THE FUTURE OF CLL TREATMENT: WHAT'S NEXT?

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1

WELCOMING REMARKS

THE FUTURE OF CLL TREATMENT: WHAT'S NEXT?

Lizette Figueroa-Rivera, MA
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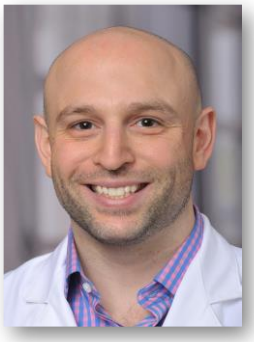
2

DISCLOSURES

THE FUTURE OF CLL TREATMENT: WHAT'S NEXT?



Dr. Adam Kittai

Consultation:

AbbVie, Astra-Zeneca, BeiGene, BMS, Eli Lilly

Grant Support:

Astra-Zeneca, BeiGene

Speakers Bureau:

BeiGene

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3

The Future of CLL Treatment: What's next?

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4

Disclosures

- **Consulting: Abbvie, AstraZeneca, BeiGene, Bristol-Myers Squibb**
- **Research Funding: AstraZeneca, BeiGene**
- **Speaking Engagements: AstraZeneca, BeiGene**

5

5

Contents

1) Watch and Wait
2) Frontline therapy, Doublets and Triplets
3) Refractory Disease
4) Richter Transformation
5) Future therapies

6

6

Watch and wait

7

7

Active Surveillance

8

8

Active Surveillance – When should we treat my disease?

Marrow failure

Massive or progressive splenomegaly

Massive or progressive lymphadenopathy

Progressive lymphocytosis

Autoimmune cytopenias NOT responding to other treatment

Organ threatening disease

Progressive B-Symptoms

Hallek et al Blood 2018

9

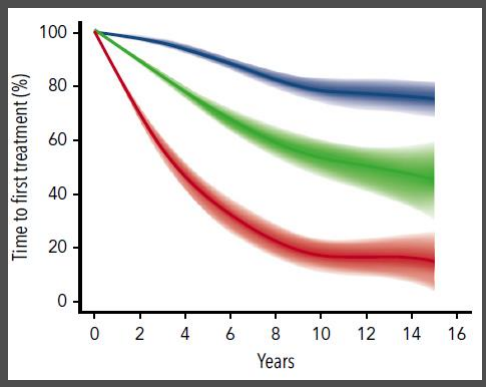
9

How long will I be in active surveillance?

1 point for each:
-Unmutated IGHV

-Absolute lymphocyte count >15,000

-Palpable lymph nodes



Risk group	Score
Low risk	0
Intermediate risk	1
High risk	2-3

Condoluci et al Blood 2020

10

10

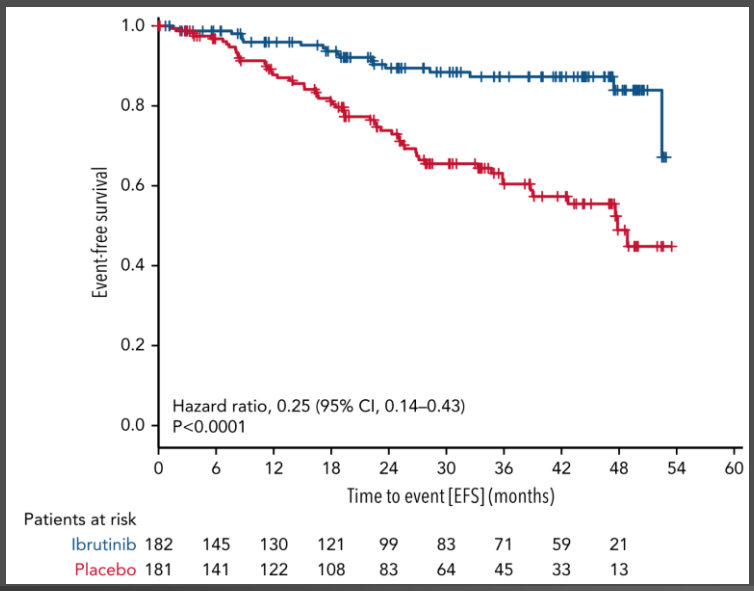
What can I do while on active surveillance?

1) Live your life
2) Exercise/ Healthy Diet
3) Immunizations
4) Cancer Screenings
5) Infections, consider IVIG

11

11

Why can't we start treatment now?

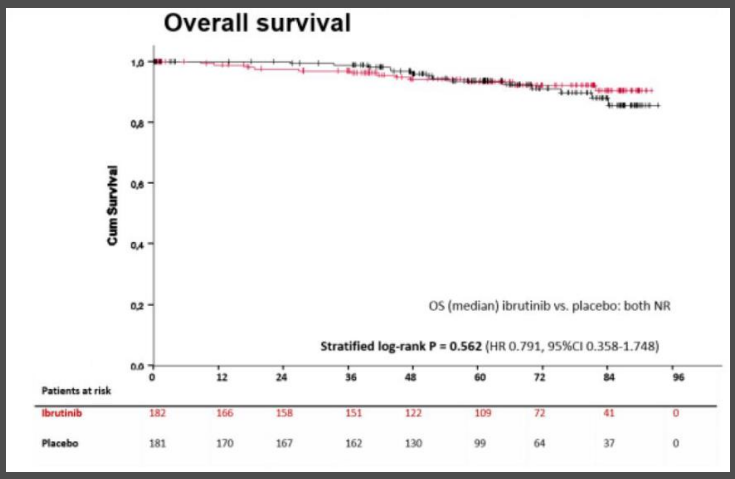


12

Langerbeins et al Blood 2022, Langerbeins et al Hematological Oncology 2023

12

Why can't we start treatment now?



13

Langerbeins et al Blood 2022, Langerbeins et al Hematological Oncology 2023

13

Why can't we start treatment now?

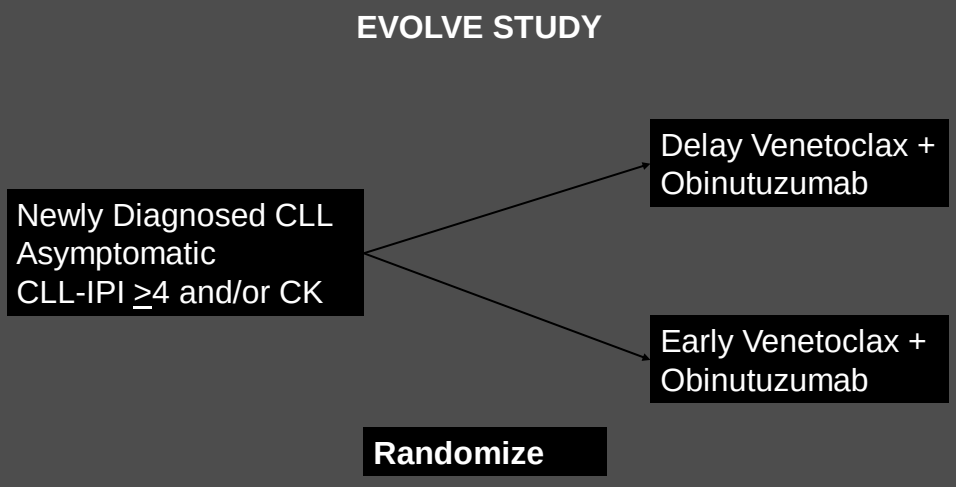
	Ibrutinib (n = 158)			Placebo (n = 155)		
	Any grade	Grade 1-2	Grade ≥3	Any grade	Grade 1-2	Grade ≥3
Total no. of events	1593	1426	167	1015*	885	129
Any AE, n (%)	150 (94.9)	70 (44.3)	80 (50.6)	147 (94.8)	80 (51.6)	67 (43.2)

14

Langerbeins et al Blood 2022, Langerbeins et al Hematological Oncology 2023

14

Are there any trials for patients on active surveillance?



