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Lenalidomide (Revlimid) + rituximab for relapsed/refractory follicular lymphoma and marginal zone lymphoma

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LAY SUMMARY

Lymphoma is the most common type of blood cancer. Lymphoma occurs when cells of the immune system called lymphocytes (a type of white blood cell) become cancerous, growing and multiplying uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, or other organs, and form a mass called a tumour. Lymphomas can be broadly classified into two types, fast-growing (aggressive) and slow-growing (indolent), Follicular lymphoma and marginal zone lymphoma are both slow-growing types of lymphoma. These lymphomas can be difficult to diagnose as symptoms may be vague (e.g. fatigue, weight loss, enlarged lymph nodes) or there may be no symptoms. Some people will not need treatment for many years, and a few will never need treatment. For patients who need treatment, the most common initial treatment is rituximab with chemotherapy. If the cancer does not respond to this therapy it is called “refractory”, and if the cancer returns after response to the initial treatment it is called “relapsed”. The condition can become more difficult to treat if it is relapsed or refractory, as there are fewer treatment options available.

The drug combination of lenalidomide (oral capsules) and rituximab (by intravenous injection) has the potential to be an effective treatment for relapsed or refractory follicular and marginal zone lymphoma. The drug combination is being developed for patients that are eligible for rituximab monotherapy or for patients that need an alternative to standard chemotherapy regimens, where rituximab alone would be considered sub-optimal.

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TARGET GROUP

Follicular Lymphoma (FL) and Marginal Zone Lymphoma (MZL), relapsed/refractory – second-line or later lines+; lenalidomide in combination with rituximab

TECHNOLOGY

DESCRIPTION

Lenalidomide (REVLIMID®, also known as CC-5013 and CDC-501) is an immunomodulatory compound with anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Immunomodulatory properties of lenalidomide include increased number and activation of T cells and natural killer (NK) cells leading to direct and enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) via increased secretion of interleukin-2 and interferon-gamma, increased numbers of natural killer T cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.[1] The drug inhibits angiogenesis (the process of making new blood vessels), and induces tumour cell apoptosis directly and indirectly by inhibition of bone marrow stromal cell support, by anti-angiogenic and anti-osteoclastogenic effects, and by immunomodulatory activity. This agent also promotes G1 cell cycle arrest and apoptosis of malignant cells. Lenalidomide is formulated as capsules for oral route of administration.[2]

Lenalidomide is an immunomodulatory drug that targets Cereblon (CRBN), a substrate receptor of the cullin 4 ring E3 ligase complex. Binding of lenalidomide to CRBN results in recruitment, ubiquitination and subsequent proteasomal degradation of lymphoid restricted transcription factors Aiolos and Ikaros (Gandhi, 2014; Lu, 2014; Krönke, 2014). In malignant B-cells degradation of these substrates results in apoptosis whilst in T cells it results in activation (Bjorklund, 2015; Hagner, 2015; Gandhi, 2014). Lenalidomide also enhances the ex vivo proliferation of CD4+ and CD8+ T cells from follicular lymphoma (FL) patients' ex vivo with a concomitant increase in production of cytokines including IL-2 and IFN-γ, which leads to indirect activation of NK cells. Lenalidomide also directly increases NK cell activation by increasing the expression of activating receptors, secretion of cytokines, and proliferation from FL ex vivo (Celgene study report 8195-014). Impaired T-cell immunologic synapse formation is an active immunosuppressive mechanism in tumour infiltrating T-cells from FL patients (Ramsay, 2009). In FL, in particular, lenalidomide has been shown to restore defective immunological synapse formation via cytoskeletal reorganization in autologous ex vivo co-cultures of cells with FL cells (Ramsey, 2009) and increase natural killer cells in the blood (Fowler, 2014).[a]

Lenalidomide may reduce or prevent the growth of cancer cells. Lenalidomide has also been shown to restore the immune cells' ability to attack and kill tumour cells, an ability that may be inhibited by follicular lymphoma and other lymphomas.[3]

While rituximab's primary mechanism is to target NK cells to malignant FL cells resulting in improved killing of target cells (ADCC), the NK cells remain impaired. Lenalidomide can directly increase NK cell activation, secretion of cytokines and proliferation as well as repair immune synapses (Gribben 2015). Lenalidomide synergistically enhances the apoptotic activity of rituximab against NHL cells via an NK mediated mechanism (Zhu, 2008) as well as enhancing direct apoptosis in FL and MZL cell lines (Celgene Study report 8195-014; Celgene Study report 8195-008), and directly and indirectly activate, repair and increase NK cells, while further augmenting the activity of rituximab, thereby resulting in superior activity of R2 due to complementary mechanisms of action.[a]

[a] Information provided by the company.

