Improving Outcomes for Patients With Chronic Lymphocytic Leukemia

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Welcome and Introductions

Financial Disclosures

Mazyar Shadman, MD, MPH

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- Consultant: Janssen Pharmaceuticals

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Product Disclosure

This activity may include discussion of agents that have not yet been approved by the U.S. Food and Drug Administration and investigational uses of approved products. Please consult prescribing information and practice guidelines for detail regarding safe and effective use of therapeutic agents.

Learning Objectives

At the conclusion of this continuing education activity, the oncology advanced practice provider will be better able to:

- Evaluate data regarding mechanistic activity, efficacy, and safety of approved and emerging therapeutic options for CLL
- Devise risk-stratified treatment plans for patients with CLL
- Plan strategies for managing adverse events (AEs) associated with approved therapies for CLL

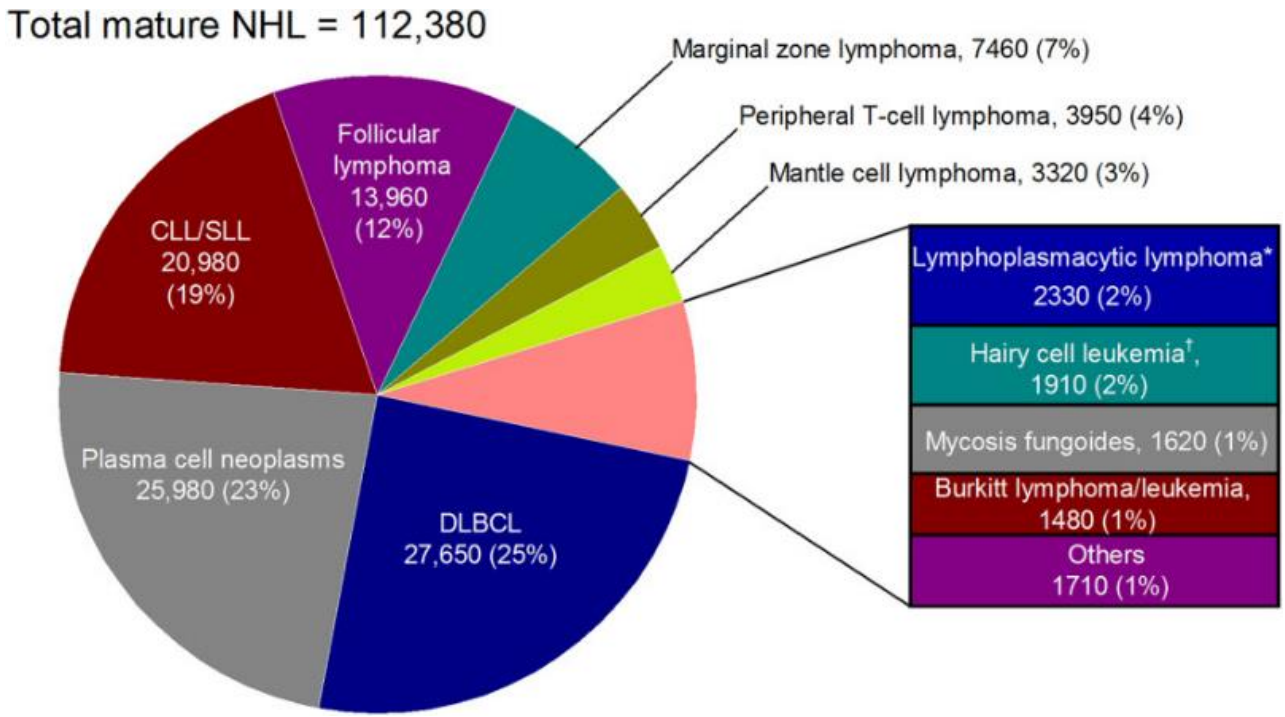
CLL/SLL

- Most common leukemia in adults in Western world
  - ~30% of leukemias
  - Anticipated new cases/deaths in 2019 20,720/3,930
- A disorder of morphologically mature but immunologically less mature lymphocytes
- Lymphocyte count ≥5000 mm^3 for diagnosis
- Immunophenotype includes CD5+/CD23+ B cells
- Primarily occurs in middle-aged and older adults
- Considered an indolent disease
- Large variation in survival between patients—from several months to a normal life expectancy

American Cancer Society. *Cancer Facts & Figures 2019*; NCCN Practice Guidelines in Oncology. CLL/SLL Guidelines. V1.2020.

SLL, small lymphocytic lymphoma.

Incidence of Mature Non-Hodgkin Lymphoid Neoplasia 2016



Teras L, et al. *CA Cancer J Clin*. 2016;66:443-59.

*Includes Waldenström macroglobulinemia. †Includes Hairy cell leukemia variant.

Presenting Symptoms of CLL

Asymptomatic in 60% of patients	
Enlarged lymph nodes	Petechiae
Recurring infections	Mucocutaneous bleeding
Early satiety	Fatigue
Abdominal discomfort	Night sweats
Abdominal fullness	Weight loss

Rodrigues CA, et al. *Rev Bras Hematol Hemoter.* 2016;38:346-57; www.cancer.gov/types/leukemia/hp/cll-treatment-pdq; https://www.cancer.org/ancer/chronic-lymphocytic-leukemia/detection-diagnosis-staging/signs-symptoms.html.

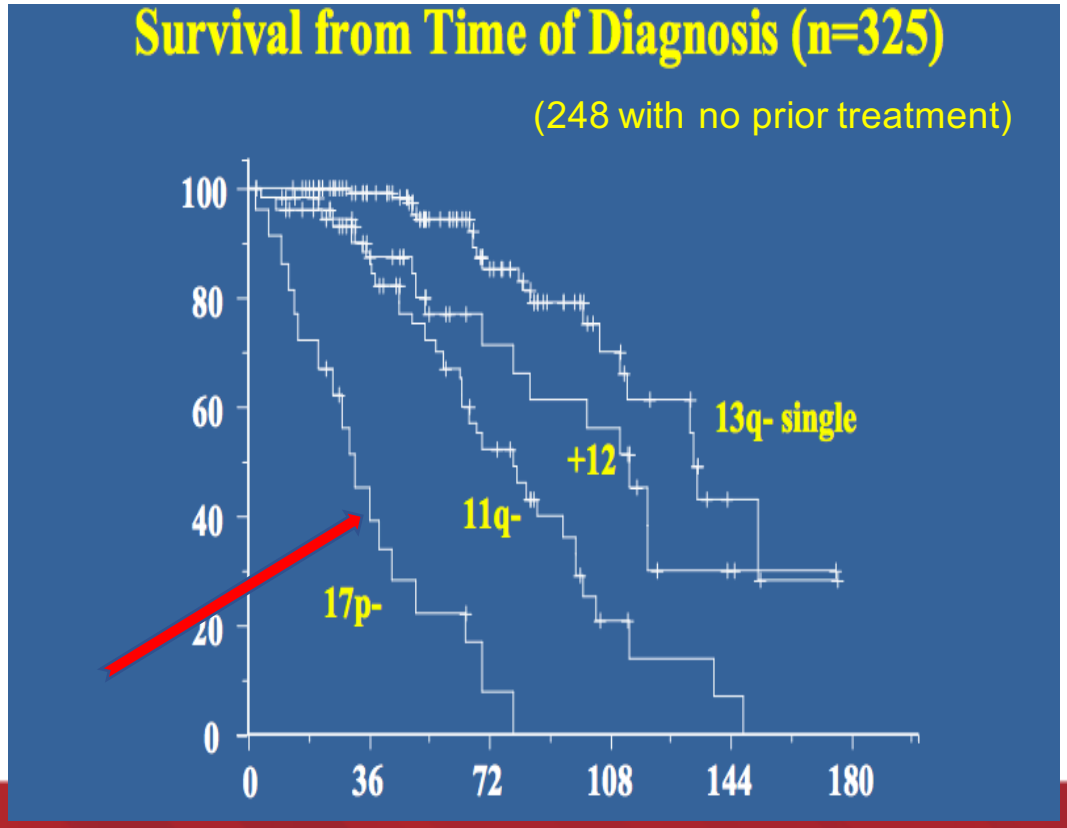
Diagnostic Work-Up: Essential

- Peripheral blood flow cytometry
- Physical exam
- Performance status
- B symptoms
- CBC with differential/platelets
- Comprehensive metabolic panel
- LDH
- Hepatitis B screen
- Bone marrow biopsy and aspirate, lymph node biopsy optional
- Fertility considerations

Molecular Biomarkers for CLL

	FISH	Karyotype	Mutations
Unfavorable	del(17p) del(11q)	Complex (>3 abnormalities) (>5?)	*TP53* Unmutated *IGHV* (≤2%) NOTCH-1 SF3B1 BIRC3 ATM
Neutral	Normal +12		
Favorable	del(13q) (sole abnormality)		Mutated *IGHV* (>2%)

Prognostic Value of FISH for CLL



Abnormality	Patients, %	Median Time to Treatment, mo	Median OS, mo
del(17)(p13.1)	7	9	32
del(11)(q22.3)	17	13	79
Trisomy 12	14	33	114
del(13)(q14)	55	49	133
None detected	18	92	111

Döhner H, et al. *N Engl J Med*. 2000;343:1910-6.

