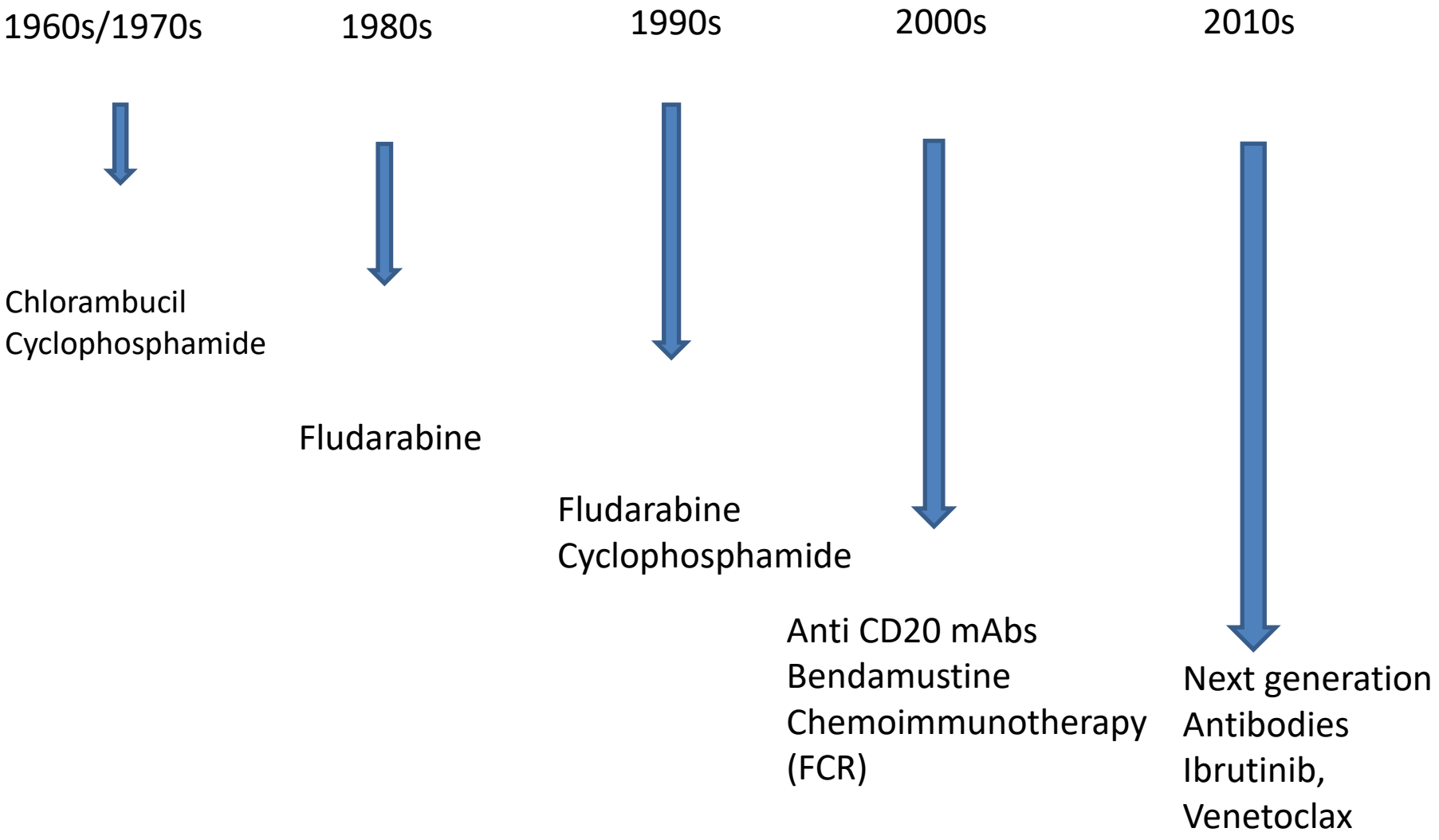
Management of CLL in NZ

Astra Zeneca Trial site news

CLL: Evolution of Therapy



Do not dwell in the past,

do not dream of the future,

concentrate the mind on the

present moment.

The Buddha

Why do we not treat all patients with CLL?

- CLL is generally a chronic and incurable disease. No evidence that treating early is likely to cure CLL
- Some patients with early stage CLL remain stable and do not progress without treatment
- Average age of presentation is 70 and some treatment options are not well tolerated.
- Treatment carries long term toxicity eg further reducing immunity, increasing risk of other malignancies.

Treatment Indications

- Anemia and/or low platelets (hemoglobin <10 g/dL or platelets <100 x10^9/L)
- Enlarged spleen (≥6 cm below the left costal margin)
- Symptomatic enlarged lymph nodes (≥10 cm in longest diameter)
- Lymphocyte count increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months. (Assuming initial lymphocyte count >30)
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- Symptomatic or functional non lymph node involvement (e.g. skin, kidney, lung, spine)
- Constitutional symptoms:
  - Unintentional weight loss of ≥10% within the previous 6 months;
  - Significant fatigue (i.e. inability to work or perform usual activities);
  - Fevers higher than 38.0°C for 2 or more weeks; or
  - Drenching night sweats for ≥1 month without evidence of infection

Hallek M et al. *Blood.* 2018;131:2745-2760.

