whom was bridged to allo-SCT; all 4 patients had splenomegaly at baseline. It is noteworthy that 2 of the 4 BMCRs, were observed in patients with high-risk genetic features. Fifteen patients (42%) with baseline splenomegaly had spleen responses; 9 patients (60%) had a ≥50% reduction in spleen size, including 5 (42%) with splenomegaly of ≥5 cm at baseline.

Based on preliminary clinical activity observed in the current study and increasing scientific and clinical knowledge of CMML, the protocol was amended (Amendment 7) to add Stage 3A for patients with CMML. Enrollment in Stage 2 was closed; however, patients with CMML or MF already enrolled were allowed to continue study participation in Stage 2.

5 Design of Study

5.1 Description of the Type/Design of Study to be Conducted and Purpose

This is a non-randomized, open-label, multicenter study, divided into multiple stages.

Chronic Myelomonocytic Leukemia and MF patients consented and enrolled with Amendment 6 or prior, who are currently on active treatment or in survival follow-up, will continue to be

followed according to the schedule of events in Amendment 6. These patients will not be reconsented under Amendment 7 or beyond.

Stage 3A (CMML):

Stage 3A is a 2-arm, non-randomized, open-label multicenter study stage in patients with CMML intended to identify clinically important responses that connote clinical benefit and potential endpoints to inform the design of a pivotal Stage 3B in patients with CMML (to be added under the auspices of a separate amendment), as well as gather data on CD123 expression on pDCs and monocytes in CMML.

Stage 3A will enroll 2 populations of patients with CMML, those with CMML-1 or CMML-2 who are refractory/resistant/intolerant to HMAs, or HU, or intensive chemotherapy; and patients with treatment naïve CMML-1 or CMML-2 with molecular features associated with a poor prognosis.

In Stage 3A, patients will be administered tagraxofusp at a dose of 12 mcg/kg as a 15-minute IV infusion once daily on Day 1 to 3 of a 21-day cycle (C1 to C4) and then on Day 1 to 3 of a 28-day cycle (C5 and beyond). The dosing period may be extended for dose delays up to Day 10 of each cycle.

Efficacy assessments will include bone marrow (aspirate and biopsy), peripheral blood (complete blood count [CBC] and differential with percent monocytes, neutrophils, neutrophil precursors, immature myeloid cells, and blasts), hepatosplenomegaly by MRI or CT, other extramedullary disease (e.g., cutaneous disease, disease-related serous effusions), symptom score analysis by the MPN-SAF TSS, cytogenetic burden, molecular response, reduced dependence on transfusion, reduced risk of infection, and survival status.

Safety will be assessed throughout the duration of the study; safety assessments will include physical examinations, vital sign measurements, ECGs, clinical laboratory evaluations, adverse event (AE) reporting (including DLTs, AEs, SAEs), and reasons for treatment discontinuation due to toxicity.

Blood samples for immunogenicity assessments will be collected for the detection of tagraxofusp reactive antibodies.

Plasmacytoid dendritic cells (pDCs) and CD123 expression will be assessed centrally on all bone marrow and peripheral blood samples by flow cytometry and immunohistochemistry prior to the start of and during treatment. Additionally, leukocyte populations will be monitored in CMML.

Exploratory assessments for CMML patients will include peripheral blood for the evaluation of cytokine IL-10, CD14+/CD16-, CYTOF (Mass cytometry), and NGS sequencing at selected sites prior to the start of and during treatment.

5.2 Data Safety Review Committee

A Data Safety Review Committee (DSRC), which will include investigators and representatives from the Sponsor, will convene periodically to review data from Stages 2 and 3A of the study. The DSRC will also convene in the event of identification of unexpected AEs, or AEs occurring at a frequency or severity not previously anticipated or following deaths on-study which are considered treatment related and/or not related to the underlying disease and sequelae.

5.3 Data Collection and Study Completion

When sufficient information is available to enable assessment of the primary endpoint and selected secondary endpoints, data collection may cease. The **Study Completion** date for the entire study will be the date beyond which study data are no longer entered into the primary database and the database is locked.

6 Study Objectives

6.1.1 Stage 3A

Objectives of Stage 3A in patients with CMML are:

- To characterize the safety profile of tagraxofusp.
- To obtain preliminary evidence of response to tagraxofusp therapy as assessed by the MDS/MPN 2015 criteria (Savona 2015), with the addition of a stable disease category, and to obtain data relative to additional clinical parameters that may be used in determination of therapeutic benefit.

The MDS/MPN 2015 criteria (Savona 2015) represent the current consensus criteria for evaluation of clinical benefit in patients with CMML, beyond those specified in the IWG-MDS criteria (Cheson 2006). Thus, as an inherent component of the design of Stage 3A, responses to treatment are assessed using the MDS/MPN 2015 criteria. The hematology community has recognized that a lack of a stable disease (SD) category in the 2015 MDS/MPN IWG criteria creates considerable uncertainty in the categorization of patients on any CMML study. Therefore, a SD category, defined as those patients not belonging to any of the defined categories in the 2015 criteria, has been added as a response category.

The purpose of Stage 3A is to evaluate the clinical benefit derived from individual components, or variations thereof, of the MDS/MPN 2015 criteria that may allow for a prospective definition of a primary efficacy endpoint, that will provide the primary evidence of efficacy for regulatory decision-making in the planned confirmatory cohort (Stage 3B; to be added under the auspices of a separate amendment).

7 Populations to be Studied

Stage 3A will include patients with CMML as follows:

- Patients with 2016 WHO-defined CMML, including those with

- CMML-1 or CMML-2 who are refractory/resistant/intolerant to HMAs, or HU, or intensive chemotherapy; and
- Treatment naïve CMML-1 or CMML-2 with molecular features associated with a poor prognosis.

7.1 Patient Selection Criteria

7.1.1 Inclusion Criteria

Patients meeting all of the following criteria may be considered for enrollment:

1. The patient is ≥ 18 years old.
2. The patient has a life expectancy of > 6 months.
3. The patient has an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2.
4. The patient has adequate baseline organ function, including cardiac, renal, and hepatic function:
   - Left ventricular ejection fraction (LVEF) ≥ institutional lower limit of normal as measured by multigated acquisition scan (MUGA) or 2-dimensional (2-D) echocardiogram (ECHO) within 28 days prior to start of therapy and no clinically significant abnormalities on a 12-lead electrocardiogram (ECG).
   - Serum creatinine ≤ 1.5 mg/dL.
   - Serum albumin ≥ 3.2 g/dL (or ≥ 32 g/L) in the absence of receipt of IV albumin within the previous 72 hours.
   - Bilirubin ≤ 1.5 mg/dL.
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 times the upper limit of normal (ULN).
   - Creatine phosphokinase (CPK) ≤ 2.5 times the ULN.
   - Absolute neutrophil count (ANC) ≥ 0.5×10^9/L.
5. If a woman of child-bearing potential (WOCBP), the patient has a negative serum or urine pregnancy test within 1 week prior to tagraxofusp treatment (intervals shorter than 1 week are acceptable, if required by institutional guidelines).
6. The patient (either male or female) agrees to use acceptable contraceptive methods for the duration of time in the study, and to continue to use acceptable contraceptive methods for 1 week after the last tagraxofusp infusion.
7. The patient has signed informed consent prior to initiation of any study-specific procedures or treatment.
8. The patient is able to adhere to the study visit schedule and other protocol requirements, including follow-up for response assessments.

9. Patient has a 2016 WHO-defined diagnosis of CMML (persistent monocytosis ≥ 1×109/L for at least 3 months, with other causes excluded, and monocytes ≥ 10% of WBC in peripheral blood, no criteria and no previous history of CML, ET, PV, and acute promyelocytic leukemia; if eosinophilic, neither PDGFRA, PDGFRB, FGFR1 rearrangements nor PCM1-JAK2 translocation; < 20% blasts in peripheral blood and bone marrow aspirate; > 1 following criteria: dysplasia in > 1 myeloid lineage, acquired clonal cytogenetic or molecular abnormality in hematopoietic cells).
10. Patient has 2016 WHO-defined CMML-1 (2-4% blasts in peripheral blood and/or 5-9% blasts in bone marrow) and CMML-2 (5-19% blasts in peripheral blood and/or 10-19% blasts in bone marrow, and/or presence of Auer rods) (Arber 2016).
11. Patient is refractory/resistant/intolerant, as defined for the purposes of this study (in the absence of a standard definition for CMML) below, to HMAs, or HU, or intensive chemotherapy, including:
    - **Resistance/intolerance to HU** is defined as:
      - Uncontrolled myeloproliferation, (platelets > 400×10^9/L **and** WBC > 10×10^9/L after 3 months of at least 2 g/day of HU); **or**
      - Myelosuppression at a clinically relevant dose; **or**
      - Presence of unacceptable HU-related non-hematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU.

    Conventional definition for HMA failure is defined for the purposes of this study (in the absence of a standard definition for CMML) as:

    - Disease progression following at least 4 to 6 cycles of 5-azacitidine or decitabine; or
    - Relapse after achieving response; or
    - Intolerance to 5-azacitidine or decitabine at the prescribed dose.

    OR

    Patient is classified as high-risk based on the presence of morphological features, as described by the 2016 WHO prognostic system (Arber 2016), and the clinical and molecular features described in molecularly-integrated prognostic systems, such as the Groupe Français des Myélodysplasies (GFM), Mayo Molecular Model (MMM), and the CMML specific prognostic model (CPSS-Mol) (Woo 2020) and thus is not expected to benefit from HMAs.
12. Patient is ineligible for an immediate allo-SCT.

7.1.2 Exclusion Criteria

Patients meeting any of the following criteria are not eligible for enrollment in any study stage:

1. Patient has persistent clinically significant toxicities Grade ≥ 2 from previous therapies, including cytotoxic chemotherapy, targeted therapies, biological therapies, or immunotherapies, not readily controlled by supportive measures (excluding alopecia, nausea, and fatigue).
2. Patient has received treatment with any disease-related therapy, including radiation therapy within 14 days of study entry.
3. Patient has received an allo-SCT within 3 months of study entry.
4. Patient has received treatment with another investigational agent within 14 days of study entry or concurrent treatment with another investigational agent.
5. Patient has previously received treatment with tagraxofusp or has a known hypersensitivity to any components of the drug product.
6. Patient has an active malignancy and/or cancer history (excluding myeloproliferative disorders and concomitant myeloid malignancies as specified in the inclusion criteria) that can confound the assessment of the study endpoints. Patients with a past cancer history (within 2 years of entry) and/or ongoing active malignancy or substantial potential for recurrence must be discussed with the Sponsor before study entry. Patients with the following neoplastic diagnoses are eligible: non-melanoma skin cancer, carcinoma in situ (including superficial bladder cancer), cervical intraepithelial neoplasia, or organ-confined prostate cancer with no evidence of progressive disease.
7. Patient has clinically significant cardiovascular disease (e.g., uncontrolled or any New York Heart Association Class 3 or 4 congestive heart failure, uncontrolled angina, history of myocardial infarction, unstable angina, or stroke within 6 months prior to study entry, uncontrolled hypertension or clinically significant arrhythmias not controlled by medication).
8. Patient has uncontrolled, clinically significant pulmonary disease (e.g., chronic obstructive pulmonary disease, pulmonary hypertension) that, in the Investigator's opinion, would put the patient at significant risk for pulmonary complications during the study.
9. Patient has known active or suspected disease involvement of the central nervous system (CNS). If suspected due to clinical findings, CNS disease should be ruled out with relevant imaging and/or examination of cerebrospinal fluid.
10. Patient is receiving immunosuppressive therapy, with the exception of corticosteroids as specified in the inclusion criteria and tacrolimus, for treatment or prophylaxis of graft-versus-host disease (GVHD). If the patient has been on immunosuppressive treatment or prophylaxis for GVHD, the treatment(s) must have been discontinued at least 14 days prior to study drug and there must be no evidence of Grade ≥ 2 GVHD.
11. Patient has uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, disseminated intravascular coagulation, or psychiatric illness that would limit compliance with study requirements.
12. Patient is pregnant or breast feeding.
13. Patient has known human immunodeficiency virus (HIV).

14. Patient has evidence of active or chronic Hepatitis B or Hepatitis C infection.
15. Patient is oxygen-dependent.
16. Patient has any medical condition that in the Investigator's opinion places the patient at an unacceptably high risk for toxicities.
17. Patient requires corticosteroid therapy at a dose of > 20 mg daily for > 7 days or has had changes to their steroid regimen within 28 days of screening.
18. Patient has 2016 WHO-defined transformation to leukemia.
19. Patient has AML M4 (French-American-British subtype; myelomonocytic). (Note: if this is suspected, the NPM1 gene must be assessed to determine eligibility).

7.2 Replacement of Patients

At the discretion of the Sponsor, additional patients may be enrolled to provide sufficient patient data for analysis after a patient prematurely withdraws from the study.

8 Treatment of Subjects

8.1 Tagraxofusp Description and Storage

Tagraxofusp Injection is a biologic fusion protein comprised of recombinant human IL-3 genetically fused to truncated DT protein. Tagraxofusp targets the IL-3R, which is overexpressed on the CSCs and bulk of various leukemias and hematopoietic malignancies relative to normal hematopoietic stem cells and other hematopoietic cells.

Tagraxofusp is prepared in liquid or lyophilized formulations; study sites may be provided with either of the following:

- Tagraxofusp Injection is a preservative-free, sterile, clear, colorless solution supplied in single-dose glass vials containing 1 mL of sterile tagraxofusp solution (1mg/vial) that should be stored in a freezer between -25°C and -15°C (-13°F and 5°F).
- Tagraxofusp for Injection (lyophilized powder), 1.0 mg is supplied in single-use, sterile, 2 mL glass vials packaged in labeled, single-vial cartons (study drug) and should be stored between 2°C and 8°C (36°F – 46°F).

Documentation stating the product's expiry date will be provided with each shipment.

8.2 Study Treatment Administration Schedule

Patients will receive 12 mcg/kg of tagraxofusp by IV infusion once daily for 3 consecutive days (or 3 doses over a period not to exceed 10 days if postponement is required to allow for toxicity resolution) of a cycle in the absence of PD or other withdrawal criteria.

A treatment cycle is 21 days in C1-4 and 28 days in C5 and beyond.

The total per-patient dose is calculated based on patient body weight in kg at baseline (C1D1). This dose will be recalculated if there is a 10% or greater change from baseline in body weight.

The first cycle 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 ambulatory care setting that is equipped for intensive monitoring of patients with hematopoietic malignancies undergoing treatment, per the Investigator's discretion, institutional guidelines, and capabilities. Patients will be monitored for at least 1 hour (or longer at the Investigator's discretion) following the administration of each infusion of tagraxofusp in Cycle 2 and beyond.

Patients with evidence of ongoing disease control during treatment (without evidence of clinically significant PD or intolerable toxicity) may receive repeated cycles of tagraxofusp even if an overall response, in the judgment of the Investigator, is not attained.

Refer to Section 8.2.1 for details regarding required pre-medication, patient monitoring procedures, and dose modification procedures for the management of tagraxofusp-related toxicity.

8.2.1 Tagraxofusp Premedication, Dose Preparation and Administration

8.2.1.1 Premedication

Patients will receive the following premedication 60 minutes (±15 minutes) before each tagraxofusp infusion:

- Acetaminophen 650 mg by mouth (PO) (or equivalent dose of paracetamol).
- Diphenhydramine 50 mg IV (or equivalent dose of another H_1-histamine antagonist).
- Methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid).
- Famotidine 20 mg IV (or an equivalent dosage of another H_2-histamine antagonist).

8.2.1.2 Tagraxofusp Dosage Preparation

Tagraxofusp is administered as a 15-minute IV infusion. Tagraxofusp is prepared for administration by the pharmacy. The total per-patient dose is calculated based on the patient's baseline body weight in kg (at baseline, C1D1) including one decimal place (mcg/kg dose × patient weight in kg [example: 12 mcg/kg × 70.3 kg]). (The dose will be recalculated if there is a 10% or greater change from baseline in body weight.) Additional dose preparation instructions and required supplies are described in detail within the Pharmacy Manual.

8.2.1.3 Inpatient and Outpatient Setting for Dose Administration

The first cycle 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 ambulatory care setting that is equipped for intensive monitoring of patients with hematopoietic malignancies undergoing

treatment, per the Investigator's discretion and institutional guidelines and capabilities. Patients will be monitored for at least 1 hour (or longer at the Investigator's discretion) following each tagraxofusp infusion in Cycle 2 and beyond.

8.2.2 Patient Monitoring Procedures During the Tagraxofusp Dosing Period

During each cycle, testing and procedures that may result in withholding of a scheduled tagraxofusp infusion, (largely based on unresolved manifestations of fluid retention and/or other relevant acute toxicities during daily dosing), include findings from clinical examination including but not limited to vital signs, and clinical laboratory parameters, detailed below, and as indicated in the applicable Schedules of Events (Table 2 and Table 3 for Stage 2; Table 4 and Table 5 for Stage 3A).

