Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Adult Chronic Lymphoblastic Leukaemia (CLL)

Introduction

The word *leukaemia* can literally be translated to mean 'white blood' and is used to describe a variety of cancers that begin in the blood-forming cells (lymphocytes) of the bone marrow.

CLL

Leukaemias are divided into two major types:

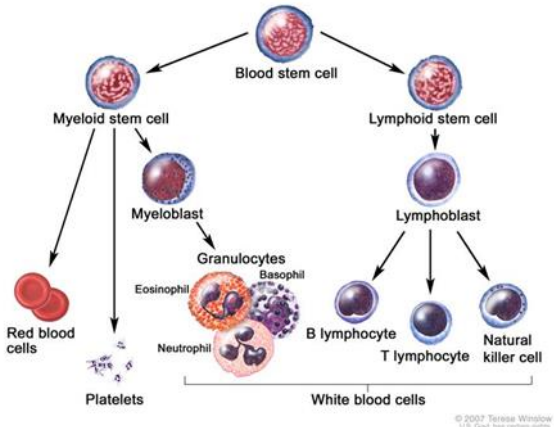
- Acute Leukaemia which usually progresses quickly with many immature white cells
- Chronic Leukaemia which progresses more slowly and has more mature white cells

Both leukaemia and lymphomas (Hodgkin's Lymphoma and non-Hodgkin's lymphomas) are cancers of lymphocytes. The difference is that leukaemia starts in the bone marrow while lymphomas originate in lymph nodes and then spread to the bone marrow or other organs.

White blood cells (*leukocytes*) evolve from immature cells referred to as *blasts*. Malignancy of these blast cells is the source of leukaemias.

Chronic Lymphoblastic Leukaemia

Chronic lymphoblastic leukaemia (CLL) is a type of slow growing leukaemia that affects developing *B-lymphocytes* (also known as B-cells).These cells are specialised white blood cells. Under normal conditions they produce immunoglobulins (also called antibodies) that help protect individuals against infection and disease. In people with CLL, lymphocytes undergo a malignant (cancerous) change and become leukaemic cells.



[Picture Credit: Blood Cell Development]

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Flores, J.C., Gracia-Lavedan, E., Benavente, Y., Amiano, P., Romaguera, D., Costas, L., Robles, C., Gonzalez-Barca, E., de la Banda, E., Alonso, E., Aymerich, M., Campo, E., Dierssen-Sotos, T., Marcos-Gragera, R., Rodriguez-Suarez, M.M., Solans, M., Gimeno, E., Garcia Martin, P., Aragones, N., Shivappa, N., Hébert, J.R., Pollan, M., Kogevinas, M., de Sanjose, S., Castaño-Vinyals, G. & Casabonne, D. 2020.

"Chronic inflammation plays a role in the development of chronic lymphocytic leukaemia (CLL), and diet might modulate chronic inflammation. This study aims to evaluate the association between the dietary inflammatory index (DII®) and CLL. A total of 366 CLL cases and 1643 controls of the Spanish multicase-control (MCC) Spain study were included. The inflammatory potential of the diet was assessed using the energy-adjusted dietary inflammatory index (E-DII) based on 30 items from a validated semi-quantitative food frequency questionnaire. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression models controlling for potential confounders. Overall, a modest, non-statistically significant, positive association was observed between CLL and E-DII scores (OR for a one-unit increase in E-DII: 1.05 (CI 95%: 0.99, 1.12), *p*-value = 0.09 and by tertiles: OR_{T2vsT1}: 1.20 (CI 95%: 0.90, 1.59); OR_{T3vsT1}: 1.21 (CI 95%: 0.90, 1.62), *p* trend = 0.21). These results were independent from disease severity (*p*-het: 0.70), time from diagnosis (*p*-het: 0.67) and CLL treatment received (*p*-het: 0.56). No interactions were detected. In conclusion, the consumption of a diet with high pro-inflammatory components was not significantly associated with CLL. Changes towards a more pro-inflammatory dietary pattern in younger generations not included here warrant future research."

