CLL and Frontline Therapies

James Davis, PharmD, BCOP
Assistant Professor – MUSC College of Pharmacy
Clinical Pharmacist – MUSC Hollings Cancer Center
Email: Davisjaa@musc.edu
@thisisJamesD

Disclosure of Conflicts of Interest

James Davis, PharmD, BCOP has no relevant financial relationships to disclose.

Exploring Upfront Treatment Options in CLL

Objectives

Upon completion of this program, participants will be able to:

- Examine the different prognostic markers in chronic lymphocytic leukemia (CLL) and their influence on therapy selection.
- Explore appropriate treatment strategies for CLL based on patient specific factors, safety, and efficacy data.
- Review treatment implications for CLL patients in the COVID-19 era

Patient Case

LH is a 65yo female who is referred to her oncologist for WBC of 125k and PLT 75k with pronounced fatigue and night sweats. She has a PMH of DMII, CKD, GERD, and poorly controlled HTN. Pathology confirms CLL diagnosis and cytogenetic analysis reveals a 17p deletion. She reports medication compliance to metformin, lisinopril, omeprazole, and carvedilol.

What considerations should be made regarding upfront CLL treatment?

Overview

Indolent

Slow growing leukemia/lymphoma

Mature B-cell

Accumulation of clonal B cells in peripheral blood, bone marrow, and/or lymphoid tissues

Symptoms

Many are asymptomatic

Others: B-symptoms, cytopenias, painful adenopathy, organ dysfunction

Incidence

More common in Western countries

Estimated 20,160 new cases and 4,410 new deaths in 2022

Goals

- Prolong survival
- Disease control
- Quality of life
- Incurable

Hallek M. *Am J Hematol*. 2019;94:1266-1287; Hallek M, et al. *Blood*. 2008;111:5446-5456; Brenner H, et al. *Blood*. 2008;111:4916-4921; Maddocks KJ, et al. *J Hematol Oncol.* 2009;2:29; SEER Cancer Stat Facts. Chronic lymphocytic leukemia. seer.cancer.gov/statfacts/html/clyl.html Accessed April 18, 2022.

Disease Staging and Prognostic Factors

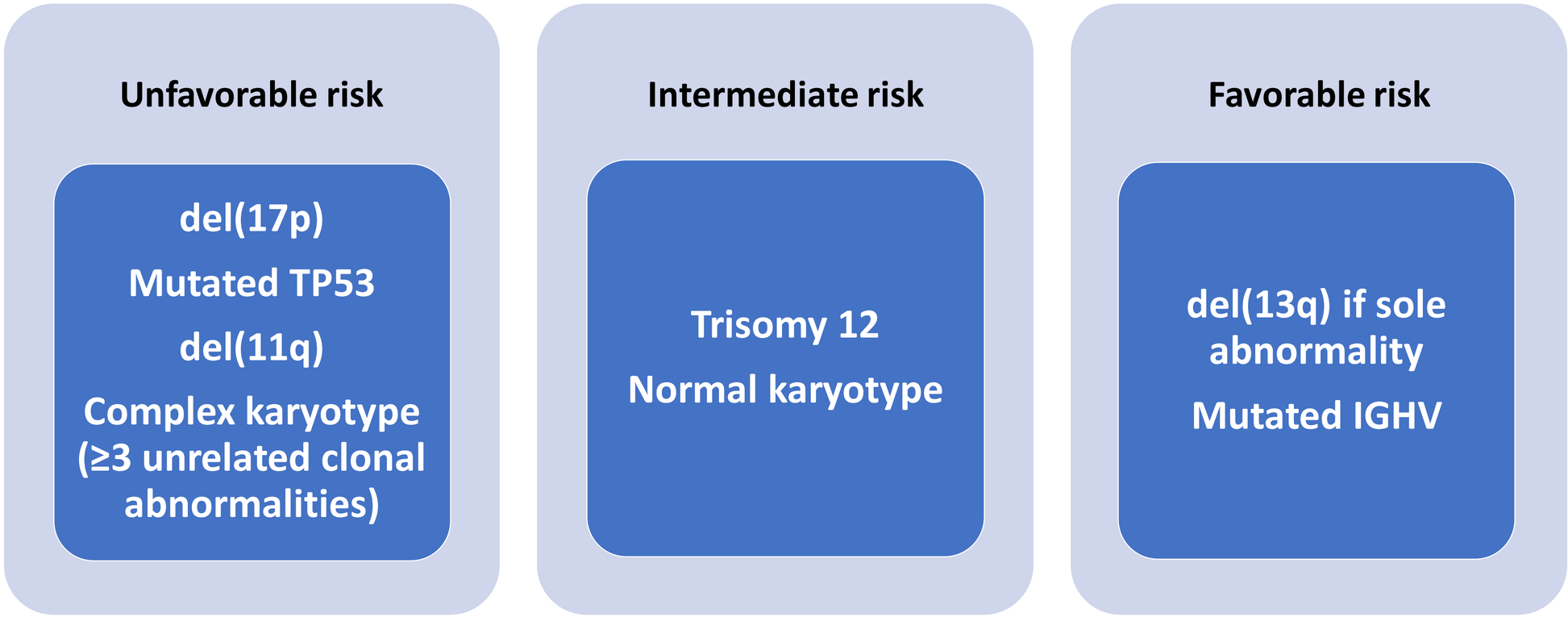
- SLL and CLL considered the same B-cell malignancy
  - CLL: ≥5000 clonal lymphocytes in peripheral blood
  - SLL: presence of lymphadenopathy and/or splenomegaly and <5000 clonal lymphocytes in peripheral blood
- Staging: Rai or Binet staging
- International Prognostic Index: Stratifies into risk groups
- **Poor prognosis**
  - **Del(17p)/*TP53* mutation**
    - **Worse outcomes with conventional chemo**
  - **Unmutated immunoglobulin heavy-chain variable (IGHV) decreased survival when using conventional chemotherapy treatments**
  - Absence of del(13q)
  - Presence of del(11q), complex karyotype

Rai Staging

Stage	Characteristics	Treatment
0	Lymphocytosis	Surveillance
I	+ lymphadenopathy	Consider treatment if symptomatic or progressive disease
II	+ splenomegaly and/or hepatomegaly	
III	+ anemia (hemoglobin < 11.0 g/dL)	Treatment
IV	+ thrombocytopenia (platelets < 100,000/mm3)	

Hallek M, et al. *Blood.* 2018;131(25):2745-2760; Damle RN, et al. *Blood.* 1999;94(6):1840-1847; Stilgenbauer S, et al. *Haematologica.* 2007;92(9):1242-1245; Patel K, Pagel JM. *J Hematol Oncol*. 2021;14:69; Gribben JG. *Hematol Educ.* 2014;8(1):69-74; NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CLL/SLL. V.3.2022.

