Tagraxofusp is being investigated for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN). Previously known as natural killer (NK) cell leukaemia/lymphoma, BPDCN was categorized by the World Health Organization under acute myeloid leukaemia (AML) but now has its own separate designation under myeloid neoplasms. BPDCN is a rare blood cancer derived from the precursors of cells called plasmacytoid dendritic cells.

Tagraxofusp is a fusion protein formed by combining interleukin-3 (IL-3) and truncated diphtheria toxin (DT). It causes inactivation of protein synthesis, and death of the target cell. Treatment for BPDCN has included therapies that are used for AML, acute lymphoblastic leukaemia (ALL), or lymphoma. If licensed, tagraxofusp will offer the first prospectively studied treatment option for BPDCN for which there are limited treatment options and a significant unmet medical need.
PROPOSED INDICATION

Treatment naïve and previously treated patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).a

TECHNOLOGY

DESCRIPTION

Tagraxofusp (SL-401/Elzonris) is a recombinant fusion protein containing the full-length human interleukin-3 (IL-3) coupled to the catalytic (C) and translocation (T) domains of a truncated diphtheria toxin (DT) via a Met-His linker. BPDCN blasts overexpress the IL-3 receptor α (IL-3R α or CD123). The IL-3 domain of tagraxofup binds to CD123 receptor, which is then internalised, leading to translocation of the DT-A fragment to the cytosol, followed by adenosine diphosphate (ADP) ribosylation of elongation factor 2, inactivation of protein synthesis, and apoptosis of the target cell.1

Tagraxofusp is being developed for the treating patients with treatment naïve and previously treated patients with BPDCN. The registrational phase I/II clinical trial (NCT02113982) was conducted in 3 stages. A cycle of therapy is 21 days. Stage 1 was a dose-escalation stage. During stages 2-3, patients were treated at the maximum tested dose at which multiple dose limiting toxicities are not observed during stage 1.2 Stage 4 was for continued access to the treatment for patients with first-line or relapsed/refractory BPDCN. 12ug/kg/day is the recommended dose. b

INNOVATION AND/OR ADVANTAGES

The mechanism of tagraxofusp cytotoxicity differs from other available therapeutics, and because tagraxofusp inhibits protein synthesis, the agent is able to kill relatively dormant blast cells. Furthermore, the tagraxofusp payload DT is not a substrate for P-glycoprotein and other drug efflux pumps that are associated with multidrug resistance.1

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Tagraxofusp does not currently have Marketing Authorisation in the EU for any indication.3

- Tagraxofusp is a designated orphan drug in the EU in November 2015 for the treatment of BPDCN4 and AML.c
- Tagraxofusp was designated Breakthrough Therapy for the treatment of BPDCN by the FDA in August 2016.5
- A biologics license application was accepted by the US FDA for tagraxofusp in June 2018 and granted priority review.6

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a Information provided by company
b Information provided by company
c Information provided by company
Tagraxofusp is in phase I/II development for AML in first complete remission (CR) with minimal residual disease, advanced high risk myeloproliferative neoplasms (MPN) and relapsed/refractory multiple myeloma in combination with pomalidomide.7

# PATIENT GROUP

## DISEASE BACKGROUND

Blastic plasmacytoid dendritic cell neoplasm (BPDCN), previously known as natural killer (NK) cell leukaemia/lymphoma, was categorised by the World Health Organization under acute myeloid leukaemia (AML) but now has its own separate designation under myeloid neoplasms.8 BPDCN is a rare, clinically aggressive haematological malignancy derived from the precursors of plasmacytoid dendritic cells and characterised by co-expression of CD123, CD4 and CD56. The aetiology of BPDCN is unknown.9

BPDCN usually presents with cutaneous lesions with or without bone marrow involvement. Patients typically present with asymptomatic, solitary or multiple skin lesions that can be variable in size (from a few millimeters to 10 centimeters), shape and colour, and can appear as nodules, plaques or bruise-like infiltrates. The skin lesions can be associated with erythema, hyperpigmentation, purpura or ulceration lymphadenopathy, and splenomegaly. Cytopenias due to bone marrow involvement can be present at diagnosis or may occur at disease progression.9

