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HEALTH TECHNOLOGY BRIEFING
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Duvelisib for Relapsed or Refractory Chronic Lymphocytic Leukaemia

NIHRIO ID	31246	**NICE ID**	10655
Developer/Company	Secura Bio Inc	**UKPS ID**	661121

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Duvelisib is an anti-cancer drug in clinical development for adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) after at least two prior therapies. CLL is a type of cancer in which too many white blood cells are produced. As these cells develop abnormally, they are unable to function and fight infection and reduce the production of healthy blood cells. The disease is chronic and develops slowly. Treatment for CLL is complex and depends on several factors, including extent of disease, previous treatment, patient's age, symptoms, and general state of health.

Duvelisib is an oral medicinal product which acts by blocking the enzyme (a type of protein) PI3K involved in the replication and survival of cancerous B-cells (a type of immune cell) and primary CLL tumour cells. Duvelisib prolongs survival time without any progression of the disease in patients with CLL who have received two or more prior lines of treatment. If licensed, duvelisib would increase the available treatment options for relapsed or refractory CLL after at least two prior therapies.

PROPOSED INDICATION

Treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) after at least two prior therapies.[a]

TECHNOLOGY

DESCRIPTION

Duvelisib (ABBV-954, INK-1197, IPI-145, Copiktra) is an anti-neoplastic agent which acts as a strong reversible inhibitor of the isoform gamma and delta of the enzyme phosphoinositide-3-kinase (PI3K). PI3K plays a very important role in innate and adaptative immunity and the inhibition of the form delta and gamma has been very important for the suppression of immunity. The activity of PI3K gamma and delta is restricted to hematopoietic cells and it is necessary for normal B cell development. In lymphomas, the activation of PI3K is enlarged to promote unlimited growth and survival. Hence, inhibition of PI3K can provide an inhibition of the signaling from B cell receptor (BCR), inhibition of a cytokine signaling from the microenvironment and enhancement of anti-tumour immunity.[1]

Duvelisib is in clinical development for the treatment of relapsed or refractory CLL. In the phase III clinical trial (NCT02004522), patients aged 18 years and older will receive oral administration of duvelisib supplied as 5 mg and 25 mg formulated capsules.[2]

INNOVATION AND/OR ADVANTAGES

Duvelisib prolongs the survival time without any progression of the disease as compared to ofatumumab in patients with CLL who have received two or more prior lines of treatment.[3] Duvelisib is also an important option for rituximab-refractory patients. As an oral monotherapy, it reduces the need for hospital visits; displaces infusions or combinations including infusions; as well as saving substantial healthcare delivery costs per patient. Duvelisib also reduces fatigue, which is a major cause of impaired quality of life (QoL) in CLL.[a]

It has been reported that inactivation of PI3K produces a significant resistance to tumorigenesis. This data suggests that inhibition of PI3K can facilitate recognition and elimination of tumour cells.[1]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Duvelisib does not currently have Marketing Authorisation in the EU/UK for any indication.

Duvelisib has an orphan drug designation in the EU in 2013 for the treatment of chronic lymphocytic leukaemia.[4]

Duvelisib is in phase II and III clinical development for the following indications:[5]

- Refractory indolent non-Hodgkin Lymphoma.
- Indolent non-Hodgkin Lymphoma.
- COVID-19.
- Maintenance after autologous Stem Cell Transplant in T-Cell and indolent B-Cell Lymphomas.

[a] Information provided by Secura Bio Inc on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Chronic lymphocytic leukaemia (CLL) is a type of cancer that affects the blood and bone marrow.[6] In CLL, the bone marrow produces too many white blood cells (lymphocytes), which are not fully developed and do not work properly. These abnormal white blood cells stop the bone marrow from producing enough healthy blood cells, and then accumulate in the blood and certain organs, where they cause complications.[6-8] CLL tends to progress slowly over many years and over time this can cause a range of problems, such as an increased risk of picking up infections, persistent tiredness, swollen glands in the neck, armpits or groin, and unusual bleeding or bruising.[7] Relapsed CLL is the term for disease that responded to therapy but, after 6 or more months, stopped responding; and refractory disease is the term for CLL that does not result in a remission (but may be stable) or disease that gets worse within 6 months of the last treatment.[9]

