BC CANCER

Provincial Health Services Authority

So Many Choices!
Navigating the Evolving World of CLL/SLL Treatments

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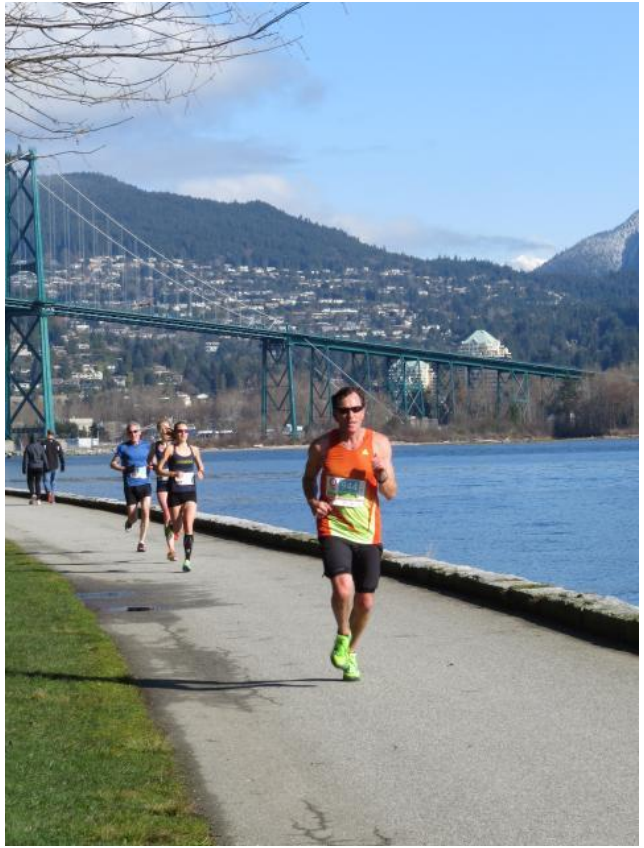
Typical CLL story

- 67 year old man, runner
- Knee pain
- Lab work ordered: CBC

Told he has…

"Leukemia"



Goals of CLL/SLL Treatment

Goals of therapy
- ➢Prolong survival
- ➢Improve quality of life

- CLL is incurable (today)
- Studies have shown that early treatment *does not* prolong survival, and may worsen quality of life due to side effects
- May develop resistance to drugs and would not be able to use them when the disease progresses
- All Guidelines recommend **Active Surveillance** for patients without any symptoms

When to consider treatment?

2018 IWCLL Guidelines: Evidence of "active" disease:

- Worsening blood counts: hemoglobin < 100, platelets <100
- Massive or enlarging spleen (>6 cm below ribs) or lymph nodes (>10 cm)
- Rising lymphocyte count: "lymphocyte doubling time" < 6 months
- Disease related symptoms
  - Unintentional weight loss more than 10% over 6 months
  - Cannot work or do usual activities due to fatigue
  - Fevers for 2 or more weeks without infection
  - Drenching night sweats for more than 1 month without infection
- Autoimmune problems not responding to steroids
- Disease involving other organs causing symptoms (e.g. skin, kidney, lungs)

Hallek, IWCLL Guidelines, Blood, 2018

Back to the case: Runner with CLL

- Active surveillance for 3 years, now 70 years old
- Up to date on vaccines: COVID19, yearly influenza, shingles, pneumonia, RSV
- Regular prostate, colon, skin cancer screening
- Continues exercising, balanced diet, support through patient community
- Begins to feel more fatigued, unable to run more than 20 minutes, lymph nodes in neck growing and becoming uncomfortable, blood counts decreasing – hemoglobin 105, platelets 80, lymphocytes 110