Lenalidomide is licensed in the EU for the treatment of:

- multiple myeloma as monotherapy in patients who have had a stem cell transplant
- multiple myeloma in combination with dexamethasone for previously untreated patients not suitable for stem cell transplant
- in combination with melphalan and prednisone for previously untreated patients not suitable for stem cell transplant
- in combination with dexamethasone for patients who have received at least one prior therapy
- myelodysplastic syndromes associated with deletion 5q cytogenetic abnormality as monotherapy for patients who need blood transfusions to manage their anaemia
- mantle cell lymphoma as monotherapy for patients with relapsed/refractory disease[4,5]

The most common side effects reported with lenalidomide for the treatment of multiple myeloma are: bronchitis (inflammation of the airways in the lungs), nasopharyngitis (inflammation of the nose and throat), cough, gastroenteritis (inflammation of the stomach and intestines with diarrhoea and vomiting), upper respiratory tract infection (cold), tiredness, neutropenia (low levels of neutrophils, a type of white blood cell), constipation, diarrhoea, muscle cramps, anaemia, thrombocytopenia (low platelet counts), rash, back pain, insomnia (difficulty sleeping), decreased appetite, fever, peripheral oedema (swelling, especially of the ankles and feet), leucopenia (low white blood cell counts) and weakness.[4]

The most common side effects reported with lenalidomide for the treatment of myelodysplastic syndromes are: neutropenia, thrombocytopenia, diarrhoea, constipation, nausea (feeling sick), itching, rash, tiredness and muscle spasms.[4]

The most common side effects reported with lenalidomide for the treatment of mantle cell lymphoma are: neutropenia, anaemia, diarrhoea, tiredness, constipation, fever and rash.[4]

The most serious side effects reported with lenalidomide are: neutropenia, venous thromboembolism (blood clots in the veins) including pulmonary embolism (blood clots in the lungs), lung infections including pneumonia, kidney failure, febrile neutropenia (neutropenia with fever), diarrhoea and anaemia.[4]

For the full list of side effects reported with lenalidomide see the Summary of Product Characteristics (SmPC).[5]

Rituximab (MabThera) is an anti-neoplastic agent. It is a monoclonal antibody that binds to a specific protein (the CD20 marker on the surface of the cell) that is found on the surface of some B-cells, including some lymphoma cancer cells. The drug does not target stem cells (B-cell progenitors) in the bone marrow which lack the CD20 marker on the surface of the cells. Following binding to lymphoma cancer cells, rituximab is thought to trigger a host cytotoxic immune response against the cancer cells. Rituximab is formulated as a solution for intravenous infusion and subcutaneous route of administration.[2]

Rituximab is licensed in the EU for the treatment of:

- Follicular lymphoma
- Diffuse large B-cell non-Hodgkin's lymphoma
- Chronic lymphocytic leukaemia
- Severe rheumatoid arthritis
- Granulomatosis with polyangiitis
- Microscopic polyangiitis[4]

Depending on the condition it is used to treat, rituximab may be given on its own, or with chemotherapy, methotrexate or a corticosteroid.[4]

The most common side effects with rituximab intravenous infusions are reactions related to the infusion (such as fever, chills and shivering) while most common serious side effects are infusion reactions, infections and heart-related problems. Similar side effects are seen when rituximab is injected under the skin, with the exception of reactions around the injections site (pain, swelling and rash), which occur more frequently with the skin injections. For the full list of side effects reported with rituximab, see the SmPC.[4,5]

In the phase III trial (NCT01938001) patients receive rituximab 375mg/m^2 intravenous every week in Cycle 1 (Days 1, 8, 15 and 22) on Day 1 of every 28 day cycle from Cycles 2 to 5, and receive either lenalidomide 20mg or placebo in capsule form on Days 1 to 21 every 28 days up to 12 cycles.[3]

Lenalidomide in combination with rituximab does not currently have Marketing Authorisation in the EU for any indication.

