


# CLL in New Zealand: Future directions & priorities

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LBC, Auckland

14 October 2020




# CLL in New Zealand: Future directions & priorities

**Priority #1:** BTK inhibitor for relapsed CLL

**Priority #2:** Reforming first-line therapy

**Priority #3:** Preventing infections

**Future treatment concepts**



# CLL in New Zealand: Future directions & priorities



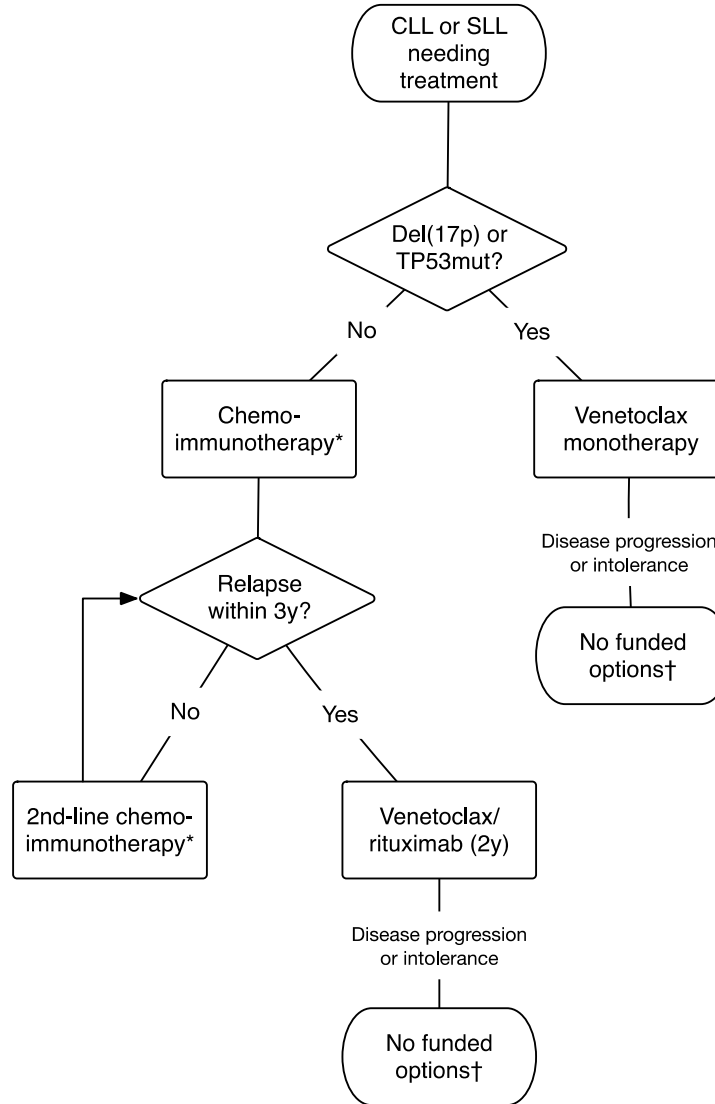
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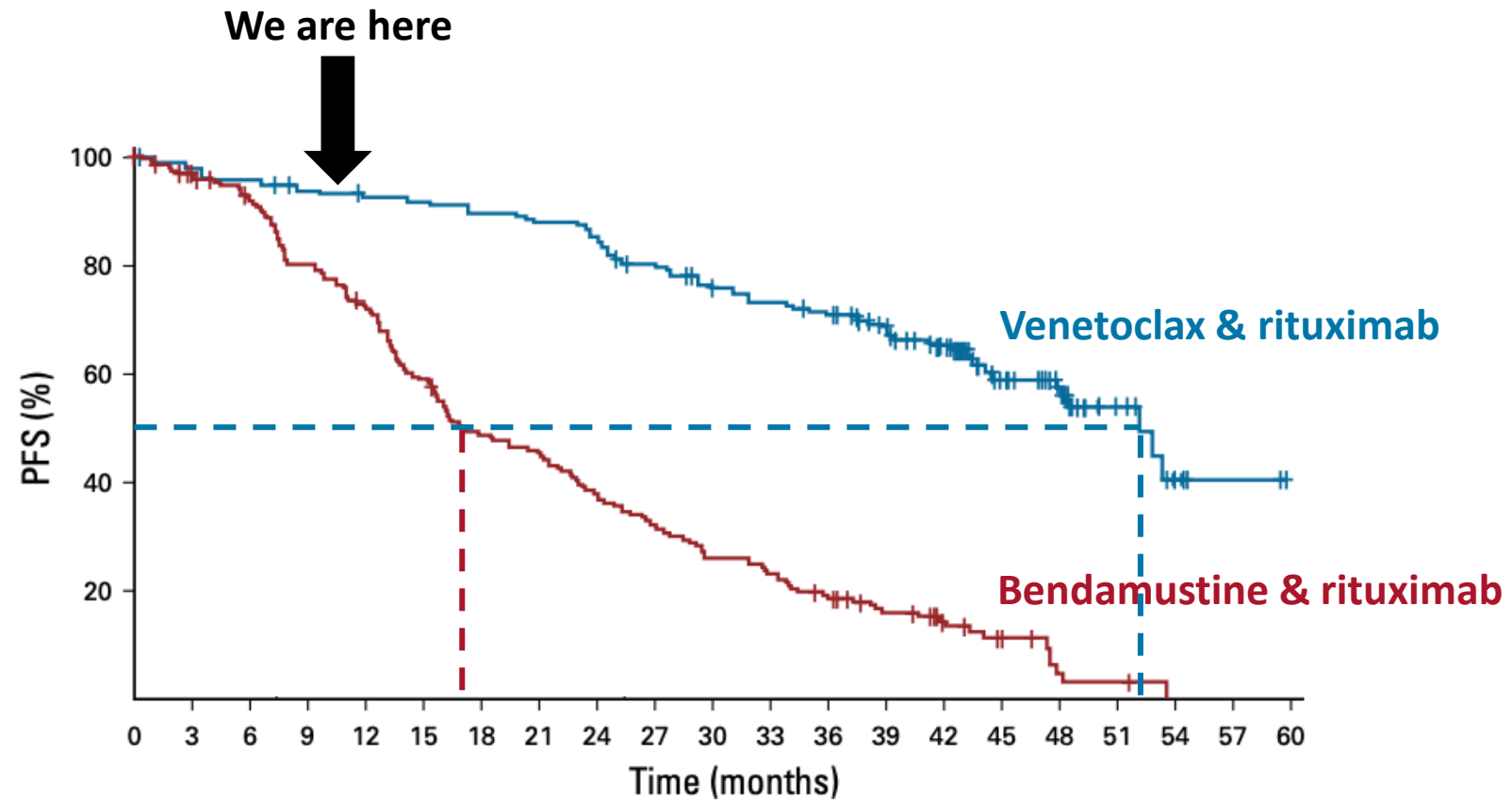
# Current PHARMAC-funded pathway