Incidence of Adult Chronic Lymphoblastic Leukaemia in South Africa

In providing the incidence figures of Leukaemia in South Africa, the outdated National Cancer Registry (2017) does not make provision for the reporting of the different types of Leukaemia – it also does not differentiate between acute and chronic Leukaemia - neither does it provide for different statistics for cases of adult and childhood Leukaemia - except in the 'Frequency of Histologically Diagnosed Cancer in South Africa' Section of the Registry .

According to the National Cancer Registry (2017) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2017:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	338	1:634	0,85%
Asian males	7	1:1 000	1,72%
Black males	151	1:1 357	1,12%
Coloured males	29	1:862	0,58%
White males	151	1:209	0,72%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	230	1:1 289	0,55%
Asian females	8	1:1 010	0,62%
Black females	106	1:2 410	0,56%
Coloured females	25	1:1 074	0,53%
White females	91	1:455	0,52%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Males 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	82	21	29	33	54	61	42	16
Asian males	0	0	3	1	1	1	1	0
Black males	66	10	19	16	16	19	4	1
Coloured males	7	2	1	4	8	3	6	1
White males	9	9	6	12	31	38	3	14

Group - Females 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	40	17	20	28	31	39	37	18
Asian females	1	1	0	6	2	3	1	0
Black females	32	10	17	12	15	14	2	4
Coloured females	1	3	0	5	4	6	5	1
White females	6	3	3	11	10	16	29	13

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Risk Factors for Adult Chronic Lymphoblastic Leukaemia

There are very few risk factors for adult chronic lymphoblastic leukaemia (CLL).

Certain chemical exposures – some studies have linked exposure to Agent Orange, a herbicide used during the Vietnam War, to an increased risk for CLL. Some other studies have suggested that farming and long-term exposure to some pesticides may be linked to an increased risk for CLL, but more research is needed.

Leon, M.E., Schinasi, L.H., Lebailly, P., Beane Freeman, L.E., Nordby, K.C., Ferro, G., Monnereau, A., Brouwer, M., Tual, S., Baldi, I., Kjaerheim, K., Hofmann, J.N., Kristensen, P., Koutros, S., Straif, K., Kromhout, H. & Schüz, J. 2019.

BACKGROUND: Pesticides are commonly used in agriculture, and previous studies endorsed the need to further investigate the possible association between their use and risk of lymphoid malignancies in agricultural workers.

METHODS: We investigated the relationship of ever use of 14 selected pesticide chemical groups and 33 individual active chemical ingredients with non-Hodgkin lymphoid malignancies (NHL) overall or major subtypes, in a pooled analysis of three large agricultural worker cohorts. Pesticide use was derived from self-reported history of crops cultivated combined with crop-exposure matrices (France and Norway) or self-reported lifetime use of active ingredients (USA). Cox regression models were used to estimate cohort-specific hazard ratios (HRs) and 95% confidence intervals (CIs), which were combined using random effects meta-analysis to calculate meta-HRs.

RESULTS: During follow-up, 2430 NHL cases were diagnosed in 316 270 farmers accruing 3 574 815 person-years under risk. Most meta-HRs suggested no association. Moderately elevated meta-HRs were seen for: NHL and ever use of terbufos (meta-HR = 1.18, 95% CI: 1.00-1.39); chronic lymphocytic leukaemia/small lymphocytic lymphoma and deltamethrin (1.48, 1.06-2.07); and diffuse large B-cell lymphoma and glyphosate (1.36, 1.00-1.85); as well as inverse associations of NHL with the broader groups of organochlorine insecticides (0.86, 0.74-0.99) and phenoxy herbicides (0.81, 0.67-0.98), but not with active ingredients within these groups, after adjusting for exposure to other pesticides.

CONCLUSIONS: Associations of pesticides with NHL appear to be subtype- and chemical-specific. Non-differential exposure misclassification was an important limitation, showing the need for refinement of exposure estimates and exposure-response analyses.

