CLL Research

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BC CANCER
Provincial Health Services Authority

UBC
a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA

Disclosures

Consulting: Arima Genomics, AstraZeneca, Chugai, Ely Lilly, Kite/Gilead, Roche, Veracyte

Research funding: Roche/Genentech

Patents: named inventor on patents related to using gene expression to identify subtypes of aggressive B-cell lymphomas – one of which is licensed to nanoString Technologies

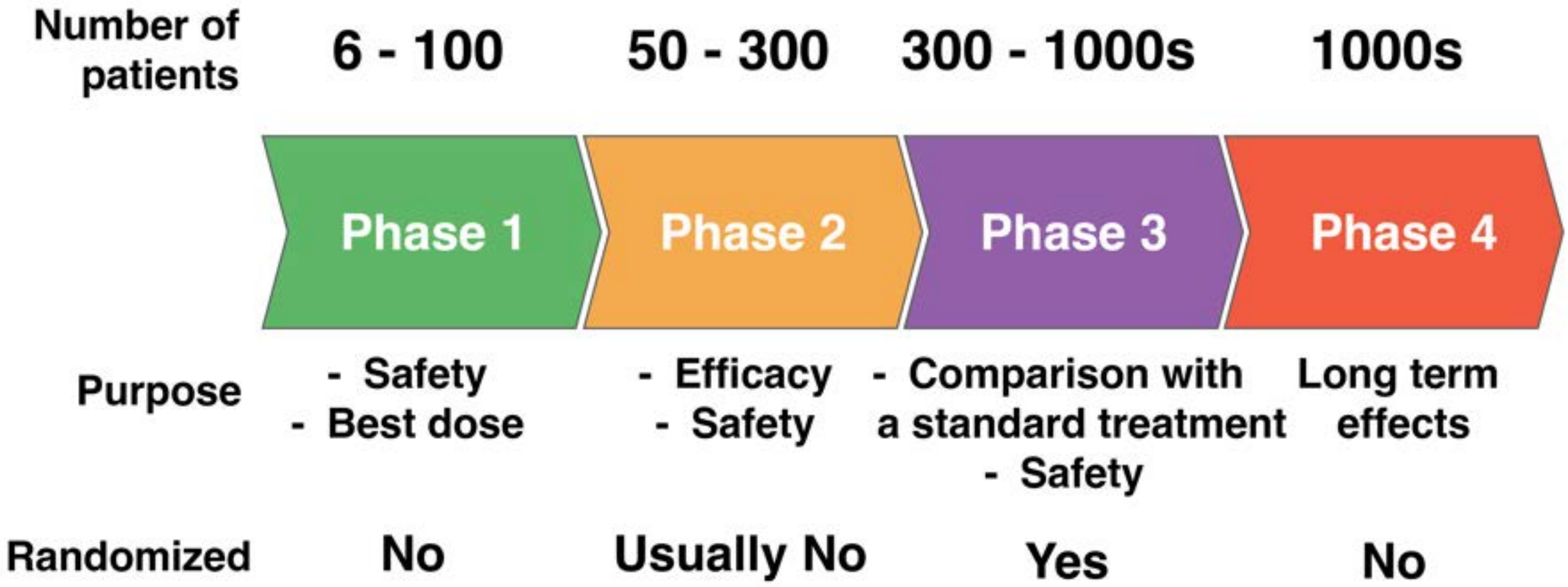
Outline

- Clinical trials – does the treatment work (better) and is it safe?
- Health economics – can (and should) we afford it?
- Understanding how CLL and treatments affect quality of life – side effects and more
- Qualitative research – what are your priorities and values?
- Generating real world evidence – does this work for our patients?
- Translational studies – understanding the biology of CLL and how it can be targeted more effectively

Clinical trials

Does the treatment work (better) and is it safe?

Clinical trial “phases”



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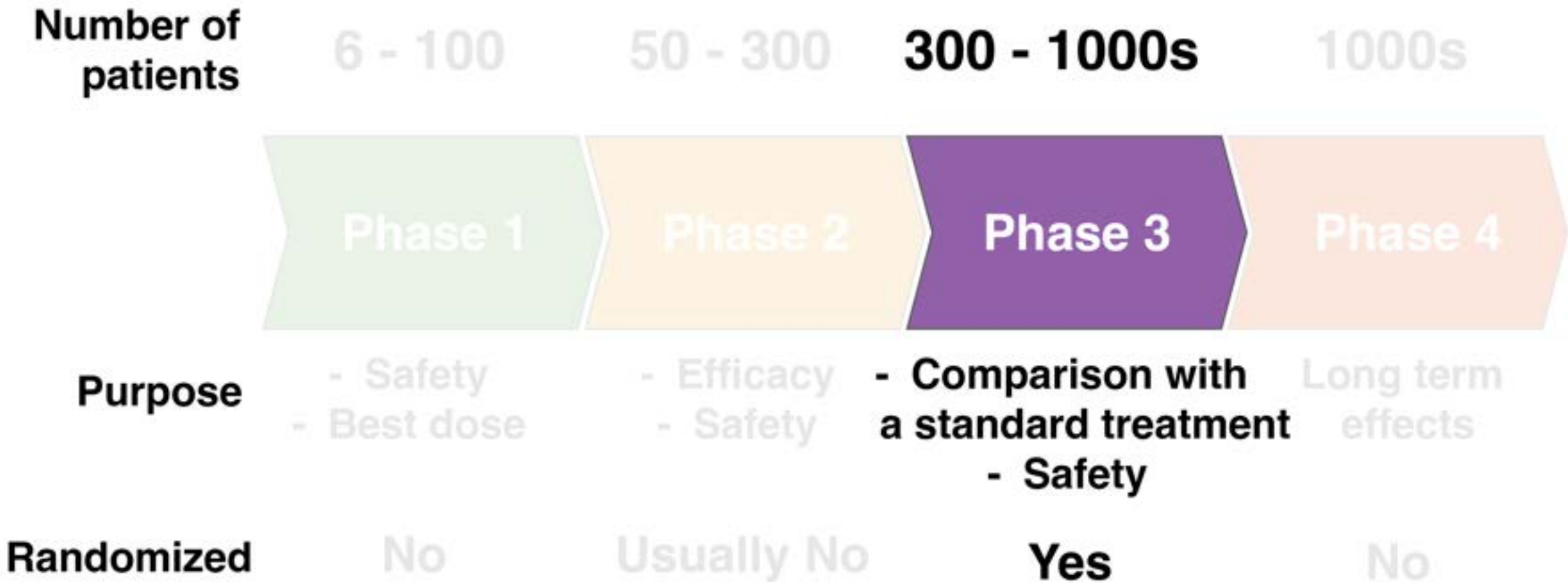

