Introduction to MBL/CLL/SLL: a case-based approach

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Disclosures for Dr. V Banerji

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- AI was used to generate images and tables.

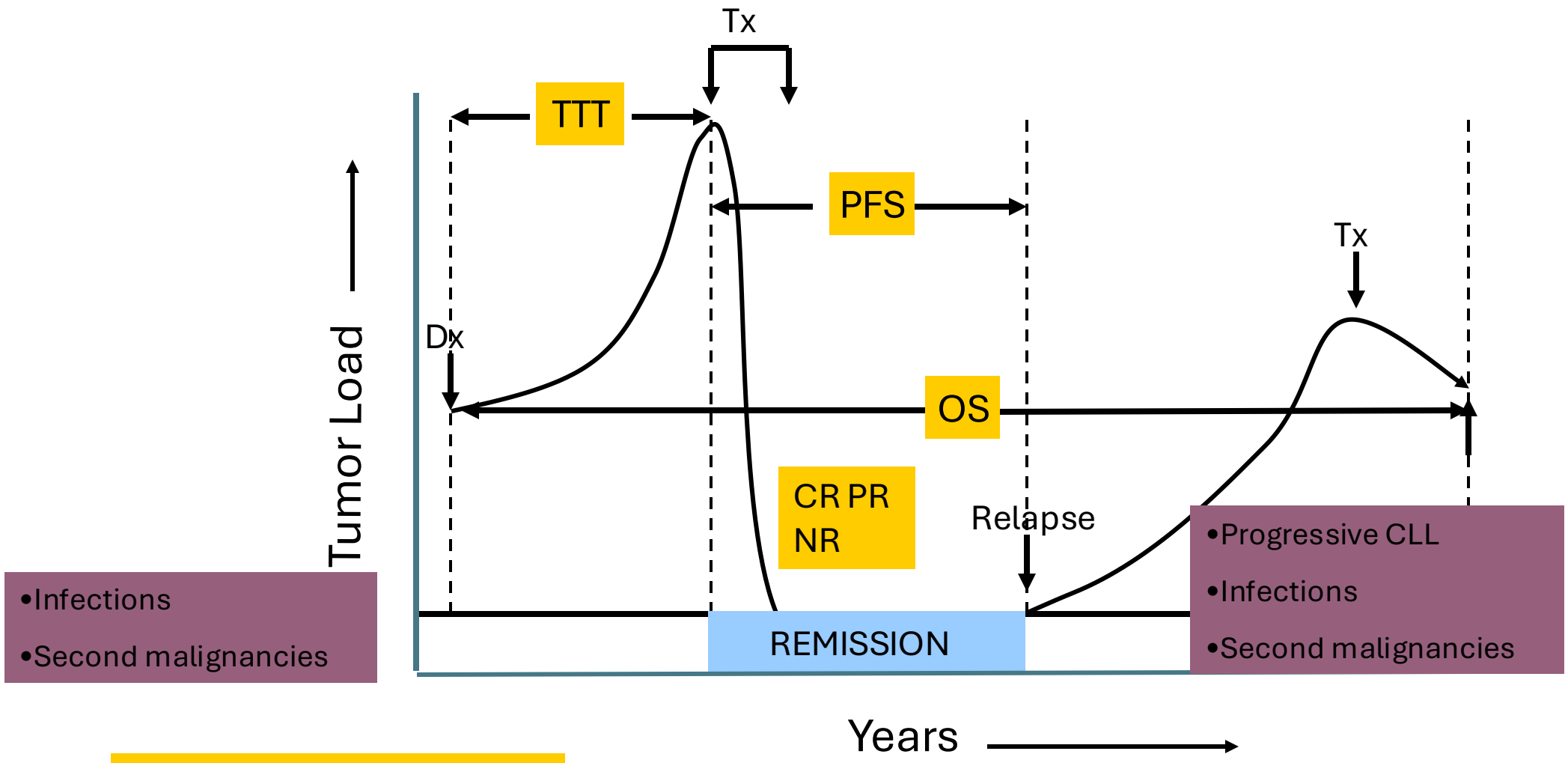
Objectives

- Understand the role of symptoms is treatment decision making
- Understand the role and impact of molecular testing in treatment decisions
- Understand continuous versus time limited treatment
- Understand the accessibility issues and tolerability

Approach to the Patient with CLL/SLL

- DO NO HARM
- Incurable disease for pts >65 age
  - Quality of Life
- “Active observation”
- ~~Chemotherapy~~ Treatment
- Bone Marrow Transplant (age <65) Have only done 2 in the last 10 years

CLL/SLL: Cancer as a Chronic Disease



CR = complete remission

PR = partial remission

NR – no response

Slide modified from Dr Johnston

TTT = Time to Treatment

PFS = Progression Free Survival

OS = overall survival

Case 1

89 year old with a new diagnosis of CLL.

Abnormal White blood cell count, and a Lymphocyte count of 10. Hemoglobin and Platelets are normal and no symptoms.

Monitoring in Survivorship- Cancer as a Chronic Disease

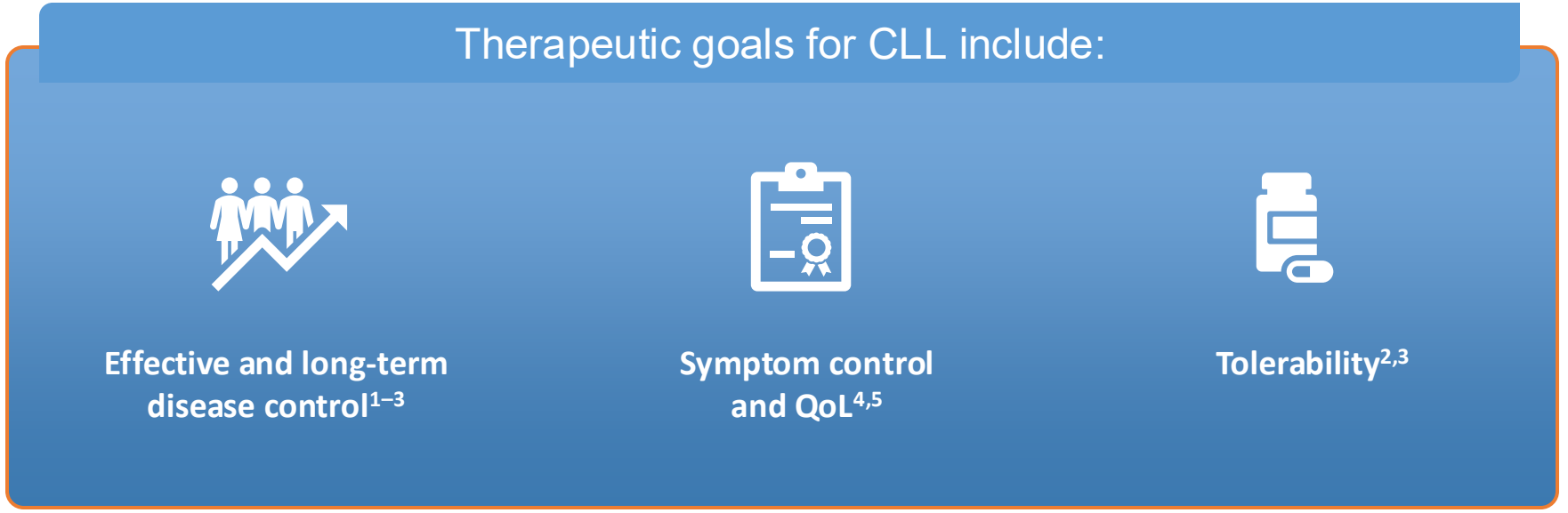
- CBC (complete blood count) , differential plus reticulocyte count
- Basic Chemistry, Kidney and Liver function
- Beta 2 microglobulin
- Immunoglobulins And Free light Chains
- (annually, and CBC Biochemistry for routine follow ups) frequency depends on stage and clinical picture

Survivorship

- Infection Prevention: Immunizations: Flu, Covid, Pneumonia, Shingrix, Hepatitis

- Second Cancer Screening: Age appropriate or symptom driven when highly suspicious (ex blood in poop). Derm/Primary care skin review

Primary Goals of CLL Treatment



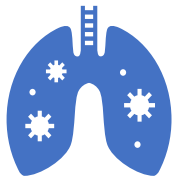
1. Stilgenbauer S et al. *Am Soc Clin Oncol Educ Book*. 2015:164-175. 2. Thompson PA et al. *Future Oncol.* 2015;11(4):641-657. 3. Furman RR. *Clin Adv Hematol Oncol*. 2017;15(8)(suppl 10):1-20. 4. Molica S. Quality of life in chronic lymphocytic leukemia: a neglected issue. *Leuk Lymphoma*. 2005;46(12):1709-14. 5. Cancer.Net. https://www.cancer.net/cancer-types/leukemia-chronic-lymphocytic-cll/types-treatment. Last updated October 2017. Accessed May 2021.