Lenalidomide in combination with rituximab is also under development for the treatment of patients with:

- previously untreated follicular lymphoma (NCT01650701, NCT01476787)
- relapsed or refractory mantle cell lymphoma (NCT01996865)
- untreated ABC type diffuse large B-cell lymphoma (NCT02285062)
- relapsed or refractory small lymphocytic non-Hodgkin lymphoma (NCT00848328)
- previously untreated indolent non-Hodgkin's lymphoma (NCT01316523)
- chronic lymphocytic leukaemia/small lymphocytic lymphoma (NCT01446133).[2]

INNOVATION and/or ADVANTAGES

The efficacy of initial treatment with rituximab-chemotherapy in treating non-Hodgkin's lymphomas (NHL) is often limited by relapses after initial response due to the development of resistance, as well as toxicity, and often does not result in permanent cure. Many patients eventually relapse or cannot tolerate current cytotoxic approaches, necessitating the need to re-initiate treatment or for alternative treatment strategies. In prior clinical trials, the synergistic effects of lenalidomide in combination with monoclonal antibodies, particularly rituximab, have shown preliminary efficacy in patients with both previously untreated first-line and relapsed/refractory indolent NHL, including rituximab-refractory, setting a precedent for the use of the lenalidomide-rituximab combination containing options for patients with indolent lymphoma such as FL and MZL.[6]

The combination of lenalidomide and rituximab may eliminate the cancer by restoring the immune system's ability to attack and eliminate cancer cells.[3]

If licensed, lenalidomide in combination with rituximab, a combination immunotherapy, will offer an additional treatment option for patients with relapsed/refractory FL and MZL, who currently have few effective therapies available.

DEVELOPER

Celgene

AVAILABILITY, LAUNCH or MARKETING

Lenalidomide was designated an orphan drug in EU for the following indications:

- multiple myeloma in December 2003
- myelodysplastic syndrome in March 2004
- B-cell chronic lymphocytic leukaemia in November 2007
- diffuse large B-cell lymphoma in May 2011
- mantle cell lymphoma in October 2011
- marginal zone lymphoma in October 2011
- follicular lymphoma in January 2013[2]

Lenalidomide was given the following designations in the USA for the following indications:

- orphan drug designation for multiple myeloma in September 2001
- fast track designation for myelodysplastic syndrome in April 2003
- orphan drug designation for myelodysplastic syndrome in January 2004
- orphan drug designation for B-cell chronic lymphocytic leukaemia in July 2007
- orphan drug designation for mantle cell lymphoma in April 2009
- orphan drug designation for diffuse large B-cell lymphoma in March 2011
- orphan drug designation for follicular lymphoma in September 2013
- orphan drug designation for extra-nodal marginal zone B-cell lymphoma (mucosa-associated lymphoid tissue or MALT-lymphoma) in April 2015
- orphan drug designation for splenic marginal zone B-cell lymphoma in January 2017
- orphan drug designation for nodal marginal zone B-cell lymphoma in January 2017[2]

Rituximab was given orphan drug designation in the USA for the following cancer indications:

- B-cell non-Hodgkin lymphoma in June 1994
- Chronic lymphocytic leukaemia in January 2004 and August 2016
- Follicular lymphoma in August 2016
- Diffuse large B-cell lymphoma in September 2016[7]

PATIENT GROUP

BACKGROUND

Lymphoma is the most common type of blood cancer. The two main forms of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. These cancerous lymphoma cells can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumour. The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B-cells) and T lymphocytes (T-cells).[8]

Follicular lymphoma (FL) is the most common indolent (slow- growing) form of NHL, accounting for approximately 12% of all B-cell NHLs. Common signs and symptoms of FL include enlargement of the lymph nodes in the neck, underarms, abdomen, or groin, as well as fatigue, shortness of breath, night sweats, and weight loss. Often, patients with FL have no obvious symptoms of the disease at diagnosis.[8]

Follicular lymphoma can occur at any age, but the average age at diagnosis is around 65 years. In most cases, there is no known cause for FL. Some acquired genetic changes are common in FL, but it is not known what causes them. Around 1 in 5 people with FL never need treatment or the lymphoma does not cause problems for many years.[9]