OS, overall survival.

CLL Staging Systems

Rai Staging System

Rai Stage	Modified Rai Stage	Characteristics
0	Low	• Lymphocytosis in peripheral blood and bone marrow only
I II	Intermediate	• Lymphocytosis and enlarged lymph nodes • Lymphocytosis and enlarged spleen and/or liver
III IV	High	• Lymphocytosis and anemia (hemoglobin <11 g/dL) • Lymphocytosis and thrombocytopenia (platelets <100 X 10^9/L)

Rai KR, et al. *Blood*. 1975;46:219-34; Binet J, et al. *Cancer*. 1981;48:198-206;
NCCN Practice Guidelines in Oncology. CLL/SLL Guidelines. V1.2020.

Updated 2018 International Workshop on CLL Guidelines to Initiate Therapy (IWCLL)

Any one of the following criteria should be met to initiate CLL therapy:
Progressive marrow failure, hemoglobin <10 g/dL or platelet count of <100 x 10^9/L
Massive (≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly
Massive (≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
Autoimmune complications of CLL that are poorly responsive to corticosteroids
Symptomatic extranodal involvement (eg, skin, kidney, lung, spine)
Disease-related symptoms, including: • Unintentional weight loss of ≥10% within the previous 6 months • Significant fatigue • Fever ≥100.5º F for 2 or more weeks without evidence of infection • Night sweats for ≥1 month without evidence of infection

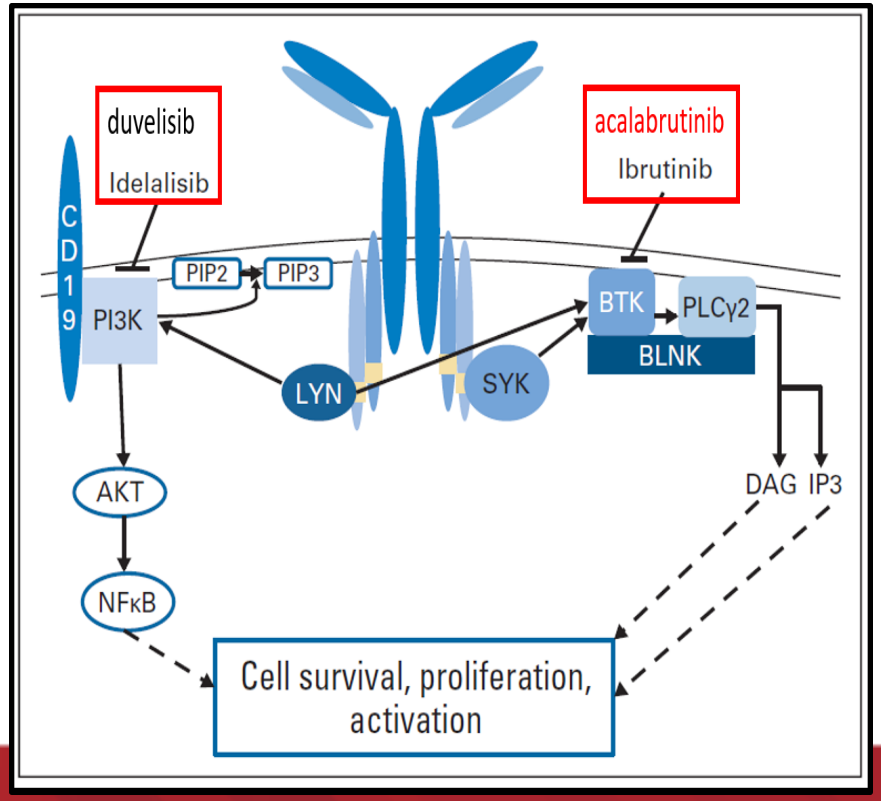
Hallek M, et al. *Blood*. 2018;131:2745-60.

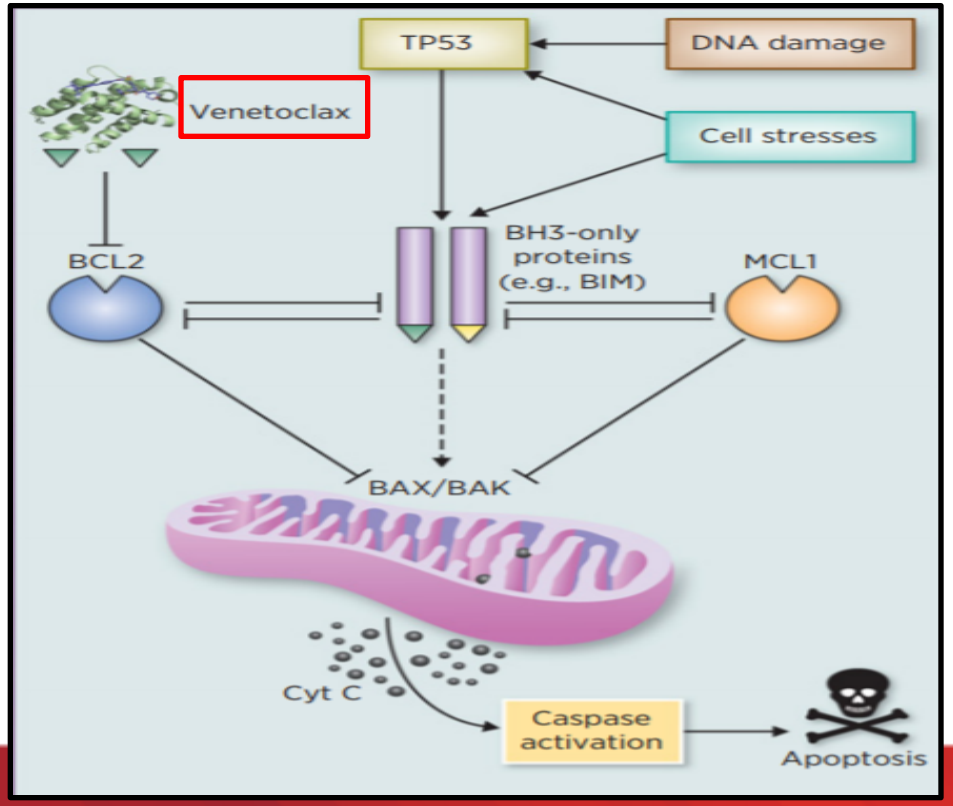
Prior to Starting Therapy for CLL

- All patients who meet 2018 IWCLL criteria should be offered therapy
- TP53 is one of the most important prognostic and predictive biomarkers
  - Should be determined prior to therapy
  - Prefer both CLL-FISH and next-generation sequencing (NGS) panel
  - Some patients will have TP53 on NGS but no del(17p) on FISH
- *IGVH* mutational status

Parikh SA. *Blood Cancer J*. 2018;8:93.

BCR Pathway Inhibitors vs BCL-2 Antagonists

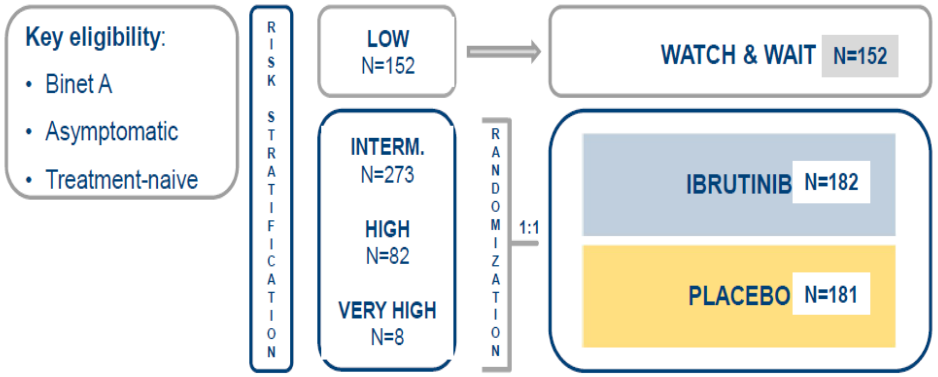




Byrd JC, et al. *J Clin Oncol*. 2014;32:3039-47; Roberts AW, et al. *Clin Cancer Res*. 2017;23:4527-33.

Is There a Role for Early Treatment, Without Meeting 2018 IWCLL Criteria?