Secondary Goals of treatment

Improved outcomes

Decreased genomic instability

Immune system Reset?



Immune reset = decreased second cancers and infections?

4 X fold risk of skin cancers, 2 fold greater risk of solid tumours

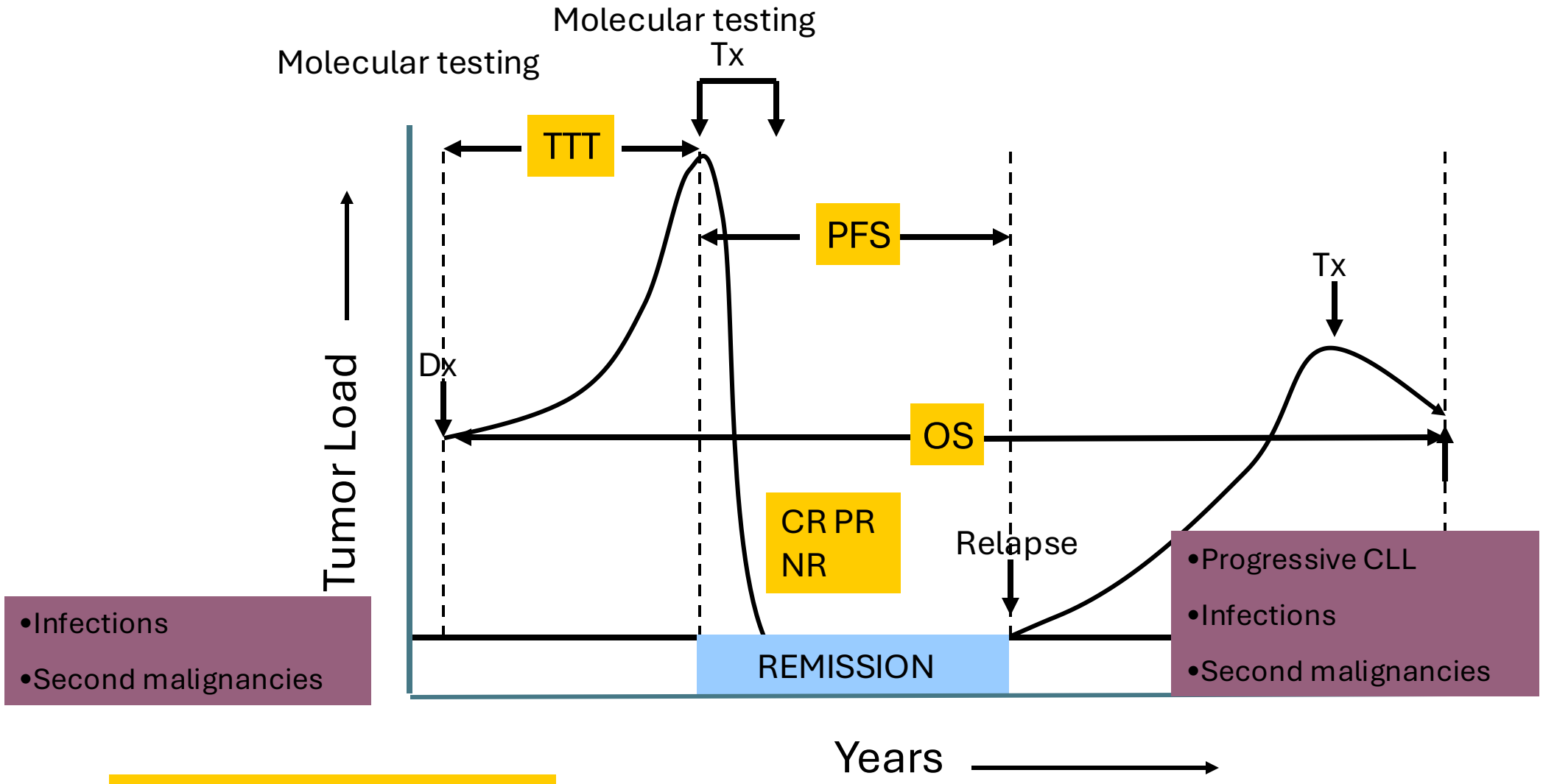
Thompson and Weirda Blood 2016

Indications for treatment

1. Rapid increase in lymphocytes with fall in hemoglobin/platelets
   - (doubling time <6 months, Hgb<110, PLT<100)
2. Uncomfortable large lymph nodes/spleen
3. Severe symptoms, eg, fatigue, Nights sweats, weight loss
4. Immune problems

A high lymphocyte count alone is not an indication for treatment

CLL/SLL: Cancer as a Chronic Disease



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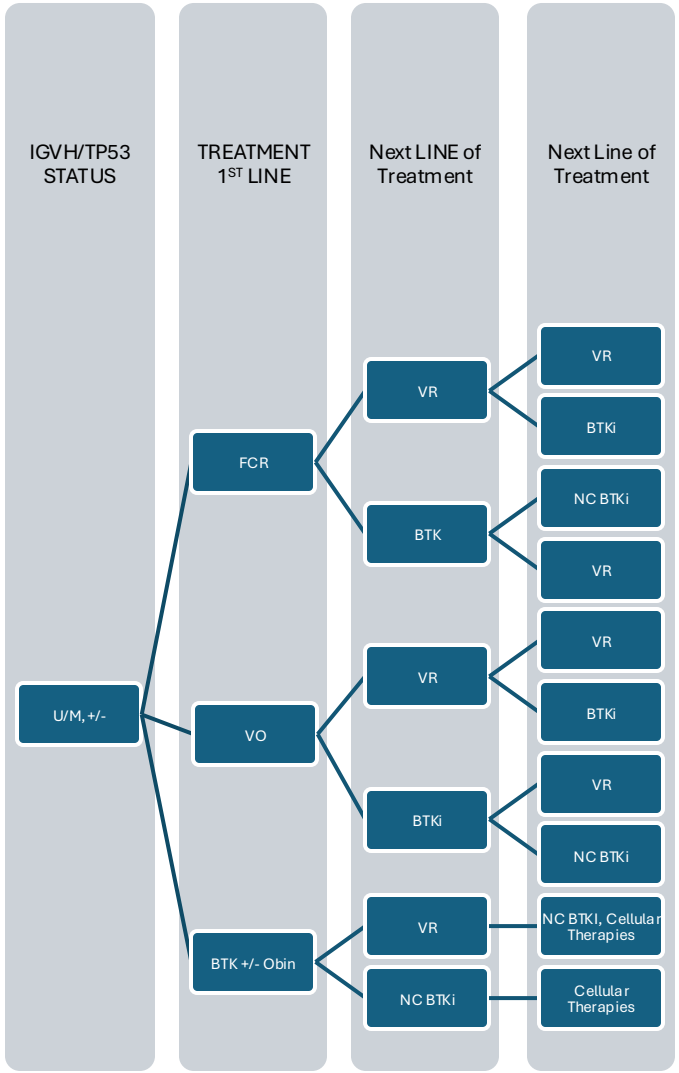
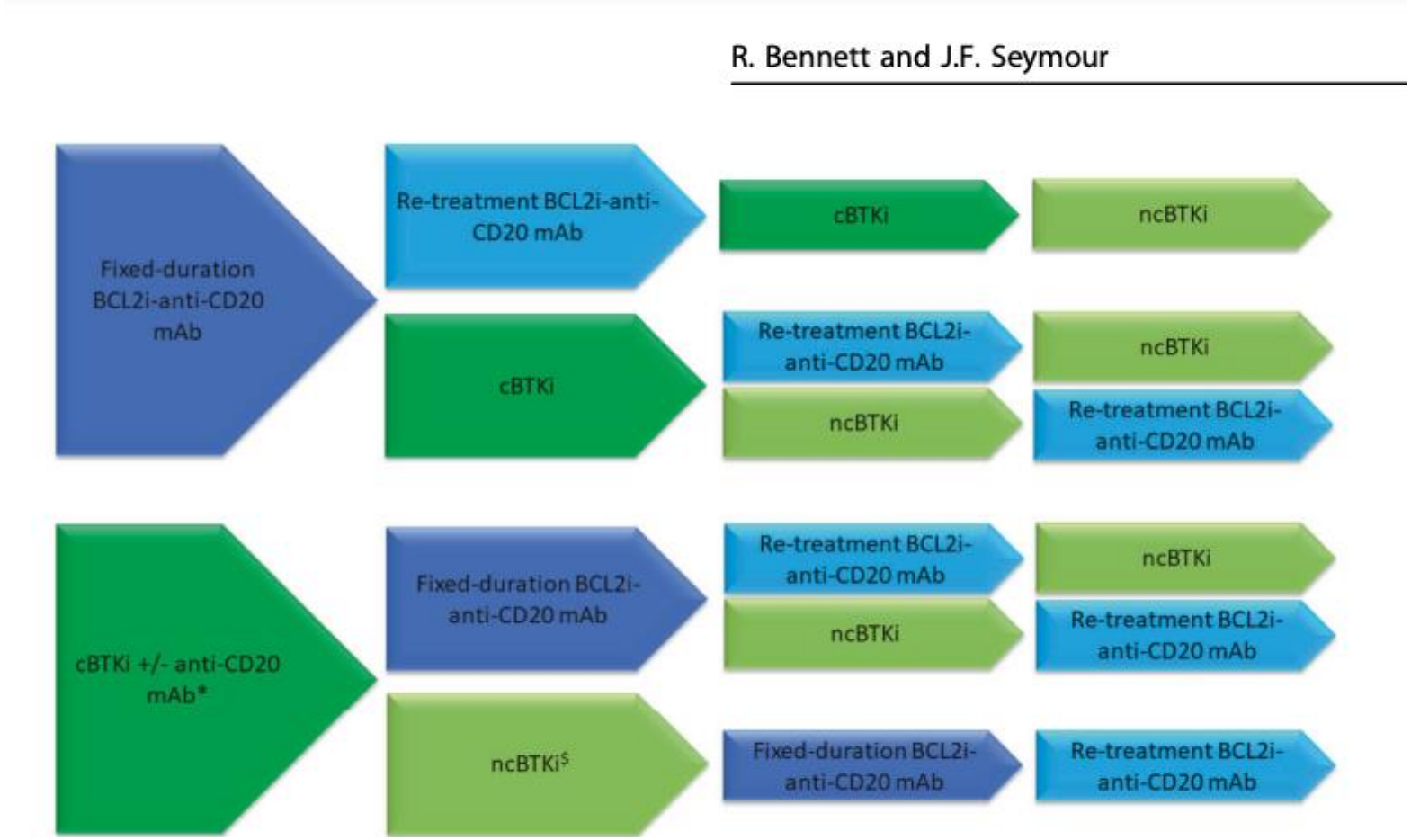
Drug Sequencing in CLL