Marginal zone lymphoma (MZL) is another type of indolent B-cell NHL that develops from B-cells that are normally found at the edge of areas of lymph node tissue. MZL lymphomas are slow-growing, and many people live with these lymphomas for many years, only needing treatment occasionally, if at all. There are three types of MZL:

- Mucosa-associated lymphoid tissue (MALT) lymphoma. MALT lymphomas are uncommon (around 1 in 13 cases of NHL). A MALT lymphoma can develop almost anywhere in the body, but it most commonly develops in the stomach. MALT lymphoma can occur at any age, but they are most common in people in their 50s and 60s. MALT lymphoma develops in areas where MALT tissue has formed a response to inflammation caused by a chronic infection, or an autoimmune condition. Gastric MALT lymphoma has been strongly linked to infection by *Helicobacter pylori*. Most people with gastric MALT lymphoma have persistent indigestion, but this is likely to be related to the *H. pylori* infection rather than the lymphoma. Most people with non-gastric MALT lymphoma have no symptoms at all, and the lymphoma is found when they have a test for something else.[9]
- Splenic MZL account for fewer than 2 in 100 cases of NHL. Splenic MZL can affect people of any age but is most common in people in their 60s. In most cases, it is not known what causes splenic MZL. This type of lymphoma is more common in people who have had certain infections, particularly hepatitis C virus, but also Epstein-Barr virus or malaria. Splenic MZL usually causes enlargement of the spleen, which may cause abdominal pain or discomfort, although some people have no symptoms of splenic MZL.[9]
- Nodal MZL account for fewer than 2 in 100 cases of NHL. Nodal MZL can affect people of any age but is most common in people in their 60s. In most cases, it is not known what causes nodal MZL, but it is most common in people who have been infected with hepatitis C virus. Nodal MZL commonly causes swollen lymph nodes, usually in the neck or groin; the lumps are not usually painful.[9]

CLINICAL NEED and BURDEN OF DISEASE

Follicular lymphoma typically follows an indolent course with a median overall survival (OS) of 7-10 years. Although FL responds well to the initial treatment, which typically is rituximab monotherapy or rituximab-containing chemotherapy regimen, this disease is characterized by recurrent relapses or progressions with progressively shorter intervals in between lines of treatment. This problem of increasingly shorter period of effectiveness of standard of care treatments is due to the development of refractoriness or resistance to chemotherapy or rituximab itself. Eventually in patients with multiple relapses, regardless of stage, most FL patients die of lymphoma because they have run out of effective treatment options. Therefore, for patients with relapsed/ refractory disease, although re-treatment with rituximab alone or in combination with chemotherapy is commonly used, the effectiveness of these treatments in patients with relapsed FL is suboptimal.

A goal in the field of FL has been to identify additional effective treatment options for relapsed/ refractory FL. One approach to provide patients with more or better treatment options is to enhance the activity of rituximab single agent through combination strategies with agents with novel mechanism of action to reverse the immunosuppression and decreased ADCC that is often seen in patients with relapsed FL. One advantage of this approach is that it utilizes a mechanism of action

different from cytotoxic chemotherapy and thus has the potential of being effective in settings where chemotherapy may have lost its effectiveness. In addition, agents that improve the immune system are not cytotoxic agents and thus avoid the toxicities more typically associated with combination chemotherapy.

In 2015/16 in England there were 23,325 finished consultant episodes (FCEs) with ICD-10 primary diagnosis C82 Follicular lymphoma, and 22,668 hospital admissions. Of these admissions, 20,286 were day cases.[10] Cancer registrations tables for England in 2015 reported that there were 2,142 new registrations of follicular lymphoma (ICD-10 code C82) and calculated a directly age-standardised incidence rate of 4.3 per 100,000 population for males, and 4.2 per 100,000 population for females. These tables also reported 210 registrations of death from follicular lymphoma (ICD-10 code C82) in 2015, calculating a directly age-standardised rate of 0.4 per 100,000 deaths for both males and females.[11]

In 2015/16 in England there were 1,600 FCEs and 728 FCE bed days with ICD-10 primary diagnosis C88.4 MALT lymphoma. There were 1,559 hospital admissions, of which 1,393 were day cases. In 2015/16 in England there were 6,805 FCEs and 4,662 FCE bed days with ICD-10 primary diagnosis C83.0 Small cell B-cell lymphoma (includes splenic and nodal MZL). There were 6,591 hospital admissions, of which 5,939 were day cases.[10] It was not possible to identify data specifically for MZL in the published cancer registrations tables for England.

