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What Patients and Care Partners Need to Know about Treating CLL (and SLL!)

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Disclosures

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Overview

Types of CLL/SLL Treatments

How to choose the right therapy

Treatments at time of relapse

Sequencing of therapies

Treatments in the pipeline

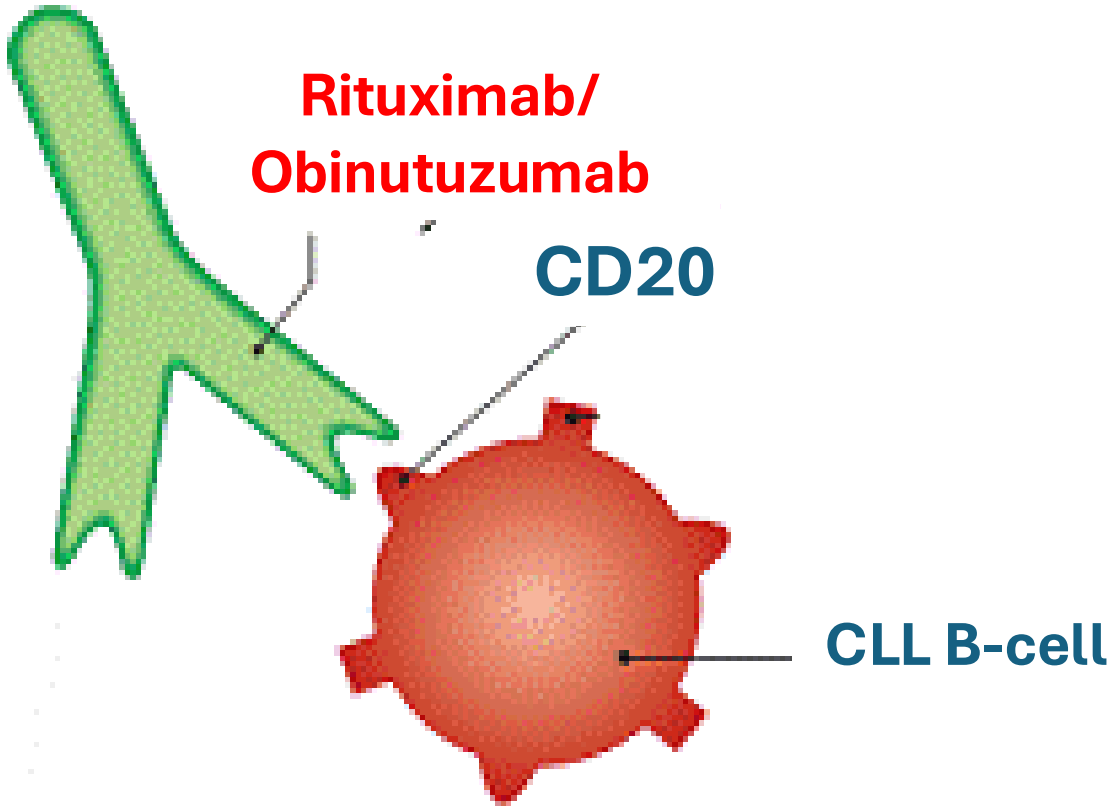
CLL/SLL Treatment Types

- Chemotherapy
- Monoclonal antibodies
- “Targeted” therapy
- Immunotherapy
- Cellular therapy
- Radiation or surgery - rare

Chemotherapy

- Strong drugs which kill any fast-growing cells in the body
  - Cancer cells 
  - Other fast-growing cells: hair, mucosal membranes (including in mouth, esophagus, bowels), ovaries/sperm, normal blood cells 
- Often given through an IV, goes through entire bloodstream
- Eg: fludarabine, cyclophosphamide, bendamustine, chlorambucil
- May be used alone or in combination

Monoclonal antibodies (type of immunotherapy)



- Prolong survival when added to chemotherapy
- Deepen response when added to targeted therapy

- Infusion reactions
- Immunosuppression
- Decreased vaccine response

“Chemoimmunotherapy”

Chemotherapy + Monoclonal Antibody = **Chemoimmunotherapy (CIT)**

Examples:

- Fludarabine, cyclophosphamide, rituximab (FCR)
- Bendamustine, rituximab (BR)
- Chlorambucil, obinutuzumab (Chlor-O)

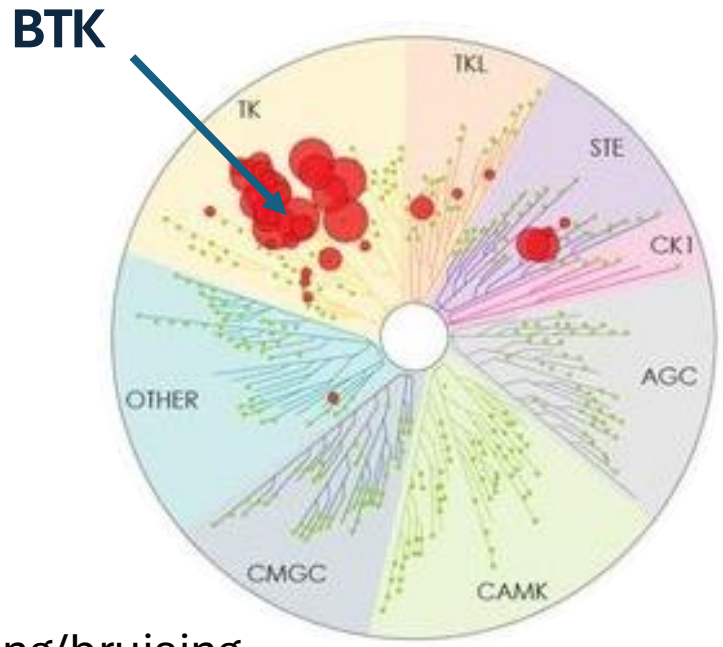
Targeted new drugs for CLL

- Ibrutinib (Imbruvica) → BTK
- Acalabrutinib (Calquence) → BTK
- Zanubrutinib (Brukinsa) → BTK
- Venetoclax (Venclexta) → BCL2
- Pirtobrutinib → “non-covalent” (reversible) BTK

Bruton's Tyrosine Kinase inhibitors (BTKi's): What's the difference?

1st generation

Ibrutinib



Bleeding/bruising
High blood pressure, arrhythmias
GI, skin/nail, joint/muscle pains

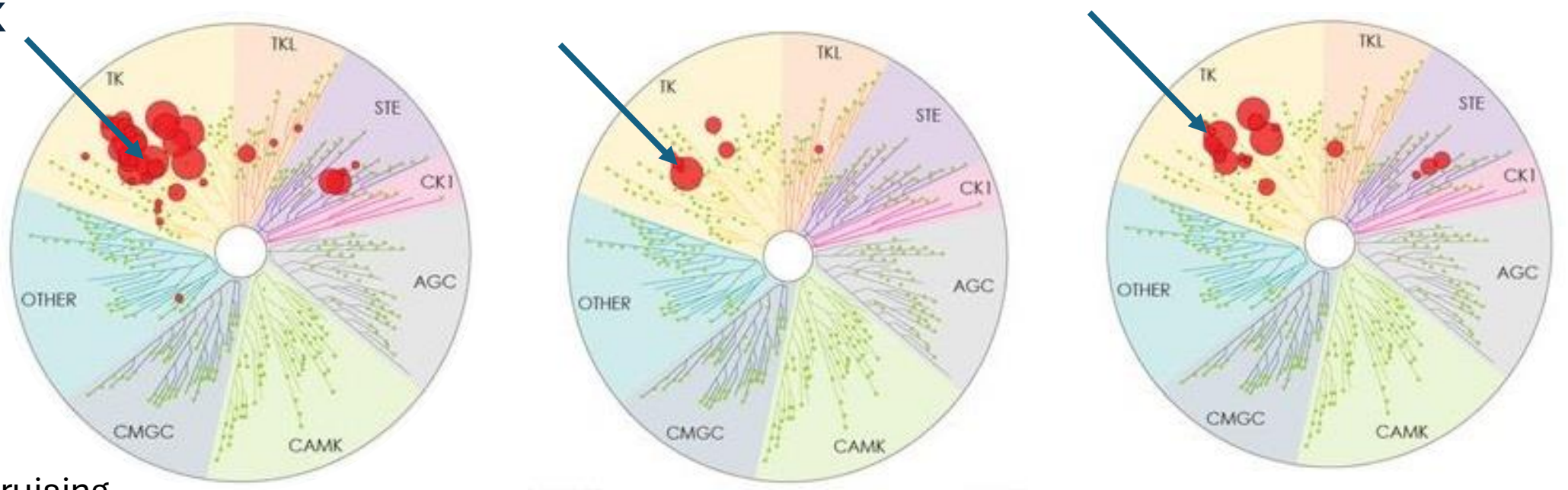
Bruton's Tyrosine Kinase inhibitors (BTKi's): What's the difference?

