UPDATES IN CHRONIC LYMPHOCYTIC LEUKEMIA WEBINAR

APRIL 4, 2023

LEUKEMIA & LYMPHOMA SOCIETY®

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WELCOMING REMARKS

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TARGET AUDIENCE

This CE activity is intended for hematologist/oncologists, oncology nurses, social workers, and other healthcare professionals involved in the care of patients with chronic lymphocytic leukemia.

EDUCATIONAL OBJECTIVES

After completing this CE activity, the participant should be better able to:

- Describe the types and subtypes of chronic lymphocytic leukemia (CLL)
- Identify tests used to diagnose disease and monitor treatment
- Explain approved and emerging treatment options for CLL
- Describe strategies to manage treatment side effects as well as long-term and late effects of treatments
- Review vaccination strategies, the impact of COVID-19, and importance of screening for secondary cancers
- Describe the role of the multidisciplinary healthcare team in managing patients with CLL

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CE DESIGNATION

Accreditation, Support and Credit

In support of improving patient care, this activity has been planned and implemented by Medical Learning Institute, Inc., and The Leukemia & Lymphoma Society. Medical Learning Institute, Inc. is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physician Continuing Medical Education

Medical Learning Institute, Inc. (MLI) designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nursing Continuing Professional Development

Approval for nurses has been obtained by the National Office of The Leukemia & Lymphoma Society under Provider Number CEP 5832 to award 1.0 continuing education contact hour through the California Board of Registered Nursing.

Social Worker Continuing Education

The Leukemia & Lymphoma Society (LLS) Provider Number 1105, is approved as an ACE provider to offer social work continuing education by the Association of Social Work Boards (ASWB) Approved Continuing Education (ACE) program. Regulatory boards are the final authority on courses accepted for continuing education credit. ACE provider approval period: 12/10/2020-12/10/2023. Social workers completing this course receive 1.0 clinical continuing education credit.

The Leukemia & Lymphoma Society (LLS) is recognized by the New York State Education Departments State Board for Social Work as an approved provider of continuing education for licensed social workers #0117. LLS maintains responsibility for the program. Social workers will receive 1.0 clinical CE contact hour for this activity.

Nurse Practitioner Credit Designation

This activity is approved for XX contact hour(s) of continuing education (which includes 0.0 hour(s) of pharmacology) by the American Association of Nurse Practitioners®. Activity ID# XXXXXXX. This activity was planned in accordance with AANP Accreditation Standards and Policies.

Interprofessional Continuing Education (IPCE) Statement

This activity was planned by and for the healthcare team, and learners will receive 1.0 Interprofessional Continuing Education (IPCE) credit for learning and change.

Support Statement

There is no commercial support associated with this CE activity.

Providers

This activity is provided by Medical Learning Institute, Inc and The Leukemia & Lymphoma Society.

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METHOD OF PARTICIPATION

There are no fees for participating in or receiving credits for this accredited activity. For information on applicability and acceptance of continuing education credit for this activity, please consult your professional licensing board.

Learners must participate in the entire CE activity and submit the online evaluation form to earn credit at the end of the presentation. Once submitted, the certificate will be generated. If you have questions regarding your certificate, please contact via email at ndane@mlieducation.org.

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FACULTY

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DISCLOSURES

William Wierda, MD, PhD, has a financial interest/relationship or affiliation in the form of:

Research Grant: AbbVie, Inc; Acerta Pharma; Bristol-Myers Squibb; Cyclacel Pharmaceuticals; Genentech, A member of the Roche Group; Gilead Sciences Inc.; Janssen Biotech Inc.; Juno Therapeutics; Kite Pharma; Loxo Oncology Inc.; Oncternal Therapeutics; Pharmacyclics LLC; Sunesis Pharmaceuticals Inc.; Xencor.

Jill Miller, MS, PA-C, has nothing to disclose.

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Planner
Lauren Berger, MPH
The Leukemia & Lymphoma Society

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Advances in Treatments for Patients with CLL/SLL

April, 2023

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Important for Selecting Treatment in CLL

- IGHV mutation status (for first line): **does not change**[1]
- del(17p) status by FISH: **can change**[2]
  - Know % of cells with deletion
- *TP53* mutation status: **can change**[2]
- Age and comorbidities are considerations
- *BTK* and *PLCG2* mutation status (in BTKi treated): **can change**[3]

1. Crombie. Am J Hematol. 2017;92:1393. 2. Chauffaille. Hematol Transfus Cell Ther. 2020;42:261. 3. Hallek. Am J Hematol. 2019;94:1266.

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BTKi- *vs.* BCL-2i-based Treatment

BTK Inhibitor[1-4]

- Easy initiation
- Continuous and indefinite therapy
- Very low TLS risk
- More cardiac risk
- Some favor in del(17p)/ mutated-*TP53*
- Activity in nodal disease

BCL-2 Inhibitor[4,5]

- Risk for TLS requires monitoring for initiation
- Includes CD20 mAb – immunosuppression
- Fixed duration
- GFR sensitivity
- Concern for del(17p)/mutated-*TP53*
- Activity in BM and blood

1. Acalabrutinib PI. 2. Ibrutinib PI. 3. Zanubrutinib PI. 4. Awan. Am Soc Clin Oncol Educ Book. 2020;40:1. 5. Venetoclax PI.

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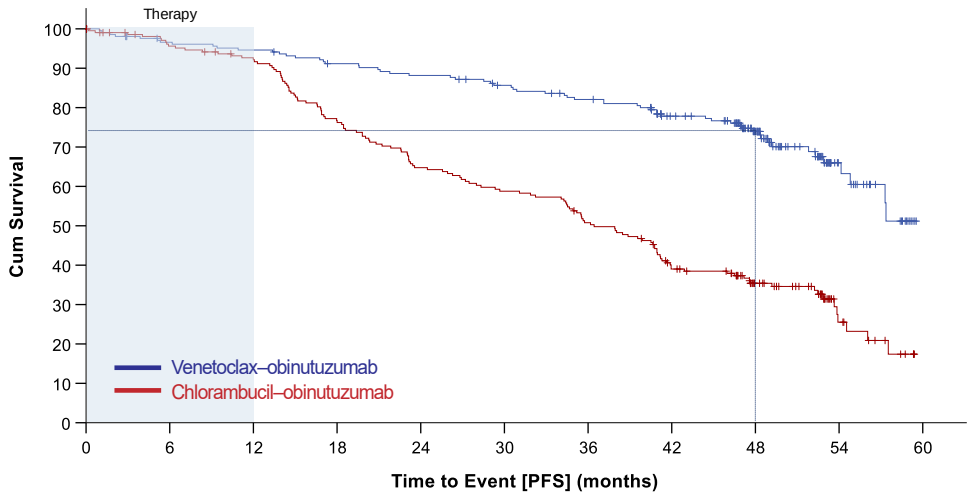
CLL 14: Progression-free Survival

Median observation time 52.4 months



Median PFS
Ven-Obi: not reached
Clb-Obi: 36.4 months

4-year PFS rate
Ven-Obi: 74.0%
Clb-Obi: 35.4%

HR 0.33, 95% CI [0.25-0.45]
P<0.0001

Al-Sawaf et al. EHA 2021, Abstract S146

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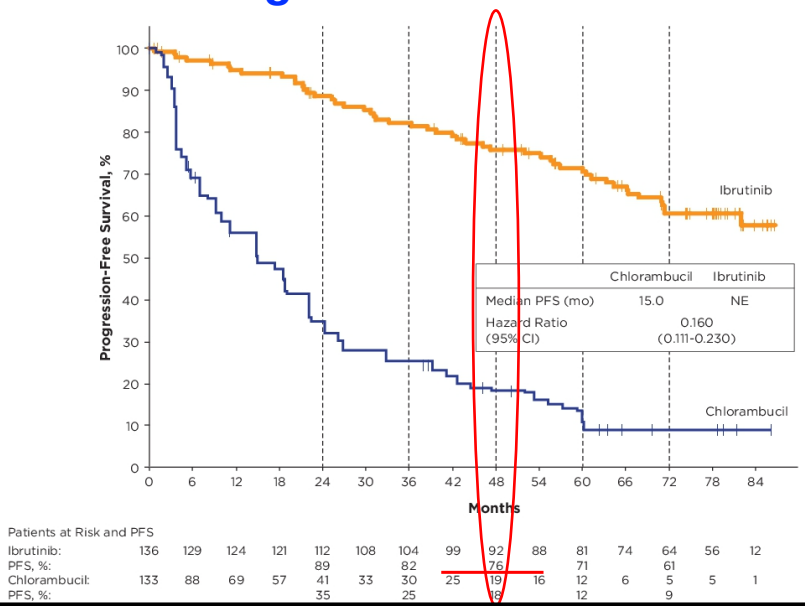
RESONATE-2: First-line, Age >65yrs
Ibrutinib Prolonged PFS Over Chlorambucil



Barr et al. ASCO 2021, Poster 7523

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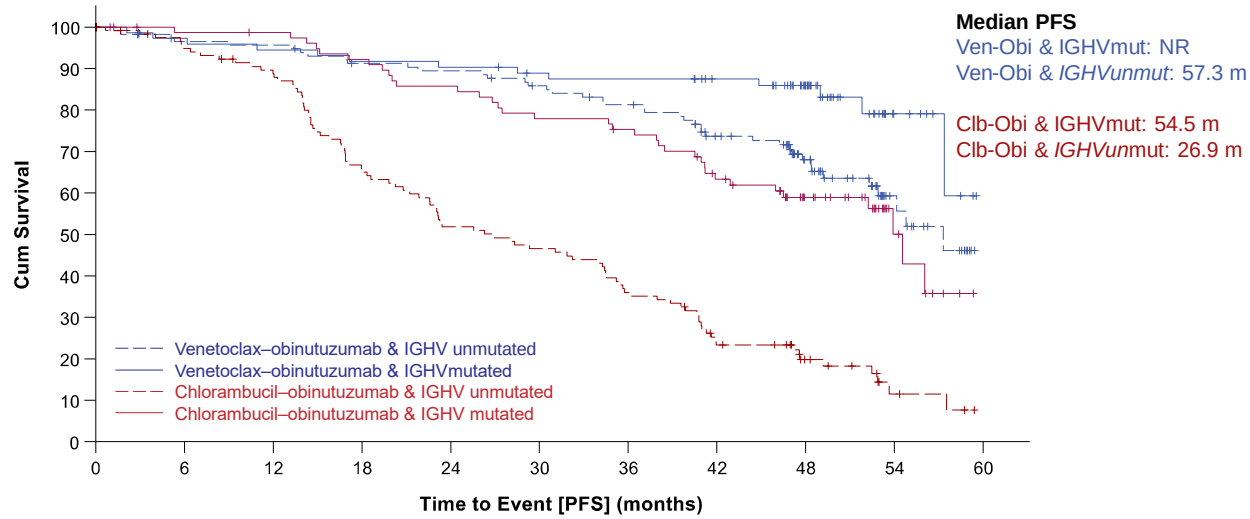
Progression-free Survival – IGHV Status