15

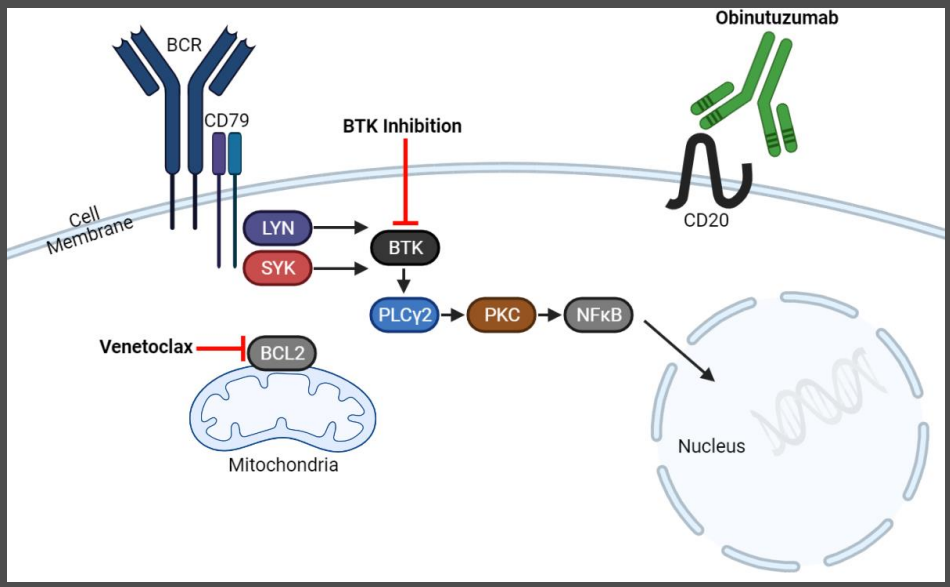
15

Frontline therapy, Doublets and Triplets

16

16

How do all of these drugs work?



17

Doc, what treatment should we use?

Patient Preference

18

Why is patient preference #1 consideration?

#1) No randomized phase 3 data

#2) The patient is the one who will get treated

#3) Our treatments generally work well for most patients

19

When do you recommend continuous therapy?

Older patients

- Cumulative data with BTKi is in the older age group

Less intensive upfront regimen

- No infusions, less monitoring → Less “time off life”

If using continuous therapy, think about cardiac Risk

- It’s complicated

20

When do you recommend time-limited therapy?

Younger patients

- Cumulative toxicity of BTKi over time

Good risk disease

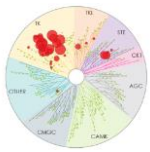
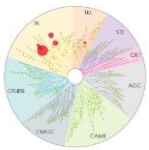
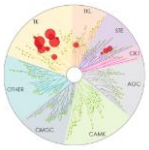
- Data in patients with TP53 aberrations

If using time-limited therapy think about kidney/cardiac function

- Increased tumor lysis and infusion reaction risk

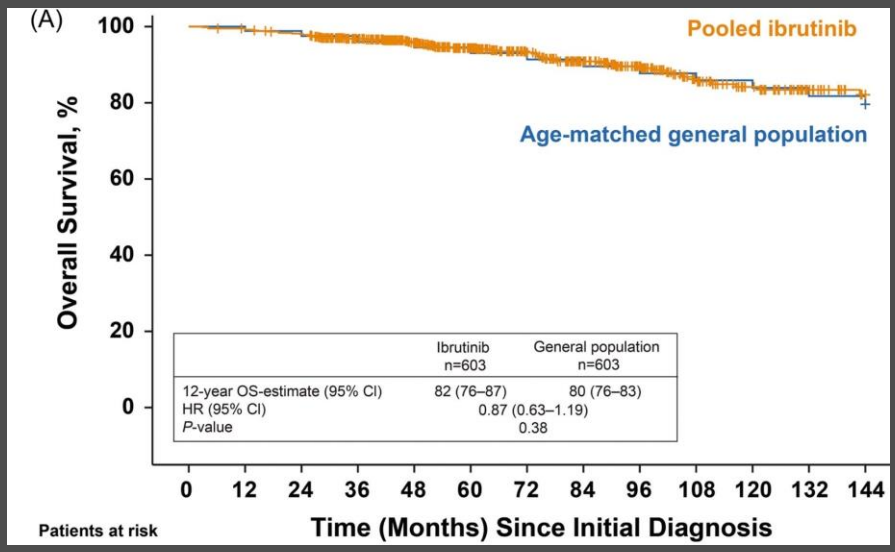
21

What are the BTK inhibitors?

	Ibrutinib	Acalabrutinib	Zanubrutinib
Canadian Approval	**CLL, MCL**	**CLL, MCL**	**CLL, MCL**
Selectivity			
Dosing	420mg PO daily (CLL, WM) 560mg PO daily (MCL ,MZL)	100mg PO BID	160mg PO BID or 320mg PO daily

22

Are patients with CLL living longer with new therapies?



Ghia et al Hemasphere 2024 23

23

Should I be worried about my heart?