Staging Systems for CLL

Rai System

Stage	Description	Modified Risk Status
0	Lymphocytosis, lymphocytes in blood >5 x 10^9/L clonal B cells and >40% lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0-I with splenomegaly, hepatomegaly, or both	Intermediate
III	Stage 0-II with hemoglobin <11.0 g/dL or hematocrit <33%	High
IV	Stage 0-III with platelets <100,000/mL	High

Binet System

Stage	Description
A	Hemoglobin ≥10 g/dL and platelets ≥100,000/mm^3 and <3 enlarged areas
B	Hemoglobin ≥10 g/dL and platelets ≥100,000/mm^3 and ≥3 enlarged areas
C	Hemoglobin <10 g/dL and/or platelets <100,000/mm^3 and any number of enlarged areas

NCCN. CLL/SLL. Version 5.2019. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

iwCLL Recommended Testing Before Treatment

Diagnostic Test	Practice Recommendation
History, physical, infection status	Always
CBC, chemistry, Igs, DAT	Always
Serum β2 microglobulin	Desirable
Marrow aspirate and biopsy	Sometimes for low blood counts
CT scan of chest, abdomen, pelvis	May be indicated
IGHV mutational status	Ideal, but not available in NZ
FISH for add(12), del(13q), del(11q), del(17p) in peripheral blood	17p should be checked
TP53 mutation	Always
Conventional karyotyping	Not generally indicated**

*Does not need to be repeated before subsequent therapy

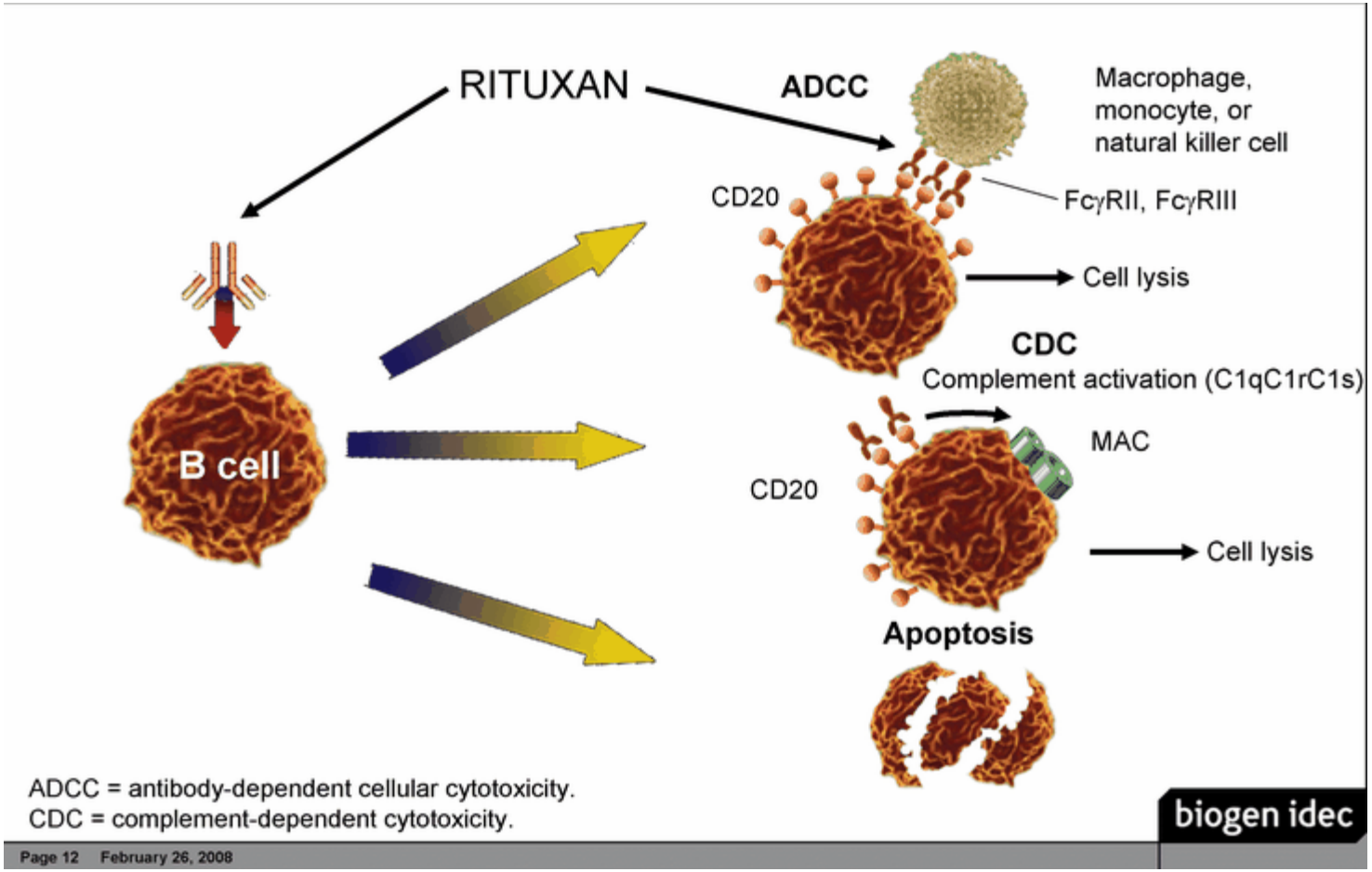
**Conventional karyotyping (with specific stimulation) may be useful before therapy, if established methodology is available

CBC = complete blood count; IGHV = immunoglobin heavy chain variable region; iwCLL = International Workshop on Chronic Lymphocytic Leukemia.

