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HEALTH TECHNOLOGY BRIEFING AUGUST 2020

CC-486 for angioimmunoblastic T-cell lymphoma

NIHRIO ID	26634	**NICE ID**	10385
Developer/Company	Celgene Ltd	**UKPS ID**	Not applicable

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

CC-486 is in development for relapsed or refractory angioimmunoblastic T-cell lymphoma (AITL). AITL is a fast-growing type of T-cell Non-Hodgkin Lymphoma marked by enlarged lymph nodes and increased antibodies in the blood. Other symptoms may include a skin rash, fever, weight loss, or night sweats. AITL is more resistant to conventional chemotherapy than other forms of lymphoma and is generally associated with a poor outcome. In relapsed or refractory disease, survival durations are in the range of only a few months meaning there is unmet medical need in this patient population.

CC-486 is an oral drug that can be incorporated into the genetic material of cells (RNA and DNA) instead of their natural building-block, cytidine. It is thought to work by altering the way the cell turns genes on and off and also by interfering with the production of new RNA and DNA. This helps to correct the problems with the maturation and growth of young blood cells in the bone marrow and to kill cancerous cells in blood cancers. If licenced, CC-486 will provide an additional therapy option for AITL patients who have relapsed or become resistant to previous treatment.

PROPOSED INDICATION

Treatment of relapsed or refractory angioimmunoblastic T-cell lymphoma (AITL) in adults after at least one line of systemic therapy.[1]

TECHNOLOGY

DESCRIPTION

CC-486 (azacitidine) is an orally administered analogue of cytidine that acts as a hypomethylating agent. It has a distinct pharmacokinetic/ pharmacodynamic profile from injectable azacitidine.[2,3] 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 CC-486 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 CC-486. Incorporation of CC-486 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.[4]

In the phase III clinical trial (NCT03593018), oral azacitidine (CC-486) 300mg was administered as a tablet during the first 14 days of 28-day cycles for European patients and oral azacitidine (CC-486) 200mg was administered on the same dosing schedule to Asian patients.[1]

INNOVATION AND/OR ADVANTAGES

Compared to B-cell Non-Hodgkin Lymphoma, AITL is more resistant to conventional chemotherapy and is generally associated with a poor outcome. In case of relapsed or refractory disease, survival durations are in the range of only a few months. Several agents have been evaluated in this setting in recent years. The response rate with these agents rarely exceeds 30% and responses are usually of limited duration.[1]

CC-486 has demonstrated clinical activity in patients with haematologic malignancies.[2,5-7]

There are recurrent mutations in patients with peripheral T-cell lymphoma (PTCL) in genes that directly or indirectly regulate cytosine methylation and hydroxymethylation, and mutations of these genes result in changes in DNA methylation levels. It is thought that treatment with the hypomethylating agents such as CC-486 could be effective for the treatment of PTCL (including AITL).[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

CC-486 is in phase III clinical development for various forms of T-cell lymphoma, myelodysplastic syndromes and acute myeloid leukemia and in phase II trials for chronic myelomonocytic leukemia, acute myeloid leukemia, ovarian cancer, pancreatic, nasopharyngeal cancer, non-small cell lung cancer, peripheral T-cell lymphoma, plasmacytoma and advanced solid tumors.[9]

PATIENT GROUP

DISEASE BACKGROUND

Patients with angioimmunoblastic T-cell lymphoma (AITL), one of the most common types of peripheral T-cell lymphoma (PTCL), typically present with advanced disease, systemic symptoms, and immune deregulation. Treatment can be challenging owing to frequent relapses after initial and subsequent therapy.[10] It is a rare and aggressive (fast-growing) form of Non-Hodgkin Lymphoma, which is a group of related malignancies that affect the lymphatic system (Lymphomas).[11,12] Lymphomas are cancers of white blood cells (lymphocytes) and can be divided depending on the type of cells, B-lymphocytes (B-cells) or T-lymphocytes (T-cells), AITL is a T-cell lymphoma, specifically a subtype of mature PTCL.[12,13] The lymphatic system functions as part of the immune system and helps to protect the body against infection and disease.[12] Refractory disease does not respond to initial treatment and may get worse or stay the same. Relapsed disease responded to initial treatment but then returned.[14]