Vital Signs: Blood pressure, heart rate, respiration rate, body temperature, and pulse oximetry are to be measured during screening and during the dosing period (usually Days 1, 2, and 3) immediately prior to infusion, immediately after completion of infusion, and 30 and 60 minutes post-infusion; and at subsequent time points in each cycle as indicated in the applicable Schedules of Events (Table 2 and Table 3 for Stage 2; Table 4 and Table 5 for Stage 3A).

Diagnostic Tests:

- During the dosing period prior to tagraxofusp infusion (usually Days 1, 2, 3) and at subsequent time points in each cycle as indicated in the applicable Schedules of Events (Table 2 and Table 3 for Stage 2; Table 4 and Table 5 for Stage 3A): CBC with differential, platelets, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, total protein, albumin, calcium, phosphorus, uric acid, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), prothrombin time (PT) or International Normalized Ratio (INR), aPTT (activated partial thromboplastin time). Additional evaluation of albumin or ALT/AST during days subsequent to treatment days may be indicated in situations where abnormalities (albumin decrease, ALT/AST increase) are noted subsequent to treatment.
- Serum albumin must be ≥ 3.2 g/dL prior to first dose of tagraxofusp in Cycle 1. During tagraxofusp dosing, serum albumin must be ≥ 3.5 g/dL. If serum albumin is reduced by ≥ 0.5 g/dL from the albumin value measured prior to tagraxofusp dosing initiation for the current cycle, withhold tagraxofusp infusion and administer 25g IV albumin. Interrupt tagraxofusp dosing 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 for the current cycle.
- For temperature ≥ 38°C, draw blood culture × 2, and collect urine for urinalysis and culture.

8.2.3 Dose Delays/Modifications and Management Procedures for Toxicities Associated with Tagraxofusp

During the dosing period for each cycle, individual tagraxofusp infusions may be delayed for up to 10 days to allow for toxicity resolution.

If dosing is resumed within a cycle, any subsequent doses in that cycle must be administered within the first 10 days of that cycle; thus, patients may receive fewer than the prescribed number of doses during a given study cycle. Tagraxofusp may be resumed after the resolution of Grade 3/4 toxicities as per Table 1.

8.2.3.1 Capillary Leak Syndrome and Associated Symptoms

CLS is associated with vascular endothelial injury related to fusion protein administration and may occur 3 – 8 days after initiation of treatment.

Patients may exhibit symptoms of **hypotension,** fluid overload, evidenced by **weight gain** or edema, nausea, and anorexia, shortness of breath and, at times, confusion and muscle injury. Findings may include **hypoalbuminemia**, reductions in blood oxygen saturation, and evidence of pulmonary edema on chest x-ray. **These symptoms may present individually or as part of CLS.**

Refer to Appendix Section 18.3 for management of patients with signs of CLS.

8.2.3.2 Chills, Anaphylaxis, and Hypersensitivity Reactions

Withhold tagraxofusp infusion for chills, anaphylaxis and hypersensitivity reactions.

Chills associated with tagraxofusp administration may be treated with meperidine 12.5-50 mg IV or morphine sulphate 1-2 mg IV (or equivalent doses of other opiates). Anaphylaxis and hypersensitivity reactions associated with rash, fever, urticaria, bronchospasm, and/or angioedema will be treated with 100 mg IV methylprednisolone (or an equivalent corticosteroid) and 25-50 mg IV diphenhydramine (or equivalent dose of another H_1-histamine antagonist). More severe symptoms will also be treated with 0.3 mL epinephrine (1:1000) IV once. Patients with anaphylactic (Grade 4) reactions or Grade $\geq$ 3 hypersensitivity reactions should not receive additional infusions of tagraxofusp.

In the setting of Grade 1-2 hypersensitivity reactions, administration of subsequent tagraxofusp infusions may be attempted provided that any systemic symptoms of the prior Grade 1-2 hypersensitivity reaction resolved within 24 hours with appropriate supportive measures. Premedication for patients with prior Grade 1-2 hypersensitivity reactions should include the agents specified in Section 8.2.1; additional premedication may be provided at the Investigator's discretion and should be discussed with the Medical Monitor or designee. Please consult Section 13.7 concerning recommended optimal reporting of tagraxofusp-related hypersensitivity reactions.

Blood (serum) samples (10 mL, for immunogenicity) will be collected anytime during the study when clinical manifestations are observed suggesting either an infusion related reaction or drug hypersensitivity.

8.2.3.3 Transaminase (AST/ALT) Elevations

In settings in which transaminases (AST/ALT) are elevated to > 5×ULN, no subsequent tagraxofusp will be administered for the duration of the cycle.

8.2.3.4 Body Temperature ≥ 38°C

For temperature ≥ 38°C, draw blood culture × 2, and collect urine for urinalysis and culture, as clinically indicated. Tagraxofusp may be administered pending resolution, provided that an appropriate evaluation for infectious etiologies has been undertaken, and provided that the Investigator determines that there is minimal likelihood of uncontrolled systemic infection including sepsis; this assessment may occur on the same day as the temperature elevation, or on subsequent days.

8.2.3.5 Serum Creatinine > 1.8 mg/dL

Withhold tagraxofusp infusion until serum creatinine resolves to ≤ 1.8 mg/dL. Dosing may resume upon recovery of serum creatinine if this occurs within the first 10 days of a cycle.

8.2.3.6 Tachycardia, Bradycardia, or Hypertension

Withhold tagraxofusp infusion for patients with a heart rate ≥ 130 bpm or heart rate ≤ 40 bpm or systolic BP ≥ 160 mmHg until resolution.

8.2.3.7 Tumor Lysis Syndrome

Treatment with cytotoxic cancer therapies in the setting of high tumor burden may cause rapid tumor lysis syndrome (TLS) and associated metabolic disturbances which can result in hyperkalemia, hyperuricemia, hyperphosphatemia and hypocalcemia. A low incidence of TLS has been reported with tagraxofusp. The Sponsor advises continued awareness of the possibility of acute and potentially life-threatening TLS in patients with high disease burden.

Serum chemistries to carefully monitor for potential laboratory or clinical TLS are included in the daily laboratory tests during tagraxofusp infusion. In the event of evidence of TLS, local standards should be followed to monitor and treat TLS. For example, IV hydration (3 L/24 hr in adults) in addition to other measures to maintain high urine output, hypouricemic agents, and additional interventions to correct electrolyte abnormalities may be given at the discretion of the Investigator.

8.2.3.8 Cytokine Release Syndrome

Cytokine release syndrome results from an excessive immune response with elevated circulating cytokines that can cause symptoms ranging from flu-like symptoms, confusion, and rigors to a potentially fatal sepsis syndrome with circulatory collapse. The Sponsor recommends vigilance

and appropriate clinical management that may include, hydration, steroids, and/or anti-IL-6 agents at the Investigator's discretion.

8.2.3.9 Other Toxicities

Hold dose for clinically significant Grade 3/4 toxicities for the current cycle, with the exception of the following Grade 3 toxicities, if deemed appropriate by the Investigator:

- Arthralgia
- Myalgia
- Fever responding to treatment with no active infection
- Nausea and/or vomiting, or diarrhea associated with suboptimal prophylaxis and/or treatment
- Reversible clinical chemistry abnormalities (refer to Sections 8.2.3.3 and 8.2.3.5 for details regarding liver transaminases, and creatinine, respectively, and Appendix Section 18.3 for details regarding albumin).

Refer to Section 8.2.3.10.1 for further instruction regarding dose delay.

8.2.3.10 Dose Modifications/Delays and Management Procedures for Other Toxicities Associated with Tagraxofusp

8.2.3.10.1 Nonhematological Toxicity

Table 1 summarizes the dose modification guidelines for tagraxofusp-related nonhematological toxicities (other than those identified in Section 8.2.3.1 through Section 8.2.3.8).

Table 1: Dose Modifications for Other Tagraxofusp-Related Nonhematological Toxicity

CTCAE Grade	Tagraxofusp Dose Delays
Any Grade 1-2 toxicities	• No dose delay
Grade 3 with resolution to Grade ≤ 1 or baseline by last day of cycle	• No dose delay
Grade 3 without resolution to Grade ≤ 1 or baseline by last day of cycle	• Delay the start subsequent cycle by up to 14 days. – If after 14 days the toxicity resolves to Grade ≤ 1 or baseline, no dose adjustment required and the cycle may start. – If after 14 days the toxicity has not resolved, monitor weekly until resolution; discuss additional dosing and schedule with the Medical Monitor.
Grade 4 (excluding transient [≤ 14 days] asymptomatic transaminase or CPK elevations) with resolution to Grade ≤ 1 or baseline by last day of cycle	• The cycle may start.
Grade 4 without resolution to Grade ≤ 1 or baseline by last day of cycle	• Delay the start subsequent cycle by up to 14 days. • If after 14 days the toxicity resolves to Grade ≤ 1 or baseline, resume dosing.

CTCAE Grade	Tagraxofusp Dose Delays
	• If after 14 days the toxicity has not resolved, monitor weekly until resolution; discuss additional dosing and schedule with the Medical Monitor

Note that delays in start of subsequent cycles greater than 3 weeks will be acceptable only after discussion with the Medical Monitor regarding the potential risk/benefit of further treatment.

8.2.3.10.2 Hematological Toxicity

Patients with neutropenia or thrombocytopenia as a consequence of their disease do not require treatment interruptions for myelosuppression. Dose modifications in these patients should be considered on a case-by-case basis and discussed with the Medical Monitor. The following guidelines can be used for these patients:

- Patients with a response and pre-cycle counts of neutrophils > 1000/μL and platelets > 50,000/μL who have sustained low counts of neutrophils < 500/μL and/or platelets < 20,000/μL for more than 2 consecutive weeks in the current cycle, may receive a subsequent cycle of tagraxofusp, at the Investigator's discretion.
- If there are persistent blasts in the peripheral blood or > 5% blasts in the bone marrow, continue treatment regardless of neutrophil and platelet count and give supportive care as needed.
- If no evidence of leukemia in the bone marrow, consider holding (postponing) therapy until recovery of neutrophils to ≥ 1000/μL and platelets ≥ 50,000/μL, then resume tagraxofusp according to guidelines mentioned above.

8.3 Treatment Discontinuation

8.3.1 Criteria for Treatment Discontinuation

Tagraxofusp treatment may be discontinued for any of the following reasons:

- Patient withdrawal of consent.
- Occurrence of unacceptable toxicity, including DLT.
- Tagraxofusp-related anaphylaxis or Grade ≥ 3 hypersensitivity reaction.
- Disease recurrence/progression.
- Intercurrent illness that prevents further administration of tagraxofusp.
- Patient non-compliance.
- Occurrence of pregnancy.
- Investigator's decision.

The reason for tagraxofusp discontinuation and the date of discontinuation should be recorded in the electronic case report form (eCRF).

8.3.2 Procedures and Follow-up after Treatment Discontinuation

The evaluation during which the Investigator determines that tagraxofusp will be discontinued should be considered the End-of-Treatment Evaluation; all tests and procedures for the End-of-Treatment Evaluation, as per the applicable Schedule of Events (Table 2 and Table 3 for Stage 2; Table 4 and Table 5 for Stage 3A) are to be performed. In addition, patients should be followed for a minimum of 30 days after the last infusion of tagraxofusp for assessment of AEs (including potential new AEs and potential change/resolution of existing AEs).

If the patient is determined to have a response at the time of discontinuation, tumor assessments should continue to be performed as described in Section 11.12 until in the judgment of the Investigator, there is evidence of relapsed or progressive disease. Beyond the End-of-Treatment Evaluation and 30-day follow up (safety/AE assessment), it is requested that subsequent follow-up occur approximately every 90 days after the last study drug dose for ascertainment of survival status.

If the patient discontinues tagraxofusp treatment and also withdraws consent for collection of future information, no further evaluations should be performed and no additional data should be collected as part of the study. The Sponsor will only retain and use any data collected before withdrawal of consent.

Please see Section 5.3 for recommendations concerning ongoing follow-up of patients alive with or without evidence of PD at the time of Study Completion/assessment of primary and critical secondary endpoints.

9 Schedules of Events: Stage 2

The schedules of events for patients with MF in Stage 2 enrolled under Amendments 7 and 8 are presented in Table 2 and Table 3. Enrollment in Stage 2 is closed, but CMML and MF patients who are already enrolled may continue receiving treatment.

Table 2: Stage 2: Schedule of Events for Screening and Cycles 1-4

Tests and Observations	Day -28 to 0 *Screening*	Days 1-3 (Up to Day 10 if Infusion(s) Held) Tagraxofusp Treatment *Pre-Infusion*	Days 1-3 (Up to Day 10 if Infusion(s) Held) Tagraxofusp Treatment *Tagraxofusp Infusion*	Cycle 1 Day 8±3[1]	Day 21±3[2] *End of Cycle*[2]	Day 28±3, Then Every 7±3 days *(Only If Delayed End of Cycle: for Toxicity Resolution)*
Informed consent form[3]	X					
Inclusion/exclusion criteria[4]	X					
Medical history	X					
ECOG performance status	X	X (Infusion 1, C1)			X	X
Physical examination including assessment of hepatomegaly and splenomegaly	X			X	X	
Pregnancy test[5]	X					
Vital signs and weight[6]	X	X	X	X	X	X
12-lead ECG[7]	X	X (MF Only: Infusion 1) (C1, C2)	X (MF Only: Infusion 1) C1, C2)			
MUGA scan or 2-D Echocardiogram[8]	X					
Hematology[9]	X	X		X	X	X
Serum chemistry[10]	X	X		X	X	X
Coagulation parameters: PT/INR, aPTT[11]	X	X		X	X	X
Urinalysis[12]	X			X	X	X
Peripheral blood for flow cytometry	X	X (Infusion 1)		X		
Bone marrow aspiration/biopsy[13]	X				X C1 and C4[14]	
MRI or CT scan of abdomen[15]	X				X C1 and C4[14]	
Pharmacokinetic sampling (patient with MF only)[16]		X (Infusion 1)				

Tests and Observations	Day -28 to 0 *Screening*	Days 1-3 (Up to Day 10 if Infusion(s) Held) Tagraxofusp Treatment *Pre-Infusion*	Days 1-3 (Up to Day 10 if Infusion(s) Held) Tagraxofusp Treatment *Tagraxofusp Infusion*	Cycle 1 Day 8±3[1]	Day 21±3[2] *End of Cycle*[2]	Day 28±3, Then Every 7±3 days *(Only If Delayed End of Cycle: for Toxicity Resolution)*
		(C1, C2)				
Immunogenicity sampling[17]		X (Infusion 1)			X	
Cytogenetic and molecular genetic testing	X				X C1 and C4	
Administration of premedications[18]		X				
Tagraxofusp administration[19]			X			
MPN-SAF TSS evaluation[20]	X				X	
Tumor response assessment[21]	X				X C1 and C4	
Vision assessment	X				X	
Prior/concomitant medications and therapies	X	X	X	X	X	X
AE and SAE monitoring	X	X	X	X	X	X

AE = adverse event; aPTT = activated partial thromboplastin time; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; IV = intravenous; MPN-SAF TSS = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; MUGA = multigated acquisition; PK = pharmacokinetics; PT = prothrombin time; SAE = serious adverse event.

1 Day 8 visit is required for C1 only and must be performed at the site.

2 The end-of-cycle evaluations (Day 21 or thereafter) may also serve as the pre-infusion evaluations for the subsequent cycles; with the exception of vital signs, these assessments do not need to be duplicated on successive days unless there is an abnormality or other clinically relevant reason for repeat evaluation.

3 Refer to protocol Section 16.3 for details.

4 Refer to protocol Section 7 (study populations) for details.

5 Urine or serum pregnancy test must be performed within 1 week prior to treatment for WOCBP.

6 Height will be measured at screening only; weight does not need to be measured more than once per day, and should be measured pre-infusion on treatment days. Vital signs should be performed after patient is sitting for 3 to 5 minutes. During dosing period, vital signs should be taken immediately prior to infusion, at 0 (i.e., immediately after completion of infusion), and at 30 and 60 minutes post-infusion.

7 All patients will have a 12-lead ECG performed at the screening visit. For MF patients only, during the days when patients are undergoing PK sampling (Cycles 1 and 2, Infusion 1), an ECG will be performed at 3 distinct time points (triplicates) within 5 minutes (±5 minutes) prior to each PK sample collection pre-infusion and at 30 and 60 minutes post-infusion.

8 A MUGA scan or 2-D ECHO to quantify LVEF must be completed within 28 days prior to start of first cycle of study drug.

9 To be collected prior to tagraxofusp infusion if during dosing period. Hematology includes WBC count with differential, RBC count, hematocrit, Hb, platelet count and immature myeloid cells (including blasts + myelocytes +metamyelocytes + promyelocytes + nucleated red blood cells).

