Submission to the Health Select Committee

on the

Funding of life saving medicines ibrutinib and venetoclax

for Chronic Lymphocytic Leukaemia (CLL)

20 June 2019

Introduction

This submission has been prepared by Neil Graham, founding executive director of CLLANZ (Chronic Lymphocytic Leukaemia Advocates New Zealand), a recently launched patient support group for people with CLL. I am also a Consultant Physician and I am living with CLL.

The submission includes the following appendices:

1. About CLL
2. International guidelines summary for use of ibrutinib and venetoclax for CLL
3. CLL therapies in New Zealand
4. Treatment outcomes observed with ibrutinib and venetoclax
5. Five patient stories

I wish to appear before the committee in support of my submission.

Submission

That the Health Select Committee:

1. **Urges PHARMAC to fund the Medsafe-approved medications ibrutinib and venetoclax** for all appropriate CLL patients, particularly the following 'high-need' subgroups who present an urgent unmet need:
    i. Patients with relapsed or refractory disease (i.e., CLL that has returned after a period of responding to treatment, or is no longer responding to chemotherapy);
    ii. Patients with 17p deletion/TP53 chromosomal abnormality, a poor prognosis subgroup of CLL;
    iii. Patients who are less able to tolerate cytotoxic chemotherapies[1] due to older age and other medical conditions

    and/or to urgently and publicly explain its rationale for further delaying funding these desperately-needed medicines.

2. **Recommends to Parliament that a review be undertaken as a matter of urgency of PHARMAC's processes and operating model in regard to modern oncological medications**:
    i. Including a specific review of PHARMAC's statutory objective:
    "*to secure for eligible people in need of pharmaceuticals the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided."*
    ii. Is this objective still applicable in today's radically different pharmaceutical environment?

[1] Medicines that are toxic to living cells, including cancer cells - fludarabine and cyclophosphamide are examples used in CLL.

iii. How does PHARMAC measure success and optimal health outcomes and how does it weigh the value of individual lives?
iv. How does PHARMAC ensure 'equity of access' to healthcare?

3. **Recommends to Parliament that a pilot rapid access solution for modern oncological medications be developed and put in place as a matter of high priority, that**
   i. Takes a risk-sharing and cost-sharing approach to negotiation with drug companies, including provisional funding only, initially, with analysis of effectiveness at the end of the provisional period.
   ii. Applies a public ICER (incremental cost-effectiveness ratio) threshold to all these medications to enable PHARMAC to achieve the best possible price for New Zealanders sooner/faster.
   iii. Adopts an analogous model to those operating well in countries like the UK, Canada and Australia, where many more modern oncological medications are funded, faster.

4. **Recommends to the Government and commends to the Parliament an immediate increase in PHARMAC's medications budget to bring it into line with other OECD countries**.
   i. Increase NZ's current allocation for medications of only 5% of the national health budget to be aligned with the OECD average of at least 10%, and
   ii. Makes this judgement and allocation in the light of budget currently allocated to preventing the loss of and saving the lives of people involved in accidents.

Overview

- I am alive and well, working as a physician, teaching, paying taxes, and enjoying all that life has to offer, because I was able to access one of these drugs. If not, I would have been dead 5 years ago.

- Not since the introduction of antibiotics almost a century ago has the world seen such death-defying therapeutics development as we are seeing now in cancer. The introduction of drugs like ibrutinib and venetoclax for CLL treatment are only two examples of many many life-changing innovations.

- The PHARMAC model (now 20 years old) of 'delaying while bargaining the price down' worked well in the early years but it is no longer fit for purpose. It does not and cannot work for revolutionary, life-saving treatments that are streaming onto the market for people in life and death situations

- It must change or it must be modified by adding a rapid access scheme, of which there are many models working in the Western world. Some of these include the ability to share the risk and cost with the pharmaceutical company's and divest if the drug does not measure up to expectations.

- PHARMAC is ignoring recommendations published in international guidelines for CLL treatment. In particular, international recommendations for patients with a specific chromosome abnormality, 17p deletion, or relapsed/refractory disease seem to have been entirely disregarded. These patients have an urgent unmet need: chemotherapy is unlikely to work for them, but ibrutinib and venetoclax are highly effective, and would afford an excellent prognosis.

- Ibrutinib and venetoclax have been shown to have a superior effect in patients in the high need subgroups of CLL described earlier. They both have high response rates and an enduring therapeutic effect. Ibrutinib and venetoclax are also relatively free of important side effects and both are oral medications, making for convenient treatment without substantial burden on healthcare resources.

- What price are we putting on a life? Please read the patient stories appended to this submission, all people leading productive lives who would all be dead or seriously sick if not for these modern drugs.

  Audrey accessed venetoclax through a clinical trial. She feels she has been given a new gift of life. She is in remission and has resumed working and leading an active life.

  Ian was able to start ibrutinib through a compassionate access programme following several years of illness and a precarious state of health. He has seen a dramatic difference to his life, with only minor side effects. He works full-time, exercises and is happy.

  Ben received treatment with ibrutinib, also through a compassionate access programme. Previously his CLL had been treated but relapsed twice. He has had no discernible side effects with ibrutinib and says without it his CLL would have returned. He feels great, is able to work and be there for his family and friends. Getting CLL is a case of bad luck but access to ibrutinib shouldn't' be left to chance.

  Graham has the high-risk deletion of the 17p chromosome, meaning his CLL is harder to treat. He describes treatment with a novel agent via a clinical trial as his "Lazarus experience", bringing him back from the near-dead. Graham's NZ born brother is an Australian citizen and would have received ibrutinib for about $40 a month if he'd been the one diagnosed with del17p CLL, while in NZ if you aren't lucky enough to be accepted onto a clinical trial or rich enough to pay you can only expect a place on death row.

- New Zealanders are dying unnecessarily, whilst the rest of the OECD has largely embraced these and many other modern oncological medications. It is a national disgrace and must change.

Ibrutinib and venetoclax should be funded for the following reasons:

1. CLL patients in the high-need subgroups outlined above lack appropriate therapy

- Current publicly funded treatments for the subgroups of high-need CLL patients described are limited by toxicity. For example, fludarabine, a chemotherapy used in the funded FCR regimen Is recommended by guidelines not to be given to patients over 70 years of age due to toxicity concerns (1). With the majority of CLL patients aged 65 years or more (2), use of fludarabine based regimens is limited.