Median observation time 52.4 months



Al-Sawaf et al. EHA 2021, Abstract S146

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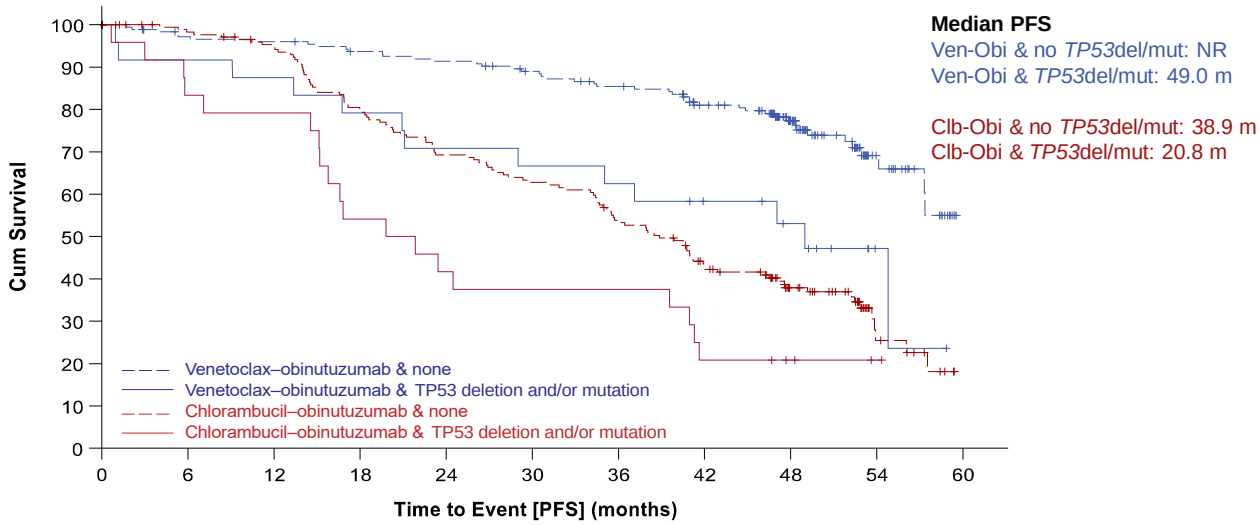
Progression-free Survival – *TP53* Status

Median observation time 52.4 months



Al-Sawaf et al. EHA 2021, Abstract S146

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Predictors of Outcomes with VEN-based Combinations (CLL13/GAIA)

- **Response (ORR and uMRD) for all subgroups; independent association of U-IGHV, *NOTCH1, BRAF/NRAS/KRAS* mutations, hCKT (≥5 abberations), and chromosome translocations with shorter PFS**

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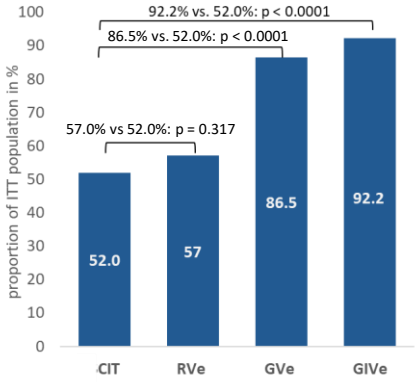
CLL13/GAIA: venetoclax-based treatments vs. CIT in younger/fit patients

Fit patients with untreated CLL: CIRS ≤ 6 & normal CrCl

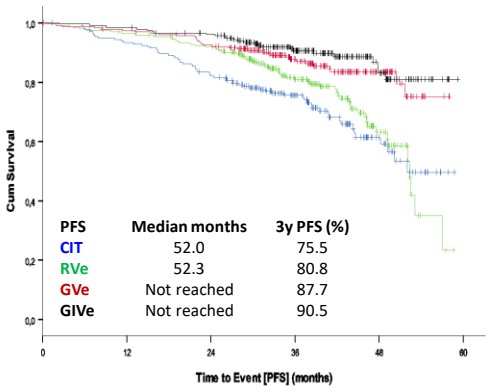
No *TP53* mutation or del(17p) in central screening

- **CIT: FCR/BR*** 6 cycles,n=230
- **RVe** 12 cycles, n=230
- **GVe** 12 cycles, n=230
- **GIVe** 15# cycles, n=230

uMRD (< 10^{-4})
at month 15 in PB by 4-colour-flow



PFS
at median FU of 38.8 months



PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RVe	52.3	80.8
GVe	Not reached	87.7
GIVe	Not reached	90.5

* ≤ 65 years: FCR, > 65 years: BR; [50% FCR / 50% BR]
# continuation of ibrutinib up to cycle 36 if MRD detectable

American Society *of* Hematology

Eichhorst et al, ASH2021 and EHA2022

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GAIA/CLL13: Multivariate analysis for CIT and RVe/GVe/GIVe

Full trial analysis for PFS

	HR	95%CI	p
GVe vs. CIT	0.42	0.27-0.65	<0.001
GIVe vs. CIT	0.33	0.21-0.52	<0.001
U-IGHV	2.43	1.70-3.47	<0.001
CKT	1.98	1.42-2.77	<0.001
Binet B/C vs. A	1.55	1.06-2.27	0.03
NOTCH1mut	1.46	1.05-2.05	0.03

U-IGHV, CKT and *NOTCH1* mutations were independent prognostic factors for CIT and RVe/GVe/GIVe.

RAS/RAF mutations were only prognostic with venetoclax therapy.

CIT for PFS

	HR	95%CI	p
U-IGHV	3.08	1.55-6.12	0.001
>65 years	2.26	1.34-3.83	0.002
NOTCH1mut	2.12	1.16-3.88	0.01
del(11q)	1.89	1.06-3.36	0.03
CKT	1.87	1.06-3.27	0.03

RVe/GVe/GIVe for PFS

	HR	95%CI	p
U-IGHV	1.85	1.20-2.84	0.005
RAS/RAFmut	1.87	1.14-3.06	0.01
CKT	1.66	1.07-2.56	0.02
b2MG>3.5mg/L	1.56	1.03-2.36	0.04
NOTCH1mut	1.54	1.02-2.33	0.04

American Society *of* Hematology

Tausch et al. ASH 2022, Abstract #345

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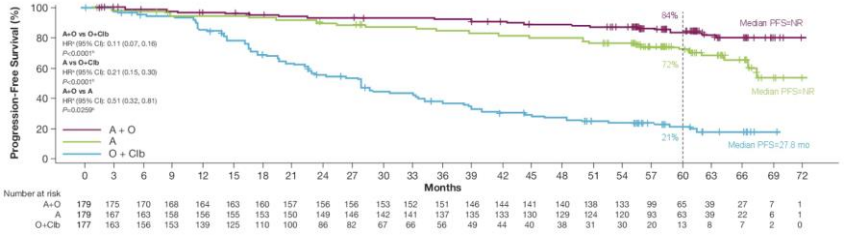
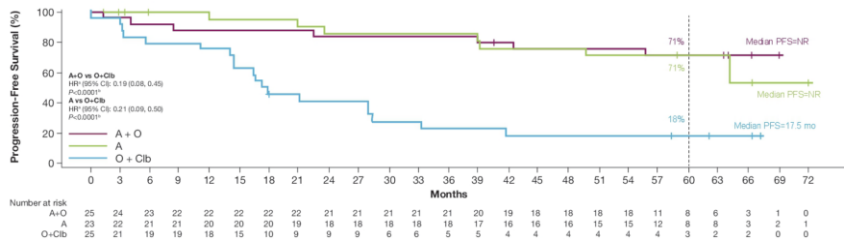
ELEVATE-TN Phase 3 Study: 5-Year Follow-Up PFS

INV-Assessed PFS



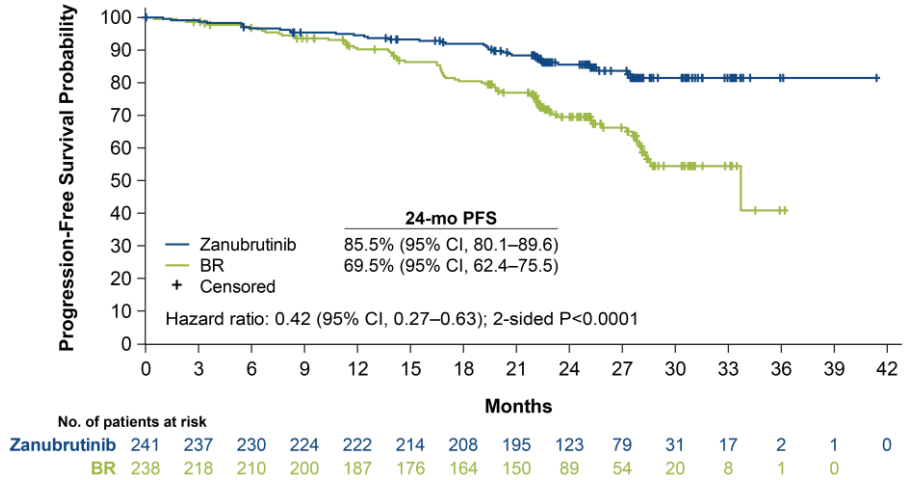
Median follow-up: 58.2 months (range, 0.0-72.0)

INV-Assessed PFS in Patients With del(17p) and/or Mutated *TP53*



Sharman JP, et al. ASCO 2022. Abstract 7539. Sharman JP, et al. EHA 2022. Abstract P666.

SEQUOIA: Progression-Free Survival Per IRC Assessment



BR, bendamustine + rituximab; IRC, independent review committee; PFS, progression-free survival.

American Society of Hematology

Tam, et al. ASH 2021, Abstract #396

First-line Ibrutinib + Venetoclax (MDACC / CAPTIVATE / GLOW / FLAIR)

- Deep remissions with IBR+VEN for most, long remissions for all uMRD (All studies)
- Higher uMRD rate for IGHV-unmutated (MDACC, GLOW, FLAIR)
- Optimal duration of treatment still unclear (longer treatment slow responders?)