1st generation

2nd generation

Ibrutinib | Acalabrutinib | Zanubrutinib

BTK



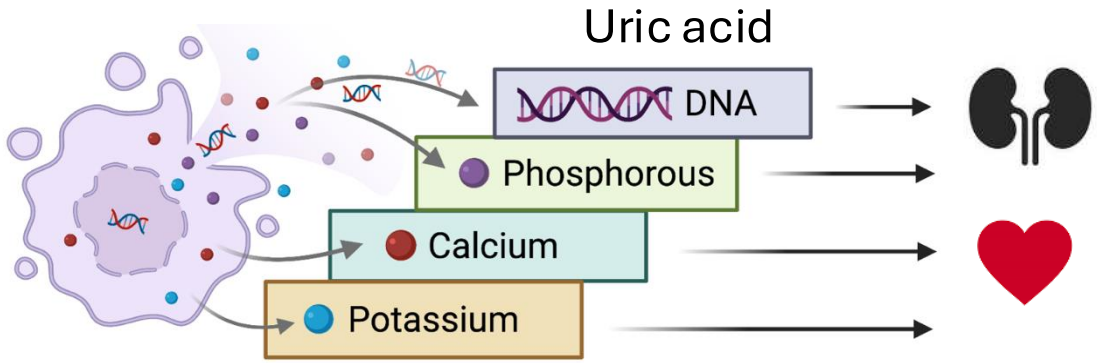
Bleeding/bruising
High blood pressure, arrhythmias
GI, skin/nail, joint/muscle pains

→ **Different targets lead to different side effects**

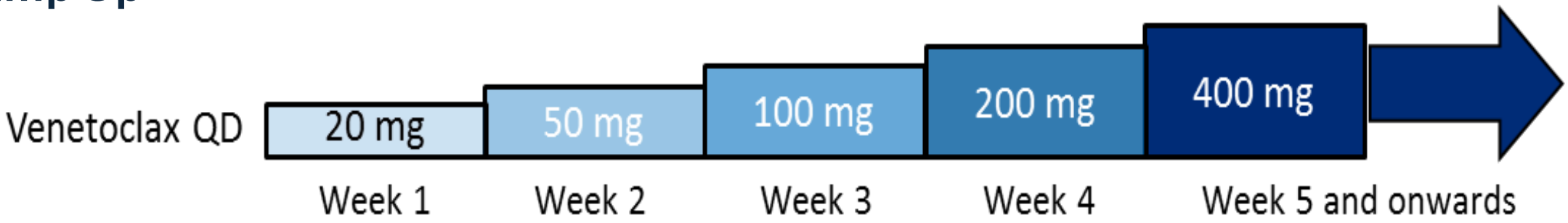
BCL2 inhibitors - Venetoclax

- Works so well that it kills cells VERY rapidly

- Risk of Tumour Lysis Syndrome
  - Cells release contents into bloodstream
  - Allopurinol, rasburicase, fluids



"Ramp Up"