The exact, underlying cause of AITL is not fully understood. It is believed that a dysfunctional immune system response to an unknown antigen ultimately leads to the development of the disorder. No specific risk factors have been confirmed to be associated with AITL. Many people have developed the disorder following the administration of certain drugs such as antibiotics, after a viral infection, or after an allergic reaction. Suspected risk factors include several viruses including the Epstein-Barr virus, cytomegalovirus, hepatitis C virus, human herpes viruses 6 and 8, and the human immunodeficiency virus. Certain infectious agents including tuberculosis and Cryptococcus have also been linked to AITL. It is not known what role, if any, that these potential risk factors play in the development of the disorder.[12]

AILT is marked by enlarged lymph nodes and hypergammaglobulinemia (increased antibodies in the blood). Other symptoms may include a skin rash, fever, weight loss, or night sweats.[11] All organ systems can potentially be affected. Researchers believe that many of the symptoms associated with AITL result from dysfunction of the immune system rather than from complications relating to tumour growth or spread. Individuals with AITL may be prone to developing certain infections due to the suppression of the immune system. Such infections can potentially cause severe, life-threatening complications.[12]

CLINICAL NEED AND BURDEN OF DISEASE

The incidence of AITL in the general population is unknown. It is estimated to account for 1-2% of all people with Non-Hodgkin Lymphoma.[12] The annual incidence rate of AITL in the UK is 0.2/ 100,000 (HMRN 2010 - 2016)[15] however it is difficult to diagnose and treat because of the presence of both B- and T-cell clones.[16] Some reports state the AITL occurs slightly more often in men than women, but others state the ratio is 1:1. Most people develop AITL in their 60s and 70s. The disorder can occur in younger adults and, although rarely, has also been reported in children.[12] AITL carries an inverse geographic tropism than other PTCL subtypes as it is more common in Europe (28.7%) than in Asia (17.9%).[13]

In the hospital episodes statistics (HES) for England in 2018-19 there were 1,658 finished consultant episodes (FCE) and 1,480 admissions, there were 1,197 day cases and 3,444 FCE bed days with the diagnosis of AILT (ICD-10 code: C86.5).[17] In 2019, there were 25 deaths in England and Wales registered with AILT as the underlying cause of death.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Therapies used to treat individuals with AITL include corticosteroids, watch and wait, single-agent chemotherapy and multiagent chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone). The initial response to multiagent chemotherapy is often good, but the overall effectiveness has largely been inadequate. Although many individuals initially experience a remission, most will eventually experience a relapse.[12]

Autologous stem cell transplantation may be considered for people with chemosensitive PTCL (that is, there has been at least a partial response to first-line chemotherapy) who are fit enough for transplantation.[19] In the relapsed and refractory settings, allogeneic Stem Cell Transplant (SCT) offers the chance for long-term remission. Choice of treatment for relapsed or refractory disease depends on whether an allogeneic SCT is planned.[10]

CURRENT TREATMENT OPTIONS

There are no NICE recommended therapies specific to AITL.

Corticosteroids, such as prednisolone, are used to treat the symptoms of AITL that result from dysfunction of the immune system.[12]

PLACE OF TECHNOLOGY

If licenced, CC-486 will provide an additional second-line or later therapy option for adult patients with relapsed/refractory AITL.