AF in ibrutinib treated patients in 3 trials:

- **–RESONATE -** AF - **5%**, Grade ≥3 AF - **3%**
- **–RESONATE-2 –** AF - **6%**
- **–ILLUMINATE -** grade ≥3 AF – **5%**

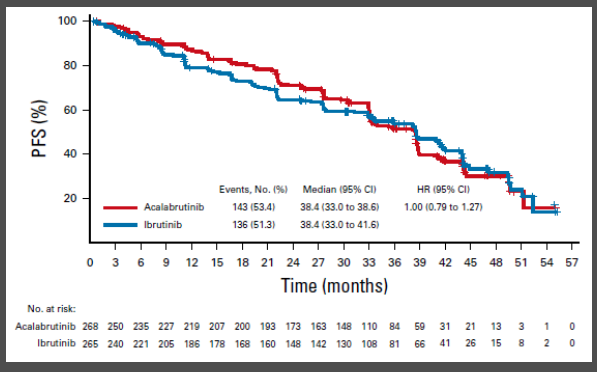
Byrd et al Blood 2019, Burger et al Leukemia 2020, Moreno et al The Lancet 2019, Ganatra et al JACC: Clinical Electrophysiology 2018

24

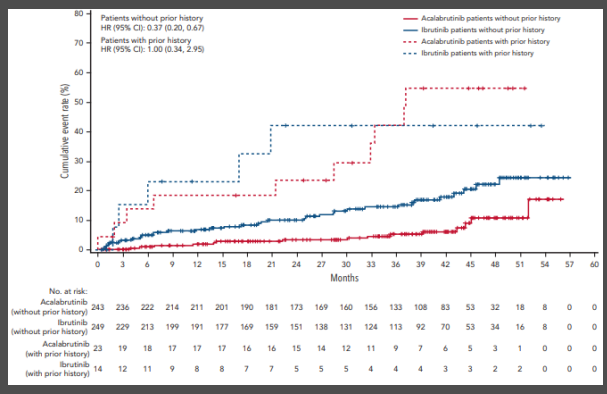
Which BTK inhibitor should we choose?

25

Have the BTK inhibitors been compared to each other?



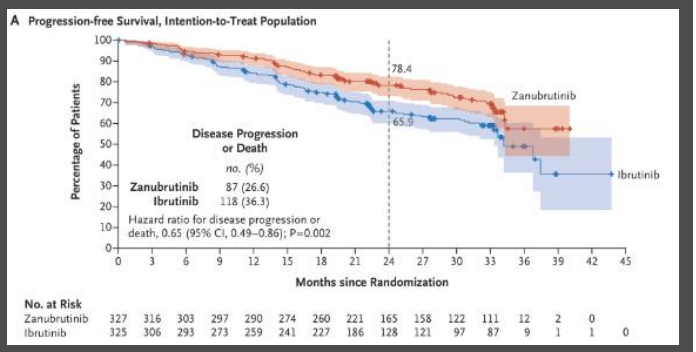
Incidence of AFib

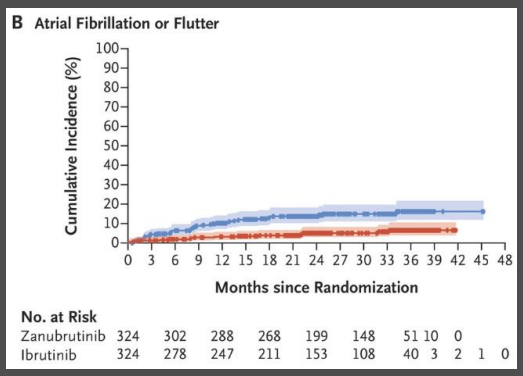


Byrd et al JCO 2021, Seymour et al Blood 2023

26

What about the new BTK inhibitor, zanubrutinib?





Brown et al NEJM 2023

27

How do I choose acalabrutinib vs. zanubrutinib?

Acalabrutinib	Zanubrutinib
Safer	Safer
Equal efficacy in RR High Risk	Improved efficacy in RR all-comers
Given twice per day	Can be given once or twice per day
Acalabrutinib headaches	Zanubrutinib has higher rates of hypertension than Acalabrutinib

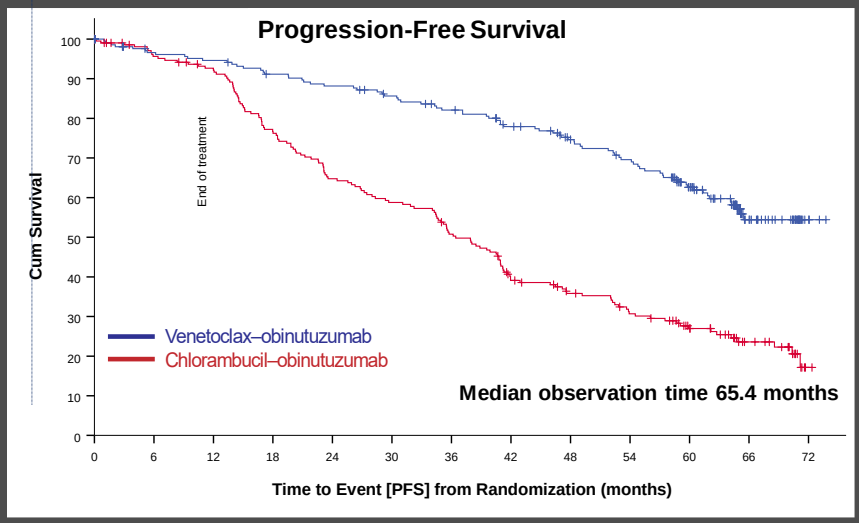
28

I want time-limited therapy, what do you recommend?

29

29

How long will I be progression-free with Venetoclax + Obinutuzumab?



Al-Sawaf O et al. Presented at: EHA; June 12, 2022 (abstract S148)

30

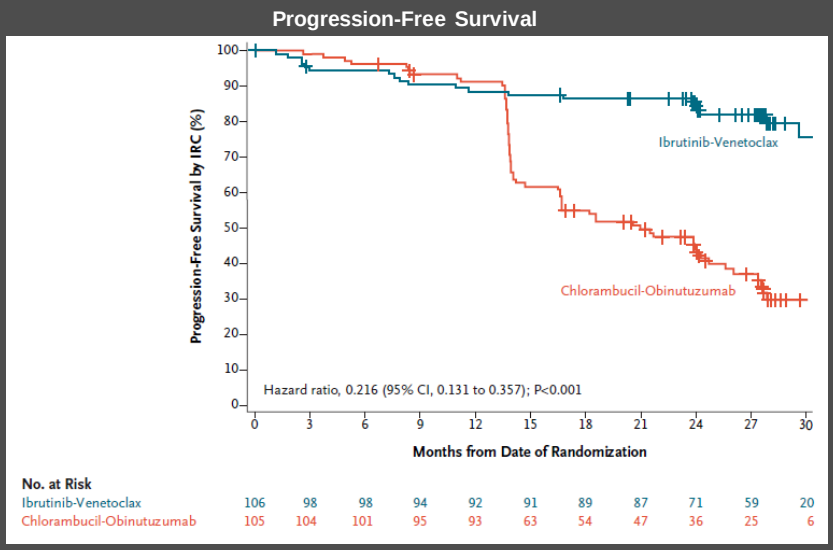
How long will I be progression-free with Venetoclax + Obinutuzumab?

