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HEALTH TECHNOLOGY BRIEFING
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CC-486 for maintenance therapy in acute myeloid leukaemia

NIHRIO ID	13666	**NICE ID**	9576
Developer/Company	Celgene Ltd	**UKPS ID**	642726

Licensing and market availability plans	Currently in phase III clinical trials

*COMMERCIAL IN CONFIDENCE

SUMMARY

CC-486 is being developed as a maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy (IC), and who are not candidates for or choose not to proceed to hematopoietic stem cell transplantation (HSCT). AML is a rapidly growing cancer of the blood and bone marrow caused by a DNA mutation in the stem cells. Although most patients with newly diagnosed AML will respond to IC, responses are often short-lived and overall survival is poor. Further post-remission therapy is necessary to achieve a durable remission.

CC-486 is a drug that can be incorporated into the genetic material of cells instead of their natural building-block, cytidine. It is thought to work by altering the way the cell turns genes on and off and interfering with the production of new RNA and DNA, leading to the death of rapidly dividing cancer cells that are not responsive to normal growth control mechanism. Its oral route of administration avoids injection-site reactions and may enhance patient convenience. The benefits of extended CC-486 dosing and long-term treatment are likely related to the impact on hypomethylation, potentially enhancing clinical activity of the drug by increasing exposure to cycling malignant cells. If licensed, CC-486 will provide an additional maintenance therapy options for older AML patients who achieved CR or CRi following IC and who are not candidates for or choose not to proceed to HSCT.

PROPOSED INDICATION

CC-486 is indicated as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy (IC) with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT).[a]

TECHNOLOGY

DESCRIPTION

The active component of CC-486 (azacitidine) is a cytidine nucleoside analog with a mechanism of action that involves incorporation into DNA and RNA.[1] It has a distinct pharmacokinetic/ pharmacodynamic profile from injectable azacitidine.[1,2] It is believed to exert its antineoplastic effects by multiple mechanisms including cytotoxicity on abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. Non-proliferating cells are relatively insensitive to azacitidine. Incorporation of azacitidine into DNA results in the inactivation of DNA methyltransferases, leading to hypomethylation of DNA. DNA hypomethylation of aberrantly methylated genes involved in normal cell cycle regulation, differentiation and death pathways may result in gene re-expression and restoration of cancer-suppressing functions to cancer cells.[3]

In the phase III clinical trial (QUAZAR AML-001, NCT01757535), 300 mg of CC-486 was administered once daily as a tablet during the first 14 days or 21 days (for AML relapse patients with 5-15% blasts in blood or bone marrow while) of 28-day cycles.[4,5]

INNOVATION AND/OR ADVANTAGES

Although most patients with newly diagnosed AML will achieve a first complete remission with standard IC, obtaining a durable remission necessarily requires either further (post remission) chemotherapy or allogeneic HSCT.[6] Many older patients with AML respond to intensive induction chemotherapy, but responses are often short-lived and overall survival (OS) is poor.[5] It has been shown that duration of first remission is predictive of response to salvage therapies and long-term outcomes. To improve outcomes, there is a need to prolong remissions, particularly in patients unable or unwilling to receive HSCT.[7]

CC-486 is an hypomethylating agent that allows for prolonged drug exposure during each treatment cycle to sustain therapeutic activity.[5] The antineoplastic effect of CC-486 is hypothesised to cause death of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanism.[8] CC-486 has demonstrated clinical activity in patients with haematologic malignancies.[1,5,9,10]

Oral administration of CC-486 avoids injection-site reactions and may enhance patient convenience compared with an injectable formulation. It allows for the evaluation of alternative doses and schedules, including extended dosing schedules. The benefits of extended CC-486 dosing and long-term treatment are likely related to the impact on hypomethylation.[7]

[a] Information provided by Celgene Ltd on UK PharmaScan

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

CC-486 does not currently have a marketing authorisation in the EU/UK for any indication.

