



WELCOMING REMARKS

HIGHLIGHTS IN THERAPY FOR CHRONIC LYMPHOCYTIC LEUKEMIA

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DISCLOSURES

HIGHLIGHTS IN THERAPY FOR CHRONIC LYMPHOCYTIC LEUKEMIA

Dr. Heather Wolfe

Consultant: None

Grant/Research Support: Schrödinger

Speaker: Curio Science



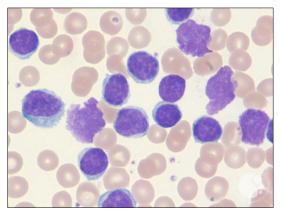
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Presentation Overview

- 1. Background
- 2. Active Surveillance
- 3. Frontline Treatment Options
- 4. Relapsed Treatment Options
- 5. Future Treatment
- 6. Survivorship Care

Chronic Lymphocytic Leukemia (CLL)

- The most common form of leukemia in adults.
- Average age at diagnosis = 72 years
- Clinical Features:
 - High white blood cell count (lymphocytosis)
 - Bone marrow suppression (anemia or low platelets)
 - -Enlarged lymph nodes
 - -Enlarged spleen
- CLL = SLL (for purpose of this talk)

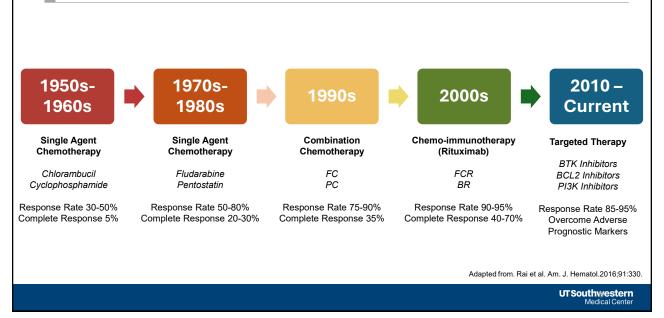


ASH Image Bank

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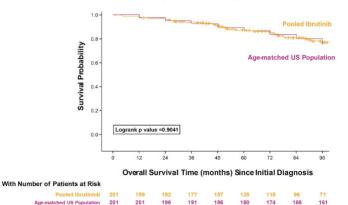
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Advances in Management of CLL



Chronic Lymphocytic Leukemia (CLL)





In the age of novel therapies, survival in 2025 approaches age matched controls (similar patients without CLL).

Burger JA. Et al. Blood (2022) 140: 4159-4161.

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Active Surveillance = "Watch and Wait"

Active Surveillance

- Active Surveillance = time between diagnosis and treatment.
- Approximately 1/3rd of patients with CLL never require treatment.
- Currently, CLL cannot be cured by current treatment options (outside of allogenic stem cell transplantation).
- Randomized trials immediate versus delayed treatment do not show improvement in long-term survival with early treatment.

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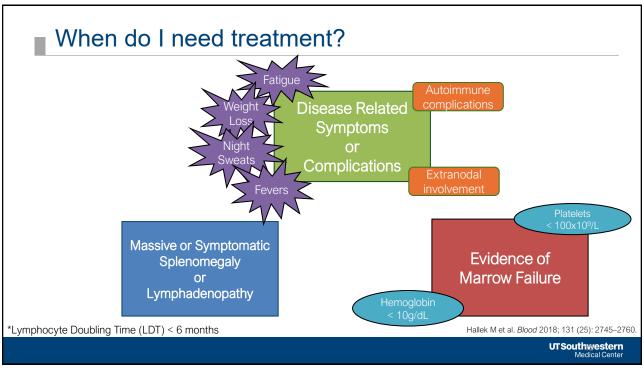
Early Intervention Trials in CLL del(17p) Inter Alfa del(11q) ECOG PS Thymidine kinase β2 microglobulin -based Sumulative Survival (%) -based Fludara CR) tibody CLI Patients Treatment-naive Asymptomatic Binet stage A Time Since Randomization (months) Nove ents? **UTSouthwestern**

Active Surveillance

- Routine visits history, physical exam, and laboratory monitoring.
- Some patients may have imaging.
- Important time for Survivorship-Based Care! (Stay Tuned...)

