

**NIHR Innovation Observatory
Evidence Briefing: SEPTEMBER 2017**

Ublituximab (TG-1101) in combination with umbralisib (TGR-1202) for chronic lymphocytic leukaemia

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LAY SUMMARY

Chronic lymphocytic leukaemia is a type of blood cancer that develops inside the bone marrows. This produces abnormal types of white blood cells (lymphocytes) which do not function properly, hence, do not protect from infections the way they should do. Chronic types of leukaemia develop slowly over a long time.

Symptoms of this cancer usually only develop at a later stage of the disease. They may include frequent infections, persistent tiredness, shortness of breath, pale skin, bleeding and bruising more easily and others. The cause of chronic lymphocytic leukaemia is not yet fully understood but risk factors may include age (older people), exposure to chemicals, family history, gender or ethnicity.

Ublituximab in combination with umbralisib is under development for the treatment of chronic lymphocytic leukaemia and other types of blood cancers. They both act in different ways to suppress the production and growth of the abnormal lymphocytes caused by bindings to certain cells and proteins in the body that produces the cancer. If licensed, it will offer an additional treatment option for patients with chronic lymphocytic leukaemia.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Chronic lymphocytic leukaemia (CLL)

TECHNOLOGY

DESCRIPTION

Umbralisib is an orally available phosphoinositide-3-kinase PI3K delta inhibitor, targeting the delta isoform with nanomolar potency and high selectivity over the alpha, beta, and gamma isoforms of PI3K. The delta isoform of PI3K is strongly expressed in cells of hematopoietic origin and is believed to be important in the proliferation and survival of B-cell lymphocytes. Inhibition of PI3K delta signalling with TGR-1202 has demonstrated robust activity in numerous pre-clinical models and primary cells from patients with hematologic malignancies.¹

TG-1101 (ublrituximab) is a monoclonal antibody that targets a unique epitope on the B-lymphocyte CD20 antigen. Ublrituximab has been bioengineered to deliver enhanced clinical activity and potency. Developed for the treatment of B-cell proliferative disorders, including Non-Hodgkin's Lymphoma and chronic lymphocytic leukaemia, the anti-CD20 antibodies target and aid in the depletion of B-lymphocytes.² Anti-CD20 antibodies have also been shown to be effective in treating select autoimmune diseases such as Rheumatoid Arthritis and Systemic Lupus Erythematosus, along with the neurological disorder Multiple Sclerosis.

The combination of umbralisib and ublrituximab suppresses proliferation and Akt phosphorylation in cancer cells while simultaneously depleting B-cells which express CD20 on their cell surface.³

In the phase III clinical trial, ublrituximab is administered as intravenous infusion dose on days 1, 8 and 15 followed by maintenance infusions and umbralisib as fixed oral daily dose.⁴

This combination product does not currently have Marketing Authorisation in the EU for any indication, however, it is under development globally for the treatment of follicular lymphoma, non-Hodgkin lymphoma, diffuse large b-cell lymphoma and marginal zone b-cell lymphoma.³

Adverse events in this combination product include neutropenia, nausea and diarrhoea.⁵

INNOVATION and/or ADVANTAGES

If licensed, ublrituximab in combination with umbralisib will offer an additional treatment option for patients with both frontline and previously treated chronic lymphocytic leukaemia.⁶

DEVELOPER

TG Therapeutics, Inc.