10 To be collected prior to tagraxofusp infusion if during dosing period. Serum chemistry incudes electrolytes and additional parameters (equivalent to Chem-20): ALT, albumin, ALP, AST, bicarbonate, bilirubin, BUN, calcium, magnesium, chloride, creatinine, glucose, LDH, phosphate, potassium, sodium, total protein, uric acid, and CPK. See Appendix Section 18.3 for administration of albumin if serum albumin decreases to < 3.0 g/dL (< 30 g/L) during treatment days or in the immediate post-treatment period.

11 In lieu of PT, INR may be measured.

12 Urinalysis includes appearance, color, pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen, and occult blood. Dipstick is acceptable.

13 Morphology and WBC differential/blast count on aspirate. Baseline must be performed within 28 days prior to the first administration of tagraxofusp. Subsequent bone marrow aspirates and biopsies will be performed at the end of C1, C4, and then every 12 weeks (±7 days). Bone marrow evaluation should also be performed at End of Treatment including patients who discontinue study therapy prior to completion of C4; if a bone marrow evaluation was performed within 4 weeks prior to the end of treatment, a repeat evaluation does not need to be performed at this time, unless clinically indicated.

14 Bone marrow and imaging studies are to be repeated at the end of C1 and C4 and then every 12 weeks (±7 days) thereafter.

15 A baseline MRI or CT scan must be performed within 28 days prior to the first administration of tagraxofusp. Subsequent imaging studies will be performed at the end of C1 and C4 and then every 12 weeks (±7 days) until there is evidence of relapsed or progressive disease. Abdominal scan is required; evaluation of chest/pelvis may be obtained at the Investigator's discretion. Scan must include measurement of spleen and liver volume. Imaging studies should also be performed at End of Treatment, including patients who discontinue study therapy prior to completion of C4; if a imaging was performed within 4 weeks prior to the end of treatment, a repeat evaluation does not need to be performed at this time, unless clinically indicated. Whenever clinically feasible, it is strongly requested that the same imaging modality (MRI or CT) at both baseline and subsequent timepoints be utilized for any given patient throughout their evaluation on-study.

16 Peripheral blood (plasma) samples (6 mL each) will be collected from patients with MF only immediately prior to the start of the infusion of tagraxofusp, then at 0 (i.e., upon completion of infusion), 15, 30, 45, 60, 90 120, 180, and 240 minutes after completion of the infusion during Infusions 1 (i.e., Day 1) in C1 and C2.

17 Peripheral blood (serum) samples (10 mL) will be collected for the detection of tagraxofusp reactive antibodies on Day 1 (pre-infusion) and Day 21 (the end of cycle collection may also serve as the pre-infusion collection for the subsequent cycle).

18 Premedications administered 60 minutes (±15 minutes) before tagraxofusp treatment: Diphenhydramine 50 mg IV (or an equivalent dose of another H_1-histamine antagonist); acetaminophen 650 mg orally (or equivalent dose of paracetamol); methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid); famotidine 20 mg IV (or an equivalent dose of another H_2-histamine antagonist).

19 Following treatment with premedication, tagraxofusp will be administered as a 15-minute infusion once daily for the first 3 consecutive days of a 21-day cycle. Individual tagraxofusp infusions may be delayed to allow for toxicity resolution, but all 3 infusions should be completed within 10 days.

20 Patients with MF should complete the MPN-SAF TSS (10-question evaluation concerning symptoms/well-being during the prior week) during screening and in every treatment cycle, prior to receiving therapy on the subsequent cycle. The MPN-SAF TSS should also be completed at End of Treatment.

21 Tumor assessments are to be performed during screening, at the end of C1 and C4, then every 12 weeks (±7 days) and at End of Treatment. These include the IWG-MRT/ELN 2013 consensus report for MF and the IWG MDS 2016 consensus report for CMML.These are detailed in Section 11.12 and Section 18.1.

Table 3: Stage 2: Study Events Schedule for Cycle 5 and Beyond in Stage 2

Procedures	Cycle 5 and Beyond				Cycles 5 and Beyond[2] 12 Weeks (i.e., every 3 cycles) ±7 Days	End-of-treatment	Safety: Through 30 Days After Last Infusion	Survival: Every 90 Days After Last Infusion
	Days 1-3 (Up to Day 10 if Infusion(s) Held) Tagraxofusp Treatment		Day 28±3[1]					
	Pre-Infusion	*Infusion*	*End of Cycle*[1]					
Concomitant medications/therapies	X		X			X		
AE and SAE monitoring	X	X	X		X	X	X	
ECOG performance status			X			X		
Physical examination including assessment of hepatomegaly and splenomegaly			X			X		
Vital signs and weight[3]	X	X	X			X		
Hematology[4]	X		X			X		
Serum chemistry[5]	X		X			X		
Coagulation parameters: PT/INR, aPTT[6]	X		X			X		
Urinalysis[7]			X					
Peripheral blood for flow cytometry	X (Infusion 1)					X		
Bone marrow aspiration/biopsy[8]					X[9]	X		
MRI or CT scan of abdomen[10]					X[9]	X		
Immunogenicity sampling[11]			X			X	X	X[12]
Cytogenetic and molecular genetic testing					X	X		
Administration of premedications[13]	X							
Administration of Tagraxofusp[14]		X						
MPN-SAF TSS evaluation[15]			X			X		
Vision assessment			X			X		
Tumor response assessment[16]					X[10]	X		

Procedures	Cycle 5 and Beyond				Cycles 5 and Beyond[2] 12 Weeks (i.e., every 3 cycles) ±7 Days	End-of-treatment	Safety: Through 30 Days After Last Infusion	Survival: Every 90 Days After Last Infusion
	Days 1-3 (Up to Day 10 if Infusion(s) Held) Tagraxofusp Treatment		Day 28±3[1]					
	Pre-Infusion	*Infusion*	*End of Cycle*[1]					
Long-term follow-up[12]							X	X

AE = adverse event; aPTT = activated partial thromboplastin time; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; MPN-SAF TSS = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; PT = prothrombin time; SAE = serious adverse event.

1 The end-of-cycle evaluations (Day 28 or thereafter) may also serve as the pre-infusion evaluations for the subsequent cycles; with the exception of vital signs, these do not need to be duplicated on successive days unless there is an abnormality or other clinically relevant reason for repeat evaluation.

2 Disease evaluation via bone marrow aspirate/biopsy and/or imaging studies (when relevant) will occur every 12 weeks (±7 days). The frequency of bone marrow evaluation may be reduced (obtained less frequently) if peripheral blood, clinical and/or imaging assessments indicate clinical stability, as per the Investigator's discretion in consultation with the Medical Monitor. The frequency of imaging assessments may also be reduced if clinical/laboratory findings indicate stability, as per the Investigator's discretion in consultation with the Medical Monitor.

3 Height will be measured at screening only; weight does not need to be measured more than once per day, and should be measured pre-infusion on treatment days. Vital signs should be performed after patient is sitting for 3 to 5 minutes. If during dosing period, vital signs should be taken immediately prior to infusion, at 0 (i.e., immediately after completion of infusion), and at 30 and 60 minutes post-infusion.

4 To be collected prior to tagraxofusp infusion if during dosing period. Hematology includes WBC count with differential, RBC count, hematocrit, hemoglobin, platelet count and immature myeloid cells (including blasts + myelocytes +metamyelocytes + promyelocytes + nucleated red blood cells).

5 To be collected prior to tagraxofusp infusion if during dosing period. Serum chemistry incudes electrolytes and additional parameters (equivalent to Chem-20): ALT, albumin, alkaline phosphatase, AST, bicarbonate, bilirubin, BUN, calcium, magnesium, chloride, creatinine, glucose, LDH, phosphate, potassium, sodium, total protein, uric acid, and CPK. See Section 18.3 for administration of albumin if serum albumin decreases to < 3.0 g/dL (< 30 g/L) during treatment days or in the immediate post-treatment period.

6 In lieu of PT, INR may be measured.

7 Urinalysis includes appearance, color, pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen, and occult blood. Dipstick is acceptable.

8 Morphology and WBC differential /blast count on aspirate. In general, bone marrow aspirates and biopsies and peripheral blood samples will be performed at the end of C1 and C4 and then every 12 weeks (±7 days) thereafter. Bone marrow evaluation should also be performed at End of Treatment; if a bone marrow evaluation was performed within 4 weeks prior to the end of treatment, a repeat evaluation does not need to be performed at this time, unless clinically indicated.

9 Bone marrow and imaging studies are to be repeated at the end of C1 and C4 and then every 12 weeks (±7 days) thereafter.

10 Imaging studies will be performed at the end of C1 and C4 and then every 12 weeks (±7 days) thereafter until there is evidence of relapsed or progressive disease. Abdominal scan is required; evaluation of chest/pelvis may be obtained at the Investigator's discretion. Scan must include measurement of spleen and liver volume. Subsequent to Week 24, for patients receiving ongoing therapy (or those who discontinue therapy but are without evidence of PD and continue to be evaluated in ongoing follow-up) the frequency of imaging studies may be reduced (obtained less frequently) if peripheral blood and/or clinical assessments indicate clinical stability, as per the Investigator's discretion, in consultation with the Medical Monitor. Imaging studies should also be performed at End of Treatment; if imaging studies were performed within 4 weeks prior to the end of

treatment, a repeat evaluation does not need to be performed at this time, unless clinically indicated. Whenever clinically feasible, it is strongly requested that the same imaging modality (MRI or CT) at both baseline and subsequent timepoints be utilized for any given patient throughout their evaluation on-study.

11 Peripheral blood (serum) samples (10 mL) will be collected for the detection of tagraxofusp reactive antibodies at the completion of every cycle and at specified points thereafter.

12 Patients will be followed for survival approximately every 90 days, until assessment of the primary objective for the study is complete for all treated patients; please consult the appropriate protocol section for description of situations in which survival and other data may be collected following study completion. Patients who undergo SCT will be followed for the occurrence of veno-occlusive disease as part of long-term follow-up. A blood sample for immunogenicity studies will be collected at least 16 weeks to up to 20 weeks after the last tagraxofusp dose.

13 Premedications administered 60 minutes (±15 minutes) before tagraxofusp treatment: Diphenhydramine 50 mg IV (or an equivalent dose of another H_1-histamine antagonist); acetaminophen 650 mg orally (or equivalent dose of paracetamol); methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid); famotidine 20 mg IV (or an equivalent doses of another H_2-histamine antagonist).

14 Following treatment with premedication, tagraxofusp will be administered as a 15-minute infusion once daily for the first 3 consecutive days of a 28-day cycle. Individual tagraxofusp infusions may be delayed to allow for toxicity resolution, but all 3 infusions should be completed within 10 days.

15 Patients with MF should complete the MPN-SAF TSS (10-question evaluation concerning symptoms/well-being during the prior week) with every treatment cycle, prior to receiving therapy on the subsequent cycle. The MPN-SAF TSS should also be completed at End of Treatment.

16 Tumor response assessments are to be conducted every 12 weeks (±7 days) and at End of Treatment, detailed in Section 11.12 and Section 18.1.

10 Schedules of Events: Stage 3A

The schedules of events for patient with CMML in Stage 3A are presented in Table 4 and Table 5.

Table 4: Stage 3A: Study Events Schedule for Screening and Cycles 1-4 for Patients with CMML

Procedures	Day -28 to 0 *Screening*	Days 1-3 (Up to Day 10 if Infusion(s) Held) Tagraxofusp Treatment *Pre-Infusion*	Days 1-3 (Up to Day 10 if Infusion(s) Held) Tagraxofusp Treatment *Tagraxofusp Infusion*	Cycle 1 Day 8±3[1]	Day 21±3[2] *End of Cycle*[2]	Day 28±3, Then Every 7±3 days *(Only if Delayed End of Cycle: for Toxicity Resolution)*
Informed consent form[3]	X					
Inclusion/exclusion criteria[3]	X					
Medical history	X					
12-lead ECG	X					
ECOG performance status	X	X (Infusion 1, C1)			X	X
Physical examination, including assessment for hepatomegaly and splenomegaly	X			X	X	
Pregnancy test[4]	X					
Vital signs and weight[5]	X	X	X	X	X	X
MUGA scan or 2-D Echocardiogram[6]	X					
Hematology[7]	X	X		X	X	X
Serum chemistry[8]	X	X		X	X	X
Coagulation parameters: PT/INR, aPTT[9]	X	X		X	X	X
Peripheral blood for flow cytometry	X	X (Infusion 1)		X		
Peripheral blood for IL-10 testing		X (Infusion 1, C1)			X C1 and C4	
Peripheral blood for translational studies (select centers)		X (Infusion 1, C1)			X C1 and C4	
Bone marrow aspiration/biopsy[10]	X				X C1 and C4[11]	
MRI or CT for assessment of hepatomegaly and splenomegaly [12]	X				X C1 and C4[11]	
Immunogenicity sampling[13]		X (Infusion 1)			X	

Procedures	Day -28 to 0	Days 1-3 (Up to Day 10 if Infusion(s) Held) Tagraxofusp Treatment		Cycle 1 Day 8±3[1]	Day 21±3[2]	Day 28±3, Then Every 7±3 days *(Only if Delayed End of Cycle: for Toxicity Resolution)*
	Screening	*Pre-Infusion*	*Tagraxofusp Infusion*		*End of Cycle*[2]	
Cytogenetic and molecular genetic testing	X				X C1 and C4	
Administration of premedications[14]		X				
Tagraxofusp administration[15]			X			
MPN-SAF TSS evaluation[16]	X				X	
Baseline/tumor response assessment[17]	X				X C1 and C4[11]	
Vision assessment	X				X	
Prior/concomitant medications/therapies (including concomitant platelet and RBC transfusions)	X	X	X	X	X	X
AE and SAE monitoring	X	X	X	X	X	X

AE = adverse event; aPTT = activated partial thromboplastin time; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; MPN-SAF TSS = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; MUGA = multigated acquisition; PT = prothrombin time; SAE = serious adverse event.

1 Day 8 visit is required for C1 only and must be performed at the site.

2 The end-of-cycle evaluations (Day 21 or thereafter) may also serve as the pre-infusion evaluations for the subsequent cycles; with the exception of vital signs, these assessments do not need to be duplicated on successive days unless there is an abnormality or other clinically relevant reason for repeat evaluation.

3 Refer to protocol Section 16.3 (Patient Information and Informed Consent) and Section 7 (Populations to be Studied) for details.

4 Urine or serum pregnancy test must be performed within 1 week prior to treatment for WOCBP.

5 Height will be measured at screening only; weight does not need to be measured more than once per day, and should be measured pre-infusion on treatment days. Vital signs should be performed after patient is sitting for 3 to 5 minutes. During dosing period, vital signs should be taken immediately prior to infusion, at 0 (i.e., immediately after completion of infusion), and at 30 and 60 minutes post-infusion.

6 A MUGA scan or 2-D ECHO to quantify LVEF must be completed within 28 days prior to start of first cycle of study drug.

7 To be collected prior to tagraxofusp infusion if during dosing period. Hematology includes WBC count with differential, RBC count, hematocrit, Hb, platelet count, and immature myeloid cells (including blasts + myelocytes +metamyelocytes + promyelocytes + nucleated red blood cells) (for safety assessments as well as efficacy assessments at the end of each cycle in between bone marrow assessments).

8 To be collected prior to tagraxofusp infusion if during dosing period. Serum chemistry incudes electrolytes and additional parameters (equivalent to Chem-20): ALT, albumin, ALP, AST, bicarbonate, bilirubin, BUN, calcium, magnesium, chloride, creatinine, glucose, LDH, phosphate, potassium, sodium, total protein, uric acid, and CPK. See Appendix Section 18.3 for administration of albumin if serum albumin decreases to < 3.0 g/dL (< 30 g/L) during treatment days or in the immediate post-treatment period.

9 In lieu of PT, INR may be measured.

10 Morphology and WBC differential/blast count on aspirate. Baseline must be performed within 28 days prior to the first administration of tagraxofusp. Subsequent bone marrow aspirates and biopsies will be performed at the end of C1 and C4 and then every 12 weeks (±7 days) thereafter. Bone marrow evaluation should also be performed at

End of Treatment including patients who discontinue study therapy prior to completion of C4; if a bone marrow evaluation was performed within 4 weeks prior to the end of treatment, a repeat evaluation does not need to be performed at this time, unless clinically indicated.

11 Bone marrow aspirate and imaging studies are to be repeated at the end of C1 and C4 and then every 12 weeks (±7 days) thereafter.