The population likely to be eligible to receive lenalidomide in combination with rituximab could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Duvelisib for treating relapsed follicular lymphoma after 2 systemic therapies. (TA10209). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Ibrutinib for treating relapsed or refractory follicular lymphoma (TA10223). Expected date of issue to be confirmed.
- NICE technology appraisal. Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab (TA472). August 2017.
- NICE technology appraisal. Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma (TA226). August 2014.
- NICE technology appraisal. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (TA137). February 2008.
- NICE quality standard. Haematological cancers (QS150). June 2017.
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE guideline. Suspected cancer: recognition and referral (NG12). June 2015.
- NICE evidence summary. Non-Hodgkin's lymphoma: rituximab subcutaneous injection (ESNM46). September 2014.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Ophthalmic Pathology Service (All Ages). D12/S(HSS)/b.
- 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

- European Society for Medical Oncology. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 2016.[12]
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines on Oncology: Non-Hodgkin's Lymphomas: Follicular Lymphoma. March 2015.[13]
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines on Oncology: Non-Hodgkin's Lymphomas: Marginal Zone Lymphomas. March 2015.[14]
- European Society for Medical Oncology. ESMO Consensus Guidelines: Marginal Zone Lymphoma, Mantle Cell Lymphoma, Peripheral T-cell Lymphoma. 2013.[15]
- British Society for Haematology. Guidelines on the Investigation and Management of Follicular Lymphoma. December 2011.[16]

CURRENT TREATMENT OPTIONS

Follicular lymphoma usually grows slowly. Although it is difficult to cure, it is usually kept under control for many years, with treatment needed only occasionally.[9] Once the condition has progressed to the extent that patients need treatment, many have first-line induction with rituximab in combination with chemotherapy (R‑chemotherapy) that induces a response in most people. This is followed by rituximab maintenance therapy.[17] Other patients are treated with rituximab alone, without the addition of chemotherapy.

Second-line treatment for FL depends on the timing of relapse following first-line treatment and the chemotherapy agents used first-line:[17]

- R-chemotherapy should be offered to patients who are rituximab-naïve, and should also be given if the patient had previously responded to rituximab.[16]
- disease that remains under control for some time on rituximab maintenance, or after it has stopped, is likely to be treated with further R‑chemotherapy (in combination with another chemotherapy agent) in preference to bendamustine monotherapy.[17]
- rituximab monotherapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).[18]
- in clinical practice, bendamustine monotherapy may be offered to patients with FL that does not respond to induction treatment with R-chemotherapy, or for disease that relapses early-on in the 2-year rituximab maintenance period.[17] However, NICE was unable to recommend the use in the NHS of bendamustine for the treatment of indolent non-Hodgkin's lymphoma that is refractory to rituximab or a rituximab-containing regimen because no evidence submission was received from the manufacturer or sponsor of the technology.[19]

- Y-Ibritumomab radio-immunotherapy may be offered to patients with relapsed FL, especially those who are refractory to rituximab or chemotherapy and for those who are intolerant or unwilling to have further chemotherapy.[16]
- In Wales, from April 2017 idelalisib is recommended as an option for use as monotherapy for the treatment of adults with FL that is refractory to two prior lines of treatment, in circumstances where the approved Wales Patient Access Scheme (WPAS) is utilised or the price is equivalent/lower than the WPAS price.[20,21] In 2014, NICE was unable to make a recommendation about the use in the NHS of idelalisib for treating follicular lymphoma that is refractory to two prior lines of treatment because no evidence submission was received from Gilead Sciences for the technology.[22]
- In August 2017, NICE recommended obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance as an option for treating adults with refractory follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen, if the conditions in the managed access agreement for obinutuzumab are followed.[17]
- NCCN guidelines recommend chemoimmunotherapy, rituximab monotherapy, lenalidomide +/- rituximab, radioimmunotherapy, idelalisib, or fludarabine + rituximab.[13]