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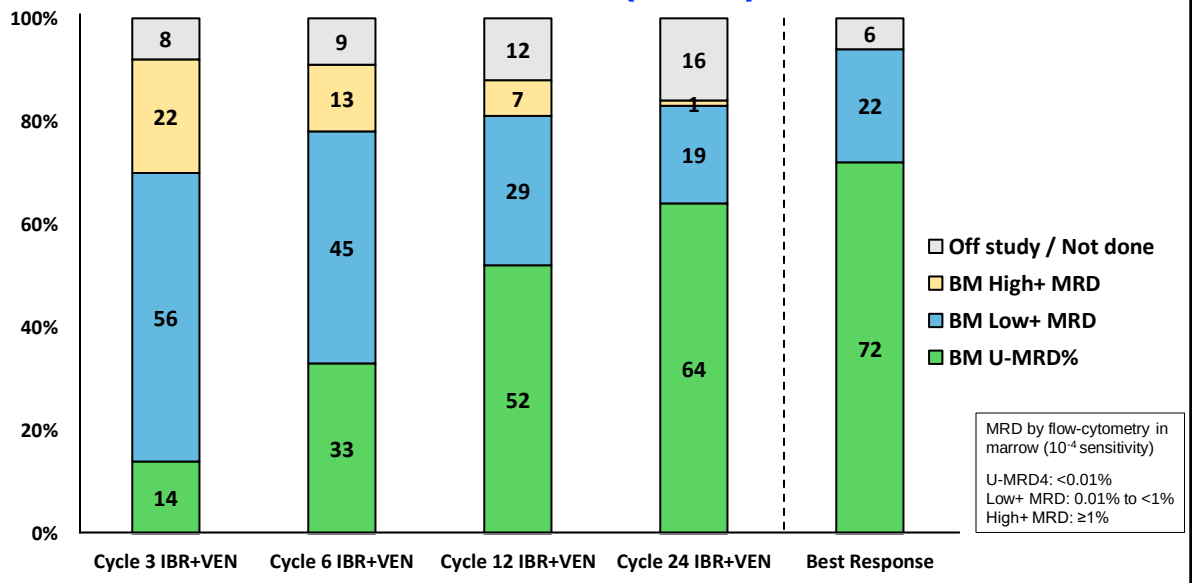
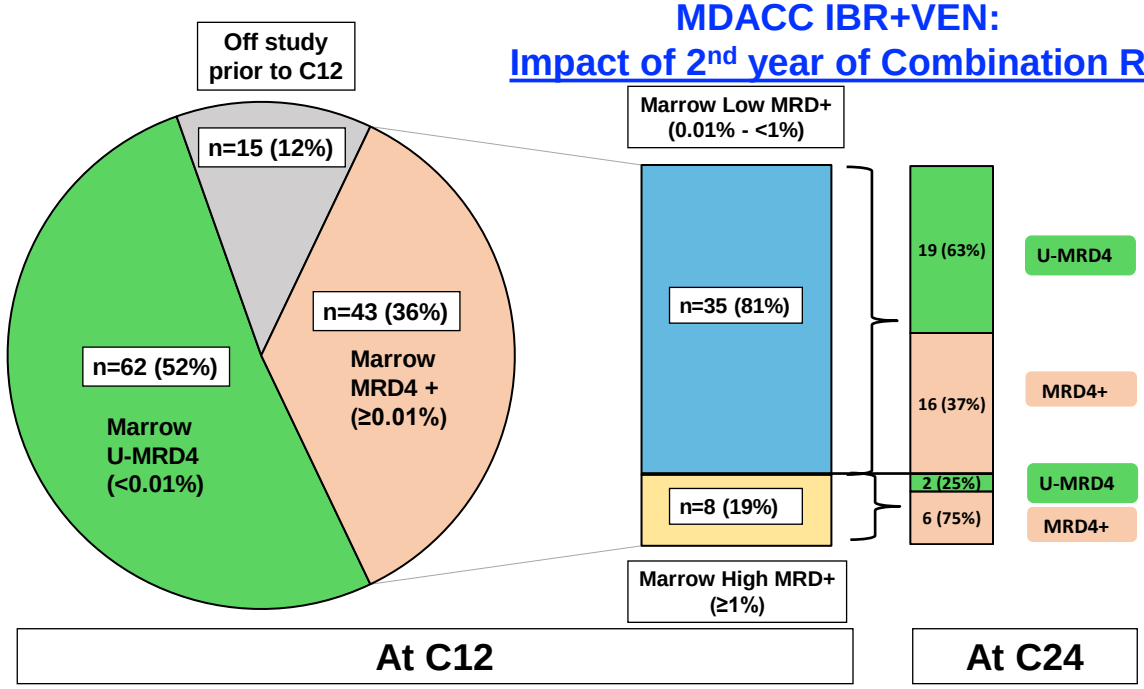
MDACC IBR+VEN: Marrow MRD Response at Serial Time-Points Intent-to-Treat (N=120)



Jain et al. ASH 2022, Abstract #95

22

MDACC IBR+VEN: Impact of 2nd year of Combination Rx



Jain et al. ASH 2022, Abstract #95

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MDACC IBR+VEN: Baseline Variables and U-MRD4 Over Time

	U-MRD at 6 mo IBR+VEN		U-MRD at 12 mo IBR+VEN		U-MRD as best response	
Variables	**Odds ratio**	**P-value**	**Odds ratio**	**P-value**	**Odds ratio**	**P-value**
Age	1	0.91	0.98	0.25	0.98	0.25
IGHV-M	0.41	0.19	0.37	0.09	0.25	0.01
FISH [del(17p) vs others)	0.46	0.29	1.17	0.81	0.65	0.42
Cyto (CK vs others)	0.68	0.53	1.38	0.56	0.97	0.96
Del(17p) / *TP53*-m	0.39	0.08	0.83	0.68	0.56	0.21
SF3B1-m	1.7	0.24	0.77	0.56	1.36	0.55
NOTCH1-m	0.76	0.53	0.62	0.24	1.16	0.75

Jain et al. ASH 2022, Abstract #95

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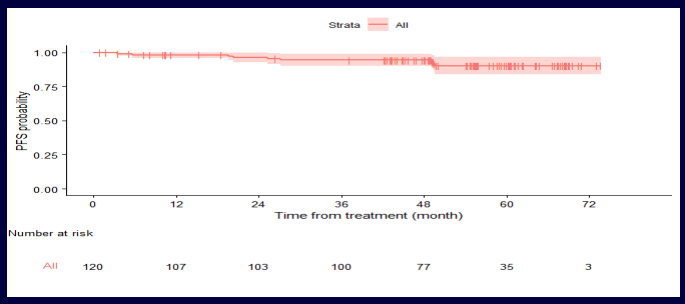
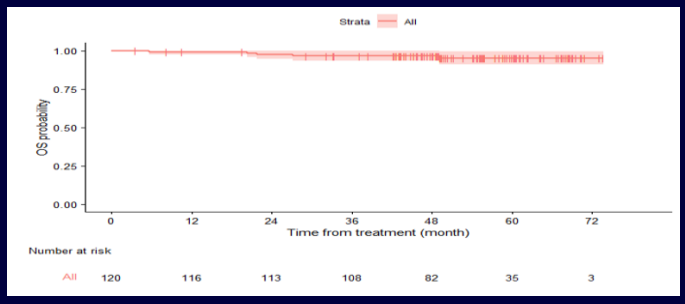
MDACC IBR+VEN: PFS and OS (N=120)



4-year PFS = 94.5%
(95% CI, 90.3-98.9%)



4-year OS = 96.6%
(95% CI, 93.3-99.9%)

Jain et al. ASH 2022, Abstract #95

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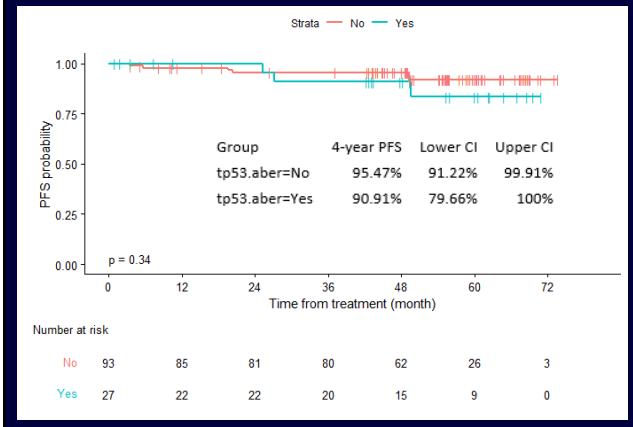
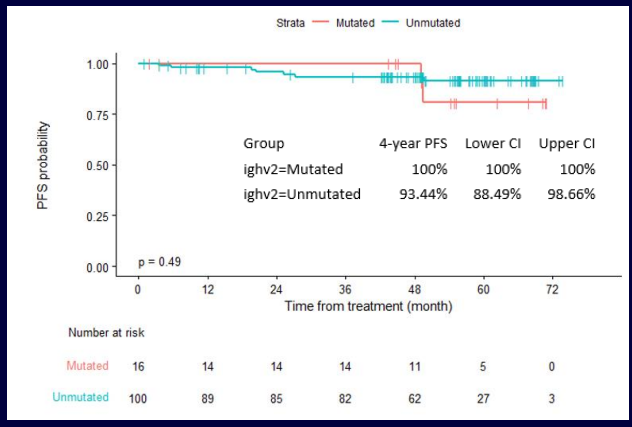
MDACC IBR+VEN: PFS by Genomic Subgroups



TP53 aberrant status



IGHV mutation status

Jain et al. ASH 2022, Abstract #95

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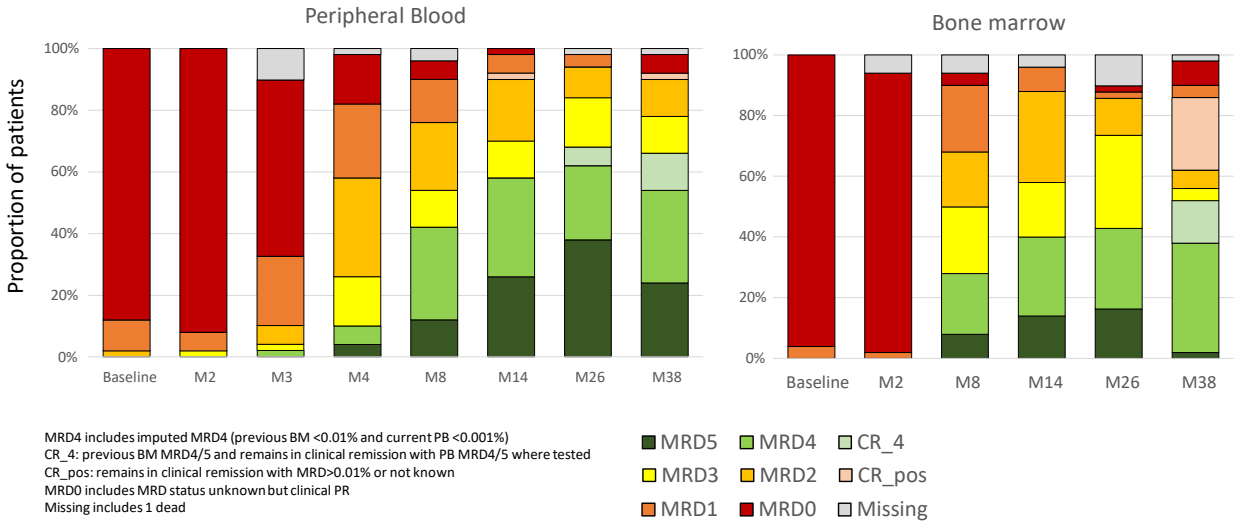
IBR + VEN for R/R CLL
PB and BM MRD responses at various time points



MRD4 includes imputed MRD4 (previous BM <0.01% and current PB <0.001%)
CR_4: previous BM MRD4/5 and remains in clinical remission with PB MRD4/5 where tested
CR_pos: remains in clinical remission with MRD>0.01% or not known
MRD0 includes MRD status unknown but clinical PR
Missing includes 1 dead

Date of data lock: 01-Nov-2022

Munir et al. ASH 2022, Abstract #91

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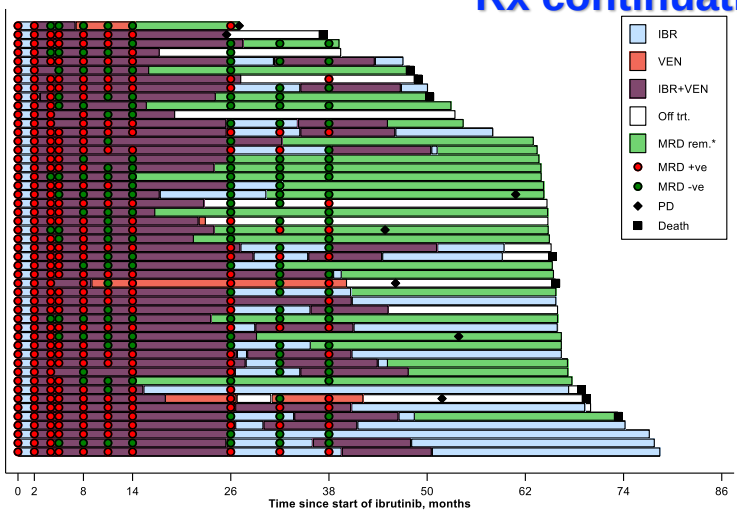
IBR + VEN for R/R CLL
Change in MRD after Rx discontinuation and Rx continuation



* Stopped treatment due to MRD negative remission

- 9 patients continued on ibrutinib after 60 months
- 11 disease progression
- 9 Deaths
- 17 patients continue in uMRD ($<10^{-4}$) after discontinuation at any time point

Date of data lock: 6-Nov-2020

Munir et al. ASH 2022, Abstract #91

Date of data lock: 01-Nov-2022

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Select Ongoing First-line Phase III Clinical Trials