Family history – first-degree relatives (parents, siblings or children) of CLL patients have more than twice the risk for Adult Chronic Lymphoblastic Leukaemia.

Sex – CLL is slightly more common in males than females.

Gene mutations – scientists know that most cases of leukaemia are associated with specific gene mutations, but in most cases, it is not clear what causes those mutations.

Age – it is largely a disease of older adults. Being middle-aged or older – the average age of diagnosis is 72 years.

A Second Cancer – Individuals with CLL often has a higher risk of developing a second cancer.

Signs and Symptoms of Adult Chronic Lymphoblastic Leukaemia

CLL is usually discovered during a routine blood test. Sometimes symptoms occur that may be caused by CLL or by other conditions.

The following include signs and symptoms of CLL:

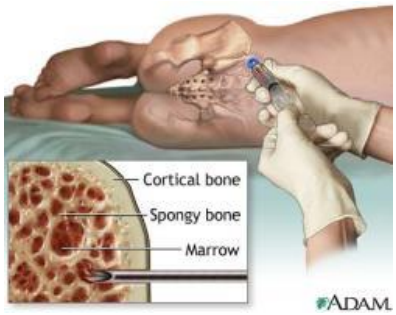
- Painless swelling of the lymph nodes in the neck, underarm, abdomen, or groin
- Feeling tired most of the time
- Fever with recurring infections
- Sweating at night
- Bruises without history of really injury
- Weight loss without trying to lose weight
- Enlargement of the spleen
- Rapid heartbeat
- Rapid breathing

Diagnosis of Adult Chronic Lymphoblastic Leukaemia

The following tests may be used to diagnose CLL:

Blood tests: a complete blood count (CBC; a routine blood test) is the first test used to begin the process of diagnosing CLL. It measures the number of different types of cells in a sample of a person's blood.

Bone marrow aspiration and biopsy: CLL can usually be diagnosed with blood tests because the cancerous cells are easily found in the blood.



[Picture Credit: Bone Marrow Aspiration]

Bone marrow has both a solid and a liquid part. A bone marrow biopsy is the removal of a small amount of solid tissue using a needle. An aspiration removes a sample of fluid with a needle. The sample(s) are then analysed by a pathologist (a doctor who specialises in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease).

For some patients, a bone marrow aspiration and biopsy may be used to help determine prognosis (chance of recovery) or provide more information about the reasons that other blood counts may be abnormal.

Flow cytometry and cytochemistry: in these tests, cancer cells are treated in the laboratory with chemicals or dyes that provide information about the leukaemia and its subtype.

Molecular testing: the doctor may recommend running laboratory tests on the leukaemia cells to identify specific genes, proteins, chromosome changes, and other factors unique to the leukaemia.

Imaging tests: Sometimes imaging tests may be recommended to find out the parts of the body affected by CLL or to find out whether particular symptoms may be related to CLL. Imaging tests may also be used to see how well treatment is working.

- An X-ray is a way to show if cancer is growing in lymph nodes in the chest
- A computed tomography (CT or CAT) scan (a three-dimensional picture of the inside of the body) can detect lymph nodes with CLL around the heart, windpipe, lungs, and abdomen, and pelvis.

Imaging tests are rarely needed to diagnose CLL, but they are sometimes used before treatment to determine which parts of the body are affected by CLL.

Afacan-Öztürk, H.B., Falay, M., Albayrak, M., Yıldız, A., Öztürk, Ç.P., Maral, S. & Özet, G. 2019.
BACKGROUND: Immunophenotyping has a central role in CLL. However, CLL is a very heterogenous disease, both morphologically and immunophenotypically; thus, its diagnosis may prove a challenge. We investigated CD81 ex-pression in the differential diagnosis of CLL and MCL.
METHODS: We retrospectively examined CD81 expression with 8 color Multiparameter Flow cytometry devices in 101 CLL and 19 MCL cases.
RESULTS: We found negative CD81 expression in CLL cases whereas it was positive in MCL cases.
CONCLUSIONS: Our results suggest that CD81 may be a valuable marker for the differential diagnosis of CLL. We are of the opinion that it should be definitely included in the diagnostic algorithm for CLL.