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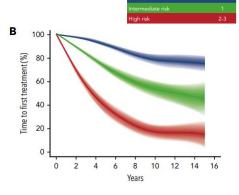


Risk Stratification

International Prognostic Score for Early-Stage CLL (IPS-E):

- Unmutated IGHV
- Absolute Lymphocyte Count > 15,000/microL
- Palpable lymph nodes

	# of Risk Factors	1 Year Treatment	5 Year Treatment
Low-Risk	0	< 1%	8%
Intermediate-Risk	1	3%	28%
High-Risk	2 or 3	14%	65%

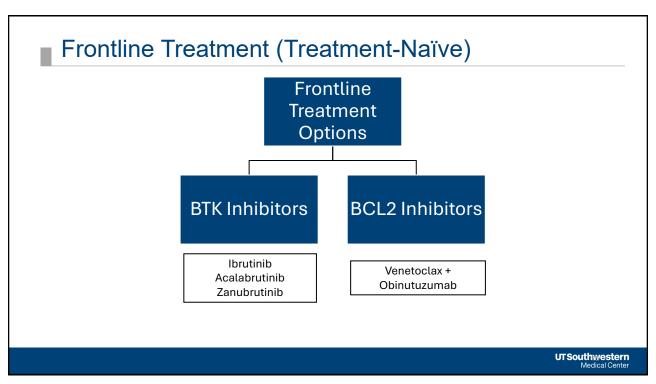


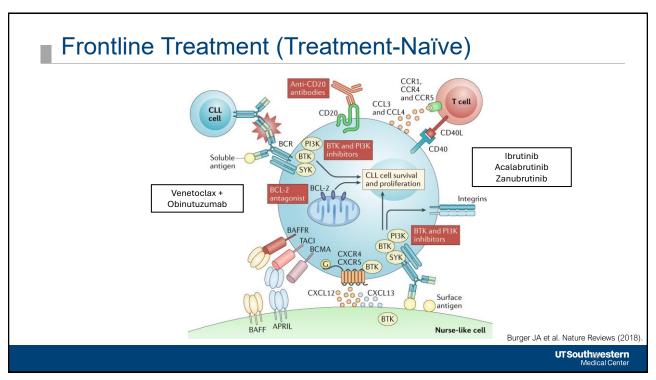
Condoluci A et al. Blood 2020; 135(21):1859.

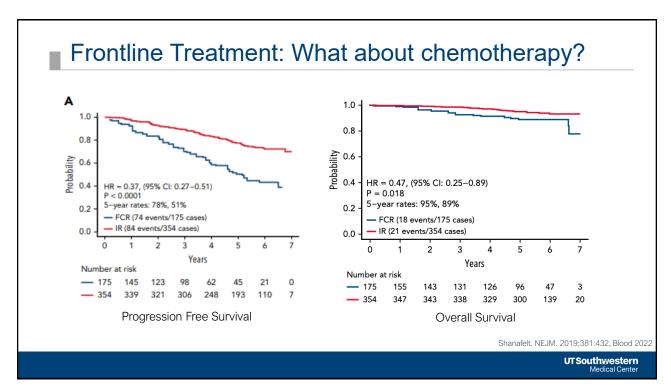
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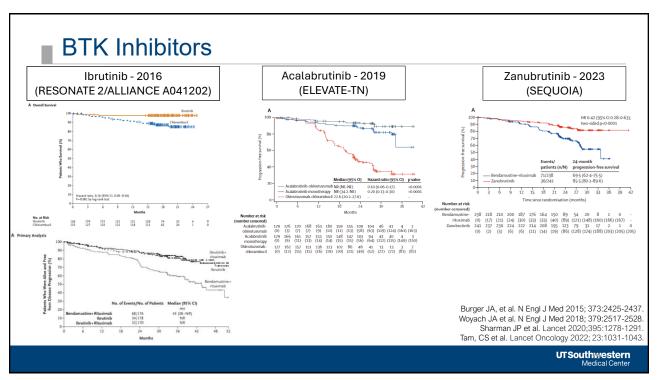
Frontline Treatment







