Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING FEBRUARY 2019

Lenalidomide in addition to R-CHOP chemotherapy for diffuse large B-cell lymphoma

NIHRIO ID	14917	**NICE ID**	10116 (9663)
Developer/Company	Celgene Ltd	**UKPS ID**	645633

Licensing and market availability plans	Currently in pre-registration.

SUMMARY

Lenalidomide in addition to a chemotherapy combination known as R-CHOP is in clinical development for newly diagnosed, previously untreated adult patients with diffuse large B-cell lymphoma (DLBCL) of the subtype known as activated B-cells (ABC) type. DLBCL is a cancer affecting a type of white blood cells called lymphocytes or B-cells. It is the most common form of non-Hodgkin lymphoma among adults. DLBCL is an aggressive cancer and although it can be cured in more than half of people affected, it remains a serious and life threatening disease. Treatment does not work as well for patients with the ABC type compared to patients with other DLBCL types who receive standard treatment.

Lenalidomide is a derivative of thalidomide and in DLBCL works by blocking the development of tumour cells, preventing the growth of blood vessels within tumours and stimulating some of the specialised cells of the immune system to attack the cancerous cells. It is administered orally in addition to current standard of therapy R-CHOP. The addition of lenalidomide to R-CHOP for this population subgroup may improve effectiveness and prognosis.

PROPOSED INDICATION

Untreated activated B-cell (ABC) type diffuse large B-cell lymphoma, stage II to IV – first line.[a]

TECHNOLOGY

DESCRIPTION

Lenalidomide (Revlimid) is a thalidomide analogue and an immunomodulatory drug with anti-neoplastic,, antiangiogenic, and pro-erythropoietic properties.[1] Lenalidomide inhibits the secretion of pro-inflammatory cytokines and increases the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibits cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Lenalidomide is effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but is much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions.[2]

The mechanism of action of lenalidomide remains to be fully characterised, however it has been demonstrated that lenalidomide inhibits the expression of cyclooxygenase-2 (COX-2), but not COX-1, in vitro.[2] Lenalidomide's activity is based on modulation of tumour-cell microenvironment and on stimulating the activity of effector cells, such as cytotoxic T and natural killer cells. Lenalidomide enhanced T-cell and NK-cell effector function to eliminate tumour B cells and it had a role in the restoration of impaired T-cell activity and formation of immunologic synapses.[3]

Lenalidomide is currently in development in a phase III trial for newly diagnosed patients who have previously untreated activated B-cell (ABC) type diffuse large B-cell lymphoma (DLBCL).[4] In the currently ongoing phase III trial (NCT02285062; EudraCT 2013-004054-21), lenalidomide (5, 10 or 15 mg hard capsules) is administered in addition to R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).[5] The proposed lenalidomide average dose is 15mg, days 1-14 for 21-day cycle for 6 cycles.[a]

INNOVATION AND/OR ADVANTAGES

The addition of rituximab to R-CHOP improves the outcome of patients with DLBCL. However about 40% of patients relapse or do not respond to initial chemo immunotherapy and patients with a relapsed DLBCL have a poor prognosis. The biological complexity of DLBCL suggests that a tailored therapeutic approach based on the biological and molecular signature might be a promising strategy. Gene-expression profiling has shown DLBCL's with the ABC phenotype are associated with an unfavourable outcome when treated with R-CHOP. The addition of lenalidomide to R-CHOP appears to mitigate the negative prognostic impact of the ABC phenotype.[6,7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lenalidomide is indicated as follows:[8]

- Multiple myeloma

As monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

As combination therapy (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

[a] Information provided by Celgene on UK PharmaScan

In combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

- Myelodysplastic syndromes

As monotherapy is indicated for the treatment of adult patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

- Mantle cell lymphoma

As monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.