\* FCR, BR or OChI front-line; FCR or OChI at relapse  
† OChI is funded at relapse (if not used prior) but outcomes poor

# Priority #1: BTK inhibitor(s) for relapsed CLL

Venetoclax/rituximab is not curative

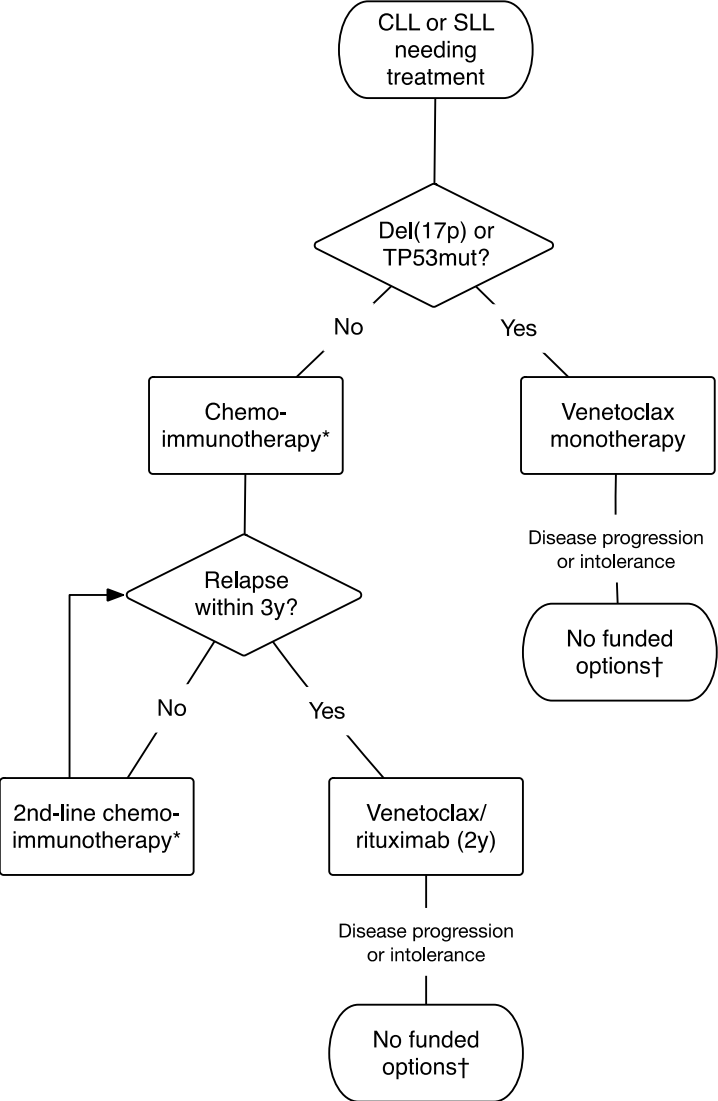


# Leading BTK inhibitors

BTK inhibitor	Dosing	Common side effects	Approved in NZ?	Funded in NZ?	Funded in Australia?
Ibrutinib (Janssen)	Once daily	Infections Bruising/bleeding Atrial fibrillation Diarrhoea Rash	<b>YES</b>	<b>NO</b>	<b>YES</b> (since Oct 2017)
Acalabrutinib (AstraZeneca)	Twice daily	Infections Headache Diarrhoea	<b>NO</b> NZ application in preparation; TGA- and FDA-approved	<b>NO</b>	<b>YES</b> (since Sept 2020)
Zanubrutinib (BeiGene)	Twice daily	Infections Diarrhoea Rash Neutropenia	<b>NO</b> FDA-approved for relapsed mantle cell lymphoma	<b>NO</b>	<b>NO</b>

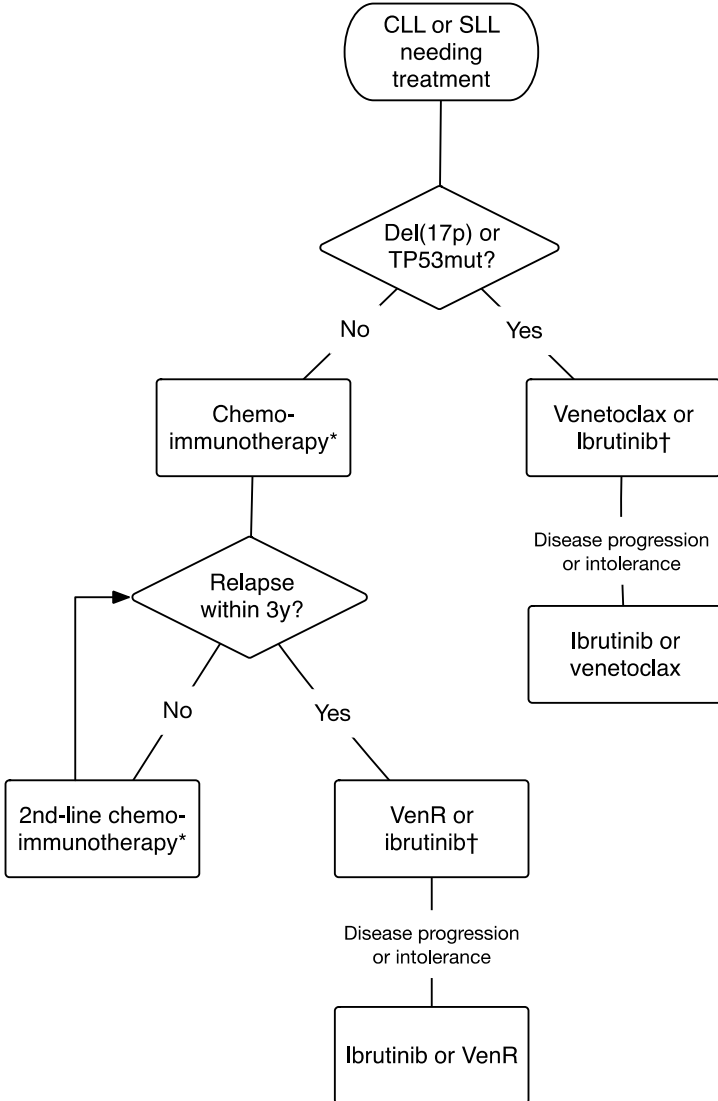
*Note: No published head-to-head comparisons of BTK inhibitors in CLL yet*