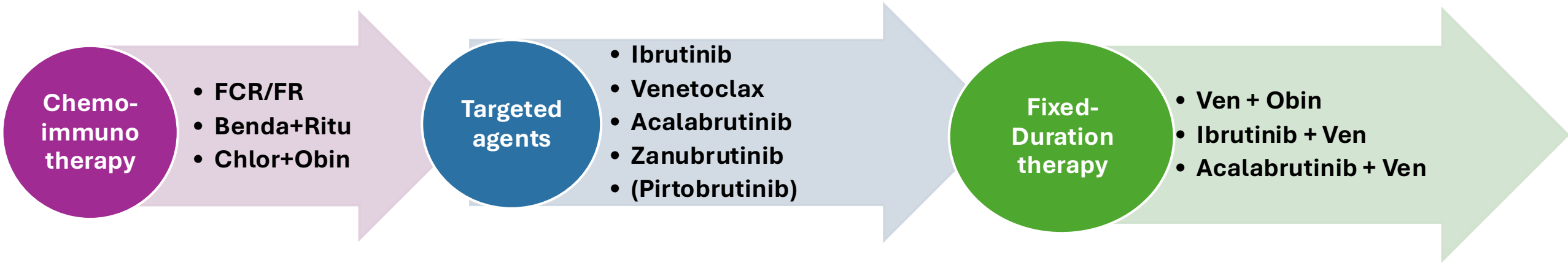


“Fixed-Duration” Therapy

Combine drugs to get **deep remissions** and allow us to **stop therapy**

- Venetoclax + Obinutuzumab (12 mos)
- Ibrutinib + Venetoclax (15 mos)
- Acalabrutinib + Venetoclax (15 mos)

The Changing Landscape of CLL/SLL Treatment in Canada



As of May 2026

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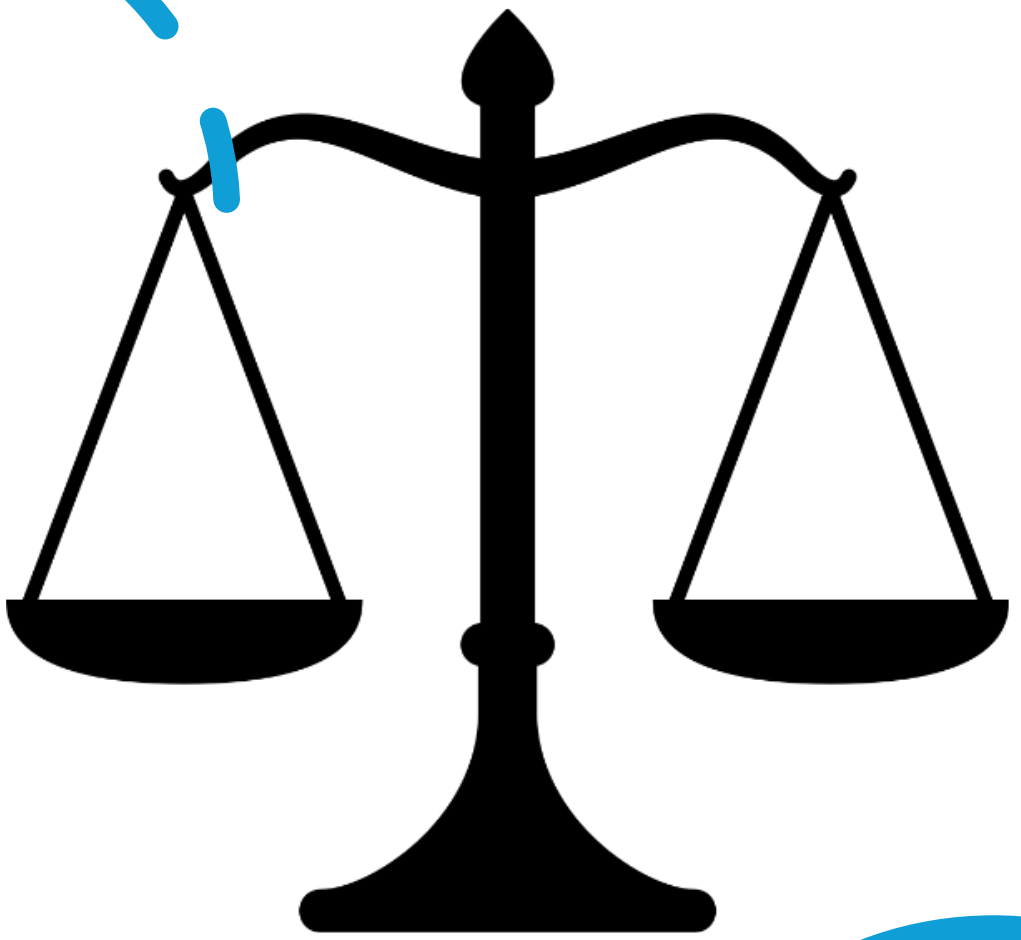
Which is the best therapy for me?