CLINICAL TRIAL INFORMATION

Trial	**ORACLE, NCT03593018, 2017-003909-17;** Randomized Phase 3 Study Evaluating the Efficacy and the Safety of Oral Azacitidine (CC-486) Compared to Investigator's Choice Therapy in Patient With Relapsed or Refractory Angioimmunoblastic T Cell Lymphoma **Phase III** - Recruiting **Location:** United Kingdom, Austria, Belgium, Denmark, France, Finland and Sweden **Primary completion date:** Dec 2021
Trial design	Randomised, parallel assignment, open label
Population	N = 86 (planned), aged 18 years and older, relapsed (after partial or complete response) or refractory AITL after at least one line of systemic therapy
Intervention(s)	Oral azacitidine (CC-486) 300mg during day 1-14 of 28-days cycle for European patients, oral azacitidine (CC-486) 200mg during day 1-14 of 28-days cycle for Asian patients
Comparator(s)	Romidepsin 14mg/m² on days 1, 8 and 15 of a 28-days cycle (Treatment until progression, patient decision or toxicity) or Bendamustine 120mg/m² on days 1 and 2 of a 21-days cycle (during 6 cycles) or Gemcitabine 1200mg/m² on days 1, 8 and 15 of a 28-days cycle (during 6 cycles)
Outcome(s)	Primary Outcome(s): • Progression Free Survival (PFS) [Time Frame: 18 months after first randomisation (when 18 events will occur)]

	• Progression Free Survival (PFS) [Time Frame: 35 months after first randomisation (when 61 events will occur)] See trial record for full list.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

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

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Quality Standards. Haematological cancers (QS150). 2017.
- NICE guidance. Non-Hodgkin's lymphoma (NG52). July 2016.
- NICE cancer service guidance. Improving outcomes in haemato-oncology cancer. Public health guidance (CSG3). December 2009.

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.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

- European Society for Medical Oncology. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.[20]
- London Cancer. Guidelines for the management of non-- - Hodgkin's and Hodgkin's lymphoma in adults. 2015.[21]
- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Non-Hodgkin's lymphomas. 2014.[22]
- European Society for Medical Oncology. ESMO Consensus conferences: guidelines on malignant lymphoma. Part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. 2013.[23]
- British Committee for Standards in Haematology. Guidelines for the Management of Mature T-cell and NK-cell Neoplasms (Excluding cutaneous T-cell Lymphoma). 2013.[24]

ADDITIONAL INFORMATION

Celgene Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data

from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

1 Clinicaltrials.gov. Efficacy and Safety of Oral Azacitidine Compared to Investigator's Choice Therapy in Patients With Relapsed or Refractory AITL. *Trial ID: NCT03593018*. 2018;Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03593018.

2 Garcia-Manero G, Gore SD, Cogle C, Ward R, Shi T, Macbeth KJ, et al. Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011 Jun 20;29(18):2521-7. Available from: https://doi.org/10.1200/jco.2010.34.4226.

3 Griffiths EA, Carraway HE, Chandhok NS, Prebet T. Advances in non-intensive chemotherapy treatment options for adults diagnosed with acute myeloid leukemia. *Leukemia Research*. 2020 Apr;91:106339. Available from: https://doi.org/10.1016/j.leukres.2020.106339.

4 electronic Medicines Compendium. *Vidaza 25 mg/ml powder for suspension for injection.* 2019. Available from: https://www.medicines.org.uk/emc/product/6468 [Accessed 13 July 2020].

5 Savona MR, Kolibaba K, Conkling P, Kingsley EC, Becerra C, Morris JC, et al. Extended dosing with CC-486 (oral azacitidine) in patients with myeloid malignancies. *American Journal of Hematology*. 2018;93(10):1199-206. Available from: https://doi.org/10.1002/ajh.25216.

6 Laille E, Shi T, Garcia-Manero G, Cogle CR, Gore SD, Hetzer J, et al. Pharmacokinetics and Pharmacodynamics with Extended Dosing of CC-486 in Patients with Hematologic Malignancies. *PloS one*. 2015;10(8):e0135520-e. Available from: https://doi.org/10.1371/journal.pone.0135520.

7 Abaza Y, Kantarjian H, Garcia-Manero G, Estey E, Borthakur G, Jabbour E, et al. Long-term outcome of acute promyelocytic leukemia treated with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab. *Blood*. 2017 Mar 9;129(10):1275-83. Available from: https://doi.org/10.1182/blood-2016-09-736686.