For gastric MALT lymphomas the first-line treatment is *H.pylori* eradication therapy. For patients who fail to respond to this treatment, and for non-gastric MALT lymphomas, R-chemotherapy is the best choice when treatment is needed, although there is no standard best chemotherapy to be recommended. Beside clinical trials, a therapeutic approach similar to other indolent lymphomas can be followed.[15] Patients with advanced disease are typically treated in a similar way to those with advanced FL.[23]

For splenic MZL, first-line therapeutic options are splenectomy, rituximab alone or R-chemotherapy.[15] Patients with disease progression after initial therapy are candidates for therapy similar to that for FL.[23]

For nodal MZL, no specific treatment recommendation is available, but the disease is usually disseminated and treatment should be planned according to the therapeutic principles adopted for FL.[15] Patients with disease progression after initial therapy are candidates for therapy similar to that for FL.[23]

EFFICACY and SAFETY

Trial	AUGMENT, NCT01938001, EudraCT-2013-001245-14; lenalidomide + rituximab vs placebo + rituximab; phase III
Sponsor	Celgene
Status	Ongoing
Source of Information	Trial registry[24],GlobalData[25]
Location	EU (incl UK), USA and other countries
Design	Double-blind, randomised, parallel group, placebo-controlled
Participants	N=358; aged ≥18 years; follicular lymphoma (grade 1, 2 or 3a) or marginal zone lymphoma; relapsed, refractory or progressive disease after treatment with systemic therapy and must not be rituximab-refractory
Schedule	Randomised to rituximab 375mg/m^2 intravenous every week in cycle 1 (Days 1, 8, 15 and 22) on day 1 of every 28 day cycle from cycles 2 to 5 and

	lenalidomide 20mg by mouth on days 1 to 21 every 28 days up to 12 cycles; or rituximab 375mg/m^2 intravenous every week in cycle 1 (Days 1, 8, 15 and 22) on day 1 of every 28 day cycle from cycles 2 to 5 and placebo identical matched capsule on days 1 to 21 every 28 days up to 12 cycles.
Follow-up	Active treatment for 12 cycles (48 weeks), follow-up 5 yrs from last subject randomised.
Primary Outcomes	Progression-free survival (PFS) for follicular lymphoma (FL) and marginal zone lymphoma (MZL) using IRC 2001 IWG criteria
Secondary Outcomes	All outcomes are for FL and MZL • Overall response rate • Durable complete response rate • Complete response rate • Duration of response • Duration of complete response • Overall survival • Incidence of adverse events • Event free survival • Time to next anti-lymphoma therapy for FL and MZL
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Anticipated primary completion date reported as December 2017

Trial	MAGNIFY, NCT01996865; lenalidomide + rituximab followed by lenalidomide vs rituximab; phase III
Sponsor	Celgene
Status	Ongoing
Source of Information	Trial registry[26],GlobalData[27]
Location	EU (not UK), USA
Design	Randomised, parallel group, active-controlled
Participants	N=500 (planned); aged ≥18 years; follicular lymphoma (grade 1, 2 or 3a), marginal zone lymphoma or mantle cell lymphoma; relapsed, refractory or progressive disease after last treatment with systemic therapy
Schedule	Arm I (lenalidomide + rituximab followed by lenalidomide): Induction Period (12 cycles): lenalidomide 20mg (10mg if creatinine clearance ≥ 30 mL/min but < 60 mL/min) by mouth (PO) daily (QD) on days 1 to 21 of every 28-day cycle during cycles 1 through 12 and rituximab 375mg/m^2 intravenously (IV) every week in cycle 1 on days 1, 8, 15, and 22 and on day 1 of every 28-day cycle during cycles 3, 5, 7, 9, and 11, followed by a Maintenance Period (lasting 18 cycles) that includes lenalidomide 10mg PO QD on days 1 to 21 of every 28-day cycle during cycles 13 to 30 and rituximab 375mg/m^2 IV on day 1 of every 28-day cycle during cycles 13, 15, 17, 19, 21, 23, 25, 27, and 29 followed by a Maintenance Period (up to Progressive Disease) receiving lenalidomide 10mg PO QD on days 1 through 21 of every 28 day cycle until the disease progresses.