Trial	Subgroup	N	Status*	MRD	Treatment Arms			
GAIA/CLL13 (NCT02950051)	Fit pts	926	Enrolled	Co-Primary	IbrVenOb	VenOb	VenR	FCR/BR
EA9161 (NCT03701282)	Fit, 18-69 yo	720	Enrolled	Secondary	IbrVenOb	IbrOb		
A041702 (NCT03737981)	≥70 yo	454	Enrolled	Secondary	IbrVenOb	IbrOb		
ACE-CL-311 (NCT03836261)	All pts	780	Enrolling	Secondary	AcaVenOb	AcaVen		FCR/BR
CRISTALLO (NCT04285567)	Fit pts [no del(17p)]	165	Enrolling	Primary	VenOb			FCR/BR
CLL17 (NCT04608318)	All pts	897	Enrolling	Secondary	IbrVen	VenOb	Ibr	
GCLLSG (NCT05197192)	High-risk	650	Enrolling	Secondary	AcaVenOb	VenOb		
MAJIC (NCT05057494)	All	600	Enrolling	Secondary	AcaVen	VenOb		

*Status as of September 2022

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Advances in Treatments for Rel / Ref CLL ASH 2022

- **ALPINE: Zanubrutnib superior PFS and ORR over ibrutinib in R/R CLL**
- **Venetoclax consolidation feasible in patients on IBR ≥12 months with potential for clinical benefit (discontinue treatment, long remission)**
- **Pirtobrutinib effective for prior BTKi-treated CLL, including with C481 mutation**
- **BTK-degrader (NX-2127) tolerated with activity – novel mechanism of action**
- **New BCL2 inhibitors (BGB-11417 and Lisaftoclax) have activity and being combined with cBTKi and CD20 mAb**
- **Protein kinase C-beta inhibitor (PKCβi) - MS-553 tolerated with activity in BTKi-treated CLL being evaluated alone and in combinations**

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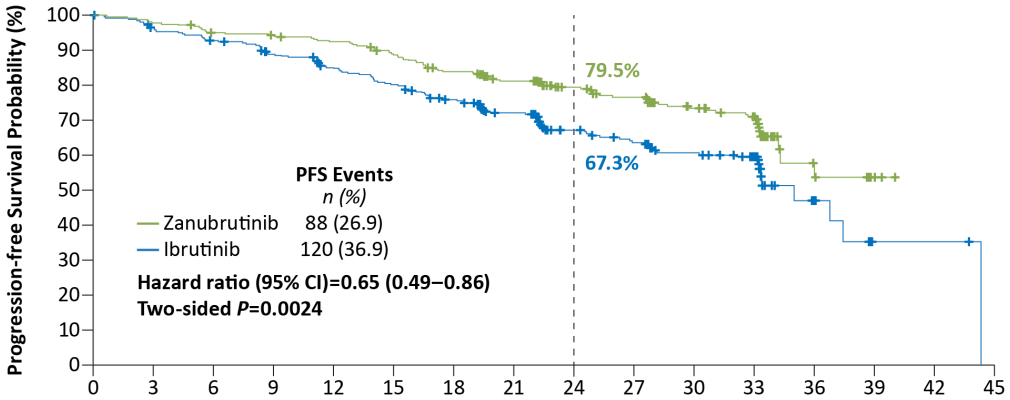
ALPINE: Zanubrutinib PFS by IRC Superior to Ibrutinib

Median study follow-up of 29.6 months



No. at Risk															
Zanubrutinib	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0
Ibrutinib	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2	0

Data cutoff: 8 Aug 2022

American Society of Hematology

Brown et al. ASH 2022, LBA-6

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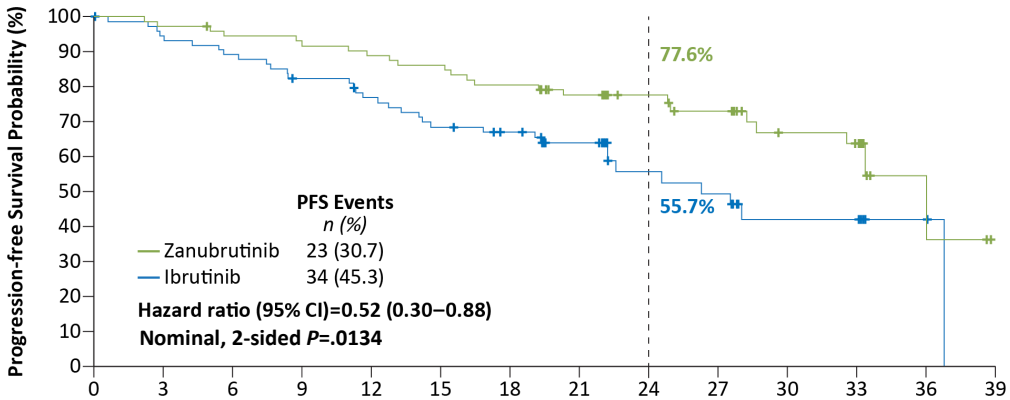
ALPINE: Zanubrutinib Improved PFS in Patients with del(17p)/*TP53*^{mut}



No. at Risk													
Zanubrutinib	75	71	68	67	64	62	58	49	35	30	21	19	3	0
Ibrutinib	75	70	66	60	55	49	45	34	18	16	10	10	2	0

PFS data assessed by IRC

Data cutoff: 8 Aug 2022

American Society of Hematology

Brown et al. ASH 2022, LBA-6

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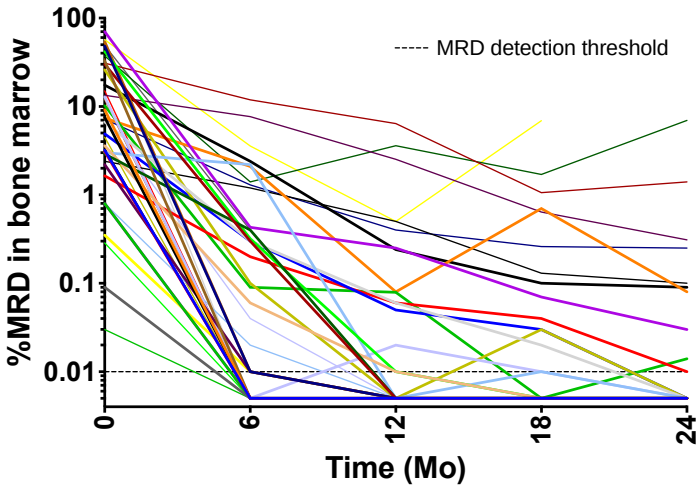
Venetoclax added to ibrutinib in high-risk CLL

MRD results



- **CLL/SLL on IBR ≥12 mo with measurable MRD, no PD, ≥1 high-risk feature:**
  - Del(17p) and/or TP53-m
  - Del(11q)
  - Complex karyotype
  - Elevated B2M
- 17/45 pts (38%) post-C6 and 26/45 (57%) post-C12 achieved U-MRD4.
- 6/16 patients MRD+ at C12 converted to U-MRD4 at C24
- Best cumulative rate of U-MRD4 in bone marrow was 33/45 (73%)
- **32/45 (71%) had U-MRD4 at the completion of venetoclax**

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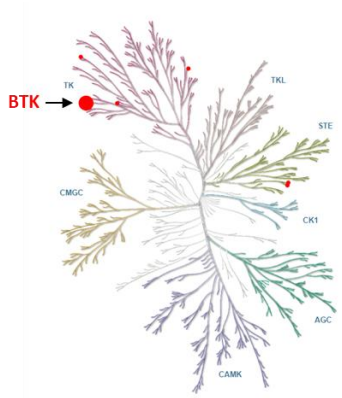
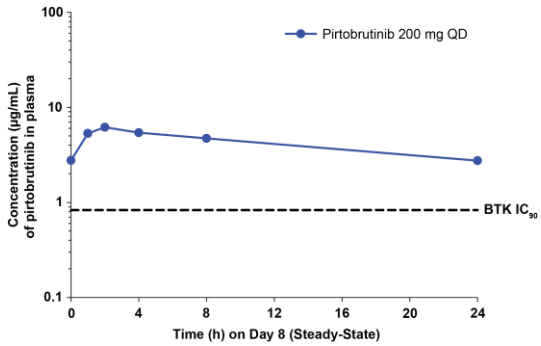
Pirtobrutinib: Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

Highly Selective for BTK[6,7]



Plasma Exposures Exceeded BTK IC_{90} Throughout Dosing Interval



- Inhibits both wildtype and C481-mutant BTK with equal low nM potency, and has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval regardless of intrinsic rate of BTK turnover
- Pirtobrutinib is well tolerated and demonstrates promising efficacy in poor-prognosis B-cell malignancy patients following prior therapy, including prior cBTKi[1]

cBTKi, covalent Bruton tyrosine kinase inhibitor. [6]Mato et al, *Lancet*, 2021:397:892-901. [7]Brandhuber et al. *Clin. Lymphoma Myeloma Leuk*. 2018.18:S216. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

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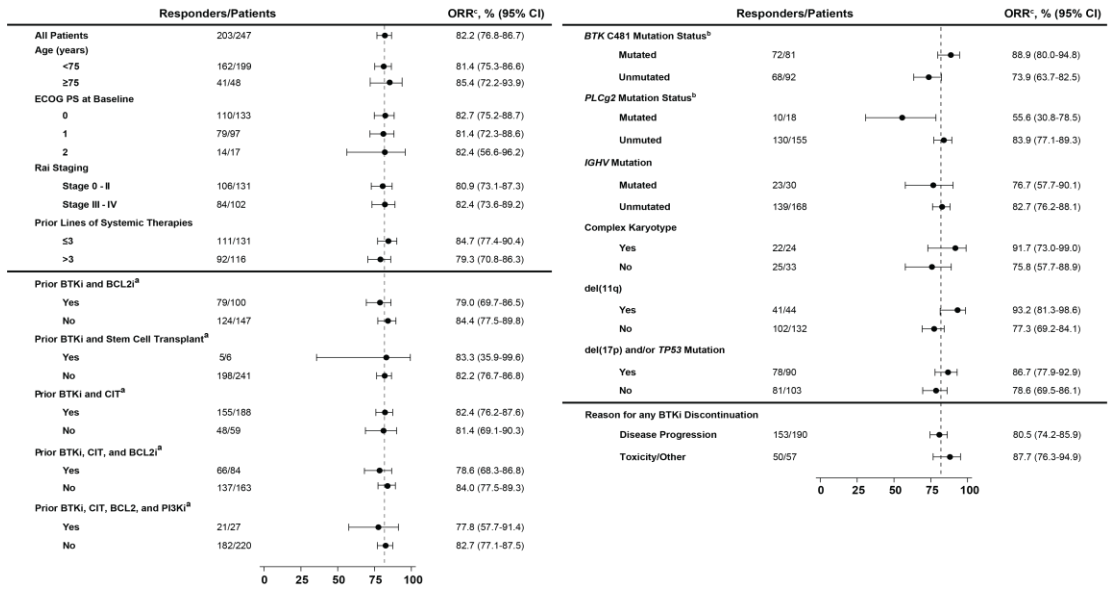
Pirtobrutinib:
Overall Response Rate in CLL/SLL Subgroups



Data cutoff date of 29 July 2022. [a]Prior therapy labels indicate that patients received at least the prior therapy, rows are not mutually exclusive. [b]Patients with available mutation data who progressed on any prior BTKi. [c]Response includes partial response with lymphocytosis. Response status per iwCLL 2018 according to independent review committee assessment.