- A subset of patients may achieve durable remissions with other treatments; however, most will relapse within a few years and therefore require alternative treatments to achieve a response to therapy (3).

- With a lack of options for patients who relapse, or become refractory to current treatments, there exists a substantial unmet clinical need for effective and well tolerated therapies for the high-need subgroups (i.e., del17p, relapsed/refractory) of CLL patients in New Zealand.

2. International guidelines for CLL treatment consistently recommend ibrutinib and venetoclax based on the body of clinical evidence for each

- Whilst there are no specific CLL guidelines developed in New Zealand, experts in CLL refer to international evidence based and peer reviewed guidelines. These international guidelines are created, reviewed and updated in alignment with clinical evidence published in peer reviewed journals. This is typically the same evidence provided to PHARMAC in funding submissions for new therapies (i.e., high quality randomised controlled trials).

- Examples of recommendations from the National Comprehensive Cancer Network (NCCN) (1); the European Society of Medical Oncologists (ESMO) (4); and the British Society for Haematology (BSH) (5) include:

  - *In first-line therapy, ibrutinib is the preferred treatment option for frail patients with significant comorbidities (NCCN);*
  - *Ibrutinib and venetoclax are included as preferred options for patients with relapsed or refractory disease, regardless of their age and comorbidities (NCCN);*
  - *Ibrutinib is the preferred treatment option for first-line therapy of patients with del17p (NCCN);*
  - *In relapsed/refractory patients with CLL and del17p, ibrutinib monotherapy, venetoclax plus rituximab and venetoclax monotherapy are listed as preferred regimens (NCCN);*
  - *Ibrutinib is the treatment of choice in front-line therapy for patients with TP53 disruption (del17p) (BSH);*
  - *Ibrutinib monotherapy is a treatment of choice for patients with CLL who are refractory to chemoimmunotherapy, have relapsed after chemoimmunotherapy, or for whom re-treatment with chemoimmunotherapy is inappropriate (BSH);*
  - *Venetoclax is the treatment of choice for patients who fail BCR inhibitor therapy (BSH);*
  - *It is recommended that patients with TP53 mutation/del17p are treated with ibrutinib in front-line (ESMO);*
  - *Patients unsuitable for BCR inhibitor therapy may be treated with the BCL2 inhibitor venetoclax (ESMO);*
  - *If relapse occurs within 24-36 months after chemoimmunotherapy, or if the disease does not respond to any first-line therapy, the therapeutic regimen should be changed. Treatment options include ibrutinib, and if the patient failed BCR inhibitor therapy, venetoclax (ESMO).*

- These examples represent the subgroup of high-need CLL patients described earlier. Many guidelines also recommend the use of targeted therapies in other subgroups of CLL. This submission, however, has focussed on those at greatest need of new therapy options in New Zealand.

3. PHARMAC's own clinical advisory committees have recommended ibrutinib and venetoclax be funded with medium to high priority based on the available clinical evidence

- Ibrutinib has been recommended for funding and prioritised in 2016, however remains unfunded. Venetoclax has been recommended for funding and is undergoing assessment for prioritisation.

- A summary of the evidence for ibrutinib and venetoclax from clinical trials in the high-need CLL patients is provided in appendix 4. Key findings include:

  - *Ibrutinib significantly reduces the risk of death or disease progression by 87% compared with ofatumumab in patients with relapsed/refractory CLL ($p<0.0001$) (6);*
  - *With up to 7 years follow-up, the estimated overall survival rate for relapsed/refractory patients treated with ibrutinib is 52% (7);*
  - *91% of patients with relapsed/refractory CLL who had progressed on ibrutinib and were then treated with ibrutinib were still alive at 12 months with follow-up ongoing (8);*
  - *Venetoclax + rituximab significantly reduces the risk of death or disease progression by 84% compared to bendamustine + rituximab in patients with relapsed/refractory CLL ($p<0.001$) (9);*
  - *With up to 7 years follow-up, median overall survival is 57 months for ibrutinib treated patients with relapsed/refractory del17p CLL (7);*
  - *The estimated survival rate at 5-years for front-line ibrutinib treatment of del17p CLL is 85% (3);*
  - *Venetoclax + rituximab reduced the risk of death or disease progression by 87% compared with bendamustine + rituximab at 2 years follow-up (10);*

- *The estimated rate of overall survival at 2 years is 73% for venetoclax treated patients with relapsed/refractory del17p patients (11).*

- These targeted treatments are changing outcomes for the better around the world, in New Zealand, however, they remain frustratingly out of reach for the people who need them.

4. ***New Zealanders with high-need CLL have been failed by the existing economic model of medication access***

   - Highly effective treatments for people with CLL are ready and waiting to be made available to the New Zealanders who desperately need them; however, they're stuck in a waiting game, despite PHARMAC's own committees recommending they be funded.

   - With a lack of public funding, people are dying of CLL who would have survived if they lived in Australia, or other countries, where these medications are funded.

   - In appendix 5 of this submission there are several stories of New Zealanders who have been failed by the public funding system, however, they've accessed ibrutinib and venetoclax on compassionate grounds or within a clinical trial. Without this access they may not have been alive today to share their stories.

   - Relying on compassionate access, self-funding or a clinical trial is neither sustainable nor acceptable. Self-fund and you live, can't afford to and you die represents a model in crisis.

Recommendations

Submission

That the Health Select Committee:

5. **Urges PHARMAC to fund the Medsafe-approved medications ibrutinib and venetoclax** for all appropriate CLL patients, particularly the following 'high-need' subgroups:
   iv. Patients with relapsed or refractory disease (i.e., CLL that has returned after a period of responding to treatment, or is no longer responding to treatment);
   v. Patients with 17p deletion/TP53 chromosomal abnormality, a poor prognosis subgroup of CLL;
   vi. Patients older than 70 who need treatment, but who generally are unable to tolerate conventional cytotoxic chemotherapy (i.e., medicines that are toxic to living cells, including cancer cells - fludarabine and cyclophosphamide are examples used in CLL).

   and/or to urgently and publicly explain its rationale for further delaying funding these desperately-needed medicines;

6. **Recommends to Parliament that a review be undertaken as a matter of urgency of PHARMAC's processes and operating model in regard to modern oncological medications**:
   v. Including a specific review of PHARMAC's statutory objective:
   "*to secure for eligible people in need of pharmaceuticals the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided."*

vi. Is this objective still applicable in today's radically different pharmaceutical environment?
vii. How does PHARMAC measure success and optimal health outcomes and how does it weigh the value of individual lives?
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7. **Recommends to Parliament that a pilot rapid access solution for modern oncological medications be developed and put in place as a matter of high priority, that**
   iv. Takes a risk-sharing and cost-sharing approach to negotiation with drug companies, including provisional funding only, initially, with analysis of effectiveness at the end of the provisional period.
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   iii. Increase NZ's current allocation for medications of only 5% of the national health budget to be aligned with the OECD average of at least 10%, and
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Summary

Internationally accepted guidelines for CLL treatment cannot be followed in New Zealand because PHARMAC does not fund the required treatments.