	Arm II (lenalidomide + rituximab followed by rituximab): Induction Period (12 cycles): lenalidomide 20mg PO QD (10mg if creatinine clearance ≥ 30 ml/min but < 60 ml/min) on days 1 to 21 of every 28-day cycle during cycles 1 to 12 and rituximab 375mg/m^2 IV every week in cycle 1 on days 1, 8, 15, and 22 and on day 1 of every 28-day cycle during cycles 3, 5, 7, 9, and 11, followed by a Maintenance Period for 18 cycles that includes: rituximab 375mg/m^2 IV on day 1 of every 28-day cycle during cycles 13, 15, 17, 19, 21, 23, 25, 27, and 29.
Follow-up	5 yrs from last subject randomised.
Primary Outcomes	Progression-free survival (PFS) for follicular lymphoma (FL), marginal zone lymphoma (MZL) and mantle cell lymphoma (MCL) using IRC 2001 IWG criteria
Secondary Outcomes	All outcomes are for FL, MZL and MCL • Overall response rate • Complete response rate • Duration of response • Duration of complete response • Incidence of adverse events • Time to next anti-lymphoma therapy • Time to treatment failure • Time to histological transformation
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Anticipated primary completion date reported as February 2021

ESTIMATED COST and IMPACT

COST

Lenalidomide is already marketed in the UK for the treatment of multiple myeloma; a pack of 21 x 20mg capsules (the strength given in the phase III trial) costs £4,169.[28]

Rituximab is already marketed in the UK as a concentrate for solution for infusion vials for the treatment of a number of lymphomas (including in combination with other chemotherapy); cost for 100mg/10ml concentrate range from £314 to £349, and for 500mg/500ml concentrate range from £786 to £873.[29]

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

REFERENCES

[1] Revlimid® United States Package Insert [USPI], 2017. Available from: https://media.celgene.com/content/uploads/revlimid-pi.pdf [Accessed 12 October 2017]

[2] GlobalData. *Drug Overview: Lenalidomide.* Available from: https://pharma.globaldata.com/ProductsView.aspx?ProductType=0,1&ProductID=27629 [Accessed 26 September 2017]. Login required

[3] Clinical Trials.gov. *Rituximab plus Lenalidomide for patients with relapsed/refractory indolent non-Hodgkin's lymphoma (follicular lymphoma and marginal zone lymphoma) (AUGMENT): NCT01938001.* Available from: https://clinicaltrials.gov/show/NCT01938001 [Accessed 26 September 2017]

[4] European Medicines Agency. *Revlimid*. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000717/human_med_001034.jsp&mid=WC0b01ac058001d124 [Accessed 27 September 2017]

[5] Electronic Medicines Compendium (eMC). *Revlimid*. Available from: http://www.medicines.org.uk/emc/medicine/19841 [Accessed 27 September 2017]

[6] Arora M, Gowda S and Tuscano J. A comprehensive review of lenalidomide in B-cell non-Hodgkin lymphoma. *Therapeutic Advances in Hematology*. 2016; 7(4):209-221. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4959641/ [Accessed 27 September 2017]

[7] GlobalData. *Drug Overview: Rituximab.* Available from: https://pharma.globaldata.com/ProductsView.aspx?ProductType=0,1&ProductID=62014 [Accessed 26 September 2017]. Login required

[8] Lymphoma Research Foundation. *Follicular lymphoma.* Available from: http://www.lymphoma.org/site/pp.asp?c=bkLTKaOQLmK8E&b=6300155 [Accessed 25 September 2017]