CLL-12 Study – Early Intervention With Ibrutinib

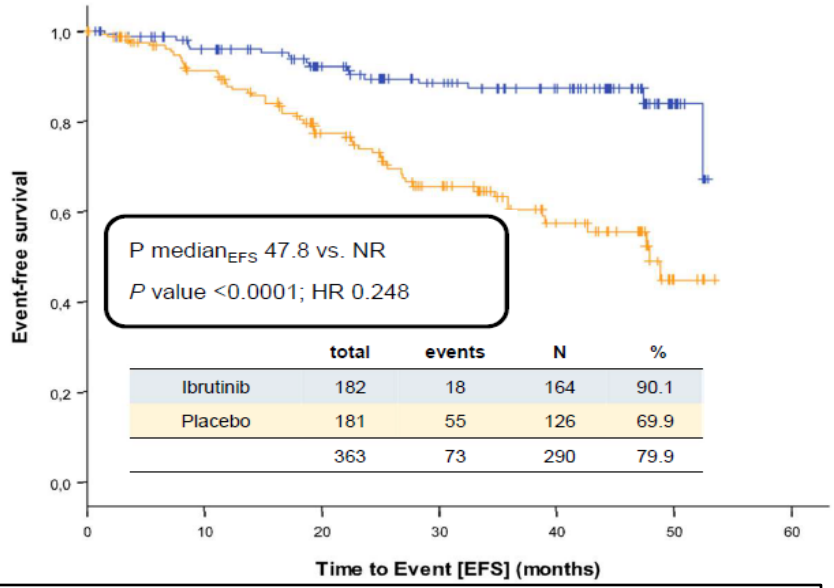


Phase 3, placebo-controlled, double-blind, multicenter trial

Primary endpoint EFS: time from randomization until symptomtatic PD, new treatment, death

Secondary endpoints: survival, PFS, TFS, TTNT, ORR, safety

π_2 : median EFS from 24 to 48 months with ibrutinib (superiority test)

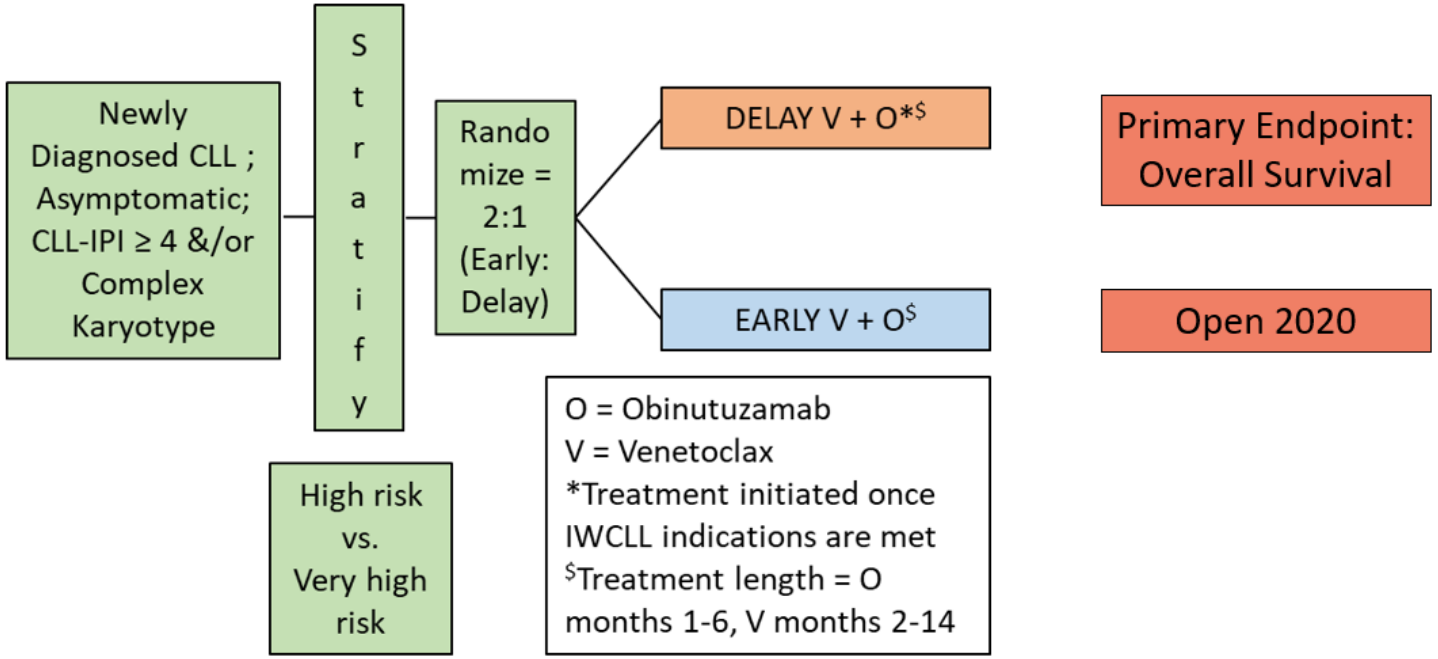


	total	events	N	%
Ibrutinib	182	18	164	90.1
Placebo	181	55	126	69.9
	363	73	290	79.9

- No OS benefit
- Study is powered for OS, so longer follow-up would be interesting
- **Early intervention with ibrutinib is NOT recommended at this time**

Langerbeins P, et al. 15-ICML 2019. Abstract 007.

Upcoming US Intergroups Early Intervention Trial with Venetoclax



Courtesy of Dr. Deborah Stephens (study PI).

SWOG
Leading cancer research. Together.

Suggested Regimens for Frontline Treatment of CLL/SLL Without del(17p)/*TP53* Mutation

Frail with significant comorbidity OR Age ≥65 y and younger patients with significant comorbidities	Age <65 y without significant comorbidities
Preferred first-line regimens:	Preferred first-line regimens:
• **Ibrutinib** • **Venetoclax + obinutuzumab**	• **Ibrutinib** • **Venetoclax + obinutuzumab**
Other recommended regimens:	Other recommended regimens:
• Bendamustine + anti-CD20 monoclonal antibody (not recommended for frail patients) • Chlorambucil + anti-CD20 monoclonal antibody • **High-dose methylprednisolone + rituximab** • **Ibrutinib + obinutuzumab** • **Onibutuzumab** • Chlorambucil • **Rituximab**	• Bendamustine + anti-CD20 monoclonal antibody • FCR (fludarabine, cyclophosphamide, rituximab) • FR (fludarabine, rituximab) • **High-dose methylprednisolone + rituximab** • **Ibrutinib + rituximab** • PCR (pentostatin, cyclophosphamide, rituximab)

NCCN Practice Guidelines in Oncology. CLL/SLL Guidelines. V1.2020.

Suggested Regimens for Relapsed/Refractory Treatment of CLL/SLL Without del(17p)/*TP53* Mutation

Frail with significant comorbidity OR Age ≥65 y, and younger patients with significant comorbidities	Age <65 y without significant comorbidities	Maintenance therapy
Preferred relapsed/refractory regimens:	Preferred relapsed/refractory regimens:	Post second-line:
• **Acalabrutinib** • **Ibrutinib** • **Venetoclax + rituximab** • **Duvelisib** • **Idelalisib + rituximab**	• **Acalabrutinib** • **Ibrutinib** • **Venetoclax + rituximab** • **Duvelisib** • **Idelalisib + rituximab**	• **Lenalidomide** • **Ofatumumab**
Other recommended regimens:	Other recommended regimens:	
• **Alemtuzumab +/- rituximab** • Chlorambucil + rituximab • Reduced-dose FCR or PCR • **HDMP + rituximab** • **Idelalisib** • **Lenalidomide +/- rituximab** • **Obinutuzumab** • **Ofatumumab** • **Venetoclax** • **Dose-dense rituximab** • Bendamustine, rituximab +/- ibrutinib or idelalisib	• **Alemtuzumab +/- rituximab** • Bendamustine + rituximab • FC + ofatumumab • FCR • **HDMP + rituximab** • **Idelalisib** • **Lenalidomide +/- rituximab** • **Obinutuzumab** • **Ofatumumab** • PCR • **Venetoclax** • Bendamustine, rituximab +/- ibrutinib or idelalisib	

NCCN Practice Guidelines in Oncology. CLL/SLL Guidelines. V1.2020.

HDMP, high-dose methylprednisolone.

Suggested Regimens for Treatment of CLL/SLL With del(17p)/*TP53* Mutation: Complete Absence of Chemotherapy

First-line	Relapsed/Refractory
Preferred regimens:	Preferred regimens:
• **Ibrutinib** • **Venetoclax + obinutuzumab**	• **Acalabrutinib** • **Ibrutinib** • **Venetoclax + rituximab** • **Duvelisib** • **Idelalisib + rituximab** • **Venetoclax**
Other recommended regimens:	Other recommended regimens:
• **Alemtuzumab +/- rituximab** • **HDMP + rituximab** • **Obinutuzumab**	• **Acalabrutinib** • **Alemtuzumab +/- rituximab** • **HDMP + rituximab** • **Idelalisib** • **Lenalidomide +/- rituximab** • **Ofatumumab**

NCCN Practice Guidelines in Oncology. CLL/SLL Guidelines. V1.2020.