The cause of CLL is unknown, however genetic mutation in the DNA of blood-producing cells can cause these blood cells to produce abnormal, ineffective lymphocytes.[8] It mostly affects people over the age of 60 and is rare in people under 40. Children are almost never affected.[7] Other factors that may increase the risk of CLL include: sex (more likely in men); race (more likely in whites); family history of blood and bone marrow cancers; and exposure to chemicals.[7,8,10]

Many people with CLL have no early symptoms. Those who do develop signs and symptoms may experience: enlarged, but painless, lymph nodes; fever; pain in the upper left portion of the abdomen, which may be caused by an enlarged spleen; night sweats, and weight loss.[8]

CLINICAL NEED AND BURDEN OF DISEASE

CLL is the most common leukaemia in the Western world with an incidence of 4.2 per 100,000 a year. The incidence increases to more than 30 per 100,000 a year at an age of >80 years.[11] Around 3,800 people are diagnosed with CLL in the UK each year.[6] The median age at diagnosis is 72 years. About 10% of CLL patients are reported to be younger than 55 years.[11]

There are around 970 CLL deaths in the UK every year, that's more than 2 everyday (2016-2018). In females and males in the UK, CLL accounted for around 380 and 570 deaths respectively in 2018. Mortality rates for CLL in the UK are highest in people aged 90+ (2016-2018).[12]

Generally, around 85 out of 100 people (around 85%) will survive their leukaemia for 5 years or more after being diagnosed. Younger people tend to do better than older people. For those younger than 60, around 95 out of 100 (around 95%) will survive their leukaemia for 5 years or more after diagnosis.[13]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for CLL is complex and depends on a number of factors, including the extent of the disease, whether it has been treated before, and the patient's age, symptoms and general state of health.[4] The treatment pathway for CLL include:[7]

- Chemotherapy
- Targeted cancer drugs
- Radiotherapy
- Stem cell or bone marrow transplantation

CURRENT TREATMENT OPTIONS

Drug therapies and treatments that can be used to treat relapsed or refractory CLL include:[9,14]

- Acalabrutinib
- Venetoclax alone or with rituximab
- Ibrutinib alone
- Idelalisib with rituximab
- Combinations of ibrutinib or venetoclax with anti-CD20 antibodies
- Allogeneic stem cell transplantation
- Alemtuzumab alone or in combination

PLACE OF TECHNOLOGY

Duvelisib offers a pharmacological treatment option for adult patients with relapsed or refractory CLL after at least two prior therapies.

CLINICAL TRIAL INFORMATION

Trial	**DUO; NCT02004522; IPI-145-07;** A Phase 3 Study of Duvelisib Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma **Phase III** – ongoing **Location(s):** US, EU, UK and other countries **Primary completion date:** May 2017
Trial design	Randomised, parallel assignment, open label
Population	N=319; Subjects with relapsed or refractory CLL or Small Lymphocytic Lymphoma (SLL); all sexes; aged 18 years and older
Intervention(s)	Duvelisib (oral) – supplied as 5mg and 25mg formulated capsules
Comparator(s)	Ofatumumab (IV) – supplied in single use vials at 100mg/5mL and 1000mg/50mL
Outcome(s)	Primary Outcome Measures : Progression-free Survival (PFS) [Time Frame: From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 3 years] See trial record for full list of outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

ESTIMATED COST

Cost of duvelisib was confidential at the time of producing this briefing.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Acalabrutinib for treating chronic lymphocytic leukaemia (TA689). April 2021.
- NICE technology appraisal. Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia (TA561). February 2019.
- NICE technology appraisal in development. Venetoclax for treating chronic lymphocytic leukaemia (TA487). November 2017.
- NICE technology appraisal. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (TA429). January 2017.
- NICE technology appraisal guidance. Idelalisib for treating chronic lymphocytic leukaemia (TA359). October 2015.
- NICE technology appraisal. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (TA193). July 2010.
- NICE technology appraisal guidance. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (TA29). September 2001.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- 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.

OTHER GUIDANCE

- London Cancer Alliance. Pan-London Haemato-Oncology Clinical Guidelines. 2020.[15]
- European Society for Medical Oncology. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2015.[16]
- British Journal of Haematology. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. 2012.[17]

ADDITIONAL INFORMATION

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