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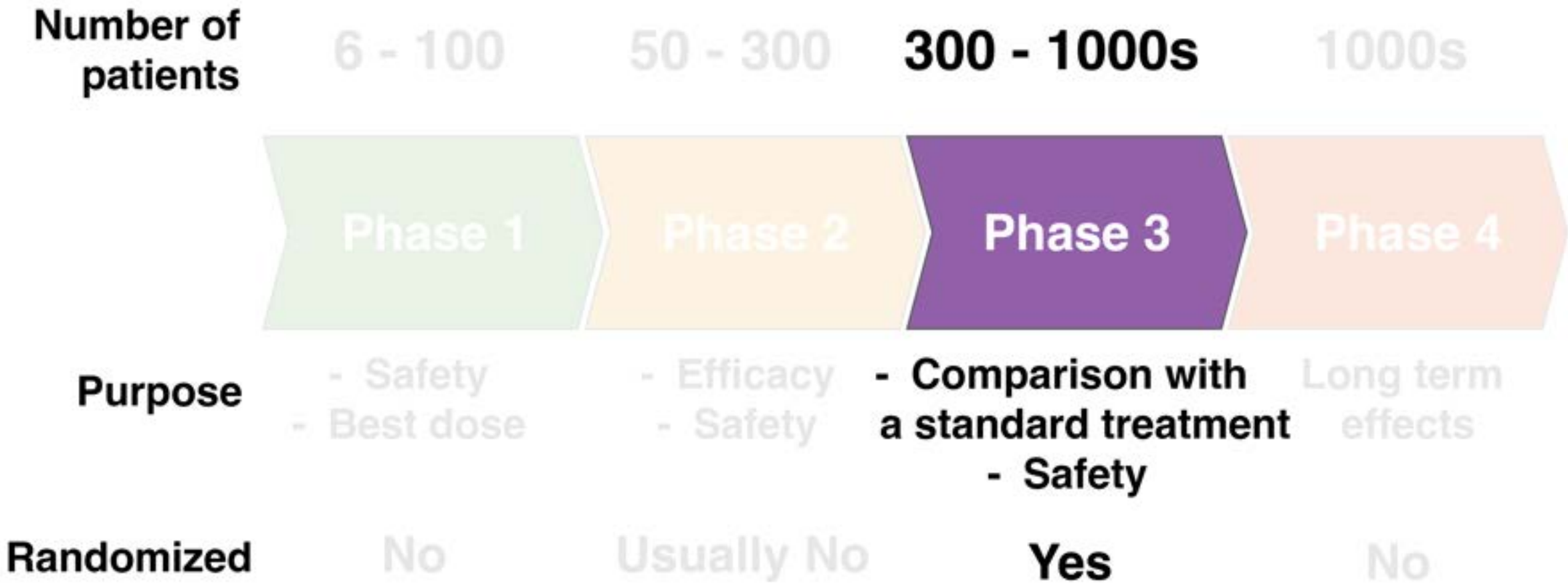

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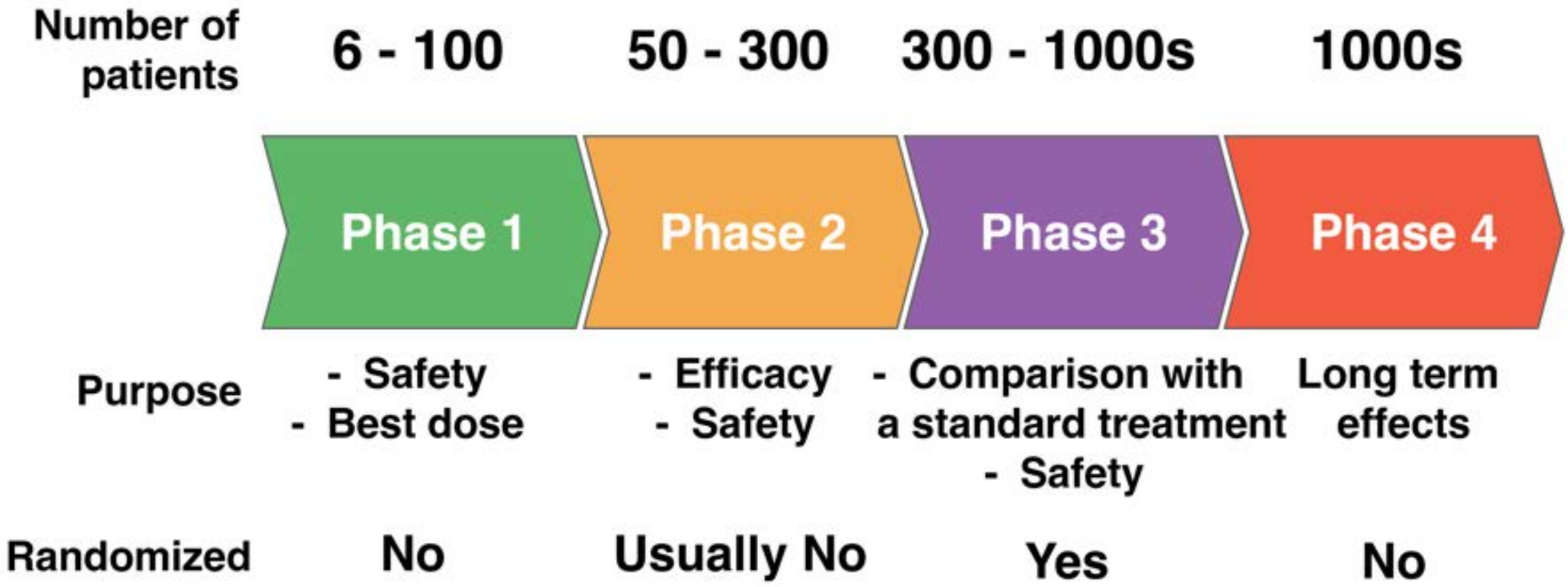