→ Meets IWCLL criteria for treatment

CLL/SLL Treatment Types

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

Chemotherapy

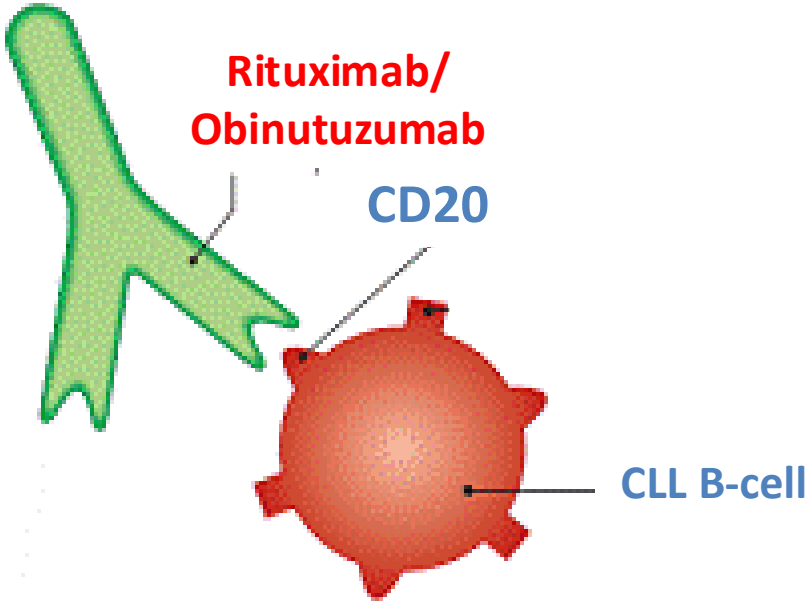
- Strong drugs which kill any fast-growing cells in the body
  - Cancer cells
  - Other fast-growing cells: hair, mucosal membranes (including in mouth, esophagus, bowels), ovaries/sperm, normal blood cells

- 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 (Obinutuzumab)

- 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

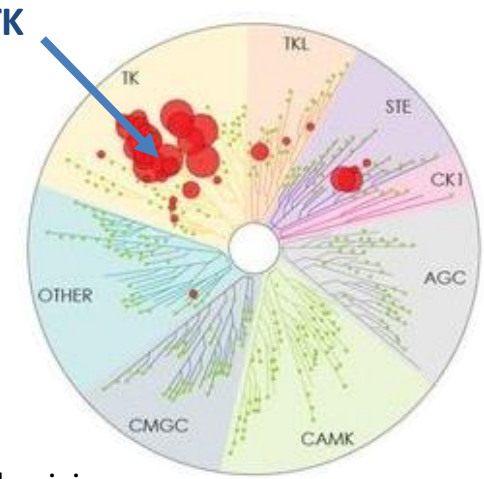
- Ibrutinib (Imbruvica) → BTK
- Acalabrutinib (Calquence) → BTK
- Zanubrutinib (Brukinsa) → BTK
- Venetoclax (Venclexta) → BCL2
- Idelalisib (Zydelig) → PI3K
- Pirtobrutinib → “non-covalent” (reversible) BTK