# Current PHARMAC-funded pathway




\* FCR, BR or OChI front-line; FCR or OChI at relapse  
 † OChI is funded at relapse (if not used prior) but outcomes poor

# Near-term goal (by late 2021)



\* FCR, BR or OChI front-line; FCR or OChI at relapse  
 † Choice depends on disease, comorbidities, patient preference



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**Priority #1:** BTK inhibitor for relapsed CLL



**Priority #2:** Reforming first-line therapy

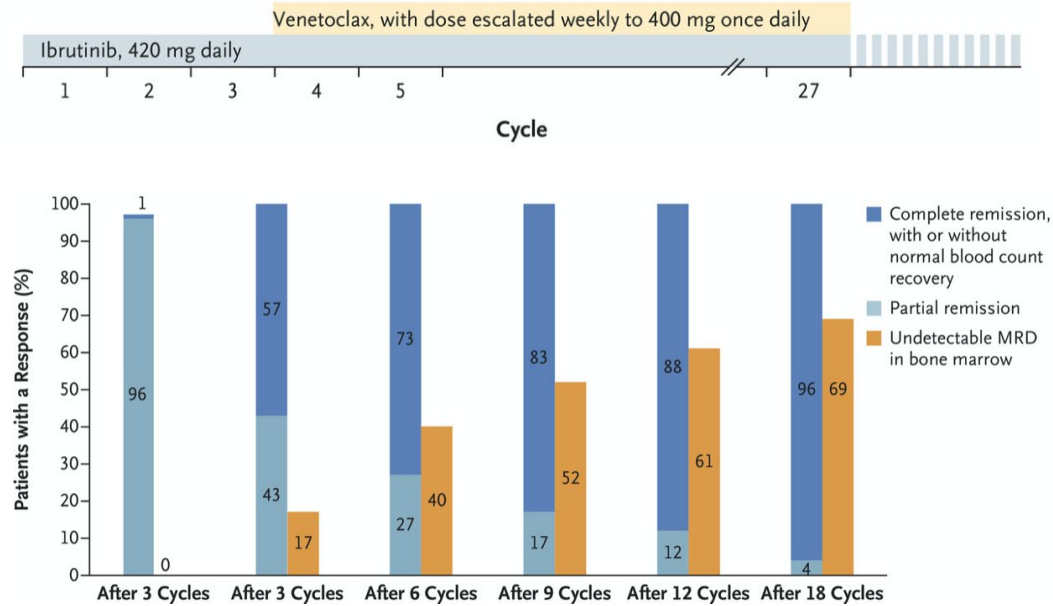