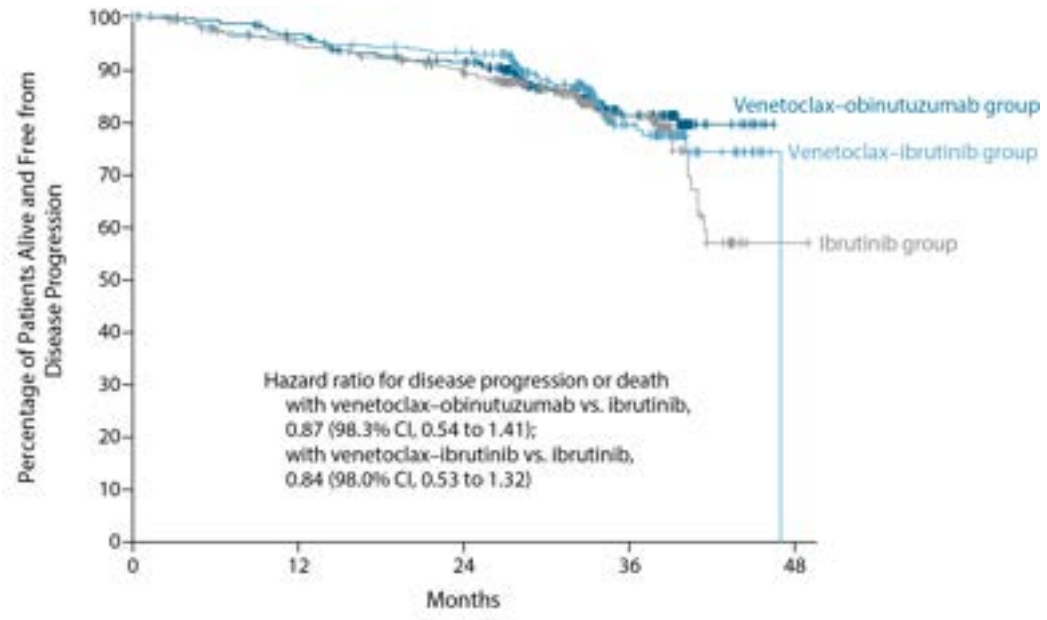
A Phase 3 example – CLL17

- **Investigator initiated – asking an important and relevant question:**

Are fixed duration treatments as effective as continuous treatments?

- **Very broad inclusion criteria – pretty much everyone who needed treatment was included**
- **Well designed and sufficiently large to answer the question**
- **The three treatments were equally effective – all 3 are funded at BC Cancer**

Arms:
Ibrutinib – continuous
Venetoclax – ibrutinib – fixed duration
Venetoclax – Obinutuzumab – fixed duration



No. at Risk					
Venetoclax–obinutuzumab	303	278	256	77	0
Venetoclax–ibrutinib	305	278	267	82	0
Ibrutinib	301	267	243	94	1

Al-Sawaf N Engl J Med 2026

Clinical trials open at BC Cancer

First treatment: Investigator initiated

Randomized Phase 3 study comparing starting early with venetoclax-obinutuzumab (experimental arm) vs starting the same treatment when treatment is indicated (standard arm) in “high-risk” but asymptomatic CLL

At relapse: Pharma sponsored

Phase 1/2 open label study of a BTK degrader in patients whose CLL has come back after 2 or more lines of treatment

How do we prioritize trials:

High quality, relevant question

If a randomized trial, would we be happy with our patients going on either arm – “equipoise”

Balance – aim for a trial for new patients and a trial for patients at the time of relapse

Health economics

Can (and should) we afford it?

From clinical trial to the patient

Step 1: Regulatory approval – Health Canada
Can the drug be used?

Step 2: Reimbursement recommendation – Canada's Drug Agency
Should the drug be publicly funded?

Step 3: Price negotiation – led by one of Provinces

Step 4: Provinces make the drug available

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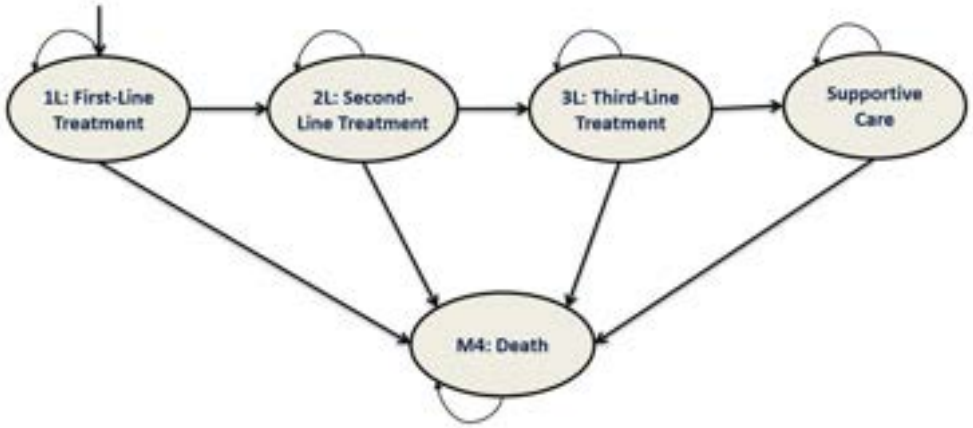
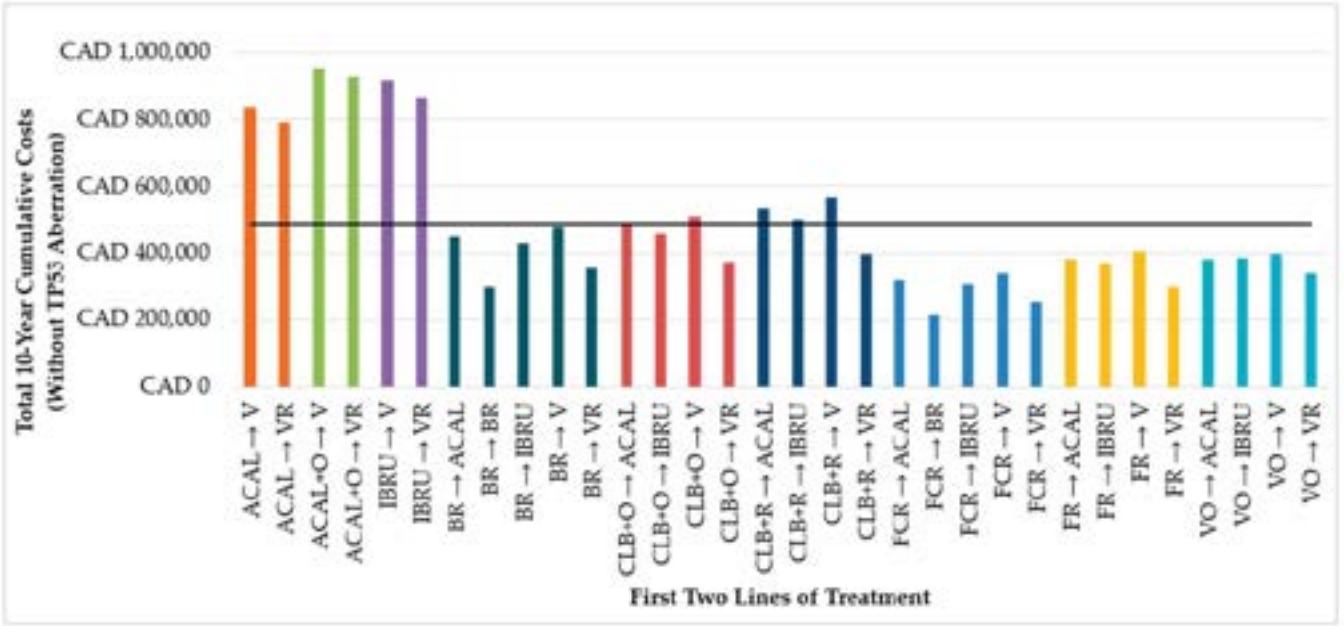
Looking at economic impact