Bennet & Seymour BCJ 2024

Case 1

- 50 yr male
- Diagnosed with CLL in 2015

- Rai Stage 0 chronic lymphocytic leukemia, Zap70 positive, CD38 negative, beta-2 microglobulin within normal limits.

- No medical issues, drives and has a job with benefits.

- Active observation

Case 1

- Routine follow up biannually until 2018
- Physical examination:
  - demonstrated progressive lymph nodes (2-3 CM range)
  - Spleen felt 4 cm below the rib cage
- Symptoms
  - Progressive sweats
  - Progressive fatigue

Assessing symptom burden

- Sweats: can be multifactorial
  - thyroid problems
  - heating and cooling
  - hormonal changes midlife
  - Are they affecting your quality of life?

- Fatigue/Decreased Energy : Can be multifactorial
  - How busy are you?
  - Have you noticed you have slowed down?
  - Do you have a good nights' sleep?
  - Do you have other medical issues: thyroid, sleep apnea, seasonal affective disorder, depression, anxiety or stress
  - Is the fatigue physical, mental or both
  - Is it affecting your quality of life

Why do we press the issue?

- These symptoms can be difficult to assess, and we want to make sure we have it right
- The treatments have improved a lot, but they still have side effects and risks
- We want to ensure the shared decision results in improved quality of life
- We want to ensure our interventions improve your symptoms

Age, Fitness and Kidney Function

Age : less than 65 versus greater than 65

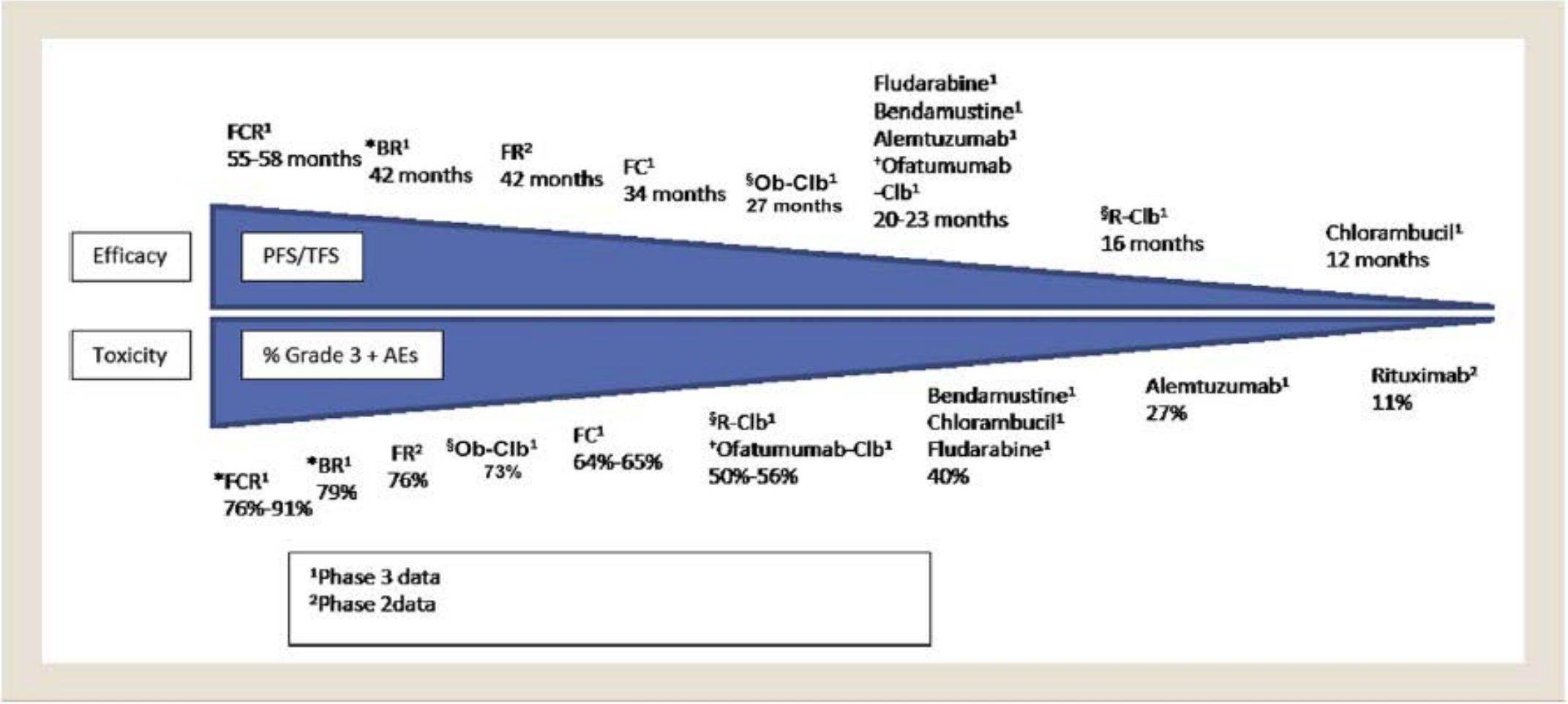
- Transplant eligibility
- Type of chemotherapy

Fitness: Comorbidity Index Rating Scale (CIRS)

- Do you have heart disease?, diabetes? etc.…
- Less than 6 =Fit
- Greater than 6 = Medical issues

Kidney function: Drugs are cleared by the kidneys if they don’t work well this can lead to side effects

Progression Free Survival (PFS) and Toxicity Free Survival



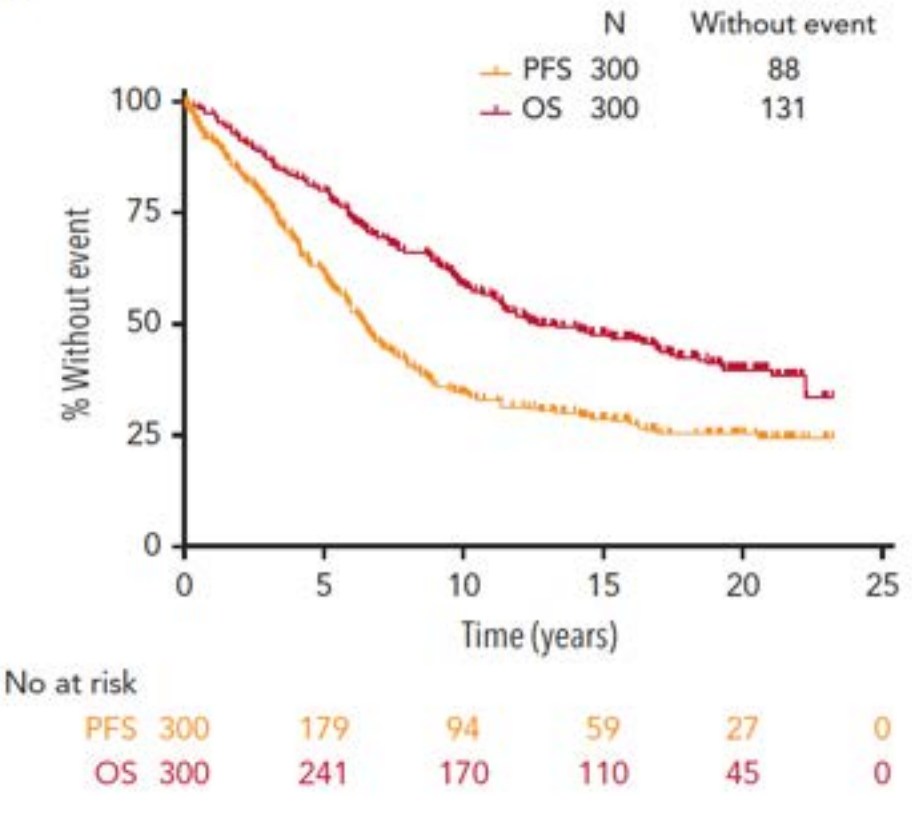
Abbreviations: AE = Adverse Event; BR = Bendamustine With Rituximab; FC = Fludarabine and Cyclophosphamide; FCR = Fludarabine and Cyclophosphamide With Rituximab; FR = Fludarabine With Rituximab; Ob-Clb = Chlorambucil With Obinutuzumab; PFS = Progression-free Survival; R-Clb = Chlorambucil With Rituximab; TFS = Treatment-free Survival.
* *Updated From Eichhorst et al*[44,45]; † *Updated From Hillmen et al*[52]; § *Updated From Goede et al.*[50]