Staging of Adult Chronic Lymphoblastic Leukaemia
Two systems for staging of CLL are in use. Both systems are based upon results of a physical examination and blood tests. Staging of CLL helps determine how likely it is that a patient will develop serious problems related to his/her illness.

The Rai System – the Rai system is based on an analysis of how the body is affected by the abnormal lymphocytes. There are five stages. The higher numbers indicate a more advanced stage of the disease.

The Binet System – This system considers the five possible sites where lymphocytes can collect (lymph nodes in the neck, armpit and groin, and lymphocyte-containing channels in the spleen and liver, and also whether anaemia or low platelet counts are present.

Treatment of Adult Chronic Lymphoblastic Leukaemia
Individuals who do not have symptoms of chronic lymphoblastic leukaemia are usually not treated for their disease. They are, however, usually monitored regularly with blood tests and physical examinations.

PDQ Adult Treatment Editorial Board. 2019. Chronic Lymphocytic Leukemia Treatment (PDQ®): Health Professional Version.
"Treatment of chronic lymphocytic leukemia (CLL) ranges from periodic observation with treatment of infectious, hemorrhagic, or immunologic complications to a variety of therapeutic options, including steroids, alkylating agents, purine analogs, combination chemotherapy, monoclonal antibodies, and transplant options. Because this disease is generally not curable, occurs in an elderly population, and often progresses slowly, it is most often treated in a conservative fashion. In asymptomatic patients, treatment may be deferred until the patient becomes symptomatic as the disease progresses. Since the rate of progression may vary from patient to patient, with long periods of stability and sometimes spontaneous regressions, frequent and careful observation is required to monitor the clinical course."

Treatment of localised adult CLL – individuals who have Stage I chronic lymphoblastic leukaemia are sometimes treated with radiation therapy. This refers to the exposure of tissues to high-energy X-rays in order to slow or stop their growth.

Treatment of advanced or symptomatic CLL – individuals with advanced or symptomatic CLL are generally treated first with chemotherapy.

Jiang, L., Malik, N., Acedo, P. & Zawacka-Pankau, J. 2019.
"p53 is a tumor suppressor, which belongs to the p53 family of proteins. The family consists of p53, p63 and p73 proteins, which share similar structure and function. Activation of wild-type p53 or TAp73 in tumors leads to tumor regression, and small molecules restoring the p53 pathway are in clinical development. Protoporphyrin IX (PpIX), a metabolite of aminolevulinic acid, is a clinically approved drug applied in photodynamic diagnosis and therapy. PpIX induces p53-dependent and TAp73-dependent apoptosis and inhibits TAp73/MDM2 and TAp73/MDM4 interactions. Here we demonstrate that PpIX is a dual inhibitor of p53/MDM2 and p53/MDM4 interactions and activates

apoptosis in B-cell chronic lymphocytic leukemia cells without illumination and without affecting normal cells. PpIX stabilizes p53 and TAp73 proteins, induces p53-downstream apoptotic targets and provokes cancer cell death at doses non-toxic to normal cells. Our findings open up new opportunities for repurposing PpIX for treating lymphoblastic leukemia with wild-type *TP53*."

Treatment of relapsed CLL – if relapse occurs six or more months after treatment ends, it is often possible to successfully use the same chemotherapy regimen again or use another chemotherapy treatment.

Treatment of refractory (resistant) CLL – if a person's disease is refractory or relapses sooner than six months after treatment ends, the options for treatment may be limited.

Removal of the spleen (splenectomy) – a number of individuals with CLL will develop an enlarged spleen. While this often responds to treatment with chemotherapy or radiation, removal of the spleen may provide longer lasting benefits including increases in red blood cell and platelet counts.

Bone marrow transplantation – bone marrow transplantation (also called hematopoietic cell transplantation) is being more seriously considered as a therapy for CLL, especially for patients under the age of 55.