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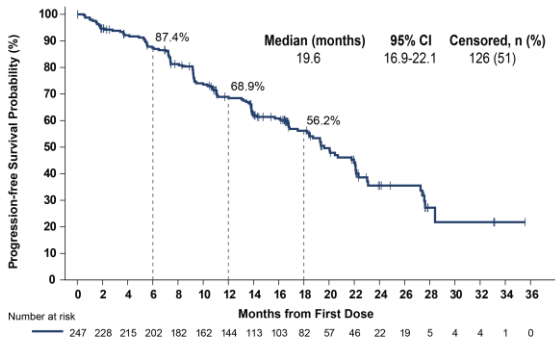
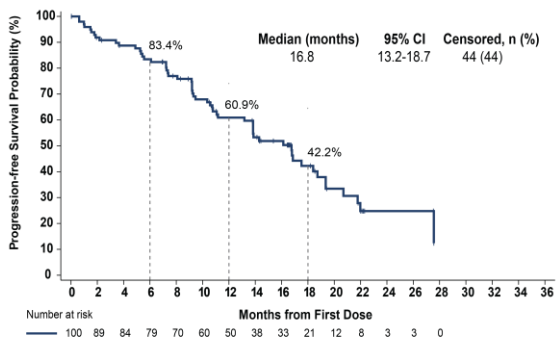
Pirtobrutinib:
Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

All prior BTKi patients
Median prior lines = 3



- Median follow-up of 19.4 months for patients who received prior BTKi

Prior BTKi and BCL2i patients
Median prior lines = 5



- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment.

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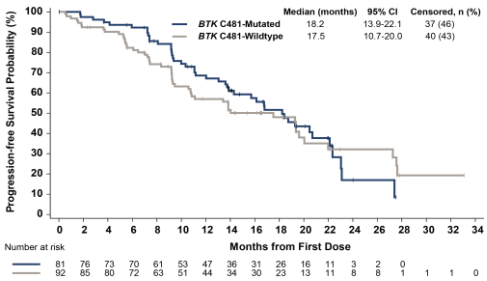
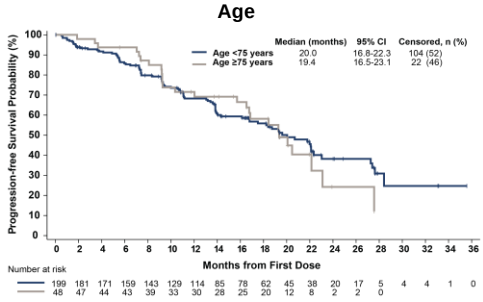
Pirtobrutinib: Progression-Free Survival in CLL/SLL Subgroups

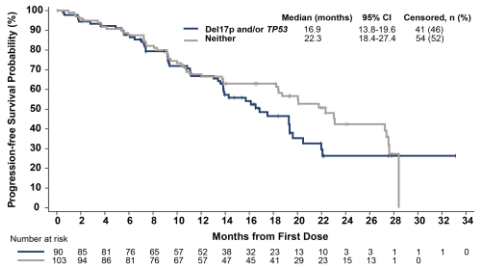
***BTK* C481 mutation status[a,b]**



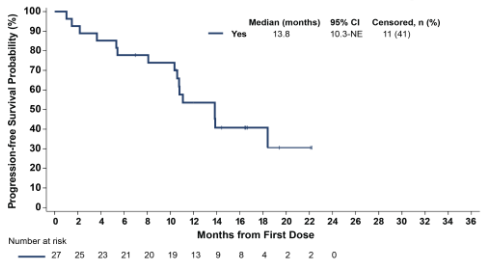
Age



del(17p) and/or *TP53* mutation[a]



Prior BTKi, CIT, BCL2i, and PI3Ki therapy



Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment. [a]*BTK* C481 mutation status, del(17p), and *TP53* mutation status were centrally determined and based on pre-treatment samples. [b]Patients with available mutation data who progressed on any prior BTKi.

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Pirtobrutinib: Safety Profile

	CLL/SLL (n=317)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	31.5%	1.9%	3.5%	0.3%
Neutropenia[a]	32.5%	26.8%	19.6%	14.8%
Diarrhea	26.5%	0.6%	8.8%	0.3%
Contusion	24.3%	0.0%	16.4%	0.0%
Cough	24.3%	0.0%	1.6%	0.0%
Covid-19	24.0%	5.0%	1.6%	0.0%
Nausea	18.9%	0.0%	3.2%	0.0%
Abdominal pain	18.0%	1.6%	2.2%	0.3%
Dyspnea	17.4%	0.9%	0.6%	0.0%
Headache	17.4%	0.6%	5.4%	0.3%
Upper respiratory tract infection	16.4%	0.3%	3.5%	0.0%
Back pain	16.1%	0.9%	0.9%	0.0%
Anemia	15.1%	8.8%	4.7%	2.2%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	30.3%	0.0%	19.6%	0.0%
Rash[d]	17.0%	0.3%	5.7%	0.3%
Arthralgia	18.3%	0.9%	4.1%	0.0%
Hemorrhage/Hematoma[e]	12.3%	2.2%	4.1%	0.9%
Hypertension	14.2%	3.5%	3.8%	0.3%
Atrial fibrillation/flutter[f,g]	3.8%	1.3%	1.3%	0.3%

Median time on treatment for the CLL/SLL safety population was 16.5 months
Discontinuations due to treatment-related AEs occurred in 2.8% (n=9) of CLL/SLL patients
Dose reductions due to treatment-related AEs occurred in 4.7% (n=15) of CLL/SLL patients

Data cutoff date of 29 July 2022. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of 12 total afib/aflutter TEAEs in the CLL/SLL safety population, 3 occurred in patients with a prior medical history of atrial fibrillation.

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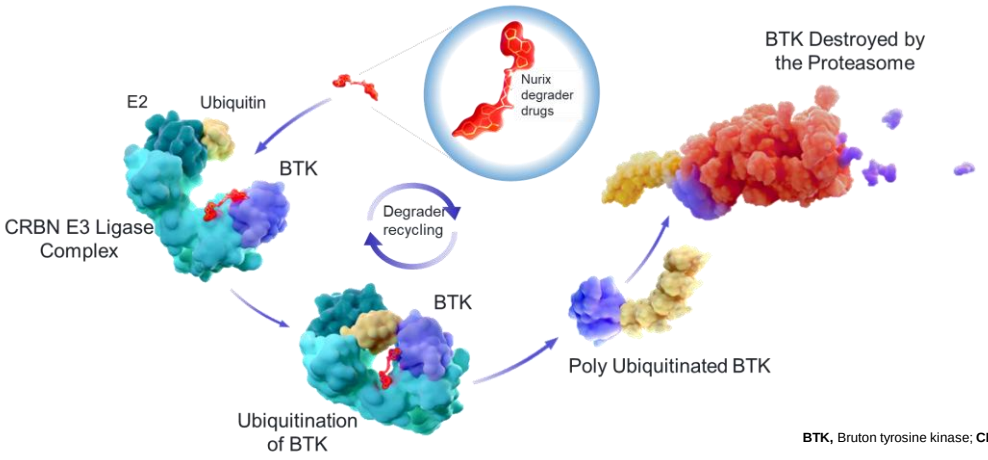
NX-2127: first-in-class targeted protein degrader of BTK

Utilizing the ubiquitin-proteasome pathway to degrade BTK, a well-validated target in B-cell malignancies



BTK, Bruton tyrosine kinase; **CRBN,** cereblon

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NX-2127 safety summary (all participants) by dose

AEs: all grades, n (%)	All doses (n=36)	100 mg* (n=22)	200 mg (n=8)	300 mg (n=6)
Fatigue	19 (53)	13 (59)	5 (63)	1 (17)
Neutropenia[a]	14 (39)	5 (23)	5 (63)	4 (67)
Contusion[b]	10 (28)	4 (18)	3 (38)	3 (50)
Thrombocytopenia[c]	9 (25)	5 (23)	2 (25)	2 (33)
Hypertension	9 (25)	5 (23)	2 (25)	2 (33)
Anemia	8 (22)	6 (27)	2 (25)	0
Constipation	7 (19)	7 (32)	0	0
Dyspnea	7 (19)	4 (18)	3 (38)	0
Pruritis	7 (19)	5 (23)	1 (13)	1 (17)
Atrial fibrillation/Atrial flutter[d]	6 (17)	3 (14)	2 (25)	1 (17)
Diarrhea	6 (17)	5 (23)	1 (13)	0
Petechiae	6 (17)	4 (18)	1 (13)	1 (17)
Rash	6 (17)	5 (23)	1 (13)	0

[a]Aggregate of "neutropenia" and "neutrophil count decreased" [b] Includes episodes of bruising and other similar verbatim terms [c]Aggregate of "thrombocytopenia" and "platelet count decreased" [d]Cases were confounded by risk factors such as: age >80 years (4 cases), history of hypertension (4 cases), male sex (3 cases), and history of prior AF on ibrutinib (2 cases)
*18 of the 22 patients treated at the 100 mg qd dose had CLL

Data cutoff: September 21, 2022

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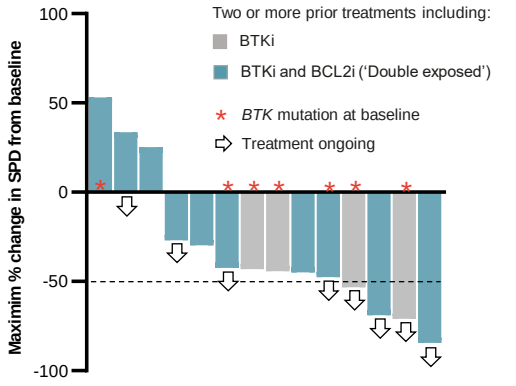
NX-2127 preliminary efficacy (patients with CLL)

Disease-evaluable patients	n=15
Objective response rate,[a] % (95% CI)	33 (12–62)
Best response, n (%)	
CR	0 (0)
PR	5 (33.3)
SD	5 (33.3)
PD	2 (13.3)
NE[b]	3 (20)

[a]Objective response rate includes CR + CRi + nPR + PR-L + PR
[b]Patients who discontinued after a single assessment of SD are considered as NE



***One patient, not shown above, with prior BTKi and BCL2i treatment and with a *BTK* mutation detected at baseline, had no nodal disease at baseline. Their treatment is ongoing with a PR**

BCL2i, B-cell lymphoma-2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **CR**, complete response; **CRi**, complete response with incomplete count recovery; **NE**, not evaluable; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease

Data cutoff: September 21, 2022

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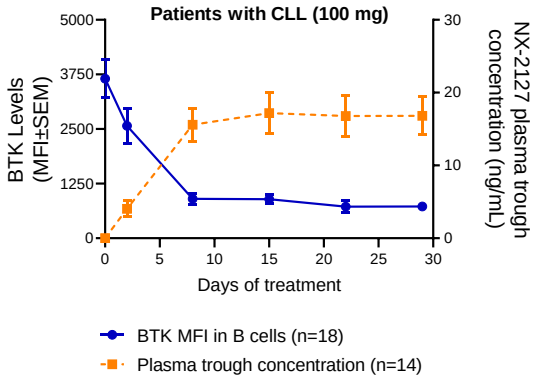
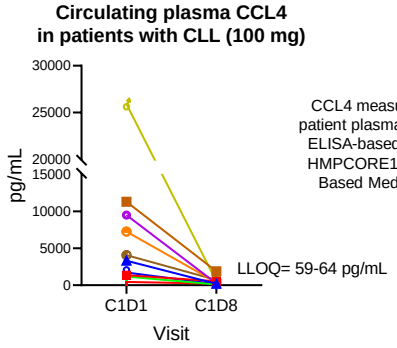
NX-2127 leads to robust BTK degradation and decrease in B-cell activation





