National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: May 2018

Ublituximab in combination with ibrutinib for high risk chronic lymphocytic leukaemia

NIHRIO (HSRIC) ID: 9735 NICE ID: 9742

LAY SUMMARY

Chronic lymphocytic leukaemia (CLL) is a type of cancer in which too many white blood cells are produced. These cells develop abnormally and are unable to function and fight infection. They also prevent the production of other healthy blood cells. As the disease is chronic, it develops very slowly over time. CLL is one of the most common type of leukaemia in adults, usually occurring in the elderly population. High risk CLL is cancer that does not get better with treatment. General symptoms of CLL include: fatigue, frequent infections, swollen lymph nodes (commonly in the neck, armpits and groin), anaemia, easy bruising/bleeding, enlarged spleen (causing tender lump in upper left abdomen), night sweats and weight loss.

The combination of ublituximab (intravenous infusions) and ibrutinib (oral capsules) is being developed as a new treatment option for patients with high risk CLL. Both drugs act in different unique ways to improve the body's natural defence to fight the cancer cells and their combined effect may significantly reduce symptoms of the disease and increase survival. If licensed, the combination of ublituximab and ibrutinib will offer an additional treatment option for patients with high risk CLL who have received other previous treatment. This combination has the potential to improve effectiveness by offering a quicker time to response and a greater depth of response compared with ibrutinib alone.

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.

TARGET GROUP

Chronic lymphocytic leukaemia (high risk) – second line; in combination with ibrutinib

TECHNOLOGY

DESCRIPTION

Ublituximab (TG-1101) is a monoclonal antibody that targets a unique epitope on the B-lymphocyte CD20 antigen. Ublituximab has been bioengineered to deliver enhanced clinical activity and potency. Developed for the treatment of B-cell proliferative disorders, including Non-Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukaemia (CLL), anti-CD20 antibodies target and aid in the depletion of B-lymphocytes.[1]

Ibrutinib is a potent, small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, leading to sustained inhibition of BTK enzymatic activity. BTK, a member of the Tec kinase family, is an important signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in the pathogenesis of several B-cell malignancies, including mantle cell lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and chronic lymphocytic leukaemia (CLL).[2]

The addition of ublituximab to ibrutinib is in the phase III clinical trial (NCT02301156) in previously treated CLL patients with high-risk cytogenetic features. Ublituximab was given by intravenous infusions (IV) at a dose of 900 mg on days 1, 8 and 15 of cycle 1 and day 1 of cycles 2-6 in combination with 420 mg ibrutinib orally once daily. Patients in the combination arm who had not progressed received quarterly infusions of ublituximab maintenance at 900 mg.[3]

Ublituximab is currently in phase III clinical development for patients with other hematologic malignancies and patients with multiple sclerosis.[1]

Ublituximab does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

Ibrutinib is effective in patients with chronic lymphocytic leukaemia (CLL), however, treatment resistance remains a problem. Ublituximab is a novel, type 1, anti-CD20m monocional antibody that binds to a unique epitope on the CD20 antigen, distinct from other treatment options of CLL such as rituximab, ofatumumab and obinutuzumab, and has been glycoengineered to exhibit a low-fucose fragment crystallizable (Fc) region, thereby demonstrating enhanced antibody-dependent cellular cytotoxicity (ADCC).[4]

In a phase II study evaluating the combination therapy of ibrutinib and ublituximab for patients with relapsed/refractory CLL, 20 of the 45 enrolled patients with high risk features had an overall response rate of 95% with three patients (15%) achieving negative minimal residual disease and the median time to response was 8 weeks.[4]

If licensed, the combination of ublituximab and ibrutinib will offer an additional second-line treatment option for patients with high risk CLL with a potential to improve effectiveness by offering a quicker time to response and a greater depth of response for patients with relapsed and refractory CLL compared with ibrutinib alone.[4]

DEVELOPER

TG Therapeutics

REGULATORY INFORMATION/ MARKETING PLANS

Ublituximab is a designated orphan drug in the USA for CLL granted in August 2010.[5]

The recombinant chimeric monoclonal antibody against CD20 is a designated orphan drug in the EU for CLL granted in November 2009.[6]

PATIENT GROUP

BACKGROUND

Chronic lymphocytic leukaemia (CLL). is a type of B lymphocyte cancer. B lymphocytes are a type of white blood cells (leukocytes). In CLL, abnormal white blood cells develop from the lymphoid blood stem cells. These leukaemia cells are unable to function as normal lymphocytes and can accumulate in the blood and bone marrow, preventing the production of healthy blood cells. As a chronic leukaemia, CLL develops slowly over time.