The most common side effects of lenalidomide are relative to the condition for which is used as treatment, however common to all different approved indications is neutropenia, diarrhoea, constipation, nausea, tiredness and rash.[9]

Lenalidomide as monotherapy or in combination with other medicinal products is in phase III and phase II clinical trials for a range of conditions including multiple myeloma, mantle cell lymphoma and anaemia.[10]

Lenalidomide was designated orphan drug in the EU in 2011 for the treatment of diffuse large B-cell lymphoma.[11]

PATIENT GROUP

DISEASE BACKGROUND

Non-Hodgkin's lymphoma (NHL) is a type of cancer of the lymphatic system, and diffuse large B-cell lymphoma (DLBCL) is the most common high grade variant.[12] DLBCL develops from abnormal mature B-cells. The abnormal cells are larger than normal, healthy B-cells, and are spread diffusely throughout the tumour, wiping out the normal structure of the lymph node. The causes of lymphoma are not known, but most people diagnosed with DLBCL are aged 65 years and over, and the disease affects slightly more men than women.[13]

The first symptoms of DLBCL are usually painless lumps, often in the neck, armpit or groin, which are enlarged lymph nodes. DLBCL can also develop in lymph nodes deep inside the body which cannot be felt from the outside. DLBCL can be hard to diagnose as people have different symptoms depending what organs and tissues are affected, but diagnosis can be confirmed by a biopsy. Stage I and II are 'early-stage' DLBCL. 'Advanced-stage' DLBCL is stage III and stage IV. Most people have advanced-stage DLBCL when they are diagnosed.[13]

Three distinct molecular subgroups of DLBCL according to cell-of-origin: germinal centre B-cell (GCB), activated B-cell (ABC) and type III/unclassifiable by gene expression profiling (GEP) had been discovered and it has been demonstrated that the ABC subtype of DLBCL as determined by GEP is independently associated with inferior Progression Free Survival and Overall Survival when patients are treated with R-CHOP only.[14]

CLINICAL NEED AND BURDEN OF DISEASE

The latest available Cancer Registration Statistics, England, 2016 showed 4,754 new registrations of DLBCL (ICD-10 code C83.3).[15] For hospital activity, in 2017/18 there were 35,148 admissions with primary diagnosis of DLBCL (ICD-10 code C83.3), resulting in 85,833 bed days and 27,918 day cases.[16]

Overall, non-Hodgkin Lymphoma (ICD-10 code C82-C86) European Age-standardised incidence rates are projected to decrease from 27.11 per 100,000 (equivalent to 13,509 observed cases) in 2014 to 26.47 per 100,000 (18,621 projected cases) in 2035.[17]

In England in 2016, there were a total of 1,194 registrations of death due to Diffuse non-Hodgkin's lymphoma (ICD-10 code C83) in people aged 20 and over, of which approximately 63% were men.[15]

The age-standardised one-year and five-year survival rates for NHL (all subtypes combined) in England over the period 2011 and 2015 show that 78% of men are expected to survive for at least 1 year, with 64.9% surviving 5 years or more. The survival rates for women are slightly higher with 80.5% expected to live for 1 year and 69.4% for at least 5 years.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

DLBCL is an aggressive cancer that needs immediate treatment. The aim of treatment in most patients is complete remission and cure.[19] A combination of chemotherapy and the monoclonal antibody rituximab, with or without radiation therapy, can lead to disease remission in a large number of patients with this form of lymphoma.[20]

CURRENT TREATMENT OPTIONS

In the UK, the most widely used treatment for DLBCL presently is the combination known as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). The R-CHOP regimen is usually given in 21-day cycles (once every 21 days) for an average of 6 cycles. However, the length and number of cycles given can vary based on the patient's individual disease and health status. In certain cases 14-day cycles may be used, and for limited stage disease (Stage I or II) 3-4 cycles may be used followed by radiation therapy.[20] Steroids can also be given to enhance the effect of the chemotherapy.[21]

PLACE OF TECHNOLOGY

If licenced, lenalidomide in addition to R-CHOP may offer a more effective treatment option for newly diagnosed, untreated DLBCL patients of the ABC-type. This combination treatment has the potential to improve prognosis in this population for which the current standard of treatment is not as effective as in other DLBCL subtypes.