New Zealanders are dying because of inability to fund these life-saving therapies in CLL. This does not happen in other western countries, because of these medications being funded by public health services.

New Zealand should adopt funding and supply models of countries like Australia, where more cancer medications are publicly funded and available. This is reflected in cancer treatment outcomes when comparing the two countries.

The world will look at New Zealand as a first world country with third world outcomes in oncological therapeutics, once the success story of modern oncology evolves further.

A national revolution in this public health issue is gaining momentum and will continue. PHARMAC's stance and the outcomes in cancer will not be tolerated.

Providing funding for ibrutinib and venetoclax is urgent and essential for New Zealanders with high-need CLL.

Background to this submission

Ibrutinib was first registered by Medsafe in New Zealand in 2015 and subsequently prioritised for funding by PHARMAC in 2016. Venetoclax was registered in 2017 and has also been prioritisation for funding. PTAC have requested further advice from CaTSoP on the relative priority of both. Both are targeted treatments for

CLL proven to increase survival without the need for the addition of toxic chemotherapy and both remain unfunded in New Zealand.

Ibrutinib and venetoclax are recommended by international guidelines as preferred treatments for CLL patients with del17p, patients with relapsed/refractory disease and for patients unable tolerate chemotherapy (1, 4, 5). Both are widely funded in other OECD countries, including Australia.

These two medications have been shown to have a superior effect in patients in the high need subgroups of CLL described earlier. They both have high response rates and an enduring therapeutic effect. For example, 5 years post diagnosis, 85% of CLL patients with del17p treated first line with ibrutinib and 54% of CLL patients with del17p treated at relapse are still alive (3). Ibrutinib and venetoclax are also relatively free of important side effects and both are oral medications, making for convenient treatment without substantial burden on healthcare resources (6, 9).

The economic model of medication access in New Zealand for modern oncological medications seems to be self-fund and you live, can't afford to and you die. The lack of funding means people are dying of CLL who would have survived had they lived in Australia. In appendix 5 of this submission there are five stories of New Zealanders who have accessed ibrutinib, venetoclax and other novel treatments on compassionate grounds. These people are well, working, and enjoying life. Without access to the novel treatments that they received on compassion grounds or via clinical trials many would not be alive to share their stories.

Most New Zealanders can't afford to self-fund their cancer medication. Unless they can generate community or compassionate funding or become part of a drug trial (often difficult because of exclusion criteria), they are left with treatment unlikely to work, or no treatment, and death. Whilst this happens, the people of many other OECD countries, where these drugs are funded, reap the benefits of increased survival.

PHARMAC, in its two plus decades of existence has rightly received global acknowledgment for initiatives to improve value for money for New Zealand's drug budget. Their response to therapeutic innovations in cancer, however, has been anachronistic. Not since the introduction of antibiotics almost a century ago has the world seen such death-defying therapeutics development as we are seeing now in cancer. PHARMAC has responded with a strategy of rationing by delay. They ask for more statistical data, when many other countries' public funding-equivalents have accepted the data and conclusions as valid in cancer survival studies.

High-profile guidelines written by international experts in CLL are developed, peer-reviewed and updated based on available clinical evidence. Strong recommendations are made for ibrutinib and venetoclax use, particularly in patients with del17p and for patients with relapsed/refractory CLL (see appendix 2) (1, 4, 5). International guidelines state that FCR has no place in the management of del17p because of such poor response rates (1). Ibrutinib and venetoclax are consistently recommended. How PHARMAC can fly in the face of international expert opinion is hard to rationalise.

With the current model and budget, PHARMAC do not fund these medications. New Zealanders are dying unnecessarily, whilst the rest of the OECD has largely embraced modern oncological medications. It is a national disgrace and must change.

ABBREVIATIONS

BCR	B-cell receptor
BCL2	B-cell lymphphoma-2
BR	Bendamustine plus rituximab
BSH	British Society for Haematology
BTK	Bruton's tyrosine kinase (BTK is a BCR-associated enzyme, ibrutinib inhibits BTK)
CaTSoP	Cancer Treatments Subcommittee of PTAC
Chemoimmunotherapy	Combination of chemotherapy with a monoclonal antibody
CLL	Chronic lymphocytic leukaemia
CLLANZ	Chronic Lymphocytic Leukaemia Advocates New Zealand
del17p	Deletion of 17p (chromosomal abnormality, typically signalling poor prognosis in CLL)
ESMO	European Society for Medical Oncology
ITP	Immune thrombocytopenia
ICER	Incremental Cost Effectiveness Ratio
FCR	Fludarabine plus cyclophosphamide plus rituximab
MAB	Monoclonal antibody
NCCN	National Comprehensive Cancer Network
PI3K	Phosphoinositide 3-kinase
PTAC	Pharmacology and Therapeutics Advisory Committee
QALY	Quality adjusted life years

APPENDICES

APPENDIX 1 – ABOUT CLL

CLL is a lymphoproliferative disorder characterised by uncontrolled growth of mature B cells accumulating in peripheral blood, bone marrow and lymph nodes and spleen (12, 13).

CLL is the most common adult leukaemia in the western world and in New Zealand. It is predominantly a disease of the elderly with an average age at diagnosis of 72 years (14, 15). There are approximately 200 new cases of CLL diagnosed each year in New Zealand. The estimated number of New Zealanders living with CLL is over 2000, and about 70 die from their illness each year (16).

CLL is characterised by a variable clinical course, with some patients having an aggressive disease leading to early mortality, while others have a more indolent disease requiring little or no intervention (17). Although the majority of patients experience an indolent disease course, it is still considered an incurable disease.