High risk or relapsed/refractory CLL is cancer that does not get better with treatment.[7] Refractory CLL is when some people do not respond to treatment while relapsed CLL is when some respond to treatment but develop CLL again after initial treatment. High risk would generally be regarded as the subgroup of patients who require treatment for progressive disease but also show features suggesting that they are expected to have a poorer outcome than average.[8]

CLL is one of the most common types of leukaemia in adults. It is most common in those over 60 years old and rarely occurs in those under 40 years old.[9] Because CLL develops slowly, people often have no symptoms in early stages. General symptoms of CLL include: fatigue, frequent infections, swollen lymph nodes (commonly in the neck, armpits and groin), anaemia, easy bruising/bleeding, enlarged spleen (causing tender lump in upper left abdomen), night sweats and weight loss.[10]

Various risk factors CLL have been identified, including: a family history of CLL, exposure to electromagnetic radiation, the presence of a compromised immune system (HIV/AIDS patients or individuals on immunosuppressive medication) and exposure to certain hair dyes. CLL is also more common in men and people of Australian, American and European origin.[11] Several genetic changes have also been identified and are regularly tested for as part of a CLL diagnosis. Deletions or mutations in these genes can change CLL prognosis and treatment. 30-50% people with CLL have a 13q deletion which results in an extremely slow developing type of CLL that may not require treatment for many years.[12]

CLINICAL NEED and BURDEN OF DISEASE

In 2015, the crude incidence rate of CLL (ICD-10: C91.1) in England was 5.9 per 100,000 population and in the UK, the crude incidence rate of CLL was 5.7 per 100,000 population.[13]

In 2014, CLL accounted for less than 1% of cancer deaths in the UK. There were 628 (61%) CLL deaths in males and 405 (39%) CLL deaths in females (male: female ratio of 16:10). This equates to a crude mortality rate of 2 per 100,000 in males and 1 per 100,000 in females.[14]

In 2016-17, there were 25,509 admissions for chronic lymphoid leukaemia of B-cell type (ICD-10:C91.1) in England, resulting in 13,926 bed days and 26,404 finished consultant episodes.[15]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Leukaemia (chronic lymphocytic, relapsed) – oftamumab (maintenance) (GID – TAG482). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Leukaemia (chronic lymphocytic) – idealalisib (with oftamumab) (GID – TA10008). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Idelalisib with bendamustine and rituximab for previously treated chronic lymphocytic leukaemia (GID – TA10109). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia (GID – TA10160). Expected February 2019.
- NICE technology appraisal. Venetoclax for treating chronic lymphocytic leukaemia (TA487). November 2017.
- NICE technology appraisal. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (TA429). January 2017.
- NICE technology appraisal. 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. Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (TA119). February 2007.

NHS ENGLAND and POLICY GUIDANCE

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

- Follows et al. Interim statement from the BCSH CLL Guidelines Panel. 2017[16]
- Ladetto et al. ESMO consensus conference on malignant lymphoma: general perspectives and recommendations for prognostic tools in mature B-cell lymphomas and chronic lymphocytic leukaemia. 2016[17]
- Eichhorst et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015[18]
- Agrawal. Chronic Lymphocytic Leukaemia Guidelines. 2015[19]
- Oscier et al. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. 2012[20]

CURRENT TREATMENT OPTIONS

Treatment options for relapsed/refractory CLL will vary mainly according to response to previous treatments.