- **Typically looking at the ICER: the additional cost of the drug vs the current treatment per quality adjusted life year (QALY)**
- **But what about treatment sequencing and total costs?**

Markov Model





Guinan et al Cancers 2024

Quality of life and side effects

How to capture and measure this

Measuring side effects – the old way

- Every side effects is recorded and given a grade (how severe it is) using a standardized dictionary (CTCAE)
- Report the amount of each grade of toxicity, focusing on severe toxicity

This is great for many toxicities and treatments that are short but…

"low grade" diarrhea for months or years will have a massive impact of quality of life

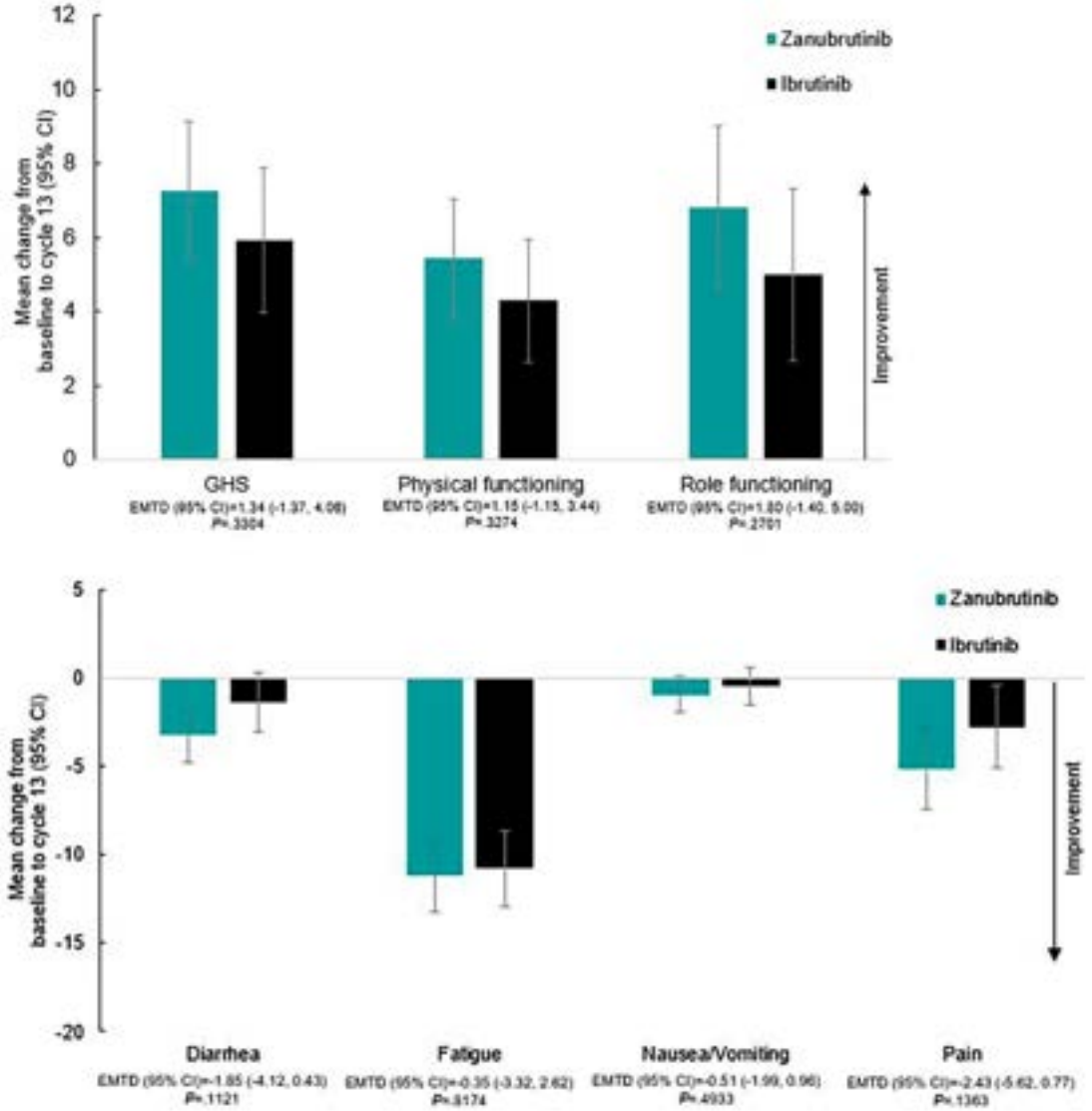
Solutions:

1. New ways to measure toxicity – "Toxicity over time"
2. Ask patients about quality of life – Patient Reported Outcomes

Thanarajasingam et al Lancet Haematol 2022

Patient reported outcomes

- **Standardized questionnaires are completed by the patient at set intervals**
- **A number of different tools are available and can be customized for the study**
- **A balance of getting all the relevant information and burden on the patient**



An example from the ALPINE study comparing zanubrutinib and ibrutinib at the time of CLL relapse – baseline vs 12 months

Tam et al Curr Med Res Opin 2023

Qualitative research

What are your priorities and values?