12 A baseline MRI or CT scan must be performed within 28 days prior to the first administration of tagraxofusp. Subsequent imaging studies will be performed at the end of C1 and C4 and then every 12 weeks (±7 days) until there is evidence of relapsed or progressive disease. Abdominal scan is required; evaluation of chest/pelvis may be obtained at the Investigator's discretion. Scan must include measurement of spleen and liver volume. Subsequent to Week 24, for patients receiving ongoing therapy (or those who discontinue therapy but are without evidence of PD and continue to be evaluated in ongoing follow-up) the frequency of imaging studies may be reduced (obtained less frequently) if peripheral blood and/or clinical assessments indicate clinical stability, as per the Investigator's discretion, in consultation with the Medical Monitor. Imaging should also be performed at End of Treatment, including patients who discontinue study therapy prior to completion of C4; if a imaging was performed within 4 weeks prior to the end of treatment, a repeat evaluation does not need to be performed at this time, unless clinically indicated. Whenever clinically feasible, it is strongly requested that the same imaging modality (MRI or CT) at both baseline and subsequent timepoints be utilized for any given patient throughout their evaluation on-study.

13 Peripheral blood (serum) samples (10 mL) will be collected for the detection of tagraxofusp reactive antibodies on Day 1 (pre-infusion) and Day 21 (the end of cycle collection may also serve as the pre-infusion collection for the subsequent cycle).

14 Premedications administered 60 minutes (±15 minutes) before tagraxofusp treatment: Diphenhydramine 50 mg IV (or an equivalent dose of another H_1-histamine antagonist); acetaminophen 650 mg orally (or equivalent dose of paracetamol); methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid); famotidine 20 mg IV (or an equivalent dose of another H_2-histamine antagonist).

15 Following treatment with premedication, tagraxofusp will be administered as a 15-minute infusion once daily for the first 3 consecutive days of a 21-day cycle. Individual tagraxofusp infusions may be delayed to allow for toxicity resolution, but all 3 infusions should be completed within 10 days.

16 Patients complete the MPN-SAF TSS (10-question evaluation concerning symptoms/well-being during the prior week) during screening and with every treatment cycle, prior to receiving therapy on the subsequent cycle. The MPN-SAF TSS should also be completed at End of Treatment.

17 Tumor assessments will be performed during screening, at the end of C1 and C4, then every 12 weeks (±7 days) and at End-of-Treatment per the 2015 MDS/MPN criteria, as detailed in Section 11.12 and Section 18.1.

Table 5: Stage 3A: Study Events Schedule for Cycle 5 and Beyond for Patients with CMML

Procedures	Cycle 5 and Beyond			Cycles 5 and Beyond[2] 12 Weeks (i.e., every 3 cycles) ±7 Days	End-of-treatment	Safety: Through 30 Days After Last Infusion	Survival: Every 90 Days After Last Infusion
	Days 1-3 (Up to Day 10 if Infusion(s) Held) Tagraxofusp Treatment		Day 28±3[1]				
	Pre-Infusion	*Infusion*	*End of Cycle*[1]				
Concomitant medications/therapies (including platelet and RBC transfusions)	X		X		X		
AE and SAE monitoring	X	X	X	X	X	X	
ECOG performance status			X		X		
Physical examination including assessment of hepatomegaly and splenomegaly			X		X		
Vital signs and weight[3]	X	X	X		X		
Hematology[4]	X		X		X		
Serum chemistry[5]	X		X		X		
Coagulation parameters: PT/INR, aPTT[6]	X		X		X		
Peripheral blood for flow cytometry	X (Infusion 1)				X		
Bone marrow aspiration/biopsy[7]				X[8]	X		
MRI or CT for assessment of hepatomegaly and splenomegaly[9]				X[8]	X		
Immunogenicity sampling[10]			X		X	X	X[11]
Cytogenetic and molecular genetic testing				X	X		
Administration of premedications[12]	X						
Administration of Tagraxofusp[13]		X					
MPN-SAF TSS evaluation[14]			X		X		
Vision assessment			X		X		
Tumor response assessment[15]				X[8]	X		
Long-term follow-up[11]						X	X

AE = adverse event; aPTT = activated partial thromboplastin time; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; MPN-SAF TSS = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; PT = prothrombin time; SAE = serious adverse event.

1 The end-of-cycle evaluations (Day 28 or thereafter) may also serve as the pre-infusion evaluations for the subsequent cycles; with the exception of vital signs, these assessments do not need to be duplicated on successive days unless there is an abnormality or other clinically relevant reason for repeat evaluation.

2 Disease evaluation via bone marrow aspirate/biopsy and/or imaging studies (when relevant) will occur every 12 weeks (±7 days). The frequency of bone marrow evaluation may be reduced (obtained less frequently) if peripheral blood, clinical and/or imaging assessments indicate clinical stability, as per the Investigator's discretion in consultation with the Medical Monitor. The frequency of imaging assessments may also be reduced if clinical/laboratory findings indicate stability, as per the Investigator's discretion in consultation with the Medical Monitor.

3 Height will be measured at screening only; weight does not need to be measured more than once per day, and should be measured pre-infusion on treatment days. Vital signs should be performed after patient is sitting for 3 to 5 minutes. If during dosing period, vital signs should be taken immediately prior to infusion, at 0 (i.e., immediately after completion of infusion), and at 30 and 60 minutes post-infusion.

4 To be collected prior to tagraxofusp infusion if during dosing period. Hematology includes WBC count with differential, RBC count, hematocrit, hemoglobin, platelet count, and immature myeloid cells (including blasts + myelocytes +metamyelocytes + promyelocytes + nucleated red blood cells) (for safety assessments as well as efficacy assessments at the end of each cycle in between bone marrow assessments).

5 To be collected prior to tagraxofusp infusion if during dosing period. Serum chemistry incudes electrolytes and additional parameters (equivalent to Chem-20): ALT, albumin, alkaline phosphatase, AST, bicarbonate, bilirubin, BUN, calcium, magnesium, chloride, creatinine, glucose, LDH, phosphate, potassium, sodium, total protein, uric acid, chloride, and CPK. See Appendix Section 18.3 for administration of albumin if serum albumin decreases to < 3.0 g/dL (< 30 g/L) during treatment days or in the immediate post-treatment period.

6 In lieu of PT, INR may be measured.

7 Morphology and WBC differential /blast count on aspirate. In general, bone marrow aspirates and biopsies will be performed at the end of C1 and C4 and then every 12 weeks (±7 days) thereafter. Bone marrow evaluation should also be performed at End of Treatment; if a bone marrow evaluation was performed within 4 weeks prior to the end of treatment, a repeat evaluation does not need to be performed at this time, unless clinically indicated.

8 Bone marrow aspirate and imaging studies are to be repeated at the end of C1 and C4 and then every 12 weeks (±7 days) thereafter.

9 Imaging studies will be performed at the end of C1 and C4 and then every 12 weeks (±7 days) until there is evidence of relapsed or progressive disease. Abdominal scan is required; evaluation of chest/pelvis may be obtained at the Investigator's discretion. Scan must include measurement of spleen and liver volume. Imaging studies should also be performed at End of Treatment; if imaging was performed within 4 weeks prior to the end of treatment, a repeat evaluation does not need to be performed at this time, unless clinically indicated. Whenever clinically feasible, it is strongly requested that the same imaging modality (MRI or CT) at both baseline and subsequent timepoints be utilized for any given patient throughout their evaluation on-study.

10 Peripheral blood (serum) samples (10 mL) will be collected for the detection of tagraxofusp reactive antibodies at the completion of every cycle and at specified points thereafter.

11 Patients will be followed for survival approximately every 90 days, until assessment of the primary objective for the study is complete for all treated patients; please consult the appropriate protocol section for description of situations in which survival and other data may be collected following study completion. Patients who undergo SCT will be followed for the occurrence of veno-occlusive disease as part of long-term follow-up. A blood sample for immunogenicity studies will be collected at least 16 weeks to up to 20 weeks after the last tagraxofusp dose.

12 Premedications administered 60 minutes (±15 minutes) before tagraxofusp treatment: Diphenhydramine 50 mg IV (or an equivalent dose of another H_1-histamine antagonist); acetaminophen 650 mg orally (or equivalent dose of paracetamol); methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid); famotidine 20 mg IV (or an equivalent doses of another H_2-histamine antagonist).

13 Following treatment with premedication, tagraxofusp will be administered as a 15-minute infusion once daily for the first 3 consecutive days of a 28-day cycle. Individual tagraxofusp infusions may be delayed to allow for toxicity resolution, but all 3 infusions should be completed within 10 days.

14 Patients should complete the MPN-SAF TSS (10-question evaluation concerning symptoms/well-being during the prior week) with every treatment cycle, prior to receiving therapy on the subsequent cycle. The MPN-SAF TSS should also be completed at End of Treatment.

15 Tumor response assessments are to be conducted every 12 weeks (±7 days) and at End of Treatment, detailed in Section 11.12, and Section 18.1.

11 Study Procedures

11.1 Patient Selection

Patients with CMML who meet the inclusion/exclusion criteria will be recruited for enrollment into the study. Patients will be advised of the clinical protocol by the Investigator. If the patient is interested and is potentially eligible for participation in the study, he/she will be provided with the informed consent form (ICF) to review and sign. The ICF includes a detailed explanation of the study design and the potential risks and benefits of treatment. Patients who agree to participate in the study will be provided with a copy of the signed consent form; the original signed consent document will be filed in the patient's medical record. Only eligible and consenting patients will be entered into the study. No study procedures will be performed until the patient's written informed consent is obtained.

Patients will be screened by the Investigator or study nurse/coordinator prior to study entry. All patients enrolled on the study will be entered into a patient registration log at each site. Each screened patient will be assigned a sequential patient/study identification number with digits indicating site number and patient study number (e.g., XX-YYY, where XX denotes site number and YYY denotes patient study number as assigned at screening). Original screening records and source documents should be kept for all patients, including those who fail to meet the study eligibility requirements and any completed eCRFs should be retained for monitoring and auditing. Each patient's data obtained from subsequent evaluations should be recorded and evaluated in the source documents and eCRF. Prior to treatment, the Investigator will re-confirm patient eligibility criteria and assignment of the correct patient study number.

11.2 Medical History

Medical history includes current and past medical conditions and smoking history, date of MPN diagnosis, history of infections related to primary disease, prior treatment, response to prior treatment, and date of relapse, if applicable. Information concerning any prior malignancy diagnoses with particular focus on cytotoxic therapies received for prior malignancies (e.g., dates/duration of anthracycline for prior breast cancer) is to be collected whenever feasible.

11.3 Prior and Concomitant Medication

Medications taken within 28 days prior to the first study drug dose and throughout the study are to be collected and recorded. For patients with CMML, all transfusions (pRBC and platelets) within 8 weeks prior to the first tagraxofusp dose also are to be recorded. For patients with MF, all transfusions (pRBC and platelets) within 12 weeks prior to the first tagraxofusp dose are to be recorded.

11.4 ECOG Performance Status

See Section 18.2 for the ECOG-PS scoring guide.

11.5 Physical Examination

Physical examination includes evaluation by body system, weight, and height (screening only) performed at screening, and at subsequent time points as indicated in the applicable Schedules of Events (Table 2 and Table 3 for Stage 2; Table 4 and Table 5 for Stage 3A). Note that physical examination includes assessment for hepatomegaly and splenomegaly by palpation, with findings records as centimeters below the right costal margin and left costal margin, respectively. Of note, a spleen response by palpation must be confirmed by imaging studies to show reduction in spleen volume (or liver volume in splenectomized patients; refer to the response criteria outlined in Appendix 18).

11.6 Vital Signs

Vital signs include temperature, heart rate, respiration rate, pulse oximetry, and blood pressure. Collection should occur after the patient has been sitting for 3-5 minutes. Vital signs are to be measured at the time points indicated in the applicable Schedules of Events (Table 2 and Table 3 for Stage 2; Table 4 and Table 5 for Stage 3A).

11.7 Electrocardiograms

All patients will have a 12-lead ECG performed during screening.

For patients with MF in Stage 2, during days when pharmacokinetic (PK) samples are drawn (C1 and C2, Infusion 1), an ECG will be performed at 3 distinct time points (triplicates) within 5 minutes (±5 minutes) prior to selected PK sample collections as follows: pre-infusion, and at 30 and 60 minutes post-infusion. An ECG should be performed after the patient is supine for 5 minutes.

11.8 Imaging Studies

After all other entry criteria have been met for an individual patient, a baseline spleen (and liver) volume assessment by MRI or CT scan is required and should be performed within 28 days prior to the first administration of tagraxofusp. Subsequent imaging studies will be performed as indicated in the applicable Schedules of Events (Table 2 and Table 3 for Stage 2; Table 4 and Table 5 for Stage 3A). An abdominal scan is required; evaluation of chest/pelvis may be obtained at the Investigator's discretion.

MRI is the preferred modality as it provides an objective measure of spleen (and liver) volume and does not expose study subjects to ionizing radiation. CT may be used where MRI is not available or suitable for study subjects. Imaging studies will be reviewed locally.

Whenever clinically feasible, it is strongly requested that the same imaging modality at both baseline and subsequent time points be utilized for any given patient throughout their evaluations on-study.

11.9 Cardiac Function: MUGA/2-D Echocardiogram

A MUGA scan or 2-D ECHO to quantify LVEF must be completed during screening within 28 days prior to start of first cycle of study drug. A minimum LVEF is stipulated as a criterion for study inclusion (see Section 7.1.1).

11.10 Clinical Laboratory Tests

The following assessments should be done at the time points indicated in the applicable Schedules of Events (Table 2 and Table 3 for Stage 2; Table 4 and Table 5 for Stage 3A) and processed by the local laboratory.

- Hematology: Scheduled hematology assessments should at minimum include WBC count, differential WBC (lymphocytes, monocytes, basophils, eosinophils, and neutrophils), RBC count, hematocrit, Hb, platelet count and immature myeloid cells (including blasts + myelocytes + metamyelocytes + promyelocytes + nucleated red blood cells) (for safety assessments as well as for efficacy assessments at the end of each cycle in between bone marrow assessments).
- Serum albumin: May be a component of the serum chemistry panel. See Appendix Section 18.3 for administration of albumin if serum albumin decreases to < 3.0 g/dL during treatment days or in the immediate post-treatment period.
- Serum chemistry and electrolytes: ALT, albumin, alkaline phosphatase (ALP), AST, bicarbonate, bilirubin (total, direct, and indirect), BUN, calcium, chloride, CPK, creatinine, glucose, LDH, magnesium, phosphate, potassium, sodium, total protein, and uric acid.
- Coagulation parameters: PT and/or INR and aPTT.
- Urinalysis (MF patients only): Appearance, color, pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen, and occult blood.

Detailed instructions for collecting, processing, storing, and shipping the samples are provided in the Laboratory Manual.

11.10.1 Urine or Serum Pregnancy Test

A urine or serum pregnancy test will be performed locally within 1 week prior to treatment for WOCBP. The pregnancy test should be performed at the clinical research site and processed by the local laboratory.

11.11 Vision Assessment

All patients will be questioned regarding any changes from baseline in visual acuity and/or color vision. Patients who have experienced any ≥ Grade 2 study drug-related changes in vision (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], v4.03, Grade) will have an ophthalmologic consultation and/or examination performed. In the event any abnormalities are detected, the patient will be followed up as per the recommendations

of the consulting ophthalmologist. Management of treatment-related ocular disorders with inflammatory characteristics should include corticosteroid eye drops and/or other measures, as indicated by an ophthalmologist. In the setting of persistent study drug-related ocular disorders ≥ Grade 2, consultation with the study's Medical Monitor is required.

11.12 Tumor Assessments

Tumor assessments must be performed at baseline within 28 days prior to the first administration of tagraxofusp, and on the scheduled specified in Table 2 and Table 3 for Stage 2 and Table 4 and Table 5 for Stage 3A.

Response assessment is performed by means of the following:

- **MF (Stage 2)**: The IWG-MRT/ELN 2013 criteria (see Table 6 in Appendix Section 18.1).
- **CMML (Stage 2)**: The IWG MDS 2006 criteria (see Table 7 in Appendix Section 18.1).
- **CMML (Stage 3A):** MDS/MPN 2015 criteria (see Table 8 in Appendix Section 18.1).

After Baseline, tumor response assessments are performed at the end of C1 and C4 and then every 12 weeks (±7 days) thereafter, at End-of-Treatment, and at other timepoints if clinically warranted.

11.12.1 Cytogenetic and Molecular Genetic Testing

Cytogenetic testing should be done on bone marrow aspirate samples and 20 metaphases assessed, when possible. Peripheral blood can be used for the analysis in patients with high circulating blast counts. The number of metaphases counted and analyzed, and abnormal karyotype will be collected in the CRF.

Molecular genetic testing by next-generation sequencing (NGS) will be done on peripheral blood or bone marrow aspirate samples and will be analyzed for the following mutations:

- Patients with MF: *JAK2V617F, CALR*, and *MPL*. For 'triple-negative' MF patients, complementary clonal markers, such as *ASXL1, EZH2, IDH1, IDH2*, and *SRSF2* are recommended; additional clonal markers such as *TP53, TET2, DNMT3A*, and *CBL* are useful for risk-stratification.
- Patients with CMML: *TET2, ASXL1, DNMT3A, EZH2, IDH1, IDH2, BCOR, SRSF2, U2AF1, SF3B1, ZRSR2, CBL, KRAS, NRAS, NF1, JAK2, RUNX1, SETBP1, NPM1*, and *FLT3* are recommended by the ELN/EHA 2018 guidelines for patients being considered for active treatments, including stem cell transplant. Of these genes, an analysis of the following **4** genes is considered mandatory for risk assessment according to accepted risk scoring systems: *ASXL1, NRAS, RUNX1*, and *SETBP1*.