CLL Risk Categories

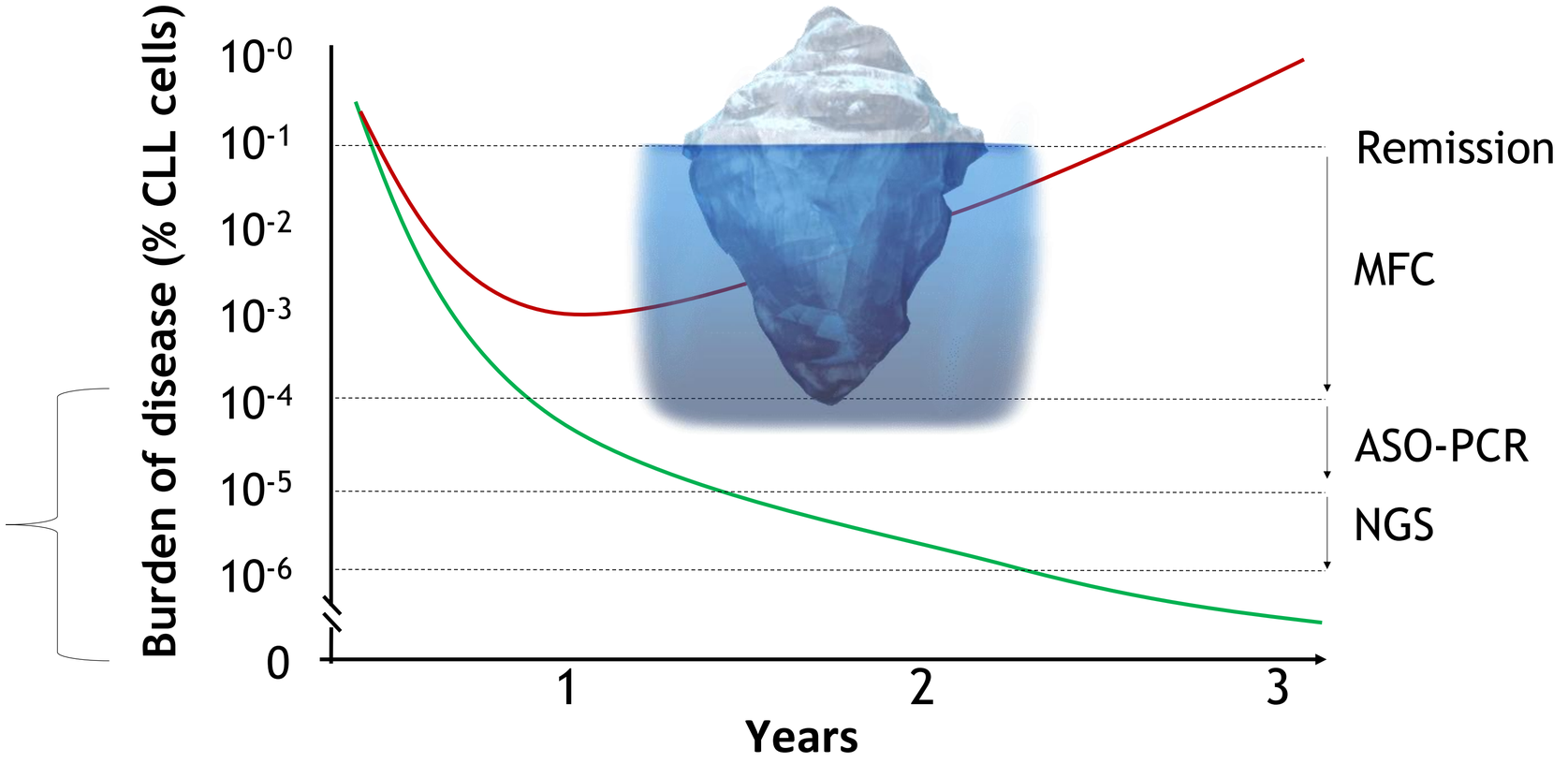


del(17p)/TP53 mutant status guides the choice of therapy in newly diagnosed patients.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CLL/SLL. V.3.2022.

Minimal Residual Disease (MRD)

- Undetectable minimal residual disease (MRD):
  - ≤0.01% (10^{-4})
  - ≤1 CLL cell in 10,000 normal leukocytes



ASO-PCR, allele-specific oligonucleotide polymerase chain reaction; MFC, multiparametric flow cytometry; NGS, next-generation sequencing.

Del Giudice I, et al. *Front Oncol*. 2019;9:689.

Current and Future Utilization of MRD

Current

- Emerging predictor of efficacy
- Not indicated in routine practice
- Patients not achieving MRD- should not have treatments changed
- Patients who were once MRD- and now MRD+ should not have treatments changed
- Provides prognostic information (except BTKi)

Future

- May be helpful to identify patients who can stop therapy
- May be helpful to identify patients who need to continue and/or switch therapy
- May guide which combination strategies are most effective

Wierda WG, et al. *Leukemia*. 2021;35(11):3059-3072.

Frontline CLL/SLL Treatment

Exploring Upfront Treatment Options

Treatment Approaches

Continuous – BTK inhibitors

- Acalabrutinib
- Ibrutinib
- Zanubrutinib

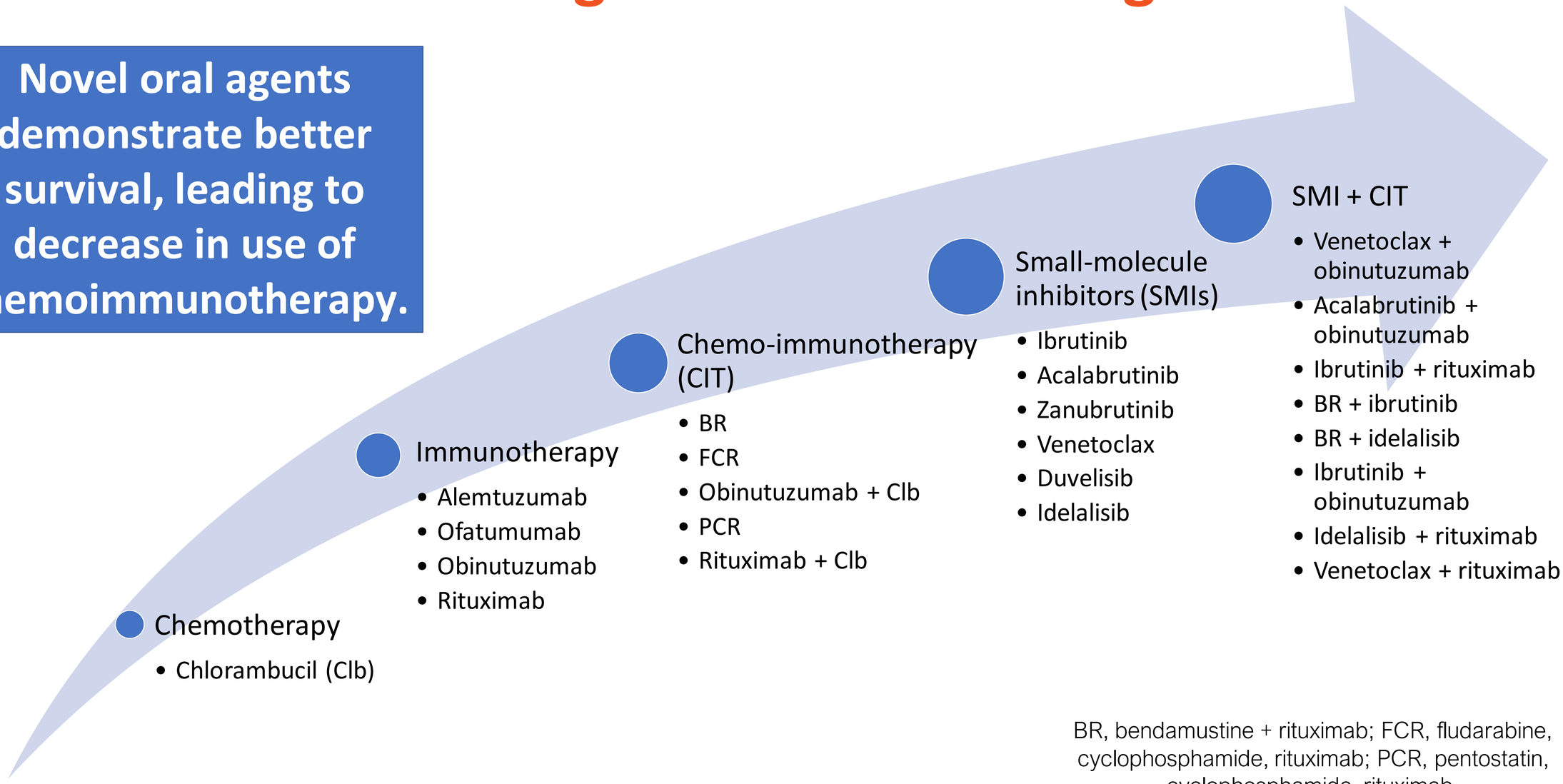
Fixed duration – BCL2i + CD20 mAb

- Venetoclax/Obinutuzumab

BTK, Bruton's Tyrosine Kinase; mAb, monoclonal antibody

Evolving Treatment Paradigm

Novel oral agents demonstrate better survival, leading to decrease in use of chemoimmunotherapy.



BR, bendamustine + rituximab; FCR, fludarabine, cyclophosphamide, rituximab; PCR, pentostatin, cyclophosphamide, rituximab.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CLL/SLL. V.3.2022.