CLINICAL TRIAL INFORMATION

Trial	**ROBUST, NCT02285062, 2013-004054-21 (EudraCT); adults aged 18 to 80 years old; lenalidomide vs. placebo, both in addition to R-CHOP; phase III**
Sponsor	Celgene
Status	Ongoing

Source of Information	Trial registry;[4] Publication[22]
Location	EU (not inc UK), US, Canada, Japan and others
Design	Randomised; placebo/controlled, parallel assignment
Participants	n=570; aged 18-65 years; newly diagnosed, previously untreated histologically proven DLBCL
Schedule	Randomised to either: • Lenalidomide (15 mg, days 1 to 14) plus R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for 6 cycles of 21 days each (R-CHOP21 x 6) • placebo plus R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for 6 cycles of 21 days each (R-CHOP21 x 6)
Follow-up	Active treatment for 6 cycles (1 cycle = 21 days long) and follow up for 5 years
Primary Outcomes	• Progression Free Survival [Time Frame: Up to 5 years from the time the last patient is randomized]
Secondary Outcomes	• Overall Survival [Time Frame: Up to 5 years from the time the last patient is randomized] • Complete Response Rate [Time Frame: Up to 5 years from the time the last patient is randomized] • Duration of Complete Response [Time Frame: Up to 5 years from the time the last patient is randomized] • Time to Next Lymphoma Treatment [Time Frame: Up to 5 years from the time the last patient is randomized] • Objective Response Rate [Time Frame: Up to 5 years from the time the last patient is randomized] • Health Related Quality of Life [Time Frame: Up to 5 years from the time the last patient is randomized] • Event Free Survival [Time Frame: Up to 5 years]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as August 2022

ESTIMATED COST

The NHS indicative price of lenalidomide (Revlimid) 15mg capsules for oral use is £3,969.00 for a 21 capsule packet.[1]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). 2016
- NICE Quality Standards. Haematological cancers (QS150). 2017

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

- The British Committee for Standards in Haematology. Guidelines for the management of diffuse large B - cell lymphoma. 2016.[7]
- The European Society for Medical Oncology. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2015.[23]

REFERENCES

1 British National Formulary (BNF). *Lenalidomide.* 2017. Available from: https://doi.org/10.18578/BNF.601622646 [Accessed 29 January 2019].

2 Drugbank.ca. *Lenalidomide.* 2019. Available from: https://www.drugbank.ca/drugs/DB00480 [Accessed 29 January 2019].

3 Chiappella A, Vitolo U. Lenalidomide in Diffuse Large B-Cell Lymphomas. *Advances in Hematology*. 2012;2012:5. Available from: http://dx.doi.org/10.1155/2012/498342 10.1155/2012/498342.

4 Clinicaltrials.gov. *Efficacy and Safety Study of Lenalidomide Plus R-CHOP Chemotherapy Versus Placebo Plus R-CHOP Chemotherapy in Untreated ABC Type Diffuse Large B-cell Lymphoma (ROBUST). Trial ID: NCT02285062*. 2014. Status: Active, not recruiting Available from: https://clinicaltrials.gov/ct2/show/NCT02285062 [Accessed 29 January 2019].

5 EU Clinical Trials Register. *Study of lenalidomide plus R-CHOP chemotherapy versus placebo plus R-CHOP chemotherapy in untreated diffuse large B-cell lymphoma. Trial ID: 2013-004054-21/ES*. 2014. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-004054-21/ES [Accessed 6 February 2019].

6 Castellino A, Chiappella A, LaPlant BR, Pederson LD, Gaidano G, Macon WR, et al. Lenalidomide plus R-CHOP21 in newly diagnosed diffuse large B-cell lymphoma (DLBCL): long-term follow-up results from a combined analysis from two phase 2 trials. *Blood Cancer Journal*. 2018 2018;8(11):108. Available from: 10.1038/s41408-018-0145-9.

7 Chaganti S, Illidge T, Barrington S, McKay P, Linton K, Cwynarski K, et al. Guidelines for the management of diffuse large B-cell lymphoma. *Br J Haematol*. 2016;174(1):43-56. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/bjh.14136 doi:10.1111/bjh.14136.

