Tagraxofusp (Elzonris®) in blastic plasmacytoid dendritic-cell neoplasm (BPDCN)

General information

Drug description [1]	Indication [2]
Tagraxofusp (SL-401) is a CD123-directed cytotoxin consisting of human interleukin-3 fused to truncated diphtheria toxin.	Tagraxofusp is indicated as monotherapy for the first-line treatment of adult patients with BPDCN.

Current treatment [3]

- 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.
- 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.
- Treatment may have included therapies used for acute myeloid leukaemia (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.
- Standard frontline therapy has not been established for patients with advanced-stage BPDCN; thus, participation in a clinical trial should be encouraged.

Regulatory status

EMA [2, 4]	FDA [5, 6]
Approval status for this indication: On 12 November 2020, the CHMP adopted a positive opinion following a re-examination procedure, recommending the granting of a marketing authorisation for the medicinal product Elzonris®, intended for the treatment of BPDCN. UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 07/01/2021 The full indication is: ❖ Tagraxofusp is indicated as monotherapy for the first-line treatment of adult patients with BPDCN. **Other indications**: none ✓ **Orphan status** ✓ **Medicine under additional monitoring** ✓ **Marketing authorisation under exceptional circumstances**	**Approval status for this indication**: On 21 December 2018, the FDA approved tagraxofusp-erzs, for BPDCN in adults and in paediatric patients 2 years and older. **Other indications**: none

Costs [7]

Elzonris® concentrate for solution for infusion 1 mg/ml = € 24,600.00 (ex-factory price)

Posology [8]

- Tagraxofusp should be administered under the supervision of a physician experienced in the use of anti-cancer agents.
- Appropriate resuscitation equipment should be available.
- The first cycle of Elzonris® should be administered in the in-patient setting. Patients should be monitored for signs and symptoms of hypersensitivity or capillary leak syndrome until at least 24 hours after the last infusion.
- **Pre-medication:**
  - Patients should be pre-medicated with a H1-histamine antagonist (e.g. diphenhydramine hydrochloride), a H2-histamine antagonist (e.g. ranitidine), a corticosteroid (e.g. 50 mg intravenous methylprednisolone or equivalent) and paracetamol approximately 60 minutes prior to the start of infusion.

Warnings and precautions [8]

- **Traceability:** In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- **Capillary leak syndrome** (CLS):
  - CLS, including life-threatening and fatal cases have been reported with most events occuring during the first five days of the first cycle of treatment.

- The most frequent signs and symptoms of CLS included weight increased, hypoalbuminemia and hypotension.
- The incidence of weight increased, hypoalbuminemia, hypotension, and blood alkaline phosphatase increased are all higher among patients who experienced CLS compared to patients that did not experience CLS. Renal failure and acute kidney injury have been reported in two patients with BPDCN and in one patient with AML secondary to CLS.
- Before initiating therapy, ensure that the patient has adequate cardiac function and serum albumin ≥ 3.2 g/dL. During treatment, regularly monitor serum albumin levels prior to the initiation of each dose, or more often as clinically indicated. Additionally, assess patients for other signs/symptoms of CLS including weight gain, new onset or worsening oedema, including pulmonary oedema, and hypotension including haemodynamic instability.
- Patients should be made aware of identifying CLS symptoms and when to seek immediate medical attention. Intravenous albumin supplementation and dosing interruptions may be required.

❖ **Hypersensitivity reactions**:
- Severe hypersensitivity reactions have been reported with Tagraxofusp.
- Commonly reported reactions include rash (generalised / maculo-papular); wheezing; pruritus; angioedema; swelling face; and flushing.
- Monitor patients for hypersensitivity reactions during treatment. Depending on the severity and the required interventions, temporarily withhold treatment and resume after symptoms have resolved.

❖ **Haematological abnormalities**:
- Thrombocytopenia and neutropenia have been reported in patients treated with tagraxofusp monotherapy.
- The majority of events were reported in cycle 1 and cycle 2 of treatment, were not dose-limiting and did not recur in subsequent cycles.
- Patients should be routinely monitored and treated as clinically indicated.

❖ **Tumour lysis syndrome**:
- Tagraxofusp can cause tumour lysis syndrome (TLS), which may be fatal as a result of its rapid anti-tumour activity.
- Identify TLS based on clinical presentation and symptoms, including acute renal failure, hyperkalaemia, hypocalcaemia, hyperuricaemia, or hyperphosphataemia from tumour lysis.
- Patients considered at high risk for TLS due to high tumour burden should be managed as clinically indicated, including correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care.

❖ **Hepatotoxicity:**
- Treatment with tagraxofusp has been associated with elevations in liver enzymes.
- Acute hepatic failure and liver encephalopathy has been reported in a patient treated with tagraxofusp at a higher dose (16 mcg/kg).
- During treatment, regularly monitor ALT and AST levels prior to the initiation of each dose. Temporarily withhold treatment if transaminases rise to greater than 5 times the upper limit of normal and resume treatment when transaminase elevations are ≤ 2.5 times the upper limit of normal.

❖ **Choroid plexus lesions**:
- Choroid plexitis was identified during non-clinical studies.
- While not observed in clinical studies, if clinical symptoms or signs suggestive of central nervous system (CNS) damage occur, full neurological examination is advised.

❖ **CNS-involved BPDCN**:
- The passage of tagraxofusp through the blood brain barrier is unknown. Other treatment alternatives should be considered if CNS disease is present.