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

1st generation

Ibrutinib

BTK



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

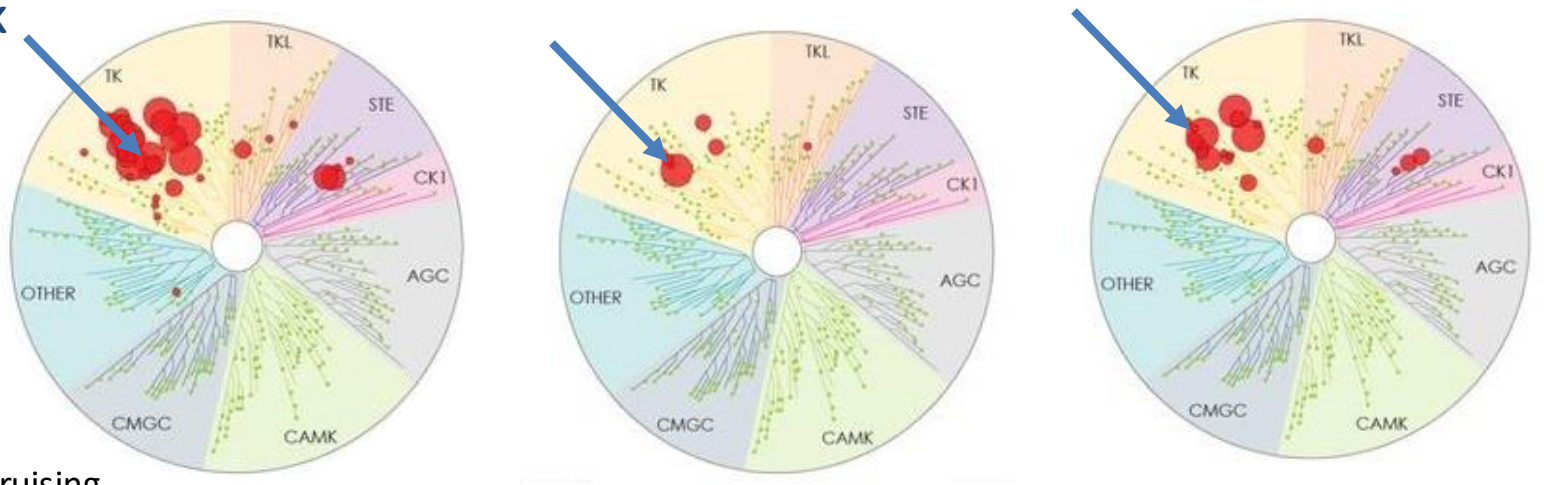
2nd generation

Ibrutinib

Acalabrutinib

Zanubrutinib

BTK



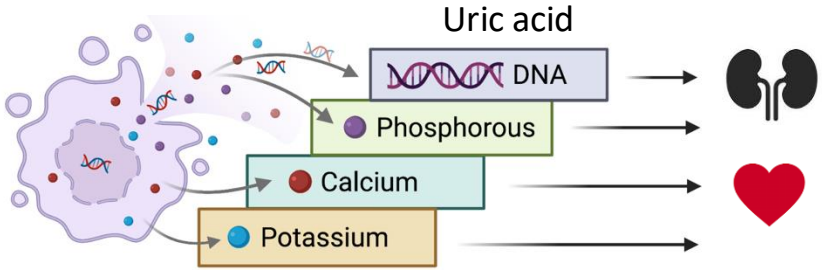
Bleeding/bruising
High blood pressure, arrhythmias
GI, skin/nail, joint/muscle pains

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

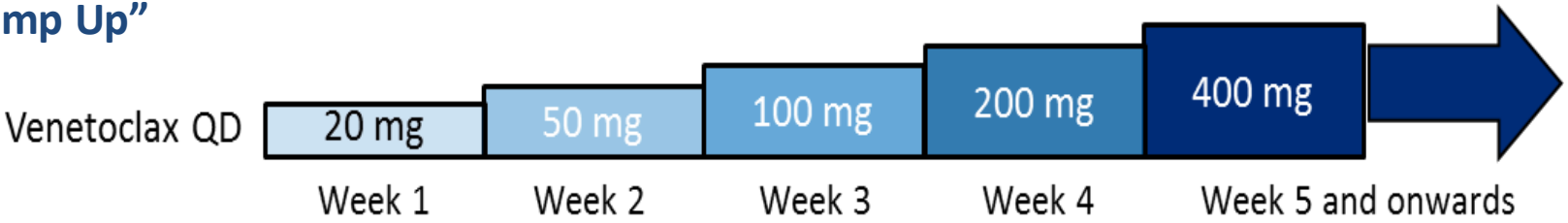
BCL2 inhibitors - Venetoclax

- Works so well that it kills cells VERY rapidly

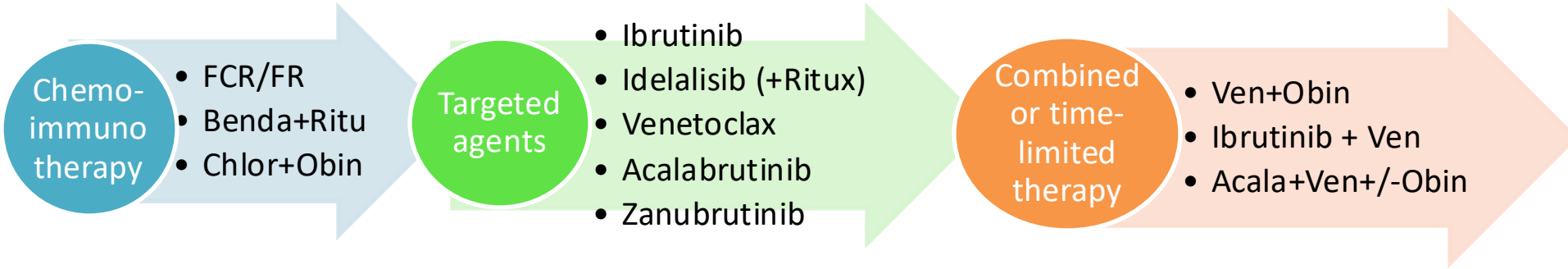
- Risk of Tumour Lysis Syndrome
  - Cells release contents into bloodstream
  - Allopurinol, rasburicase, fluids