What are the funded options for treating CLL in NZ?
First line treatment for younger patients

- Younger fit patients (generally <65-70 years)
- FCR, Fludarabine, Cyclophosphamide, Rituximab
- Fludarabine and Cyclophosphamide are pills taken for 3-5 days once per month
- Fludarabine is a purine analogue and targets lymphocytes. Cyclophosphamide is an alkylating agent that also targets lymphocytes.
- Rituximab is an antibody, directed against B lymphocytes given by infusion once per month.
- Treatment last up to 6 months

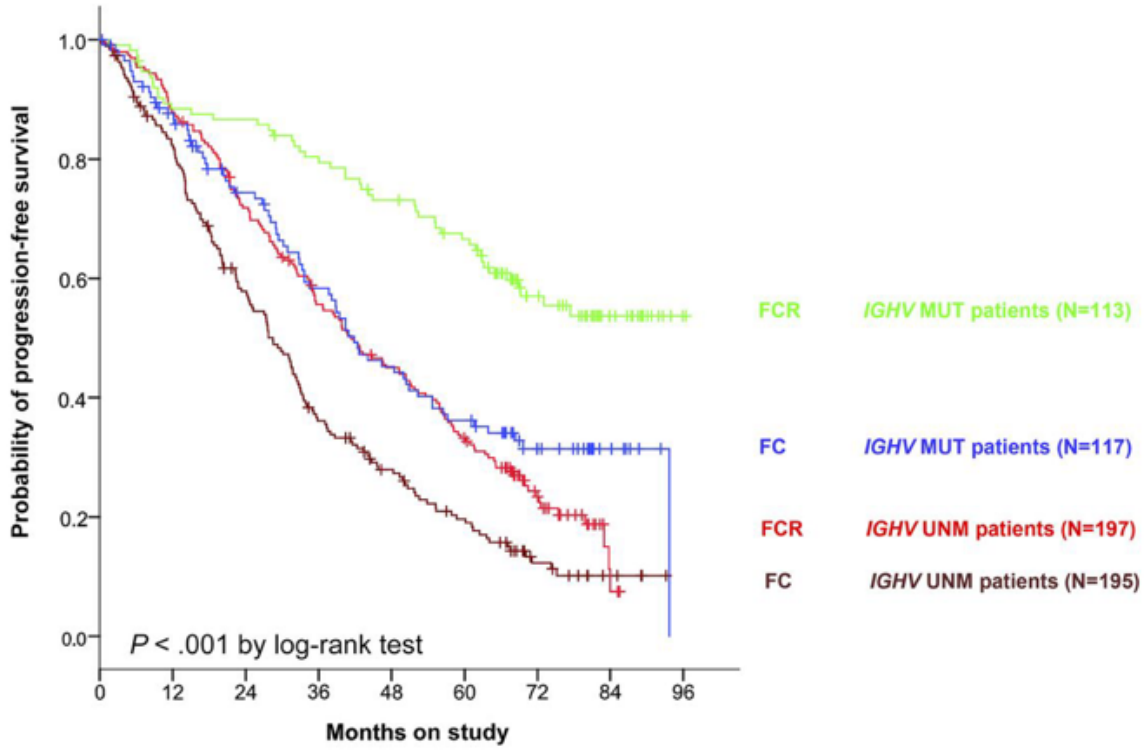
Rituximab: Mode of Action



FCR v FC: CLL 8 Study
Progression free survival, PFS. EHA 2018.

PFS is superior for patients with IGHV-mutated disease compared with unmutated.

PFS is superior in patients receiving FCR v FC



Older patients: first line treatment

- Bendamustine and Rituximab
- Bendamustine is given intravenously for 2 days once per month and Rituximab by infusion one day once per month
- Bendamustine is a combination of purine analogue and alkylating agent
- Treatment lasts for up to 6 months
- Better tolerated than FCR in older patients but not as effective as FCR in younger patients

