Report loncastuximab tesirine - Zynlonta®

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: loncastuximab tesirine **Brand Name:** Zynlonta **Originator/licensee:** ADC Therapeutics (NL) B.V **Classification:** NCE **ATC code:** L01FX22 **Orphan Status:** **Eu:** Yes **Us:** Yes **Mechanism of action:** loncastuximab tesirine is a monoclonal antibody and drug conjugate that delivers SG3199, a PBD dimer cytotoxin, to B-cell malignancies by targeting CD19. Upon binding to CD19, loncastuximab tesirine is internalised and SG3199 is released, resulting in the formation of highly cytotoxic DNA interstrand cross-links, which cause cell-death [1].	**Authorized Indication:** **EMA:** loncastuximab tesirine as monotherapy is indicated for the treatment of adult patients with relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy [1]. **FDA:** loncastuximab tesirine is a CD19-directed antibody and alkylating agent conjugate indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low grade lymphoma, and HGBL [2]. **Route of administration:** IV **Licensing status** **EU CHMP P.O. date:** 15/07/2022 **FDA M.A. date:** 23/01/2021 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** No **-----** **ABBREVIATIONS:** **AE:** adverse event **CHMP**: Committee for Medicinal Products for Human Use **CI:** confidence interval **DLBCL**: Diffude large B-cell lymphoma **ECOG**: Eastern Coperative Oncology Group **HGBL**: high-grade B-cell lymphoma **M.A.**: marketing authorization **NHL:** Non-Hodgkin's lymphoma **ORR:** Overall Response Rate **PBD:** pyrrolobenzodiazepine **Pts**: patients **SAE:** serious adverse event **TEAE**: treatment emergent adverse events	**Summary of clinical EFFICACY:** LOTIS-2 (NCT03589469) were a multicenter, open-label, single-arm, phase II trial in pts aged ≥ 18 years with relapse or refractory DLBCL after two or more multiagent systemic treatments, who had measurable disease and ECOG performance status 0-2. The primary endpoint was ORR, defined as the proportion of pts with best overall response of complete or partial response*. Eligible pts (*n*=145) received loncastuximab tesirine ev on day 1 of each 21-day cycle, at 150 µg/kg for two cycles, then 75 µg/kg thereafter, for up to 1 year or until disease relapse or progression, unacceptable toxicity, death, major protocol deviation, pregnancy, or patient, investigator, or sponsor decision. 70 of 145 pts had complete or partial response (overall response rate 48.3% [95% CI 39.9 – 56.7]); 35 had complete response and 35 had partial response [3]. *according to the 2014 Lugano classification, assessed by central review. **Summary of clinical SAFETY:** At least one TEAE was reported in 143 (99%) of 145% pts. The most common grade 3 or higher TEAEs were neutropenia (37 [26%] of 145 pts), thrombocytopenia (26 [18%]), and increased gamma-glutamyltransferase (24 [17%]). At least one serious TEAE was reported in 57 (39%) of 145 pts; 22 (15%) pts had SAEs that were considered at least possibly related to loncastuximab tesirine, the most common of which were febrile neutropenia (four [3%]), anaemia (two [1%]), pleural effusion (two [1%]), non-cardiac chest pain (two [1%]) and pericardial effusion (two [1%]). 77 (53%) of 145 pts died during the study period. Most deaths (60 [78%] of 77) were due to disease progression; five (6%) of 77 pts died from fatal TEAEs (all of which were considered unrelated or unlikely to be unrelated to treatment) and 12 (16%) died after the AE reporting period [3]. **Ongoing studies:** • ***For the same indication:*** Yes • ***For other indications:*** Yes [7]. **Discontinued studies (for the same indication):** No	**Cost of therapy:** The estimated cost of loncastuximab tesirine is not yet known. **Epidemiology:** DLBCL is the most common subtype of NHL: one in three cases of NHL is represented by DLBCL. Pts usually respond to first-line treatments, however in 40% of the cases the disease is recurrent [4]. The crude incidence for DLBCL in Europe is 3.8/100 000/year [5]. ----- **POSSIBLE PLACE IN THERAPY** Currently, there are 3 FDA-approved autologous CAR-T cell products for the treatment of relapsed or refractory large B-cell lymphoma after ≥2 lines of systemic therapy: axicabtagene ciloleucel (axi-cel, Yescarta®), tisagenlecleucel (tisa-cel, Kymriah®), and lisocabtagene maraleucel (liso-cel, Breyanzi®) [6]. **OTHER INDICATIONS IN DEVELOPMENT** Non-Hodgkin's lymphoma, Diffuse large B cell lymphoma, Follicular lymphoma, Mantle-cell lymphoma, Marginal zone B-cell lymphoma, Post-transplant lymphoproliferative disorder [7]. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** No **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Axicabtagene ciloleucel *Service reorganization: No *Possible off label use: Yes ----- **References:** [1]. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/zynlonta [2]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761196s000lbl.pdf [3]. https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S147020452100139X.pdf?locale=it_IT&searchIndex= [4].https://www.osservatoriomalattierare.it/i-tumori-rari/altri-tumori-rari/14242-linfoma-diffuso-a-grandi-cellule-b-benefici-duraturi-dalla-terapia-con-polat uzumab-vedotin [5] https://www.annalsofoncology.org/article/S0923-7534(19)47184-6/pdf [6]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8172085/pdf/nihms-1699512.pdf [7]. https://adisinsight.springer.com/drugs/800044648

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