- Clinical trial results
  - Efficacy – how well does it work?
  - Safety – what are the side effects?
- Prognostic markers
- “Fitness”, comorbidities
- Values and preferences
- Cost and availability



How do treatments compare (First-Line)?

Trial	Winner
CIT vs BTK inhibitors	BTK inhibitors
CIT vs Venetoclax + Obinutuzumab	Ven + Obin
CIT vs. Ibrutinib + Venetoclax	Ibrut + Ven
CIT vs. Acalabrutinib + Venetoclax	Acala + Ven

→ Clinical trials have consistently shown that novel agents work better than CIT in keeping the cancer away longer **(Progression-Free Survival)** and in some cases, helping patients live longer **(Overall Survival)**

How do treatments compare (First-Line)?

Trial	Winner
• Ibrutinib vs. 2nd gen (Acala/Zanu)	2nd generation
• Acalabrutinib vs Zanubrutinib	? (=)
• BTKi vs. Ven+Obin or Ven+BTKi	EQUAL
• Ven+Obin vs. Ven+BTKi	Trials ongoing

→ Second generation BTK inhibitors favoured over ibrutinib as single-agent
→ No clear difference between Acalabrutinib and Zanubrutinib
→ Fixed-duration therapy is **equivalent** to continuous BTK monotherapy for most cases
→ Unclear what's better between different time-limited options

Pros and cons of novel agent strategies

Continuous (Acalabrutinib or Zanubrutinib)
Daily pills, easy
May be better for high-risk disease (stay in remission longer)
Unclear if/when can stop
Development of resistance mutations
Side effects: - Bleeding/bruising - High blood pressure, arrhythmias - GI, skin/nail, joint/muscle pains - Medication interactions

Pros and cons of novel agent strategies

Continuous (Acalabrutinib or Zanubrutinib)	Fixed-Duration (Ven-Obin, Acala-Ven)
Daily pills, easy	More intensive (ramp up, IV treatment)
May be better for high-risk disease (stay in remission longer)	Less time in remission for high-risk disease (although unclear if any downside of start/stop)
Unclear if/when can stop	Only 12-15 months
Development of resistance mutations	Less resistance mutations
Side effects: - Bleeding/bruising - High blood pressure, arrhythmias - GI, skin/nail, joint/muscle pains - Medication interactions	Side effects: - Infusion reactions (obin) - Vaccine responsiveness (obin) - Same side effects for BTK inhibitors (but shorter time)

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What about at time of relapse?

Questions to ask

❖Did treatment stop because of **progression of CLL/SLL** or due to **side effects** or **planned**?

- If Progression → switch drug class
- If Side Effects → can consider repeating same drug class with new option
- If Planned (Fixed-duration) → can consider repeating one or both drugs

❖Repeat prognostic testing (new deletion 17p, TP53 mutation?)

❖Resistance mutation testing?

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What do we know about sequencing?