Bendamustine and Rituximab in CLL, German Study Group, 2012

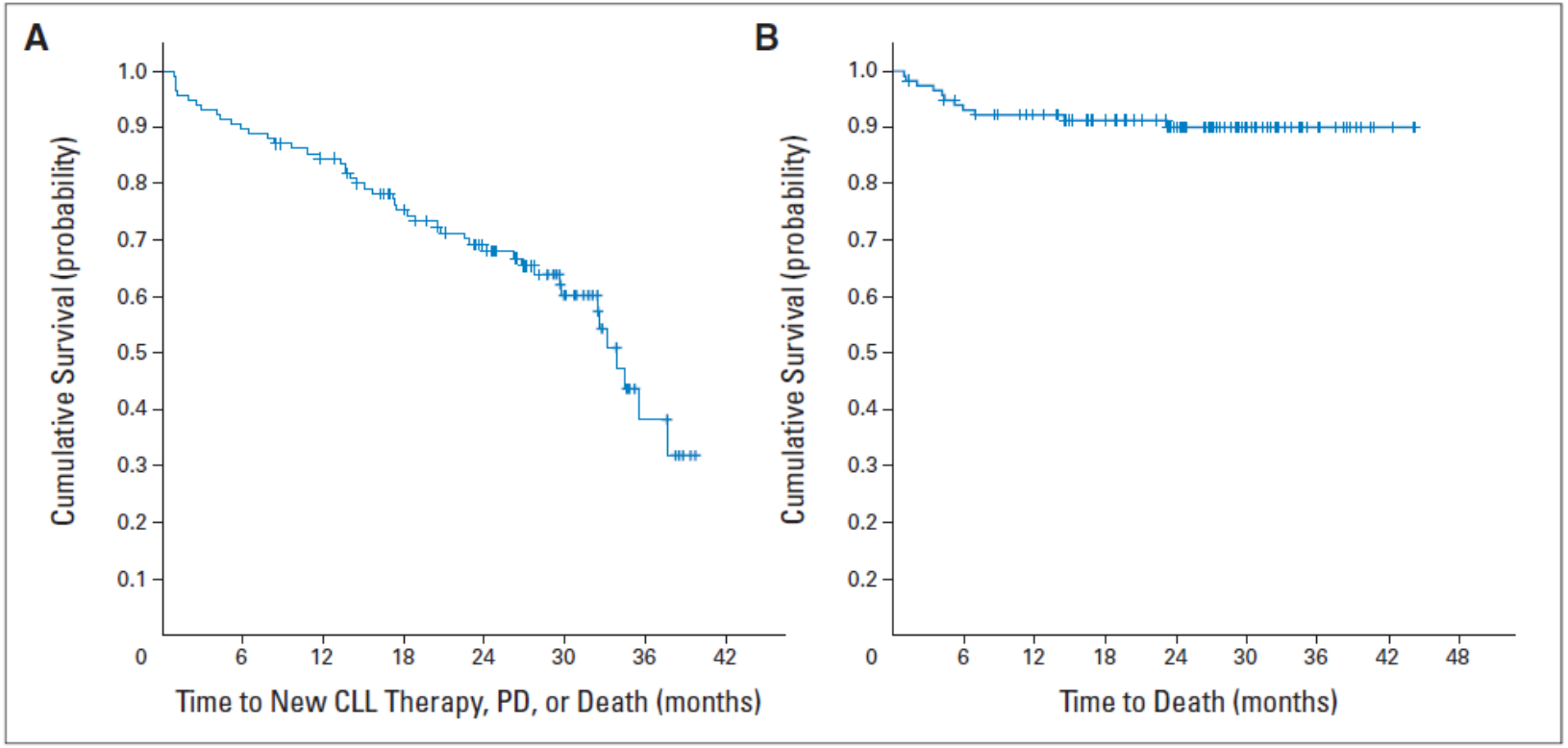
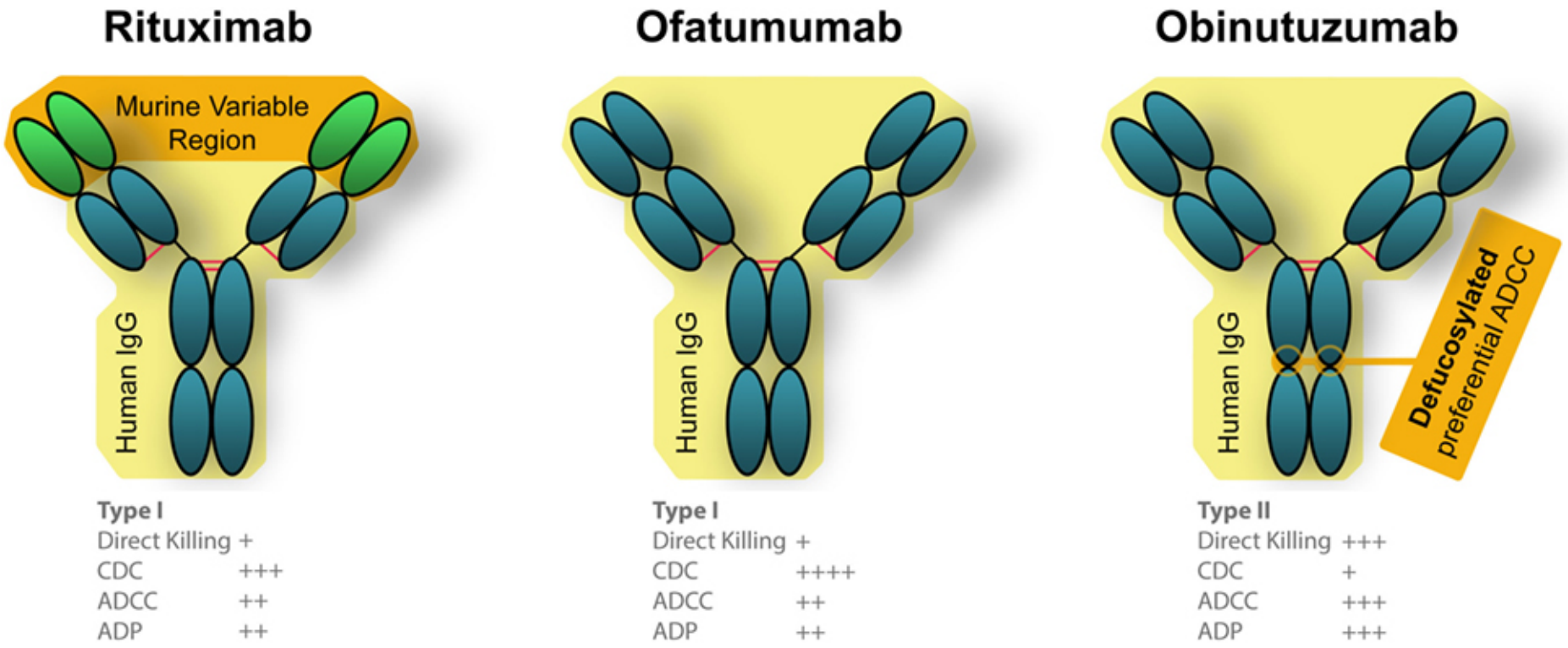