The overall 5-year relative survival is approximately 84% in men and 85% in women (2). Once a patient relapses, average survival is poor as there is often a shorter duration of response to treatment (18, 19).

Most patients do not require therapy at initial diagnosis. Treatment is generally reserved for patients with advanced, symptomatic or aggressive disease. Patients requiring therapy are assigned a regimen based on their relative physical fitness. In the treatment of CLL, three different patient groups based on fitness are distinguished to help guide the approach to therapy and are commonly used worldwide (20, 21).

1. 'Go-go' - **medically fit** patients with no or mild comorbidity and a normal life expectancy.
2. 'Go-slow' - **medically less fit (unfit)** patients with multiple or severe comorbidities and an unknown life expectancy.
3. 'No-go' - **medically frail** patients with fatal comorbidities and a reduced life expectancy.

Several genetic mutations play an important role in the progression of CLL and contribute to a poor prognosis. Deletion of the short (p) arm of chromosome 17 (del 17p) is one of the poorest prognostic factors in CLL as it results in the loss of gene TP53 which is involved in preventing proliferation of abnormal cells with mutated DNA (22, 23).

Studies show for patients with del17p the median time from diagnosis to treatment is 9 months compared to 92 months for those with no mutations (24). These patients are often resistant and do not respond to conventional therapies and therefore median OS is also lower (32 vs. 111 months in patients with no abnormalities) (24).

Current publicly funded treatment in New Zealand for CLL patients with relapsed/refractory and/or del17p disease is limited.

The introduction of newer targeted treatments, such as ibrutinib and venetoclax provide the potential to forego chemotherapy, substantially increase survival, and preserve quality of life, particularly for those CLL patients in New Zealand with relapsed/refractory disease, or those at any stage with poor prognosis del17p disease (6-8, 25-27).

APPENDIX 2 – INTERNATIONAL GUIDELINES SUMMARY FOR USE OF IBRUTINIB AND VENETOCLAX FOR CLL

Table 1 - Summary of CLL treatment recommendations for ibrutinib and venetoclax based on published international guidelines

Guideline	Recommendations	Citation
National Comprehensive Cancer Network (NCCN)	In first-line therapy, ibrutinib is the preferred treatment option for frail patients with significant comorbidities (e.g., not able to tolerate purine analogs) or patients aged ≥65 years and younger patients with significant comorbidities. Ibrutinib is also the preferred regimen for patients <65 years of age without significant comorbidities in first-line therapy. Ibrutinib and venetoclax are included as preferred options for patients with relapsed or refractory disease, regardless of their age and comorbidities. Ibrutinib is the preferred treatment option for first-line therapy of patients with del17p. In relapsed/refractory patients with CLL and del (17)p, ibrutinib monotherapy, venetoclax plus rituximab and venetoclax monotherapy are listed as preferred regimens.	Wierda et al (2019) (1)
British Society for Haematology	Ibrutinib is the treatment of choice in front-line therapy for patients with TP53 disruption (including del17p). Ibrutinib monotherapy is a treatment of choice for patients with CLL who are refractory to chemoimmunotherapy, have relapsed after chemoimmunotherapy, or for whom re-treatment with chemoimmunotherapy is inappropriate. Venetoclax in combination with rituximab might also become an option for BCR inhibitor naïve patients. Venetoclax is the treatment of choice for patients who fail BCR inhibitor therapy.	Schuh et al (2018) (5)
European Society for Medical Oncology (ESMO)	It is recommended that patients with TP53 deletion/mutation (including del17p) are treated with ibrutinib in front-line. Patients unsuitable for BCR inhibitor therapy may be treated with the BCL2 inhibitor venetoclax. If relapse occurs within 24-36 months after chemoimmunotherapy, or if the disease does not respond to any first-line therapy, the therapeutic regimen should be changed. Treatment options include ibrutinib, and if the patient failed BCR inhibitor therapy, venetoclax.	ESMO Guidelines Committee (2017) (4)

Source: Wierda et al (2019) (1); Schuh et al (2018) (5); ESMO Guidelines Committee (2017) (4).
BCL2, B-cell lymphoma-2; BCR, B-cell receptor; CLL, Chronic lymphocytic leukaemia; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network.

APPENDIX 3 - CLL TREATMENTS IN NZ

Table 2 - Classes of CLL treatments …

Chemotherapy drugs	Steroids	Monoclonal antibodies	Targeted agents
Chlorambucil	Prednisone	Rituximab	Venetoclax
Fludarabine	Dexamethasone	Obinutuzumab	Ibrutinib
Cyclophosphamide		Alemtuzumab	Idelalisib
Bendamustine		Ofatumumab	

Funded in New Zealand
*Registered but not funded in New Zealand
**Not registered / available in New Zealand

Table 3 - New Zealand registration dates and funding status for ibrutinib and venetoclax

Targeted treatment	Year of registration	Funding application received	Indication/ line of therapy	First prioritised	Date completed	Status
Ibrutinib	2015	2015	Relapsed/ refractory CLL, del17p	2016	-	Unfunded (recommended by PTAC and CaTSoP)
		2018	1st line CLL for unfit patients	-	-	Unfunded (full evaluation when funded for other populations)
Venetoclax	2017	2017	Relapsed/ refractory CLL, no suitable [alternative] treatment	-	-	Unfunded (under assessment)
		2017	Relapsed/refractory CLL, del17p	-	-	Unfunded (under assessment)

APPENDIX 4 - TREATMENT OUTCOMES OBSERVIED WITH IBRUTINIB AND VENETOCLAX

Table 4 - Summary of Ibrutinib and venetoclax outcomes for patients with del17p CLL