AVAILABILITY, LAUNCH or MARKETING

TGR-1202 (umbralisib) in combination with TG-1101 (ublrituximab) received FDA orphan drug designation for the treatment of chronic lymphocytic leukaemia in January 2017.^{7,8}

According to a press release in January 2017, the company anticipates to commence a regulatory filing for the combination product in 2018.⁶

PATIENT GROUP

BACKGROUND

Leukaemia is a blood cancer that develops in the bone marrow inside the bones. In most types of this cancer abnormal white blood cells are produced, which get into the bloodstream and circulate round the body. They do not work properly and hence do not protect from infections the way they should. A distinction is made between acute and chronic leukaemia. Acute leukaemias tend to develop quickly and get rapidly worse, whereas the chronic types develop slowly over a long time.⁹ Whether leukaemia is lymphocytic or myeloid depends on which bone marrow cells the cancer starts in. Myeloid leukaemias start in myeloid blood stem cells (white blood cells other than lymphocytes, red blood cells or platelet-making cells), lymphocytic leukaemias start in the blood stem cells that become lymphocytes (white blood cells).¹⁰ There are three types of these lymphocytes: B lymphocytes that make antibodies to help fight infection; T lymphocytes that help B lymphocytes make the antibodies that help fight infection; natural killer cells that attack cancer cells and viruses. In chronic lymphocytic leukaemia (CLL) the bone marrow produces too many immature B lymphocytes, which prevent the bone marrow from producing normal, healthy cells.¹¹

CLL usually only shows symptoms at a later stage of the disease. It might therefore only be picked up during a blood test that is carried out for another reason. If symptoms develop, they may include frequent infections, anaemia with persistent tiredness, shortness of breath and pale skin, bleeding and bruising more easily, fever, night sweats, swollen glands in your neck, armpits or groin, or unintentional weight loss.¹²

Risk factors for CLL are not completely understood yet, however, they might include exposure to certain chemicals, family history, gender or race/ethnicity.¹³ CLL is most common in Australia, the USA and Europe. Studies have shown that the risk increases in men who are affected by diabetes. People who have conditions such as pneumonia, sinusitis, shingles infection, auto immune haemolytic anaemia, chronic osteoarthritis or inflamed prostate have a slightly increased risk of developing CLL.¹⁴

CLINICAL NEED and BURDEN OF DISEASE

In 2014, there were 3,515 new cases of CLL in the UK. In that year, it accounted for 1% of all new cancer cases in the UK. CLL is more common in men, affecting 2,200 males and 1,300 females in 2014. The crude incidence rate shows that there are 7 new CLL cases for every 100,000 males in the UK, and 4 for every 100,000 females. 59% of CLL cases each year in the UK are diagnosed in people aged 70 and over. Incidence rates in the UK are highest in people aged 85+. 1 in 155 men and 1 in 260 women will be diagnosed with CLL during their lifetime.¹⁵ Five-year relative survival for CLL in women in England is 73%, for men it is 67%.¹⁶

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- 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. Idelalisib for treating chronic lymphocytic leukaemia (TA359). October 2015
- NICE technology appraisal. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (TA343). June 2015
- NICE technology appraisal. Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia (TA344). June 2015
- NICE technology appraisal. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (TA216). February 2011
- NICE technology appraisal. Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab (TA202). October 2010
- NICE technology appraisal. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (TA193). July 2010
- NICE technology appraisal. Rituximab for the first-line treatment of chronic lymphocytic leukaemia (TA174). July 2009
- NICE technology appraisal. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (TA29). September 2001

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2017 Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 16068/P

OTHER GUIDANCE

Oscier D, Dearden C, Eren E, Fegan C, Follows G, Hillmen P, Illidge T, Matutes E, Milligan DW, Pettitt A, Schuh A. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. *British journal of haematology*. 2012 Dec 1;159(5):541-64.

CURRENT TREATMENT OPTIONS

CLL is not considered curable with standard treatments, with the possible exception of stem cell transplants in a small number of younger/fitter patients. Treatment options however slow down disease progression. The usual way to treat patients is chemotherapy to kill the cancer cells, biological therapy that uses monoclonal antibodies to strengthen the immune system, radiation therapy to relieve symptoms or stem cell transplant using healthy stem cells from a donor.¹¹

Most patients undertaking chemotherapy will take three main medications in treatment cycles lasting 28 days:

- fludarabine
- cyclophosphamide
- rituximab.