There are two main types of stem cell transplant:

Allogeneic transplant – the patient is given stem cells from a donor, ideally a brother or sister with a similar genetic make-up. If the patient does not have a 'matched' sibling, an unrelated person with a partially matched genetic make-up may be used.

Autologous transplant – the patient's own stem cells are removed before the high dose chemotherapy or radiation is given.

Prognosis (outlook) for Adult Chronic Lymphoblastic Leukaemia

The prognosis (chance of recovery) for patients with CLL depends on:

The stage of the disease

- Whether the CLL gets better with treatment or has recurred (come back)
- Whether the CLL progresses to lymphoma or prolymphoblastic leukaemia
- The patient's general health

Eyre, T.A., Roeker, L.E., Fox, C.P., Gohill, S.H., Walewska, R., Walter, H.S., Forconi, F., Broom, A., Arumainathan, A., Brander, D.M., Allan, J.N., Schuster, S.J., Hill, B.T., Lansigan, F., Cheson, B.D., Lamanna, N., Coombs, C.C., Barr, P.M., Skarbnik, A.P., Shadman, M., Ujjani, C.S., Pearson, L., Pagel, J.M., Jacobs, R. & Mato, A.R. 2020.

"Elderly chronic lymphocytic leukaemia (CLL) patients treated outside of trials have notably greater toxicity with the Bruton's tyrosine kinase inhibitor ibrutinib compared to younger patients. It is not known whether the same holds true for the B-cell lymphoma 2 inhibitor venetoclax. We provide a

comprehensive analysis of key safety measures and efficacy in 342 patients comparing age categories ≥75 and <75 years treated in the relapsed, refractory non-trial setting. We demonstrate that venetoclax has equivalent efficacy and safety in relapsed/refractory CLL patients who are elderly, the majority of whom are previous ibrutinib-exposed and therefore may otherwise have few clear therapeutic options."

Ahmadvand, M., Eskandari, M., Khakpour, G., Pashaiefar, H., Manoochehrabadi, S., Yaghmaie, M., Montazer-Zohour, M. & Naghavi, A. 2018.
Background: Chronic lymphocytic leukemia (CLL) is a type of malignancy in which the bone marrow makes too many lymphocytes. MicroRNAs (miRNAs) are endogenous short (~22-nucleotides) non-protein-coding regulatory RNA molecules with key roles in cellular and molecular processes linked to different cancers including CLL. Re-cently, some investigations have demonstrated that miR-125a downregulation is correlated with the expression of P53, NRG1 and ERBB2.
Methods: In this study, samples including 38 patients with CLL and 25 healthy individuals were collected. We used quantitative real-time PCR (qRT-PCR) to assess the expression of miR-125a in plasma of the CLL patients in comparison with healthy controls. Moreover, we used the Kyoto Encyclopedia of Genes and Genomes (KEGG) signaling pathway analysis on miR-125a targets in the DAVID database in order to investigate the potential role of miR-125a in cancer pathways. MiR-125a exerted a variety of roles in the cancer pathway via downregulating target genes including ERBB2.
Results: The expression of miR-125a dramatically decreased (~2-fold) in the patients with CLL compared with the healthy controls ($p = 0.03$). Furthermore, overexpression of miR-125a was associated with different CLL staging and B symptoms (all at $p < 0.05$). The KEGG pathway enrichment analysis demonstrated the eight statistically related KEGG signaling pathways with miR-125a targetome.
Conclusions: The results suggested that the miR-125a expression level could be a novel potential biomarker for CLL prognosis.

Supportive Care
Watch and Wait. People with CLL who have minimal changes in their blood counts and no symptoms are usually managed with observation alone. Patients may have medical examinations and periodic testing to determine whether the disease is stable or beginning to progress.

People are often concerned when they receive a diagnosis of CLL and then learn that they will not begin treatment right away. It is important to know that the watch and wait approach is the current standard of care for people with CLL who have minimal changes in their blood counts and no symptoms.