Regimen	Median follow-up	Outcomes	Study
Ibrutinib Relapsed/refractory del17p patients	67 months	Estimated survival rates at 7 years: - 42% OS rate; - 22% PFS rate. Median OS: 57 months. Median PFS: 26 months.	Byrd et al (2018) (7) PCYC-1102/1103 NCT01105247
Ibrutinib Relapsed/refractory del17p patients	27.6 months (extended analysis)	Estimated survival rates at 2 years: - 75% OS rate; - 63% PFS rate. Median PFS: not reached (95% CI, 27.7-not reached). Median OS: not reached (95% CI, 29.5-not reached). Overall response was reported in 83% of patients.	O'Brien et al (2016) (26) RESONATE-17 NCT01744691
Ibrutinib Treatment naïve and relapsed/ refractory patients with TP53 aberration	57 months	Estimated survival rates at 5 years in TP53 cohort: - 74% ibrutinib PFS rate for treatment naïve patients; - 19% ibrutinib PFS rate for relapsed/refractory patients; - 85% ibrutinib OS rate for treatment naïve patients; - 54% ibrutinib OS rate for relapsed/refractory patients. Overall response at 6 months reported in 96% (TP53 cohort).	Ahn et al (2018) (3) NCT01500733
Ibrutinib Relapsed/refractory del17p	28 months	Estimated survival rates at 30 months: - 69% OS rate; - 57% PFS rate. Median OS: 59.3 months. Overall response at 28 months reported in 85%.	Jones et al (2018) (28) Meta-analysis of: NCT01105247; NCT01578707; NCT01744691.
Ibrutinib Relapsed/refractory del17p	44 months	Median PFS: 40.1 months. Estimated PFS rate at 3 years: 53%.	Byrd et al (2019) (6) RESONATE NCT01578707
Ibrutinib Relapsed/refractory del17p	19 months	Estimated survival rates at 18 months: - 83% OS rate; - 71% PFS rate.	Brown et al (2018) RESONATE NCT01578707
Venetoclax + rituximab vs. Bendamustine + rituximab (BR) Relapsed/refractory del17p	23.8 months	Estimated survival rates at 2 years: - 82% venetoclax + rituximab PFS rate vs. 28% BR PFS rate, (HR, 0.13; 95% CI, 0.05-0.29).	Seymour et al (2018) (10) MURANO NCT02005471
Venetoclax Relapsed/refractory del17p	26.6 months	Estimated survival rates at 24 months: - 73% OS rate; - 54% PFS rate. Estimated median PFS 27.2 months.	Stilgengaur et al (2018) (11) M13-982 NCT01889186
Venetoclax Relapsed/refractory del17p	12.1 months	Estimated survival rates at 12 months: - 87% OS rate; - 72% PFS rate.	Stilgengaur et al (2016) (27) M13-982 NCT01889186

CI confidence interval; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

Table 5 - Summary of ibrutinib and venetoclax outcomes for patients with relapsed/refractory CLL

Regimen	Median follow-up	Outcomes	Study
Ibrutinib	67 months	Estimated survival rates at 7 years: - 52% OS rate; - 32% PFS rate.	Byrd et al (2018) (7) PCYC-1102/1103 NCT01105247
Ibrutinib	61.5 months	Estimated survival rates at 5 years: - 60% OS rate; - 44% PFS rate.	O'Brien et al (2018) (29) PCYC-1102/1103 NCT01105247
Ibrutinib	35.2 months	Estimated survival rates at 30 months: - 79% OS rate; - 69% PFS rate.	Byrd et al (2015) (30) PCYC-1102/1103 NCT01105247
Ibrutinib	20.9 months	Estimated survival rates at 2 years: - 83% OS rate; - 75% PFS rate.	Byrd et al (2013) (31) PCYC-1102/1103 NCT01105247
Ibrutinib vs. Ofatumumab	44 months	Estimated survival rates at 3 years: - 74% ibrutinib OS vs. 65% ofatumumab OS; - 59% ibrutinib PFS vs. 3% ofatumumab PFS. Median PFS: Ibrutinib not reached, vs. ofatumumab 8.11 months, (HR, 0.13; 95% CI, 0.099-0.178; P<0.0001). Median OS: Not reached for either arm.	Byrd et al (2019) (6) RESONATE NCT01578707
Ibrutinib vs. Bendamustine + rituximab (BR)	34.8 months	Estimated survival rates at 3 years: - 82% ibrutinib OS; - 68% ibrutinib PFS. Median PFS: Ibrutinib not reached vs. BR 14.3 months, (HR, 0.206; 95% CI, 0.159–0.265; P < 0.0001). Median OS: Not reached for either arm.	Fraser et al (2018) (32) HELIOS NCT01611090)
Ibrutinib vs. Ibrutinib + rituximab	36 months	Estimated survival rates at 3 years: - 92% ibrutinib OS vs. 89% ibrutinib + rituximab OS; - 86% ibrutinib PFS vs. 87% ibrutinib + rituximab PFS.	Burger et al (2019) (33)* NCT02007044
Venetoclax (patients progressed on either ibrutinib or idelalisib)	24 months	Estimated survival rates at 24 months: - 76% venetoclax OS rate; - 52% venetoclax PFS rate. Median PFS: Venetoclax 24.7 months. Median OS: Venetoclax not reached. Overall response was achieved in 70% of patients.	Byrd et al (2018) (25) NCT02141282
Venetoclax (patients progressed post ibrutinib)	14 months	Estimated survival rates at 12 months: - 91% OS rate; - 75% PFS rate. Median PFS: Venetoclax 24.7 months (95% CI, 19.2-not reached). Median OS: Venetoclax not reached (27.8-not reached). Overall response was achieved in 65% of patients.	Jones et al (2018) (8) M14-032 NCT02141282
Venetoclax (patients progressed post idelalisib)	14 months	Estimated survival rates at 12 months: - 94% OS rate; - 79% PFS rate. Median PFS: not reached. Median OS: not reached. Overall response was achieved in 67% of patients.	Coutre et al (2018) (34) M14-032 NCT02141282
Venetoclax + rituximab vs. Bendamustine + rituximab (BR)	36 months	Estimated survival rates at 3 years: - 88% venetoclax + rituximab OS rate vs. 80% BR OS rate; - 71% venetoclax + rituximab PFS rate vs. 15% BR PFS. Median PFS: Venetoclax + rituximab not reached vs.17 months BR, (HR, 0.16; 95% CI, 0.12-0.23; p<0.001). Median OS not reached.	Kater et al (2019) MURANO NCT02005471

Venetoclax + rituximab vs. Bendamustine + rituximab (BR)	23.8 months	Estimated survival rates at 2 years: - 85% venetoclax + rituximab PFS rate vs. 36% BR PFS rate (HR, 0.17; 95% CI, 0.11-0.25; p<0.001); - 92% venetoclax + rituximab OS rate vs. 87% BR OS rate (HR, 0.48; 95% CI, 0.25–0.90).	Seymour et al (2018) (10) MURANO NCT02005471

* 13% (27/208) of patients were treatment-naïve.