Fig 2. (A) Event-free survival and (B) overall survival for all patients in the intent-to-treat group. CLL, chronic lymphocytic leukemia; PD, progressive disease.

Upfront Treatment for patients with significant co-morbidities and/ or advanced age

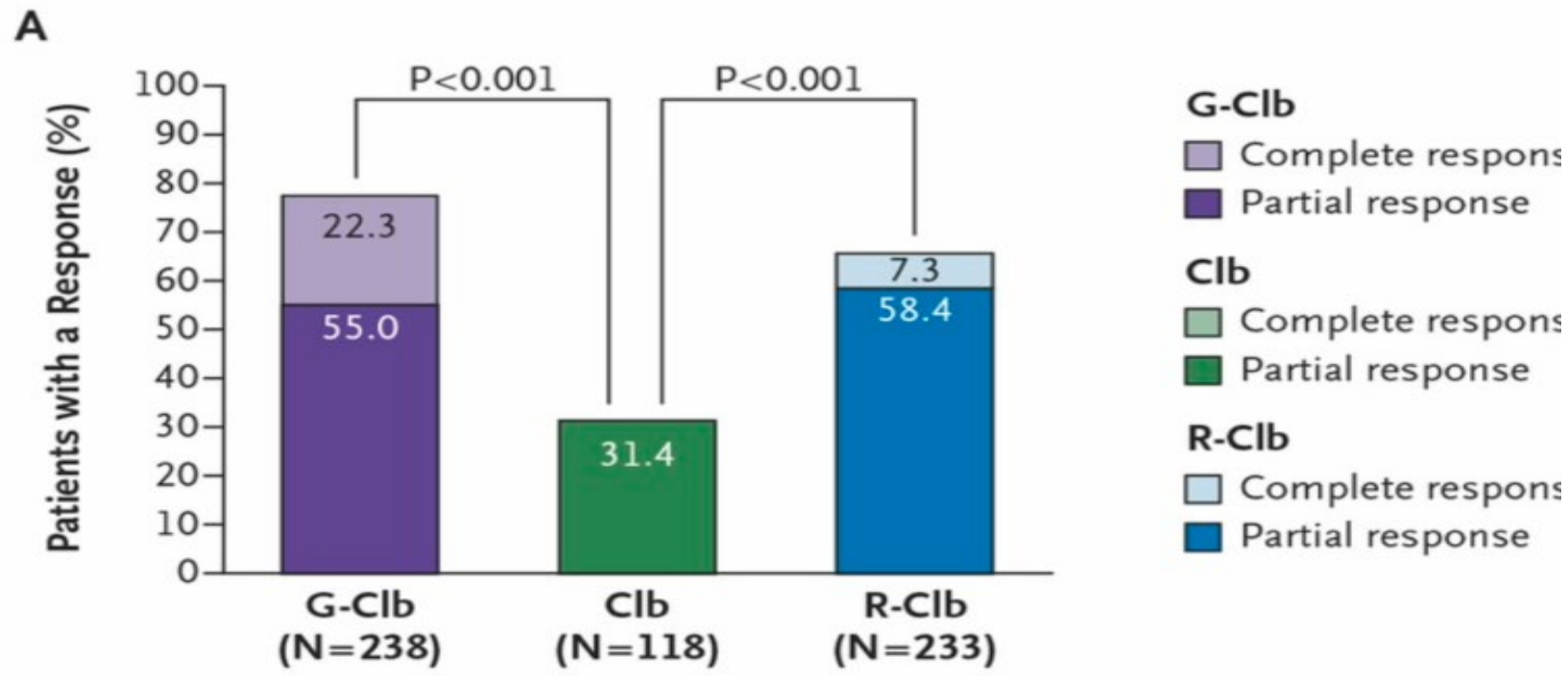
- Chlorambucil and Obinutuzumab (anti CD20 antibody)
- The chlorambucil is given orally, generally twice per month
- Obinutuzumab is given as an infusion once per month
- Generally low toxicity regime
- 6 month regime