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.
Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Sharman, J.P., Egyed, M., Jurczak, W., Skarbnik, A., Pagel, J.M., Flinn, I.W., Kamdar, M., Munir, T., Walewska, R., Corbett, G., Fogliatto, L.M., Herishanu, Y., Banerji, V., Coutre, S., Follows, G., Walker, P., Karlsson, K., Ghia, P., Janssens, A., Cymbalista, F., Woyach, J.A., Salles, G., Wierda, W.G., Izumi, R., Munugalavadla, V., Patel, P., Wang, M.H., Wong, S. & Byrd, J.C. 2020.

Background: Acalabrutinib is a selective, covalent Bruton tyrosine-kinase inhibitor with activity in chronic lymphocytic leukaemia. We compare the efficacy of acalabrutinib with or without obinutuzumab against chlorambucil with obinutuzumab in patients with treatment-naive chronic lymphocytic leukaemia.

Methods: ELEVATE TN is a global, phase 3, multicentre, open-label study in patients with treatment-naive chronic lymphocytic leukaemia done at 142 academic and community hospitals in 18 countries. Eligible patients had untreated chronic lymphocytic leukaemia and were aged 65 years or older, or older than 18 years and younger than 65 years with creatinine clearance of 30-69 mL/min (calculated by use of the Cockcroft-Gault equation) or Cumulative Illness Rating Scale for Geriatrics score greater than 6. Additional criteria included an Eastern Cooperative Oncology Group performance status score of 2 or less and adequate haematologic, hepatic, and renal function. Patients with significant cardiovascular disease were excluded, and concomitant treatment with warfarin or equivalent vitamin K antagonists was prohibited. Patients were randomly assigned (1:1:1) centrally via an interactive voice or web response system to receive acalabrutinib and obinutuzumab, acalabrutinib monotherapy, or obinutuzumab and oral chlorambucil. Treatments were administered in 28-day cycles. To reduce infusion-related reactions, acalabrutinib was administered for one cycle before obinutuzumab administration. Oral acalabrutinib was administered (100 mg) twice a day until progressive disease or unacceptable toxic effects occurred. In the acalabrutinib-obinutuzumab group, intravenous obinutuzumab was given on days 1 (100 mg), 2 (900 mg), 8 (1000 mg), and 15 (1000 mg) of cycle 2 and on day 1 (1000 mg) of cycles 3-7. In the obinutuzumab-chlorambucil group, intravenous obinutuzumab was given on days 1 (100 mg), 2 (900 mg), 8 (1000 mg), and 15 (1000 mg) of cycle 1 and on day 1 (1000 mg) of cycles 2-6. Oral chlorambucil was given (0·5 mg/kg) on days 1 and 15 of each cycle, for six cycles. The primary endpoint was progression-free survival between the two combination-therapy groups, assessed by independent review committee. Crossover to acalabrutinib was allowed in patients who progressed on obinutuzumab-chlorambucil. Safety was assessed in all patients who received at least one dose of treatment. Enrolment for this trial is complete, and the study is registered at ClinicalTrials.gov, NCT02475681.

Findings: Between Sept 14, 2015, and Feb 8, 2017, we recruited 675 patients for assessment. 140 patients did not meet eligibility criteria, and 535 patients were randomly assigned to treatment. 179 patients were assigned to receive acalabrutinib-obinutuzumab, 179 patients were assigned to receive acalabrutinib monotherapy, and 177 patients were assigned to receive obinutuzumab-chlorambucil. At median follow-up of 28·3 months (IQR 25·6-33·1), median progression-free survival was longer with acalabrutinib-obinutuzumab and acalabrutinib monotherapy, compared with obinutuzumab-chlorambucil (median not reached with acalabrutinib and obinutuzumab vs 22·6 months with obinutuzumab, hazard ratio [HR] 0·1; 95% CI 0·06-0·17, p<0·0001; and not reached with acalabrutinib monotherapy vs 22·6 months with obinutuzumab, 0·20; 0·13-0·3, p<0·0001). Estimated