BTK Inhibitors



BTKi Related Adverse Effects

Atrial Fibrillation Hypertension Bone and Joint Pain

Bleeding Infection Diarrhea

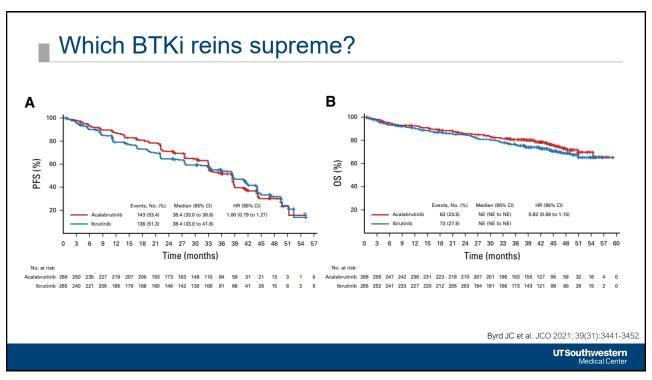
Fatigue Skin Changes Low Blood Counts

	Phase 2,	Phase 3	RESONATE	Phase 3 RE	SONATE2
Adverse event	follow-up	Follow-up	Follow-up	Follow-up	Follow-up
	21 mo ⁶ (n = 85)	9 mo ⁴ (n = 195)	19 mo ^{16,17} (n = 195)	18 mo ⁵ (n = 135)	21 mo ¹⁸ (n = 135)
Atrial fibrillation All grades Grade ≥3	3 (4)	10 (5)	13 (7)	8 (6)	14 (10)
	0	6 (3)	7 (4)	2 (1)	6 (4)
Bleeding All grades Grade ≥3	14 (16)	86 (44)	NR	NR	9 (7)
	4 (5)	2 (1)	4 (2)	6 (4)	8 (6)
Infection All grades Grade ≥3	NR	137 (70)	NR	NR	NR
	NR	47 (24)	59 (30)	NR	31 (23)
Arthralgia All grades Grade ≥3	23 (27) 0	34 (17) 2 (1)	44 (23) NR	22(16) 2 (1)	27 (20) 3 (2)
Myalgia All grades Grade ≥3	16 (19) 1 (1)	19 (10) 1 (1)	NR NR	NR NR	NR NR

Table 1. Frequency of highlighted adverse events on selected landmark ibrutinib studies

Stephens DM, et al. Blood (2019) 133(12):1298-1307.

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Which BTK Reins Supreme?

TABLE 2. Most Common AEs Occurring in \geq 10% (any grade) or \geq 5% (grade 3 or higher) of Patients in Either Treatment Arm

			266)		263)
	Event	Any Grade	$\text{Grade} \geq 3$	Any Grade	Grade ≥ 3
\Rightarrow	Diarrhea ^{a,b}	92 (34.6)	3 (1.1)	121 (46.0)	13 (4.9)
	Headache ^{a,b}	92 (34.6)	4 (1.5)	53 (20.2)	0
	Cougha	77 (28.9)	2 (0.8)	56 (21.3)	1 (0.4)
	Upper respiratory tract infection	71 (26.7)	5 (1.9)	65 (24.7)	1 (0.4)
	Pyrexia	62 (23.3)	8 (3.0)	50 (19.0)	2 (0.8)
	Anemia	58 (21.8)	31 (11.7)	49 (18.6)	34 (12.9)
	Neutropenia	56 (21.1)	52 (19.5)	65 (24.7)	60 (22.8)
	Fatigue ^b	54 (20.3)	9 (3.4)	44 (16.7)	0
\star	*Arthralgia ^a	42 (15.8)	0	60 (22.8)	2 (0.8)
$\frac{1}{\sqrt{2}}$	- Hypertension ^{a,b}	23 (8.6)	11 (4.1)	60 (22.8)	23 (8.7)
	Nausea	47 (17.7)	0	49 (18.6)	1 (0.4)
	Pneumonia	47 (17.7)	28 (10.5)	43 (16.3)	23 (8.7)
	Thrombocytopenia	40 (15.0)	26 (9.8)	35 (13.3)	18 (6.8)
	Dyspnea	37 (13.9)	6 (2.3)	23 (8.7)	1 (0.4)

	Acalabrutinib (n = 266)		Ibrutinib (n = 263)		
Event	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	
Bronchitis	34 (12.8)	3 (1.1)	23 (8.7)	2 (0.8)	
Constipation	31 (11.7)	0	37 (14.1)	2 (0.8)	
Contusiona	31 (11.7)	0	48 (18.3)	1 (0.4)	
Nasopharyngitis	29 (10.9)	0	27 (10.3)	0	
Dizziness	28 (10.5)	0	26 (9.9)	0	
Vomiting	28 (10.5)	1 (0.4)	36 (13.7)	3 (1.1)	
Peripheral edema	26 (9.8)	0	38 (14.4)	1 (0.4)	
Rash	26 (9.8)	2 (0.8)	33 (12.5)	0	
Myalgia	25 (9.4)	2 (0.8)	27 (10.3)	1 (0.4)	
Atrial fibrillation ^a	24 (9.0)	12 (4.5)	41 (15.6)	9 (3.4)	
Urinary tract infection ^a	22 (8.3)	3 (1.1)	36 (13.7)	6 (2.3)	
Back pain ^a	20 (7.5)	0	34 (12.9)	2 (0.8)	
Epistaxis	19 (7.1)	1 (0.4)	28 (10.6)	1 (0.4)	
Muscle spasms ^a	16 (6.0)	0	35 (13.3)	2 (0.8)	
Dyspepsia ^a	10 (3.8)	0	32 (12.2)	0	