On 1 September 2020, CC-486 was approved by the Food Drug Administration (FDA) for the continued treatment of adult patients with AML who achieved first CR or CRi following intensive IC and who are not able to complete intensive curative therapy.[11]

CC-486 is in phase III clinical development for various forms of T-cell lymphoma, myelodysplastic syndromes and in phase II trials for chronic myelomonocytic leukaemia, ovarian cancer, pancreatic cancer, nasopharyngeal cancer, non-small cell lung cancer, peripheral T-cell lymphoma, plasmacytoma and advanced solid tumors.[12]

PATIENT GROUP

DISEASE BACKGROUND

AML (also referred to as acute myelogenous leukaemia, acute myeloblastic leukaemia, acute granulocytic leukaemia, and acute nonlymphocytic leukaemia) is a rapidly growing cancer of the blood and bone marrow, with a poor prognosis if left untreated.[13] AML is caused by a DNA mutation in the stem cells in your bone marrow that produce red blood cells, platelets and infection-fighting white blood cells. The mutation causes the stem cells to produce immature white blood cells which do not have the infection-fighting properties of fully developed white blood cells.[14] As these abnormal cells build up in the blood and bone marrow, the amount of healthy red blood cells and platelets decrease. The leukaemic cells can eventually spread to other parts of the body including the lymph nodes and the spleen.[15]

The cause of genetic mutation in AML is not known, however, a number of factors may increase the risk of developing AML including radiation exposure, exposure to benzene, smoking, previous cancer treatment, blood disorders, genetic disorders, being overweight or obese and autoimmune conditions.[14,16] AML is also more common in older people. The risk of AML increases from around 50 years and is greatest in those aged between 85 and 89 years.[16]

The symptoms of AML usually develop over a few weeks, becoming more severe as the number of immature white blood cells increases.[17] Symptoms of AML include:[17,18]

- tiredness and breathlessness (anaemia) resulting from a low red blood cell count
- bleeding (such as nosebleeds) or bruising easily resulting from a low platelet count
- frequent infections resulting from abnormal white blood cell count
- general weakness
- high temperature
- weight loss
- pain in bones or joints
- sweating
- flat red or purple spots on the skin
- swollen lymph nodes
- feeling of fullness or discomfort in the abdomen
- pale skin

Outcomes for elderly patients with AML are inferior to those of younger patients. In general, there is often a higher rate of induction deaths and drug resistance, and poorer recurrence free survival (RFS) and OS. These data are confounded by co-morbid medical conditions and a reluctance to stratify those aged over 60 to appropriate risk-adapted therapy. Even in those

deemed fit enough for intensive chemotherapy, although initial CR rates of up to 50% in some studies can be obtained, relapses are common and OS is poor.[19]

Adult AML survivors who achieve CR after enduring rigorous months of induction and consolidation therapy suddenly transition into a period of "watchful waiting"— integrating back into life while not knowing if and when their cancer may recur. Survivors also face disease and treatment sequelae manifesting as medical complications, deficits in quality of life and function, and persistent symptoms.[20]

CLINICAL NEED AND BURDEN OF DISEASE

In 2017, there were 4,102 registrations of newly diagnosed cases of AML (ICD-10 code: C92) and the directly age-standardised rate per 100,000 population of newly diagnosed cases was 9.8 among males and 6.2 among females in England.[21] More than 40 out of 100 (40%) new cases are in people aged 75 and over.[15]

There are around 2,600 AML deaths in the UK every year, that's around 7 every day (2015-2017). In 2017, AML accounted for 2% of all cancer deaths in the UK with 1,100 deaths reported in females and 1,600 deaths in males.[22]

Survival statistics for people with AML diagnosed in England between 2008 and 2010 showed that younger people have a better prognosis:[23]

- In people aged between 25 and 64, almost 40 out of 100 people (almost 40%) will survive their leukaemia for 5 years or more after they are diagnosed.
- In people aged 65 or older, around 5 out of 100 people (around 5%) will survive their leukaemia for 5 years or more after diagnosis.

The 2019-2020 Hospital Episodes Statistics for England recorded a total of 60,812 finished consultant episodes (FCE) for myeloid leukaemia (ICD-10 code: C92), resulting in 56,835 hospital admissions, 141,224 FCE bed days and 45,936 day cases.[24]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The main treatment for AML is chemotherapy. Other treatments include radiotherapy, growth factors, stem cell or bone marrow transplants, and targeted cancer drugs. Supportive treatments may be needed to help with infections or side effects of treatment. These include anti-sickness medicines, painkillers, blood transfusions, platelet infusions, and antibiotics.[25]