Detailed instructions for collecting, processing, storing, and shipping the samples are provided in the Laboratory Manual.

11.12.2 Bone Marrow Examinations Including Biological / Target / Correlative Studies

Bone marrow aspirate and biopsy samples will be collected during screening within 28 days prior to the first administration of tagraxofusp and at the end of C1 and C4 and then every 12 weeks (±7 days) thereafter, and at End-of-Treatment. Plasmacytoid dendritic cells (pDCs) and CD123 expression will be assessed by flow cytometry and immunohistochemistry in all bone marrow samples by a central laboratory.

Consult the Laboratory Manual regarding information on the collection, handling, labeling, and shipping of samples.

11.13 Immunogenicity Studies

Peripheral blood samples (10 mL) will be collected (serum red top tube, no additive) for the detection and characterization of tagraxofusp reactive antibodies according to the schedule provided below.

- C1-4: Day 1 (pre-infusion) and Day 21 (± 3 days).
- C5 and beyond: End of cycle (D28 [± 3 days]).
- End-of-Treatment.
- 30 days after last infusion.
- At least 16 weeks and to up to 20 weeks after last infusion.
- If there are clinical manifestations suggesting either an infusion related reaction or drug hypersensitivity, an immunogenicity sample should be obtained, as indicated in Section 8.2.3.2.

Detailed instructions for collecting, processing, storing, and shipping the samples will be provided in the Laboratory Manual.

11.14 Translational Studies/Exploratory assessments

- Flow cytometry: Cells expressing high levels of CD123 have been described in the bone marrow of CMML patients and an excess of CD123 expressing pDCs has been shown to correlate with regulatory T cell accumulation and an increased risk of acute leukemia transformation (Lucas 2019). Additionally, $CD14^{+}/CD16^{-}$ monocytes have been indicated to be a specific biomarker that distinguish CMML from confounding diagnoses (Selimoglu-buet 2015). pDCs in addition to leukocyte populations (MF) and monocyte subsets (CMML) will be assessed centrally in bone marrow and peripheral blood by flow cytometry. Samples will be collected at the following time points:
    - Screening or C1D1 (pre-infusion)
    - All Cycles: Day 1

- C1: Day 8
- End of Treatment

- Cytokine IL-10: It has been observed that CMML patients with decreased IL-10 expression have poor overall survival when compared to patients with elevated expression of IL-10 (Niyongere 2019), which suggests that cytokine IL-10 can be a prognostic marker of overall survival (Niyongere 2019). Peripheral blood samples will be collected for the detection of the cytokine IL-10 for CMML patients at the following time points.
  - C1: Day 1 (pre-infusion) and Day 21 (± 3 days)
  - C4: End of cycle (Day 21 [± 3 days]).
- In addition to central laboratory analysis of CD123 and monocyte cell populations, an exploratory analysis of $CD14^{+}/CD16^{-}$ flow cytometry, CYTOF (Mass cytometry), next generation sequencing in CMML patients will be examined at selected sites at the following time points:
  - C1: Day 1 (pre-infusion) and Day 21 (end of cycle)
  - C4: Day 21 (end of cycle)

Detailed instructions for collecting, processing, storing, and shipping the samples will be provided in the Laboratory Manual.

12 Concomitant Medications

12.1 Recommended Medications per Institutional Guidelines/Practices

It is recommended that patients receive the following types of prophylactic therapies/regimens per institutional guidelines/practices:

- Antibacterial: ciprofloxacin, levofloxacin, or an equivalent antibiotic.
- Antifungal: fluconazole, voriconazole, or an equivalent antifungal.
- Antiviral: acyclovir, valacyclovir, or an equivalent antiviral.

12.2 Allowed Medications/Therapies

Refer to Section 8.2.1.1 for premedications to be administered with tagraxofusp.

All patients may receive supportive care measures as clinically indicated, including prophylactic antibiotics, antihistamines, antiemetics, albumin, fluids (hydration), and supportive measures. Patients may receive growth factor support and/or blood product transfusions as per the discretion of their physician.

Albumin 25 g IV daily should be administered if serum albumin is < 3.0 g/dL during days when treatment is withheld or in the immediate post-treatment period. (Refer to Section 18.3 for albumin administration requirements in the setting of elements of CLS.)

Corticosteroid therapy is permitted and is governed by parameters detailed in Section 12.3 (Prohibited Medications/Therapies).

Granulocyte-colony stimulating factor (G-CSF) is permitted only for the treatment of febrile neutropenia. Following a febrile neutropenic event, G-CSF prophylaxis may be considered if there is evidence of response and the Investigator determines that ongoing tagraxofusp treatment is associated with a potentially favorable risk-benefit profile (such a determination should be made in consultation with the Medical Monitor).

12.3 Prohibited Medications/Therapies

Prior to discontinuation of tagraxofusp, patients may not receive the following anticancer/ antimyeloproliferative agents: JAKi (ruxolitinib, fedratinib, and others), interferon-α, thalidomide, lenalidomide, cytotoxic chemotherapy agents (including 2-chlorodeoxyadenosine and other purine analogs), hypomethylating agents (5-aza, decitabine and others), tyrosine kinase inhibitors (including those which inhibit the BCR-ABL kinase such as imatinib), HU, and investigational anti-cancer agents.

Patients may not receive additional disease-modifying or cytoreductive agents such as danazol or anagrelide. Patients may not receive erythroid- or platelet-stimulating growth factors.

Hydroxyurea is prohibited during study participation except for cycle 1; Short-term treatment with HU beyond cycle 1 with approval of the Medical Monitor is permitted.

Ongoing corticosteroid therapy at doses of > 20 mg/day prednisone (or equivalent) for > 7 days is not permitted; however transient increases in corticosteroid doses in the setting of infections or other “stress” settings are allowed.

13 Adverse Events and Safety Evaluation

The AE reporting period for a patient treated in the study begins with provision of consent and is continuous through 30 days after the last tagraxofusp infusion. All AEs that occur in treated patients during the AE reporting period must be reported to the Sponsor or designee, whether or not the event is considered related to tagraxofusp. Any known untoward event that occurs beyond the AE reporting period (30 days after the last tagraxofusp infusion) that the Investigator assesses as related to tagraxofusp should also be reported as an AE.

All patients should be monitored for at least 1 hour (or longer at the Investigator’s discretion) following the administration of each tagraxofusp infusion. The Investigator or designated medical staff responsible for study conduct and safety evaluations, should be available during the administration of tagraxofusp and follow-up to assess, treat, or report as necessary any AE or SAE that may occur.

13.1 Definitions

All observed or volunteered AEs regardless of suspected causal relationship to tagraxofusp will be reported as described below.

13.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a study patient who is administered a medicinal product (drug or biologic); the event may or may not have a causal relationship with the medicinal product. Examples of AEs include, but are not limited to the following:

- Clinically significant symptoms and signs including:
  - Worsening of signs and symptoms of the disease under study; disease progression without worsening of signs and symptoms as assessed by bone marrow aspiration or other methods should not be reported as AEs.
  - Signs and symptoms resulting from drug overdose, abuse, misuse, withdrawal, sensitivity, dependency, interaction, or toxicity.
  - All possibly related and unrelated illnesses, including the worsening of a preexisting illness.
  - Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (hip fracture from a fall secondary to dizziness), the medical condition (dizziness) and the outcome of the accident (hip fracture from a fall) should be reported as 2 separate AEs.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat confirmatory test).
- Laboratory abnormalities that meet any of the following (Note: merely repeating abnormal test, in the absence of any of the below conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE):
  - Test result that is associated with accompanying symptoms
  - Test result that requires additional diagnostic testing or medical/surgical intervention
  - Test result that leads to significant additional concomitant drug treatment or other therapy
  - Test result that is considered to be an AE by the Investigator or Sponsor

Note that veno-occlusive disease occurring post-SCT and any changes in visual acuity and/or color vision will be followed as AEs of special interest.

13.1.2 Serious Adverse Event (SAE)

An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Results in death;
- Is life-threatening (at immediate risk of death);
- Requires admittance to the hospital or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth disfigurements among the offspring of the patients;
- Events with medical significance or needing medical intervention to prevent the occurrence of any of the above events.

Medical judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Serious also includes any other event that the Investigator or Sponsor judges to be serious, or which is defined as serious.

AEs associated with in-patient hospitalization, or prolongation of an existing hospitalization, are considered serious. Any initial admission, even if the duration is less than 24 hours is considered serious. In addition, any transfer within the hospital to an acute/intensive care unit is considered serious. However, the following hospitalizations should not be considered serious:

- Hospitalization or prolonged hospitalization in the absence of precipitating clinical AEs, as follows:
  - Admission for treatment of preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition
  - Administrative admission (e.g., for a yearly physical examination)
  - Protocol-specified admission during the study (e.g., admission for tagraxofusp treatment)
  - Preplanned treatments or surgical procedures
  - Admission exclusively for the administration of blood products

Progress of the disease under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal during the study or within the safety reporting period. If the disease under study has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE of CTCAE Grade 5 intensity. Disease progression is NOT an SAE; however some sequelae of disease progression (i.e., pain, thrombocytopenia) may be reported as AEs or SAEs (generally not related to investigational therapy).

The onset date of an SAE is defined as the date on which the event initially met serious criteria (e.g., the date of admission to a hospital). The end date is the date on which the event no longer met serious criteria (e.g., the date the patient was discharged from a hospital).

13.2 Period of Observation

Clinical signs and symptoms, and AEs (regardless of relationship to study drug) will be collected for treated patients continuously from provision of consent to 30 days following the last infusion of tagraxofusp. All SAEs and AEs judged to be related to study drug will be collected throughout the AE reporting period.

Conditions that the patient experienced prior to the provision of consent should be recorded in the patient medical history section of the eCRF. All the AEs should be followed-up at the Investigator's discretion until the symptoms dissipate or become stable even if AEs continue beyond the period of observation. AEs unresolved at the end of the observation period will be considered "ongoing" with an undetermined outcome; however, if after the period of observation completes but prior to the completion of the study, additional outcome information becomes available, it will be reported. The severity of the signs, symptoms, or AEs should be determined using the CTCAE, v4.03. A complete CTCAE list can be downloaded at http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

All clinically meaningful abnormal test results should be retested. Abnormal test results that are difficult to associate with the study drug should be followed until normalized or until the abnormity could be clearly attributed to another cause. Abnormal test results should not be reported as AEs unless they meet the criteria outlined in Section 13.1.1.

13.3 Pre-existing Conditions

A pre-existing condition will not be reported as an AE unless the condition worsens by at least one CTCAE grade during the study. The pre-existing condition, however, must be recorded in the medical history eCRF as a pre-existing condition and all related concomitant medication administered for the condition recorded in the concomitant medication eCRF.

13.4 Pregnancy

WOCBP and men with partners of childbearing potential must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 1 week after the study in such a manner that the risk of pregnancy is minimized. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy with documented serum follicle-stimulating hormone level ≥ 35 mIU/mL). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products, such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy,

are practicing abstinence, or whose partner is sterile (e.g., vasectomy), should be considered to be of childbearing potential.

WOCBP must have a negative serum or urine pregnancy test during screening within 1 week before the first study drug dose. If the pregnancy test is positive, the patient must not receive study therapy and must not be enrolled in the study.

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that the risk of failure is minimized.

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. This information will be included in the ICF that must be signed by the patient.

In addition, all WOCBP or fertile men with partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect they or their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If following initiation of study drug, it is subsequently discovered that a patient is pregnant or may have been pregnant at the time of exposure to study therapy, including during at least 1 week after product administration, study therapy will be permanently discontinued in an appropriate manner. Exceptions to discontinuation may be considered for life-threatening conditions only after consultation with the Sponsor and Medical Monitor or as otherwise specified in this protocol. The Investigator must immediately notify the Sponsor and Medical Monitor of this event.

Protocol-required procedures for study discontinuation and follow-up must be performed on the patient unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the Investigator must report to the Sponsor follow-up information regarding the course of the pregnancy of the patient/patient's partner, including perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

13.5 Documentation and Reporting of Adverse Events by Investigator

The Investigator is to report all directly observed AEs and AEs spontaneously reported by the patient using concise medical terminology. In addition, each patient will be questioned about AEs at each clinic visit following initiation of treatment. The question asked will be "Since your last clinic visit have you had any health problems?" or a similar question to assess health status.

The AE reporting period for this study begins after provision of written informed consent and ends 30 days after the last tagraxofusp infusion. All AEs are to be reported on the AE eCRFs.

All AEs that occur in study patients during the AE reporting period must be reported to the Sponsor, whether or not the event is considered study drug-related. In addition, any untoward

event that occurs beyond the AE reporting period that the Investigator assesses as related to the investigational product should also be reported as an AE.

Each AE is to be classified by the Investigator as serious or non-serious. This classification of the gravity of the event determines the reporting procedures to be followed. If a SAE occurs, reporting will follow local and international regulations, as appropriate.

For any event that meets one of the SAE criteria, the Investigator must notify the Safety Contact **within 24 hours** of the knowledge of the occurrence. To report the SAE, complete the SAE form and email to the Safety Contact (email address listed below) within 24 hours of awareness.

Safety Contact Information: E-mail: [redacted]

Each SAE should be followed until resolution, or until such time as the Investigator determines its cause or determines that, it has become stable.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to the Safety Contact via e-mail. All SAEs are also to be recorded in the eCRF.

The Sponsor will report AEs, which are unexpected and reported as serious and associated with use of the study drug, to the applicable regulatory authorities and all participating sites. For events that are fatal or life-threatening, unexpected, and associated with use of the investigational product, a 7-Day Alert Report will be submitted to the applicable regulatory authorities within 7 calendar days of receipt of the SAE information. For all other events that are serious, unexpected, and associated with the use of the investigational medicinal product, a written report will be made no more than 15 calendar days from the date the Sponsor learns of the event.

13.6 Assessment of Causal Relationship to Tagraxofusp

In this study, the investigational medicinal product is tagraxofusp. The relationship of an AE to the investigational product should be classified using the following guidelines:

- Related: A temporal relationship exists between the event onset and administration of tagraxofusp. It cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies. In case of cessation of the dose, the event abates or resolves and reappears upon re-challenge.
- Not Related: Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered probably not or not related to tagraxofusp. It should be emphasized that ineffective study drug treatment should not be considered as causally related in the context of AE reporting (in other words, disease progression is not considered an AE; however some sequelae of disease progression may be reported as AEs and should generally be reported as AEs not related to investigational therapy).

An Investigator who is qualified in medicine and has an active license to practice in the geographic location where the patient is being treated must make the determination of relationship to the investigational product for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. The following factors for study drug relationship should be referenced when making a determination of "related" or "not related."

- The temporal sequence from study drug administration: The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication/therapy: The other medications the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question. Transfusions of pRBCs or platelets after enrollment (first dose) will be captured as concomitant medication/therapy.
- Known response pattern for this class of study drug: Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug: The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

13.7 Grading of Adverse Event Severity

To report AEs on the eCRFs, the Investigator will use the severity grading as described in NCI CTCAE, v4.03.

Every effort should be made by the Investigator to assess the AE according to CTCAE criteria. If the Investigator is unable to assess severity because the term is not described in NCI CTCAE, Version 4.03, severity of MILD, MODERATE, SEVERE, LIFE-THREATENING, or DEATH may be used to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

- Mild (Grade 1): does not interfere with patient's usual function
- Moderate (Grade 2): interferes to some extent with patient's usual function
- Severe (Grade 3): interferes significantly with patient's usual function
- Life-threatening (Grade 4): results in immediate risk of patient's death

- Death (Grade 5): results in patient's death

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious events.

It is requested that when reporting AEs for which potentially redundant CTCAE terms exist, investigators utilize the more clinically-oriented terminology (for example, "anemia" is preferable to "hemoglobin decreased").

It is also requested that in the setting of a hypersensitivity reaction or suspected hypersensitivity reaction considered by the Investigator to be related to investigational therapy, that investigators report both the specific symptoms associated with the reaction (i.e., "urticaria," "chills," "dyspnea") and also report the appropriate term indicating the hypersensitivity reaction ("allergic reaction," or "infusion-related reaction" or "anaphylaxis" if appropriate [General Disorders and Immune System Disorders; CTCAE v4.03]).

14 Statistical Analysis

14.1 General Considerations

Analyses will be performed on all patients that received any quantity of tagraxofusp (i.e., all treated patients). The baseline value for a given variable is defined as the last measurement for the variable prior to the first infusion of tagraxofusp. Cycle 1 Day 1 for each individual patient is defined as the date the patient receives their first infusion of tagraxofusp.