First-line Treatment for Patients Without del(17p) or *TP53* Mutation: Summary

- **Venetoclax and Obinutuzumab**
  or
- **Ibrutinib**

- **No head-to-head comparison**
- **Both are reasonable options**
- **Consider patient and disease factors**
- **Look at pros and cons for each**

- FCR: only reasonable if
  - Mutated *IGHV*
  - Younger than 65
  - Fit
  - No evidence of del(17p)
  - No evidence of *TP53* mutation
  - [No evidence of del(11q)]
- BR: if ibrutinib or venetoclax are not used for any reason and if patient does not meet FCR criteria

Frontline Therapy [no del(17p), no *TP53* mutation)

Historical studies from the "chemo era"

Study	Treatments	N	Result	Outcome	Notes
German CLL10	FCR vs BR	564	FCR > BR	PFS but not OS	No benefit if >65 AML/MDS: 5% with FCR
German CLL11	CHL-obino vs CHL-ritux vs CHL	780	CHL-obino > CHL-ritux > CHL	PFS and OS	
RESONATE-2	Ibrutinib vs CHL	269	Ibrutinib > CHL	PFS and OS	

Eichhorst B, et al. *Lancet Oncol*. 2016;17:928-42; Eichhorst B, et al. ASH 2016. Abstract 4382; Goede V, et al. *N Engl J Med*. 2014;370:1101-10; Goede V, et al. *Leukemia*. 2015;29:1602-4; Burger JA, et al. *N Engl J Med*. 2015;373:2425-37.

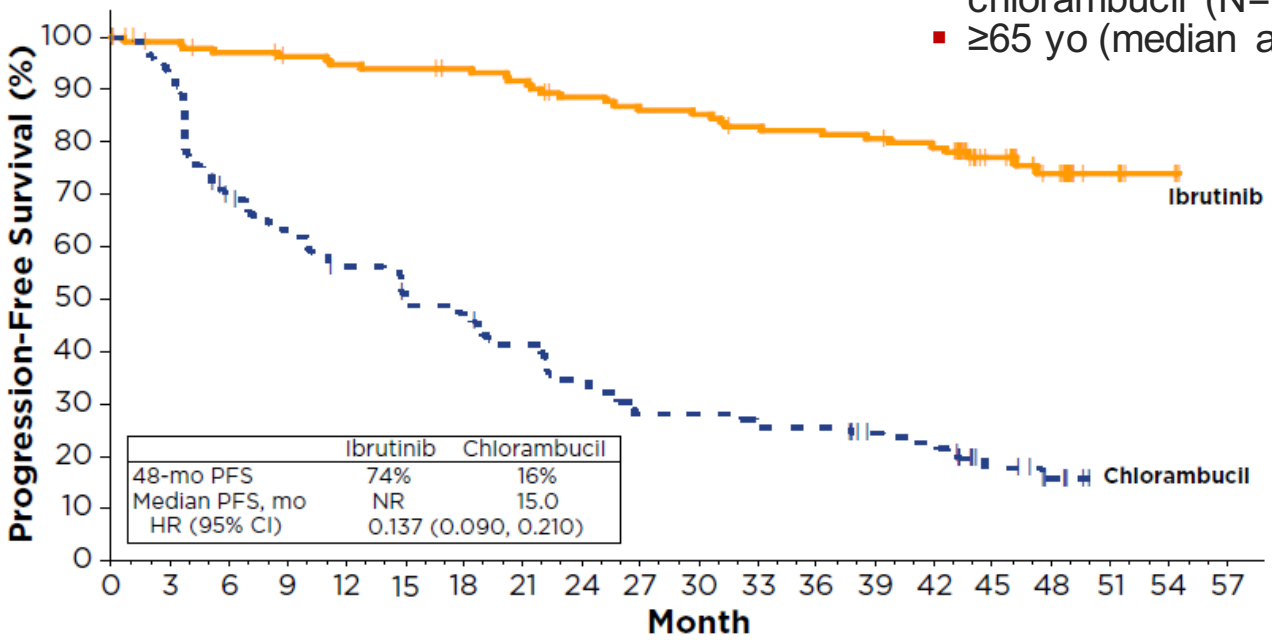
Novel Agents Are Rapidly Changing the Treatment Landscape of CLL/SLL

- Prognostic factors for CLL:
  - *IGHV*
  - Cytogenetics: del(13p), del(11q), del(17p), trisomy 12
  - Flow cytometry: CD38, CD49d, ZAP70
  - Serum biomarkers: thymidine kinase, β2-microglobulin
- With development of novel agents, outcome of patients with higher-risk disease improving (eg, del(17p))
- In patients with *TP53* abnormalities and those with early relapse after chemoimmunotherapy, outcome significantly improved (eg, 5-year survival improved from <40% to >80% with ibrutinib)

Dreger P, et al. *Blood*. 2018;132:892-902.

Ibrutinib Monotherapy in TN CLL: Phase III RESONATE-2 Trial After 4 Years

- Randomized to ibrutinib or chlorambucil (N=269)
- ≥65 yo (median age 73)



Burger JA, et al. EHA 2018. Abstract PF343.

TN, treatment-naïve.

Ibrutinib and Rituximab vs FCR in TN CLL/SLL *Phase III E1912 Trial*

Demographics

- ≤70 yo
- No del(17p)
- Treatment naïve

Treatment Arms (N=529)

- Ibrutinib + rituximab (n=354)
- FCR (n=175)

Survival Outcomes

- PFS was superior (median f/u of 33.4 months) in the ibrutinib + rituximab arm; independent of age, sex, PS, stage, del(11q23) status, and *IGHV* unmutated patients (HR=0.352; 95% CI 0.223-0.558, *P*<0.0001)
- OS was also favorable in the IR arm (HR=0.168, 95% CI 0.053-0.538; *P*=0.0003)

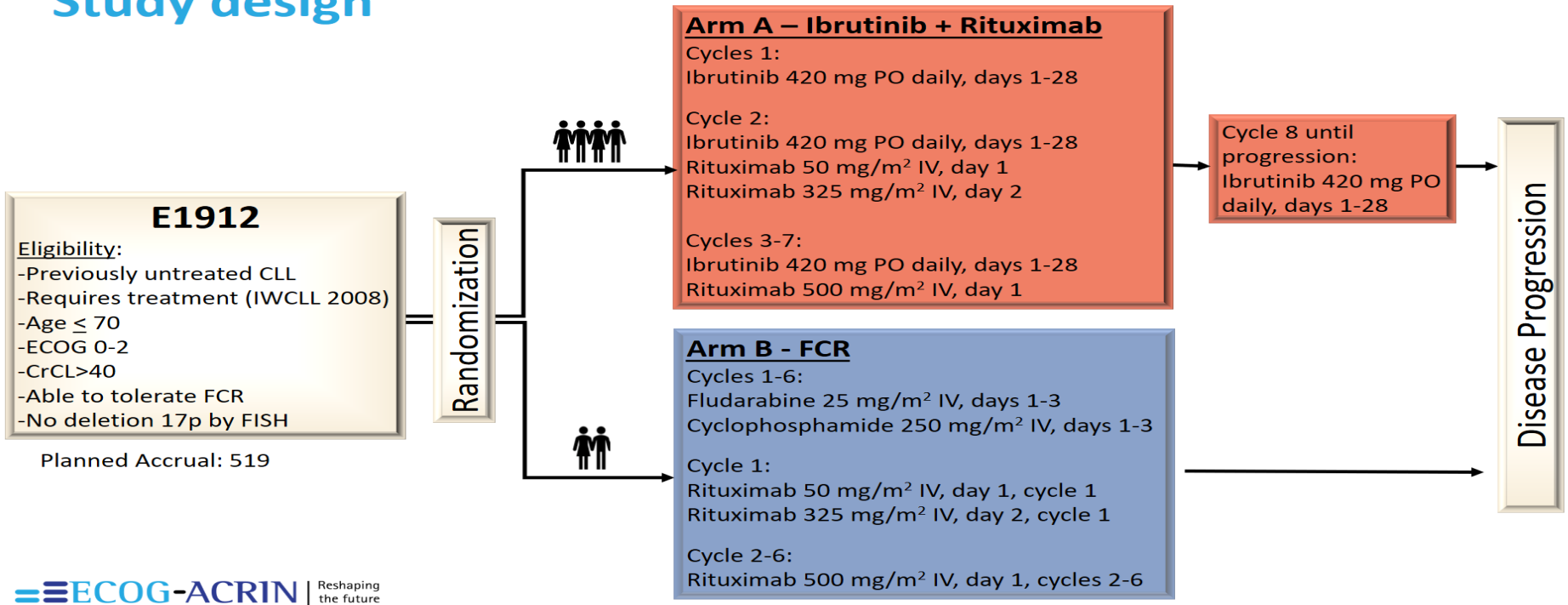
Safety

Grade 3/4 Adverse Event	Ibrutinib + Rituximab	FCR
All	58%	72%
Neutropenia	23%	44%
Infectious complications	7.1%	17.7%

Shanafelt TD, et al. ASH 2018. Abstract LBA4.