[9] Lymphoma Association. *Follicular lymphoma.* Available from: https://www.lymphomas.org.uk/about-lymphoma/types/non-Hodgkin-lymphoma/follicular-lymphoma#follicular-lymphoma [Accessed 25 September 2017]
[10] NHS Digital. *Hospital Admitted Patient Care Activity, 2015-16*. Available from: http://www.content.digital.nhs.uk/catalogue/PUB22378 [Accessed 25 September 2017]
[11] Office for National Statistics. *Cancer Registration Statistics.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 25 September 2017]
[12] European Society for Medical Oncology. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2016; 27(Supplement 5): 83-90.
[13] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines on Oncology: Non-Hodgkin's Lymphomas: Follicular Lymphoma. Available from: https://www.tri-kobe.org/nccn/guideline/hematologic/nhl/english/foll.pdf [Accessed 12 October 2017]
[14] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines on Oncology: Non-Hodgkin's Lymphomas: Marginal Zone Lymphomas. Available from: https://www.tri-kobe.org/nccn/guideline/hematologic/nhl/english/mzl.pdf [Accessed 12 October 2017]
[15] European Society for Medical Oncology. ESMO Consensus Guidelines: Marginal Zone Lymphoma, Mantle Cell Lymphoma, Peripheral T-cell Lymphoma. *Annals of Oncology*. 2013; 24(4): 857-877. Available from: http://www.esmo.org/Guidelines/Haematological-Malignancies/Marginal-Zone-Lymphoma-Mantle-Cell-Lymphoma-Peripheral-T-cell-Lymphoma [Accessed 26 September 2017]
[16] British Society for Haematology. *Guidelines on the Investigation and Management of Follicular Lymphoma.* Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2011.08969.x/full [Accessed 25 September 2017]
[17] NICE technology appraisal. *Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab (TA472).* Available from: https://www.nice.org.uk/guidance/ta472 [Accessed 26 September 2017]
[18] NICE technology appraisal. *Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (TA137)*. Available from: https://www.nice.org.uk/guidance/ta137 [Accessed 12 October 2017]
[19] NICE technology appraisal. *Bendamustine for the treatment of indolent (low grade) non-Hodgkin's lymphoma that is refractory to rituximab (terminated appraisal) (TA206).* October 2010. Available from: https://www.nice.org.uk/guidance/TA206 [Accessed 12 October 2017]
[20] All Wales Medicines Strategy Group. *Idelalisib (Zydelig), Reference No. 2597.* Available from: http://www.awmsg.org/awmsgonline/app/appraisalinfo/2597 [Accessed 26 September 2017]
[21] Lymphoma Association. *Newer drugs for lymphoma: targeted therapies*. Available from: https://www.lymphomas.org.uk/about-lymphoma/treatment/newer-drugs-lymphoma-targeted-therapies [Accessed 26 September 2017]
[22] NICE technology appraisal. *Idelalisib for treating follicular lymphoma that is refractory to 2 prior treatments (terminated appraisal) (TA328)*. December 2014. Available from: https://www.nice.org.uk/guidance/ta328 [Accessed 12 October 2017]
[23] Freedman AS, Friedberg JW. *Treatment of marginal zone (MALT) lymphoma*. Available from: http://cursoenarm.net/UPTODATE/contents/mobipreview.htm?24/34/25120?source=see_link [Accessed 26 September 2017]
[24] Clinical Trials.gov. *Rituximab plus Lenalidomide for patients with relapsed/refractory indolent non-Hodgkin's lymphoma (follicular lymphoma and marginal zone lymphoma) (AUGMENT): NCT01938001.* Available from: https://clinicaltrials.gov/show/NCT01938001 [Accessed 26 September 2017]
[25] GlobalData. *Clinical Trial Profile Overview*. Available from: https://pharma.globaldata.com/ClinicalProductsView.aspx?id=Location&ClinicalID=Xg@D5NKEVA7@aaHUx2jlVg [Accessed 26 September 2017]. Login required
[26] Clinical Trials.gov. *Lenalidomide Plus Rituximab Followed by Lenalidomide Versus Rituximab Maintenance for Relapsed/Refractory Follicular, Marginal Zone or Mantle Cell Lymphoma. (MAGNIFY): NCT01996865*. Available from: https://clinicaltrials.gov/ct2/show/NCT01996865?term=NCT01996865 [Accessed 12 October 2017]
[27] GlobalData. *Clinical Trial Profile Overview.* Available from: https://pharma.globaldata.com/ClinicalProductsView.aspx?id=ProductPreview&ClinicalID=xJrRXyVbW1fk53h413c/bA [Accessed 12 October 2017]. Login required

[28] British National Formulary. *Lenalidomide*. Available from: https://www.medicinescomplete.com/mc/bnf/current/PHP5713-lenalidomide.htm?q=lenalidomide&t=search&ss=text&tot=12&p=1#_hit [Accessed 25 September 2017]
[29] British National Formulary. *Rituximab.* Available from: https://www.medicinescomplete.com/mc/bnf/current/PHP5662-rituximab.htm?q=rituximab&t=search&ss=text&tot=18&p=1#_hit [Accessed 25 September 2017]