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Glasdegib for Acute Myeloid Leukaemia (AML) – first line

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LAY SUMMARY

Acute myeloid leukaemia (AML) is an aggressive type of blood cancer that starts from certain types of young white blood cells called granulocytes or monocytes in the bone marrow. The bone marrow is the soft inner part of the bones, where new blood cells are made. AML usually develops over a few weeks and becomes increasingly more severe. If left untreated it would cause death with a few weeks or months. AML incidence is strongly related to age.

Glasdegib is an oral drug under development for the treatment of AML. It is a drug that has the potential to stop the growth of cancer cells. If licensed, glasdegib may offer an additional treatment option for patients with AML.

TARGET GROUP

Acute Myeloid Leukaemia (AML), (patients older than 60 years) – first line; in combination with chemotherapy

TECHNOLOGY

DESCRIPTION

Glasdegib (PF-04449913; PF-4449913) is an oral therapy that is under development for the treatment of different types of haematological malignancies including AML. It acts by inhibiting the smoothened (SMO) receptor, thereby disrupting the hedgehog (Hh) signalling pathway.[1] SMO is one of the main components of the Hh pathway, it is a heptahelical transmembrane G-protein coupled–receptor that initiates Hh cytoplasmic signalling.[2] The Hh signaling pathway plays an important role in cellular growth, differentiation and repair. Glasdegib is a small-molecule inhibitor of the Hh signaling pathway with potential antineoplastic activity.[3]

In the phase II clinical trial (NCT01546038), glasdegib is administered orally and continuously for 28-days in combination with chemotherapy in patients with AML or Myelodysplastic Syndrome.[4]

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

Glasdegib is also in phase II development for Chronic myeloid leukaemia; Colorectal cancer; Myelodysplastic syndromes; Myelofibrosis; Non-small cell lung cancer; and in Phase I/II development for Chronic myelomonocytic leukaemia.[5]

INNOVATION and/or ADVANTAGES

Glasdegib is the first SMO/Hh pathway inhibitor reported to show clinical benefit in patients with AML who are ineligible for intensive chemotherapy.[1] Therefore, if licensed, glasdegib may offer an additional treatment option for patients with AML.

DEVELOPER

Pfizer ltd

AVAILABILITY, LAUNCH or MARKETING

Glasdegib is a designated orphan drug in the USA for the treatment of AML.[6]

PATIENT GROUP

BACKGROUND

Leukaemia is cancer of the white blood cells. Acute leukaemia means it progresses rapidly and aggressively, and usually requires immediate treatment. Acute leukaemia is classified according to the type of white blood cells affected.[7] There are five types of white blood cell (leucocyte). These are divided into two main classes

- Granulocytes (includes Neutrophils, Eosinophils and Basophils)
- Agranulocytes (includes Lymphocytes and Monocytes).[8]

Acute myeloid leukaemia (AML) is a type of blood cancer that starts from young granulocytes or monocytes in the bone marrow. The bone marrow is the soft inner part of the bones, where new blood cells are made.[9]

The symptoms of AML usually develop over a few weeks and become increasingly more severe. Symptoms can include: pale skin, tiredness, breathlessness, frequent infections, unusual and frequent bleeding, such as bleeding gums or nosebleeds. In more advanced cases, AML can make the patient extremely vulnerable to life-threatening infections or serious internal bleeding.[7]

AML patient may experience a number of complications. These can be caused by the condition itself, although they can also occur as a side effect of treatment. Some of the main complications associated with AML are:[7]

- Weakened immune system: this is a common complication of AML. Even if patient's blood is restored to normal working order with treatment, many of the medications that are used to treat AML can temporarily weaken the immune system.
- Bleeding: patient will bleed and bruise more easily due to the low levels of in their blood. Bleeding may also be excessive. Serious bleeding can occur inside the skull, lung or inside the stomach.
- Infertility: many of the treatments that are used to treat AML can cause infertility. This is often temporary, but in some cases can be permanent.[7]

The causes of AML are unknown. There are a number of factors that may increase a person's risk of developing AML. The following are known risk factors of AML:[10]

- Exposure to radiation
- Smoking
- Exposure to benzene
- Cancer treatments: rarely, some anti-cancer treatments such as chemotherapy or radiotherapy can cause leukaemia.
- Blood disorders: such as myelodysplasia or myeloproliferative disorders
- Genetic disorders: such as Down's syndrome and Fanconi anaemia