- Daily treatment with NX-2127 resulted in a fast and sustained suppression of BTK (CD19+) as measured in patient whole blood using a flow cytometry assay. BTK suppression target of 80% reached consistently (data not shown here)
- Robust decrease of plasma CCL4 by Cycle 1 Day 8 and suppression was maintained through Cycle 2 Day 1, consistent with clinically observed lymphocytosis occurring in majority of patients with nodal disease by Cycle 1 Day 8
- NX-2127 treatment also resulted in degradation of cereblon neo-substrate Ikaros

BTK, Bruton's tyrosine kinase; **CCL4**, C–C motif ligand 4; **LLOQ**, lower limit of quantification

Data cutoff: September 21, 2022

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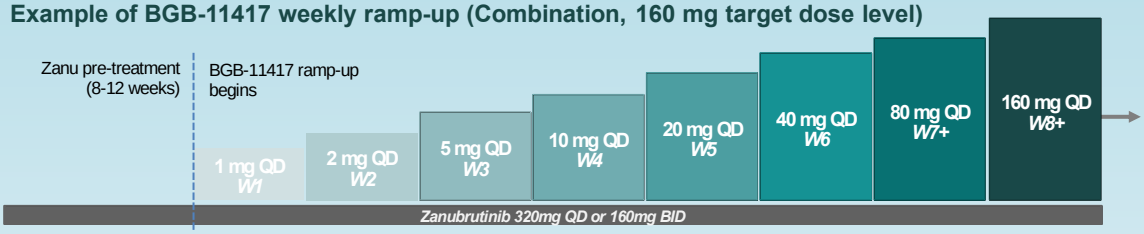
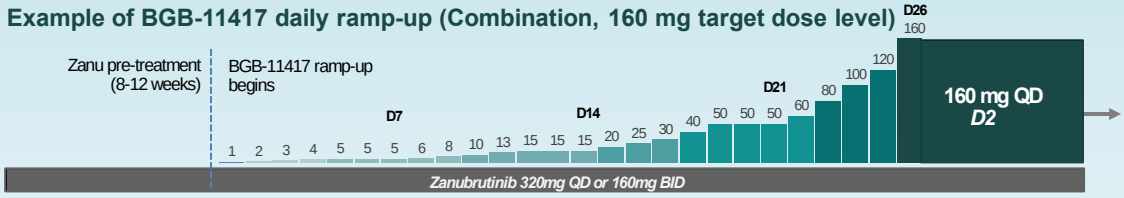
BGB-11417 (BCL2i) + Zanubrutinib: Dose Ramp-Up Schedules

Example of BGB-11417 weekly ramp-up (Combination, 160 mg target dose level)



Example of BGB-11417 daily ramp-up (Combination, 160 mg target dose level)



- TLS prophylaxis included hydration, started 24-48 hrs prior to first dose. Allopurinol started 2-3 days prior to first dose and rasburicase as indicated. Hospitalization for observation was initially required for each new ramp-up dose level for first 3 dose levels but the requirement has been removed per SMC

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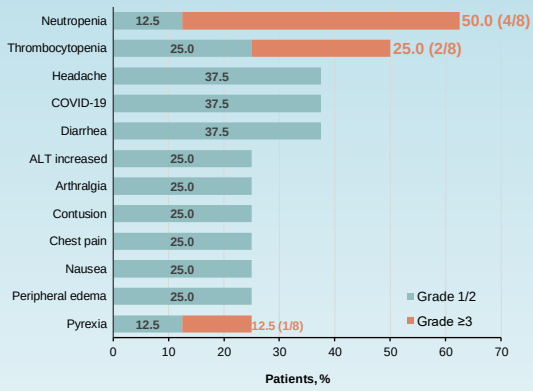
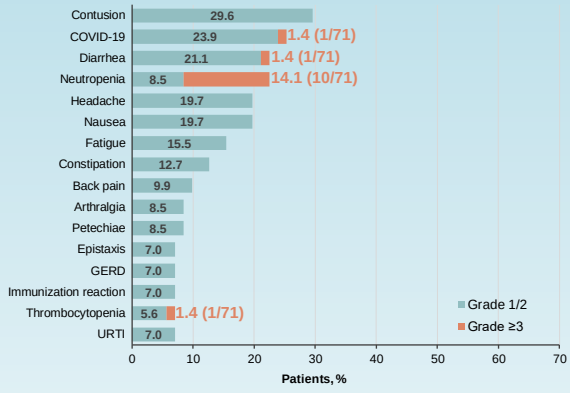
BGB-11417 (BCL2i) ± Zanubrutinib Most Frequent Adverse Events

BGB-11417 Monotherapy, n=8
(Events in ≥2 Patients)



BGB-11417 + Zanubrutinib, n=71[a,b]
(Events in ≥5 Patients)



[a]Includes 21 patients who are still in zanubrutinib pretreatment phase and have not yet received BGB-11417. [b]Includes 46 patients who are TN.

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BGB-11417 (BCL2i) ± Zanubrutinib
Overall Response Rate

Response, n (%)	R/R BGB-11417 (n=8)	R/R BGB-11417 + zanubrutinib (n=25)	TN BGB-11417 + zanubrutinib (n=46)
Treated with BGB-11417	**8**	**24**	**26**
Efficacy evaluable	**6**	**20[a]**	**11[a]**
ORR, n (%)	4 (67)	19 (95)	11 (100)
CR	2 (33)[b]	6 (30)[c]	2 (18)[d]
PR	2 (33)[e]	13 (65)[f]	9 (82)[g]
SD	2 (33)	1 (5)	0
PD	0	0	0
Median follow-up, months (range)	13.4 (1.4-21.9)	11.1 (2.2-18.6)	3.5 (0.4-9.7)

[a]n=2 (R/R) and n=11 (TN) have responded after zanubrutinib pretreatment but have not yet had response assessment on combination treatment: they are not included here. [b]40 mg: n=1; 80 mg: n=1. [c]40 mg: n=1; 80 mg: n=2; 160 mg: n=3. [d]160 mg: n=2. [e]40 mg: n=1; 80 mg: n=1. [f]40 mg: n=2; 80 mg: n=3; 160 mg: n=3 ; 320 mg: n=5. [g]160 mg: n=9.
CR, complete response; ORR, overall response rate; PR, partial response; SD, stable disease.

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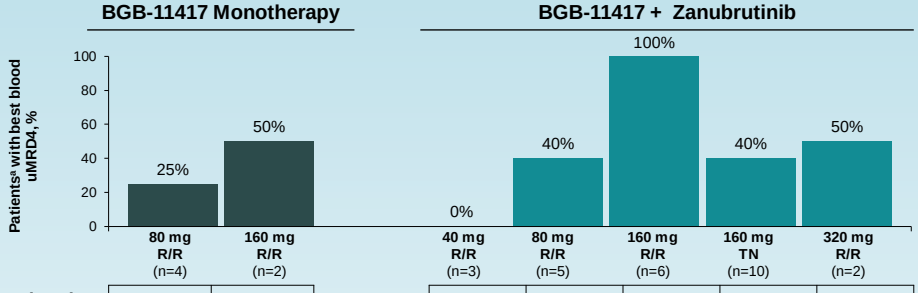
BGB-11417 (BCL2i) ± Zanubrutinib
Blood Minimal Residual Disease

- Blood MRD negativity was observed at **≥80 mg** after **6 months** (mono and combo in R/R CLL/SLL)
- **uMRD rate increased with longer follow-up and higher dose** (160 mg and 320 mg are immature)



	80 mg R/R (n=4)	160 mg R/R (n=2)	40 mg R/R (n=3)	80 mg R/R (n=5)	160 mg R/R (n=6)	160 mg TN (n=10)	320 mg R/R (n=2)
Median treatment duration months, range	**20.2** (15.9-23.8)	**14.3** (13.9-14.7)	**17.1** (16.4-17.8)	**15.0** (10.7-16.3)	**12.1** (9.8-13.7)	**8.2** (5.7-8.6)	**9.3** (9.0-9.5)
Median time to blood uMRD4[b], months, range	**12.2** (12.2-12.2)	**7.4** (7.4-7.4)	**0**	**9.5** (6.7-12.2)	**8.1** (4.6-10.4)	**6.6** (4.9-6.9)	**7.1** (7.1-7.1)

Data cutoff date: 29 October 2022.
MRD was measured by ERIC flow cytometry with 10^{-4} sensitivity. [a]In MRD-evaluable population, which was defined as patients who tested at least 1 postbaseline MRD sample. [b]From BGB-11417 first dose to first blood uMRD4; uMRD4 is defined as CLL cells out of total nucleated cells less than 10^{-4}.

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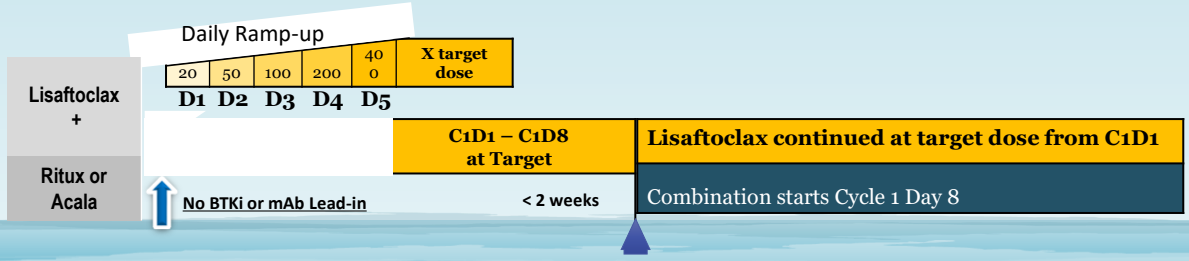
Lisaftoclax (APG-2575) (BCL2i): Daily Ramp-up as Monotherapy and in Combination with Rituximab or Acalabrutinib

Lisaftoclax daily ramp-up to target dose and continued once daily as monotherapy or in combination

Lisaftoclax + combination: lisaftoclax daily ramp-up, combination treatment starts < 2 weeks



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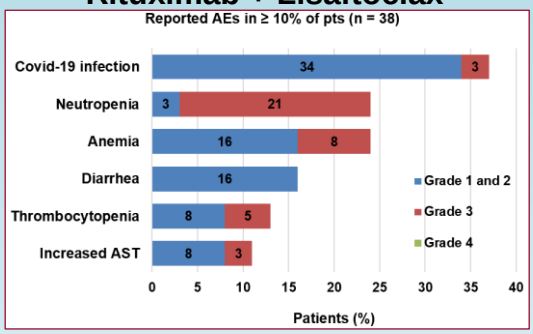
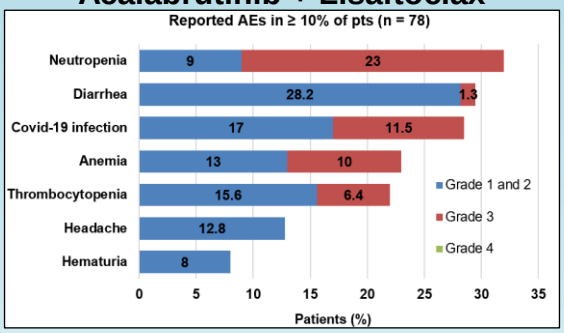
Lisaftoclax Safety: Combinations

Rituximab + Lisaftoclax



Grade 3/4 AEs in ≥ 2% of pts, no. (%)	
Neutropenia	8 (21)
Clinical TLS	1 (2.7)

Acalabrutinib + Lisaftoclax



Grade 3/4 AEs in ≥ 2% of pts, no. (%)	
Neutropenia	18 (23)
Covid-19 infection	9 (11.5)
Atrial fibrillation	3 (3.8)
Abscess	2 (3)

AST, aspartate aminotransferase
TLS, tumor lysis syndrome

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Lisaftoclax: Efficacy Summary