Anti-CD 20 antibodies in CLL



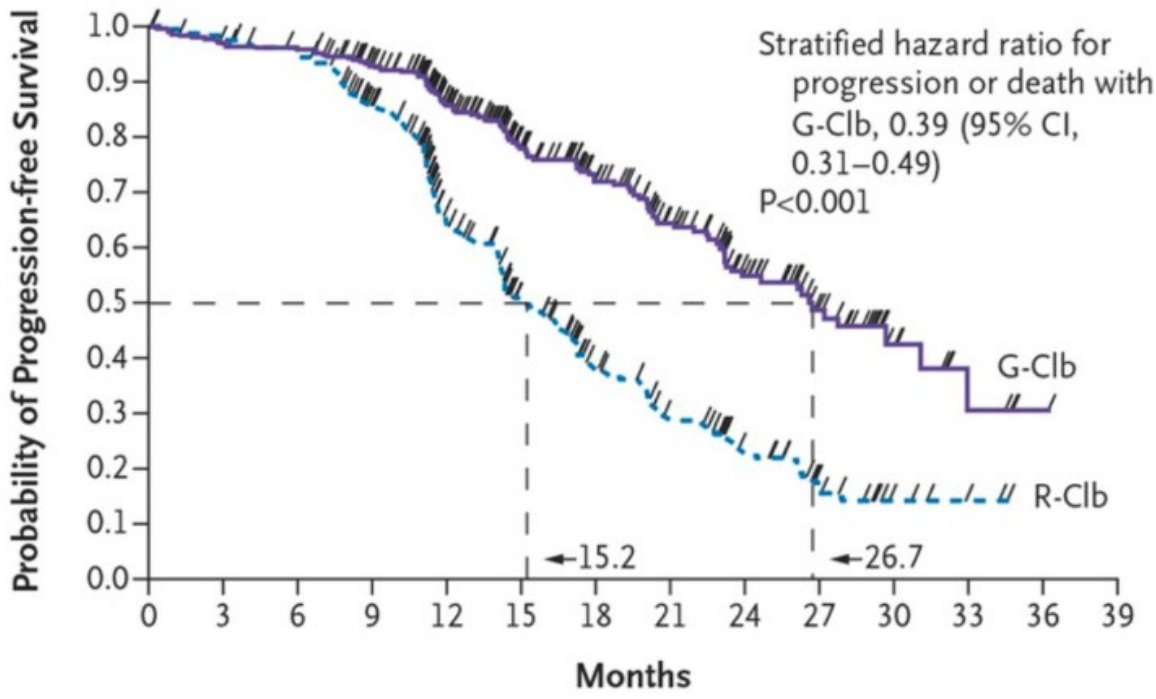
Frontiers in.org

Study comparing Chlorambucil, versus Chlorambucil and Rituximab versus Chlorambucil and Obinutuzumab



Goede et al, NEJM 2014,370:1101

Progression free survival of patients on Chlorambucil and Obinutuzumab versus Chlorambucil and Rituximab



No. at Risk

G-Clb	333	307	302	278	213	156	122	93	60	34	12	4	1	0
R-Clb	330	317	309	259	163	114	72	49	31	14	5	2	0	0