IN 2018

- I had a young fit man and he got FCR.
  - I didn’t have molecular testing

FCR Long Term Data

A



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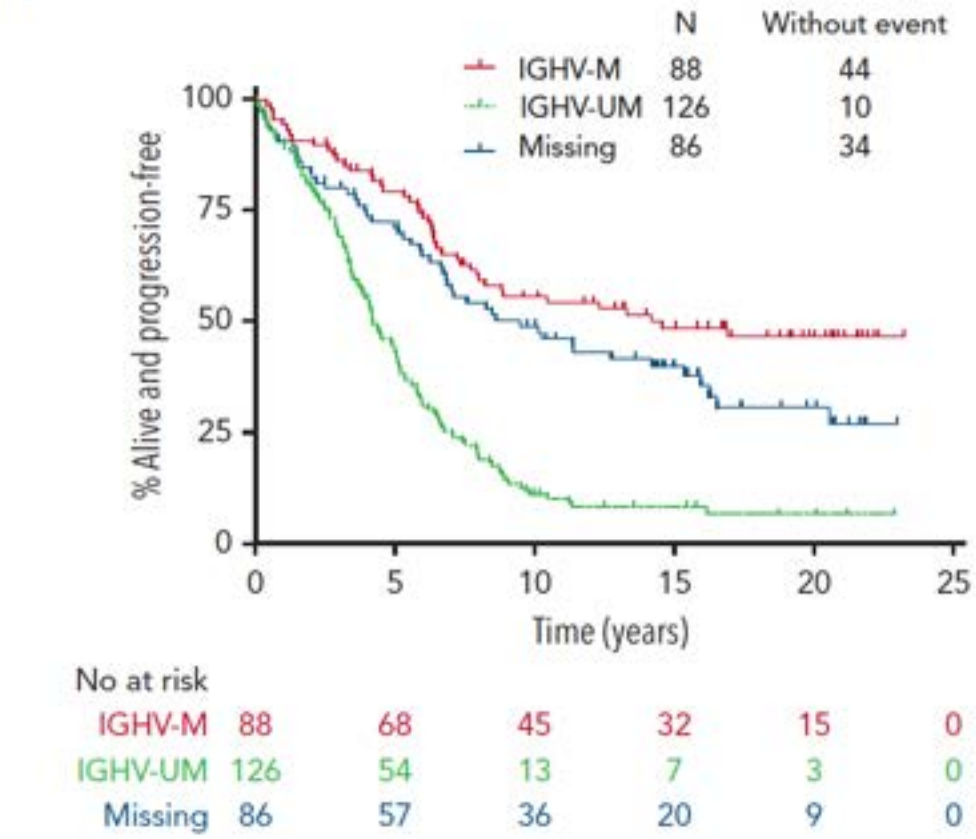

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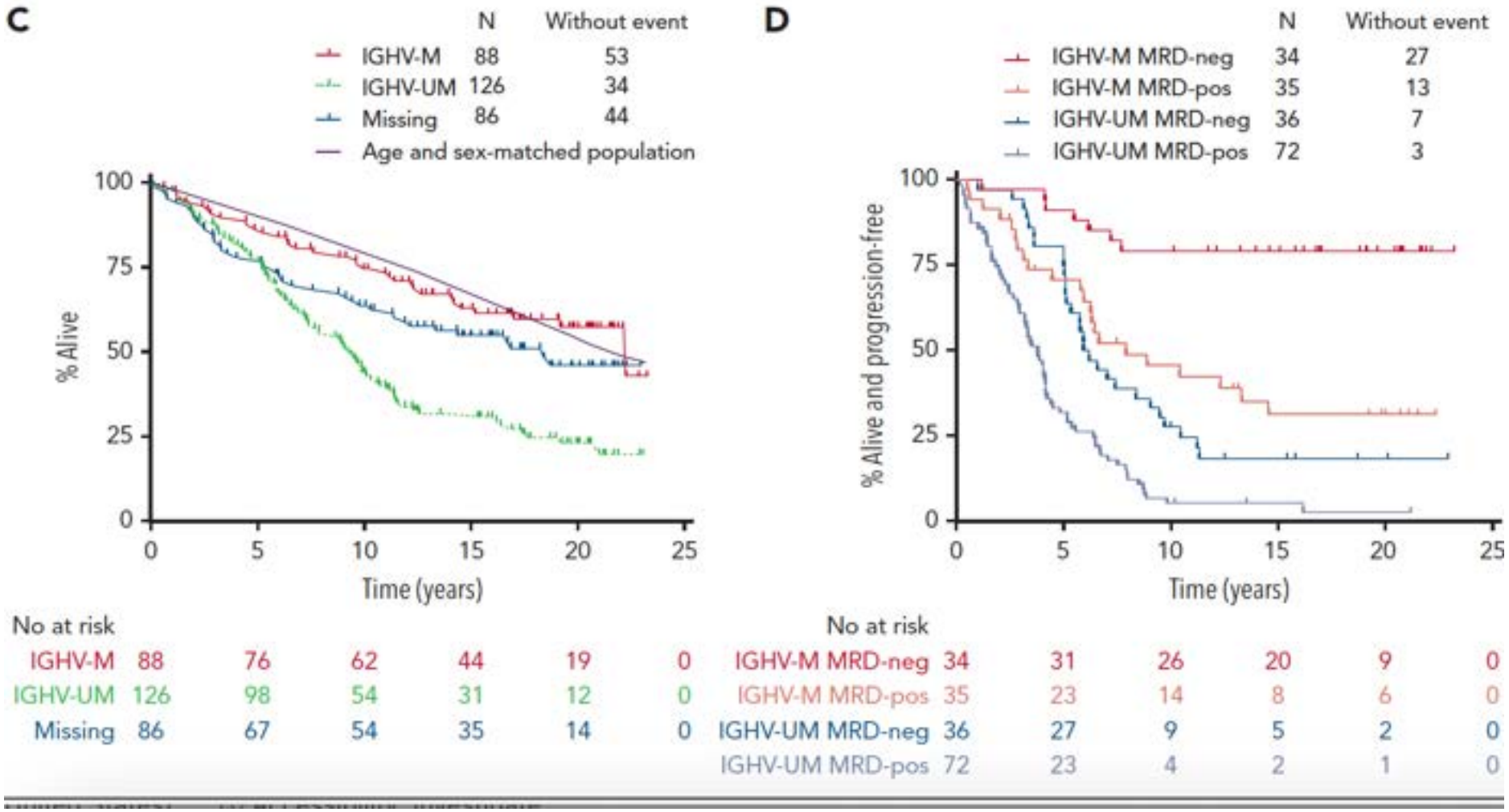


Blood 23 NOVEMBER 2023 | VOLUME 142, NUMBER 21 1

Second cancers, Acute Myeloid Leukemia/ Myelodysplastic Syndrome

- 96 patients (32%) developed 106 other Cancers
- solid tumors other than skin cancers, n = 42 (14%);
- nonmelanoma skin cancer, n = 34 (11%);
- myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), n = 19 (6.3%);
- other hematologic neoplasms, n = 6 (2%);
- and melanoma, n = 5 (1.7%).
- Richter transformation occurred in 29 patients (9.7%).

Disease Classification

- High Risk- P53 abnormalities
- Intermediate Risk: Unmutated, del11q, trisomy 12, Normal Fish
- Low risk- del 13q, IgHV mutated

In 2025

- Young fit (<65) IgHV Mutated and no P53 abnormality What would you like to receive ？ If the following regimens were funded in Canada.