Guidelines recommend the use of:

- Medicinal products:
    - Bendamustine – for those where fludarabine based treatment is inappropriate[21]
    - Ibrutinib (alone) – for those who have had at least 1 prior therapy or for those with 17p deletion/TP53 mutation and in whom chemo-immunotherapy is unsuitable[22]
    - Rituximab in combination with fludarabine and cyclophosphamide – for people with relapsed or refractory CLL[23]
    - Venetoclax in patients:[24]
        - with a 17p deletion or TP53 mutation and whose disease has progressed after a B-cell receptor pathway inhibitor or
        - without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor and

- Stem cell and bone marrow transplant – high dose chemotherapy and radiotherapy followed by transplantation of stem cells from a genetically similar donor (allogenic).[25]

- Radiotherapy –should be considered for patients for whom chemo-immunotherapy has been ineffective or is contra-indicated and can provide effective palliation in cases with symptomatic bulky lymphadenopathy.[26]

Other treatment options intended for secondary effects of CLL and/or CLL treatment include:[27]

- Supportive therapies for CLL e.g. immunoglobulin replacement therapy – to help prevent/treat infections
- Antibiotic, antifungal and antiviral medications – to treat infections in CLL patients
- Granulocyte-colony stimulating factor (G-CSF) injections – to boost white blood counts
- Blood transfusions – to treat severe anaemia or bleeding and bruising problems

EFFICACY and SAFETY	
Trial	NCT02013128, UTX-IB-104; Ublituximab in combination with Ibrutinib in Select B-cell Malignancies; phase I/II
Sponsor	TG Therapeutics, Inc.
Status	Completed.
Source of Information	Trial registry[28]
Location	USA
Design	Single group assignment
Participants	N=62; aged 18 years and older; confirmed Mantle Cell lymphoma (MCL) open for enrolment; refractory to or relapsed after at least 1 prior treatment regimen; eastern Cooperative Oncology Group (ECOG) score of 0 to 2
Schedule	Subjects received ublituximab intravenous (IV) infusion dose on days 1, 8 and 15 followed by maintenance infusions and ibrutinib fixed oral daily dose. Subjects received ublituximab IV fusion in combination with ibrutinib at an oral daily dose for subjects with CLL MCL.
Follow-up	-
Primary Outcomes	• To evaluate the safety of ublituximab in combination with ibrutinib in patients with select B-cell malignancies [Time Frame: 28 days (1 cycle of therapy)] • To determine the incidence of adverse events, any potential abnormal laboratory results and any dose-limiting toxicities
Secondary Outcomes	Overall response rate [Time frame: up to 1 year]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	-

Trial	GENUINE Study, NCT02301156, UTX-IB-301; high-risk CLL; Ublituximab in Combination with Ibrutinib Versus Ibrutinib alone; phase III
Sponsor	TG Therapeutics, Inc.
Status	Completed
Source of Information	Trial registry,[29] abstract,[30] press release[3]
Location	USA, Israel
Design	Randomised, parallel assignment

Participants	n=126; aged 18 years and older; relapsed/refractory CLL requiring treatment
Schedule	Randomised to ublituximab intravenously at a dose of 900 mg on days 1, 8 and 15 of cycle 1 and day 1 of cycles 2-6 followed by maintenance quarterly infusions at 900 mg and every 3 cycles thereafter in combination with ibrutinib orally at 420 mg once daily; or ibrutinib orally at 420 mg once daily alone
Follow-up	Median follow up: 11.4 months
Primary Outcomes	• Overall Response Rate (ORR) - Every 8-12 weeks, up to 2 years
Secondary Outcomes	• Complete response (CR) rate • Safety • Duration of response (DoR) • Time to response (TTR) • Progression-Free Survival (PFS) • Minimal residual disease (MRD) negativity
Key Results	• The GENUINE study met its primary endpoint, demonstrating that ublituximab in combination with ibrutinib yields superior ORR to ibrutinib alone in high-risk CLL: - ORR 78% (UTX+IB) vs.45% (IB), p<0.001 - CR rate 7% vs. 0 (secondary endpoint) - MRD rate 19% vs 2% (secondary endpoint), p<0.01 • Secondary endpoint shows trend (HR=0.559) in improvement of PFS however not statistically significant at time of analysis • With the exception of infusion related reactions, ublituximab did not alter the safety profile of ibrutinib monotherapy
Adverse effects (AEs)	The most common adverse events (reported in ≥10% of the combination treated subjects) included: • Infusion reaction • Diarrhoea • Fatigue • Insomnia • Nausea • Headache • Arthralgia • Cough • Abdominal pain • Stomatitis • Upper Respiratory Infection • Dizziness • Contusion • Anaemia • Peripheral Edema
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of ublituximab is not yet known.