8 electronic Medicines Compendium (eMC). *Revlimid.* 2018. Available from: https://www.medicines.org.uk/emc/product/347 [Accessed 6 February 2019].
9 European Medicines Agency (EMA). *European public assessment report (EPAR) for Revlimid.*: 2017. Report No.: EMA/113870/2017. Available from: https://www.ema.europa.eu/documents/overview/revlimid-epar-summary-public_en.pdf.
10 Clinicaltrials.gov. *Search: lenalidomide | Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation, Unknown status Studies | Interventional Studies | Phase 3.* 2018. Available from: https://clinicaltrials.gov/ct2/results?term=lenalidomide&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&recrs=m&age_v=&gndr=&type=Intr&rslt=&phase=2 [Accessed 30 January 2019].
11 European Medicines Agency (EMA). *Public summary of opinion on orphan designation: Lenalidomide for the treatment of diffuse large B-cell lymphoma* 2011. Report No.: EU/3/11/868. Available from: https://www.ema.europa.eu/documents/orphan-designation/eu/3/11/868-public-summary-opinion-orphan-designation-lenalidomide-treatment-diffuse-large-b-cell-lymphoma_en.pdf.
12 Cancer Research UK. *High grade NHL.* 2018. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/high-grade [Accessed 29 January 2019].
13 Lymphoma Action. *Diffuse large B-cell lymphoma.* 2018. Available from: https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/diffuse-large-b-cell-lymphoma [Accessed 29 January 2019].
14 Gleeson M, Jack A, Cunningham D, Counsell N, McWhirter N, Chalkley R, et al. The Activated B-Cell Subtype of Diffuse Large B-Cell Lymphoma As Determined By Whole Genome Expression Profiling on Paraffin Embedded Tissue Is Independently Associated with Reduced Overall and Progression Free Survival in the Rituximab Era: Results from the UK NCRI R-CHOP 14 v 21 Phase III Trial. *Blood*. 2016;128(22):1746. Available from: http://www.bloodjournal.org/content/128/22/1746.abstract.
15 Office for National Statistics (ONS). *Cancer Registration Statistics, England, 2016*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland
16 NHS Digital. *Hospital Admitted Patient Care Activity, 2017-18*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18 [Downloaded 27 November 2018].
17 Cancer Research UK. *Selected Cancers, Number of Projected and Observed Cases and European Age-Standardised Incidence Rates per 100,000 people by Cancer Type and Sex.* Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Four [Downloaded 9th March 2018].
18 Office for National Statistics (ONS). *Cancer Survival in England: adults diagnosed between 2011 and 2015 and followed up to 2016.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Downloaded March 2017].
19 National Institute for Health and Care Excellence (NICE). *Guideline Scope: Non-Hodgkin's lymphoma: diagnosis and management of non-Hodgkin's lymphoma*. Available from: https://www.nice.org.uk/guidance/ng52/documents/nonhodgkins-lymphoma-final-scope2.
20 Lymphoma Research Foundation. *Diffuse Large B-Cell Lymphoma: Treatment Options.* 2018. Available from: https://www.lymphoma.org/aboutlymphoma/nhl/dlbcl/dlbcltreatment/ [Accessed 30 January 2019].
21 Macmillan Cancer Support. *Diffuse large B-cell lymphoma.* 2019. Available from: https://www.macmillan.org.uk/information-and-support/lymphoma/lymphoma-non-hodgkin/understanding-cancer/types-of-non-hodgkin-lymphoma/diffuse-large-b-cell-lymphoma.html#153279 [Accessed 31 January 2019].

22 Nowakowski GS, Chiappella A, Witzig TE, Spina M, Gascoyne RD, Zhang L, et al. ROBUST: Lenalidomide-R-CHOP versus placebo-R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. *Future oncology (London, England)*. 2016;12(13):1553-63. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27089170 10.2217/fon-2016-0130.

23 Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2015;26(suppl_5):v116-v25. Available from: doi:10.1093/annonc/mdv304.

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.