Recent Update at EHA 2023
6 year Follow-up – OS data
Ven + Obin – 78.7%
Chlor + Obin – 69.2%
HR – 0.69, p = 0.052

Al-Sawaf O et al. Presented at: EHA; June 12, 2022 (abstract S148)

31

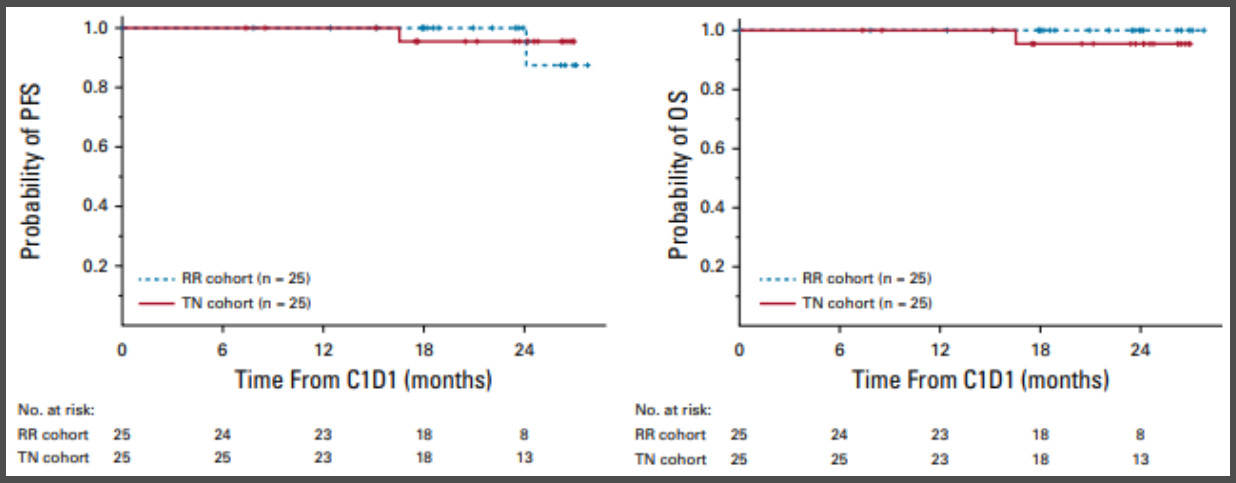
I heard ibrutinib plus venetoclax was an option?



Kater et al NEJM Evidence 2022

32

Ibrutinib + Venetoclax + Obinutuzumab



Rogers et al JCO 2020

33

What is the latest data on venetoclax regimens?

Eligibility

Treatment-naive, fit patients with CLL, **no *TP53*** aberrations (**centrally screened**)

- **CIT** FCR ≤65y, BR >65y
- **RV** rituximab, venetoclax | FD 12 months
- **GV** obinutuzumab, venetoclax | FD 12 months
- **GIV** obinutuzumab, ibrutinib, venetoclax | 12-36 months

Primary Endpoints

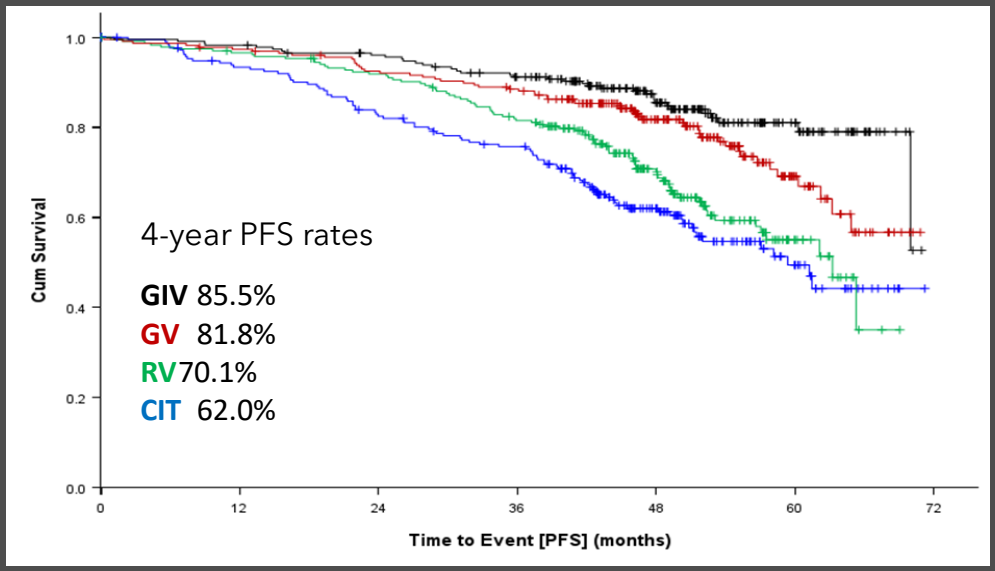
1. **uMRD rate** at MO15
2. **Progression-free survival**

Furstenau et al ASH 2023

34

34

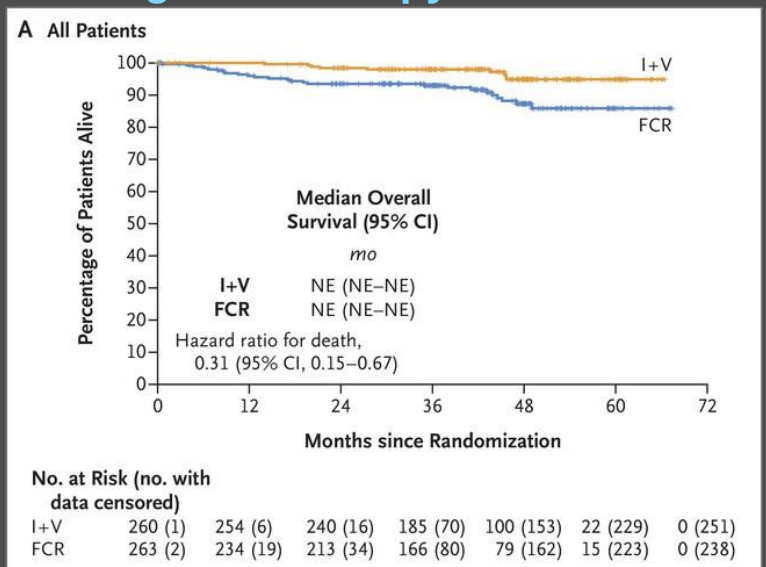
Progression-free survival



Furstenau et al ASH 2023 35

35

What about MRD guided therapy?



Munir et al NEJM 2024 36

36

What about toxicity of ibrutinib + venetoclax?