Changing Treatment Landscape

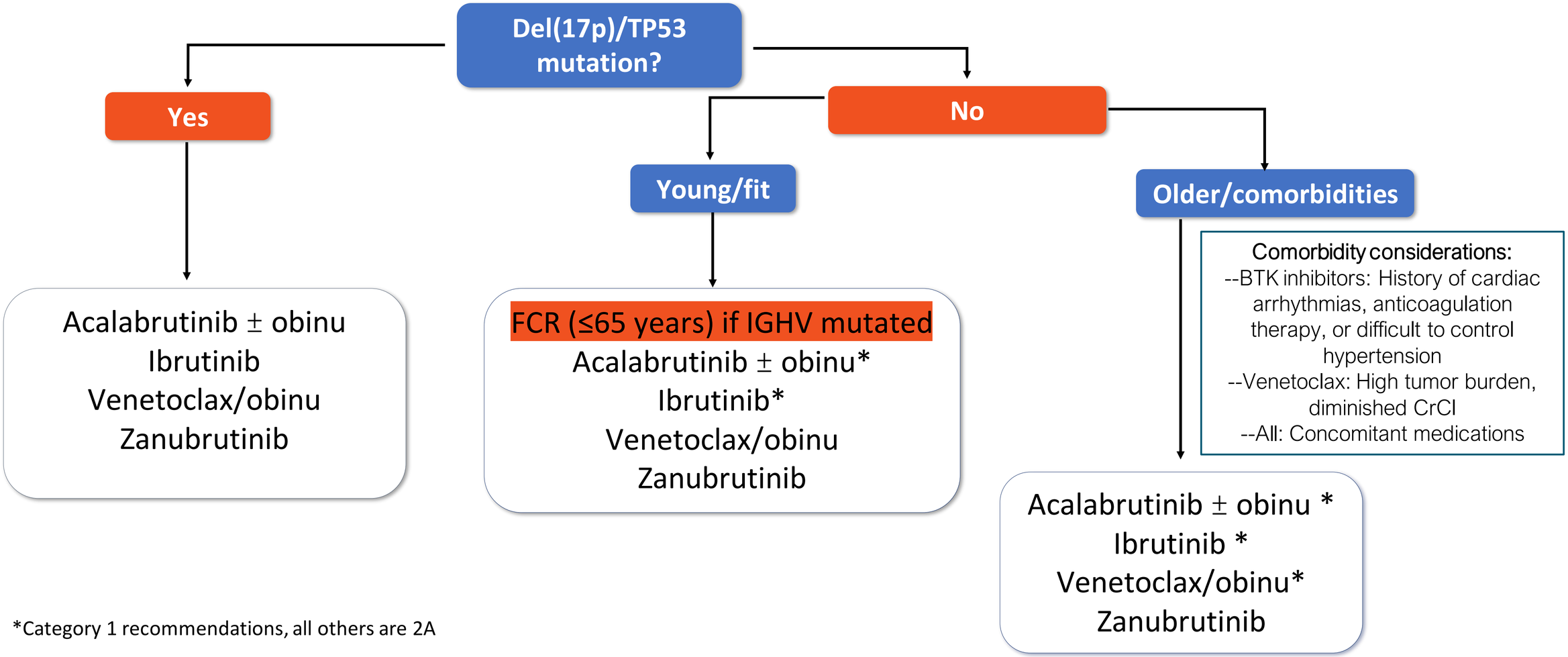
Population	Old Standard	New Standard
Young/Fit	FCR or BR	BTKi Venetoclax/obinu FCR*
Older/Fit	BR	BTKi Venetoclax/obinu
Elderly/Comorbidities	Clb + Obinutuzumab	BTKi Venetoclax/obinu

*FCR an option for IGHV mutated patients

BR, bendamustine + rituximab; FCR, fludarabine, cyclophosphamide, rituximab; Clb, Chlorambucil; BTKi, Bruton's Tyrosine Kinase inhibitor; obinu, obinutuzumab

Adapted from Brem EA, O'Brien S. *JCO Oncol Pract.* 2022;18(2):109-113; Shanafelt TD, et al. *N Engl J Med*. 2019;381(5):432-443; Burger JA, et al. *Leukemia*. 2020;34(3):787-798; Moreno C, et al. *Lancet Oncol.* 2019;20(1):43-56; Sharman JP, et al. *Lancet*. 2020;395(10232):1278-1291; Al-Sawaf O, et al. *Lancet Oncol*. 2020;21(9):1188-1200; Tam CS, et al. *Blood*. 2021; 138 (suppl 1): Abstract 396. Imbruvica. Prescribing information. Pharmacyclics; December 2020; Calquence. Prescribing information. AstraZeneca; November 2019; Brukinsa. Prescribing information. BeiGene; September 2021; October 2020