Qualitative research

Aiming to understand what goes into making decisions:

- **priorities, values and barriers**
- **patients, families, health care workers and payers**

Example: What goes into the decision to choose between time limited vs continuous treatment for your CLL?

Our tools:

- **Questionnaires**
- **Structured interviews**
  - **One-on-one and large groups**
- **Discrete choice experiments**

Generating real world evidence

How does the treatment work for our patients?

Real world evidence – BC Cancer

- BC Cancer is ideally placed to produce real world outcomes
- Population of 5.6 million
- BC Cancer has the mandate to provide cancer care to all patients across the Province

BC Provincial CLL database

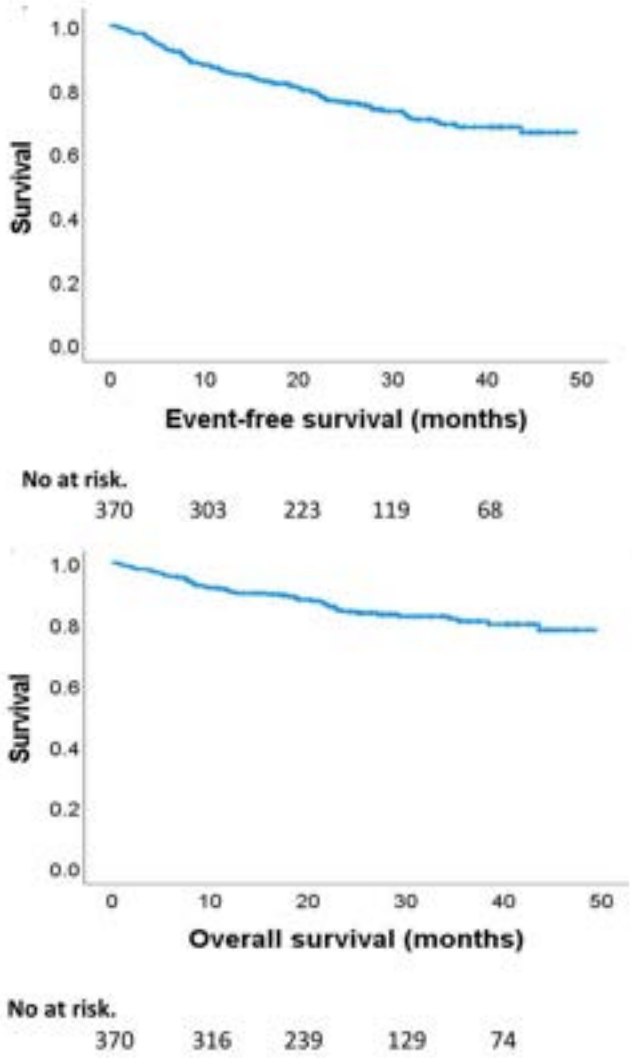
- Established in 2007 by Drs. Gerrie, Toze, Ramadan, Connors and Bruyere
- Collates patient characteristic, pathology information, treatment and outcomes
- Research Ethics Board Approved
- First project included 100 patients

Over 6,000 patients are in the database now

Ibrutinib in the real world

- Examined what happened when ibrutinib became available for treatment of CLL in British Columbia
- Mainly used at the time of relapse during the study period

1. Outcomes looked very similar to the clinical trials
2. 35% of patients had stopped using ibrutinib with half being due to toxicity
   - toxicity is very important