Ibrutinib and Rituximab vs FCR in TN CLL/SLL *Phase III E1912 Trial*

Study design



ECOG-ACRIN cancer research group | Reshaping the future of patient care

Shanafelt TD, et al. *N Engl J Med*. 2019;381:432-43.

Ibrutinib + Rituximab Improves PFS and OS in Younger Patients With CLL vs FCR

Phase III E1912 Study

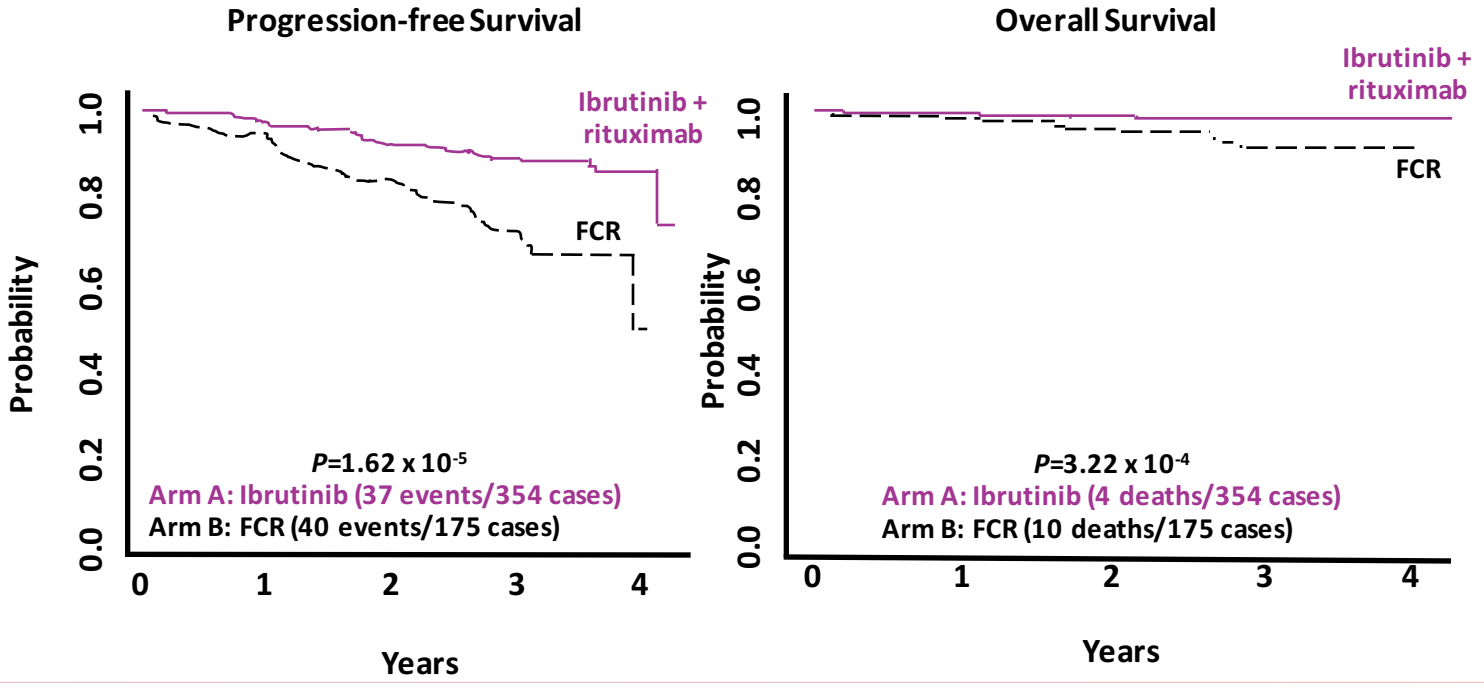
- Ibrutinib + rituximab vs FCR in younger patients with newly diagnosed CLL
- HR for PFS in ITT population: 0.35
- HR for OS in ITT population: 0.17

Baseline characteristics		IR n=354	FCR n=175	Total
Median age (y)		58	57	58
Age ≥ 60		41.0%	40.0%	40.6%
Female		33.3%	31.4%	32.7%
ECOG = 0		63.8%	62.3%	63.3%
Rai stage 0		3.1%	5.1%	3.8%
Rai stage I-II		52.8%	53.7%	53.1%
Rai stage III-IV		44.1%	41.1%	43.1%
FISH deletion	**11q**	**22.0%**	**22.3%**	**22.2%**
	Trisomy 12	19.8%	15.4%	18.3%
	13q deletion	34.2%	33.1%	33.8
B2M >3.5 mg/L		51.9%	48.0%	50.6%
IGHV unmutated*		75.0%	61.7%	71.1%

Shanafelt TD, et al. ASH 2018. Abstract LBA4.

*Tested in 437 (82%) patients.

Ibrutinib and Rituximab vs FCR in TN CLL/SLL *Phase III E1912 Trial*

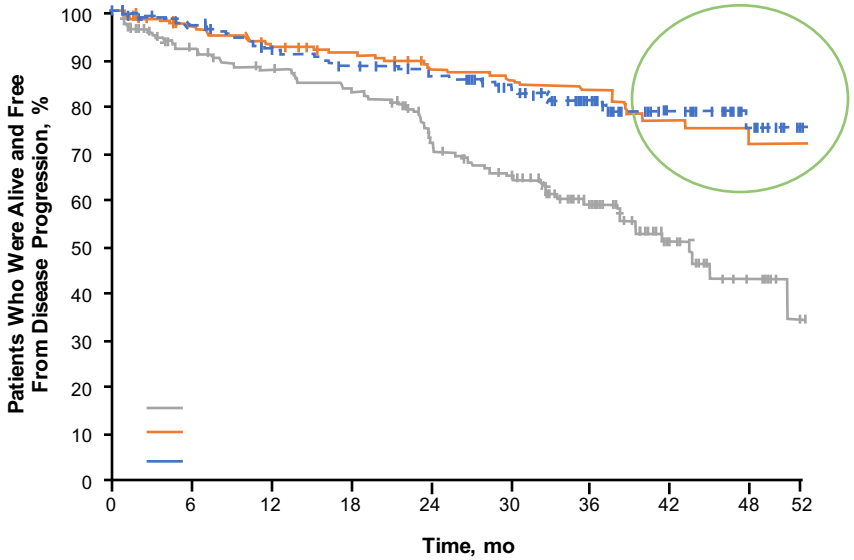


Shanafelt TD, et al. ASH 2018. Abstract LBA4.

Ibrutinib-Based Therapy Improves PFS vs Bendamustine-Rituximab in Older CLL Patients

Phase III A041202 Study

- Ibrutinib ± rituximab versus BR in older patients with newly diagnosed CLL
- Improved PFS with ibrutinib regimens vs BR
  - HR for PFS = 0.39 (ibrutinib alone); 0.38 (ibrutinib + rituximab)
- No difference in PFS between ibrutinib arms

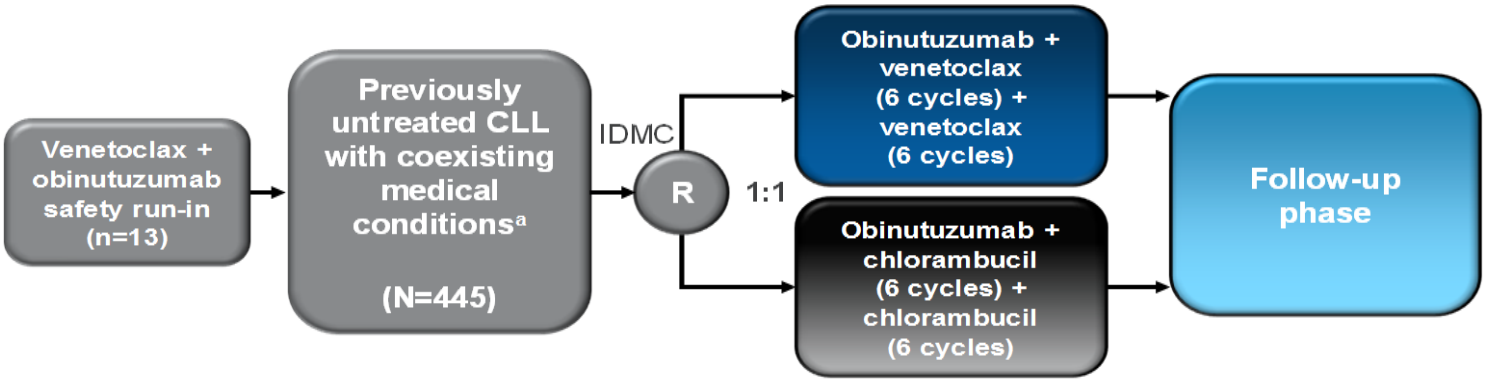


	Events/Patients, n	Median, mo (95% CI)
Bendamustine + rituximab	68/176	43 (38-NR)
Ibrutinib	34/178	NR
Ibrutinib + rituximab	32/170	NR

Take-home point: Ibrutinib therapy improves PFS versus BR in older patients; no differences in OS noted at this time

Woyach J, et al. *N Engl J Med*. 2018;379:2517-28.