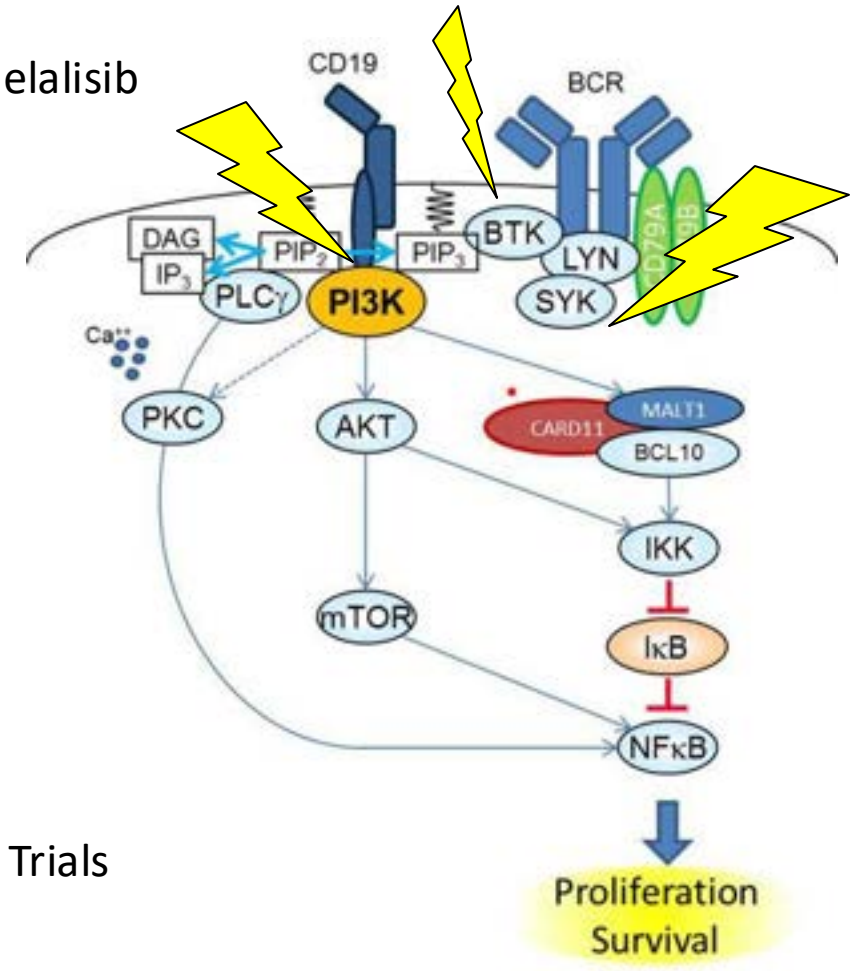
- FCR
- Ven Obin
- Ibrutinib/Ven
- Acala/ Ven
- Continuous BTKi

Novel targeted agents-Personalized Medicine?

Ibrutinib, acalabrutinib, Zanubrutinib, Pirtobrutinib

Idelalisib

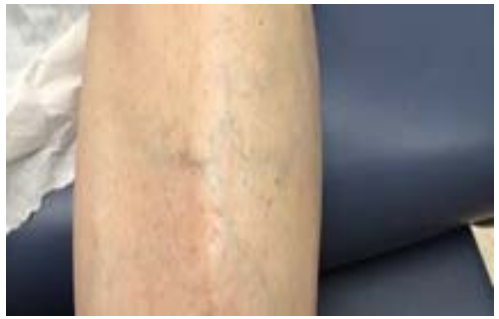
Fostamatinib

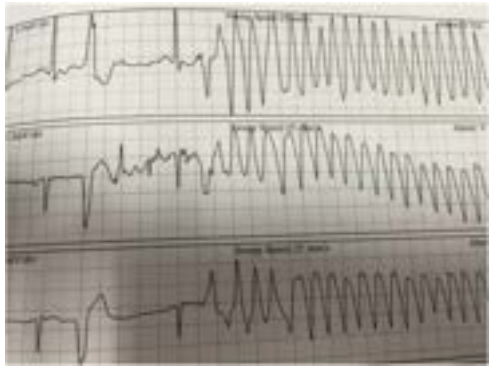


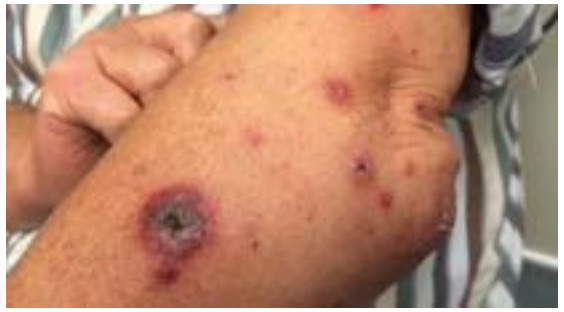
Currently in Clinical Trials

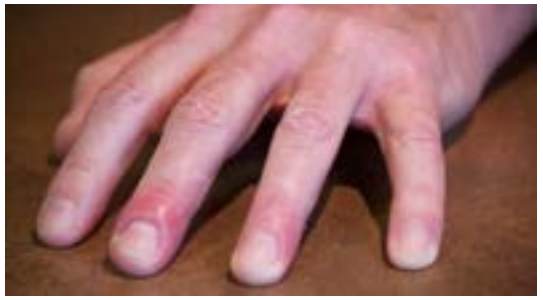
Side Effects of BTK inhibitors

- Heart Rhythm abnormalities
- High Blood pressure
- Heart failure
- Bruising/Bleeding
- Skin infections
- Nail changes
- Paronychia
- Infections