Goede et al, NEJM 2014, 370:1101

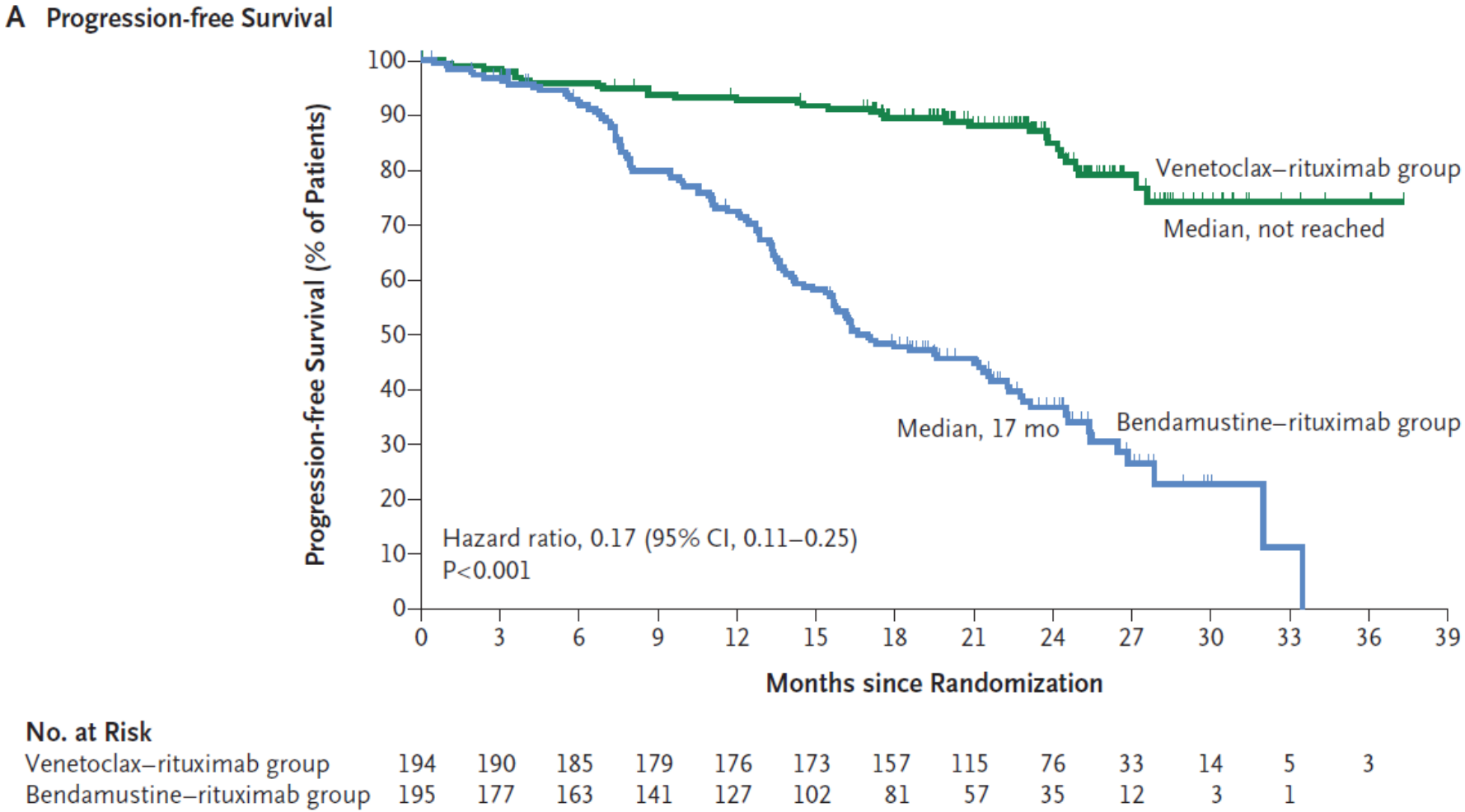
Relapsed Patients

- Previous FCR:
  - May be repeated if relapse after 3 years
  - Venetoclax is available for patients who relapse within 3 years
  - Consider Chlorambucil and Obinutuzumab

Venetoclax in CLL

- Targets Bcl2 inducing apoptosis or cell death
- Developed in Melbourne
- Given orally
- Effective in CLL patients with poor prognosis eg unmutated and del 17p.
- Funded in NZ for
    - upfront management of patients with del 17 or p53 mutation
    - Patients who relapse within 3 years of previous treatment. Is combined with Rituximab and given for 2 years
- Generally well tolerated but risk of cell lysis with initial treatment

Murano study of Venetoclax and Rituximab v Bendamustine and Rituximab in relapsed CLL



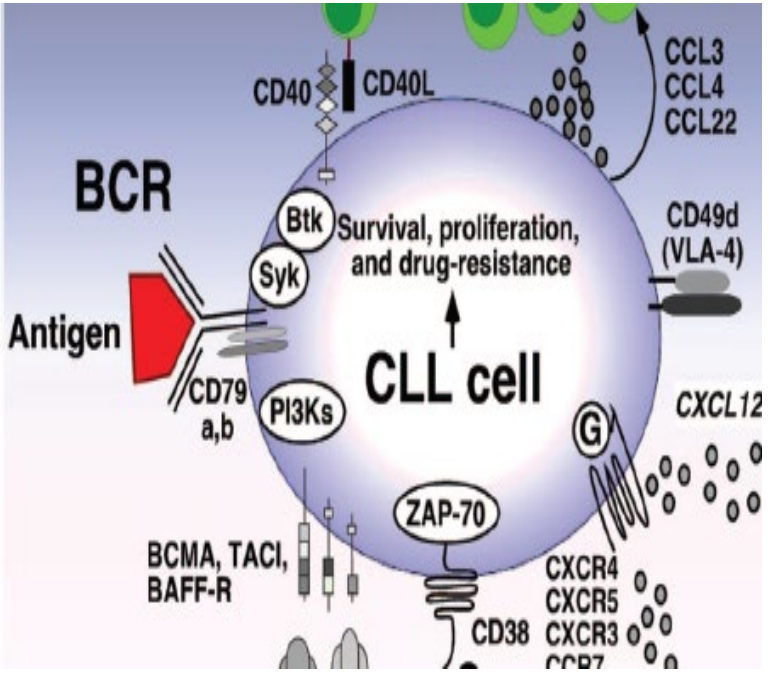
J Seymour, NEJM, March 22, 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Richard R. Furman, M.D., Steven E. Coutre, M.D., Ian W. Flinn, M.D., Ph.D., Jan A. Burger, M.D., Ph.D., Kristie A. Blum, M.D., Barbara Grant, M.D., Jeff P. Sharman, M.D., Morton Coleman, M.D., William G. Wierda, M.D., Ph.D., Jeffrey A. Jones, M.D., M.P.H., Weiqiang Zhao, M.D., Ph.D., Nyla A. Heerema, Ph.D., Amy J. Johnson, Ph.D., Juthamas Sukbuntherng, Ph.D., Betty Y. Chang, Ph.D., Fong Clow, Sc.D., Eric Hedrick, M.D., Joseph J. Buggy, Ph.D., Danelle F. James, M.D., and Susan O'Brien, M.D.