The aim of post remission consolidation therapy is to reduce relapse risk. There is no 'standard' post-remission therapy.[19] Therapeutic strategies include consolidation chemotherapy, allogeneic transplantation, or high-dose therapy and autologous stem cell transplant. Consolidation treatment should reflect the patients' disease risk group, stem cell donor availability and patient eligibility for transplant. Patients with de novo AML with standard or favourable risk karyotype, and good performance status (ECOG 0-2) should be considered for 'curative' therapy with intensive chemotherapy. However, the optimal induction, and consolidation regimens are unknown.[26]

CURRENT TREATMENT OPTIONS

Midostaurin is recommended, within its marketing authorisation, as an option in adults for treating newly diagnosed acute FLT3-mutation-positive myeloid leukaemia with standard

daunorubicin and cytarabine as induction therapy, with high-dose cytarabine as consolidation therapy, and alone after complete response as maintenance therapy.[27]

PLACE OF TECHNOLOGY

If licensed, CC-486 will provide an additional maintenance therapy options adult AML patients who achieved CR or CRi following IC with or without consolidation treatment, and who are not candidates for or choose not to proceed to HSCT.

CLINICAL TRIAL INFORMATION

Trial	**QUAZAR AML-001;** NCT01757535; 2012-003457-28; A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Compare Efficacy and Safety of Oral Azacitidine Plus Best-supportive Care Versus Best Supportive Care as Maintenance Therapy in Subjects With Acute Myeloid Leukemia in Complete Remission **Phase III –** Active, not recruiting **Location(s):** EU (incl. UK), USA, Canada and other countries **Primary completion date:** Jul 2019
Trial design	Randomised, parallel assignment, quadruple-blinded
Population	N=472 (actual); subjects with a diagnosis of de novo AML or AML secondary to prior myelodysplastic disease or chronic myelomonocytic leukaemia (CMML), and who have achieved first Complete remission (CR)/ Complete remission with incomplete blood count recovery (CRi) following induction with or without consolidation chemotherapy; aged 55 or older
Intervention(s)	300 mg of CC-486 daily for the first 14 days of each 28 days treatment cycle; or 21 days for AML relapse patients with 5-15% blasts in blood or bone marrow while on study[5]
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: Overall Survival (OS) [Time frame: 60 months] See trial record for full list of other outcomes
Results (efficacy)	CC-486 is the first therapy used in the maintenance setting to provide statistically significant and clinically meaningful improvements in both OS and RFS in pts with AML in remission following induction chemotherapy, with or without consolidation:[5] • At a median follow-up of 41.2 months, OS was significantly improved with CC-486 *vs.* placebo (PBO): median OS was 24.7 months *vs.* 14.8 months from time of randomization, respectively (*P*=0.0009; HR 0.69 [95%CI 0.55, 0.86]). • Relapse-free survival (RFS) was also significantly prolonged: median RFS was 10.2 months in the CC-486 arm, compared with 4.8 months in the PBO arm (*P*=0.0001; HR 0.65 [95%CI 0.52, 0.81]) • OS and RFS benefits of CC-486 were demonstrated regardless of baseline cytogenetic risk, the number of

	prior consolidation cycles received, and CR/CRi status. CC-486 did not adversely impact overall health-related quality of life (HRQoL) *vs.* PBO, as assessed by mean changes from baseline in HRQoL measures during treatment.
Results (safety)	CC-486 had a manageable safety profile generally consistent with that of injectable azacitidine:[5] • Median exposure to CC-486 was 12 cycles (range 1-80) and to PBO was 6 cycles (1-73) • The most frequently reported adverse events (AEs) with CC-486 and PBO were grade 1 or 2 gastrointestinal (GI) events, including nausea (64% and 23%, respectively), vomiting (59% and 10%), and diarrhoea (49% and 21%). • The most common grade 3-4 AEs were neutropenia (CC-486, 41%; PBO, 24%), thrombocytopenia (23% and 22%), and anaemia (14% and 13%). Serious AEs were infrequent, mainly infections, which occurred in 17% of pts in the CC-486 arm and 8% of pts in the PBO arm. Few AEs led to treatment discontinuation, most often GI events (CC-486, 5%; PBO, 0.4%).

ESTIMATED COST

The estimated cost for CC-486 is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE cancer service guidance. Improving outcomes in haemato-oncology cancer. Public health guidance (CSG3). December 2009.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Guidelines for Leukaemia and other Myeloid Disorders – AML. 13-2H-106
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a

OTHER GUIDANCE

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ADDITIONAL INFORMATION

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