Treatment Algorithm

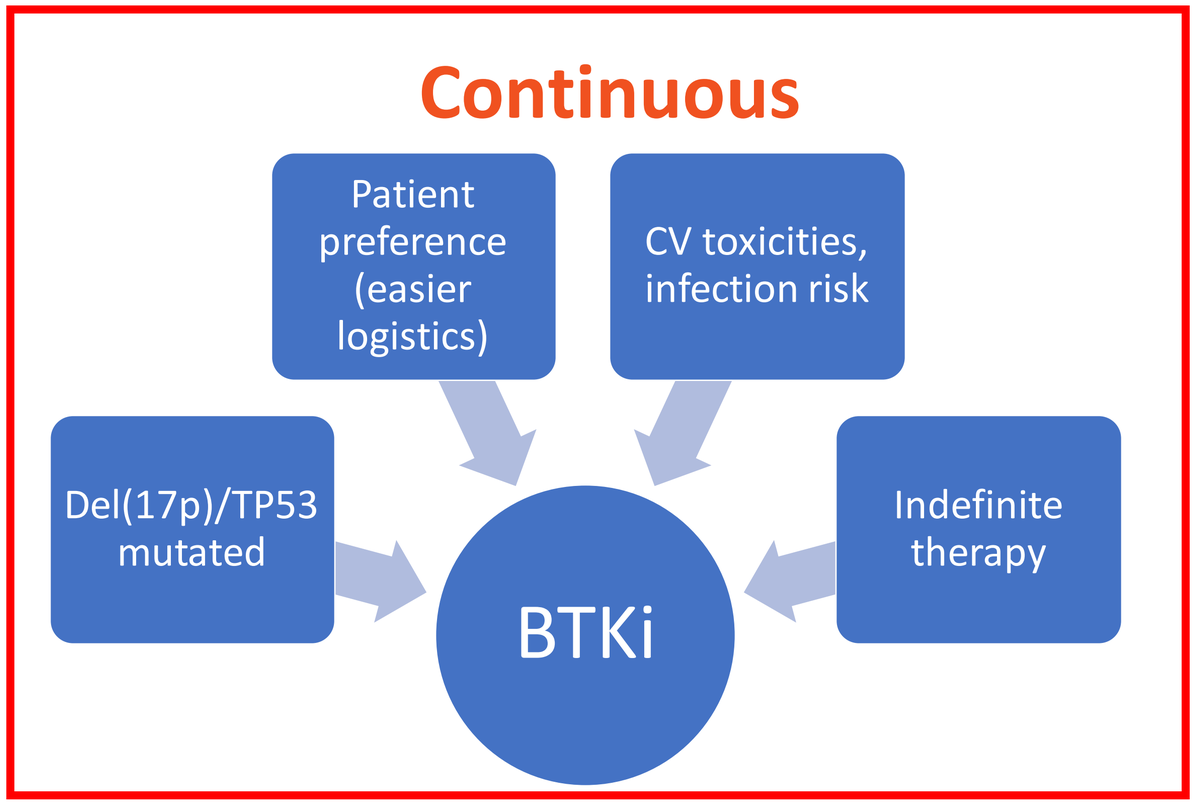


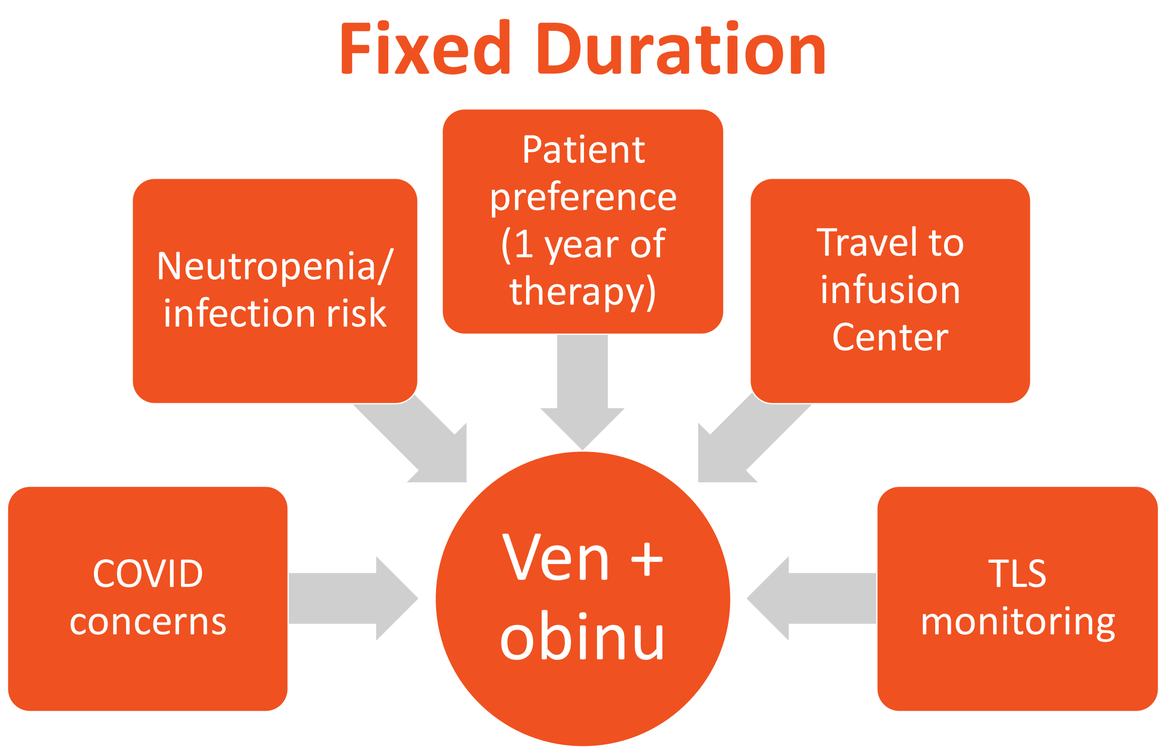
*Category 1 recommendations, all others are 2A

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CLL/SLL. V.3.2022.

How to Choose? Continuous vs Fixed Duration?

- Both continuous therapy with BTKi and fixed-duration therapy with venetoclax/obinutuzumab are excellent options for frontline CLL





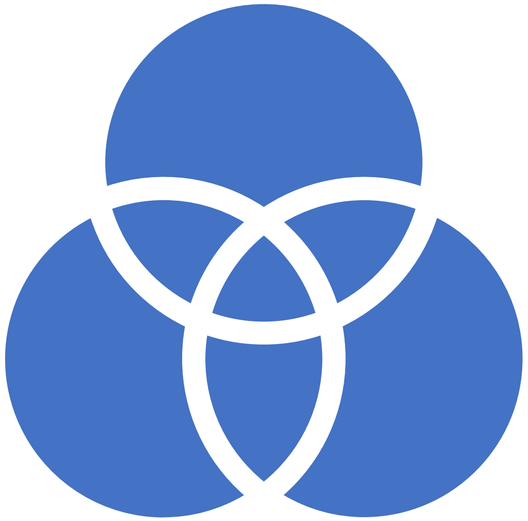
*No head-to-head trials; based on opinion. CV, cardiovascular; TLS, tumor lysis syndrome

Brem EA, O'Brien S. *JCO Oncol Pract.* 2022;18(2)109-113.

BTKi Comparison

- All-cause irreversible (covalent) inhibition of BTK
- Highest selectivity = Lowest off-target effects

- **acalabrutinib > zanubrutinib > ibrutinib**
  - Ibrutinib
    - Inhibits ITK, TEC, BMX, RLK/TXK, EGFR, HER2, HER4, BLK, JAK3
  - Zanubrutinib
    - Less activity on ITK and TEC
  - Acalabrutinib
    - Does not inhibit EGFR, IL2-inducible T-cell kinase (ITK), TEC

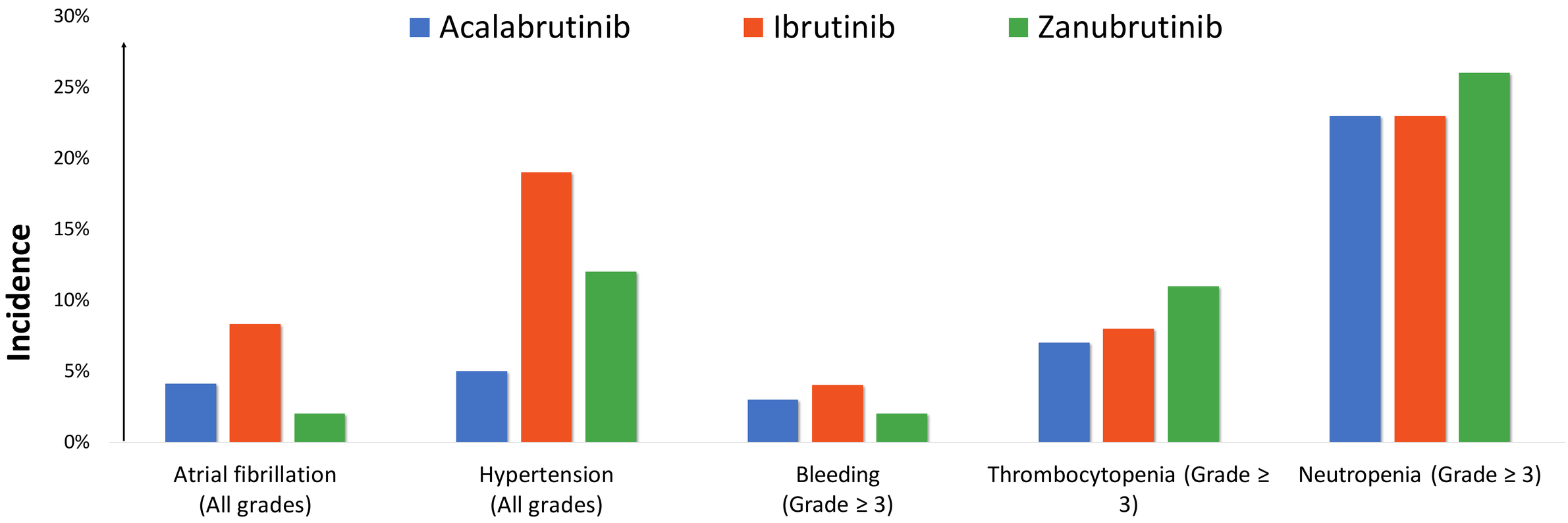


EGFR, epidermal growth factor receptor; ITK, IL2-inducible T-cell kinase; HER, human epidermal growth factor receptor.

Wen T, et al. *Leukemia*. 2021;35:312-332; Berglöf A, et al. *Scand J Immunol*. 2015;82(3):208-217.

Toxicity Comparison

AEs from Prescribing Information*



*Cross-trial comparisons should be interpreted with caution.

Imbruvica. Prescribing information. Pharmacyclics LLC; December 2020; Calquence. Prescribing information. AstraZeneca; November 2019; Brukinsa. Prescribing information. BeiGene; September 2021; Venclexta. Prescribing information. AbbVie Inc; December 2021.