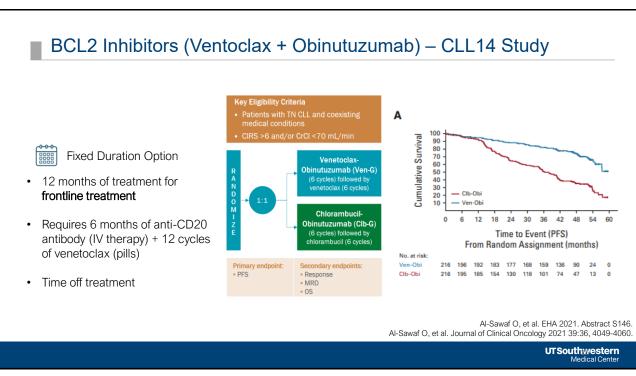
Byrd JC et al. JCO 2021; 39(31):3441-3452.

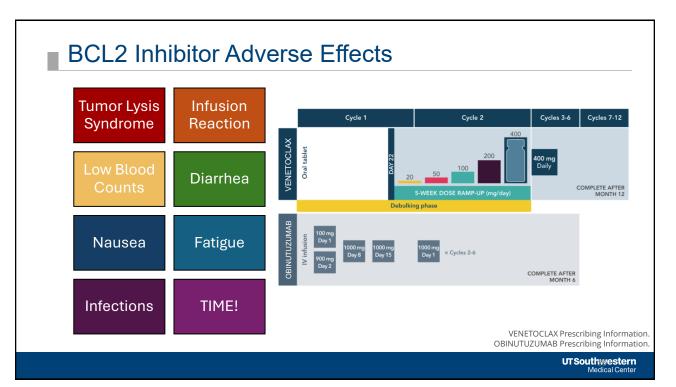
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Which BTK Reins Supreme? (ALPINE) Table 2. Adverse Events that Occurred during Treatment (Safety Population). Zanubrutinib (N=324) Ibrutinib (N=324) C Overall Survival number of patients (percent) 100-318 (98.1) 321 (99.1) 90 Grade ≥3 adverse events 218 (67.3) 228 (70.4) Zanubrutinib Grade ≥3 adverse events reported in >2% of the patients in either trial group 80-Percentage of Patients ++ Ibrutinib 70-Neutropenia 52 (16.0) 45 (13.9) 60-Hypertension 48 (14.8) 36 (11.1) 50-Covid-19-related pneumonia 23 (7.1) 13 (4.0) Covid-19 40-Deaths 22 (6.8) 16 (4.9) 19 (5.9) 26 (8.0) no. (%) Pneumonia 30-Decreased neutrophil count 17 (5.2) 14 (4.3) Zanubrutinib 48 (14.7) 20-4 (1.2) Syncope 9 (2.8) Ibrutinib 60 (18.5) 9 (2.8) 12 (3.7) 10-Hazard ratio for death, 0.76 (95% CI, 0.51-1.11) 7 (2.2) 8 (2.5) Atrial fibrillation 6 (1.9) 12 (3.7) Increased blood pressure 4 (1.2) 10 (3.1) No. at Risk 136 (42.0) 162 (50.0) 310 303 56 50 Events leading to dose reduction 40 (12.3) 55 (17.0) 325 314 307 297 290 283 271 255 200 171 156 124 Ibrutinib Events leading to dose inter-ruption 162 (50.0) 184 (56.8) Events leading to treatment discontinuation 50 (15.4) 72 (22.2) 33 (10.2) Events leading to death 36 (11.1) Brown JR et al. NEJM 2023; 388:319-32. UTSouthwestern Medical Center