CLL14: Venetoclax + G vs CHL + G in First-line CLL With Comorbidities



Primary endpoint:

- PFS as assessed by investigator[3]

Secondary endpoints[3]:

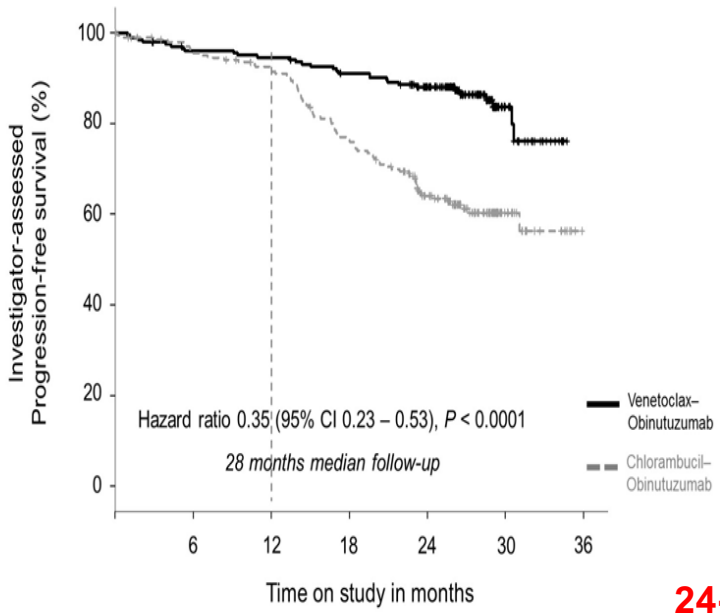
- PFS as assessed by IRC
- MRD
- ORR
- CR rate
- DOR
- EFS
- OS
- TTNT
- Safety

[a]CIRS >6 and/or CrCl <70 mL/min

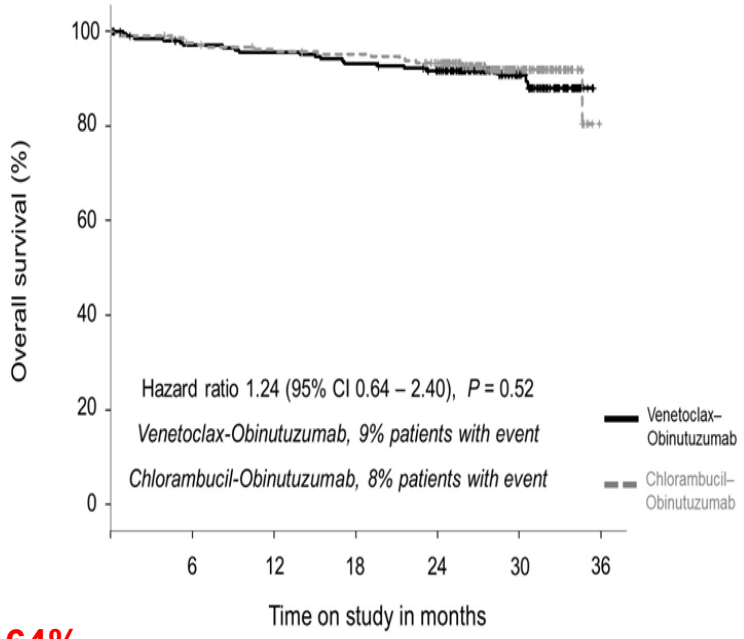
12% were *TP53* deleted and/or mutated

CLL14: Venetoclax + G vs CHL + G in First-line CLL With Comorbidities

PROGRESSION-FREE SURVIVAL



OVERALL SURVIVAL



24-month PFS:
Ven-G: 88%; CHL-G: 64%

Fischer K, et al. *N Engl J Med*. 2019;380:2225-36.

MRD-negative: Ven-G vs Other Regimens

Chemo-free

Treatment	Duration (m)	BM MRD (ITT)
Ven-G[1]	12	**57%**
IB-G[2]	until PD	20%
FCR[3]	6	27%
BR[3]	6	11%
CHL-G[1]	12	17%
iFCR[4]	6	84%
iFCG[5]	12	91%

[1]CLL-14 ; [2]iLLUMINATE; [3]CLL-10; [4]DCFI, [5]MDACC.

MRD, measurable residual disease; ITT, intent to treat.

Venetoclax + Ibrutinib in First-line CLL

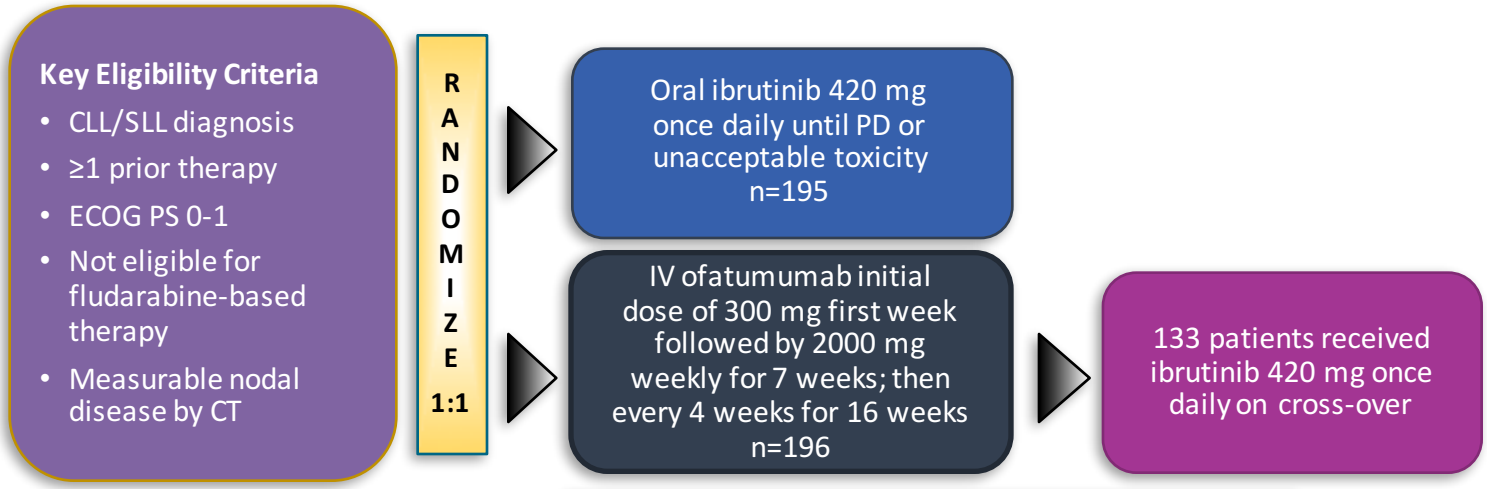
- Previously untreated high-risk, older patients administered ibrutinib monotherapy followed by venetoclax → combined therapy
- 96% CR or CR with incomplete count recovery
  - 69% of patients had remission with undetectable MRD in bone marrow
- 1-year PFS 98%, OS 99%
- Responses in older patients and across all high-risk subgroups

Jain N, et al. *N Engl J Med*. 2019;380:2095-103.

First Treatment Choice: Ibrutinib vs. Ven-G in the Frontline Setting

Ibrutinib	Ven-G
Long-term efficacy data available	Time-limited treatment
Easier to start	Better tolerated and easier to continue
Preferred in patients who: • Can't follow the ramp-up schedule for venetoclax • Significant/unstable renal issues	Preferred in patients with: • Cardiac issues (arrythmia, HTN) • Bleeding issues
Studied against stronger regimens (FCR and BR)	Deep remissions (at MRD level) – would expect the same in younger patients
Ven is effective at the time of ibrutinib progression	Less is known about effectiveness of ibrutinib after Ven progression (ASH 2019 ?)