CLINICAL NEED and BURDEN OF DISEASE

European age standardised incidence rates of AML in England and Wales in 2014 were 5.2 and 6.5 per 100,000 respectively. AML accounted for less than 1% of all new cancer cases in the UK, and 32% of all leukaemia types combined in 2014. AML incidence is strongly related to age, with the highest incidence rates being in older males and females. In the UK in 2012-2014, on average each year almost 6 in 10 (55%) cases were diagnosed in people aged 70 years and over. Age-specific incidence rates rise gradually from around age 40-44 years and more steeply from around age 60-64 years, with the highest rates in the 85-89 years age group in males, and the 90+ year age group in females.[11]

Acute myeloid leukaemia (AML) accounted for 2% of all cancer deaths in the UK in 2014. The European age-standardised mortality rates in the UK were 4.3 per 100,000. These rates do not differ significantly between the constituent countries of the UK for either sex.[12]

Five-year relative survival for AML in in England (14%) and Wales (12%) are similar to the average for Europe (15%). Five-year relative survival for AML in women in England (16%) is below the average for Europe (18%). No five-year survival data is available for Wales.[13]

In 2015 to 2016, there were 42,809 admissions for myeloid leukaemia (ICD-10: C92.0) in England, resulting in 122,696 bed days and 45,599 finished consultant episodes.[14]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Leukaemia (acute myeloid, relapsed, refractory) - vosaroxin (ID746). Expected publication date: TBC
- NICE technology Appraisal guidance in development. Gemtuzumab ozogamicin for untreated de novo acute myeloid leukaemia (ID982). Expected publication date: 25 July 2018.
- NICE technology appraisal in development. Midostaurin for untreated acute myeloid leukaemia (ID894). Expected publication date: 25 April 2018
- NICE technology appraisal. Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts (TA399). July 2016.
- NICE clinical guideline. Haematological cancers – improving outcomes (NG47). May 2016.
- NICE technology appraisal. Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (TA218). March 2011.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). February 2017
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

- Cancer Care Ontario. Systemic Treatment of Acute Myeloid Leukemia (AML). 2016.[15]
- London Cancer. Acute Myeloid Leukaemia Guidelines. Version 1.0. 2015-16.[16]
- European Society for Medical Oncology. Acute myeloblastic leukaemias in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2013.[17]
- Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet.[18]

CURRENT TREATMENT OPTIONS

Chemotherapy is the main treatment for AML. The treatment is in two phases:

- Getting rid of the AML (induction): usually the patient is given two or more different chemotherapy drugs in cycles of treatment. The 2 main drugs are cytarabine and daunorubicin.[19]
- Treatment to stop AML coming back (consolidation): When there are no signs of the leukaemia, it is in remission. The patient gets treatment to stop it coming back (consolidation). Combinations of chemotherapy can be used in this phase. These include: amsacrine, high dose cytarabine, etoposide, daunorubicin, fludarabine, idarubicin. Some people have high dose chemotherapy and then a bone marrow or stem cell transplant.[19]

NICE pathways for AML recommends Azacitidine as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have acute myeloid leukaemia 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.[20] Azacitidine is not recommended, within its marketing authorisation, for treating acute myeloid leukaemia with more than 30% bone marrow blasts in people of 65 years or older who are not eligible for haematopoietic stem cell transplant.[21]