"Ramp Up"



The Changing Landscape of CLL/SLL Treatment in Canada



As of April 2025

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

Back to the case

- 67 year old man, knee injury, diagnosed with CLL after routine CBC
- No symptoms at diagnosis
- 3 years later, fatigue, enlarging lymph nodes causing symptoms, worsening hemoglobin and platelets
- Prognostic testing: **IGHV unmutated, trisomy 12 → "intermediate risk"**
- No access to *TP53* mutation testing
- Mild high blood pressure, otherwise healthy
- Active, travels frequently since retirement, spends time with grandchildren

Possible treatments

1. Chemoimmunotherapy: Bendamustine and rituximab (6 months)
2. BTK inhibitors: Ibrutinib, Acalabrutinib, Zanubrutinib (indefinite)
3. Venetoclax and obinutuzumab (1 year)
4. Ibrutinib and venetoclax (1 year)
5. *Acalabrutinib and venetoclax (1 year)*

"Time-limited"
"Fixed-duration"

→ How do these compare?

How do treatments compare?

	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?

	Winner
• Ibrutinib vs. 2nd gen (Acala/Zanu)	2nd generation
• Acalabrutinib vs Zanubrutinib	? (=)
• Venetoclax + Obin vs. BTK inhibitor	Trials ongoing
• Venetoclax + Obin vs. BKT inhibitor + Ven	Trials ongoing

→ Second generation BTK inhibitors favoured over ibrutinib as single-agent
→ No clear difference between Acalabrutinib and Zanubrutinib
→ Unclear what's better between BTK monotherapy and "time-limited" options OR between different time-limited options

Pros and cons of novel agent strategies

"Indefinite" 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

★ BTKi may not be funded for good-risk CLL/SLL in some provinces (as a first-line treatment option)

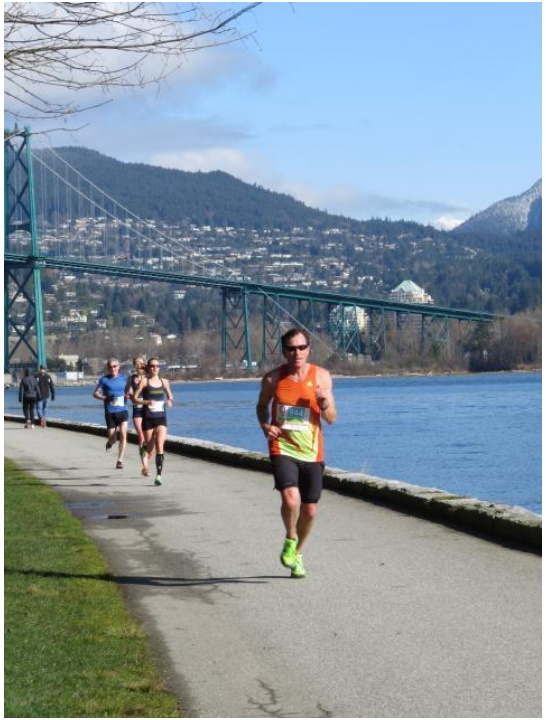
Pros and cons of novel agent strategies

"Indefinite" Acalabrutinib or Zanubrutinib	"Time Limited" (Ven-Obin, Ibrut-Ven, Acala-Ven)
Daily pills, easy	More intensive (IV treatment, ramp up)
May be better for high-risk disease ★ (stay in remission longer)	Less time in remission for high-risk disease (although unclear if any downside to start/stop)
Unclear if/when can stop	Only 12-15 months
Development of resistance mutations	Less resistance mutations (almost none)
Side effects: - Bleeding/bruising - High blood pressure, arrhythmias - GI, skin/nail, joint/muscle pains - Medication interactions	Side effects: - Infusion reactions (obin) - Immunosuppression and vaccine responsiveness (obin) - Same side effects for BTK inhibitors (but shorter duration) - GI, low white blood cells (venetoclax)

★ BTKi may not be funded for good-risk CLL/SLL in some provinces (as a first-line treatment option)

Back to the case

- 70 year old man with CLL needing treatment
- IGHV unmutated, trisomy 12 – “intermediate”
- Mild high blood pressure, otherwise healthy
- Active, travels, spends time with family
- After discussion of pros/cons, elected time-limited therapy with Venetoclax +Obinutuzumab
- Tolerated well, attained a remission at 15 months
- Now well, back to traveling and running!