**Priority #3:** Preventing infections

**Future treatment concepts**



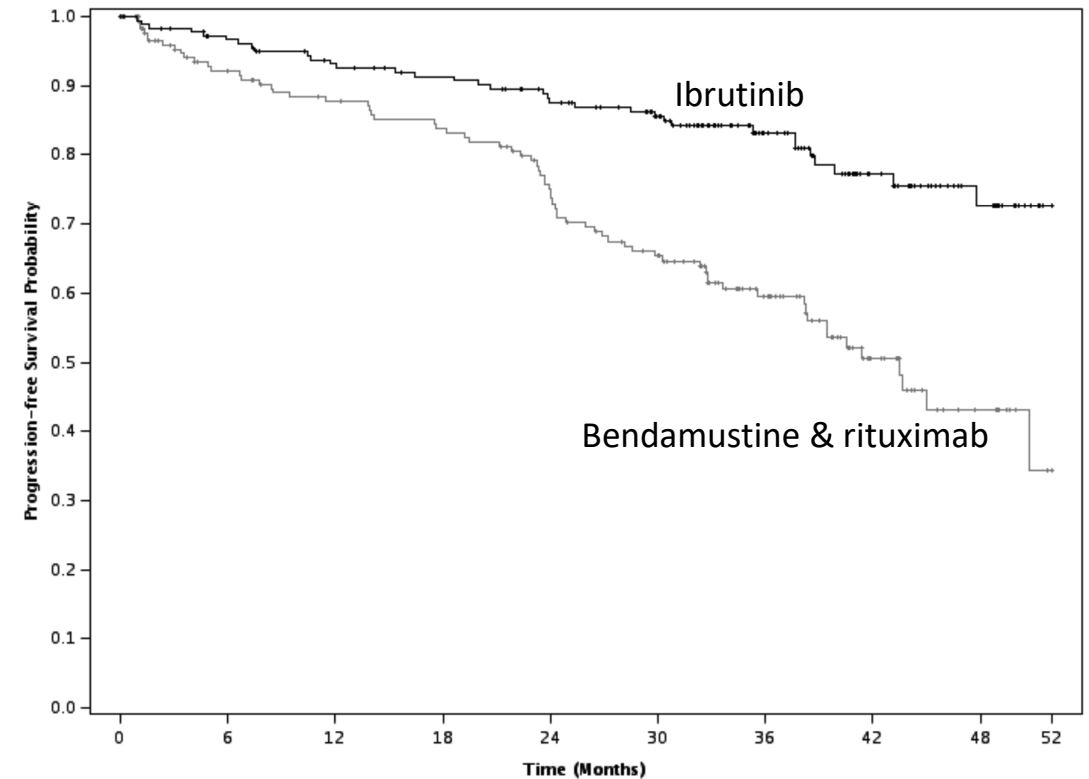
# Reforming first-line therapy

1. Fixed-duration ib Brutinib & venetoclax results in very deep CLL remissions



N Engl J Med 2019; 380: 2095-103

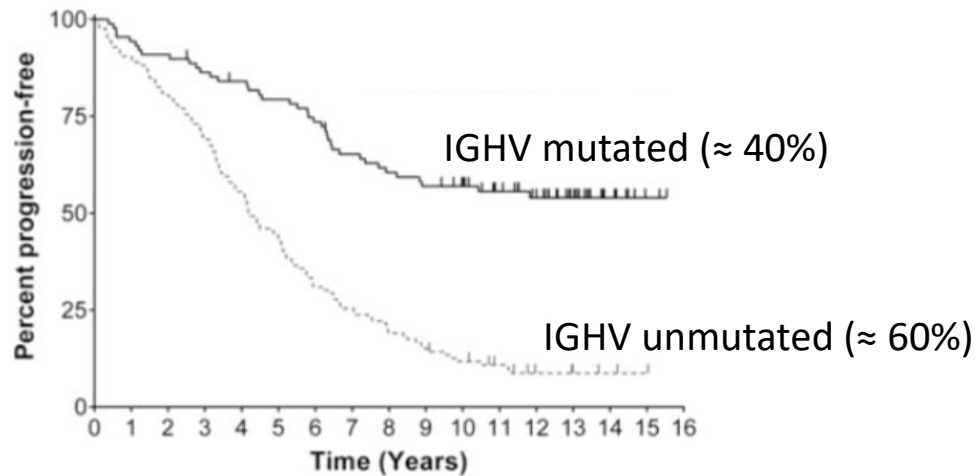
2. Long-term ib Brutinib is better than lower-intensive chemotherapies



N Engl J Med 2018; 379: 2517-28

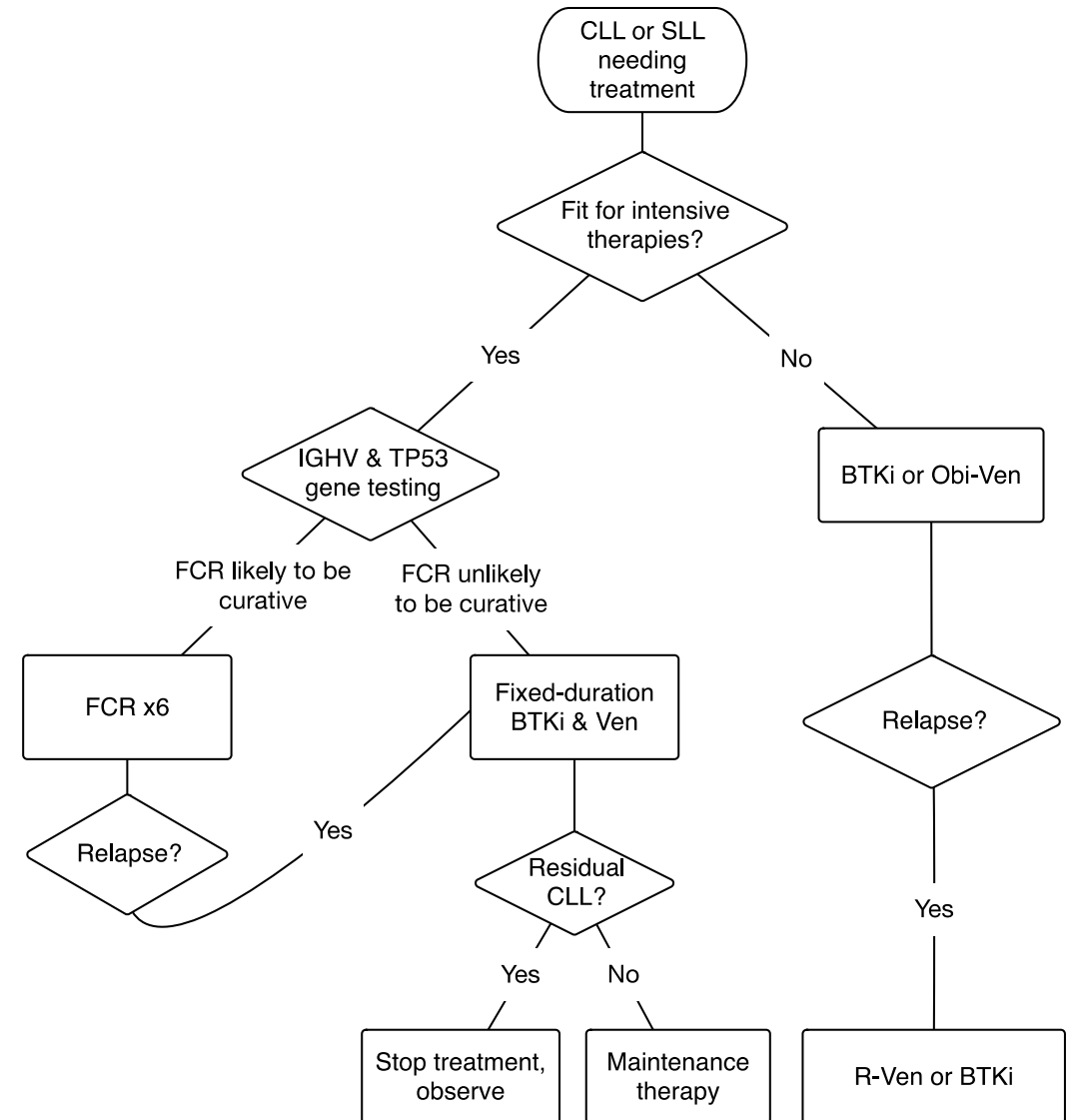
# Medium-term goal (2023?)