❖ **Women of childbearing potential/contraception:**
- In women of childbearing potential, a negative pregnancy test should be obtained within 7 days prior to initiation of therapy. Effective contraception should be used before the first dose is administered and for at least one week after the last dose.

❖ **Hereditary fructose intolerence**:
- Patients with hereditary fructose intolerance (HFI) must not be given this medicinal product unless strictly necessary. A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

❖ **Sodium sensitivity:**
- This medicinal product contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially 'sodium-free'.

Study characteristics [1, 8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)

NCT02113982, STML-401-0114	47	Tagraxofusp (IV) at a dose of 7 µg or 12 µg/kg of body weight on days 1 to 5 of each 21-day cycle	-	Combined rate of complete response and clinical complete response among patients who had not received previous treatment for BPDCN	single-arm, non-randomized, multistage, open-label, multicenter	-	Stemline Therapeutics and the Leukemia and Lymphoma Society Therapy Acceleration Program	[1]

Efficacy (I vs. C)	**Safety** (I vs. C)
Combined rate of complete response and clinical complete response (assessed in 13 patients who were enrolled in stage 3): 54% (95% CI, 25-81). **Combined rate of complete response and clinical complete response** (in 29 patients who had not been previously treated and had who received the higher dose of tagraxofusp, 12 µg per kilogram): 72% (95% CI, 53-87). **Median time until response**: 43 days (range, 14-131) **Overall response rate** (partial response or better): 90%. **Median duration of the primary outcome:** not reached at the time of this analysis **Median duration of follow-up:** 19 months (range, 1-42). 13 of the 29 previously untreated patients (45%) were successfully **bridged to stem-cell transplantation** while they were in remission after treatment with tagraxofusp. At the time of the analysis (median follow-up, 25 months), **survival probabilities** in this group were 59% at 18 months and 52% at 24 months. **Results in previously treated patients (n=15)** **Overall response rate:** 67% (95% CI, 38-88). **Median time until response**: 24 days (range, 17-48), with a median duration of response of 2.8 months (range, 0.7-14.0). **1** previously treated patient who had disease remission while receiving tagraxofusp underwent **allogeneic stem-cell transplantation.** Median duration of **OS**: 8.5 months **UPDATE:** **Confirmatory cohort, n=13:** **CR/CRc[1] rate:** 54% (95% CI, 25.1-80.8) **Median duration of CR/CRc[2], months:** NE **Overall response rate:** 77% (95% CI, 46.2-95.0) **Bridge to stem cell transplant, rate:** 46% (95% CI, 19.2-74.9) **Median OS:** 18.9 (5.2-NE) **12-month survival:** 53.8% (95% CI, 24.8-76.0) **18-month survival:** 53.8% (95% CI, 24.8-76.0) **24-month survival:** 46.2% (95% CI, 19.2-69.6) **Treatment-naïve BPDCN, n=65**	**No previous treatment (n=32):** **Grade ≥3 AEs**: n=25/32 (78%) **SAEs:** n=13/32 (41%) **Death[4]:** n=2/32 (6%) **Previous treatment (n=15):** **Grade ≥3 AEs:** n=13/15 (87%) **SAEs:** n=10/15 (67%) **Death[5]**: n=1/15 (7%) Among the 44 patients who received the higher dose of tagraxofusp (12 µg/kg), **CLS** was reported in 8 (18%); of these patients, 6 (14%) had a grade 2 event, 1 (2%) had a grade 4 event, and 1 (2%) had a grade 5 event (death). One additional death occurred in a patient who had received tagraxofusp at a dose of 7 µg/kg before the implementation of additional safety measures[6].

[1] CRc=clinical complete response; defined as complete response with residual skin abnormality not indicative of active disease.

[2] Duration of CR/CRc includes patients bridged to stem cell transplantation.

[4] From any cause

[5] From any cause

[6] After this death during stage 1, the protocol was amended to provide mitigation strategies, including a requirement of normal cardiac function to participate in the study and thresholds for early signs of capillary leak syndrome within a treatment cycle.

CR/CRc rate: 57% (44.0-62.9) **Median duration of CR/CRc[3], months:** 7.3 **Overall response rate:** 75% (95% CI, 63.1-85.2) **Bridge to stem cell transplant, rate:** 32% (95% CI, 21.2-45.1) **Median OS:** 12.3 (9.3-35.9) **12-month survival:** 52.2% (95% CI, 38.5-64.2) **18-month survival:** 48.2% (95% CI, 34.6-60.5) **24-month survival:** 40.9% (95% CI, 27.5-53.9)	

Risk of bias - study level (case series) [9]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	yes	yes	partial	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	no	yes	yes	yes	yes

Overall risk of bias: moderate

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Abbreviations: AE=adverse event, AJ=adjustment, AML=acute myeloid leukaemia, allo-HCT=allogeneic haematopoietic stem cell transplant, ALT=alanin-aminotransferase, AST=aspartate transaminase, BPDCN=blastic plasmacytoid dendritic-cell neoplasm, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CLS= Capillary Leak Syndrome, CR=complete response, CRc=clinical complete response, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HFI=hereditary fructose intolerance, HR=hazard ratio, I=intervention, Int.=intention, IV=intravenous, MG=median gain, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TLS=tumour lysis syndrome,

References:

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[3] Duration of CR/CRc includes patients bridged to stem cell transplantation.

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