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] TG Therapeutics. *Pipeline: Ublituximab (TG-1101)*. Available from: http://www.tgtherapeutics.com/pipeline/TGTX-1101.cfm [Accessed 23rd April 2018]

[2] Emc *5. Pharmacological properties*. Available from: https://www.medicines.org.uk/emc/product/3414#PHARMACOLOGICAL_PROPS [Accessed 21st May 2018]

[3] TG Therapeutics. *TG Therapeutics Announces Positive Data from Phase 3 GENUINE Trial of TG-1101 in Combination with Ibrutinib in Patients with High Risk Chronic Lymphocytic Leukemia at the 53rd Annual Meeting of the American Society of Clinical Oncology*. Available from: http://ir.tgtherapeutics.com/news-releases/news-release-details/tg-therapeutics-announces-positive-data-phase-3-genuine-trial-tg?releaseid=1028913 [Accessed 1st May 2018]

[4] Sharman JP, Farber CM, Mahadevan D, Schreeder MT, Brooks HD, Kolibaba KS, Fanning S, Klein L, Greenwald DR, Sportelli P, Miskin HP. Ublituximab (TG-1101), a novel glycoengineered anti-CD20 antibody, in combination with ibrutinib is safe and highly active in patients with relapsed and/or refractory chronic lymphocytic leukaemia: results of a phase 2 trial. *British Journal of Haematology*. 2017 Feb 1;176(3):412-20. [Accessed 3rd May 2018]

[5] U.S. Food and Drug Administration. Search Orphan Drug Designations and Approvals. Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=296609. [Accessed 3rd May 2018]

[6] European Medicines Agency. *Orphan Designation*. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2009/12/human_orphan_000720.jsp&mid=WC0b01ac058001d12b [Accessed 3rd May 2018]

[7] National Cancer Institute. *Chronic Lymphocytic Leukaemia Treatment 9PDQ) - Patient Version*. Available from https://www.cancer.gov/types/leukemia/patient/cll-treatment-pdq [Accessed 23rd April 2018]

[8] Hewamana S, Dearden C. Treatment options for high-risk chronic lymphocytic leukaemia. *Therapeutic advances in hematology.* 2011 Jun;2(3):147-59.

[9] NHS Choices. *Chronic Lymphocytic Leukaemia* - Overview. Available from: http://www.nhs.uk/conditions/leukaemia-chronic-lymphocytic/Pages/Introduction.aspx [Accessed 23rd April 2018]

[10] MacMillian Cancer Support. *Signs and Symptoms of CLL. Understanding chronic lymphocytic leukaemia* Available from: http://www.macmillan.org.uk/information-and-support/leukaemia/chronic-lymphocytic/understanding-cancer/signs-and-symptoms.html [Accessed 23rd April 2018]

[11] Cancer Research UK. *Risks and Causes. Chronic lymphocytic leukaemia*. Available from: http://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/risks-causes [Accessed 23rd April 2018]

[12] MacMillian Cancer Support. *Understanding Chronic Lymphocytic Leukaemia*: Macmillian cancer support. Available from http://www.macmillan.org.uk/information-and-support/leukaemia/chronic-lymphocytic/understanding-cancer [Accessed 23rd April 2018]

[13] 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-Zero [Accessed 20th April 2018]