≈ 75% of fitter patients are either **cured by FCR**, or enter **deep remission & stop fixed-duration** therapy;  
≈ 25% stay on maintenance therapy



## Requirements:

PHARMAC funding (esp. BTK inhibitor)  
IGHV and TP53 gene sequencing  
Minimal residual disease assessment





# CLL in New Zealand: Future directions & priorities

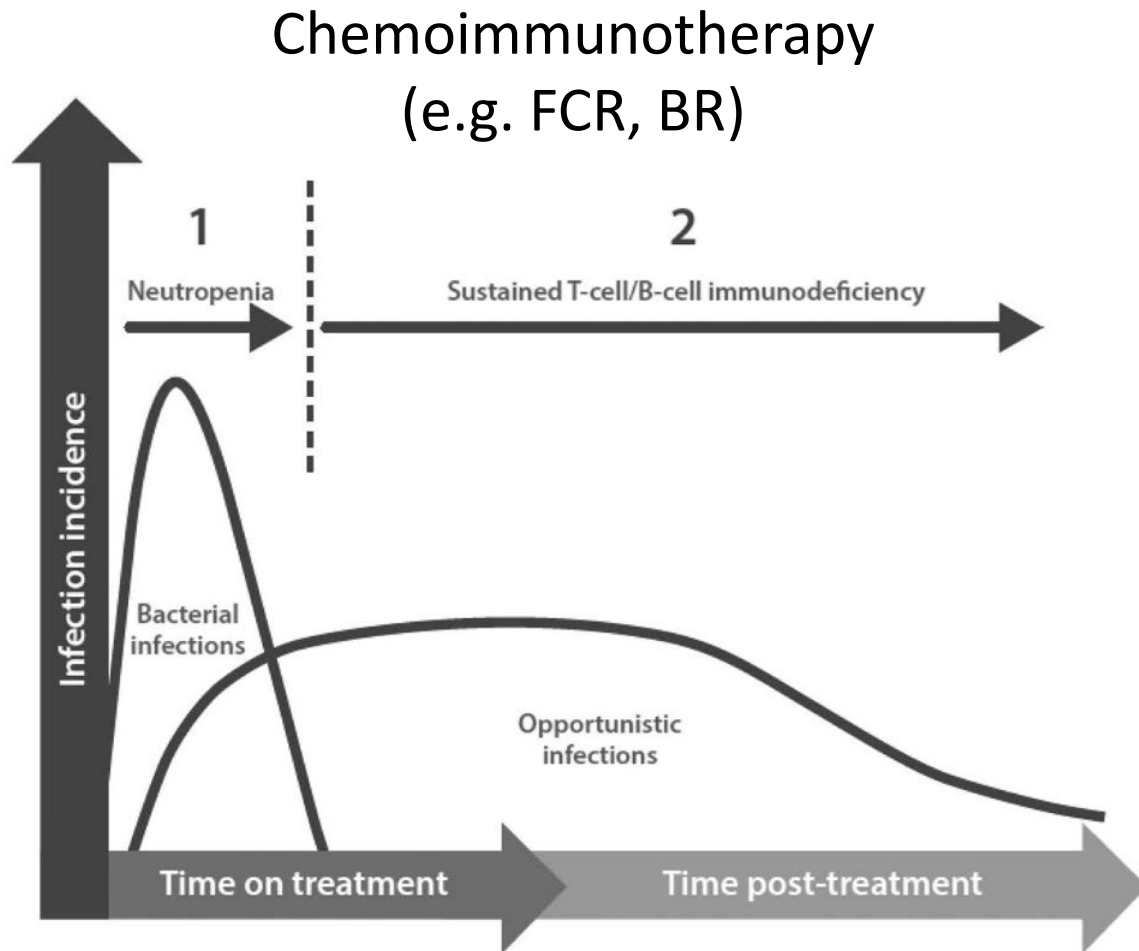
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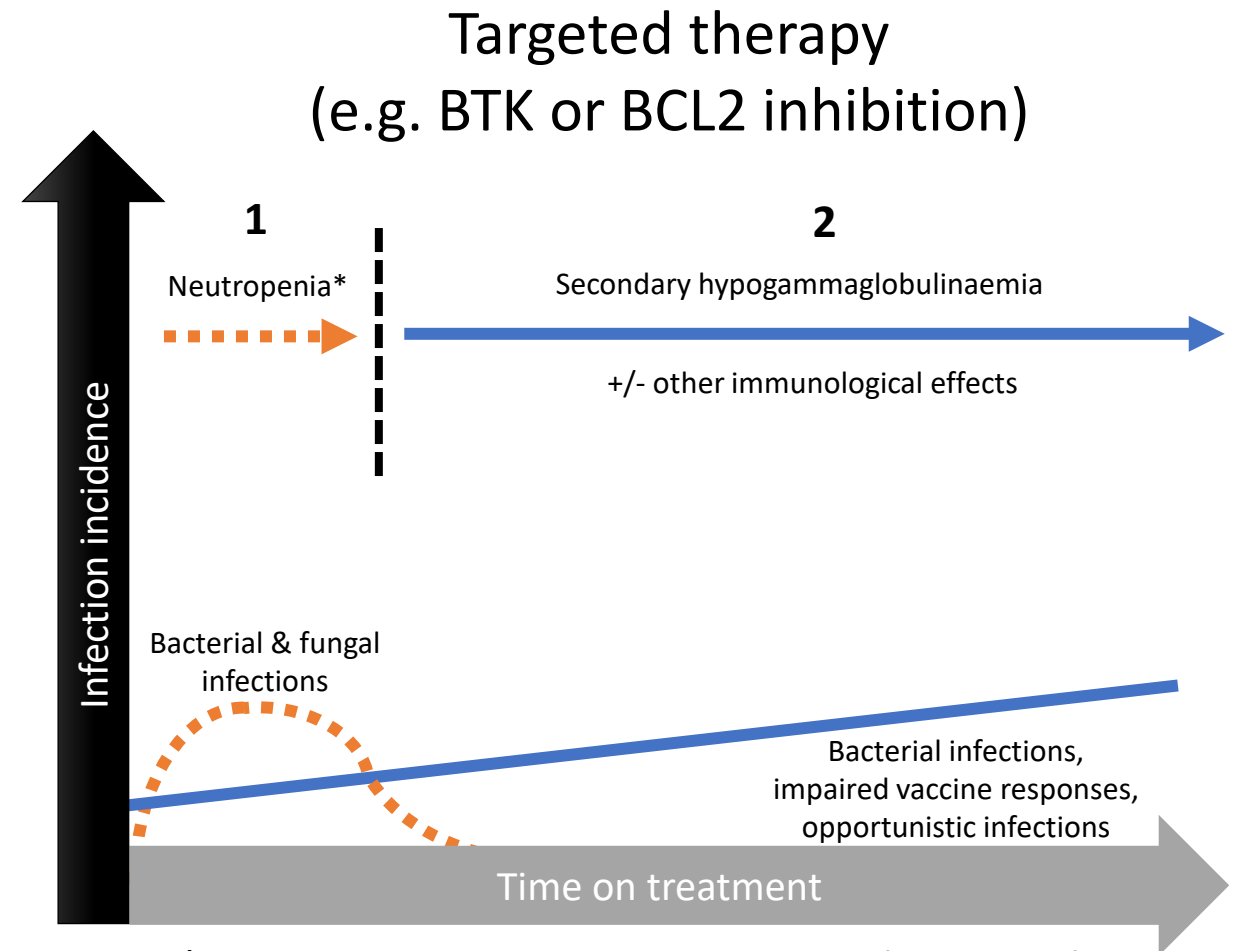
 **Priority #3:** Preventing infections