- **Not much!**
- Unclear which treatments are better first and which are better later
- “Real world” and observational studies may help to answer this question
- Clinical trials now building this into their designs

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Treatments in the Pipeline

- Non-covalent BTK inhibitors (Pirtobrutinib)
- Cellular therapy (CAR T-cell therapy)
- New targeted agents
  - BTK degraders
  - B-cell receptor inhibitors
  - Bispecific antibodies
  - New BCL2 inhibitors
  - …

Non-covalent (reversible) BTK inhibitors

Covalent BTK inhibitors
(Ibrutinib, Acala, Zanu)

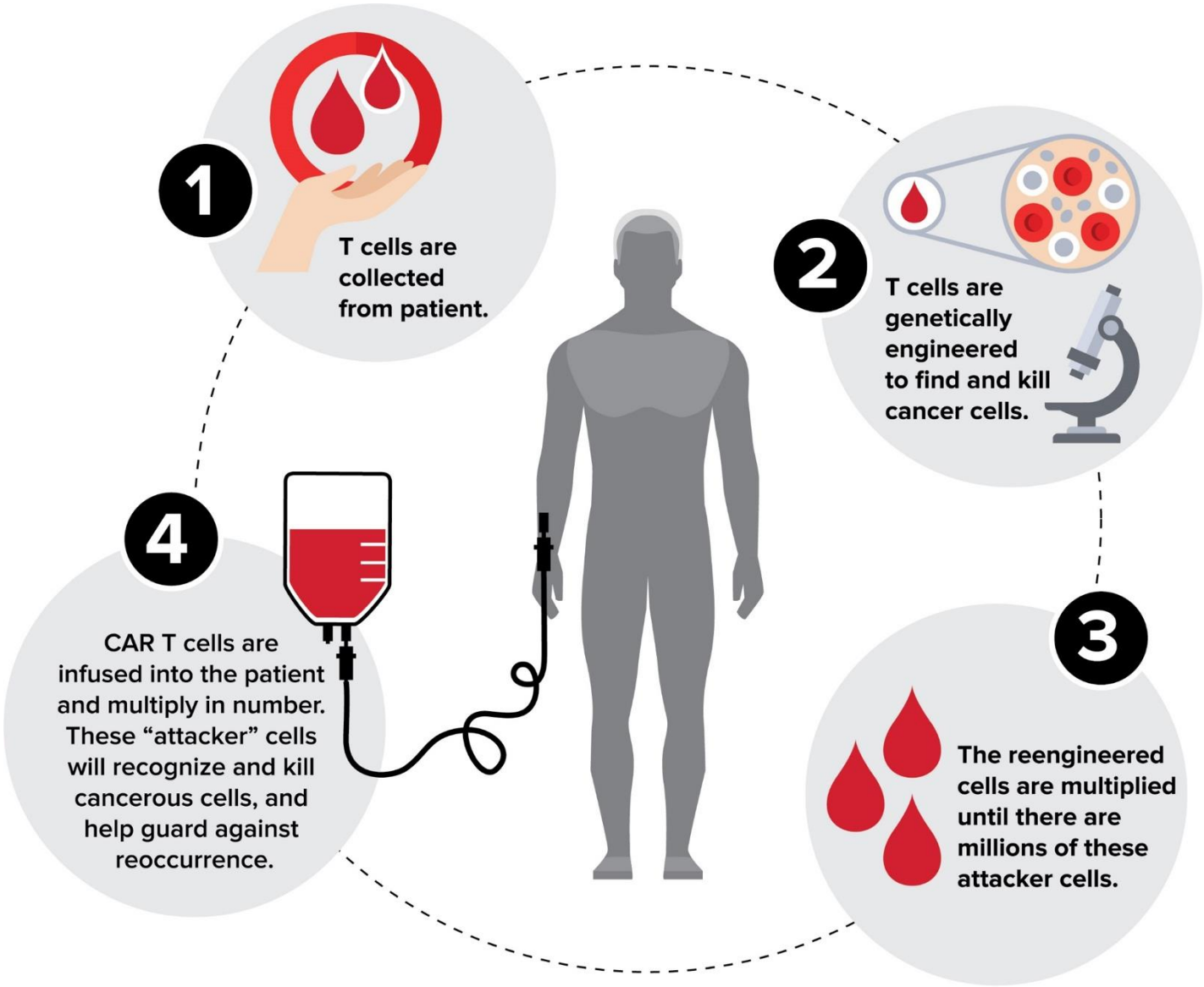
Non-covalent BTK inhibitors
(Pirtobrutinib, Nemtabrutinib)