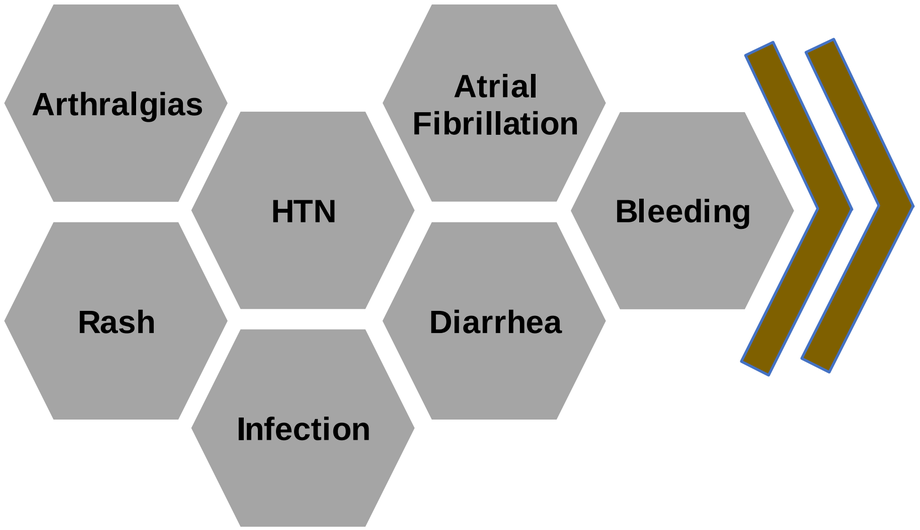
BTKi Comparison

	Acalabrutinib	Ibrutinib	Zanubrutinib
Dosing and duration of therapy	• 100 mg PO twice daily • Indefinite therapy	• 420 mg PO once daily • Indefinite therapy	• 160 mg PO twice daily **OR** 320 mg once daily • Indefinite therapy
2-year PFS (approx.)	90%	89%	86%
Unique AE	• Headache		
Select drug interactions	• CYP3A4 inhibitors/inducers • Proton Pump Inhibitors (PPIs) until new formulation is released	• CYP3A4 inhibitors: Modify dose or avoid • Strong CYP3A4 inducers: Avoid use • Warfarin	• CYP3A4 inhibitors: Modify dose and/or frequency • CYP3A4 inducers: Avoid use

Adapted from Brem EA, O'Brien S. *JCO Oncol Pract.* 2022;18(2):109-113; Shanafelt TD, et al. *N Engl J Med*. 2019;381(5):432-443; Burger JA, et al. *Leukemia*. 2020;34(3):787-798; Moreno C, et al. *Lancet Oncol.* 2019;20(1):43-56; Sharman JP, et al. *Lancet*. 2020;395(10232):1278-1291; Al-Sawaf O, et al. *Lancet Oncol*. 2020;21(9):1188-1200; Tam CS, et al. *Blood*. 2021; 138 (suppl 1): Abstract 396. Imbruvica. Prescribing information. Pharmacyclics; December 2020; Calquence. Prescribing information. AstraZeneca; November 2019; Brukinsa. Prescribing information. BeiGene; September 2021; October 2020

BTK Inhibitor Discontinuation Due to Toxicity

Most Common Reasons



11- 41%

of patients
DISCONTINUE ibrutinib

↑ **Age** **(21%)**

strong predictor for
discontinuation due to toxicity

Most adverse effects decrease with duration except hypertension

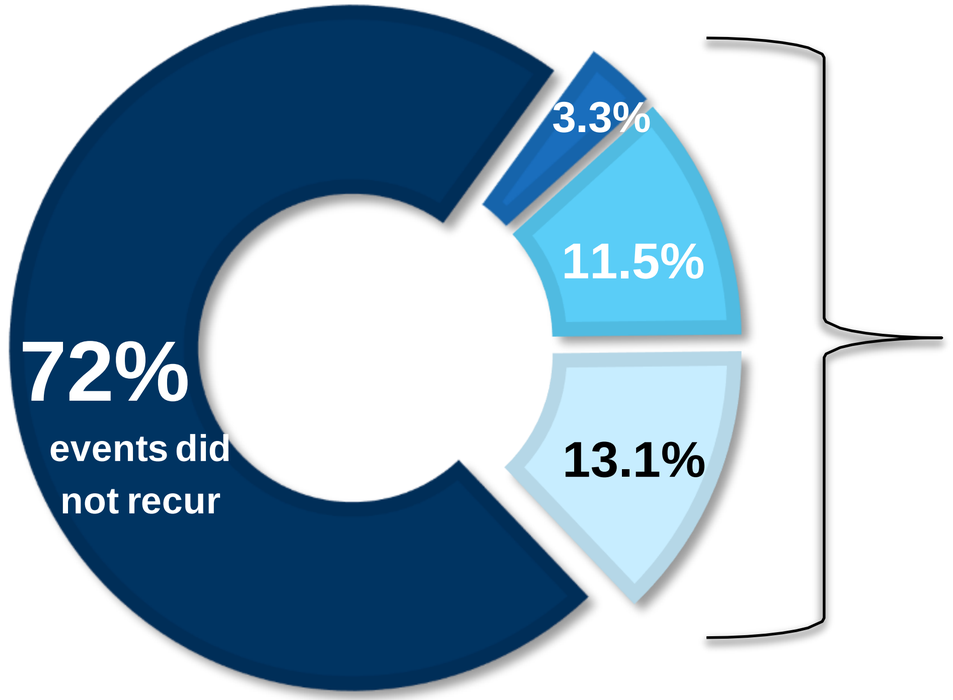
- 8% during first year
- 15% in year 2
- 20% in year 3

Mato AR, et al. Haematologica. 2018;103(5):874-879. Brown JR. Blood. 2018;131(4):379-386. Maddocks KJ, et al. JAMA Oncol. 2015;1(1):80-87. Coutre SE, et al. *Blood Adv*. 2019;3:1799-1807; Mato AR, et al. O'Brien SM, et al. *Am J Hematol*. 2019;94(5):554-562.

Acalabrutinib for Patients Intolerant to Ibrutinib

Patients intolerant to ibrutinib. Majority had grade 3/4 AE

Switched to acalabrutinib and recurrence of AEs was evaluated



27.9% AEs recurred

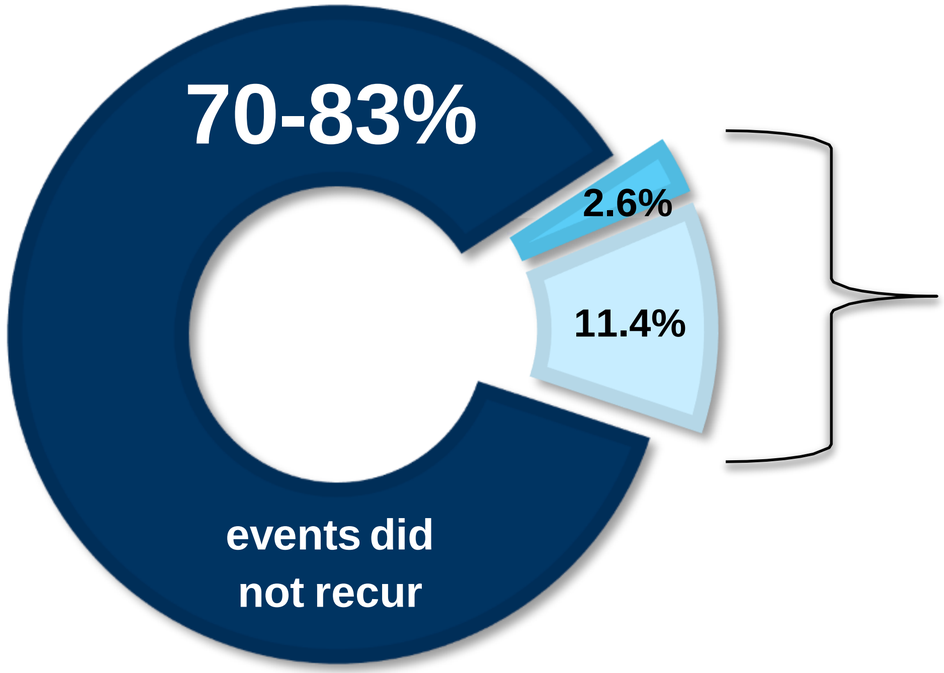
- 3.3% higher grade
- 11.5% same grade
- 13.1% lower grade

Awan FT, et al. Blood Adv. 2019;3(9):1553-1562.