**Future treatment concepts**

# Long-term oral targeted CLL therapies: a different infection risk profile



Exp Rev Hematol 2018; 11:1, 57-70



*\*Transient neutropenia common with venetoclax, less common with Btk inhibitors*

# Preventing infections during BCL2i & BTKi

Aim to vaccinate *before*, not *after*, CLL therapy

- Influenza vaccination – funded
- Pneumococcal vaccine (initial PCV13 dose funded pre-chemo; booster 23PPV dose **unfunded**)
- Zoster vaccination – Zostavax unsuitable; recombinant vaccine **unfunded**

Role of immunoglobulin replacement needs clarification

- RATIONAL trial (completed)
- RATIONALISE trial (grant application made)



Overview In Depth

Vaccine type: Subunit protein vaccine

## Schedule and administration

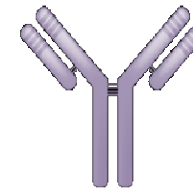
Pneumovax®23 vaccine is not part of the routine immunisation schedule but is funded for children and adults with a medical condition that increases their risk of invasive pneumococcal disease AND is listed on the Pharmaceutical Schedule. The vaccine is available for purchase by people with a medical condition that is not listed on the Pharmaceutical Schedule.

## Children aged 5 years or older, and adults

- Cochlear implant
- Complement deficiency (acquired or inherited)
- Functional asplenia
- HIV-positive
- Post-haematopoietic stem cell transplantation
- **Post-chemotherapy**
- Pre- or post-splenectomy
- Pre- or post-solid organ transplantation
- Primary immunodeficiency
- Renal dialysis


## Zostavax should not be given to:

- **Individuals with current leukaemia, lymphoma,** or other bone/marrow/lymphatic neoplasms.
- Individuals with acquired immune deficiency syndrome (AIDS) or other medical condition causing cellular immunodeficiency.
- Individuals with tuberculosis (TB).
- Anyone with severe allergy (anaphylaxis) to a previous dose of herpes zoster virus vaccine or a component of the vaccine.



# RATIONAL

**ROLE OF ANTIBIOTIC THERAPY OR IVIG ON  
INFECTIONS IN HAEMATOLOGY**



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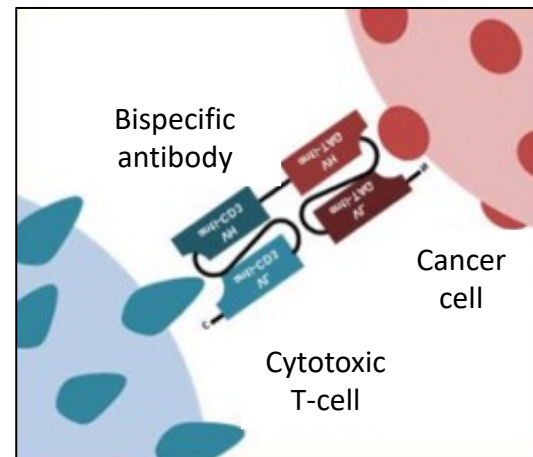
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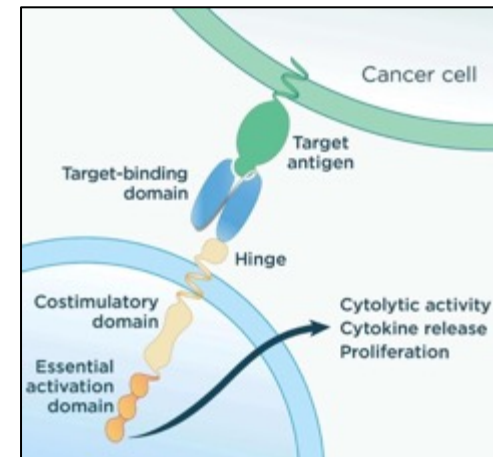
 **Future treatment concepts**

# Future treatment concepts

- 'Double refractory' CLL
  - Resistant to both BTK and BCL2 inhibitor(s)
  - Allogeneic stem cell transplantation is the standard of care
  - High-dose steroids & antibodies; new BCL2 and PI3k inhibitors
  - Redirection of patient T-cells against the tumour as an alternative