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BCL2 Inhibitors





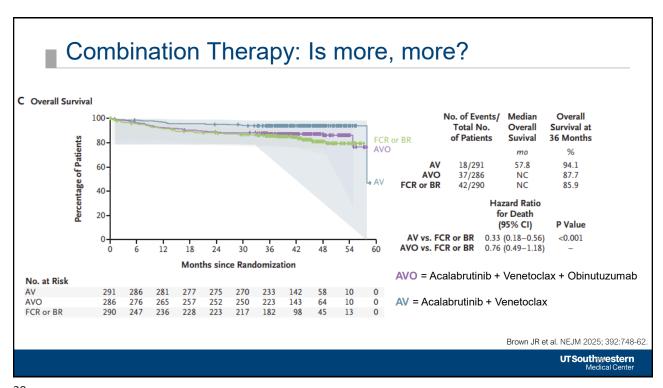
■ Frontline Treatment – Patient Factors/Preference

	BTK Inhibitor	Venetoclax + Anti-CD20 Ab
TP53 Mutation Status	Data supports continuous therapy for TP53 mutated disease	Less data for fixed duration
Duration of Therapy	Until progression or toxicity	Fixed Duration, 12 months
Comorbidities	Caution with atrial fibrillation, uncontrolled hypertension, or cardiac risk factors	High risk for tumor lysis syndrome with CKD
Medications	Risk of bleeding with antiplatelet agents or anticoagulants Dose adjustments with CYP3A4 Inhibitors	Dose adjustments with CYP3A4 Inhibitors (avoid with strong CYP3A4 inh)
Treatment Initiation	Start at full dose	Ramp-up due to TLS Risk
Follow-Up	Routine follow-up	Frequent lab/visits during ramp up

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Combination Therapy Is more, more?



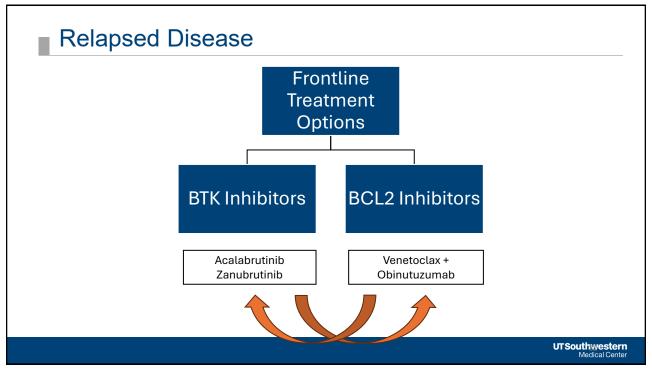
Combination Therapy: Is more, more?

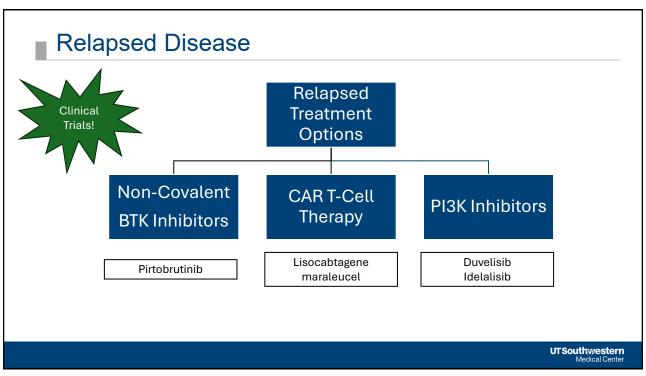
Table 2. Adverse Events and Selected Events of Clinical Interest (Safety Population).**							
Adverse Events	Acalabrutinib–Venetoclax (N = 291)		Obinutu	Acalabrutinib–Venetoclax– Obinutuzumab (N = 284)		Chemoimmunotherapy (N = 259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	
			number of pati	ents (percent)			
Events							
Hypertension	12 (4.1)	8 (2.7)	11 (3.9)	6 (2.1)	7 (2.7)	2 (0.8)	
Hemorrhage							
Any	94 (32.3)	3 (1.0)	86 (30.3)	6 (2.1)	11 (4.2)	1 (0.4)	
Major	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)	
Neutropenia‡	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)	
Infection	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)	
Second primary cancer							
Any	15 (5.2)	5 (1.7)	12 (4.2)	5 (1.8)	2 (0.8)	0	
Excluding nonmelanoma skin cancer	8 (2.7)	5 (1.7)	7 (2.5)	4 (1.4)	1 (0.4)	0	
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)	
Atrial fibrillation or flutter	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)	
Ventricular tachyarrhythmia†	2 (0.7)	0	3 (1.1)	0	0	Brown JR et al.	