Zanubrutinib for Patients Intolerant to Ibrutinib/Acalabrutinib

Patients intolerant to ibrutinib or acalabrutinib*

Patients switched to zanubrutinib and recurrence of AEs was evaluated



- 0% higher grade
- 2.6% same grade
- 11.4% lower grade

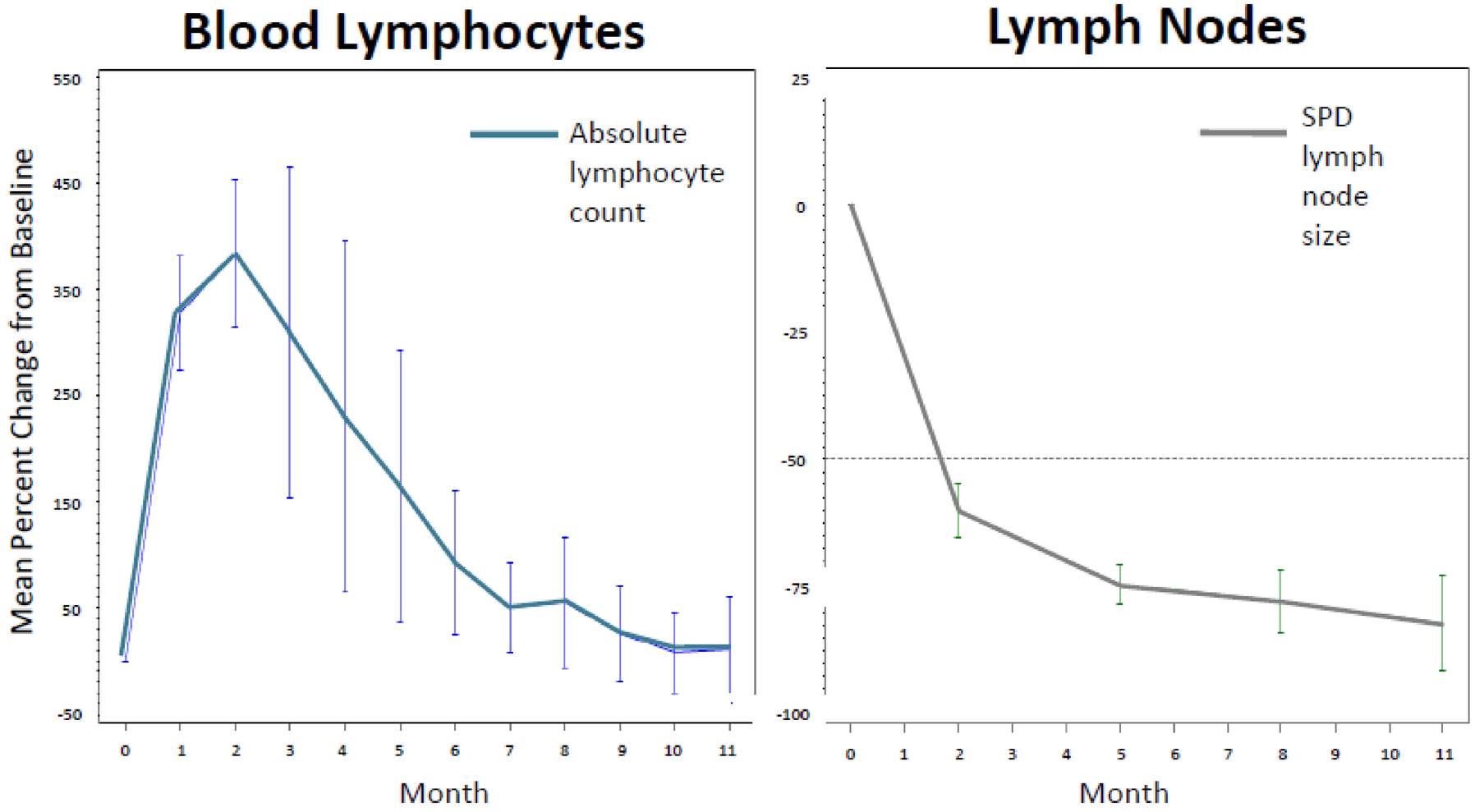
Shadman M, et al. Presented at: ASH Annual Meeting; December 2021. Abstract 626.

Combating Discontinuation Rates

- Prevention and Management of Cardiac Adverse Effects
  - Afib – control rate and rhythm, avoid warfarin due to interaction
  - Bleeding – hold 3-7 days pre/post surgical procedures, avoid warfarin
  - Hypertension – frequent monitoring, control per guidelines, consider switching BTKi if uncontrolled
- Headache (acala) – caffeine and/or acetaminophen
- Arthralgia – NSAIDs, dose reductions, or change BTKi
- Rash – hold, topical/oral steroids, dose reduce, change BTKi

Ganatra S, et al. *JACC Clin Electrophysiol*. 2018;4(12):1491-1500; de Weerdt I, et al. *Haematologica*. 2017;102(10):1629-1639; Yazdy MS, et al. *Blood*. 2019;134(suppl_1):4311; de Weerdt I, et al. *Haematologica*. 2017;102(10):1629-1639; Calquence. Prescribing information. AstraZeneca; November 2019.