Others can be tried in case these three are not an option:

- bendamustine
- chlorambucil
- ibrutinib
- idelalisib
- obinutuzumab
- ofatumumab
- prednisolone.¹⁷

With these treatments side effects are very common. These include persistent tiredness, feeling sick, an increased risk of infections, easy bruising or bleeding, anaemia, hair loss, irregular heartbeat, or allergic reactions.¹⁷

Stem cell or bone marrow transplants are used to try to cure CLL or control it for longer periods. A stem cell transplant involves a high-dose chemotherapy and radiotherapy, removing the stem cells from the blood or bone marrow of a donor and transplanting the donor stem cells directly into one of the patient's veins.¹⁷

Surgery to remove the swollen spleen or antibiotics, antifungals or antiviral medication to help reduce the risk of picking up infections during treatment are used as well in some cases. Blood transfusions may help with severe anaemia; immunoglobulin replacement therapy can help prevent infections; injections of medication called granulocyte-colony stimulating factor help boost the number of white blood cells.¹⁷

EFFICACY and SAFETY

| | |
|------------------------------|---|
| Trial | UNITY-CLL, NCT02612311, ublituximab in combination with TGR-1202 compared to obinutuzumab in combination with chlorambucil, phase III |
| Sponsor | TG Therapeutics, Inc. |
| Status | Ongoing, recruiting |
| Source of Information | Trial registry ⁴ |
| Location | UK, Poland, USA |
| Design | Randomised, active-controlled |
| Participants | N=450 (planned), = or > 18 years old, Treatment naïve or previously treated Chronic Lymphocytic Leukaemia (CLL) requiring treatment, Eastern Cooperative Oncology Group (ECOG) score of 0 to 2; |
| Schedule | Ublituximab: IV infusion dose on Days 1, 8 and 15 of month 1, and day of months 2-6, followed by maintenance infusions, TGR-1202: Fixed oral daily dose; |
| Follow-up | Not reported |
| Primary Outcomes | Progression-Free Survival (PFS) in patients with CLL treated with ublituximab in combination with TGR-1202 compared to obinutuzumab + chlorambucil |
| Secondary Outcomes | Overall response rate (ORR) in patients with CLL treated with ublituximab in combination with TGR-1202 compared to ublituximab and TGR-1202 alone |

| | |
|--------------------------------|--|
| Key Results | - |
| Adverse effects (AEs) | - |
| Expected reporting date | Estimated primary completion date September 2018. Estimated study completion date November 2018. |

ESTIMATED COST and IMPACT

COST

The cost of TGR-1202 (umbralisib) in combination with TG-1101 (ublituximab) is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|--|--|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival <input type="checkbox"/> Other | <input type="checkbox"/> Reduced symptoms or disability <input type="checkbox"/> No impact identified |
|--|--|

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|--|--|
| <input type="checkbox"/> Increased use of existing services <input type="checkbox"/> Re-organisation of existing services <input type="checkbox"/> Other | <input type="checkbox"/> Decreased use of existing services <input type="checkbox"/> Need for new services <input checked="" type="checkbox"/> None identified |
|--|--|

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|---|---|
| <input type="checkbox"/> Increased drug treatment costs <input type="checkbox"/> Other increase in costs <input type="checkbox"/> Other | <input type="checkbox"/> Reduced drug treatment costs <input type="checkbox"/> Other reduction in costs <input checked="" type="checkbox"/> None identified |
|---|---|

OTHER ISSUES

- | | |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

INFORMATION FROM

No information was received from TG Therapeutics.