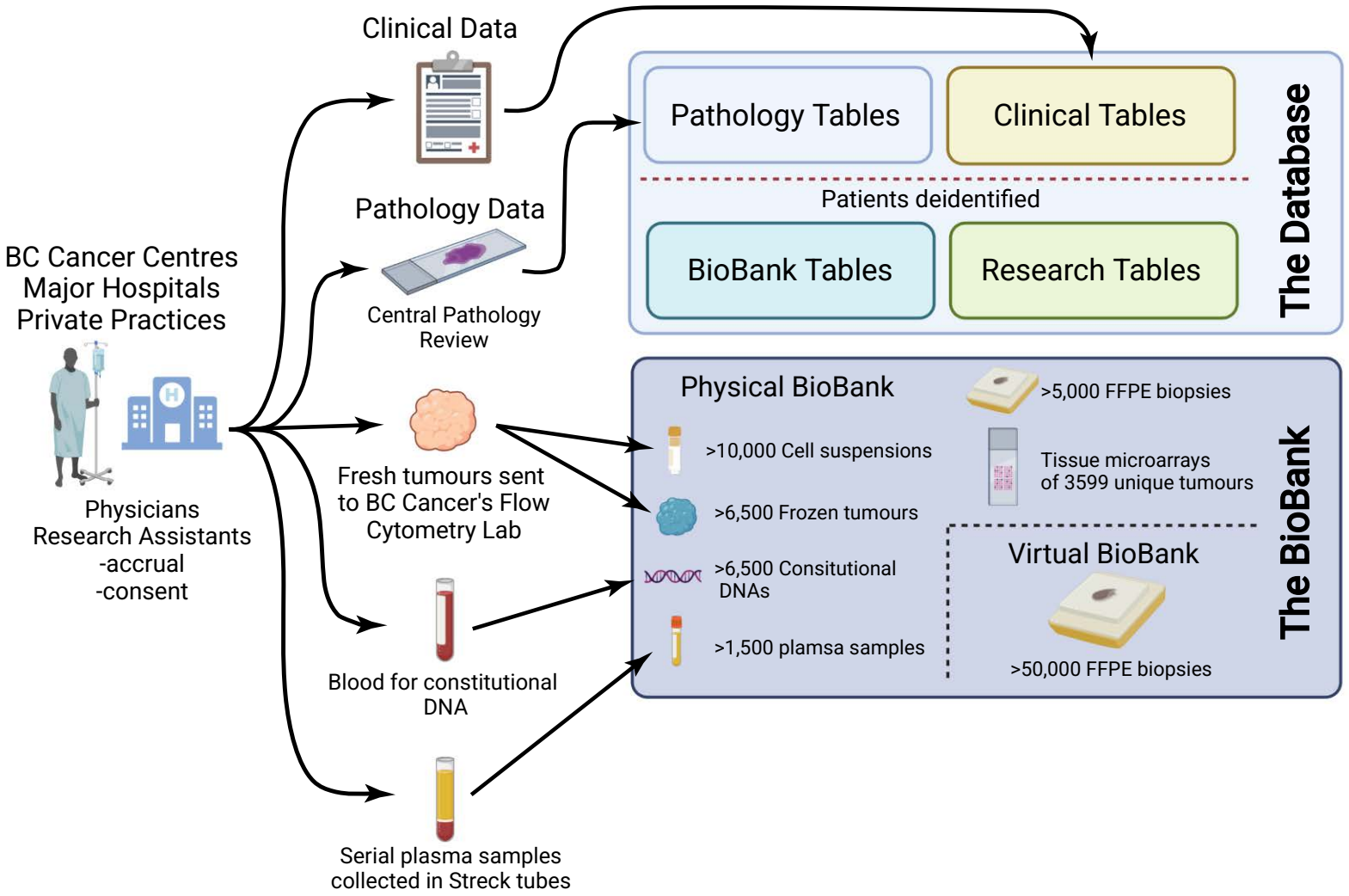


Khelifi et al Leuk Lymphoma 2023

Translational studies

Understanding the biology of CLL and how it can be targeted more effectively

Biobanking for lymphoid cancers at BC Cancer



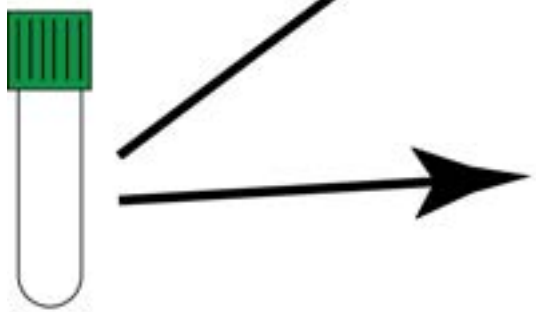
Biobanking for lymphoma and studies using patient samples has been ongoing for decades

Leverage the power of linking samples with clinical information and treatment outcomes

Understand the underlying biology and mechanisms of treatment resistance

CLL needed its own banking process

- The samples are blood which contains both the CLL cells and normal blood cells
- Ideal to have not only all the cells but also pure CLL and normal cell fractions



Flow cytometry:
confirm diagnosis
quantify CLL and normal cells
FISH studies:
what genetic abnormalities are there

Magnetic bead separation and
flow cytometry -> 3 types of sample:
1. all cells
2. pure CLL
3. pure normal

Frozen down in liquid nitrogen

So far…. 204 banked samples including 16 “serial” samples

BC CANCER FOUNDATION
partners in discovery

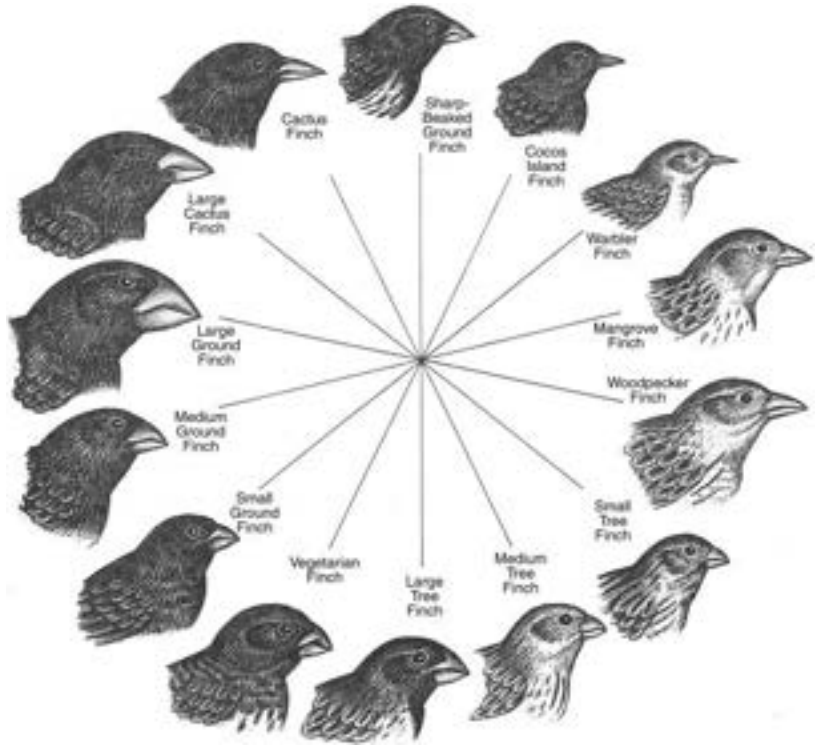
Ongoing translational projects

- **Understanding the genomic alterations in CLL**
  - **141 samples profiled using whole genome and whole transcriptome sequencing - most recently through the Marathon of Hope Cancer Centres Network**
- **Determining mechanisms of resistance to Bruton tyrosine kinase inhibitors by profiling samples taken before and after progression**
- **Understanding the biology behind how CLL turns into aggressive lymphoma**
  - **Transformation to Hodgkin lymphoma**

MARATHON OF HOPE CANCER CENTRES NETWORK
CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada
GenomeCanada
Genome BritishColumbia
BC CANCER FOUNDATION partners in discovery
Cancer Research Society

CLL – lessons from tumour evolution

- Malignant cells within a cancer are not all the same
- The make up of the cancer evolves when pressure (such as treatment) is applied
- CLL is the poster child for examining this as the cancer can be readily sampled on multiple occasions
- This research is revealing how tumours escape treatment and grow back



Darwin's finches

CLL – lessons from tumour evolution

- **BTK is a critical enzyme for CLL cells**
- **BTK inhibitors bind a pocket in the enzyme that stops it working**