[14] Cancer Research UK. *Chronic lymphocytic leukaemia (CLL) mortality statistics*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll/mortality#heading-Zero [Accessed 19th April 2018]

[15] NHS Digital. *Hospital Admitted Patient Care Activity, 2016-17*. Available from: https://digital.nhs.uk/catalogue/PUB30098 [Accessed 23 October 2017]

[16] Follows GA, Bloor A, Dearden C, Devereux S, Fox CP, Hillmen P, Kennedy B, McCarthy H, Parry-Jones N, Patten PE, Schuh10 A. Interim statement from the BCSH CLL Guidelines Panel. [Accessed 3rd May 2018]

[17] Ladetto M, Buske C, Hutchings M, Dreyling M, Gaidano G, Le Gouill S, Luminari S, Pott C, Zamò A, Zucca E, the ESMO Lymphoma Consensus Conference Panel Members. ESMO consensus conference on malignant lymphoma: general perspectives and recommendations for prognostic tools in mature B-cell lymphomas and chronic lymphocytic leukaemia. *Annals of Oncology*. 2016 Dec 1;27(12):2149-60. [Accessed 3rd May 2018]

[18] Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, Buske C. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2015 Aug 25;26(suppl_5):v78-84. [Accessed 3rd May 2018]

[19] Agrawal S. *Chronic Lymphocytic Leukaemia Guidelines*. Available from: http://www.londoncancer.org/media/123091/Chronic-Lymphocytic-Leukaemia_London-Cancer-Guidelines.pdf [Accessed 19th March 2018]

[20] 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. [Accessed 3rd May 2018]

[21] National Institute for Health and Care Excellence. *Bendamustine for the first-line treatment of chronic lymphocytic leukaemia.* Available from: https://www.nice.org.uk/guidance/ta216/chapter/1-Guidance [Accessed 1st May 2018]

[22] National Institute for Health and Care Excellence. *Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation*. Available from: https://www.nice.org.uk/guidance/ta429 [Accessed 1st May 2018]

[23] National Institute for Health and Care Excellence*. Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia.* Available from: https://www.nice.org.uk/guidance/ta193 [Accessed 1st May 2018]

[24] National Institute for Health and Care Excellence. *Venetoclax for treating chronic lymphocytic leukaemia.* Available from: https://www.nice.org.uk/guidance/ta487/chapter/1-Recommendations [Accessed 1st May 2018]

[25] Cancer Research UK. *Chronic Lymphocytic Leukaemia: Stem cell and bone marrow transplant.* Available from: http://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/treatment/stem-cell-bone-marrow-transplant [Accessed 1st May 2018]

[26] Cancer Research UK. *Chronic Lymphocytic Leukaemia: Having radiotherapy.* Available from: http://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/treatment/radiotherapy/having [Accessed 1st May 2018]

[27] MacMillan Cancer Support. *Supportive and other treatments*. Available from: https://www.macmillan.org.uk/information-and-support/leukaemia/chronic-lymphocytic/treating/supportive-and-other-treatments/supportive-therapies. [Accessed 1st May 2018]

[28] ClinicalTrials.gov *Ublituximab + Ibrutinib in Select B-cell Malignancies*. Available from: https://clinicaltrials.gov/ct2/show/record/NCT02013128 [Accessed 3rd May 2018]

[29] ClinicalTrials.gov *Ublituximab in Combination With Ibrutinib Versus Ibrutinib Alone in Patients With Previously Treated High-Risk Chronic Lymphocytic Leukemia (CLL). Available from: https://clinicaltrials.gov/ct2/show/NCT02301156* [Accessed 19th March 2018]

[30] Sharman JP, Brander DM, Mato A, Kambhampati S, Burke JM, Lansigan F, Schreeder MT, Lunin SD, Ghosh N, Zweibach A, Shtivelband MI. Ublituximab And Ibrutinib For Previously Treated Genetically High-Risk Chronic Lymphocytic Leukemia: Results Of The Genuine Phase 3 Study. *Hematological Oncology*. 2017 Jun 1;35(S2):111-2. [Accessed 3rd May 2018]