TG Therapeutics, Inc. 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 TG Therapeutics. *Pipeline – TGR-1202*. Available from <http://www.tgtherapeutics.com/pipeline/TGR-1202.cfm> [Accessed 04 September 2017]
- ² TG Therapeutics. *Pipeline – TG-1101*. Available from <http://www.tgtherapeutics.com/pipeline/TGTG-1101.cfm> [Accessed 04 September 2017]
- ³ Global Data. *Ublituximab + umbralisib tosylate*. Available from <https://pharma.globaldata.com/ProductsView.aspx?ProductType=0,1&ProductID=268838> [Accessed 04 September 2017] Log in required
- ⁴ ClinicalTrials.gov. *Ublituximab + TGR-1202 Compared to Obinutuzumab + Chlorambucil in Patients With Untreated and Previously Treated Chronic Lymphocytic Leukemia (UNITY-CLL)*. Available from <https://clinicaltrials.gov/ct2/show/NCT02612311?term=NCT02612311&rank=1> [Accessed 04 September 2017]
- ⁵ TG Therapeutics. *TG Therapeutics' Novel Combination of TG-1101 (Ublituximab) and TGR-1202 Demonstrates Compelling Early Activity and Safety Profile in Patients With Previously Treated High-Risk Chronic Lymphocytic Leukemia (CLL) and Aggressive Lymphomas*. Available from <http://ir.tgtherapeutics.com/releasedetail.cfm?ReleaseID=861007> [Accessed 04 September 2017]
- ⁶ TG Therapeutics. *TG Therapeutics Announces Orphan Drug Designation for the Combination of TG-1101 and TGR-1202 for Treatment of Chronic Lymphocytic Leukemia*. Available from <http://ir.tgtherapeutics.com/releasedetail.cfm?ReleaseID=1007058> [Accessed 04 September 2017]
- ⁷ TG Therapeutics. *TG Therapeutics Announces Orphan Drug Designation for the Combination of TG-1101 and TGR-1202 for Treatment of Chronic Lymphocytic Leukemia*. Available from <http://ir.tgtherapeutics.com/releasedetail.cfm?ReleaseID=1007058> [Accessed 04 September 2017]
- ⁸ FDA. *Ublituximab and phosphoinositide-3-kinase delta inhibitor*. Available from <https://www.accessdata.fda.gov/scripts/opdlisting/oodp/detailedIndex.cfm?cfgridkey=554216> [Accessed 04 September 2017]
- ⁹ Cancer Research UK. *About chronic lymphocytic leukaemia*. Available from <http://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/about> [Accessed 05 September 2017]
- ¹⁰ American Cancer Society. *About chronic lymphocytic leukemia*. Available from <https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/what-is-cll.html> [Accessed 05 September 2017]
- ¹¹ Leukaemia Care. *Chronic lymphocytic leukaemia*. Available from http://www.leukaemiacare.org.uk/chronic-lymphocytic-leukaemia?gclid=EAlaIqobChMIg5eJ_8-N1glVQZPtCh07JQ2rEAAyAIAAEgKOrPD_BwE [Accessed 05 September 2017]
- ¹² NHS Choices. *Chronic lymphocytic leukaemia*. Available from <http://www.nhs.uk/conditions/leukaemia-chronic-lymphocytic/Pages/Introduction.aspx> [Accessed 05 September 2017]
- ¹³ American Cancer Society. *What are the risk factors for chronic lymphocytic leukemia?* Available from <https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/causes-risks-prevention/risk-factors.html> [Accessed 05 September 2017]
- ¹⁴ Cancer Research UK. *Chronic lymphocytic leukaemia- risks and causes*. Available from <http://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/risks-causes> [Accessed 05 September 2017]
- ¹⁵ Cancer Research UK. *Chronic lymphocytic leukaemia (CLL) incidence statistics*. Available from <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll/incidence#heading-Five> [Accessed 05 September 2017]

¹⁶ Cancer Research UK. *Chronic lymphocytic leukaemia (CLL) survival statistics*. Available from <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll/survival#heading-Zero> [Accessed 05 September 2017]

¹⁷ NHS Choices. *Treating chronic lymphocytic leukaemia*. Available from <http://www.nhs.uk/Conditions/leukaemia-chronic-lymphocytic/Pages/Treatment.aspx> [Accessed 05 September 2017]