14.2 Determination of Sample Size

14.2.1 Stage 2 (Patients with CMML Previously Enrolled and Patients with MF)

An objective of Stage 2 is a preliminary assessment of response rates associated with tagraxofusp in CMML and MF. Because available anti-cancer agents are associated with very limited responses in the MPNs evaluated in this study, it is anticipated that an agent that confers a response rate ≥ 10% may be considered active and worthy of additional investigation.

Initially, a sample size of 18 patients with a particular MPN was planned for enrollment in Stage 2. Furthermore, it was planned that in settings where there is evidence that a sufficient proportion of patients have experienced improvement in components of the response criteria, that additional investigation of tagraxofusp in a given MPN may have been considered appropriate based on preliminary data.

Preliminary evidence of activity has been observed in patients with relapsed and/or refractory CMML and MF.

As of July 2021, 36 patients have been enrolled, comprising 20 patients with CMML-1 and 16 with CMML-2; median age was 69 years (range 42–81), and 75% of patients were male. Twenty-three patients (64%) had either high- or intermediate-risk genetics based on CPSS,

GFM, MMM, or ELN risk stratification systems. Prior therapies included HMA in 16 patients (43%), allogeneic stem cell transplantation (allo-SCT) in 3 (8%), and other in 12 (32%); 7 patients (19%) were high-risk and treatment naive. Overall, 16 patients (44%) had baseline palpable splenomegaly; in 12 of these patients, spleen size was ≥5 cm below left costal margin. Overall, 4 of 36 (11%) patients achieved bone marrow morphological complete responses (BMCRs), 1 of whom was bridged to allo-SCT; all 4 patients had splenomegaly at baseline. It is noteworthy that 2 of the 4 BMCRs, were observed in patients with high-risk genetic features. Fifteen patients (42%) with baseline splenomegaly had spleen responses; 9 patients (60%) had a ≥50% reduction in spleen size, including 5 (42%) with splenomegaly of ≥5 cm at baseline.

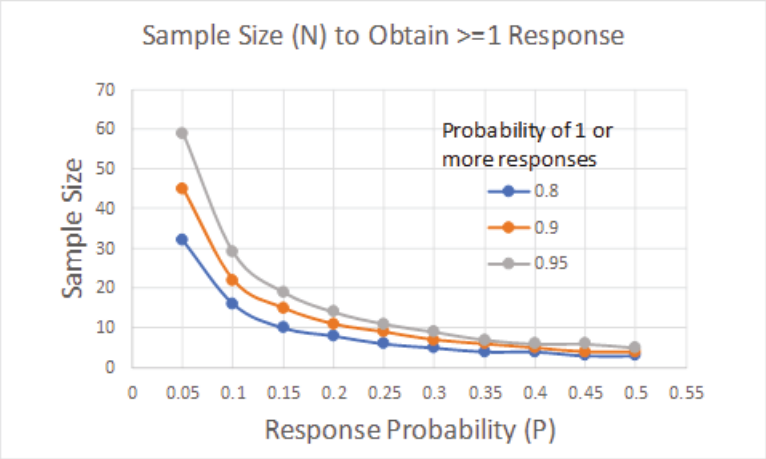
14.2.2 Stage 3A in Patients with CMML

The purpose of Stage 3A is to evaluate the clinical benefit derived from individual components, or variations thereof, of the MDS/MPN 2015 criteria that may allow for a prospective definition of a primary efficacy endpoint, that will provide the primary evidence of efficacy for regulatory decision-making in the planned confirmatory cohort (Stage 3B; to be added under the auspices of separate amendment). Individual evaluations will be performed for each of the two CMML cohorts in Stage 3A.

Approximately 20 patients with CMML may be enrolled in each of the two cohorts in Stage 3A to ensure a sufficient number of patients with specific baseline disease characteristics are enrolled to reject a meaningless rate of clinical activity in subsets of interest. (For our purposes, a meaningless rate will be taken to mean that there are no responders, using the definitions below, in the sample for each of the following subsets.) No formal stratification will be performed; however approximately 8-10 patients with baseline splenomegaly (defined as ≥ 5 cm below the left costal margin) and approximately 8-10 patients who are transfusion-dependent at baseline (receipt of at least 4 transfusions within 8 weeks before the first tagraxofusp dose) will be included in each 20-patient cohort. This intended enrollment distribution may be adjusted, depending on the actual prevalence of splenomegaly and transfusion-dependence seen in the general patient population as the study continues to enroll.

In this exploratory stage, the primary evidence of activity in each subset would be (1) a reduction in spleen volume that correlates with an improvement in symptom score or (2) conversion from transfusion-dependent to transfusion-independent. These occurrences on a per-patient basis would be considered responses within each subgroup. Clinical activity would have been demonstrated if at least 1 patient achieves either of these clinically important outcome responses. Up to 5 additional patients with either of these specific baseline characteristics may be enrolled in Stage 3A, to increase the confidence in the observed results, if necessary. It can be seen in the graph below that for any true rate of response that is ≥ 0.15, this approach would have at least 80% power to detect at least one responder. Given at least a single responder, additional methods such as confidence interval estimation or formal power calculations, may be used to determine whether to move ahead with a confirmatory Stage 3B.

The operating characteristics of this approach to sample size estimation in Stage 3A may be seen in the following graph. This graph presents the sample size required to have either an 80%, 90%, or 95% probability of at least 1 responder when the sample size is N, and the true probability of response is P.



As an example, if the true response probability were 0.15, 10 patients evaluated for a given response type would result in at least one response with 80% probability.

Other subsets of patients may be retrospectively identified in which treatment with tagraxofusp may result in clinically important outcomes, and enrichment strategies within the framework of this sample size may be applied, with the same objective of rejecting a meaningless rate of clinical activity.

14.3 Demographics and Baseline Characteristics

Demographic (e.g., gender, age, and race) and baseline characteristics (e.g., ECOG PS, height, weight, and prior therapy) will be summarized with descriptive statistics.

14.4 Analyses of Safety Data

Safety assessments include DLTs, AEs, SAEs, physical examinations, vital sign measurements, ECGs, clinical laboratory evaluations, and reasons for treatment discontinuation due to toxicity.

Treatment-emergent AEs through 30 days after the last tagraxofusp infusion will be summarized by Medical Dictionary for Regulatory Activities (MedDRA™) Version 13.1 (or higher) System Organ Class and preferred term. The incidences and percentages of patients experiencing each AE preferred term will be summarized with descriptive statistics. AEs will also be summarized by NCI CTCAE, Version 4.03 (or higher), grade and by causality (relationship to study drug). DLTs, Grade 3-4 AEs, SAEs, and AEs resulting in dose modification or treatment discontinuation will also be summarized by preferred term.

Laboratory results will be classified according to NCI CTCAE, Version 4.03. Laboratory results not corresponding to an NCI CTCAE term will not be graded. Incidences of laboratory abnormalities will be summarized with descriptive statistics.

Vital signs, physical examination results, and ECGs will be summarized with descriptive statistics.

14.5 Analyses of Efficacy Data

Efficacy assessments include ORR, CR rate, specific components of the response criteria for each indication, duration of response (DOR), progression-free survival (PFS), and OS. Refer to Appendix 18.1 for detailed response criteria established for CMML and MF. All efficacy outcomes will be presented by subgroups defined by disease.

Data from Stage 2 will be analyzed with descriptive statistical methods to provide estimates of rates of response. Stage 3A data will be analyzed with descriptive and correlation methods, with results intended to assist in the design of the confirmatory Stage 3B. Bayesian methods may also be used to determine likely values of response parameters, with Stage 2 results providing prior information for calculation of credible intervals based on Stage 3A data. Complete details of efficacy analyses will be provided in the Statistical Analysis Plan (SAP).

14.6 Pharmacokinetic and Immunogenicity Analyses

Planned PK and immunogenicity analyses will be described in separate SAPs.

14.7 Blinding

This is an open-label study.

15 Emergency Procedures

15.1 Emergency Contact

In emergencies, the Investigator should contact the Medical Monitor by telephone at the number listed on the title page of the protocol.

15.2 Emergency Identification of Investigational Products

Since this is an open-label study, the investigational treatment will be identified on the package labeling.

15.3 Emergency Treatment

During a patient’s participation in the study, the Investigator and/or institution should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory values, related to the study.

16 Ethical and Regulatory Considerations

16.1 Good Clinical Practice

As the Sponsor of this clinical study, Stemline has the overall responsibility for the conduct of the study, including assurance that the study meets the requirements of applicable regulatory authorities. Stemline will maintain compliance with the FDA Code of Federal Regulations (CFR), ICH Guideline E6, Declaration of Helsinki, and Good Clinical Practice (GCP) guidelines. The study must receive approval from an Institutional Review Board (IRB)/Ethics Committee (EC) prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

The Sponsor is responsible for obtaining IRB/EC approvals, providing Investigators with information required to conduct the study, ensuring proper investigative site monitoring, verifying that appropriate patient informed consent is obtained, and ensuring that the IRB/EC and regulatory agencies are promptly informed of significant new information regarding the study.

16.2 Delegation of Investigator Responsibilities

The Investigator must ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study drugs, and their study-related duties and functions. The Investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

16.3 Patient Information and Informed Consent

Before being admitted to the clinical study, the patient must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a language understandable to him or her. An ICF that includes both information about the study and the consent form will be prepared and given to the patient. This document will contain all ICH, GCP, and locally required regulatory elements. The ICF must specify who informed the patient and be approved by the Institution's IRB/EC. Copies of the ICF used in the study must contain the IRB/EC-approval stamp (if applicable) and version date. The Investigator must keep the original executed ICF including the patients' signatures and the signing dates properly stored in a secured location at the study site with an additional copy of the ICF included with the patients' medical chart and therapy records.

After reading the informed consent document, the patient must give consent in writing. The written informed consent will be obtained prior to conducting any study-related procedures or tests. The patient's consent must be confirmed at the time of consent by the dated signature of the person conducting the informed consent discussions. If the patient agrees to participate in the study, the patient and the Investigator must sign both copies of the ICF. A copy of the signed ICF must be given to the patient or the patient's legally authorized representative. The signed ICF

must be available for verification by the Sponsor's designated monitors or Regulatory Authority inspectors.

The date of the signed ICF will also be noted in the patient's medical chart. Patients should be informed of new information learned during the study, which may affect their decision to continue participation in the study. The Investigator should inform the patient's primary physician about the patient's participation in the study if the patient has a primary physician and if the patient agrees to the primary physician being informed.

16.4 Confidentiality

The Investigator(s) and the Sponsor or its authorized representative will preserve the confidentiality of all patients and donors participating in the study, in accordance with GCP, ICH, local regulations and to the extent applicable the Health Insurance Portability and Accountability Act of 1996 ("HIPAA").

Patient names will not be supplied to the Sponsor or its authorized representative. Only the patient study numbers and date of birth will be recorded in the eCRF, and if the patient name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor or its authorized representative. Study findings stored on a computer will be stored in accordance with local data protection laws. Patients will be told that representatives of the Sponsor, its authorized representative, IRB/EC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection law. The Investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

16.5 Protocol Amendments

Any changes that affect patient safety or welfare will be submitted to the IRB/EC and Regulatory Authority (where applicable) for approval prior to implementation. The Investigator and the Sponsor must approve all amendments. No amendment will be implemented until approved and signed by all parties. Exceptions to this are when the Investigator considers that the patient's safety is compromised.

16.6 IRB/EC Approval and Reporting

The Investigator must obtain appropriate IRB/EC approval prior to study initiation. A copy of the written approval from the IRB/EC and a copy of the approved ICF should be sent to the Sponsor or its delegate. It is also necessary to submit a list of the IRB/EC members (including their Institution affiliations, gender makeup, and occupations) or supply a statement from the IRB/EC specifying that the membership complies with applicable regulations.

The study protocol, patient information and consent form, the Investigator's Brochure, available safety information, patient recruitment materials (e.g., advertisements), information about

payments and compensation available to the patients and documentation evidencing the Investigator's qualifications should be submitted to the IRB/EC for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Any changes to the protocol must be approved by the Sponsor in writing unless the change is proposed to assure safety of the patient. In the non-emergent setting, following agreement on the proposed changes, an amendment to the protocol will be submitted to the IRB/EC for approval prior to implementation of the change. Any change made emergently must be documented in the patient's medical record.

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected AEs as soon as possible;
- Periodic reports on the progress of the study.

16.7 Closure of the Study

The Sponsor or its authorized representative has the right to close this study and the Investigator has the right to close the study at his/her site at any time. The IRB/EC must be informed, if required by legislation. Should the study be closed prematurely, all unused tagraxofusp will be reconciled with dispensing records, documented, and, if directed by the Sponsor, destroyed at the study site or returned for destruction after completion of accountability by the site monitor.

16.8 Record Retention

The Sponsor will maintain copies of correspondences, records of shipment and disposition of study drug, AEs, and other records related to the clinical study and the signed Investigator agreements. Retained records will enable the tracing of patients who have participated in the study. Notes of patients who have enrolled in the study must be retained if the patient has died.

Study documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when storage of these documents is no longer required. The Investigator should contact the Sponsor if the site's archiving arrangements change at any time.

16.9 Liability and Insurance

Liability and insurance provisions for this study are provided in the clinical trial agreement.

16.10 Financial Disclosure

Prior to study initiation the Investigator will be asked to sign a clinical trial agreement. All Investigators also will be required to sign a Financial Disclosure Form in accordance with 21 CFR Part 54; Financial Disclosure by Clinical Investigators prior to study initiation and at any time financial interest changes.

16.11 Study Monitoring and Auditing

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance to applicable government regulations with respect to current GCP and current standard operating procedures. Monitoring functions will be performed in compliance with 21CFR§812.43(d) and 21CFR§812.46. Direct access to the on-site study documentation and medical records must be ensured.

16.12 Study Monitoring and Source Data Verification

The Investigator is responsible for the validity of all data collected at the site and must accept the various monitoring procedures employed by the Sponsor. The purpose of monitoring is to verify the rights and well-being of human patients are protected; that study data are accurate, complete, and verifiable with source data; that the study is conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

Sites will be monitored to identify and reconcile any differences between the completed eCRFs and medical records, and review Source documents for accuracy, completeness, and legibility. The monitor will review completed data forms and study documentation for accuracy, completeness, and protocol compliance. In addition, the Sponsor will evaluate any protocol deviations and take corrective action as necessary.

The Sponsor will review significant new information, including unanticipated AEs and ensure that such information is provided to all reviewing IRBs/ECs. This information will also be provided to the FDA, other regulatory authorities, and Investigators worldwide in accordance with local regulations. The monitor’s responsibilities include site visits, participation in initial study sessions, review of eCRFs, source documents and results, and ensuring clear communication between the Investigator and the Sponsor.

The monitor and data manager will query any missing or spurious data with the Investigator, which should be resolved in a timely manner. A monitoring log will be maintained recording each visit, the reason for the visit, the monitor’s signature, and Investigator’s or designee’s confirmation signature.

16.12.1 Study Documentation

The Investigator must provide the Sponsor with the following documents prior to enrollment and maintain the currency of these documents throughout the course of the study.

- Completed and signed Form FDA 1572 or equivalent.
- All applicable country-specific regulatory forms.
- Current signed and dated curricula vitae for the Investigator, sub-investigators, and other individuals having significant investigator responsibility who are listed on Form FDA 1572 or equivalent, or the clinical study information form.
- Copy of the current medical license of the principal Investigator, any sub-investigators and any other individuals having significant responsibility as listed in the 1572.
- A financial disclosure form for the Principal Investigator and any other persons listed in the 1572.
- Copy of the IRB/EC approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the patient must be approved by the IRB/EC. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/EC must also be provided to the Sponsor.
- Copy of the IRB/EC-approved informed consent document.
- A list of the IRB/EC members or a Federalwide Assurance number.
- Copy of the protocol signature page signed by the Investigator.
- Fully executed clinical trial agreement, including budget.
- A written document containing the name, location, certification number, and date of certification of each laboratory to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the laboratory director’s curricula vitae and active medical license. List of normal laboratory values and units of measure for all laboratory tests required by the protocol.

The sites will also be asked to maintain a Delegation of Authority Log, pharmacy logs, temperature logs, personal patient identification log and monitoring visit logs during this study.

16.12.2 Site Audits

For the purpose of compliance with GCP and regulatory agency guidelines, it may be necessary for Sponsor authorized Quality Assurance personnel and/or authorized personnel from an external regulatory agency to conduct an audit/inspection of an investigational site. These site reviews may be planned or spontaneous and occur at any stage during the study. The purpose of an audit is to assess the quality of data with regard to accuracy, adequacy, and consistency, and

to assure that studies are conducted in accordance with GCP, the protocol, and Regulatory Agency guidelines.

The Investigator should promptly notify the Sponsor or its authorized representative of any audits by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or its authorized representative.

Electronic data systems will be in accordance with applicable aspects of 21 CFR Part 11, ICH Guidelines, GCP, and HIPAA.