Transient Lymphocytosis

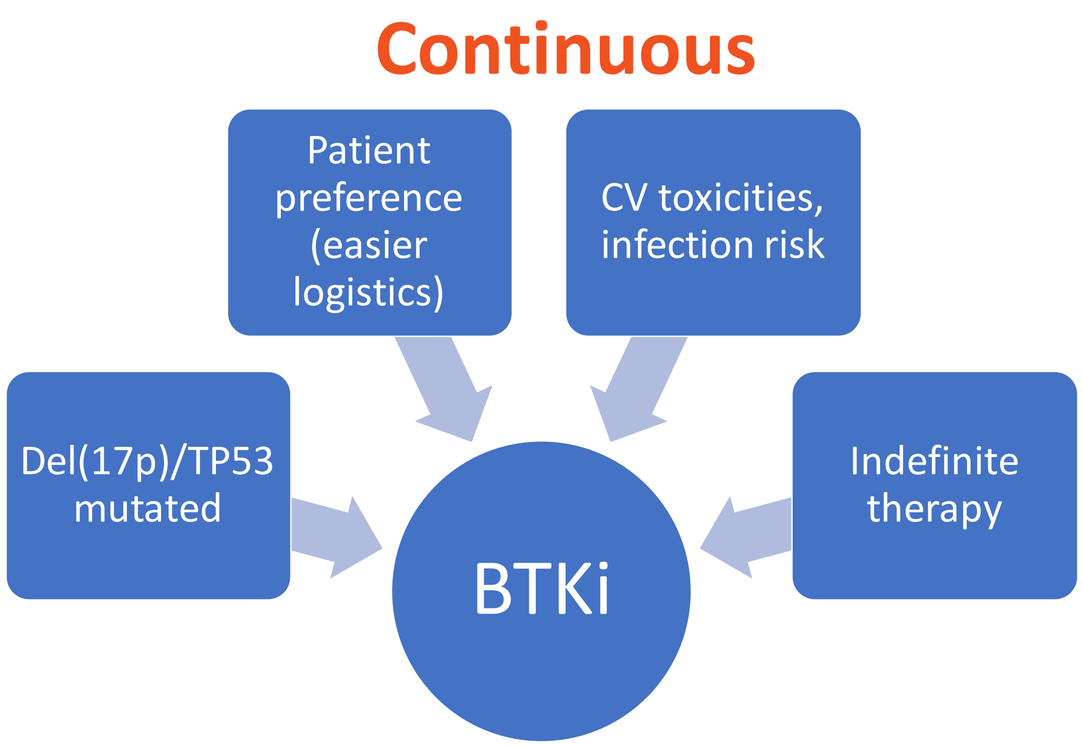


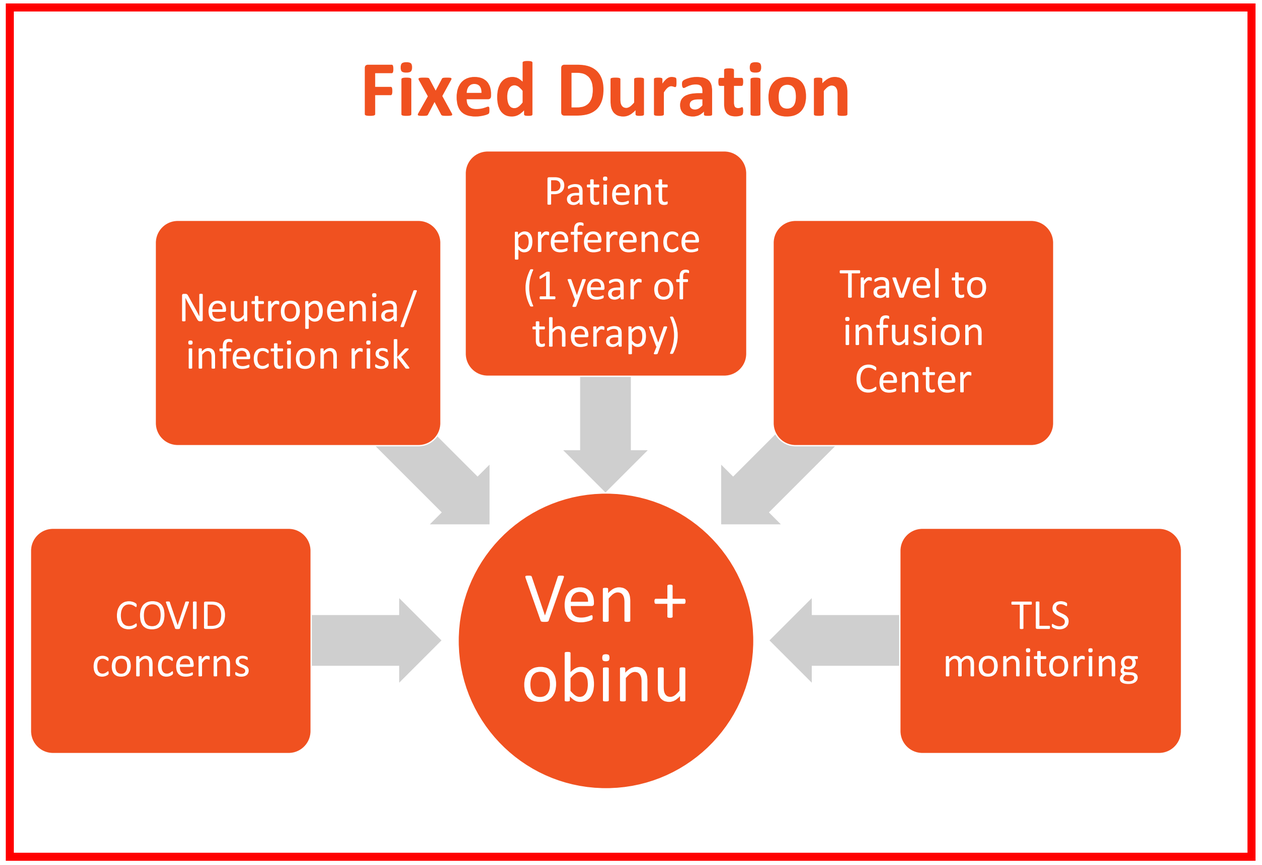
Brown JR, et al. *Blood*. 2015;126(23):2952.; Byrd JC, et al. *New EnglJ Med*. 2013;369(1):32-42.

SPD, sum of products

How to Choose? Continuous vs Fixed Duration?

- Both continuous therapy with BTKi and fixed-duration therapy with venetoclax/obinutuzumab are excellent options for frontline CLL





*No head-to-head trials; based on opinion. CV, cardiovascular; TLS, tumor lysis syndrome

Brem EA, O'Brien S. *JCO Oncol Pract.* 2022;18(2)109-113.

Venetoclax / Obinutuzumab per CLL14 Trial

CLL14 Trial

Venetoclax + Obinu

vs

Clb + Obinu

Efficacy: Improved PFS, higher rates of MRD undetectability

AE: **GI toxicity, TLS, neutropenia**

Duration of treatment: 1 year

Venetoclax + obinutuzumab FDA approved for frontline CLL therapy

Venetoclax PO 4-wk ramp up from 20 to 400 mg/day starting on Day 22 of cycle 1, then 400 mg/day until end of cycle 12 +

Obinutuzumab IV Days 1/2, 8, 15 of cycle 1, then 1000 mg Day 1 of cycles 2-6

Clb, chlorambucil; O, obinutuzumab; PFS, progression free survival; MRD, minimal residual disease

Fischer K, et al, *N Engl J Med* 2019;380:2225-2236; Al-Sawaf. EHA 2021. Abstr S146.

Tumor Lysis Syndrome: Venetoclax Ramp-Up Dosing

Ramp-up from 20 mg to 400 mg performed over 4 weeks

Venclexta. Prescribing information. AbbVie; December 2021.

TLS monitoring/prevention

- Risk-stratify patients based on tumor burden, renal function, and comorbidities
- Allopurinol) should be initiated ≥2-3 days prior to venetoclax
- Oral hydration (1.5-2.0 L) should begin 2 days before first dose and every time dose is increased

Drug Interactions – CYP3A4 and PGP

- Increase: i.e., HIV medications, antifungals, cardiac drugs, PAXLOVID
- Decrease: i.e., Anti-seizure medications, anti-tubercular agents, and St John's Wort

BTK vs BCL2 Considerations Summary

BTK Inhibitor

- Logistically very easy
- Indefinite therapy
- TLS not of concern
- More cardiac risk
- Some favor in del(17p)/*TP53* mutation

BCL2 Inhibitor

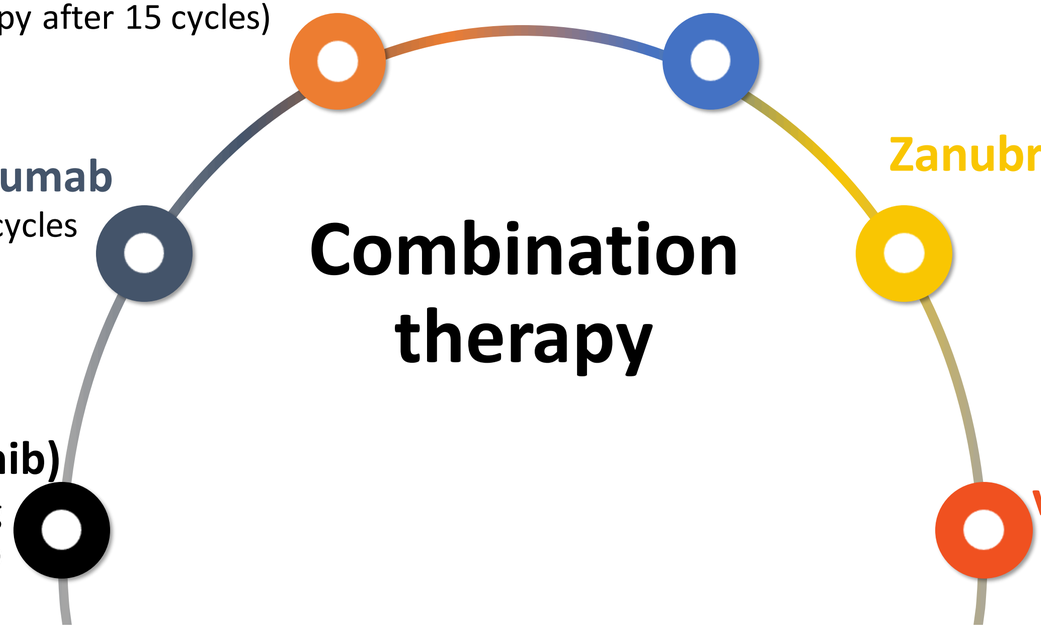
- Cumbersome initiation
- Fixed duration
- Risk for TLS requires monitoring
- Renal Function
- Question if best for high-risk patients

Finite Therapies of the Future

CAPTIVATE study (venetoclax + ibrutinib)
MRD- randomized to CONTINUE ibrutinib vs placebo
MRD+ randomized to CONTINUE ibrutinib or comb
Non-MRD directed (stop therapy after 15 cycles)

Ibrutinib + venetoclax + obinutuzumab
All discontinued after 14 cycles

CLL13 (CIT vs ven + CD20 ± ibrutinib)
Discontinue after 6–36 cycles depending on randomization arm/MRD



Acalabrutinib + venetoclax + obinutuzumab
MRD+ continued AV for 2 years and if MRD- stopped

Zanubrutinib + venetoclax + obinutuzumab
MRD assessed between 8-24 cycles
Patients with undetectable MRD could stop

GLOW study (venetoclax + ibrutinib versus chlorambucil + obinutuzumab)
All discontinued after 15 cycles

Eichhorst B, et al. Presented at: American Society of Hematology (ASH) Annual Meeting; December 2021. Abstract 642; Jain N, et al. *JAMA Oncol*. 2021;7(8):1213-1219; Rogers KA, et al. Presented at: American Society of Hematology (ASH) Annual Meeting; December 2020. Abstract 1305; Wierda WG, et al. Presented at: ASH Annual Meeting; December 2020. Abstract 123; Davids MS, et al. Presented at: ASH Annual Meeting; December 2020. Abstract 2216; Soumerai JD, et al. Presented at: ASH Annual Meeting; December 2020. Abstract 1307; Kater A, et al. European Hematology Association. 2021. Abstract LB1902.