BR, bendamustine plus rituximab; CI confidence interval; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

Table 6 - Summary of ibrutinib outcomes for patients with previously untreated CLL

Regimen	Median follow-up	Outcomes	Study
Ibrutinib	67 months	Estimated survival rates at 7 years: - 75% OS rate; - 80% PFS rate. Median OS: not reached. Median PFS: not reached.	Byrd et al (2018) (7) PCYC-1102/1103 NCT01105247
Ibrutinib	61.5 months	Estimated survival rates at 5 years: - 92% OS rate; - 92% PFS rate.	O'Brien et al (2018) (29) PCYC-1102/1103 NCT01105247
Ibrutinib	35.2 months	Estimated survival rates at 30 months: - 97% OS rate; - 96% PFS rate. -	Byrd et al (2015) (30) PCYC-1102/1103 NCT01105247
Ibrutinib	22.1 months	Estimated survival rates at 2 years: - 97% OS rate; - 96% PFS rate.	O'Brien et al (2014) (35) PCYC-1102/1103 NCT01105247
Ibrutinib vs. Chlorambucil	36 months	Estimated survival rates at 2 years: - 95% ibrutinib OS vs. 84% chlorambucil OS; - 89% ibrutinib PFS vs. 34% chlorambucil PFS. Median PFS: Ibrutinib not reached, vs. chlorambucil 15 months, (HR, 0.12; 95% CI, 0.07-0.20; P<0.0001). Overall survival: with longer follow up and despite patient crossover, ibrutinib continues to demonstrate an OS benefit compared with chlorambucil (HR, 0.43; 95% CI, 0.21-0.86; P=0.0145).	Barr et al (2018) (36) RESONATE-2 NCT01722487
Ibrutinib vs. Chlorambucil	18.4 months	Estimated OS rate at 24 months: - 98% with ibrutinib vs. 85% with chlorambucil (HR, 0.16; p<0.001). Median PFS: Ibrutinib not reached, vs. chlorambucil 18.9 months), (HR, 0.16; p<0.001).	Burger et al (2015) (37) RESONATE-2 NCT01722487
Ibrutinib vs. Ibrutinib + rituximab; or Rituximab + bendamustine	38 months	Estimated PFS rates at 2 years: - 87% ibrutinib monotherapy; - 88% ibrutinib + rituximab; - 74% rituximab + bendamustine.	Woyach et al (2018) (38) ALLIANCE NCT01886872
Ibrutinib + obinutuzumab vs. Chlorambucil + obinutuzumab	31.3 months	Estimated survival rates at 30 months: - 79% ibrutinib group vs. 31% chlorambucil group PFS; - 86% ibrutinib groups vs 85% chlorambucil group OS. -	Moreno et al (2019) (39) iLLUMINATE NCT02264574

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

APPENDIX 5 – PATIENT STORIES

Audrey Smith

I had a catering business and was used to working long hours. However, when I began to feel continuously tired, I thought I was getting older!

After two bouts of pneumonia, my Doctor sent me to haematology at Palmerston North Hospital and I was diagnosed with CLL in August 2016. It was agreed we would monitor the blood counts as I had a full and busy life... I was selling my business, moving to Hawkes Bay and I had family commitments.

In January 2018, I started treatment; rituximab and bendamustine, chemotherapy (5 x bendamustine, 4 x rituximab) on a 28-day cycle at the haematology department Palmerston North Hospital.

The results in May 2018 showed only a partial response (50% lymphocyte count decline), but residual marked lymphocytosis, persistent adenopathy, progressive anaemia, and treatment related nausea. My haematologist said she had hoped to give my results an A+, but instead it was only a B-.

The future looked very bleak and it is never a good sign when a doctor speaks to you about quality of life. However, there was a possible solution, perhaps.....

My Doctor would see I if was eligible for a trial using a drug, venetoclax. I was so thrilled to be accepted, however, before treatment could begin, I was admitted to hospital with severe pneumonia, yet again.

Treatment in Wellington with venetoclax commenced June 2018 on the VENICE - II trial.

The initial introduction of the drug was carefully monitored for 6 weeks but the immediate results were amazing! I expected to feel some side effects, however, my body adjusted very well and within the first six weeks, I just felt so much better than I had for years!

For me, venetoclax has been like miracle drug. I have been on it for one year and feel I have been given a new gift of life. I am in remission.

I have been able to resume private catering and follow an exercise regime that includes aquaerobics and walking.

I have not felt so well for about 5 years and cannot believe how lucky I have been to be accepted for the venetoclax trial as I was not in a position to self-fund.

Many others are not nearly as fortunate as myself and suffer dreadfully with the current treatment offered to CLL patients; and possibly like me, their disease does not respond well to the standard treatment. I truly believe that Pharmac should be more flexible with its funding model and look to fund this incredible drug. Without the trial, I think my quality of life would be ghastly and I would become much more of a drain on the public hospital services.

Neil Graham (submission author)

I was diagnosed with chronic lymphocytic leukaemia in 2000 just after my 50th birthday. I had several treatments over the next 15 years, but was generally well and active, and continued working as a physician with the Bay of Plenty District Health Board.

About five years ago my disease went out of control. I developed blood transfusion-dependent bone marrow failure. My lymphocytes peaked at almost one thousand times the normal range. My days were clearly numbered. The only treatment option was a new medicine that was registered but not funded in New Zealand, and I was lucky enough to become the first CLL patient to get this therapy on a compassionate access programme.

Over the following months my bone marrow largely recovered, and my wellbeing returned. I remain in a state described as "a complete remission". I am working, teaching, researching, and paying taxes. I'm physically active (e.g. 300+ km back country mountain biking in a week recently), enjoying life, and I am alive. What has happened medically to me has been remarkable, professionally and personally.

Five years on, the compassionate access programme is closed to new entrants, the medicine and others like it that have since become available are still not funded, and people are dying as a result. The treatment I'm on is funded in 23 countries with similar or lower wealth than New Zealand, the lowest on the scale being Brazil, Columbia and Albania. All 23 of these countries have looked at the same evidence reviewed by Pharmac and decided to fund this life-saving drug. But Pharmac has looked at that evidence and judged that lives such as mine are not worth saving.