Adverse Event	Ibrutinib–Venetoclax (N=252)			
	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Acute kidney injury	0	0	0	0
Anemia	24 (9.5)	2 (0.8)	0	0
Atrial fibrillation or arrhythmia	10 (4.0)	2 (0.8)	0	0
Constipation	8 (3.2)	1 (0.4)	0	0
Cough	4 (1.6)	0	0	0
Diarrhea	58 (23.0)	2 (0.8)	0	0
Dyspnea	10 (4.0)	0	0	0
Fatigue	38 (15.1)	1 (0.4)	0	0
Febrile neutropenia	0	0	0	0
Fever	5 (2.0)	0	0	0
Headache	10 (4.0)	0	0	0
Hemolysis or hemolytic anemia	0	0	0	0
Hypertension	6 (2.4)	6 (2.4)	0	0
Infections and infestations, other	1 (0.4)	0	0	0
Infusion-related reaction	0	0	0	0
Lung infection	0	0	0	0
Lymphocyte count decreased	4 (1.6)	0	0	0
Nausea	43 (17.1)	3 (1.2)	0	0
Neutropenia	23 (9.1)	16 (6.3)	10 (4.0)	0
Other	24 (9.5)	7 (2.8)	0	0
Platelet count decreased	39 (15.5)	3 (1.2)	2 (0.8)	0
Rash	26 (10.3)	1 (0.4)	0	0

Munir et al NEJM 2024

37

37

Trials of combination therapy

Ibrutinib + Venetoclax + Obinutuzumab vs. Ibrutinib + Obinutuzumab

Ibrutinib vs. Venetoclax + Obinutuzumab vs. Ibrutinib + Venetoclax

Acalabrutinib + Venetoclax + Obinutuzumab vs. Acalabrutinib + Venetoclax vs. BR/FCR

Acalabrutinib + Venetoclax vs. Venetoclax + Obinutuzumab

Venetoclax + Obinutuzumab vs. Sonrotoclax + Zanubrutinib

38

Treatment of TN CLL - Summary

1) I prefer acalabrutinib and zanubrutinib compared to ibrutinib

2) No randomized data to help decide best upfront option

3) Patient preference #1

4) High-risk disease? – Favor continuous therapy

39

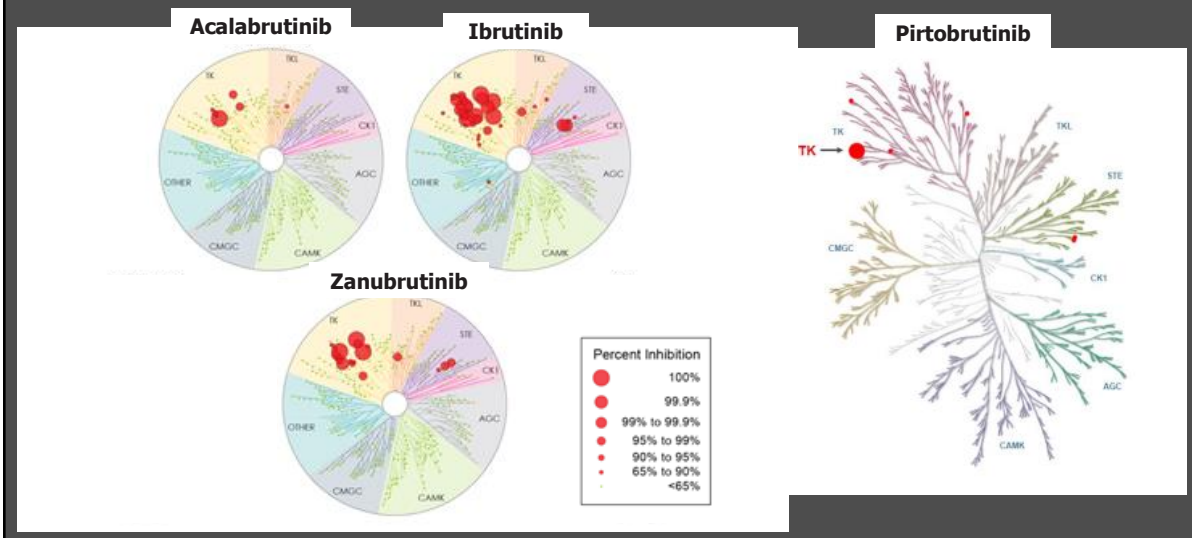
39

A new hope: Pirtobrutinib and CART

40

40

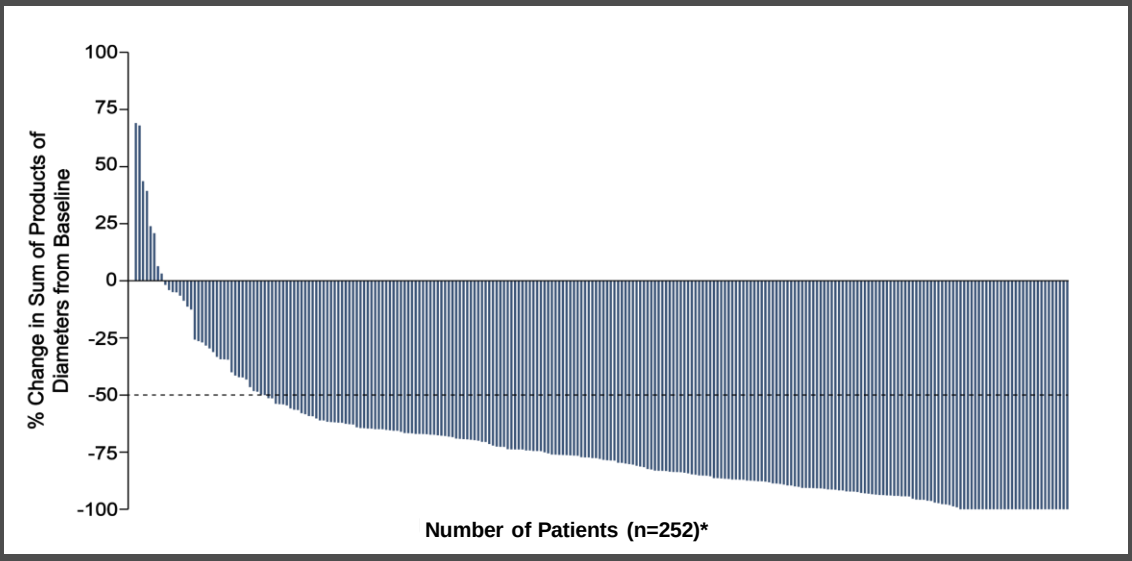
Why do you think pirtobrutinib might be a safer drug? How does it work?



Kaptein A et al *Blood*. 2018;132(Suppl 1): 1871, Barf T et al.J *Pharmacol Exp Ther. 20`7*. Mato et al Lancet 2023.