RESONATE (PCYC-1112)
Phase III Ibrutinib vs Ofatumumab in R/R CLL



Endpoints: PFS, OS, ORR, safety

Patient Characteristics

- Median age = 67
- Rai classification (high) = 57%
- Del(17p) = 32%
- Del(11q) = 31%
- Unmutated IGHV = 47%
- TP53 = 38%

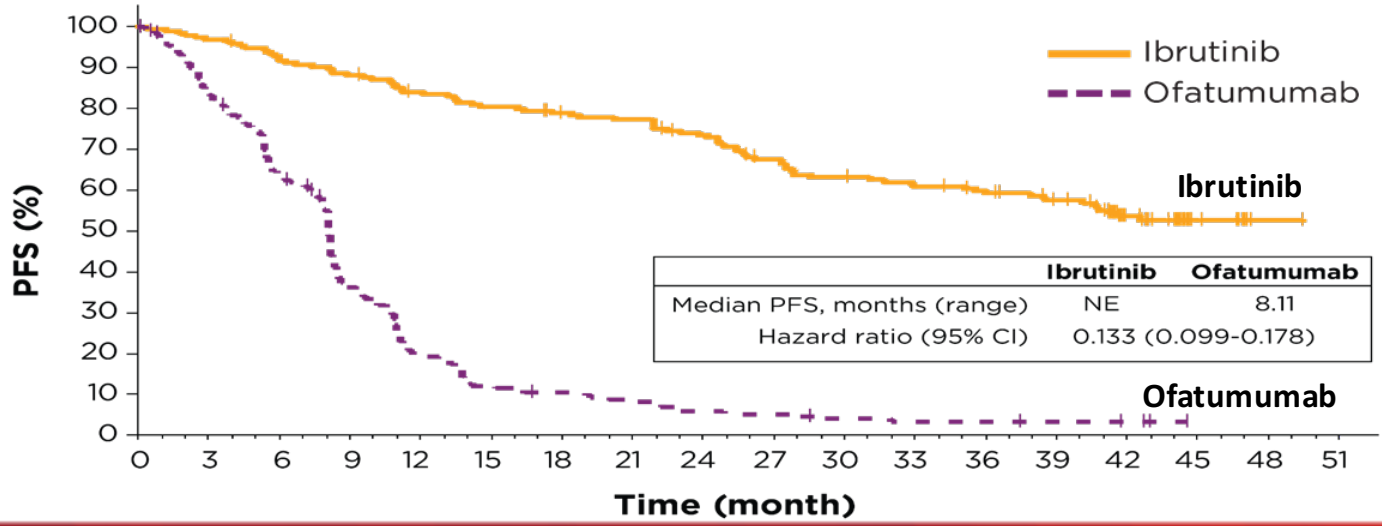
Byrd JC, et al. *Blood.* 2019;133:2031-42; FDA Prescribing Information; Clinicaltrials.gov.

ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Ibrutinib Significantly Extended PFS vs Ofatumumab (RESONATE ~4-year Update)

Updated Results (~6-year analysis) to be presented at ASCO 2019:

- At a median follow-up of 64 months, median PFS continued to be observed with ibrutinib vs ofatumumab → **44.1 vs 8.1 months** (HR 0.15; 95% CI 0.11-0.20; *P*<0.0001)



Byrd JC, et al. *Blood*. 2019;133:2031-42; Byrd JC, et al. ASCO 2017. Abstract 7510; Barr PM, et al. ASCO 2019. Abstract 7510.

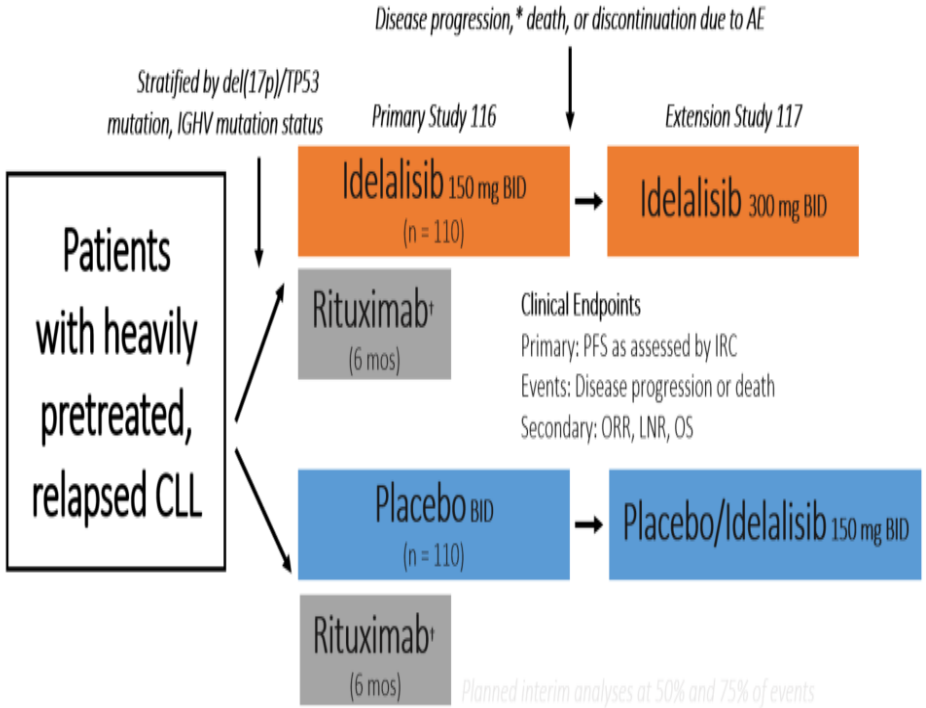
Ibrutinib in CLL
Efficacy

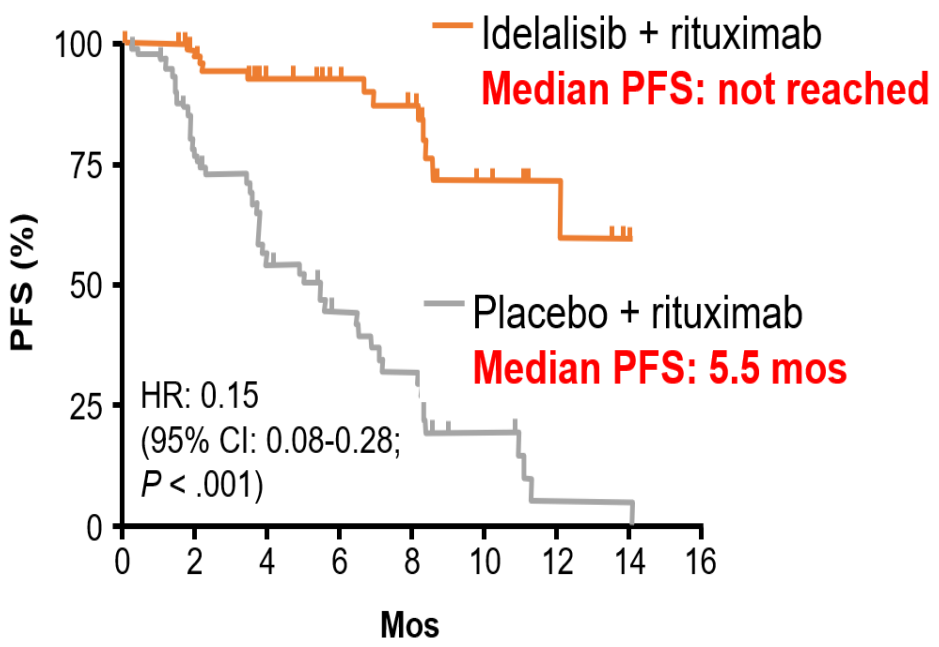
Population	Study	Phase	Follow up	Survival
Treatment naive	PCYC 1102[1] (age ≥65)	I/II	5 yrs	PFS 92% OS 92%
	RESONATE-2[2,3] (vs chlorambucil) (age ≥65)	III	4 yrs	PFS 74% (vs 16% for chlorambucil) OS 95% (vs 84% for chlorambucil)*
Relapsed/ refractory	PCYC 1102[1]	I/II	5 yrs	PFS 44% OS 60%
	RESONATE[4] (vs ofatumumab)	III	5 yrs	Median PFS 44.1 mos (vs 8.1 mos for ofatumumab)
High risk	RESONATE-17[5] [R/R, del(17p)]	II	2 yrs	PFS 63% OS 75%
	Ahn et al[6] (TP53)	II	5 yrs	PFS 74% treatment naïve; 19% R/R OS 85% treatment naïve; 54% R/R

*At 2-year follow-up.

[1]O'Brien S, et al. Blood 2018. Abstract 233; [2]Barr PM, et al. *Haematologica*. 2018;103:1502-10; [3]Burger JA, et al. EHA 2018. Abstract PF343; [4]Barr PM, et al. ASCO 2019. Abstract 7510; [5]O'Brien S, et al. *Lancet Oncol*. 2016;17:1409-18; [6]Ahn IE, et al. *Blood*. 2018;131:2357-66.

Idelalisib and Rituximab for Previously Treated Patients





Furman RR, et al. *N Engl J Med.* 2014;370:997-1007.

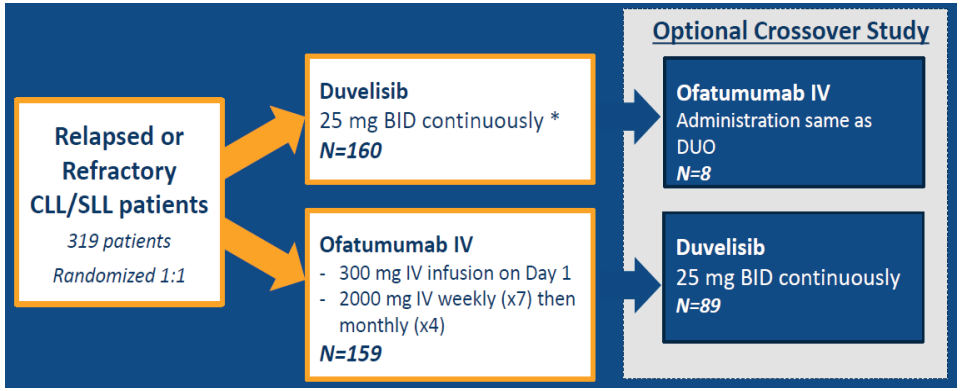
Higher Toxicity if Idelalisib Is Used in Treatment-naïve Patients!