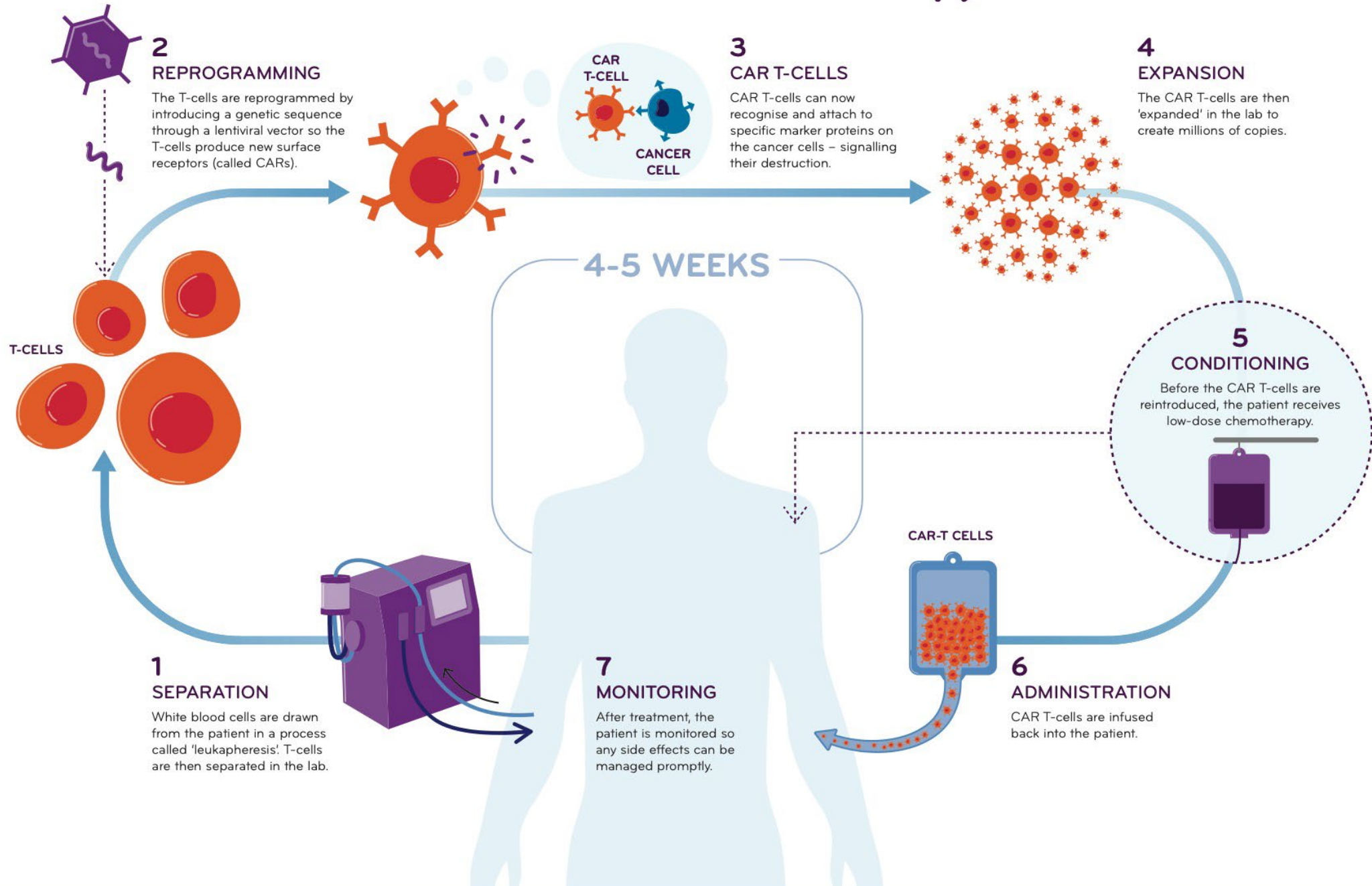
Bispecific T-cell engagers



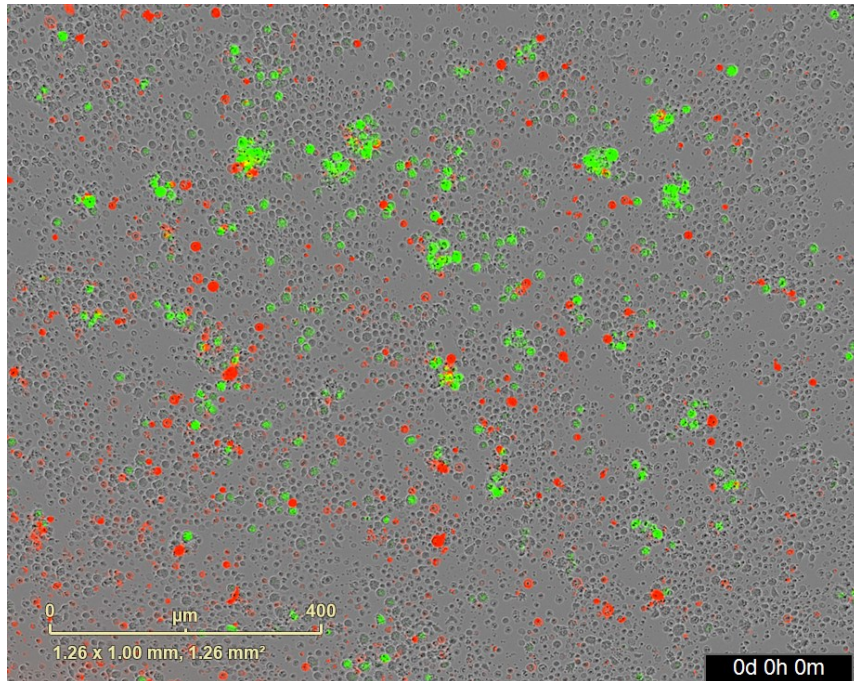
Chimeric antigen receptor  
T-cells



# CAR T-Cell Cancer Therapy



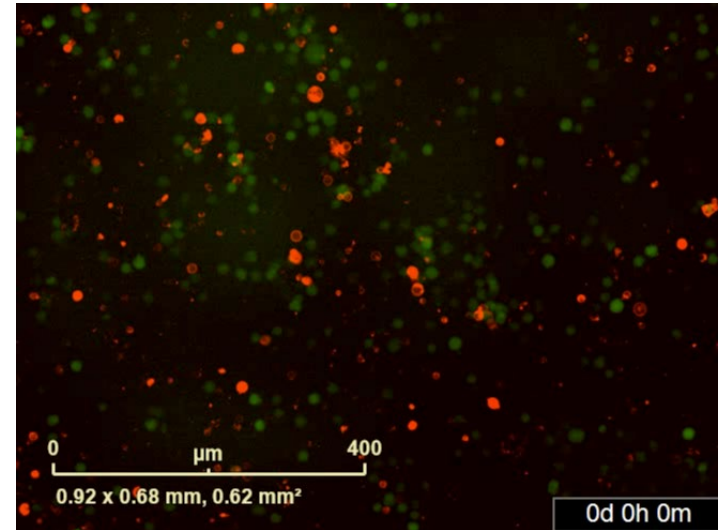
# Live cell imaging



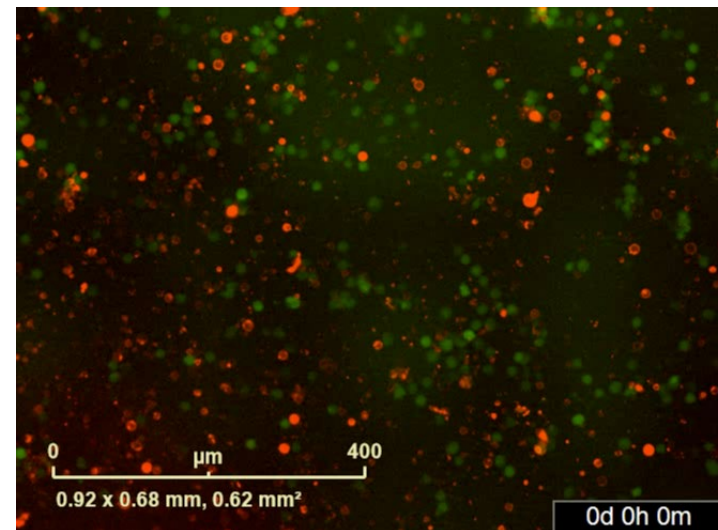
**Green** = tumour cells

**Red** = dead and dying cells

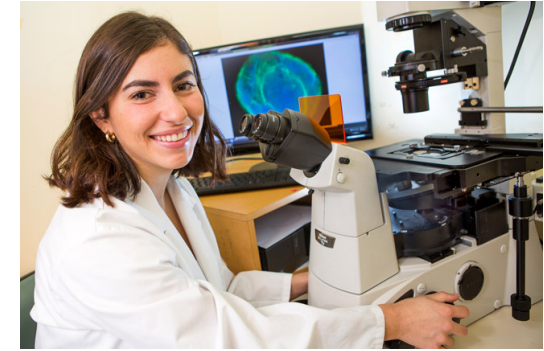
**Grey** = 1928T2z CAR T cells



Growth of control CD19<sup>-</sup> tumour cells

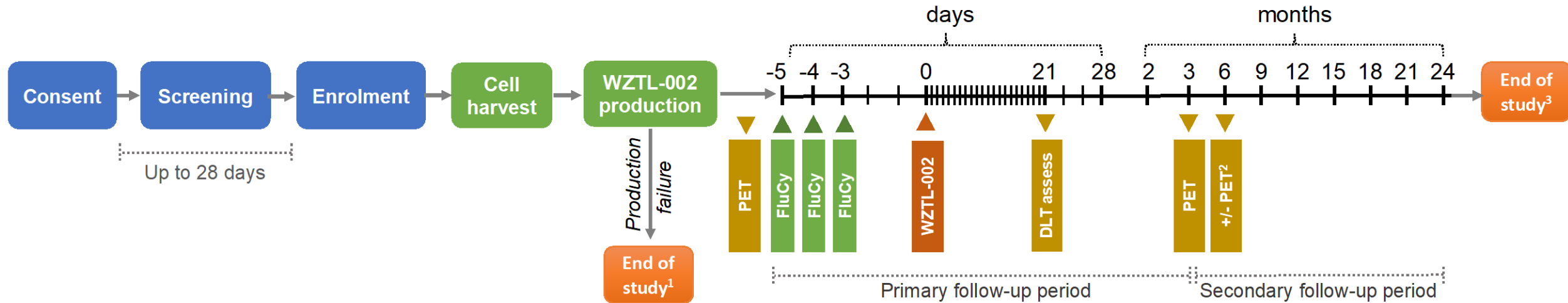


Killing of CD19<sup>+</sup> tumour cells



*Videos by Yasmin Nouri,  
John Waller Scholar*

**Note:** ENABLE is a Phase 1, first-in-human clinical trial  
 Neither the safety profile nor the effectiveness of WZTL-002 CAR T-cells is known



**Notes and abbreviations:**

- <sup>1</sup> Second attempt at cell harvest and WZTL-002 production may be considered at discretion of TMC
  - <sup>2</sup> 6 month PET scan if first PET scan post WZTL-002 treatment shows partial response
  - <sup>3</sup> Long-term follow-up through bone marrow transplant clinic and Cellular Therapies Registry enrolment
- FluCy, fludarabine and cyclophosphamide IV; PET, positron-emission tomography/computed tomography scan





# CLL in New Zealand: Summary

## Summary

**Priority #1:** PHARMAC funding of at least one BTK inhibitor for relapsed CLL

**Priority #2:** PHARMAC funding of front-line chemotherapy-free therapy for those who will benefit most

**Priority #3:** PHARMAC funding of pneumonia vaccines, and of a recombinant zoster vaccine, before CLL treatment