Mutations in C481 lead to resistance

→ Non-covalent BTK inhibitors are effective in those with resistance mutations

→ **Pirtobrutinib** now Health Canada approved for those progressing after a covalent BTK inhibitor (ibrutinib, acala, zanu) and a BCL2 inhibitor (venetoclax)

CAR T-cell therapy: “Living Drug”



- Curative for some lymphomas
- Severe toxicities (CRS, ICANS)
- FDA approved for CLL after BTK and BCL2 inhibitor, but short remissions, not curative
- Results not as promising in CLL, possibly due to “exhausted” T cells
- Studies ongoing to improve T cells prior to CART

Targeted Agents in Development

BTK Degraders	B-cell receptor pathway inhibitors	Bispecific T-cell engagers	BCL2 inhibitors
Bexobrutideg (Nx-5948) ★	PKC-beta inhibitors	CD20 x CD3 BiTE	ABBV-453
BGB-16673 ★	MS-553	Epcoritamab	BP1002
ABBV-101	MALT-1 inhibitors	Mosenutuzumab	Lisaftoclax
AC676	ABBV-525 ★	CD19 x CD3 BiTE	LP-118
Nx-2127	JNJ-67856633	AZD0486 ★	Sonrotoclax ★
UBX-303061	SGR1505	ROR1 x CD3 BiTE	
		NVG-111	

★ Ongoing or planned clinical trials in BC

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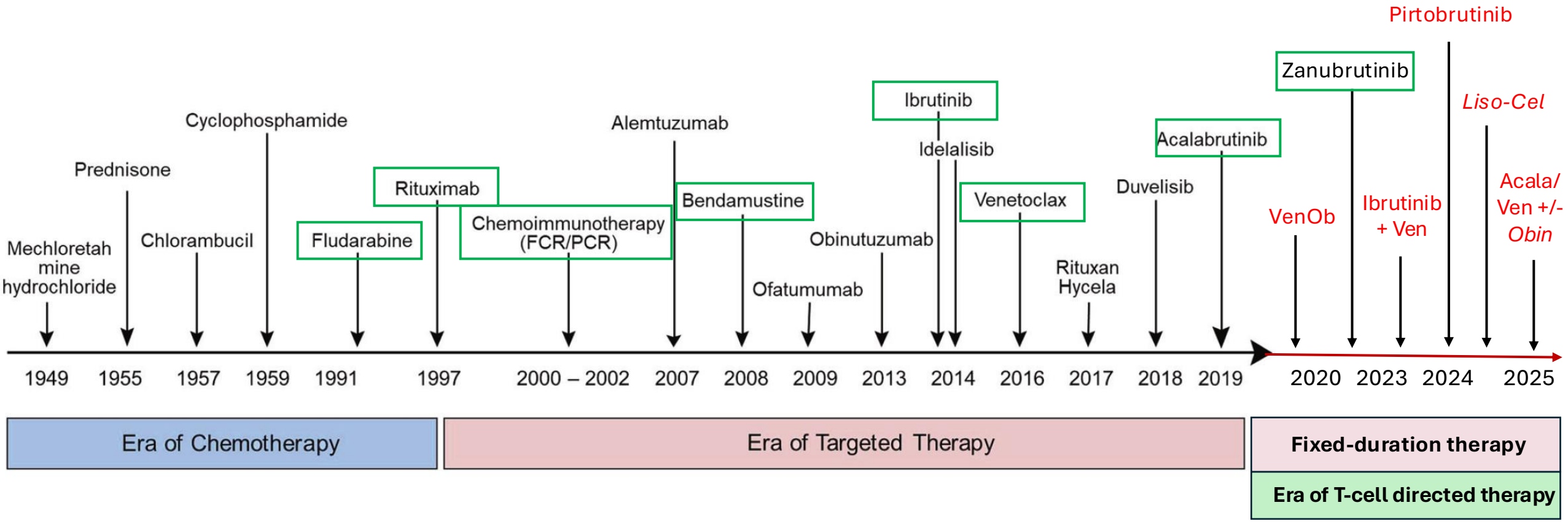
The Evolution of CLL Treatment



Adapted from Parikh et al, Nature 2020