41

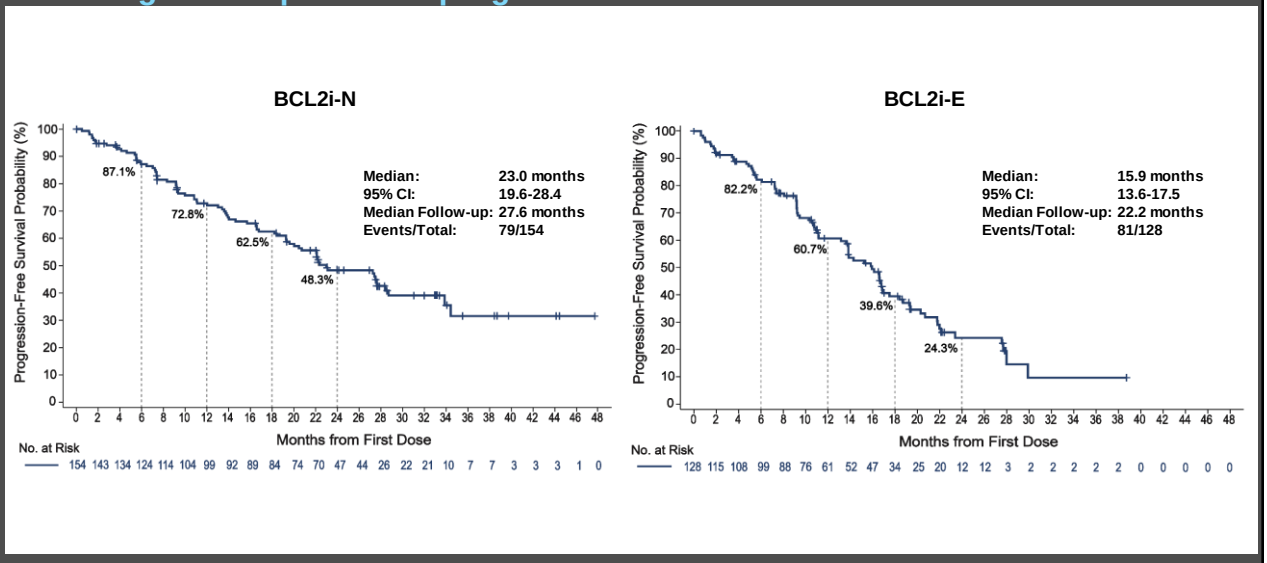
Will I attain a response to pirtobrutinib?



Mato, Woyach et al NEJM 2023

42

How long will I expect to be progression-free with Pirtobrutinib?



Mato, Woyach et al NEJM 2023

43

Pirtobrutinib Safety

Fatigue – 31.5%

Diarrhea – 26.5%

Bruising – 24.3%

Atrial Fibrillation – 3.8%

Bleeding – 42.6%

HTN – 14.2%

Infections – 71% any grade (28.1% grade ≥3)

Mato, Woyach et al NEJM 2023

44

Pirtobrutinib Summary

Pirtobrutinib is approved for the treatment of R/R CLL after cBTKi and BCL2i

Appears to be safe and effective for patients who progress on cBTKi and BCL2i

Multiple clinical trials of pirtobrutinib currently ongoing

Still work to do – PFS of 15.9 months

45

CAR-T Cell Therapy for CLL

CAR – Chimeric antigen receptor

Lisocabtagene maraleucel = Breyanzi = Liso-cel

Breyanzi = anti-CD19 CAR-T cell therapy

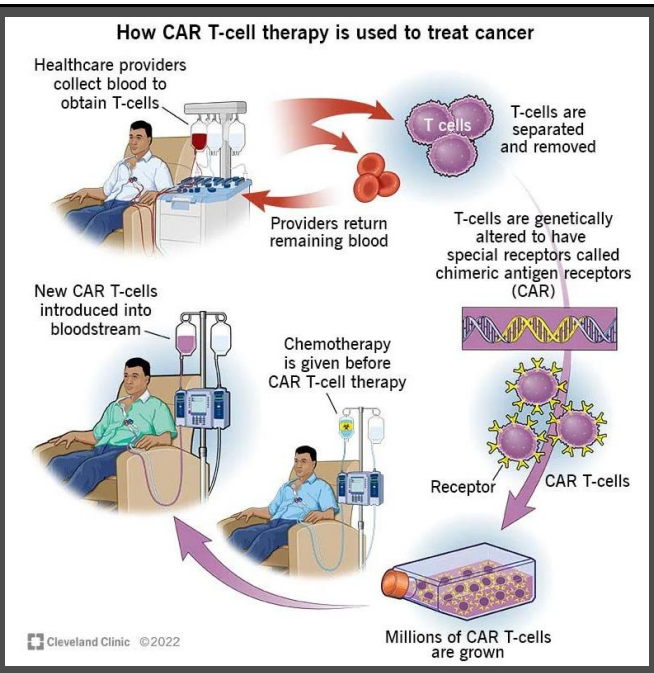
- Designed to attack the CD19 receptor on the outside of cancer
- Currently approved for the treatment of Diffuse Large B-cell Lymphoma

CAR-T cell therapy is a type of cellular therapy

- Where we use cells to attack the cancer

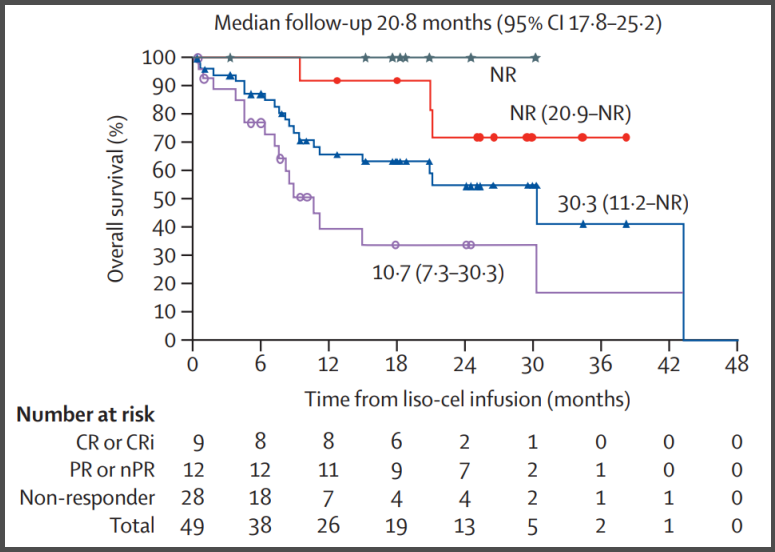
46

46



47

Is CAR-T effective in CLL?



Siddiqi et al Lancet 2023

48

48

What about CAR-T toxicity?

	Full population (n=117)
Patients with cytokine release syndrome	
Any grade	99 (85%)
Grade 1	43 (37%)
Grade 2	46 (39%)
Grade 3	10 (9%)
Grade 4	0
Grade 5	0
Time to cytokine release syndrome onset, days*	4 (1–7)
Time to cytokine release syndrome resolution, days*	6 (4–11)

Patients with neurological events†	
Any grade	53 (45%)
Grade 1	13 (11%)
Grade 2	18 (15%)
Grade 3	21 (18%)
Grade 4	1 (1%)
Grade 5	0
Time to neurological event onset, days*	7 (4–11)
Time to neurological event resolution, days*	7 (4–16)

Siddiqi et al Lancet 2023

49

49

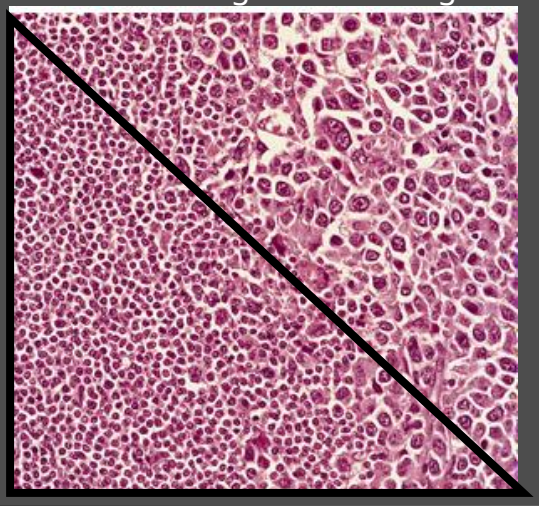
Richter Transformation

50

50

What is Richter Transformation (RT)?