## CLINICAL NEED AND BURDEN OF DISEASE

There are no formal studies on the incidence of BPDCN in the general population. In addition, the exact prevalence of BPDCN is difficult to estimate due to regular changes in disease nomenclature. The available European data reported in 2004 that its overall incidence is extremely low, accounting from 0.44% of all haematological malignancies to 0.7% of cutaneous lymphomas. Predominantly males are affected, with a sex ratio of 2.5:1. The clinical course of BPDCN is aggressive, with a reported median overall survival (OS) ranging from 12 to 16 months. The disease usually occurs in elderly patients, with a median age between 60 and 70 years.9,10

In 2015, blastic plasmacytoid dendritic cell neoplasm affected approximately 1.2 in 10,000 people in the European Union (EU).4 Applying this figure to the 2017 mid-year population of England and Wales, the estimated population affected with BPDCN in England and Wales comes to 7,049.

According to the Hospital Episodes Statistics data for England, in 2016-2017 there were 66 admissions which led to 42 day cases and 432 FCE bed days due to blastic NK cell lymphomas (ICD-10 code: C86.4).11

# PATIENT TREATMENT PATHWAY

## PATIENT PATHWAY

The clinical course of BPDCN is aggressive.9 Treatment has included therapies that are used for AML, acute lymphoblastic leukaemia (ALL), or lymphoma.9 No prognostic models are available to tailor therapy to individual cases. Consequently, no standardised therapeutic approach has been
established yet and the optimal therapy remains to be defined. In patients with isolated cutaneous disease at the onset, the efficacy of skin-directed therapies, such as surgical excision, focal radiation therapy and systemic steroids, has been evaluated in several studies. These approaches can be initially effective and may lead to the complete resolution of cutaneous lesions, but do not appear to provide a long-term benefit. Systemic relapse occurs within about 6–9 months. However, the skin-directed therapeutic approach can be a reasonable palliative option for elderly patients or those who are not eligible for systemic intensive chemotherapy.⁹

CURRENT TREATMENT OPTIONS

Prior to the release of the tagraxofusp pivotal clinical trial there have been no data or clinical trials that can define the best first treatment for patients with BPDCN.¹²

Empirical chemotherapies employed in the past for either first-line or relapsed/refractory BPDCN have been shown to carry generally poor outcomes with respect to responses, safety, tolerability, and survival.¹³,¹⁴ Treatment may have included therapies used for AML, length for which a patient responds to these treatments is usually short. After a relapse, second remissions with conventional chemotherapy are difficult to achieve. Allogeneic haematopoietic stem cell transplant (allo-HCT), especially if offered in first remission, may result in longer remissions. The current recommendation is for BPDCN patients to be evaluated for an allo-HCT as soon as possible and to begin searching for a donor.⁸ Standard frontline therapy has not been established for patients with advanced-stage BPDCN; thus, participation in a clinical trial should be encouraged.¹³

PLACE OF TECHNOLOGY

If licensed, tagraxofusp may offer an option for patients with treatment naïve and previously treated patients with BPDCN.

CLINICAL TRIAL INFORMATION

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02113982, STML-401-0114; tagraxofusp; phase I/II</th>
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<tr>
<td>Sponsor</td>
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<tr>
<td>Status</td>
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</tr>
<tr>
<td>Source of</td>
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<td>Design</td>
<td>Non-randomised, single group assignment, open label</td>
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<tr>
<td>Participants</td>
<td>n=120 (planned); aged 18 years and older; AML or BPDCN</td>
</tr>
<tr>
<td>Schedule</td>
<td>The trial was conducted in 3 stages. A cycle of therapy is 21 days. Stage 1 was a dose-escalation stage. During stages 2-3, patients are treated at the maximum tested dose at which multiple dose limiting toxicities are not observed during stage 1. 12ug/kg/day is the recommended dose.</td>
</tr>
</tbody>
</table>

FOR CONTEXT:
• Stage 1: a lead-in dose escalation stage that enrolls both first-line and R/R BPDCN, R/R AML and high-risk AML patients
• Stage 2: an expansion stage that enrolls first-line and R/R BPDCN patients (and R/R AML patients) who receive tagraxofusp at the
Follow-up

Primary Outcomes

Secondary Outcomes

Key Results

Adverse effects (AEs)

Expected reporting date

ESTIMATED COST

The cost of tagraxofusp is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

• No relevant guideline identified

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE


OTHER GUIDANCE

• No relevant guideline identified

REFERENCES

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Information provided by company
Blood Available/HLA criteria neoplasm of Organization Biology, The
NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.