	Monotherapy	Combined with rituximab	Combined with acalabrutinib	
Response Evaluable	**R/R n=43**	**R/R n=34**	**R/R n=57**	**TN n=16**
Median (range) treatment duration	16.5 (1-36)	11 (1-21)	12 (1-24)	7 (5-11)
Overall Response Rate n, (%)	29/43 (67)	27/34 (79)	56/57 (98)	16/16 (100)
Biological Characteristics, no. (%)				
TP53-mutated and/or del(17p)	N/A	5/6 (83)	11/12 (92)	4/4 (100)
Complex karyotype (≥ 3 abnormities)	N/A	5/5 (100)	15/16 (94)	7/7 (100)
Unmutated IGHV	N/A	N/A	23/25 (92)	9/9 (100)
Mutated IGHV	N/A	N/A	13/13 (100)	3/3 (100)
BTKi resistant or intolerant	4/6 (67)	0/4 (0)	7/8 (88)	N/A

Data on iwCLL CR and MRD rates not yet available

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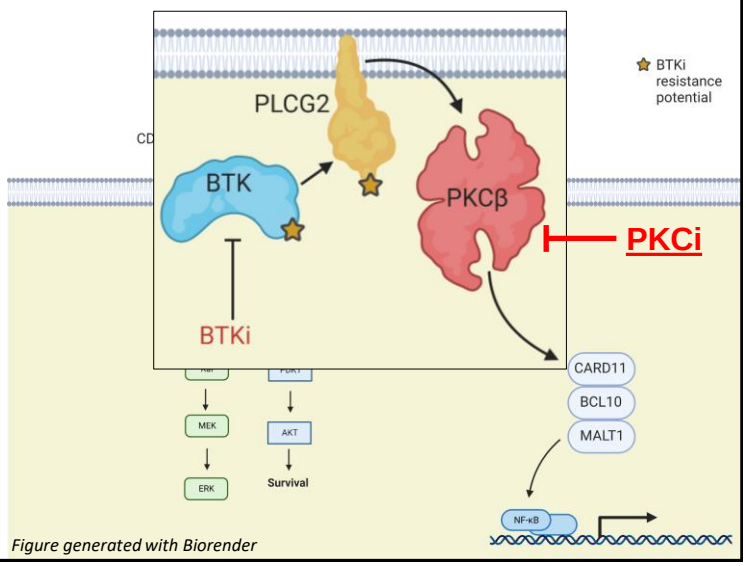
Protein Kinase C-beta Background

Resistance mutations are upstream of PKCβ

Inhibition of PKCβ has potential to overcome mutation-driven resistance



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PKCβi (MS-553)
Safety Profile in Depth

- 14 pts (33%) had Gr 3-4 TR-AE
- One Grade 4 related AE: Neutropenia
- One DLT occurred at 350 mg BID
- MTD was not reached
- **RP2D of 250 mg BID was selected**
- Six patients were dosed at above RP2D with drug withdrawn on 3 patients

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PKCβi (MS-553)
Efficacy

	R/R Mono	
Efficacy evaluable patients*	CLL/SLL N=23	Richter's N=3
Best Response	n(%)	
CR	0	0
PR	6 (26)	1 (33)
PRL	5 (22)	0
SD	11 (48)	0

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* Efficacy evaluable patients are patients who have completed at least one cycle of study drug treatment or had at least one response assessment with data cutoff as of June 20, 2022

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Conclusions

- Combined targeted therapy (BTKi + venetoclax ± CD20 mAb) in first-line results in deep remissions (uMRD) with finite-duration treatment
- Consolidation with venetoclax feasible in patients on IBR ≥12 months with potential clinical benefit
- Pirtobrutinib efficacy in prior BTKi-treated CLL
- BTK-degrader (NX-2127) tolerated with activity
- New BCL2 inhibitors (BCL2i) (BGB-11417 and Lisaftoclax) have activity and being combined with BTKi and CD20 mAb
- Protein kinase C-beta inhibitor (PKCβi) - MS-553 tolerated with activity in BTKi-treated CLL

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Thank you!

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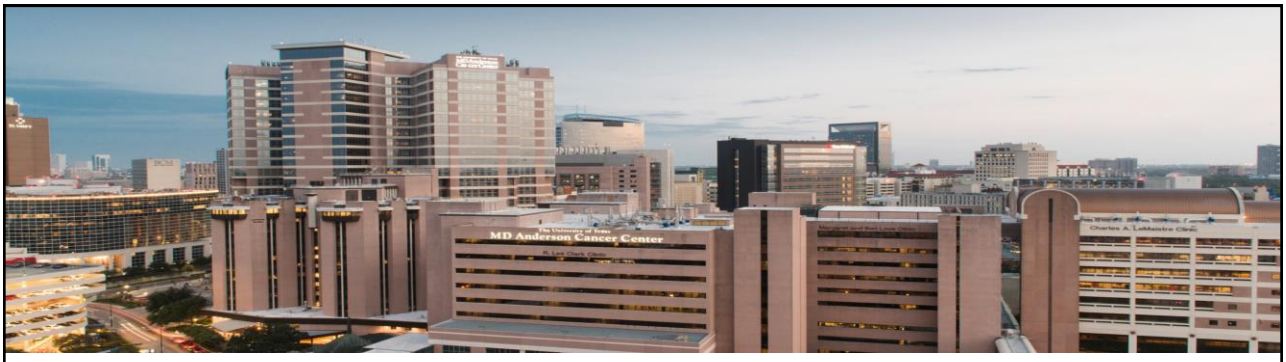

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Supportive Care Strategies for CLL

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Outline

1 MANAGEMENT OF TREATMENT ADVERSE EFFECTS

2 VACCINATIONS

3 SCREENING FOR OTHER CANCERS

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CLL Treatment Adverse Effects

Early education, patient/caregiver engagement, and a multidisciplinary team approach are key for optimal management of treatment-related toxicities.

Infections

- Infection prevention while on treatment
  - Herpes virus prophylaxis (acyclovir or valacyclovir)
  - Consider PJP prophylaxis while on treatment, particularly if using glucocorticoids
  - If neutropenic, consider growth factor support and antibacterial/antifungal coverage
  - Screen for HBV prior to starting anti-CD20 antibody treatment
- Recurrent Sinopulmonary infections – replace IgG if <500 mg/dL
- Vaccinations: stay on top of recommended schedule; consider timing of vaccine doses in relation to treatment plans

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BTKi-Associated Adverse Effects and Management

- Common AEs: GI distress, musculoskeletal pain, rash, fatigue
  - Manage symptoms to optimize compliance
  - Close monitoring during first few months of therapy (labs and symptoms)
  - Follow recommended dose modifications for Gr≥3 Aes
- Rare but serious AEs: Hemorrhage/Bleeding
  - If possible, avoid concomitant anticoagulant or antiplatelet therapy
  - Consider holding BTKi before/after surgery

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BTKi-Associated Adverse Effects and Management

- Atrial fibrillation/flutter (Gr≥3: 3-4% with ibrutinib, 1-2% with acalabrutinib and zanubrutinib)
  - Baseline ECG prior to starting treatment
  - Engage onco-cardiology early and often
  - Use blood thinners WITH CAUTION
  - Manage appropriately; NOT an absolute indication to d/c
  - Avoid CYP3A4 inhibitors
- Hypertension (Gr≥3: 8% with ibrutinib)
  - Monitor regularly (clinic and home)
  - Initiate/adjust antihypertensive therapies as needed

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Venetoclax-Associated Adverse Effects and Management

- Tumor Lysis Syndrome: risk is 2% with 5-week dose escalation and appropriate risk-stratified management
  - Hydration, uric acid reduction (allopurinol or febuxostat; rare: rasburicase)
  - Debulking prior to start of treatment
  - Vigilant lab monitoring (consider hospitalization if med/high risk)
  - Interventions based on results (post-dose lab draw must be early enough for intervention if needed)
- Neutropenia (Gr 3-4: 63%)
  - Monitor CBC regularly
  - Dose modification
  - Growth factor support
- GI distress (nausea, diarrhea)
  - Manage through symptoms
  - Dose modification if necessary

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CD20-Antibody Side Effects and Management

- Infusion-related reactions (obinutuzumab: Gr≥3 20%)
  - Infusion center should have protocol in place for reactions, to include pharmacologic interventions and dose/rate modifications
  - Premedicate with acetaminophen, antihistamine, glucocorticoid (can de-escalate with subsequent doses)
- TLS
  - Uric acid reduction
  - Hydration - po/IV fluids
  - Laboratory monitoring

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CD20-Antibody Side Effects and Management

- HBV reactivation (1%)
  - Screen for HBV prior to treatment
  - Consider antiviral therapy if positive (consult ID); consider postponing treatment until viral load is negative
- Black box warning: PML (progressive multifocal leukoencephalopathy)
  - Progressive, usually fatal, demyelinating CNS infection
  - Caused by reactivation of polyoma JC virus

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Vaccinations

Myth v. Fact

- People with CLL should not receive any vaccinations, ever. MYTH!!!
- People with CLL don't respond as well to vaccinations. FACT!!!
- People with CLL shouldn't receive vaccinations while in the middle of chemo/immunotherapy. FACT!!!
- Vaccines can give you the infection you're trying to prevent (flu/Covid). MYTH!!!

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CLL patients should NEVER receive a live/attenuated vaccine. These include:

- MMR
- Rotavirus
- Smallpox
- Varicella
- Yellow fever
- Zostavax (Zoster)
- FluMist (nasal flu vaccine)

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Recommended Vaccinations (adults 19-64 with CLL)

- Influenza (annually)
- Covid (annually??)
- Pneumococcal (new vaccines now available)
- Herpes Zoster (Shingrix x2)
- Td booster (every 10 years)
- Hib (HSCT only)

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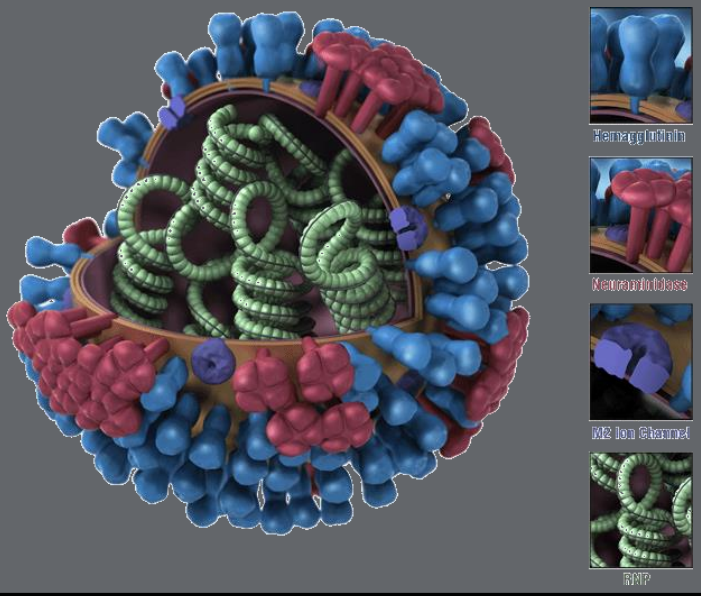
Vaccinations: Influenza



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Vaccinations: Influenza

Types of Flu Vaccines

- Inactivated or recombinant are safe and effective.
  - Flublok Quadrivalent (recombinant): only egg-free vaccine
  - Fluzone Quadrivalent: inactivated, protects against 2 Flu A and 2 Flu B viruses
  - Fluad Quadrivalent: inactivated with an adjuvant (MF59) to enhance immune response; approved for >65
- Live attenuated (or weakened; aka nasal spray/FluMist) is NOT safe for CLL patients.