8 Lemonnier F, Dupuis J, Sujobert P, Tournillhac O, Cheminant M, Sarkozy C, et al. Treatment with 5-azacytidine induces a sustained response in patients with angioimmunoblastic T-cell lymphoma. *Blood*. 2018 10/02;132:blood-2018. Available from: https://doi.org/10.1182/blood-2018-04-840538.

9 Clinicaltrials.gov. *CC-486 | Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | Phase 2, 3.* 2020. Available from: https://clinicaltrials.gov/ct2/results?term=CC-486&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 13 July 2020].

10 Moskowitz AJ. Practical Treatment Approach for Angioimmunoblastic T-Cell Lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2019 Mar;15(3):137-43. Available from: https://doi.org/10.1200/jop.18.00511.

11 National Cancer Institute. *angioimmunoblastic T-cell lymphoma.* 2020. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/angioimmunoblastic-t-cell-lymphoma [Accessed 13 July 2020].

12 Rare Disease Database. *Angioimmunoblastic T-Cell Lymphoma.* 2020. Available from: https://rarediseases.org/rare-diseases/angioimmunoblastic-t-cell-lymphoma/ [Accessed 13 July 2020].

13 Lunning MA, Vose JM. Angioimmunoblastic T-cell lymphoma: the many-faced lymphoma. *Blood*. 2017;129(9):1095-102. Available from: https://doi.org/10.1182/blood-2016-09-692541.

14 Leukemia & Lymphoma Society. *RELAPSED AND REFRACTORY.* 2020. Available from: https://www.lls.org/lymphoma/non-hodgkin-lymphoma/treatment/refractory-and-relapsed [Accessed 23 July 2020].

15 Timmins MA, Wagner SD, Ahearne MJ. The new biology of PTCL-NOS and AITL: current status and future clinical impact. *British Journal of Haematology*. 2020;189(1):54-66. Available from: https://doi.org/10.1111/bjh.16428.

16 Dearden CE, Johnson R, Pettengell R, Devereux S, Cwynarski K, Whittaker S, et al. Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma).

British Journal of Haematology. 2011;153(4):451-85. Available from: https://doi.org/10.1111/j.1365-2141.2011.08651.x.

17 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2018-19*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19

18 Office for National Statistics. *Deaths registered in England and Wales – 21st century mortality: 2019*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset

19 National Institute for Health and Care Excellence. *Non-Hodgkin's lymphoma: diagnosis and management (NG52)*. 2016. Available from: https://www.nice.org.uk/guidance/ng52 [Accessed 13 July 2020].

20 d'Amore F, Gaulard P, Trümper L, Corradini P, Kim WS, Specht L, et al. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015 Sep;26 Suppl 5:v108-15. Available from: https://doi.org/10.1093/annonc/mdv201.

21 London Cancer. *Guidelines for the management of non-- - Hodgkin's and Hodgkin's lymphoma in adults*. 2015. Available from: http://www.londoncancer.org/media/134135/Lymphoma-_London-Cancer-Guidelines-2015.pdf [Accessed 31 July 2020].

22 National Comprehensive Cancer Network. *NCCN Guidelines. Non-Hodgkin Lymphomas*. 2019. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx#site [Accessed 23 July 2020].

23 Dreyling M, Thieblemont C, Gallamini A, Arcaini L, Campo E, Hermine O, et al. ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. *Ann Oncol*. 2013 Apr;24(4):857-77. Available from: https://doi.org/10.1093/annonc/mds643.

24 British Committee for Standards in Haematology. *Guidelines for the Management of Mature T-cell and NK-cell Neoplasms (Excluding cutaneous T-cell Lymphoma)*. 2013. Available from: https://b-s-h.org.uk/media/2895/t-nhl-guideline-3-8-13-updated-with-changes-accepted-v1-rg.pdf [Accessed 23 July 2020].

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