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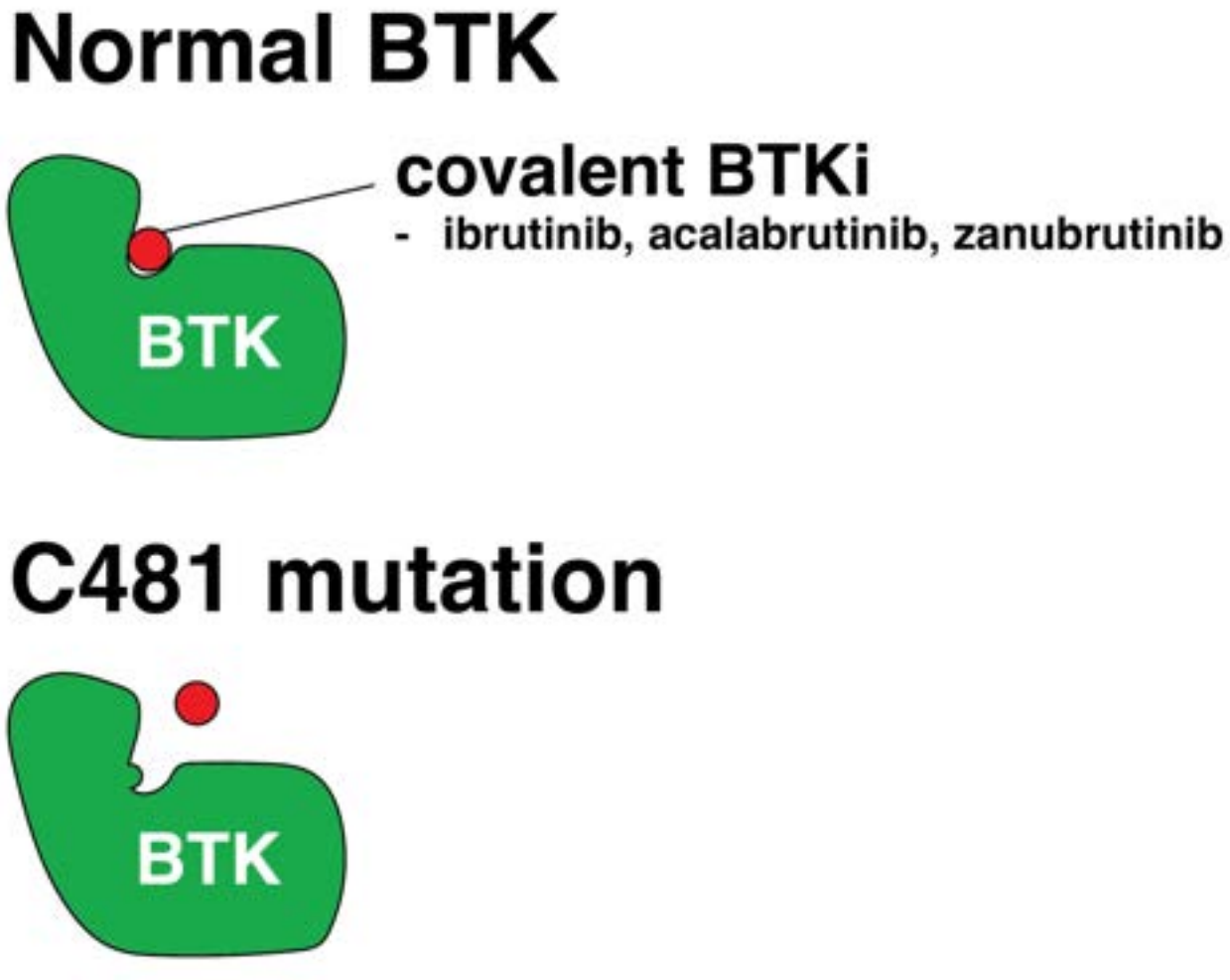
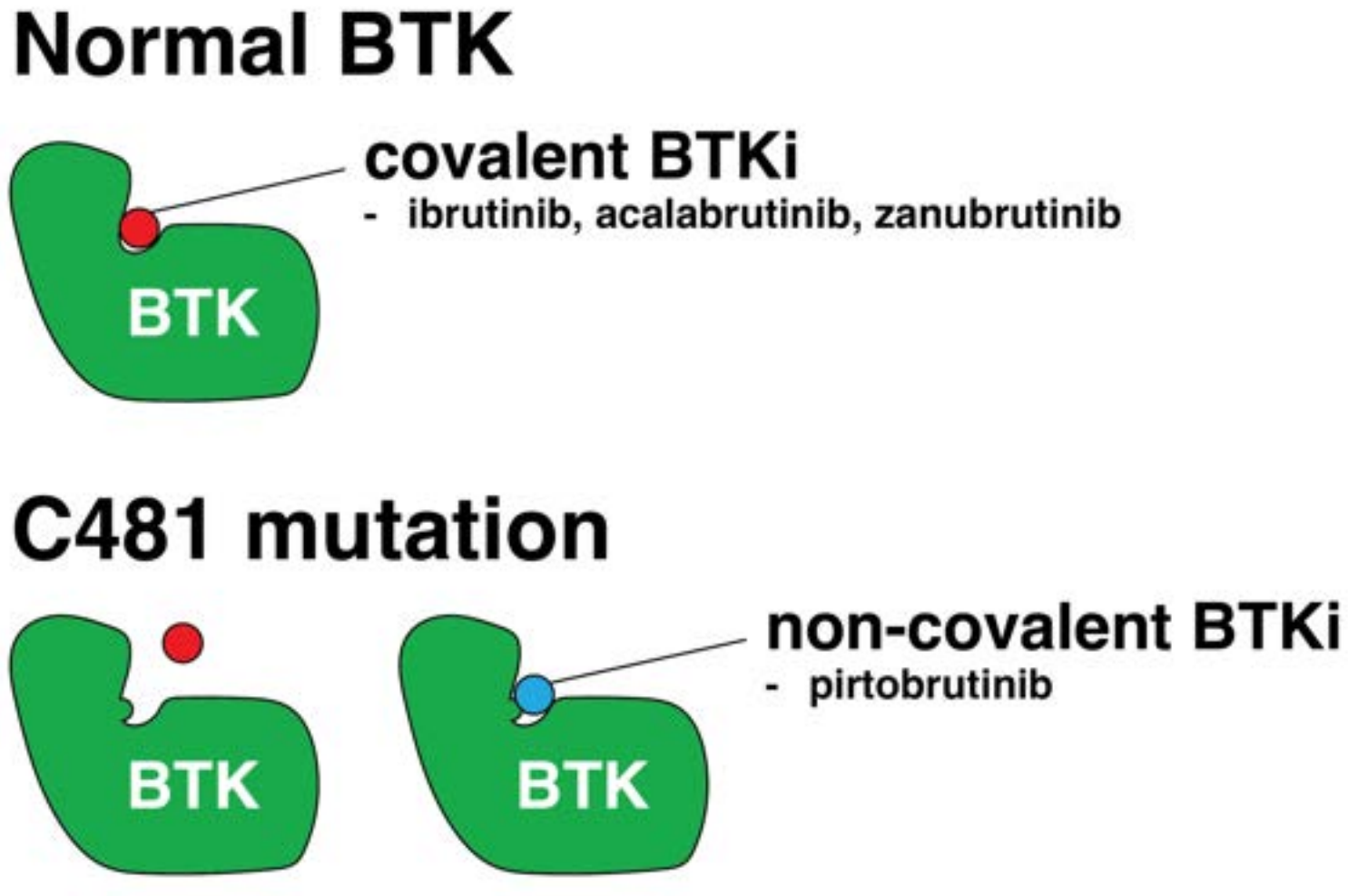
- BTK is a critical enzyme for CLL cells
- BTK inhibitors bind a pocket in the enzyme that stops it working
- A major way that CLL cells escape these drugs is mutation in part of the pocket