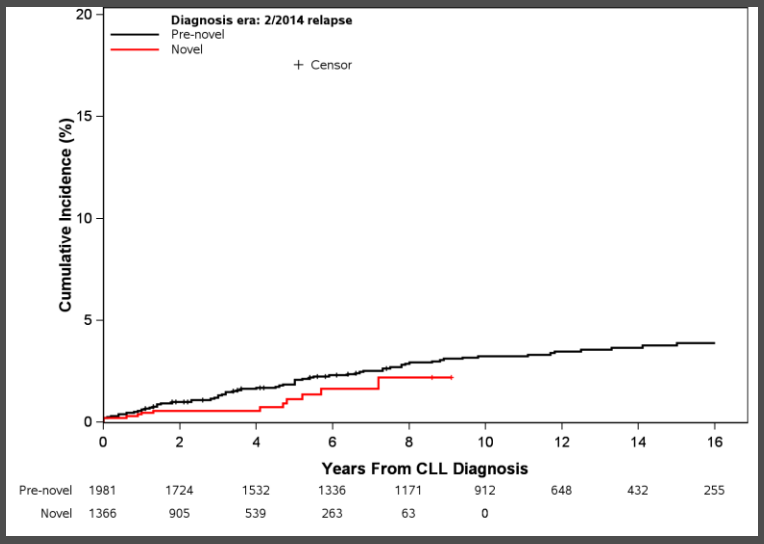
Richter Transformation: Diffuse Large B-Cell lymphoma occurring in the setting of CLL



Warnke et al Atlas of tumor pathology 1995

51

What is the risk I will get Richter Transformation?

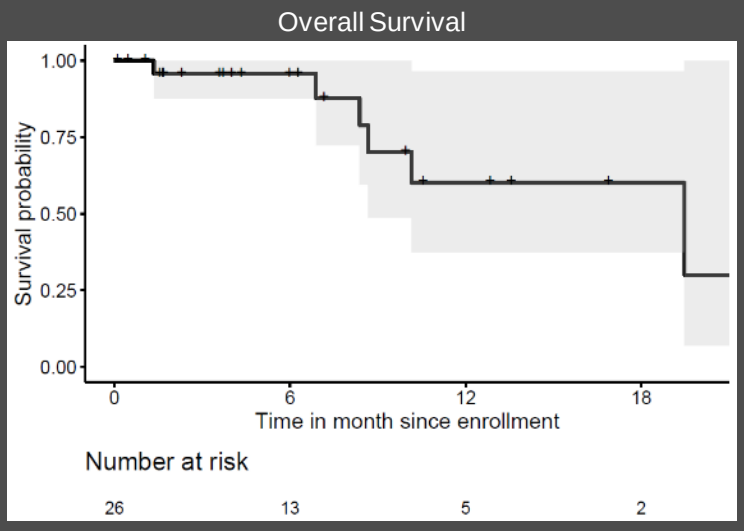


Risk Estimates	RT Incidence After Diagnosis		
	Pre-novel agent era	Novel agent era	Total
N	1981	**1366**	3347
5-year	2.1%	**1.1%**	1.8%

Hampel et al ASH 2023

52

What do you use to treat patients with RT?



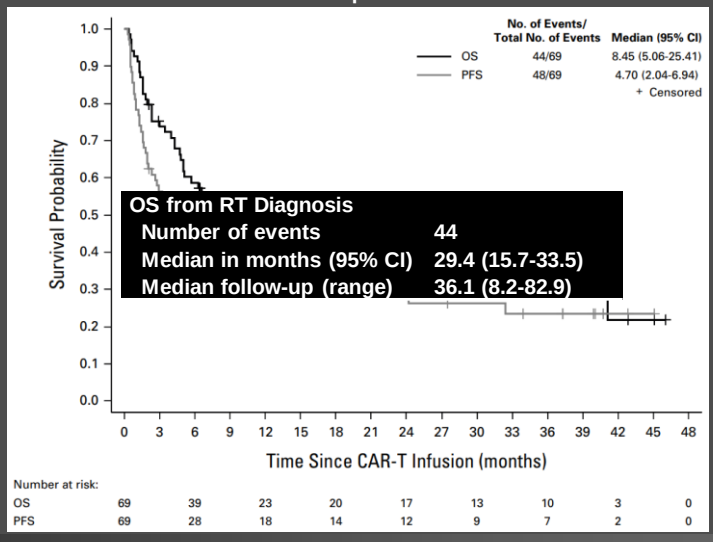
Venetoclax + RCHOP

Davids et al ICML 2023

53

If CAR-T works for CLL, how about RT?

Median follow-up – 24.13 months



Kittai, Bond et al JCO 2024

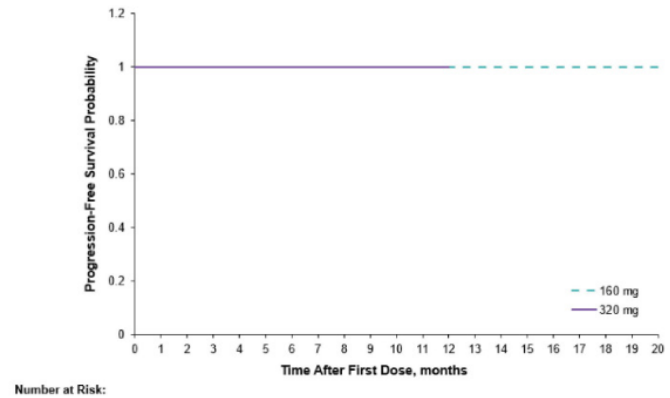
54

Drugs on the horizon

55

Sonrotoclax – A new BCL2 inhibitor

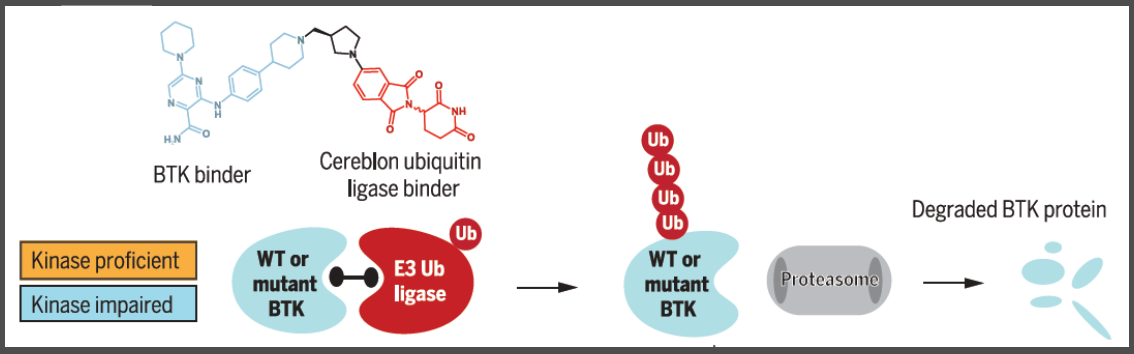
Figure. Progression-Free Survival With Sonrotoclax + Zanubrutinib in Patients With TN-CLL/SLL by Dose