Ian Hibberd

I was diagnosed with Chronic Lymphatic Leukaemia in 2006 while I was living in Hawke's Bay. At the time I was a fit and healthy marathon runner with no signs of a health issue. From 2006 until November 2012 it was a case of having quarterly blood tests and a watch and wait brief. I continued to lead a very normal lifestyle, barely noticing my affliction.

In August 2012 I moved to Lower Hutt for employment reasons (Public Servant - Ministry of Education) and in December 2012 I was admitted to the emergency ward for ITP (Immune thrombocytopenia), (platelets had a reading of 2). From December 2012 until September 2013 I had 5 courses of FCR chemotherapy, no platelet response from the treatment and the CLL was unscathed! A laparoscopic splenectomy was carried out in March 2013 and I started on a new drug eltrombopag. This was successful in stabilising my platelets and I stopped taking the drug in September 2017.

During this period, I also had a CLL relapse (progressive lymphadenopathy) and it was ascertained I was 11q deletion (11q-). In April 2015 I was given access to ibrutinib on compassionate grounds. Presently I am taking ibrutinib (280mg) daily along with co-trimoxazole (480mg) and this is maintaining my health.

The difference ibrutinib has made to my life is dramatic, with only minor side effects, I have been able to have a normal life again. I work full-time, I exercise and I'm healthy. I'm very happy with that, as previously the state of my health was precarious.

My family and I are truly grateful, for giving me another chance at life.

Ben Schrader

I'd been getting breathless while exercising and generally feeling off colour. It was just the flu, I thought. I finally went to my GP in March 2012 and he took a blood test. A few hours later I was in Wellington hospital. My red blood cell (haemoglobin) count was below safe levels and I was very sick.

Following tests, the doctors told me I had chronic lymphocytic leukaemia (CLL). It was a huge shock. Was this a death sentence? Not necessarily, I was reassured. My type of CLL started with autoimmune haemolysis anaemia, where my spleen was destroying red blood cells faster than they could be replaced. This was treated by blood transfusions and a six-month chemotherapy course. After each round I spent days throwing up and feeling crap, but the treatment worked, and I went into remission.

My CLL came back in 2015 and I had further treatment. It returned within 12 months. This time blood transfusions were unable to stop my haemolysis. I needed a splenectomy. I was in no state to have major surgery, but it was that or certain death. Happily, I came through. My haematologist suggested that my CLL might be treated with a new drug ibrutinib. The drug company was giving it to some patients with view that Pharmac would fund it once its efficacy was shown. I was accepted just before the window closed.

I've had no discernible side effects with ibrutinib and without it my CLL would have returned. The drug has allowed me to keep working and be fully available to my family and friends. I feel great. It would be wonderful if other CLL patients could too. The cause of CLL is still unknown. Getting it appears to be a case of bad luck, but access to ibrutinib shouldn't be left to chance.

Graham Adams

When your GP tells you your haematologist's report "makes for grim reading", you know you're in trouble. I had that experience in early 2015 - two years after having been diagnosed with chronic lymphocytic leukaemia (CLL) and shortly after being given the news I also had chromosome 17p deletion, the dreaded genetic marker no CLL patient wants to harbour.

The deletion of 17p has traditionally meant a very poor prognosis. Chemotherapy-based treatments simply don't work for the vast majority of such CLL patients and that was all that was on offer through the public health system when I needed treatment. I have read that its success rate is as low as five per cent.

I realised I was unlikely to get out of this predicament alive unless I had an alternative to chemotherapy. I had heard about the new targeted drugs like ibrutinib that seemed to take 17p deletion in their stride but I knew they weren't publicly funded in New Zealand - even though they were already being heralded as a "game-changer" for certain blood cancers, including high-risk CLL patients like me.

So I decided, in consultation with my haematologist, that I would use up a chunk of my retirement savings to pay for a year's supply of ibrutinib at $10,000 a month in preparation for a stem cell transplant.

And then, just as I was about to make my first $10,000 payment, I had the good fortune to learn of a clinical trial in Auckland that was designed to pit ibrutinib and obinutuzumab against an old chemotherapy agent, chlorambucil, also paired with obinutuzumab.

I was lucky enough to be accepted as a patient, but I ended up on the arm without ibrutinib and you'd have to say the chlorambucil-obinutuzumab regimen wasn't a raging success. My lymphocyte count dropped

sharply from around 200 to 12 but my lymph nodes contracted only by 20 per cent. My bone marrow was still stuffed with CLL cells.

Within a month of finishing the six-month trial, my lymphocyte count had shot up, and the lymph nodes in my neck had swollen to once again make me look like a chipmunk.

At that point, under the terms of the clinical trial, I was eligible for free access to ibrutinib, but my haematologist had a separate trial under way for a second-generation form of ibrutinib, then called BGB-3111 (now zanubrutinib).

Three and a half years later, after slow, steady improvement, my blood counts are all normal. My crushing fatigue, that in 2016 was so severe I was nearly entirely housebound and had to be wheeled along hospital corridors, has improved so dramatically that this year I have been able to average 6km walking a day.

I still tire easily but I am alive and well. I describe it as my “Lazarus experience”. Zanubrutinib has brought me back from the near-dead.

My New Zealand-born brother is an Australian citizen who lives in Brisbane. If he were to be diagnosed with CLL with 17p deletion like me, he would have access to ibrutinib for less than $40 a month under the Australian public health system. If and when that failed, he would be able to access another wonder drug, venetoclax, also for a minimal charge.

In short, Australia’s health system offers a Lazarus experience for patients with high-risk CLL while New Zealanders who aren’t lucky enough to be accepted onto a clinical trial or rich enough to pay can currently expect only a place on death row.

REFERENCES

1. Wierda W, et al. NCCN Guidelines® Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 3. 2019.

2. National Cancer Instittue Surveillane EaERPS. Cancer Stat Facts: NHL - Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) 2019 [18 June 2019]. Available from: https://seer.cancer.gov/statfacts/html/cllsll.html.

3. Ahn IE, Farooqui MZH, Tian X, Valdez J, Sun C, Soto S, et al. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. Blood. 2018;131(21):2357-66.

4. ESMO Guidelines Committee. eUpdate – Chronic Lymphocytic Leukaemia Treatment Recommendations 2017. Available from: https://www.esmo.org/Guidelines/Haematological-Malignancies/Chronic-Lymphocytic-Leukaemia/eUpdate-Treatment-Recommendations.