COVID-19 Implications

Exploring Upfront Treatment Options in CLL

COVID-19 Implications in CLL

Vaccine Efficacy Diminished in CLL

- Trials demonstrate 94-100% efficacy in immunocompetent patients
- 52-75% response in CLL patients on therapy with two doses of mRNA vaccine
- Additional 23.8% response rate with third dose in **untreated** patients
- Additional 12% response rate with third dose in **treated** patients

COVID-19 Mortality Rates Higher in CLL

Mortality Rates	
Early 2020	**33%**
Late 2020	**11%**

Parry H, et al. Blood Cancer J. 2021 Jul 30;11(7):136; Roeker LE, et al. Leukemia. 2021 Sep;35(9):2703–5; Herishanu Y, et al. Blood. 2022 Feb 3;139(5):678–85; Roeker LE, et al. Blood 2021; 138 (18): 1768–1773

COVID-19 Therapies in CLL

EVUSHELD (tixagevimab+cilgavimab)

Pre-exposure prophylaxis enables coverage ~ 6 months for patients on treatment

Oral Antiviral Therapy

- Paxlovid – hold BTKi and venetoclax
- Molnupiravir

Vaccines (12yo+)

3 primary vaccines + 2 boosters

IV Monoclonal Antibodies

- Bebtelovimab
- Remdesivir

Masking, hand hygiene, social distancing

Inpatient Support

Convalescent plasma, Tocilizumab, Corticosteroids

CDC.gov; NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CLL/SLL. V.3.2022

Patient Case

LH is a 65yo female with PMH of DMII, CKD, GERD, and poorly controlled HTN. CLL with 17p deletion. Compliance to metformin, lisinopril, omeprazole, and carvedilol.

Treatment considerations?

- del17p – consider BTKi
- Poorly controlled HTN – 2nd generation BTKi
- GERD on PPI – consider switch to H2 blocker with acala, new formulation of acala when available, or zanubrutinib
- CKD – increased TLS risk with Venetoclax, consider inpatient escalation if chosen. Venetoclax dose adjustment with carvedilol
- COVID – recommendation vaccination and Evusheld (tixagevimab+cilgavimab)

Questions?

James Davis, PharmD, BCOP

Email: Davisjaa@musc.edu

@thisisJamesD

Conclusions

- The treatment landscape for CLL has changed significantly in the past decade, with targeted therapies improving outcomes in frontline the setting
- Newer targeted therapies have shown clinical benefits, but treatment selection should be tailored on a patient-by-patient basis
- Future treatment regimens are likely to combine multiple oral agents including BTKi and BCL2 inhibitors
- COVID-19 implications should be considered when caring for CLL patients

Pivotal Studies

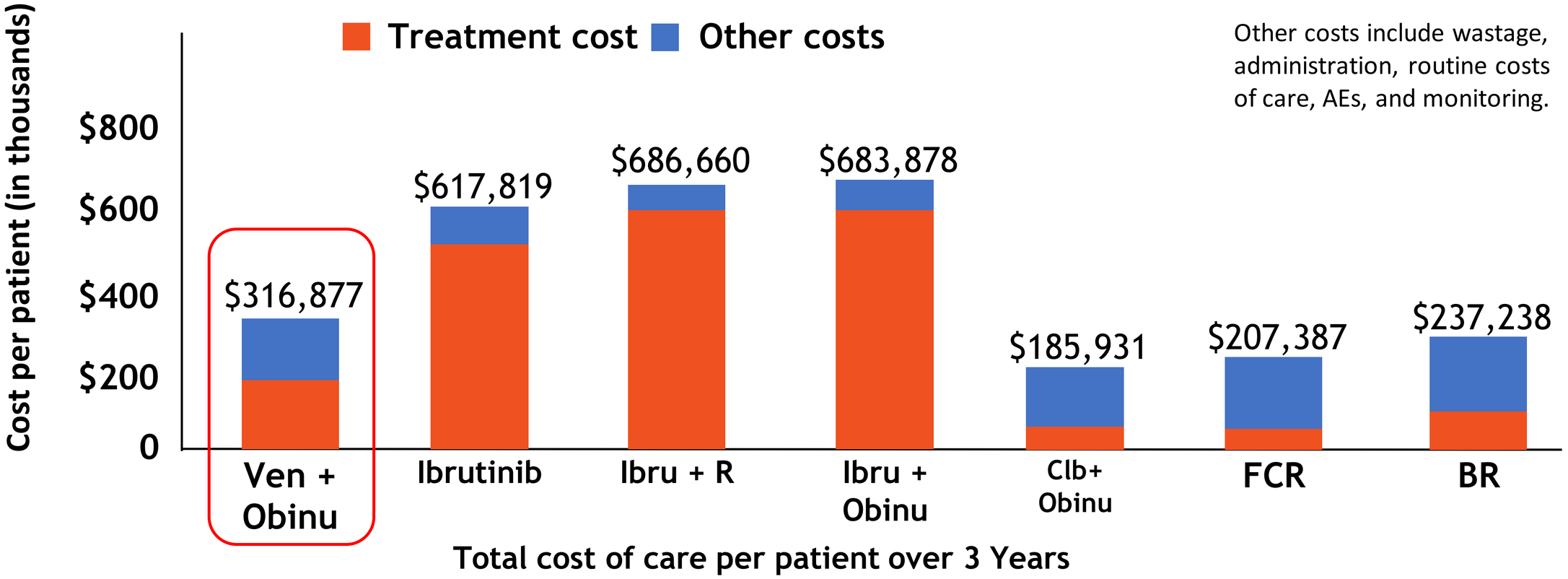
Acalabrutinib	**ELEVATE-TN** Acalabrutinib ± O vs O-Clb			
Ibrutinib	**RESONATE-2** Ibrutinib vs Clb	**ECOG 1912** Ibrutinib + R vs FCR	**iLLUMINATE** Ibrutinib + O vs O-Clb	**Alliance** Ibrutinib ± R vs BR
Venetoclax	**CLL14** Venetoclax + O vs O-Clb			
Zanubrutinib	**SEQUOIA*** Zanubrutinib + B+R / Zanubrutinib + Venetoclax			

*Additional details discussed on trials with evidence published within the past 12 months.

BR, bendamustine + rituximab; Clb, chlorambucil; ECOG, Eastern Cooperative Oncology Group; FCR, fludarabine, cyclophosphamide, and rituximab; O, obinutuzumab; R, rituximab.

Shanafelt TD, et al. *N Engl J Med*. 2019;381(5):432-443; Woyach JA, et al. *N Engl J Med*. 2018;379(26):2517-2528; Burger JA, et al. *Leukemia*. 2020;34(3):787-798; Moreno C, et al. *Lancet Oncol.* 2019;20(1):43-56; Sharman JP, et al. *Lancet*. 2020;395(10232):1278-1291; Al-Sawaf O, et al. *Lancet Oncol*. 2020;21(9):1188-1200; Tam CS, et al. *Blood*. 2021;138 (suppl 1): Abstract 396.

Finite Therapy vs Indefinite Treatment Reduces Costs



Cho SK, et al. *Pharmacoeconomics*. 2020;38(9):941-951.

BR, bendamustine + rituximab; FCR, fludarabine + cyclophosphamide + rituximab; Obinu, obinutuzumab; Clb, chlorambucil; Ibr, ibrutinib; R, rituximab; VEN, venetoclax.

BTKi Off Target Effects

Target	Effect
TEC	Platelet effects, T-cell priming
EGFR	Rash, cardiac toxicity, diarrhea
SRC	Platelet effects
BMX	Cardiac toxicity
ITK	Immune effects
JAK3	Immune effects
ERBB4	Cardiac toxicity

Berglöf A, et al. *ScandJ Immunol*. 2015;82(3):208.; Bose P, et al. *Expert OpinDrug MetabToxicol*. 2016;12(11):1381-92.; Bye AP, et al. *Blood Adv.* 2017;1(26):2610-23.; GhezD, et al. *Blood*. 2018;131(17):1955-9.; Rogers K. *Blood*. 2018;131(17):1882-4.; Rogers KA, et al. *Leukemia*. 2019;33(10):2527-30.; RuchlemerR, et al. *Mycoses*. 2019;62(12):1140-7.; ShatzelJJ, et al. *J ThrombHaemost*. 2017;15(5):835-47.; WoyachJA. *Blood*. 2018;132(18):1869-70.