Tam et al ASH 2023

56

BTK degraders



Montoya et al Science 2024

57

Bispecific Antibodies

Bi-Specific Antibody	Targets	Design
blinatumomab	CD19 x CD3	
mosunetuzumab	CD20 x CD3	
glofitamab	$(CD20)_2$ x CD3	
odronextamab	CD20 x CD3	
epcoritamab	CD20 x CD3	

Schuster et al Science 2021

58

58

Conclusions: What does the future hold?

1) Currently, great options are available for patients with CLL, that are both safe and effective.
2) New drugs being developed → focused on being safer and more effective.
3) Approvals of pirtobrutinib and CAR-T, give options to patients who are in need of therapy.
4) We are always hopeful for a cure and are driving deeper and prolonged responses with combination therapy.

59

Thanks! Questions?

Icahn School of Medicine at Mount Sinai

60

THE FUTURE OF CLL TREATMENT: WHAT'S NEXT?

Ask a question by phone:

Press star (*) then the number 1 on your keypad.

Ask a question by web:

Click "Ask a question"

Type your question

Click "Submit"

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.

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61

LLS EDUCATION & SUPPORT RESOURCES

HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET

Chat live online:
www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET

Email: www.LLS.org/ContactUs
All email messages are answered within one business day.

CLINICAL TRIAL SUPPORT CENTER
Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
www.LLS.org/Navigation

NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLSNutrition.org

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62

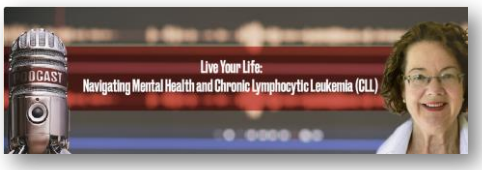
LLS EDUCATION & SUPPORT RESOURCES

Online Chats

Online Chats are free, live sessions, moderated by oncology social workers. To register or for more information, please visit **www.LLS.org/Chat**

Education Videos

View our free education videos on disease, treatment, and survivorship. To view all patient videos,
please visit **www.LLS.org/EducationVideos**



Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**

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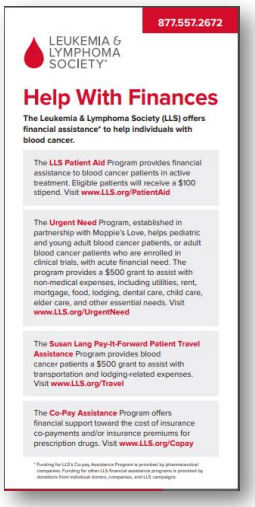
63

LLS EDUCATION & SUPPORT RESOURCES



The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: www.LLS.org/Finances

To order free materials: **www.LLS.org/Booklets**

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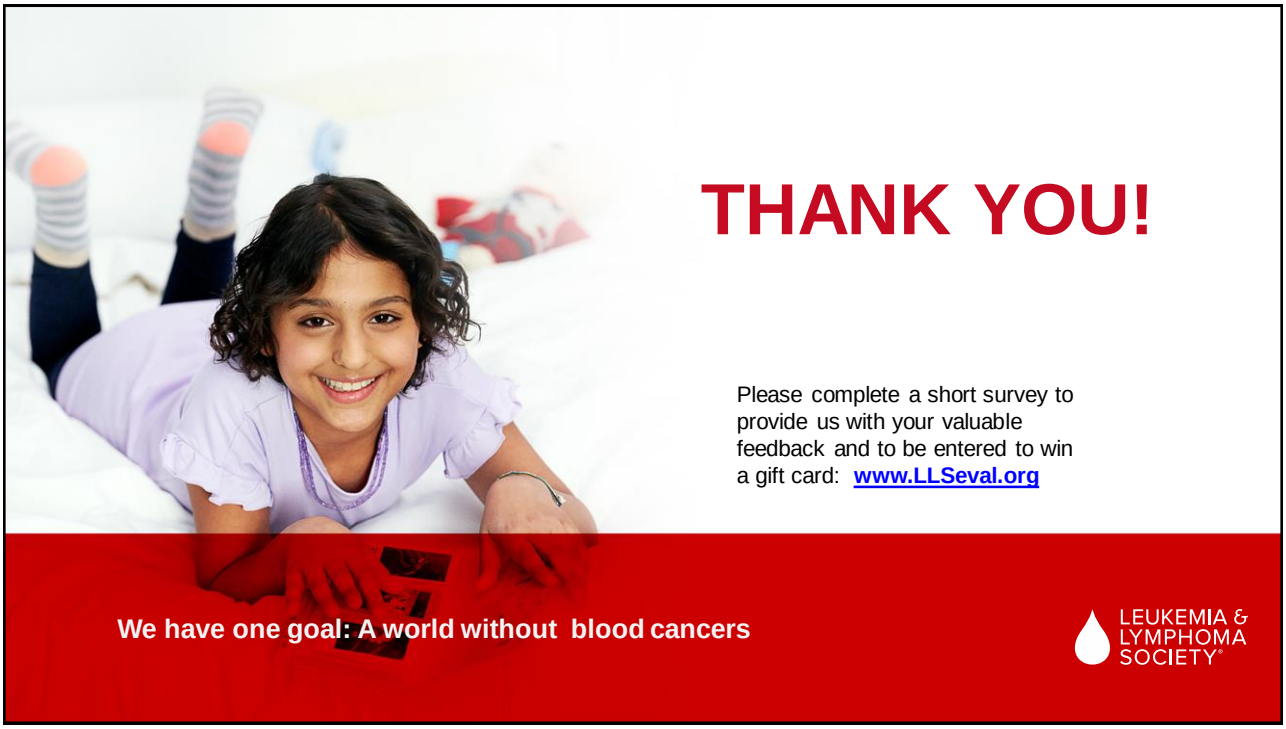
64


THANK YOU!
Please complete a short survey to provide us with your valuable feedback and to be entered to win a gift card: www.LLSeval.org
We have one goal: A world without blood cancers
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65