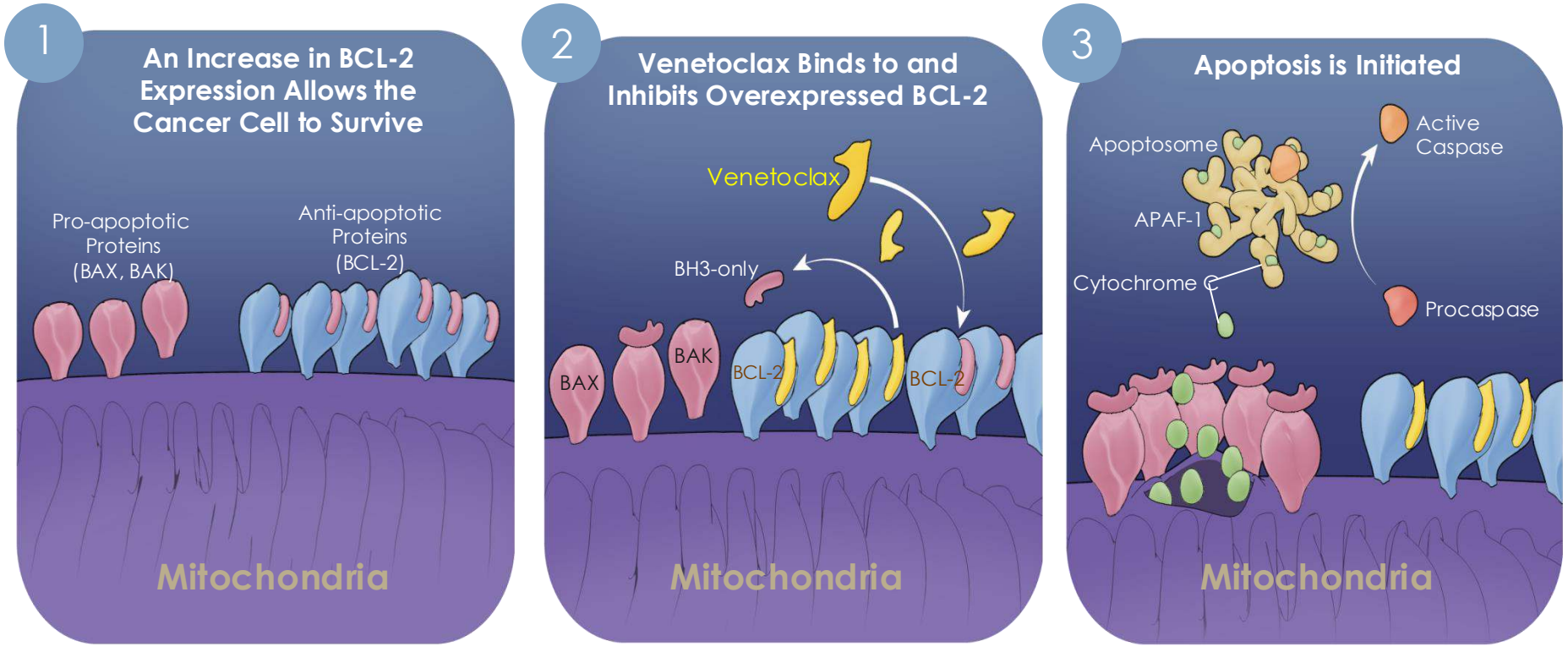






Patient permission obtained for images

Targeting Apoptosis

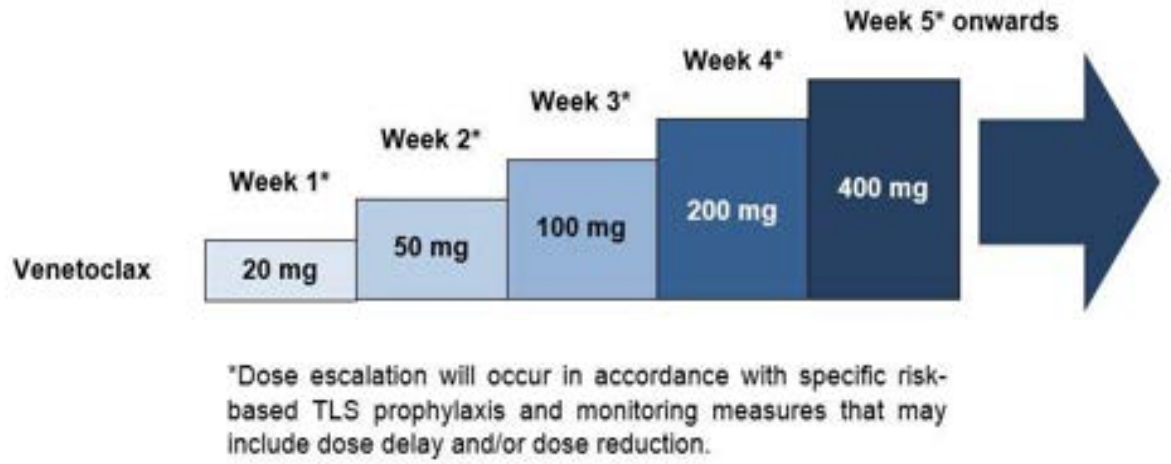


Side Effects of BCL-2 directed treatments

- Tumour Lysis Syndrome: Break down of the cancer cells that lead to mineral imbalances that could affect the heart, the kidney
- Low Blood counts
- Infections

Venetoclax Dosing and Administration[1]

DOSING GUIDELINES	**Venetoclax should be taken orally once daily until disease progression or unacceptable toxicity is observed[1]** •Take with a meal and water at approximately the same time each day •Swallowed whole and not chewed, crushed, or broken prior to swallowing
RECOMMENDED DOSAGE REGIMEN	**The starting dose of venetoclax is 20 mg once daily for 7 days[1]** •The venetoclax dose must be administered according to a weekly ramp-up schedule to the recommended daily dose of 400 mg over a period of 5 weeks as shown in the graphic below
DOSAGE FORMS AND STRENGTHS*	**Tablets[1]** •10, 50, and 100 mg



The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS.

*The Starting Pack provides the first 4 weeks of venetoclax according to the ramp-up schedule. Once the ramp-up phase is completed, the 400 mg dose is achieved using 100 mg tablets supplied in bottles.

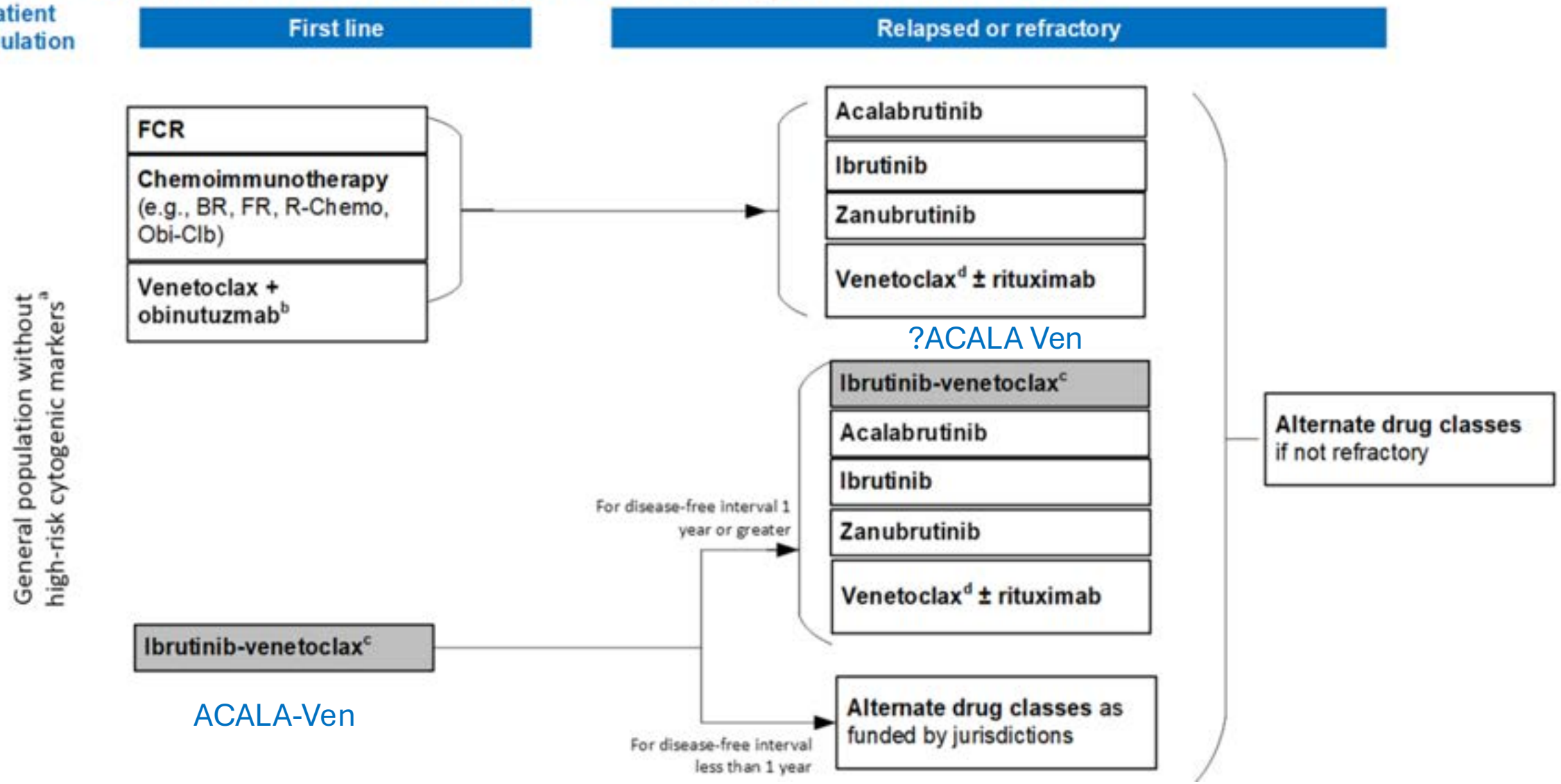
1. Venetoclax Prescribing Information AbbVie Inc & Genentech Inc; April 2016

