Glasdegib (Daurismo®) with low-dose cytarabine (LDAC) in patients with newly diagnosed acute myeloid leukaemia (AML)

General information [1]

Drug description	Indication
Glasdegib is an antineoplastic agent (inhibitor of the Hedgehog signal transduction pathway)	in combination with LDAC for the treatment of newly diagnosed de novo or secondary AML in adult patients who are not candidates for standard induction chemotherapy

Current treatment [2]

- ❖ Chemotherapy is the main treatment for AML
- ❖ The treatment is in two phases:
  - Induction: usually the patient is given two or more different chemotherapy drugs in cycles of treatment (the 2 main drugs are cytarabine and daunorubicin)
  - Consolidation: Combinations of chemotherapy can be used in this phase, these include amsacrine, high dose cytarabine, etoposide, daunorubicin, fludarabine, idarubicin. Some patients have high dose chemotherapy and then a bone marrow or stem cell transplant.
- ❖ NICE pathways for AML recommends azacitidine as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have AML with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification and if the manufacturer provides azacitidine with the discount agreed as part of the patient access scheme. Azacitidine is not recommended, within its marketing authorisation, for treating AML with more than 30% bone marrow blasts in people of 65 years or older who are not eligible for haematopoietic stem cell transplant.

Regulatory status

EMA [1]	FDA [3]
Approval status for this indication: On 30 April 2020, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Daurismo®. **UPDATE:** Date of issue of marketing authorisation valid throughout the European Union: 26/06/2020 Daurismo® is indicated, in combination with LDAC, for the treatment of newly diagnosed de novo or secondary AML in adult patients who are not candidates for standard induction chemotherapy. **Other indications**: none ✓ **Orphan status** ✓ **Medicine under additional monitoring**	**Approval status for this indication**: approved (11/2018) Daurismo® is indicated, in combination with LDAC, for the treatment of newly-diagnosed AML in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy **Other indications**: none

Costs

Currently no cost information available.

Study characteristics [4-6]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
BRIGHT 1003 NCT01546038	132[1]	**Glasdegib 100 mg** (once daily orally in 28-day cycles on a continuous basis) + **LDAC 20 mg** (subcutaneously twice daily for 10 days every 28 days)	**LDAC 20 mg** (subcutaneously twice daily for 10 days every 28 days)	OS	open-label, multicentre (Europe, North America) phase II study	-	Pfizer Inc.	Link

Efficacy (I vs. C)

Median OS in AML study population: 8.3 (6.6–9.5) months vs. 4.3 (2.9–4.9) months, HR 0.46 (95% CI, 0.29–0.71, p=0.0002)

Safety (I vs. C)

Any AE grade 3-4: n=54/84 (64.3%) vs. n=23/41 (56.1%)
SAEs: n=66/84 (78.6%) vs. n=32/41 (78.0%)
Any AE grade 5: n=24/84 (28.6%) vs. n=17/41 (41.5%)

[1] AML patients: n=116; MDS-patients: n=16

Median OS in de novo AML study population: 6.6 months vs. 4.3 months, HR 0.67 (95%CI, 0.36-1.24, p=0.0991 **Median OS in secondary AML study population:** 9.1 months vs. 4.1 months, HR 0.287 (95%CI, 0.15-0.55, p< 0.0001**CR:** n=15/88 (17.0%) vs. 1/44 (2.3%) achieved CR (p<0.05) **ORR in the AML population:** 26.9% (21/78) vs. 5.3% (2/38)	I: 1 pneumonia (1.2%) was considered as treatment-related Grade 5 AE. C: 1 sepsis (2.4%) was considered as treatment-related Grade 5 AE. **Discontinuation:** n=30/84 (35.7%) vs. 19/41 (46.3%) permanently discontinued study treatments due to AEs, with n=9/84 (10.7%) vs. n=3/41 (7.3%) discontinuing due to treatment-related (per investigator's assessment) AEs

ESMO-MCBS version 1.1

Not applicable

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	-	open-label	yes	yes[2]	high risk

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Abbreviations: AE=adverse event, AML=acute myeloid leukaemia, CHMP=Committee for Medicinal Products for Human Use, CI= confidence interval, CR=complete remission, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, HR=hazard ratio, LDAC=low-dose cytarabine, MDS=myelodysplastic syndrome, n=number, SAE=serious adverse event, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, QoL=quality of life

References:

1. European Medicines Agency (EMA). Medicines. Daurismo. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/daurismo.
2. National Institute for Health Research (NIHR). Glasdegib for Acute Myeloid Leukaemia (AML) – first line [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/migrated_new/11424-Glasdegib-in-combination-with-chemotherapy-for-Acute-Myeloid-Leukaemia-AML.pdf.
3. U.S. Food and Drug Administration (FDA). Drugs@FDA. Daurismo. Label information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210656s002s004lbl.pdf.
4. Cortes J, et al. Randomized Comparison of Low Dose Cytarabine With or Without Glasdegib in Patients With Newly Diagnosed Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome. Supplementary Materials. [Available from: https://www.nature.com/articles/s41375-018-0312-9#Sec18.
5. Cortes JE, Heidel FH, Hellmann A, Fiedler W, Smith BD, Robak T, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia (2019) 33:379–389.
6. European Medicines Agency (EMA). Daurismo: EPAR - Product Information [Available from: https://www.ema.europa.eu/en/documents/product-information/daurismo-epar-product-infomartion_en.pdf.

[2] Industry-funded; phase II, small sample-size