What about at time of relapse?

Questions to ask

- Did treatment stop because of progression of CLL/SLL or due to side effects?
  - If Progression → switch drug class
  - If Side Effects → can consider repeating same drug class with new option
- Repeat prognostic testing (new deletion 17p, TP53 mutation?)
- Resistance mutations (not ready for prime time?)

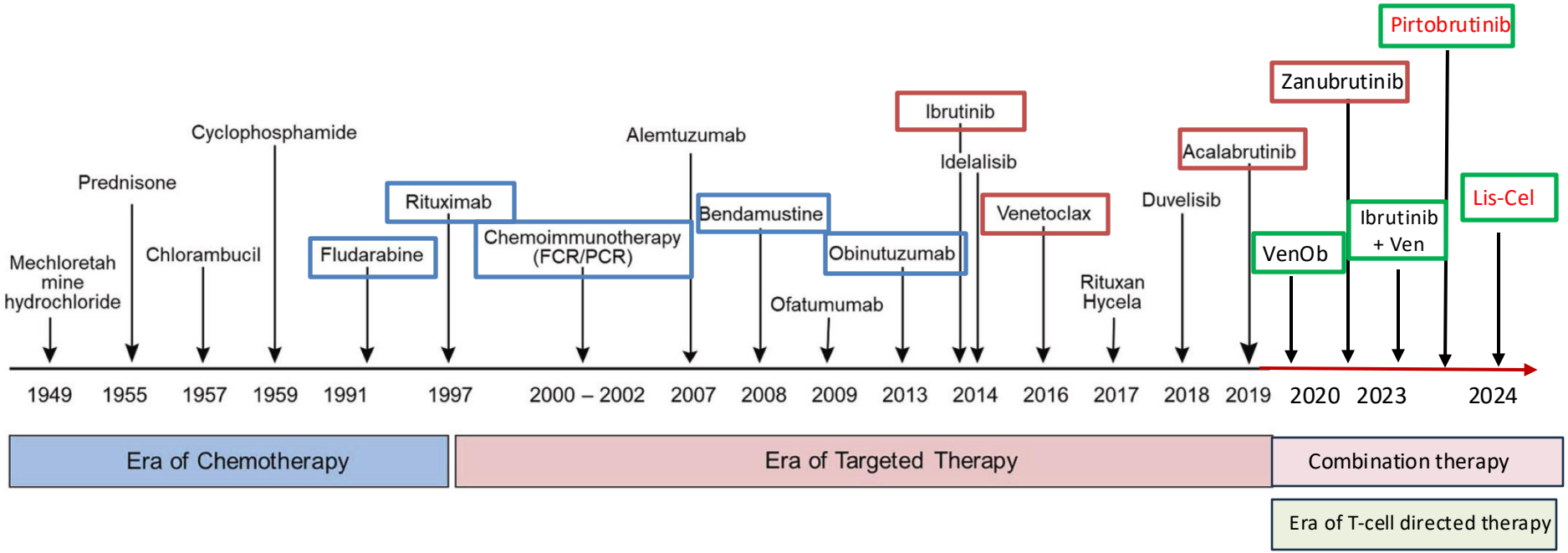
Treatment options at relapse

- Switch class of treatment (BTKi ⟷ BCL2 inhibitor)
- Repeat time-limited treatment
  - Ven-Obinutuzumab → Ven-Rituximab
  - Ibrut + Ven → Ven-Rituximab Or Ibrut + Ven
- New classes of drugs
  - Non-covalent BTK inhibitors (Pirtobrutinib)
  - Cellular therapy (CAR T-cell therapy)
  - Bispecific antibodies
  - Clinical trials (BTK degraders, new BCL2 inhibitors)
  - Stem cell transplant

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

Drug Approvals for CLL/SLL in Canada over 8 Decades!



Adapted from Parikh et al, Nature 2020