Report DARZALEX® daratumumab

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: daratumumab **Brand Name:** Darzalex® **Originator/licensee:** Janssen-Cilag International NV **Classification:** NI **ATC code:**L01XC24 **Orphan Status:** **Eu:** Yes **Us:** Yes **Mechanism of action:**daratumumab is an IgG1κ human mAb that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity [1].	**Authorized Indication:** **EMA:**daratumumab is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult pts with newly diagnosed systemic ALamyloidosis [2]. **FDA:** daratumumab, in a SC formulation with hyaluronidase, is indicated for the treatment of AL amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone in newly diagnosed pts [3]. **Route of administration:** SC **Licensing status** **EU CHMP P.O. date:**20/05/2021 **FDA M.A. date:** 15/01/2021 **EU Speed Approval Pathway:** Yes **FDA Speed Approval Pathway:** Yes ----- **ABBREVIATIONS:** **AL:** Amyloid Light-chain **ASCT:** Autologous Stem Cell Transplant **BMDex**: Bortezomib + melphalan + dexamethasone **BMPC:** Bone Marrow Plasma Cell (%) **CD38:** Cluster of Differentiation 38 **CHMP:** Committee for Medicinal Products for Human Use **CI:** Confidence Interval **CHR:** Complete Hematologic Response **CR:** Complete Response **CyBorD:** Cyclophosphamide + bortezomib + dexamethasone **IgG1κ**: Humanized Immunoglobulin G, subclass 1, κ light chain **ITT:** Intention-To-Treat **IV:** Intravenous **M.A.:** Marketing Authorization **mAb:** monoclonal Antibody **OR:** Odds ratio **PC:** Plasma Cell **P.O.:** Positive Opinion **pts:** patients **QW:** every week **Q2W:** every two weeks **Q4W:** every four weeks **SC:** Subcutaneous **TEAEs:** Treatment-Emergent Adverse Events **VGPR:** Very Good Partial Response **vs.**: versus	**Summary of clinical EFFICACY:** **ANDROMEDA (NCT03201965):** is a randomized, open label, multicenter, phase III study with a run-in phase.It was conducted to determine the safety and efficacy of daratumumab SC in combination with CyBorD compared with CyBorD alone, for the treatment of adult pts with newly diagnosed AL amyloidosis.Approximately 388 pts were randomized in a 1:1 ratio to receive CyBorD with or without SC daratumumab. *Comparator arm:(n=193)* ● **CyBorD**: dexamethasone (40 mg orally or IV dose) + cyclophosphamide (300 mg/m^2 orally or IV dose) + bortezomib (1.3 mg/m^{2}SC injection) weekly on day 1, 8, 15, 22 in every 28-day cycle for a maximum of six cycles. *Experimental arm: (n=195)* ●**CyBorD:** dexamethasone (20 mg orally or IV dose as premedication and 20 mg on the day after daratumumab dosing) + cyclophosphamide (300 mg/m^2 orally or IV dose weekly) + bortezomib (1.3 mg/m^{2}SC injection weekly) on day 1, 8, 15, 22 in every 28-day cycle for a maximum of six cycles. ● **Daratumumab:** 1800 mg SC weekly for the first eight weeks (two cycles), then Q2W for four cycles (cycles 3-6), and then Q4W until progression of disease or subsequent therapy for a maximum of two years. The primary endpoint was overall CHR*rate by ITT for up to 2.4 years from the randomization. CHR isdefined as percentage of participants who achieved CHR, according to the International Amyloidosis Consensus Criteria. Pts treated with daratumumab + CyBorD achieved a 53.3% CHR (95% CI,46.1 to 60.5), whilepts treated with CyBorD alone achieved a 18.1% CHR (95% CI, 13.0to 24.3). The study met its primary endpoint (OR = 5.1, 95% CI 3.2 to 8.2, p < 0.0001) [4-5]. **Summary of clinical SAFETY:** The most common grade 3/4 TEAEs occurring in more than 5% of pts for the experimental arm compared to the CyBorD arm included lymphopenia (13% vs. 10%), pneumonia (8% vs. 4%), diarrhoea (6% vs. 4%), cardiac failure (6% vs. 5%), neutropenia (5% vs. 3%), syncope (5% vs. 6%) and peripheral edema (3% vs. 6%).Serious cardiac events were reported by 16% of pts.A total of 56 deaths occurred: 27 in the daratumumab + CyBorD arm, 29 in the CyBorD arm [4-5]. **Ongoing studies:** ● ***For the same indication:*** Yes ● ***For other indications:*** Yes **Discontinued studies (for the same indication):**No **References:** 1. https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf 2. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/darzalex-2 3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761145s002lbl.pdf 4. https://adisinsight.springer.com/trials/700285080 5. https://clinicaltrials.gov/ct2/show/NCT03201965?term=NCT03201965&draw=2&rank=1 6. https://www.drugs.com/price-guide/darzalex-faspro 7. https://pubmed.ncbi.nlm.nih.gov/17951308/ 8. https://ashpublications.org/blood/article/136/23/2620/474251/Management-of-AL-amyloidosis-in-2020 9. https://link.springer.com/content/pdf/10.1007/s11899-020-00574-5.pdf 10. https://clinicaltrials.gov/ct2/results?cond=&term=&type=Intr&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=daratumumab&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= 11. https://clinicaltrials.gov/ct2/results?cond=AL+Amyloidosis&term=&type=Intr&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=	**Economic impact:** The price (USA) for daratumumab 1,800 mg, 15 mL, is $8,296.30 [6]. The price for one cycle of therapy (administered QW for 28 days) is: $ 33,185.2 **Epidemiology:** It is estimated that in Italy there are about 800 new cases of amyloidosis every year[7]. ----- **POSSIBLE PLACE IN THERAPY** First line treatment is recommended with combination chemotherapy regimens similar to those used in myeloma but typically using dexamethasone. Proteasome inhibitor-based regimens are a preferred choice due to better response rates and outcomes in phase II studies and a bortezomib-alkylator-steroid combination is preferred where a rapid response is desirable (cardiacinvolvement, renal impairment, severe hypoalbumina-emia, fluid retention) **- Low-risk pts, eligible for ASCT:**ASCT preceded by high-dose melphalan is the most definitive PC–directedtherapy. For induction therapy, bortezomib (if BMPC>10%) is recommended. For suboptimal responses post-ASCT(if <VGPR/CR) bortezomib-based "consolidation" therapy should be considered. **-Intermediate-risk pts, ineligible for ASCT, cardiac stage I-IIIa:** CyBorD + daratumumab (if not accessible, consider either CyBorD or BMDex). **-High-risk pts:** CyBorD + daratumumab with an intensive monitoring during therapy [8-9]. **OTHER INDICATIONS IN DEVELOPMENT** Plasma Cell Myeloma, Systemic Lupus Erythematosus, Lupus Nephritis, Refractory T-Cell Lymphoma, Relapsed T-Cell Lymphoma[10]. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:**- **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** doxycycline; daratumumab + pomalidomide; ixazomib + cyclophosphamide + dexamethasone [11]. *Service reorganization Y/N No *Possible off label use Y/N Yes

*CHR means a normalization of free AL levels and ratio, negative serum, and urine immunofixation.

Issued on May 2021