16.13 Documentation and Use of Study Findings

16.13.1 Documentation of Study Findings

Source documentation will be maintained to document the treatment and study course of a patient and to substantiate the integrity of the study data submitted for review to regulatory agencies. Source documentation for Stemline studies will include, but not be limited to, worksheets, hospital and/or clinic or office records documenting patient visits including study and other treatments or procedures, medical history and physical examination information, laboratory and special assessments results, drug accountability records, and medical consultations (as applicable).

Laboratory and diagnostic reports including but not limited to: local laboratory hematology and chemistry results, bone marrow biopsy reports, bone marrow aspirate reports, ECHO readings, and MUGA readings may be collected by the study monitor during the course of the study. Every effort should be made by the site to de-identify personal patient information from these reports and replace it with the patient study identification number.

16.13.2 Use of Study Findings

All information concerning the product, as well as any matter concerning the operation of the Sponsor, such as clinical indications for the drug, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by the Sponsor and are unpublished, are confidential and must remain the sole property of the Sponsor. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained. The Sponsor has full ownership of the eCRFs completed as part of the study.

All publications and presentations of the results of the Study are governed by the applicable provisions of the clinical trial agreement between the Sponsor and the institution. By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor. If necessary, the authorities will be notified of the Investigator’s name, address, qualifications, and extent of involvement. The Investigator may not publish or present any information on this study without the express written approval of the Sponsor. Additionally, the Sponsor may, for any reason, withhold approval for publication or

presentation. If the Investigator is to be an author of a publication manuscript prepared by the Sponsor, the Sponsor will allow the Investigator 30 days for full review of the manuscript before publication. Such manuscript or materials should be provided for Sponsor review in accordance with the specifications in the clinical trial agreement.

17 References

Aldinucci D, Olivo K, Lorenzon D, et al. The role of interleukin-3 in classical Hodgkin's disease. Leukemia Lymphoma 2005; 46(3):303-311.

Aldinucci D, Poletto D, Gloghini A, et al. Expression of functional interleukin-3 receptors on Hodgkin and Reed-Sternberg cells. Am J Pathol 2002; 160(2):585-596.

Alfonso A, Montalban-Bravo G, Takahashi K, et al. Natural history of chronic myelomonocytic leukemia treated with hypomethylating agents. Am J Hematol. 2017;92(7):599-606.

Arai N, Homma M, Abe M, et al. Impact of CD123 expression, analyzed by immunohistochemistry, on clinical outcomes in patients with acute myeloid leukemia. International Journal of Hematology 2019; 109(5):539–544.

Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-405.

Barbui T, Tefferi A, Vannucchi AM, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. Leukemia. 2018;32(5):1057-1069.

Barosi G, Tefferi A, Besses C, et al. Clinical end points for drug treatment trials in BCR-ABL1-negative classic myeloproliferative neoplasms: consensus statements from European LeukemiaNET (ELN) and International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT). Leukemia. 2015;29(1):20-6.

Black JH, McCubrey JA, Willingham MC, et al. Diphtheria toxin-interleukin-3 fusion protein (DT(388)IL3) prolongs disease-free survival of leukemic immunocompromised mice. Leukemia 2003; 17(1):155-159.

Boquet P, Silverman MS, Pappenheimer AM, Jr, Vernon WB. Binding of triton X-100 to diphtheria toxin, crossreacting material 45, and their fragments. Proc Natl Acad Sci U S A. 1976; 73(12): 4449-53.

Brunetti L, Di Battista V, Venanzi A, et al. Blastic plasmacytoid dendritic cell neoplasm and chronic myelomonocytic leukemia: a shared clonal origin. Leukemia. 2017;31(5):1238-1240.

Chauhan D, Ray A, Das DS, et al. Effect of a novel agent, SL-401, targeting interleukin-3 receptor (IL-3R) on plasmacytoid dendritic cell (pDC)-induced myeloma cell growth and osteolytic bone disease. Proc Am Soc Clin Oncol 2014; 32(15S):563s (A8599).

Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the international working group (IWG) response criteria in myelodysplasia. Blood 2006; 108(2): 419-425.

Collier RJ and Kandel J. Structure and activity of diphtheria toxin. I. Thiol-dependent dissociation of a fraction of toxin into enzymically active and inactive fragments. J Biol Chem. 1971;246(5): 1496-503.

Coston T, Pophali P, Vallapureddy R. Suboptimal response rates to hypomethylating agent therapy in chronic myelomonocytic leukemia; a single institutional study of 121 patients. Am J Hematol. 2019;94(7):767-779.

Desai A, Yan Y, Gerson SL. Concise Reviews: Cancer Stem Cell Targeted Therapies: Toward Clinical Success. Stem Cells Transl Med. 2019;8(1):75-81.

Donovan JJ, Simon MI, Draper RK, and Montal M. Diphtheria toxin forms transmembrane channels in planar lipid bilayers. Proc Natl Acad Sci U S A 1981;78(1): 172-6.

Drazin R, Kandel J, Collier RJ. Structure and activity of diphtheria toxin. II. Attack by trypsin at a specific site within the intact toxin molecule. J Biol Chem 1971;246(5):1504-10.

Duchmann M, Braun T, Micol JB, et al. Validation of response assessment according to international consortium for MDS/MPN criteria in chronic myelomonocytic leukemia treated with hypomethylating agents. Blood Cancer J. 2017 May 12;7(5):e562.

Economides MP, McCue D, Lane AA, Pemmaraju N. Tagraxofusp, the first CD123-targeted therapy and first targeted treatment for blastic plasmacytoid dendritic cell neoplasm. Expert Rev Clin Pharmacol. 2019;12(10):941-946.

Facchetti F, Cigognetti M, Fisogni S. Neoplasms derived from plasmacytoid dendritic cells. Mod Pathol. 2016;29(2):98-111.

Florian S, Sonneck K, Hauswirth AW, et al. Detection of molecular targets on the surface of CD34+/CD38-- stem cells in various myeloid malignancies. Leukemia Lymphoma 2006; 47:207-222.

Frankel EF, 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(3): 385–392.

Frolova O, Frankel AE, Korchin B, et al. IL3R-Directed Agents, SL-401 and SL-501, Inhibit the Growth of Leukemia Stem cells in CML. Blood (ASH Meeting Abstracts) 2010 116: Abstract 3403.

Gagelmann N, Ditschkowski M, Bogdanov R, et al. Comprehensive clinical-molecular transplant scoring system for myelofibrosis undergoing stem cell transplantation. Blood. 2019;133(20):2233-2242.

Germing U, Kündgen A, Gattermann N.Risk assessment in chronic myelomonocytic leukemia (CMML). Leuk Lymphoma. 2004;45(7):1311-8.

Gesner TG1, Mufson RA, Norton CR, et al. Specific binding, internalization, and degradation of human recombinant interleukin-3 by cells of the acute myelogenous, leukemia line, KG-1. J Cell Physiol. 1988;136(3):493-9.

Gordon VM, Klimpel KR, Arora N, et al. Proteolytic activation of bacterial toxins by eukaryotic cells is performed by furin and by additional cellular proteases. Infect Immun. 1995;63(1): 82-7.

Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med 2012; 366:787-98.

Harrison CN, Mesa RA, Kiladjian JJ, et al. Health-related quality of life and symptoms in patients with myelofibrosis treated with ruxolitinib versus best available therapy. Brit J Haem. 2013;162(2):229-239.

Honjo T, Nishizuka Y, Hayaishi O. Diphtheria toxin-dependent adenosine diphosphate ribosylation of aminoacyl transferase II and inhibition of protein synthesis. J Biol Chem. 1968;243(12): 3553-5.

Itzykson R, Fenaux P, Bowen D, et al. Diagnosis and Treatment of Chronic Myelomonocytic Leukemias in Adults: Recommendations From the European Hematology Association and the European LeukemiaNet. HemaSphere 2018;2(6):e150.

Itzykson R, Kosmider O, Renneville A, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. J Clin Oncol. 2013;31(19):2428-36.

Jen EY, Gao X, Li L, et al. FDA approval summary: Tagraxofusp-erzs for treatment of blastic plasmacytoid dendritic cell neoplasm. Clin Cancer Res. 2020;26(3):532-536.

Ji P, Peterson LC. Plasmacytoid dendritic cells in chronic myelomonocytic leukemia. Blood. 2014;123(21):3220.

Jordan CT, Guzman ML, Noble M. Cancer Stem Cells. N Engl J Med 2006; 355:1253-1261.

Jordan CT, Upchurch D, Szilvassy SJ, et al. The interleukin-3 receptor alpha chain is a unique marker for human acute myelogenous leukemia stem cells. Leukemia 2000; 14:1777-1784.

Kagan BL, Finkelstein A, Colombini M. Diphtheria toxin fragment forms large pores in phospholipid bilayer membranes. Proc Natl Acad Sci U S A. 1981; 78(8): 4950-4.

Kochi SK, Collier RJ. DNA fragmentation and cytolysis in U937 cells treated with diphtheria toxin or other inhibitors of protein synthesis. Exp Cell Res 1993;208(1): 296-302.

Konopleva M, Contractor R, Tsao T, et al. Mechanisms of apoptosis sensitivity and resistance to the BH3 mimetic ABT-737 in acute myeloid leukemia. Cancer Cell. 2006;10(5):375-88.

Krishnan A, Li B, Pagane M, et al. Evaluation of Combination Tagraxofusp (SL-401) and Hypomethylating Agent (HMA) Therapy for the Treatment of Chronic Myelomonocytic Leukemia (CMML). Blood. 2018 132:1809.

Lagadinou ED, Sach A, Callahan K, et al. BCL-2 inhibition targets oxidative phosphorylation and selectively eradicates quiescent human leukemia stem cells. Cell Stem Cell. 2013;12(3):329-41.

Lhermitte L, de Labarthe A, Dupret C, et al. Most immature T-ALLs express Ra-IL3 (CD123): possible target for DT-IL3 therapy. Leukemia 2006; 20:1908-1910.

Loghavi S, Sui D, Wei P, et al. Validation of the 2017 revision of the WHO chronic myelomonocytic leukemia categories. Blood Adv. 2018;2(15):1807-1816.

Lucas N, Duchmann M, Rameau P, et al. Biology and prognostic impact of clonal plasmacytoid dendritic cells in chronic myelomonocytic leukemia. Leukemia. 2019;33(10):2466-2480.

Mani B, Goswami S, Gopalakrishnan B, et al. The interleukin-3 receptor CD123 targeted SL-401 mediates potent cytotoxic activity against CD34+CD123+ cells from acute myeloid leukemia/myelodysplastic syndrome patients and healthy donors. Haematologica 2018;103(8):1288-1297.

Moyo TK, Savona MR. Therapy for Chronic Myelomonocytic Leukemia in a New Era. Curr Hematol Malig Rep. 2017;12(5):468-477.

Mughal T, Padron E, Savona M, et al. Myelodysplastic/myeloproliferative neoplasms (MDS/MPN): an international perspective and recommendations on molecular pathogenesis and clinical characterization. Haematologica 2015;100(9):1117-30.

Mughal TI, Pemmaraju N, Radich JR, et al. Emerging translational science discoveries, clonal approaches, and treatment trends in chronic myeloproliferative neoplasms. Hematological Oncology 2019;37(3):240-252.

Munoz L, Nomdedeu JF, Lopez O, et al. Interleukin-3 receptor alpha chain (CD123) is widely expressed in hematologic malignancies. Haematologica 2001; 86:1261-1269.

Naresh KN, Pavlu J. Plasmacytoid dendritic cell nodules in bone marrow biopsies of chronic myelomonocytic leukemia. Am J Hematol. 2010;85(11):893.

Niyongere S, Lucan N, Zhou JM, et al. Heterogeneous expression of cytokines accounts for clinical diversity and refines prognostication in CMML. Leukemia 2019; 33:205–216.

Padron E, Dezern A, Andrade-Campos M, et al. A Multi-Institution Phase I Trial of Ruxolitinib in Patients with Chronic Myelomonocytic Leukemia (CMML). Clin Cancer Res. 2016;22(15):3746-54.

Padron E, Komrokji R, List AF. The clinical management of chronic myelomonocytic leukemia. Clin Adv Hematol Oncol. 2014;12(3):172-8.

Pardanani A. Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management. Am J Hematol. 2019;94(3):363-377.

Park S, Labopin M, Yakoub-Agha I, et al. Allogeneic stem cell transplantation for chronic myelomonocytic leukemia: a report from the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. Eur J Haematol. 2013;90(5):355-64.

Patnaik MM, Tefferi A. Chronic myelomonocytic leukemia: 2016 update on diagnosis, risk stratification, and management. Am J Hematol. 2016;91(6):631-42.

Pophali P, Horna P, Lasho TL, et al. Splenectomy in patients with chronic myelomonocytic leukemia: Indications, histopathological findings and clinical outcomes in a single institutional series of thirty-nine patients. Am J Hematol. 2018;93(11):1347-1357.

Prager BC, Xie Q, Bao S, Rich JN.Cancer Stem Cells: The Architects of the Tumor Ecosystem. Cell Stem Cell. 2019;24(1):41-53.

Ramos F, Fernandez-Ferrero S, Suarez D, et al. Myelodysplastic syndrome: a search for minimal diagnostic criteria. Leuk Res 1999; 23:283-290.

Rapoport AP, Luhowskyj S, Doshi P, DiPersio JF. Mutational analysis of the alpha subunit of the human interleukin-3 receptor. Blood. 1996;87(1): 112-22.

Ratts R, Trujillo C, Bharti A, et al. A conserved motif in transmembrane helix 1 of diphtheria toxin mediates catalytic domain delivery to the cytosol. Proc Natl Acad Sci U S A. 2005; 102(43):15635-40.

Ratts R, Zeng H, Berg EA, et al. The cytosolic entry of diphtheria toxin catalytic domain requires a host cell cytosolic translocation factor complex. J Cell Biol. 2003;160(7): 1139-50.

Ricci C, Fermo E, Corti S, et al. RAS mutations contribute to evolution of chronic myelomonocytic leukemia to the proliferative variant. Clin Cancer Res. 2010;16(8):2246-56.

Savona MR, Malcovati L, Komrokji R, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood. 2015;125(12):1857-65.

Selimoglu-Buet D, Wagner-Ballon O, Saada V, et al. Characteristic repartition of monocyte subsets as a diagnostic signature of chronic myelomonocytic leukemia. Blood 2015;125(23), 3618-3626.

Shen Q, Ouyang J, Tang G, et al. Flow cytometry immunophenotypic findings in chronic myelomonocytic leukemia and its utility in monitoring treatment response. Eur J Haematol. 2015;95(2):168-76.

Stevens BM, Zhanga W, Pollyeaa DA, et al. CD123 CAR T cells for the treatment of myelodysplastic syndrome. Exp Hematol 2019;74:52-63,e3.

Tamari R, Mughal TI, Rondelli D, et al. Allo-SCT for myelofibrosis: reversing the chronic phase in the JAK inhibitor era? Bone Marrow Transplant. 2015 May;50(5):628-36.

Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: international working group – myeloproliferative neoplasms research and treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. Blood 2013B; 122:1395-98.

Tefferi A. Challenges facing JAK inhibitor therapy for myeloproliferative neoplasms. N Engl J Med 2012; 366:844-46.

Tefferi A. Primary myelofibrosis: 2013 update on diagnosis, risk-stratification, and management. Am J Hematol 2013A; 88:142-150.

Tehranchi R, Woll PS, Anderson K, et al. Persistent malignant stem cells in del(5q) myelodysplasia in remission. N Engl J Med 2010; 363:1025-1037.

Thiele J, Kvasnicka HM, Facchetti F, et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica 2005; 90(8):1128-1132.

Tsuneoka M, Nakayama K, Hatsuzawa K, et al. Evidence for involvement of furin in cleavage and activation of diphtheria toxin. J Biol Chem. 1993;268(35): 26461-5.

Valent P, Orazi A, Savona MR, et al. Proposed diagnostic criteria for classical CMML, CMML variants and pre-CMML conditions. Haematologica 2019. doi: 10.3324/haematol.2019.222059 [Epub ahead of print].

van Rhenen A, Feller N, Kelder A, et al. High stem cell frequency in acute myeloid leukemia at diagnosis predicts high minimal residual disease and poor survival. Clin Cancer Res 2005; 11:6520-6527.

Vergez F, Green AS, Tamburini J, et al. High levels of CD34+CD38low/-CD123+ blasts are predictive of an adverse outcome in acute myeloid leukemia: a Groupe Ouest-Est des Leucemies Aigues et Maladies du Sang (GOELAMS) study. Haematologica 2011; 96:1792-1798.

Vermi W, Facchetti F, Rosati S, et al. Nodal and extranodal tumor-forming accumulation of plasmacytoid monocytes/interferon-producing cells associated with myeloid disorders. Am J Surg Pathol. 2004 May;28(5):585-95.