Woyach et al N Engl J Med 2014

CLL – lessons from tumour evolution

- BTK is a critical enzyme for CLL cells
- BTK inhibitors bind a pocket in the enzyme that stops it working
- A major way that CLL cells escape these drugs is mutation in part of the pocket
- Non-covalent BTK inhibitors can still bind and block the pocket

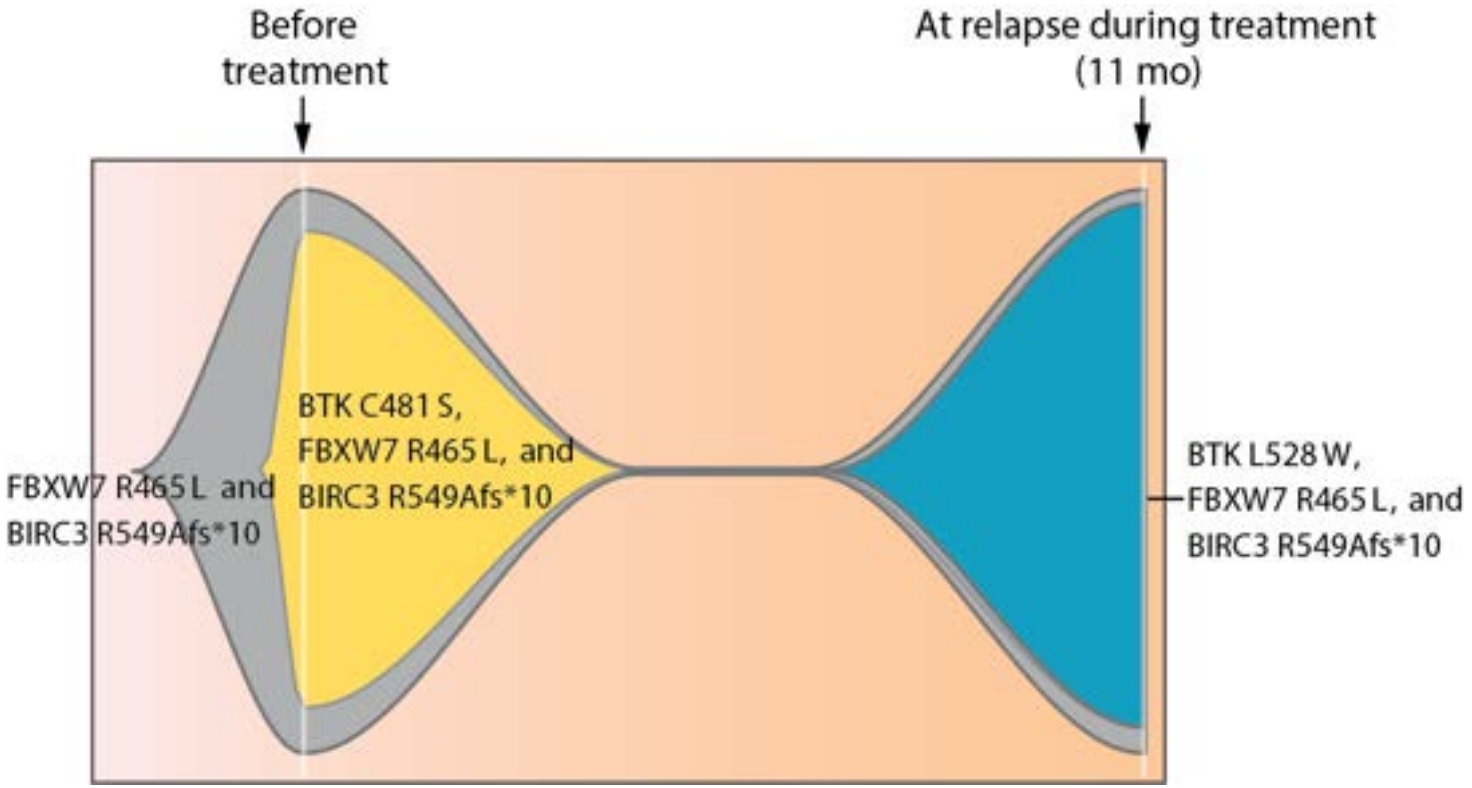


Woyach et al N Engl J Med 2014

CLL – lessons from tumour evolution

- **Treating with pirtobrutinib can get rid of the cells with the C481 mutations but, in some patients, other mutations grow out that are resistant to that drug**

- **This has implications for how we used these medications**



Wang et al N Engl J Med 2022

Concluding comments

- **CLL research, covering a number of domains, has led to massive improvement in patient outcomes in the last 10-15 years**
- **It is critical that the research continues to ask and answer questions that are most important to patients and their families**
- **We hope that you can engage with research and how the results are transitioned to patient care**