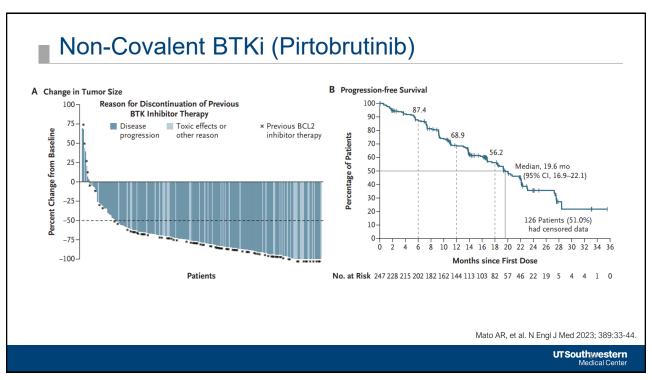
Relapsed Disease When CLL comes back...

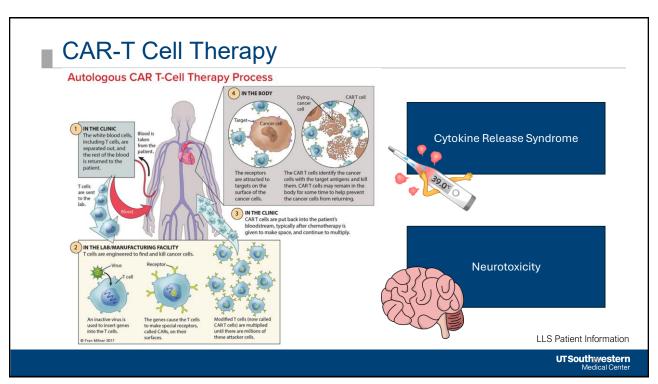
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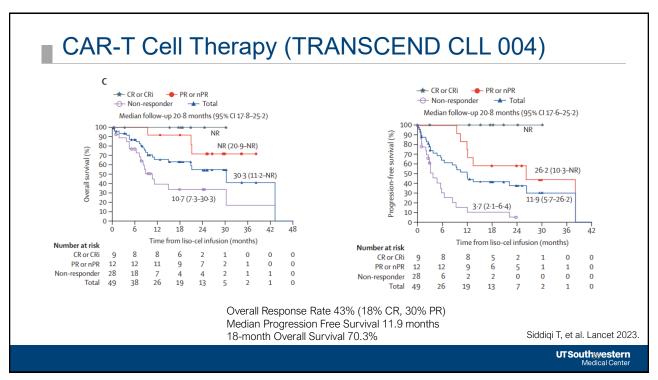
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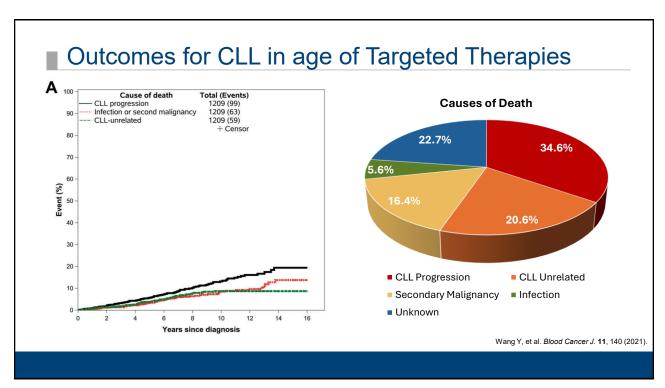
Future Treatments

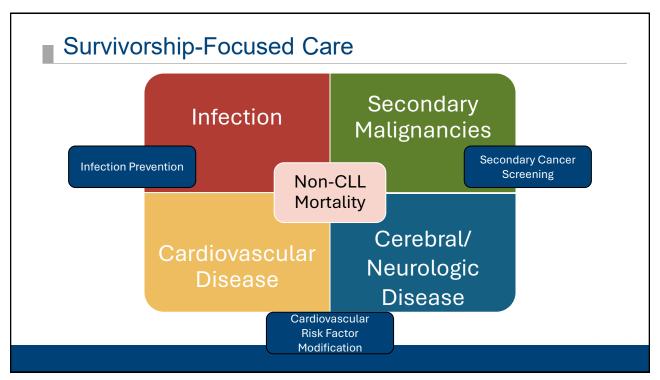
- 1. Combinations (BTKi + BCL2 +/- anti-CD20 antibody)
- 2. Non-Covalent BTKi (Nemtabrutinib)
- 3. New BCL2i (Sonrotoclax)
- 4. Bispecific Antibodies
- 5. Novel Compounds (BTK Degraders)