Questions studies are addressing

CAN WE IMPROVE OUTCOME

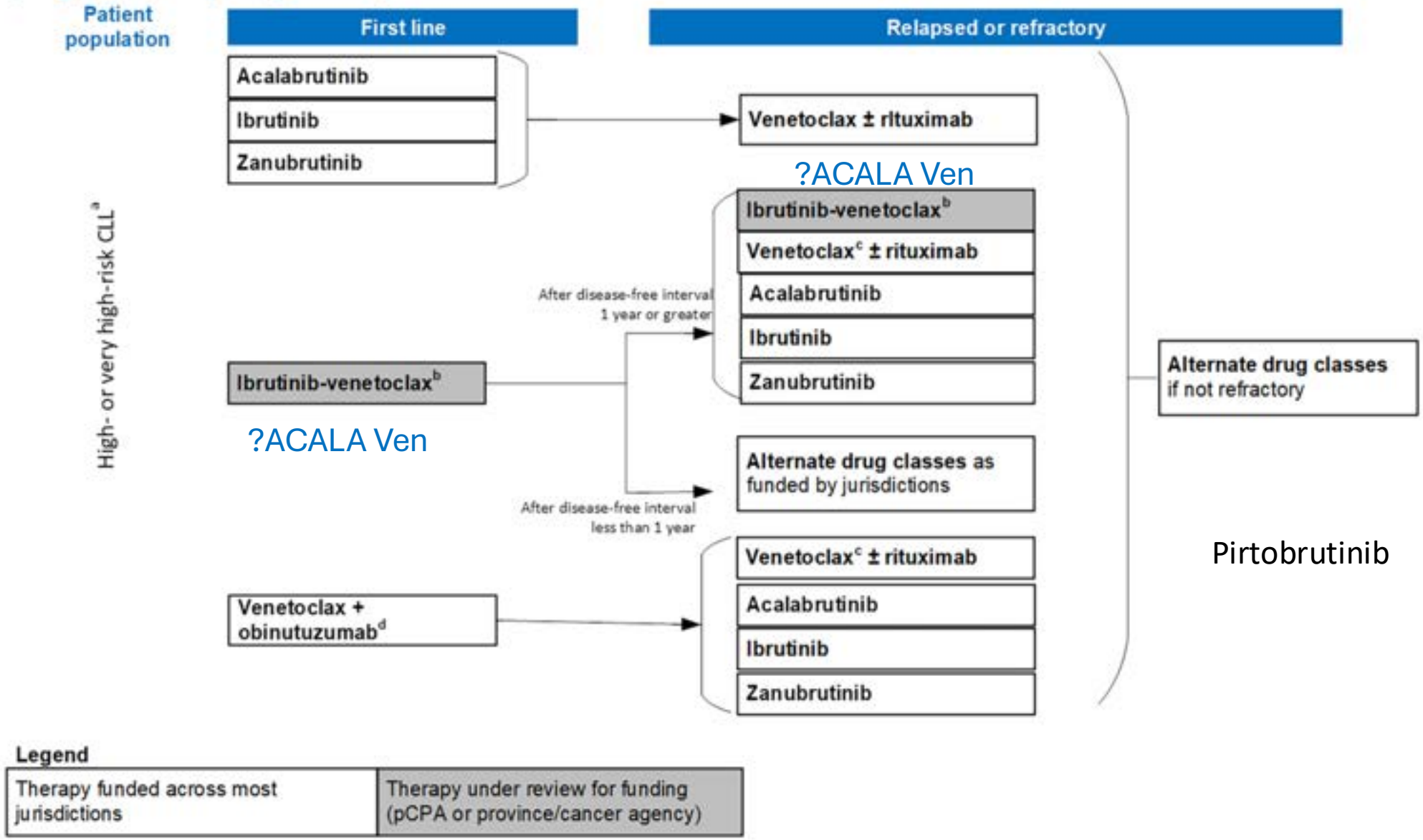
CAN WE REDUCE TOXICITY

Figure 1: Provisional Funding Algorithm Diagram for Chronic Lymphocytic Leukemia (General Population Without High-Risk Cytogenetic Markers)



CDA

Figure 2: Provisional Funding Algorithm Diagram for Chronic Lymphocytic Leukemia (High or Very High Risk)



Case 2

- 71 year old black female
  - Severe high blood pressure (on 2 BP meds)and end stage kidney disease and low kidney function, IGHV Unmutated , no P53 abnormalities. How would you treat?

  - Chlorambucil Obin
  - Ven Obin
  - Acala
  - Ibrutinib
  - Zanu
  - BTKi/BCL-2

How I start the conversation

- Its important for me to support you in this journey
- How do you come to your appointments?
- Which treatment appeals to you and why?
- What influenced your selection?

Equity Lense in Oncology

- How do we make treatments more tolerable
- How do we remove the ageist lens from treatment decision making?
- How do we make therapy more accessible?
- How do we embark on shared decision making?
- Don’t rule out therapy without talking to your friendly neighborhood Heme/onc.

Case 2

- 71 year old black female
  - Severe high blood pressure (on 2 BP meds)and end stage kidney disease and low kidney function, IGHV Unmutated , no P53 abnormalities. How would you treat?

- ~~Chlorambucil Obin~~
- Ven Obin
- Acala
- Ibrutinib
- Zanu
- BTKi/BCL-2

Case 3

50 year male with 17 p deletion

- Acala
- Ibrutinib
- Zanu
- Ibr/Ven
- Acala/Ven

80 year old female with 17p deletion

- Acala
- Ibrutinib
- Zanu
- Ibr/Ven
- Acala/Ven

Case 4

68 Year old relapsed post FCR/BR

- VenR
- Ibrutinib
- Acala
- Zanu

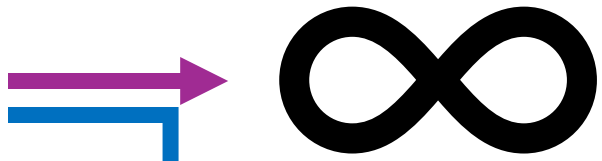
72 Year old rapidly progressing on 1st generation BTKI, previously treated with chemi-immunotherapy

- VenR
- Ibrutinib
- Acala
- Zanu
- Pirtobrutinib

In Canada the debate that exist:
time limited vs continuous therapy

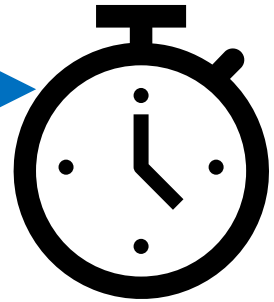
High Risk

Del 17, P53 mutation



Ibrutinib
Acalabrutinib
Zanubrutinib
Pirtobrutinib

Intermediate /Low Risk



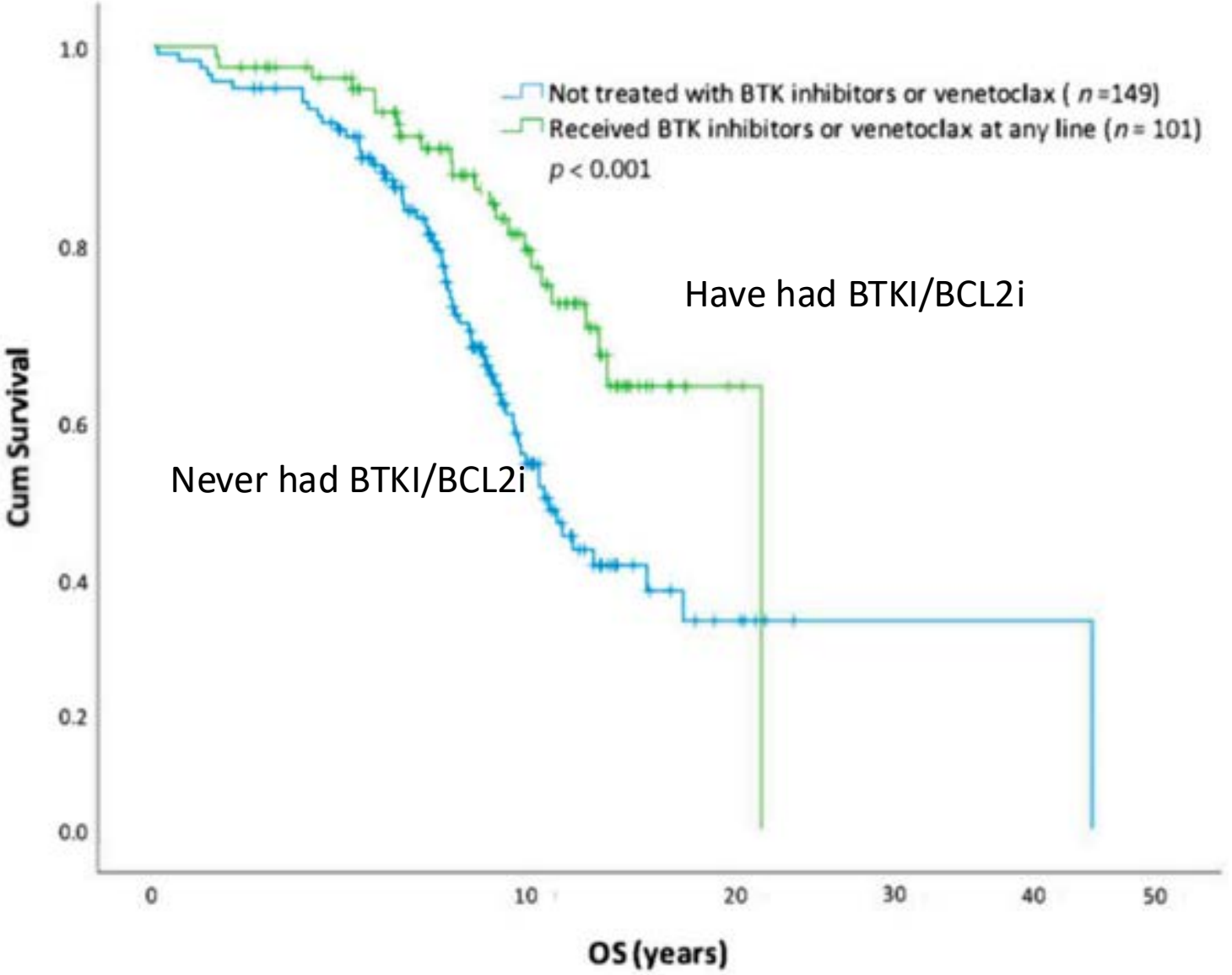
FCR
BR
Chlorambucil/Obinutuzumab
Venetoclax/Obinutuzumab
Venetoclax/Rituximab
BTKi/BCL2 Combinations

IgVH Unmutated or Mutated w/o
TP 53 abnormalities

Patient Factors: choice, coverage, accessibility

System Factors: Ease of administration
Resources, $$

Novel Agent impact on Manitoba CLL Outcomes 2010-2019



No BTK inhibitor/venetoclax	149	39	5	1	0	0
Received BTK inhibitor/venetoclax	101	42	1	0	0	0

Figure 5. Overall survival (OS) of patients with unmutated IGHV and/or TP53 aberration stratified by treatment with BTK inhibitors ($n = 98$) or venetoclax ($n = 3$) at any line of therapy.