Regular v. High Dose

- Fluzone High Dose Quadrivalent (inactivated); contains 4x the antigen of standard-dose; approved for >65

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Vaccinations: Influenza

- Vaccinate by end of October each year.
- Don't vaccinate during an acute infection.
- If possible, don't vaccinate in the middle of treatment.
- It takes 2 weeks for antibodies to develop.
- No proven benefit to getting a "booster" mid-season.
- CDC has no official recommendation of one vaccine over another.

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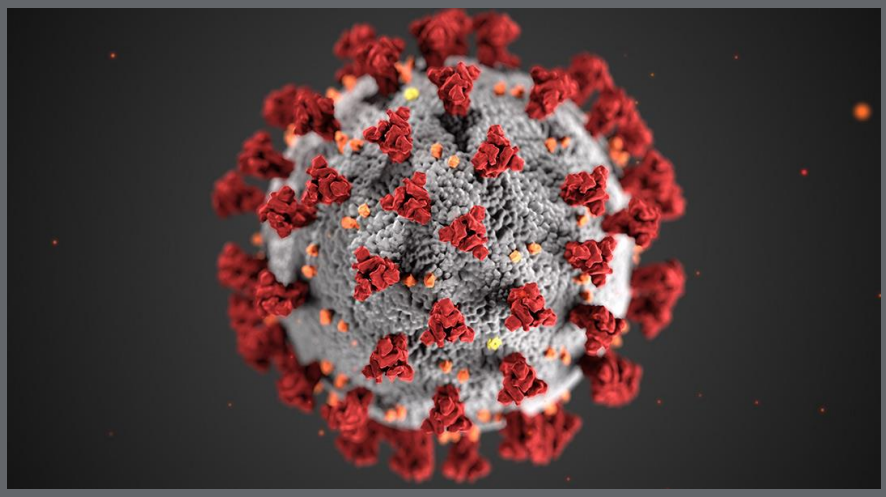
Vaccinations: COVID-19



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COVID-19 vaccination – YES, we are still recommending it for our patients!!!

Protective response rate may be lower in CLL, regardless of treatment status, but especially those receiving CD20 antibody or on B-cell pathway inhibitors. Vaccine response rates improve with boosting. T cell activation by vaccination enhances viral clearance and minimizes severity of symptoms.

- **Moderna or Pfizer**: 3 primary doses (3-4 weeks apart), followed by bivalent booster dose at least 8 weeks following primary series.
- **Novavax**: 2 primary doses (3 weeks apart), followed by bivalent booster at least 8 weeks later.
- **Janssen**: if received J&J vaccine initially, should receive a second dose with monovalent mRNA vaccine (at least 4 weeks later), then bivalent booster at least 8 weeks later.

Bivalent booster: combines ancestral strain that originated in Wuhan, China, plus Omicron strains BA.4 and BA.5 (circulating in late summer 2022)

What about Evusheld??

As of Jan 26, 2023, Evusheld is no longer authorized for use in US as current SARS-CoV-2 variants are resistant.

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Vaccinations: Pneumococcus

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Vaccinations: Pneumococcus

Protects against infection with ***Streptococcus pneumoniae,*** a significant human pathogenic bacterium.

- Pneumococcal polysaccharide (PPSV23; Pneumovax 23); since 1983 – protection wanes over 5-6 years (induces immune response via release of immunoglobulins from B cells)
- Pneumococcal conjugate vaccine (PCV13; Prevnar 13); since 2010 (T cell-dependent mechanism, resulting in durable memory B cell formation)
- Pneumococcal conjugate vaccine 15 (PCV15; Vaxneuvance); approved 2021; effective against same 13 serotypes as PCV13.
- Pneumococcal conjugate vaccine 20 (PCV20; Prevnar 20); approved 2021; effective against all serotypes of PCV13 and 6 of 7 serotypes in PPSV23.

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Pneumococcal Recommendations for Immunocompromised Adults ("simplified" by ACIP in 10/2021)

- If no prior h/o pneumococcal vaccination (or is unknown) – give either PCV15 or PCV20 (if PCV15, give PPSV23 at least 8 weeks later)
- If ONLY received PPSV23 previously – give either PCV15 or PCV20 (if PCV15, then repeat PPSV23 in 5 years up to 3 doses [but no 3rd dose if 2nd dose was given >age 65])
- If ONLY received PCV13 previously – give PCV20 at least 1 year later (or can give PPSV23 at least 8 wks later, then repeat every 5 years up to 3 doses)
- If received BOTH PCV13 and PPSV23 previously – give PCV20 at least 5 yrs after last pneumococcal vaccine
- *CLEAR AS MUD???*

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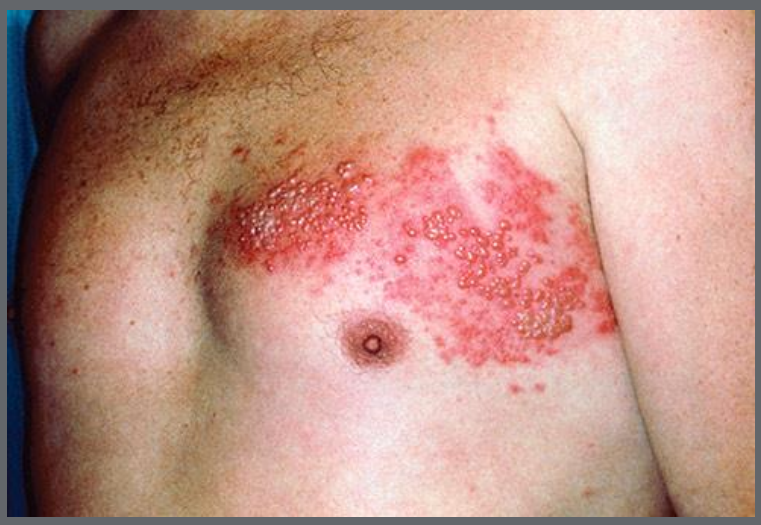
Vaccinations: Herpes Zoster



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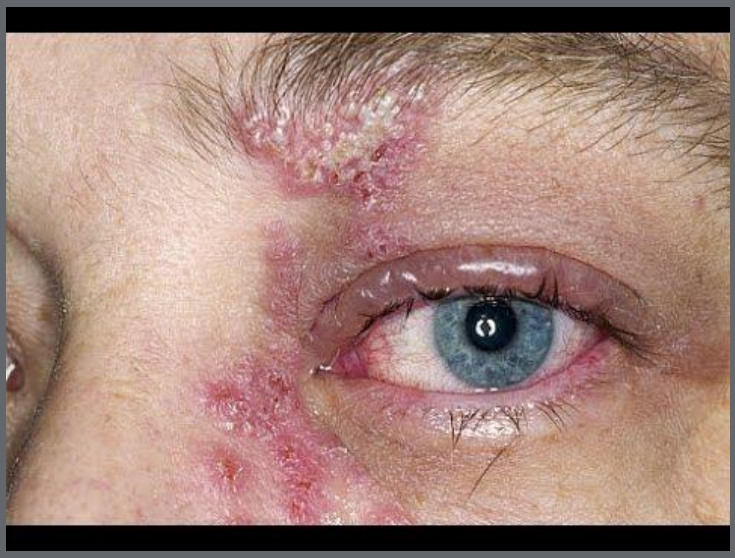

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Vaccinations: Herpes Zoster/Shingles

- Nearly 1/3 of Americans will develop shingles in their lifetime.
- Any type of cancer is associated with a 40% increased risk of developing shingles.
- Blood cancers had the highest risk: **≥3 times that of those without cancer**.
- Shingles infection can be seen as a marker of underlying malignancy.

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Vaccinations: Herpes Zoster/Shingles

- Painful, blistering rash; occurs unilaterally, following "dermatomal" (underlying nerve) distribution pattern.
- Results from reactivation of varicella-zoster virus from deep nerve roots.
- 10-13% of those who develop shingles will get post-herpetic neuralgia (PNH), lasting weeks to years following infection.

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Vaccinations: Herpes Zoster

Shingrix (Recombinant Zoster Vaccine; RZV)

- Approved in 2017; recommended for immunocompetent adults 50 and older.
- Safer and more effective than Zostavax (ZVL); recommended regardless of prior Zostavax vaccination.
- Pooled efficacy of 2 large trials: 92% effective in preventing shingles
- Antibody response in CLL patients may be slightly less for both treatment naïve and those on BTKi.

Administration

- Requires 2 doses, 2-6 months apart
- Can receive at same time as flu or pneumococcal vaccinations
- Should not be given during acute shingles infection
- No need to screen for prior varicella exposure

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Vaccinations: Tetanus and Hib

Tetanus/diphtheria booster every 10 years.

Haemophilus influenzae type B: only post-SCT

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Cancer Screening

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Cancer Screening

According to ACS, patients with CLL are at higher risk of skin cancer (all types), as well as cancers of larynx, lung, colon and soft tissue sarcoma. Following treatment with chemoimmunotherapy, risk of secondary MDS/AML is 5-6%.

Skin cancer

Annual skin exams with a dermatologist

Breast cancer

Annual MMGs for women 45-54; every 2 years 55 and older

Colorectal cancer

Colonoscopy every 5-10 years (depending on risk and history)

Lung cancer

Low-dose CT scan recommended age 55-74 with 30-pk-yr history of smoking.

Prostate cancer

PSA and physical exam

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Contact

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FREE LLS RESOURCES FOR HEALTHCARE PROVIDERS

- CME & CE courses: www.LLS.org/CE
- Fact Sheets for HCPs: www.LLS.org/HCPbooklets
- Videos for HCPs: www.LLS.org/HCPvideos
- Podcast series for HCPs: www.LLS.org/HCPpodcast

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FREE LLS RESOURCES FOR PATIENTS

- **Information Specialists** – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges (IRC).

- **Clinical Trial Nurse Navigators** – RNs provide personalized service for patients seeking treatment in a clinical trial, sift through information and provide information to bring back to their HC team (CTSC).
  - www.LLS.org/CTSC

- **Registered Dieticians** – (LLS) provides PearlPoint Nutrition Services® to patients/caregivers of all cancer types, free nutrition education and one-on-one consultations by phone or email.
  - www.LLS.org/nutrition

- **Reach out Monday–Friday, 9 am to 9 pm ET**
  - Phone: (800) 955-4572
  - Live chat: www.LLS.org/IRC
  - Email: infocenter@LLS.org
  - HCP Patient Referral Form: www.LLS.org/HCPreferral

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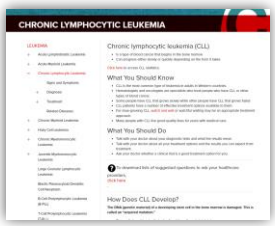
FREE LLS RESOURCES FOR PATIENTS

- **Webcasts, Videos, Podcasts, Booklets**:
  - www.LLS.org/Webcasts
  - www.LLS.org/EducationVideos
  - www.LLS.org/Podcast
  - www.LLS.org/Booklets



- **https://www.LLS.org/leukemia/chronic-lymphocytic-leukemia**
- **Support Resources**
  - Financial Assistance: www.LLS.org/Finances
    - Urgent Need
    - Patient Aid
    - Travel Assistance
  - Other Support: www.LLS.org/Support
    - LLS Regions
    - Online Weekly Chats Facilitated by Oncology SW
    - LLS Community Social Media Platform
    - First Connection Peer to Peer Program

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FREE LLS RESOURCES FOR YOUR PATIENTS

BOOKLETS AND FACT SHEETS

English – www.LLS.org/Booklets
Spanish – www.LLS.org/Materials

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Q & A

Ask a question by web:

- Click “Ask a question”
- Type your question
- Click “Submit”

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THANK YOU!

INSTRUCTIONS FOR CREDIT

Participants must complete the evaluation to receive credit. After completing this process, your certificate will automatically generate.

For questions or concerns, please contact Profeducation@LLS.org

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