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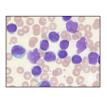
Survivorship Care

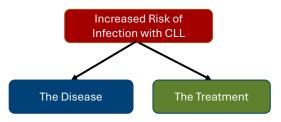




Infection Prevention

- 1. Immunoglobulin Replacement
 - Prophylactic immunoglobulin replacement (IVIG) is not recommended
 - IF IgG < 500 mg/dL + recurrent infections requiring IV antibiotics or hospitalization, IVIG is recommended
- 2. Routine Vaccination for Immunocompromised







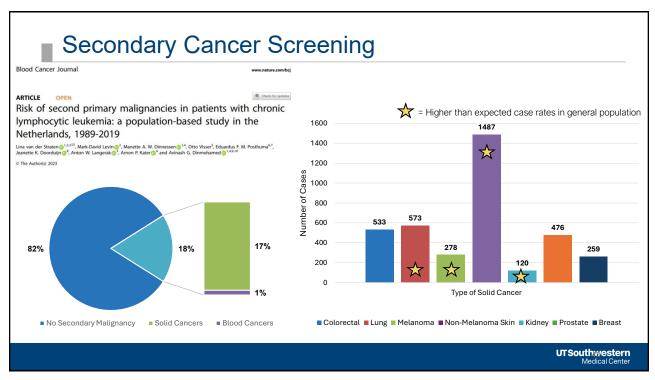
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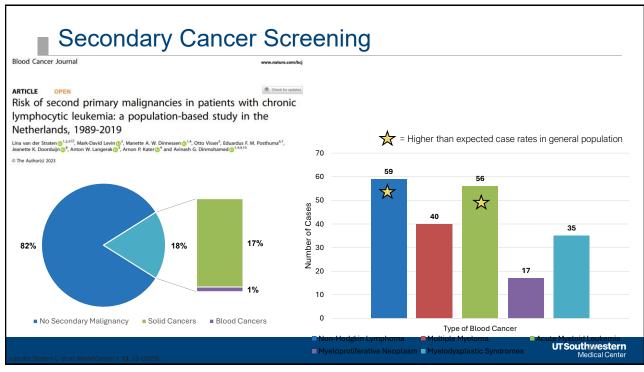
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Infection Prevention

- 1. Yearly recombinant influenza vaccine (Avoid live vaccines)
- 2. Pneumococcal vaccine series
 - 1. PCV21 or PCV20
 - 2. PCV15 => PPSV23
- 3. COVID-19 vaccine series
- 4. Recombinant Zoster vaccine series
- 5. Tetanus, diphtheria, pertussis (Tdap or Td) booster every 10 years
- 6. HPV Vaccine (consider ≤ 45 years of age)
- 7. RSV Vaccine (in patients > 60 years of age)

Advisory Committee on Immunization Practices, Recommended Adult Immunization Schedule for ages 19 years or older. United States, 2023, Centers for Disease Control and Prevention





Secondary Cancer Screening

- 1. Skin Cancer: Yearly dermatology visits
- 2. Colorectal Cancer: Screening at age 45
- 3. Breast Cancer: Mammograms every 1-2 years at age 50-74, shared decision making at age 40-49 and after 75
- **4.** Lung Cancer: Annual Low-dose CT scan in patients ≥ 50 years of age with ≥ 20 pack-year smoking history
- 5. Prostate Cancer: Shared decision making, if screening is performed PSA at age 50-75 (every 1-2 years)
- **6. Cervical Cancer:** Start at age 21 with pap smears, at age 30-65 can do pap smears with HPV testing every 5 years

US Preventative Service Task Force Published Recommendations (2016 – 2023)
American College of Physicians Clinical Guidelines & Recommendations (2017 – 2023)
American Cancer Society
National Comprehensive Cancer Network Detection, Prevention, and Risk Reduction Guidelines (2023-2024)

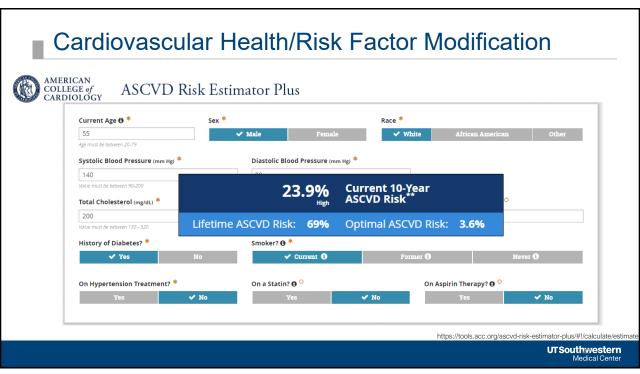
* Ask your doctor about your individual risk