progression-free survival at 24 months was 93% with acalabrutinib-obinutuzumab (95% CI 87-96%), 87% with acalabrutinib monotherapy (81-92%), and 47% with obinutuzumab-chlorambucil (39-55%). The most common grade 3 or higher adverse event across groups was neutropenia (53 [30%] of 178 patients in the acalabrutinib-obinutuzumab group, 17 [9%] of 179 patients in the acalabrutinib group, and 70 [41%] of 169 patients in the obinutuzumab-chlorambucil group). All-grade infusion reactions were less frequent with acalabrutinib-obinutuzumab (24 [13%] of 178 patients) than obinutuzumab-chlorambucil (67 [40%] of 169 patients). Grade 3 or higher infections occurred in 37 (21%) patients given acalabrutinib-obinutuzumab, 25 (14%) patients given acalabrutinib monotherapy, and 14 (8%) patients given obinutuzumab-chlorambucil. Deaths occurred in eight (4%) patients given acalabrutinib-obinutuzumab, 12 (7%) patients given acalabrutinib, and 15 (9%) patients given obinutuzumab-chlorambucil.
Interpretation: Acalabrutinib with or without obinutuzumab significantly improved progression-free survival over obinutuzumab-chlorambucil chemoimmunotherapy, providing a chemotherapy-free treatment option with an acceptable side-effect profile that was consistent with previous studies. These data support the use of acalabrutinib in combination with obinutuzumab or alone as a new treatment option for patients with treatment-naive symptomatic chronic lymphocytic leukaemia.
Funding: Acerta Pharma, a member of the AstraZeneca Group, and R35 CA198183 (to JCB).

Flinn, I.W., Gribben, J.G., Dyer, M.J.S., Wierda, W., Maris, M.B., Furman, R.R., Hillmen, P., Rogers, K.A., Padmanabhanyer, S., Quillet-Mary, A., Ysebaert, L., Walter, H.S., Verdugo, M., Klein, C., Huang, H., Jiang, Y., Lozanski, G., Pignataro, D.S., Humphrey, K., Mobasher, M. & Kipps, T.J. 2019. "This single-arm, open-label, phase 1b study evaluated the maximum tolerated dose (MTD) of venetoclax when given with obinutuzumab and its safety and tolerability in patients with relapsed/refractory (R/R) or previously untreated (1L) chronic lymphocytic leukemia. Venetoclax dose initially was escalated (100-400 mg) in a 3+3 design to define the MTD combined with standard-dose obinutuzumab. Patients received venetoclax (Schedule A) or obinutuzumab (Schedule B) first to compare safety and determine dose/schedule for expansion. Venetoclax-obinutuzumab was administered for 6 cycles, followed by venetoclax monotherapy until disease progression (R/R) or fixed-duration 1 year of treatment (1L). 50 R/R and 32 1L patients were enrolled. No dose-limiting toxicities were observed. Safety, including incidence of tumor lysis syndrome (TLS), did not differ between schedules (2 laboratory TLS per schedule). Schedule B and 400 mg dose of venetoclax was chosen for expansion. The most common grade 3-4 adverse event was neutropenia (R/R, 58% of patients; 1L, 53%). Rates of grade 3-4 infections were 29% (R/R) and 13% (1L); no fatal infections occurred in 1L. All infusion-related reactions were grade 1-2, except for 2 grade 3 events. No clinical TLS was observed. Overall best response rate was 95% (CR/CRi, 37%) in R/R and 100% (CR/CRi, 78%) in 1L patients. Rate of undetectable ($<10^{-4}$) minimal residual disease (MRD) in peripheral blood for R/R and 1L patients respectively was 64% and 91% ≥3 months after last obinutuzumab dose. Therapy with venetoclax and obinutuzumab had an acceptable safety profile and elicited durable responses and high rates of undetectable MRD. The study is registered to https://clinicaltrials.gov as NCT01685892."

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American Cancer Institute
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