NEJM, 2013

ABSTRACT

BACKGROUND

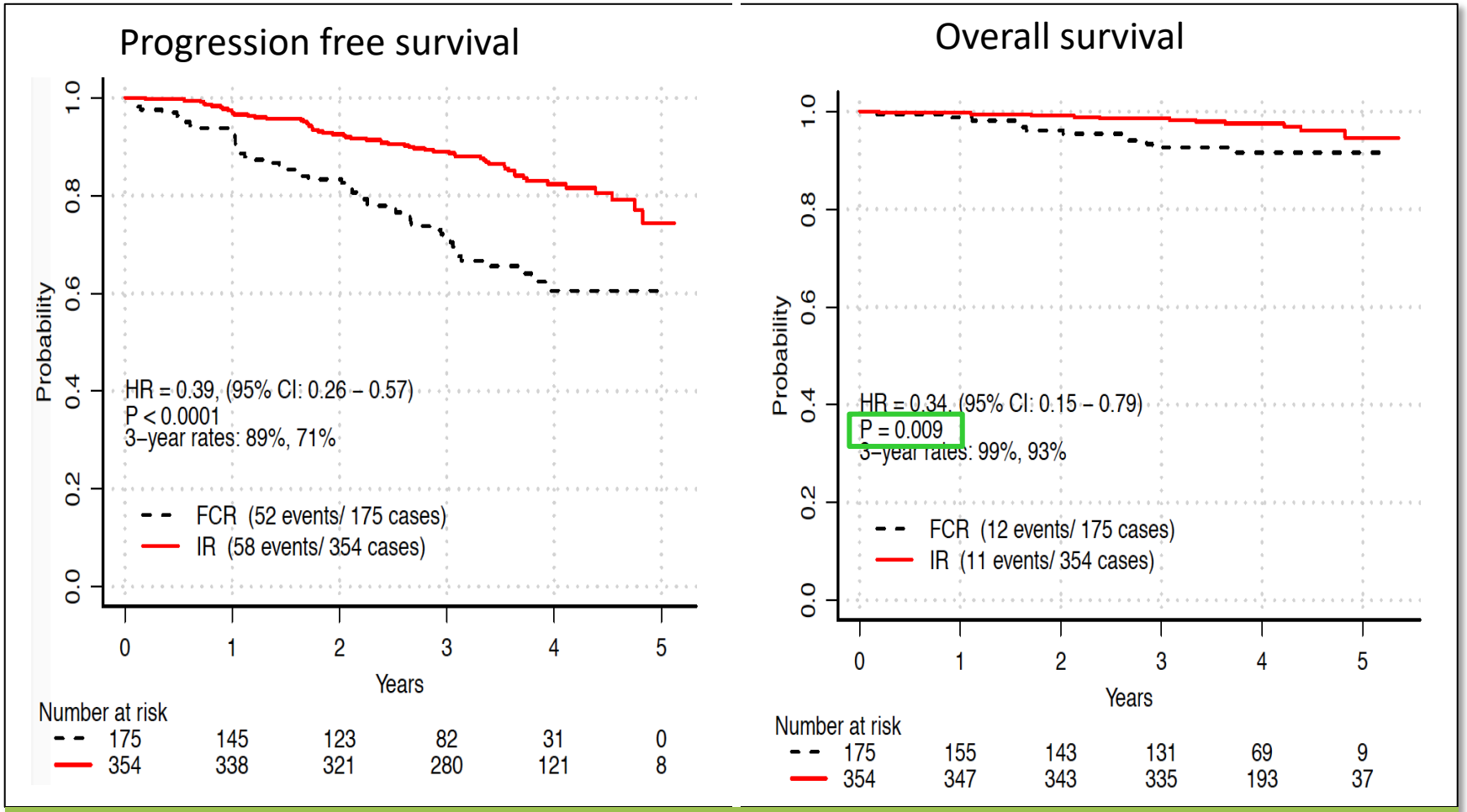
The treatment of relapsed chronic lymphocytic leukemia (CLL) has resulted in few durable remissions. Bruton's tyrosine kinase (BTK), an essential component of B-cell–receptor signaling, mediates interactions with the tumor microenvironment and promotes the survival and proliferation of CLL cells.

Ibrutinib and derivatives in CLL

- Ibrutinib targets the B cell receptor signalling in CLL cells
- Given orally and effective in patients with poor prognostic features eg unmutated and del 17.
- (Care with increased risk of bleeding, Atrial fibrillation and interaction with some medications)
- Not funded in NZ
- Derivatives include acalabrutinib and zanubrutinib, more targeted
- PI3k inhibitors and idelalasib are also effective in CLL but not at present funded in NZ

Ibrutinib and rituximab vs FCR

In Untreated Younger Patients With CLL (E1912)



With a median follow-up of 48 months, 73% of IR patients remain on treatment; Only 7% of ibrutinib treated patients progressed while on therapy

Shanafelt TD et al. *Blood.* 2019;(suppl 1):Abstract 33.

What would be ideal in NZ?

Testing for IGHV mutations

Ibrutinib or Venetoclax for upfront management in:

- Unmutated younger patients
- Patients with del 17 and p53 mutations
- Older patients

? Combining Ibrutinib and Venetoclax