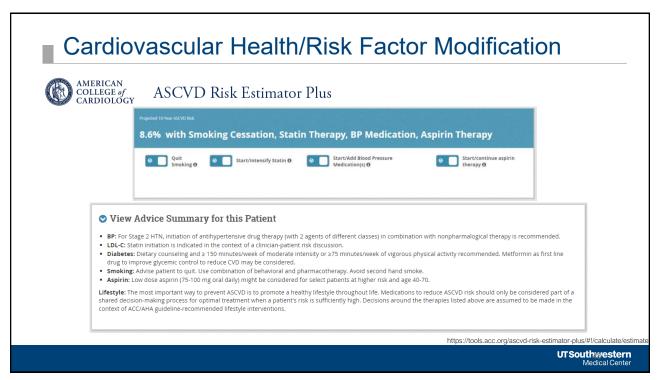
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Cardiovascular Health/Risk Factor Modification

- 1. Screen for pre-existing cardiac disease or emerging risk factors
 - · Coronary Heart Disease
 - Heart Failure
 - Atrial Fibrillation
 - High blood pressure (<u>blood pressure monitoring in clinic</u>)
 - Hyperlipidemia (routine cholesterol levels)
 - Diabetes (check HqbA1c)
 - Obesity
 - Cigarette/Tobacco Use
- 2. Discuss your family history
- 3. Review prior cancer treatment history and risk for toxicity
- 4. Assess current diet and exercise habits





Cardiovascular Health/Risk Factor Modification

- 1. Management of chronic medical conditions
 - If you have high blood pressure → adequate blood pressure control
 - If you have high cholesterol levels → dietary changes or start statin
 - If you have pre-diabetes/diabetes → dietary changes, management of diabetes
- 2. Addition of protective medications
 - · Start aspirin?
 - · Start statin?
- 3. Avoid cigarette/tobacco use
- 4. Encourage regular exercise/dietary modifications

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Additional Recommendations

- 1. Ask your doctor about vitamin D supplementation.
- 2. Engage in physical activity.
- 3. Maintain a healthy diet high in vegetables, fruits, and whole grains.
- 4. Drink alcohol sparingly.
- 5. Discontinue use of cigarettes, tobacco products, and e-cigarettes.
- 6. Practice sun safety (use SPF at least 30, avoid tanning beds, avoid sunburns, wear hats/coverage when outside).
- 7. Strive for 7-9 hours of sleep regularly.

Conclusions

- 1. Patients with CLL are living longer than ever before approaching average life expectancy!
- 2. Active surveillance is the recommended plan of treatment for most patients without indications for treatment.
- 3. When patients require treatment, frontline treatment should be tailored to the patient.
- 4. During active surveillance, it is a good time for survivorship care!
 - Remain up-to-date on vaccinations to prevent disease.
 - Establish care/follow-up with primary care team regularly for age-appropriate cancer screening, management of risk factors, and comorbid conditions.

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Thank you!

Questions?



HIGHLIGHTS IN THERAPY FOR CHRONIC LYMPHOCYTIC LEUKEMIA

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

Chat live online:

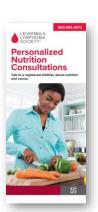
www.LLS.org/InformationSpecialists Monday to Friday, 10 a.m. to 7 p.m. ET

Email: www.LLS.org/ContactUs

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Education Videos

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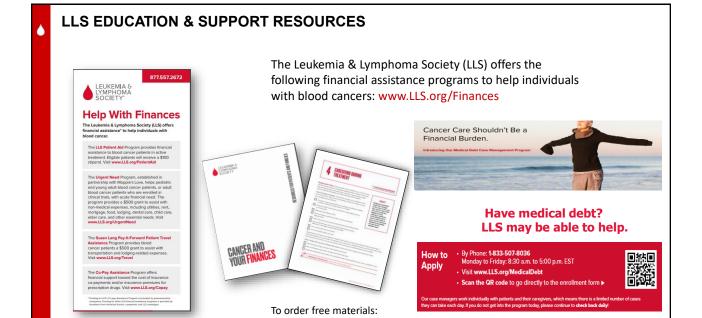
Patient Podcast

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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www.LLS.org/Booklets

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