5. Schuh AH, Parry-Jones N, Appleby N, Bloor A, Dearden CE, Fegan C, et al. Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. Br J Haematol. 2018;182(3):344-59.

6. Byrd JC, Hillmen P, O'Brien S, Barrientos JC, Reddy NM, Coutre S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. Blood. 2019;133(19):2031-42.

7. Byrd J, R F, S C, et al. Up to 7 years of follow-up of single agent ibrutinib in the Phase 1b/2 PCYC-1102 trial of first line and relapsed/refractory patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. Blood. 2018;132.

8. Jones JA, Mato AR, Wierda WG, Davids MS, Choi M, Cheson BD, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. The Lancet Oncology. 2018;19(1):65-75.

9. Kater AP, Seymour JF, Hillmen P, Eichhorst B, Langerak AW, Owen C, et al. Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study. J Clin Oncol. 2019;37(4):269-77.

10. Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. The New England journal of medicine. 2018;378(12):1107-20.

11. Stilgenbauer S, Eichhorst B, Schetelig J, Hillmen P, Seymour JF, Coutre S, et al. Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial. J Clin Oncol. 2018;36(19):1973-80.

12. Hallek M. Chronic lymphocytic leukemia: 2013 update on diagnosis, risk stratification and treatment. Am J Hematol. 2013;88(9):803-16.

13. Lobetti-Bodoni C, Bertoni F, Stussi G, Cavalli F, Zucca E. The changing paradigm of chronic lymphocytic leukemia management. Eur J Intern Med. 2013;24(5):401-10.

14. Eichhorst B, Dreyling M, Robak T, Montserrat E, Hallek M. Chronic Lymphocytic Leukemia: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Ann Oncol. 2011;22 Suppl 6:vi50-4.

15. Gribben JG. How I Treat CLL Up-Front. Blood. 2010;115(2):187-97.

16. Ministry of Health. Cancer: Historical summary 1948-2013. 2016.

17. Hock BD, McKenzie JL, McArthur L, Tansley S, Taylor KG, Fernyhough LJ. CD38 as a prognostic marker in chronic lymphocytic leukaemia at a single New Zealand centre: patient survival in comparison to age- and sex-matched population data. Intern Med J. 2010;40(12):842-9.

18. Tam CS, O'Brien S, Plunkett W, Wierda W, Ferrajoli A, Wang X, et al. Long-term results of first salvage treatment in CLL patients treated initially with FCR (fludarabine, cyclophosphamide, rituximab). Blood. 2014;124(20):3059-64.

19. Eketorp Sylvan S, Hansson L, Karlsson C, Norin S, Lundin J, Osterborg A. Outcomes of patients with fludarabine-refractory chronic lymphocytic leukemia: a population-based study from a well-defined geographic region. Leuk Lymphoma. 2014;55(8):1774-80.

20. Eichhorst BF, Busch R, Stilgenbauer S, Stauch M, Bergmann MA, Ritgen M, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood. 2009;114(16):3382-91.

21. Stilgenbauer S, Furman RR, Zent CS. Management of chronic lymphocytic leukemia. American Society of Clinical Oncology Educational Book: ASCO Meeting. 2015;35:164-75.

22. Tam CS, Stilgenbauer S. How best to manage patients with chronic lymphocytic leuekmia with 17p deletion and/or TP53 mutation? Leuk Lymphoma. 2015;56(3):587-93.

23. Zenz T, Eichhorst B, Busch R, Denzel T, Häbe S, Winkler D, et al. TP53 Mutation and Survival in Chronic Lymphocytic Leukemia. J Clin Oncol. 2010;28(29):4473-9.

24. Dohner H, Stilgenbauer S, Benner A, Leupolt E, Krober A, Bullinger L, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343(26):1910-6.

25. Byrd J, Wierda W, Davids MS, et al, editors. Durability of response to venetoclax in patients with CLL relapsed/refractory to ibrutinib and/or idelalisib. EHA; 2018.

26. O'Brien S, Jones JA, Coutre SE, Mato AR, Hillmen P, Tam C, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. The Lancet Oncology. 2016;17(10):1409-18.

27. Stilgenbauer S, Eichhorst B, Schetelig J, Coutre S, Seymour JF, Munir T, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. The Lancet Oncology. 2016;17(6):768-78.

28. Jones J, Mato A, Coutre S, Byrd JC, Furman RR, Hillmen P, et al. Evaluation of 230 patients with relapsed/refractory deletion 17p chronic lymphocytic leukaemia treated with ibrutinib from 3 clinical trials. Br J Haematol. 2018;182(4):504-12.

29. O'Brien S, Furman RR, Coutre S, Flinn IW, Burger JA, Blum K, et al. Single-agent ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. Blood. 2018;131(17):1910-9.

30. Byrd JC, Furman RR, Coutre SE, Burger JA, Blum KA, Coleman M, et al. Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood. 2015;125(16):2497-506.

31. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. The New England journal of medicine. 2013;369(1):32-42.

32. Fraser G, Cramer P, Demirkan F, Silva RS, Grosicki S, Pristupa A, et al. Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma. Leukemia. 2019;33(4):969-80.

33. Burger JA, Sivina M, Jain N, Kim E, Kadia T, Estrov Z, et al. Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. Blood. 2019;133(10):1011-9.

34. Coutre S, Choi M, Furman RR, Eradat H, Heffner L, Jones JA, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. Blood. 2018;131(15):1704-11.

35. O'Brien S, Furman RR, Coutre SE, Sharman JP, Burger JA, Blum KA, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. The Lancet Oncology. 2014;15(1):48-58.

36. Barr PM, Robak T, Owen C, Tedeschi A, Bairey O, Bartlett NL, et al. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2. Haematologica. 2018;103(9):1502-10.

37. Burger JA, Tedeschi A, Barr PM, Robak T, Owen C, Ghia P, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. The New England journal of medicine. 2015;373(25):2425-37.

38. Woyach JA, Ruppert AS, Heerema NA, Zhao W, Booth AM, Ding W, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. The New England journal of medicine. 2018;379(26):2517-28.

39. Moreno C, Greil R, Demirkan F, Tedeschi A, Anz B, Larratt L, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. The Lancet Oncology. 2019;20(1):43-56.