Yang J and Yang L et al… Banerji V Current Oncology 2023

Cost of therapies in Canada No P53 abnormality

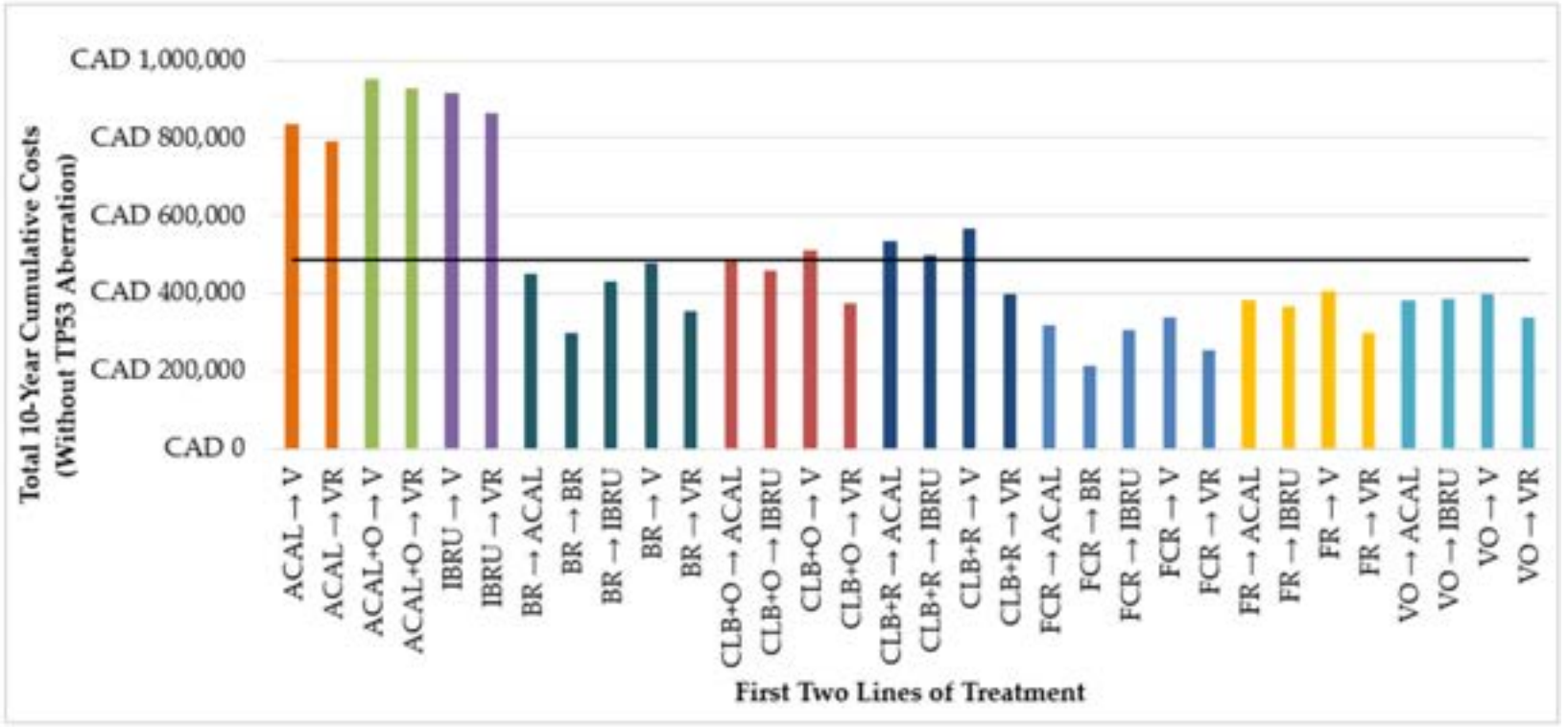


Figure 2. Total 10-year costs of treatment sequences by first two lines of treatment in patients withou TP53 aberration. ACAL: acalabrutinib, ACAL + O: acalabrutinib in combination with obinutuzumab BR: bendamustine in combination with rituximab, CAD: Canadian dollars, CLB + O: chlorambucil in combination with obinutuzumab, CLB + R: chlorambucil in combination with rituximab, FCR: fludara bine, cyclophosphamide, rituximab, FR: fludarabine in combination with rituximab, IBRU: ibrutinib V: venetoclax, VO: venetoclax in combination with obinutuzumab, VR: venetoclax in combinatio with rituximab. The black horizontal line represents the mean cost of all treatment sequences.

Guinan et al. … Hillis C, Banerji V Cancers 2024

Cost of therapies in Canada with P53 abnormalities

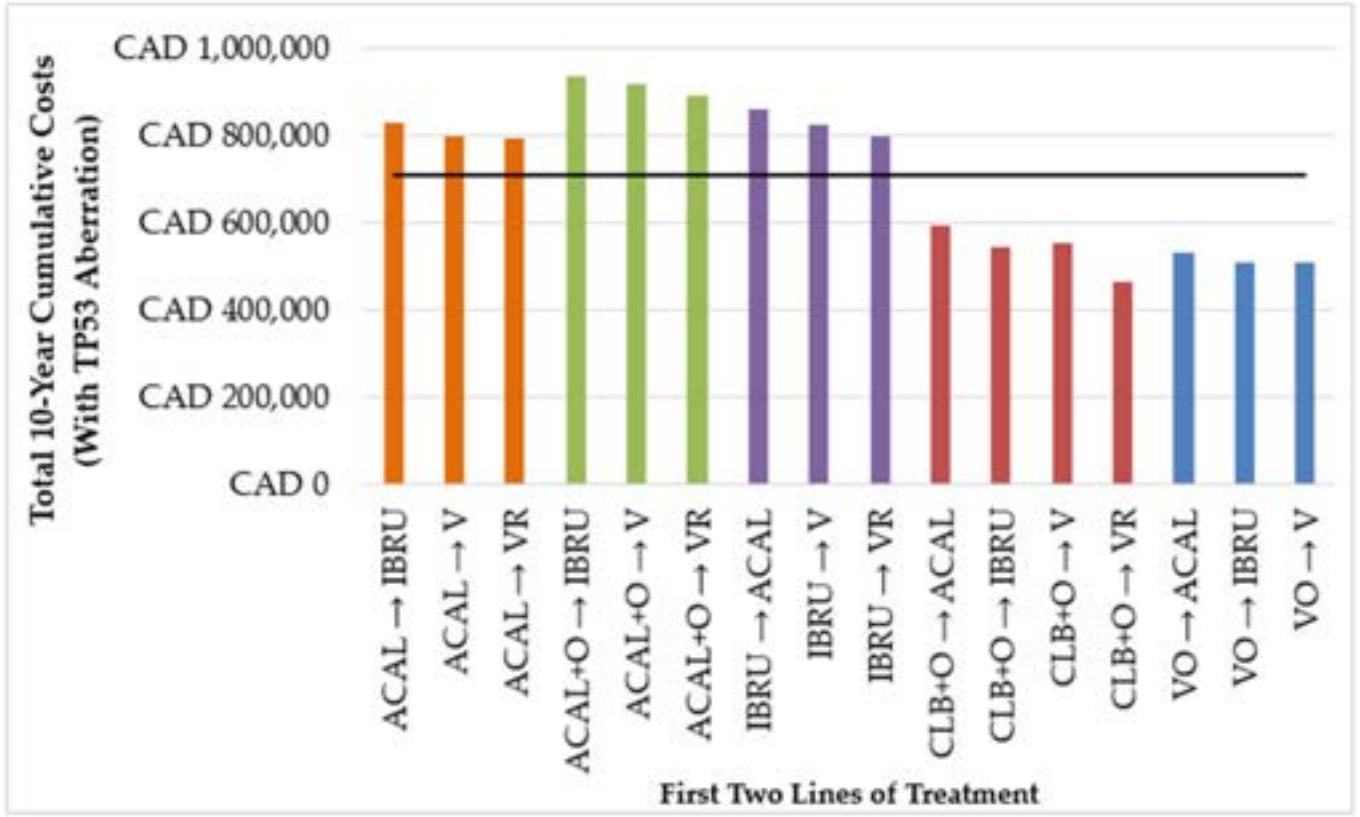


Figure 3. Total 10-year costs of treatment sequences by first two lines of treatment in patients with TP53 aberration. ACAL: acalabrutinib, ACAL + O: acalabrutinib in combination with obinutuzumab, CAD: Canadian dollars, CLB + O: chlorambucil in combination with obinutuzumab, IBRU: ibrutinib, V: venetoclax, VO: venetoclax in combination with obinutuzumab, VR: venetoclax in combination with rituximab. The black horizontal line represents the mean cost of all treatment sequences.

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Summary

- Every person has a unique story and a unique profile
- One Size doesn’t fit all