Vermi W, Soncini M, Melocchi L, et al. Plasmacytoid dendritic cells and cancer. J Leukoc Biol. 2011;90:681-690.

Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxlitinib for myelofibrosis. N Engl J Med 2012; 366:799-807.

Woo J, Choi DR, Sorer BE, et al. Allogeneic hematopoietic cell transplantation (HCT) for chronic myelomonocytic leukemia: Clinical, Cytogenetic, and Mutational Risk Factors Associated with survival. Haematologica 2020;105(3):652-660.

Yan B, Chen Q, Shimada K, et al. Histone deacetylase inhibitor targets CD123/CD47-positive cells and reverse chemoresistance phenotype in acute myeloid leukemia. Leukemia. 2019;33(4):931-944.

Zhang H, Wilmot B, Bottomly D, et al. Genomic landscape of neutrophilic leukemias of ambiguous diagnosis. Blood. 2019;134(11):867-879.

18 Appendices

18.1 Disease-specific Response Criteria

Table 6: Stage 2: Revised IWG-MRT and ELN Response Criteria for MF

Response categories	Required criteria (for all response categories, benefit must last for ≥12 weeks to qualify as a response)
CR	Bone marrow [1]: Age-adjusted normocellularity; < 5% blasts; ≤ Grade 1 MF [2] and Peripheral blood: Hemoglobin ≥ 100 g/L and < ULN; neutrophil count ≥ $1x10^9$/L and < ULN; Platelet count ≥ $100x10^9$/L and < ULN; < 2% immature myeloid cells[3] and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
PR	Peripheral blood: Hemoglobin ≥100 g/L and < ULN; neutrophil count ≥$1x10^9$/L and < ULN; Platelet count ≥$100x10^9$/L and < ULN; < 2% immature myeloid cells[3] and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or Bone marrow[1]: Age-adjusted normocellularity; < 5% blasts; ≤ Grade 1 MF[2] and Peripheral blood: Hemoglobin ≥85g/L but < 100g/L and < ULN; neutrophil count ≥$1×10^9$/L and < ULN; platelet count ≥$50×10^9$/L but < $100×10^9$/L and < ULN; < 2% immature myeloid cells[3] and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Clinical improvement (CI)	The achievement of anemia, spleen or symptom response without progressive disease or increase in severity of anemia, thrombocytopenia or neutropenia[4]
Anemia response	Transfusion independent patients: a ≥ 20g/L increase in hemoglobin level[5] Transfusion dependent patients: becoming transfusion independent[6]
Spleen response[7]	A baseline splenomegaly that is palpable 5-10cm below the LCM, becomes not palpable[8] or A baseline splenomegaly that is palpable > 10cm below the LCM, decreases by ≥ 50%[8] A baseline splenomegaly that is palpable < 5cm below the LCM is not eligible for spleen response A spleen response requires confirmation by MRI or CT showing ≥ 35% spleen volume reduction
Symptom response	A ≥ 50% reduction in the MPN-SAF TSS[9]
Progressive disease[10]	Appearance of new splenomegaly that is palpable at least 5cm below the LCM or A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or A 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm or Leukemic transformation confirmed by a bone marrow blast count of ≥ 20% or A peripheral blast content of ≥20% associated with an absolute blast count of ≥$1x10^9$/L that lasts for at least 2 weeks
Stable disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR or CI, or Loss of anemia response persisting for at least 1 month or

Response categories	Required criteria (for all response categories, benefit must last for ≥12 weeks to qualify as a response)
	Loss of spleen response persisting for at least 1 month
Cytogenetic remission	At least 10 metaphases must be analyzed for cytogenetic response evaluation and requires confirmation by repeat testing within a 6-month window CR: eradication of a preexisting abnormality PR: ≥ 50% reduction in abnormal metaphases (partial response applies only to patients with at least 10 abnormal metaphases at baseline)
Molecular remission	Molecular response evaluation must be analyzed in peripheral blood granulocytes and requires confirmation by repeat testing within a 6-month window CR: eradication of a preexisting abnormality PR: ≥50% decrease in allele burden (partial response applies only to patients with at least 20% mutant allele burden at baseline)
Cytogenetic/molecular relapse	Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing

Adapted from Tefferi, et al. Blood 2013; 122(8):1395-98.

EMH: extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven nonhematosplenic EMH). LCH: left costal margin. ULN: upper limit of normal.

1 Baseline and posttreatment bone marrow slides are to be interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.

2 Grading of MF is according to the European classification. Thiele et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica 2005; 90: 1128.
It is underscored that the consensus definition of a CR bone marrow is to be used only in those patients in which all other criteria are met, including resolution of leukoerythroblastosis. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.

3 Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, < 5% immature myeloid cells is allowed.

4 See above for definitions of anemia response, spleen response, and progressive disease. Increase in the severity of anemia constitutes the occurrence of new transfusion dependency or a ≥ 20 g/L decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the CTCAE version 4.03. In addition, assignment to CI requires a minimum platelet count of ≥ 25×10^9/L and absolute neutrophil count of ≥$0.5x10^9$/L.

5 Applicable only to patients with baseline hemoglobin of < 100g/L. In patients not meeting the strict criteria for transfusion dependency at the time of study enrollment (see as follows), but have received transfusions within the previous month, the pretransfusion hemoglobin level should be used as the baseline.

6 Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of pRBCs in the 12 weeks prior to study enrollment, for a hemoglobin level of < 85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any pRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥85g/L.

7 In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy.

8 Spleen or liver responses must be confirmed by imaging studies where a ≥35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.

9 Symptoms are evaluated by the MPN-SAF TSS. The MPN-SAF TSS is assessed by the patients themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/bad as it can be) for each item. The MPN-SAF TSS is the summation of the individual scores (0-100 scale). Symptom response requires ≥50% reduction in the MPN-SAF TSS.

10 Progressive disease assignment for splenomegaly requires confirmation by MRI or CT showing a ≥25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to posttreatment measurements.

Grading of Myelofibrosis

MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal BM.
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas.
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis.[1]
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis.[1]

Adapted from Arber et al, Blood 2016; 127(20): 2391-2405

Semiquantitative grading of BM fibrosis (MF) with minor modifications concerning collagen and osteosclerosis. Fiber density should be assessed only in hematopoietic areas.

1. In grades MF-2 or MF-3 an additional trichrome stain is recommended.

Table 7: Stage 2: Modified IWG Response Criteria for Altering Natural History of MDS (Including CMML)

Category	Response criteria (response must last at least 4 weeks)
Complete remission	Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines(1) Persistent dysplasia will be noted[1,2] Peripheral blood[3]: Hemoglobin ≥11g/dL Platelets ≥100×10^9/L Neutrophils ≥1.0×10^9/L[2] Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥50% but still > 5% Cellularity and morphology not relevant
Bone Marrow CR(2)	Bone marrow ≤5% myeloblasts and decrease by ≥50% over pretreatment[2] Peripheral blood: If hematologic improvement responses, they will be noted in addition to marrow CR[2]
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets Reduction in Hemoglobin concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic response	Complete: Disappearance of the chromosomal abnormality without appearance of new ones Partial: At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts 5-10% blasts: ≥ 50% increase to > 10% blasts 10-20% blasts: ≥ 50% increase to > 20% blasts 20-30% blasts: ≥ 50% increase to > 30% blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hemoglobin by ≥ 2 g/dL Transfusion dependence
Survival	Endpoints: Overall: death from any cause Event free: failure or death from any cause PFS: disease progression or death from MDS DFS: time to relapse Cause-specific death: death related to MDS

Adapted from Cheson, et al. Blood 2006; 108(2):419-25.

Deletions to the IWG response criteria are not shown. To convert hemoglobin from g/dL to g/L, multiply g/dL by 10.

MDS: myelodysplastic syndromes. Hgb: hemoglobin. CR: complete remission. HI: Hematologic improvement. PR: partial remission. FAB: French-American-British. AML: Acute myeloid leukemia. PFS: Progression-free survival. DFS: Disease-free survival.

1 Dysplastic changes should consider the normal range of dysplastic changes (modification) (Ramos 1999)

2 Modification to IWG response criteria

3 In some circumstances, protocol therapy may require the initiation of further treatment (e.g., consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Table 8: Stage 3A: 2015 MDS/MPN Response Criteria (Savona 2015)

Criteria for measurement of treatment response in adult MDS/MPN

CR (presence of all of the following improvements)[1]

- Bone marrow:
  - ≤ 5% myeloblasts (including monocytic blast equivalent in case of CMML)
  - Normal maturation of all cell lines and return to normal cellularity[1]
  - Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤ grade 1 fibrosis)[2]
- Peripheral blood[3]
  - WBC ≤ 10×10^9 cells/L
  - Hgb ≥ 11 g/dL
  - Platelets ≥ 100×10^9/L; ≤ 450×10^9/L
  - Neutrophils ≥ 1.0×10^9/L
  - Blasts 0%
  - Neutrophil precursors reduced to ≤ 2%
  - Monocytes ≤ 1×10^9/L
- Extramedullary disease: Complete resolution of extramedullary disease present before therapy (e.g. cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly
- Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia[1]

Note: Provisional category of CR with resolution of symptoms is removed from the original criteria.[3]

Complete cytogenetic remission

- Resolution of previously present chromosomal abnormality (known to be associated with myelodysplastic, syndrome myeloproliferative neoplasms, or MDS/MPN), as seen on classic karyotyping with minimal of 20 metaphases or FISH[4]

Partial remission

- Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining > 5% of cellularity except in cases of MDS/MPN with ≤ 5% bone marrow blasts at baseline

Marrow response

- Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above
- Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining > 5% of cellularity, or reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 months apart

Criteria for measurement of treatment response in adult MDS/MPN

Clinical benefit

Requires 1 of the following in the absence of progression or CR/partial response and independent of marrow response (response must be verified at ≥ 8 weeks) to be considered a clinical benefit. (Note: "Cord blood response" was corrected to "response".)

- Erythroid response
  - Hgb increase by ≥ 2.0 g/dL
  - Transfusion independence for ≥ 8 weeks for patients requiring at least 4 packed red blood cell transfusions in the previous 8 weeks
  - Only red blood cell transfusions given based on physician's judgement for a pretreatment Hgb of ≤ 8.5 g/dL will count in the red blood cell TI response evaluation[5]
- Platelet response
  - Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 weeks
  - Pretreatment ≤ 20×10^9/L: increase from < 20×10^9/L to > 20×10^9/L and by at least 100%
  - Pretreatment > 20×10^9/L but ≤ 100×10^9/L: absolute increase of ≥ 30×10^9/L[5]
- Neutrophil response
  - Pretreatment ≤ 0.5×10^9/L, at least 100% increase and an absolute increase ≥ 0.5×10^9/L
  - Pretreatment, > 0.5×10^9/L and ≤ 1.0×10^9/L, at least 50% increase and an absolute increase ≥ 0.5×10^9/L[5]
- Spleen response
  - Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable
- Symptom response (improvement in symptoms as noted by decrease of ≥ 50% as per the MPN-SAF TSS scoring < 20 were not considered eligible for measuring clinical benefit)[6]

1 Presence of dysplastic changes, which may be interpreted within the scope of normal range of dysplastic changes, may still exist in the presence of CR as allowed in MDS IWG. Marrow should exhibit age-adjusted normocellularity in CR.

2 If there is no significant fibrosis present on the initial bone marrow biopsy, a second biopsy is not required to prove resolution of fibrosis. Grading of fibrosis in measurement of treatment response should be according to the European Consensus System (Thiele 2005).

3 Given the current lack of a validated tool to assess complete resolution of symptoms in MDS/MPN, "CR with resolution of symptoms" (a complete resolution of disease-related symptoms as noted by the MPN-SAF TSS in presence of CR) will be a provisional category of disease response.

4 Loss of cytogenetic burden of disease (via FISH or classic karyotyping) known to adversely affect prognosis is required to reach complete cytogenetic remission. Decrease in the cytogenetic burden of disease must be by ≥ 50% (via FISH or classic karyotyping) to be indicative of a partial cytogenetic response. Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on the performance characteristics of the specific probes used.

5 Resolution of abnormal peripheral blood counts must persist for at least 2 separate analyses over at least 8 weeks. In the case of proliferative MDS/MPN, CR will include resolution of thrombocytosis to a normal platelet count ($150\text{-}450\times10^9$/L) and resolution of leukocytosis to WBC ≤10×10^9 cells/L but ≥1.5×10^9/L. Hemoglobin should be maintained >11 g/dL and platelets ≥100×10^9/L without the support of transfusions. Clinical benefit may occur when these changes occur in absence of other changes required for CR or marrow response. Platelet and packed red blood cell TI would be considered for clinical benefit, and duration of TI should be monitored. Reduction in myeloid precursors (promyelocytes, myelocytes, metamyelocytes, nucleated red blood cells) to less than appreciable levels (≤ 2-3%) and/or 1 x 10^9/L monocytosis in the absence of infection, cytokine treatment, or other reactive causes.

6 MPN-SAF TSS validation among patients with MDS/MPN is currently under way (R.A. Mesa, personal communication, 2014).

Criteria for measurement of disease progression in adult MDS/MPN

Combination of 2 major criteria, 1 major and 2 minor criteria, or 3 minor criteria from list

Major criteria

- Increase in blast count[1]
  - < 5% blasts: ≥ 50% increase and to > 5% blasts
  - 5-10% blasts: ≥ 50% increase and to > 10% blasts
  - 10-20% blasts: ≥ 50% increase and to > 20% blasts
  - 20-30% blasts: ≥ 50% increase and to > 30% blasts [2]
- Evidence of cytogenetic evolution[3]
  - Appearance of a previously present or new cytogenetic abnormality in complete cytogenetic remission via FISH or classic karyotyping.
  - Increase in cytogenetic burden of disease by ≥ 50% in partial cytogenetic remission via FISH or classic karyotyping.
- New extramedullary disease.
  - Worsening splenomegaly:

    Progressive splenomegaly that is defined by IWG-MRT: the appearance of a previously absent splenomegaly that is palpable at > 5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of > 10 cm

    Extramedullary disease outside of the spleen to include new/worsening hepatomegaly, granulocytic sarcoma, skin lesions, etc.

Minor criteria

- Transfusion dependence[4]
- Significant loss of maximal response on cytopenias ≥ 50% decrement from maximum remission/response in granulocytes or platelets
- Reduction in Hgb by ≥ 1.5 g/dL from best response or from baseline as noted on complete blood count
- Increasing symptoms as noted by increase in ≥ 50% as per the MPN-SAF TSS[5]
- Evidence of clonal evolution (molecular)[6]

1 Blasts as measured from the bone marrow.

2 Patients with development of acute myeloid leukemia from MDS/MPN; 20-30% blasts may be allowed on some clinical trials for patients with MDS/MPN.

3 Increase in cytogenetic burden of disease by ≥ 50% (via FISH or classic karyotyping). Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on specific probes used.

4 Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the past month for a hemoglobin level < 8.5 g/dL that was not associated with clinically overt bleeding. Cytopenia resulting from therapy should not be considered in assessment of progression.

5 MPN-SAF TSS validation among patients with MDS/MPN is currently under way (R.A. Mesa, personal communication, 2014).

6 The identification of new abnormalities using single nucleotide polymorphism arrays or sequencing or a clearly significant increase in mutational burden of a previously detected abnormality. Precise criteria for defining new abnormalities and what exactly constitutes a significant increase in mutational burden are open to interpretation; we suggest that this criterion should be used conservatively based on current evidence.

The hematology community has recognized that a lack of a stable disease category in the 2015 MDS/MPN IWG criteria creates considerable uncertainty in the categorization of patients on any CMML study. Therefore, the stable disease category defined as those patients not belonging to any of the defined categories in the 2015 criteria has been added as response criteria for CMML patients.

18.2 ECOG Performance Status

The ECOG performance status scale, with corresponding Karnofsky performance status score equivalents, is presented in Table 9.

Table 9 Eastern Cooperative Oncology Group Performance Status Scale, with Equivalent Karnofsky Performance Status Scores

ECOG[1]		Karnofsky[2]	
Score	**Criterion**	**%**	**Criterion**
0	Normal activity	100	Normal; no complaints; no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms but ambulatory	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self; unable to carry on normal activity or do active work
2	In bed < 50% of time	60	Requires occasional assistance but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of time	40	Disabled, requires special care and assistance
		30	Severely disabled; hospitalization is indicated though death is not imminent
4	100% bedridden	20	Very sick; hospitalization is necessary
		10	Moribund; fatal processes progressing rapidly
5	Dead	0	Dead

1 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

2 Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. Cancer. 1984;53:2002-2007.

18.3 CLS Management Guidance

Time of Presentation	CLS Sign/Symptom	Recommended Action	Tagraxofusp Dosing Management
Prior to first dose of tagraxofusp in Cycle 1	Serum albumin < 3.2 g/dL	Administer tagraxofusp when serum albumin ≥ 3.2 g/dL.	
During tagraxofusp 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 tagraxofusp 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 sign/symptom or as clinically indicated.	

[1] 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.