EFFICACY and SAFETY

Trial	NCT01546038; adults 18 Years and older; glasdegib in combination with ARA-C (LDAC) vs glasdegib in combination with Decitabine, vs glasdegib in combination with intensive chemotherapy (Daunorubicin and cytarabine); phase II
Sponsor	Pfizer
Status	Ongoing, but not recruiting
Source of Information	Trial registry;[4] Global data.[22]
Location	EU (not UK), USA, and Canada
Design	Randomised
Participants	n= 267 (planned); aged 18 years and older; AML or Refractory Anaemia with Excess Blasts type 2 (RAEB 2) High Risk Myelodysplastic Syndrome (MDS); newly diagnosed according to the WHO 2008 Classification and previously untreated.
Schedule	Study arms are: - Experimental: Arm A (Phase 1B) glasdegib in combination with low dose ARA-C (LDAC) - Experimental: Arm B (Phase 1B) glasdegib in combination with Decitabine - Experimental: Arm C (Phase 1B) glasdegib in combination with intensive chemotherapy: glasdegib administered continuously for 28 days. Daunorubicin given using 60 mg/m2 for 3-days together with cytarabine 100 mg/m2 on days 1 through 7 followed by cytarabine 1g/m2 on days 1, 3, and 5 during 2-4 cycles of consolidation therapy. - Experimental: P2 Fit (Phase II Single Arm) glasdegib in combination with intensive chemotherapy: glasdegib administered continuously for 28 days. Daunorubicin given using 60 mg/m2 for 3-days together with cytarabine 100 mg/m2 on days 1 through 7 followed by cytarabine 1g/m2 on days 1, 3, and 5 during 2-4 cycles of consolidation therapy. - P2 Unfit (Phase 2 Randomized) Patients will be randomized 2:1 (low dose ARA-C in combination with glasdegib: low dose ARA-C alone).
Follow-up	Glasdegib administered continuously for 28 days; low dose ARA-C (LDAC) administered BID on Days 1 through 10; Decitabine given for 5-days; Daunorubicin given for 3-days;

	Follow-up duration is one year, two years, or five years depending on the outcome measures. See below.
Primary Outcomes	**Current Primary Outcome Measures** - Number of participants with Dose-limiting toxicities (DLT) [Time Frame: 1 -year] (Phase 1B) - Percentage of patients with Complete Response rate [Time Frame: 2-years] - Complete response are those with repeat bone marrow showing less than 5 percent (%) myeloblasts with normal peripheral blood values. (Phase 2 Fit) - Overall Survival (OS) [Time Frame: 48 months] Time from the start of study treatment to date of death due to any cause. (Phase 2 Unfit) **Original Primary Outcome Measures** - First cycle dose limiting toxicities [Time Frame: 1 -year] - Complete Response [Time Frame: 2-years] - Complete Response with Incomplete Blood count Recovery [Time Frame: 2-years]
Secondary Outcomes	**Current Secondary Outcome Measures** - Measure of drug exposure over the dosing interval following repeated dosing [Time Frame: 2 years] Not Specified (Phase 1B; Phase 2 Fit and Unfit) - Overall Survival (OS) [Time Frame: 48 months] Time from the start of study treatment to date of death due to any cause. (Phase 1B; Phase 2 Fit) - Percentage of patients with disease-specific efficacy for AML and MDS [Time Frame: 2 years] (Phase 2 Fit and Unfit) - Percentage of patients with Complete Response rate / Complete Response rate with incomplete blood count recovery [Time Frame: 2 years] Complete response are those with repeat bone marrow showing less than 5 percent (%) myeloblasts with normal peripheral blood values. (Phase 1B; Phase 2 Unfit); Complete response with incomplete blood count recovery are those with repeat bone marrow showing less than 5 percent (%) myeloblasts with either platelets or neutrophils not recovered. - QTc Interval [Time Frame: 2 years] (Phase 1B; Phase 2 Fit and Unfit) - Disease-related gene mutation (biomarkers) [Time Frame: 2 years] (Phase 1B; Phase 2 Fit and Unfit) - Changes in analyte levels from baseline to post-treatment (biomarkers) [Time Frame: 2 years] (Phase 1B; Phase 2 Fit and Unfit) - Changes in gene expression levels from baseline to post-treatment (biomarkers) [Time Frame: 2 years] (Phase 1B; Phase 2 Fit and Unfit) - Detectable tumor Gli1 expression (biomarkers) [Time Frame: 2 years] (Phase 1B; Phase 2 Fit and Unfit) **Original Secondary Outcome Measures** - Area under the plasma concentration versus time curve (AUC) of all study drugs [Time Frame: 2 years]

	- Peak Plasma Concentration (Cmax) of all study drugs [Time Frame: 2 years] - Cumulative Incidence of Relapse [Time Frame: 5 years] - Relapse Free Survival [Time Frame: 5 years] - Event free survival [Time Frame: 5 years] - Cumulative incidence of Death [Time Frame: 5 years] - Overall Survival [Time Frame: 5 years] - QTc Interval [Time Frame: 2 years]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as Jan 2017. Estimated Study Completion Date reported as October 2019

ESTIMATED COST and IMPACT

COST

The cost of glasdegib is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs:

☐ Other reduction in costs:

☐ Other:

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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