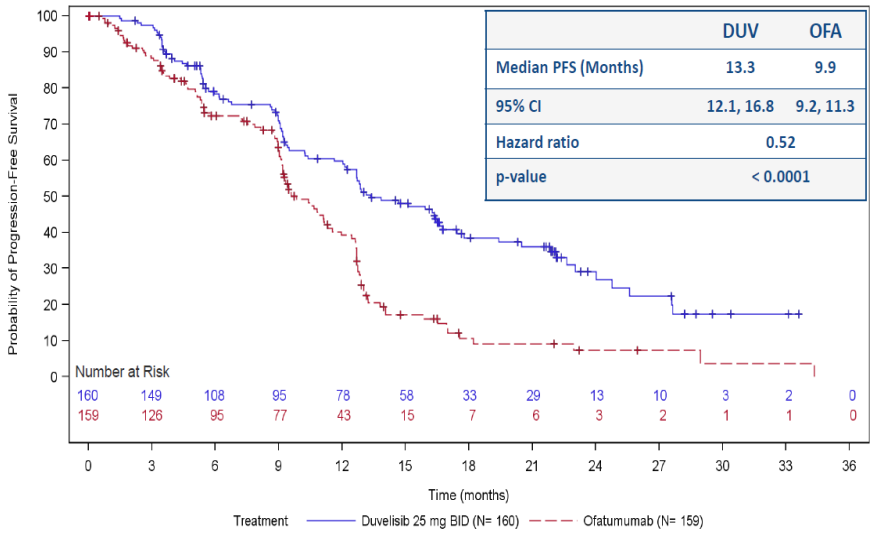
Toxicity Frequency

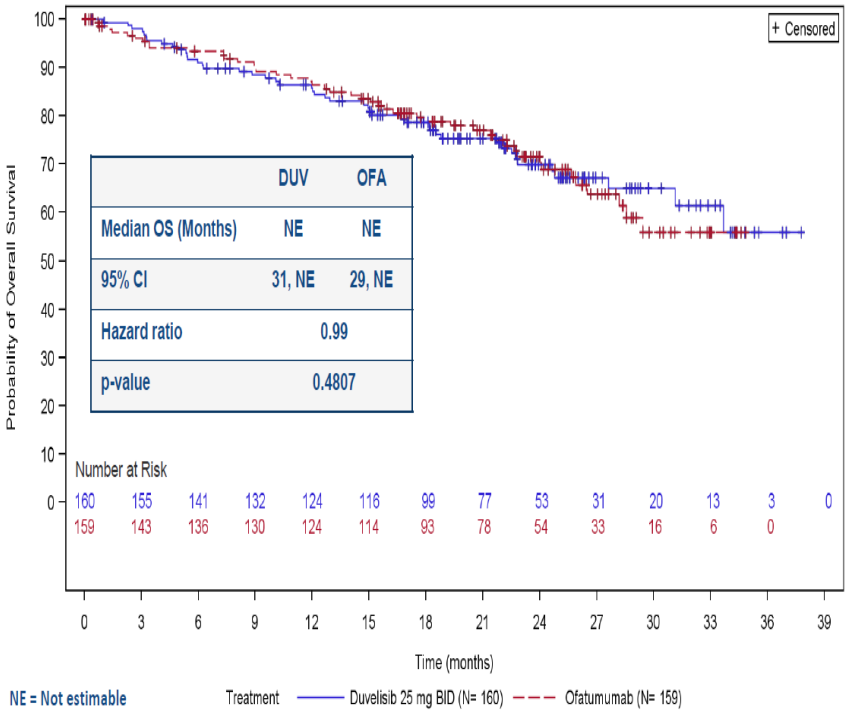
	Phase I[1]	Overall relapsed[2]	Upfront Pts ≥ 65 yo[3]	Upfront younger Pts[4]
Number of patients	54	760	64	24
Median prior treatments	5 (2-14)	≥ 1	0	0
Median age	63 (37-82)	66 (21-91)	71 (65-90)	67 (58-85)
Median time to therapy (months)	15 (0.2-49)	–	22 (0.8 – 46)	8 (0.7-16)
Grade ≥3 transaminitis	1.9%	14%	23%	52%
Grade ≥3 Colitis/diarrhea	5.6%	14%	42%	13%
Any grade pneumonitis	5.6%	3%	3%	13%

[1]Brown JR, et al. *Blood*. 2014;123:3390-7; [2]Coutre S, et al. EHA 2015. Abstract P588; [3]O'Brien SM, et al. *Blood*. 2015;126:2686-94; [4]Lampson BL, et al. ASH 2015. Abstract 497.

Duvelisib vs Ofatumumab (DUO Trial) – R/R

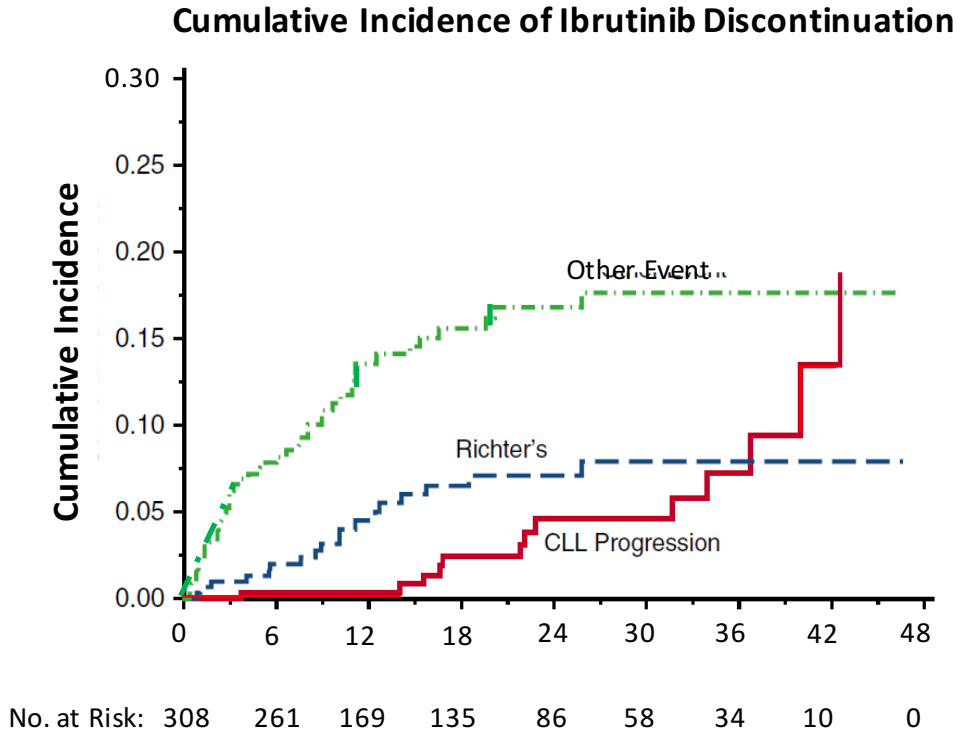






Flinn IW, et al. *Blood*. 2018;132:2446-55.

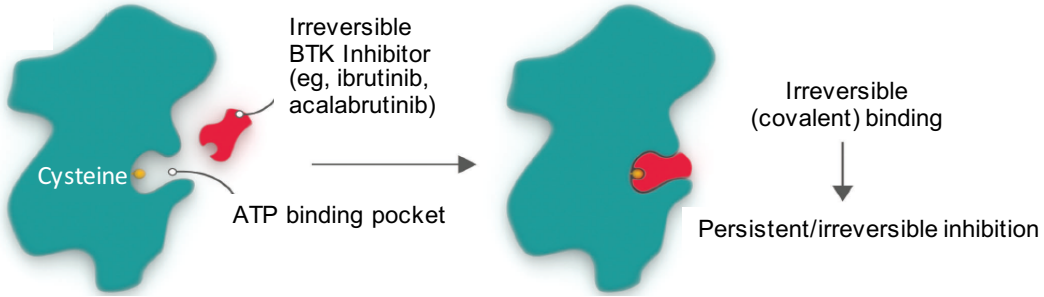
Ibrutinib in CLL
Resistance



- Progressive CLL
  - Almost never occurs during first 12 months
  - Incidence continues to increase with time
- Histologic transformation
  - Most commonly to large cell lymphoma(Richter's) or prolymphocytic leukemia
  - Occurs within first 2 years
- Poor prognosis
  - Reported median survival of 3–23 months

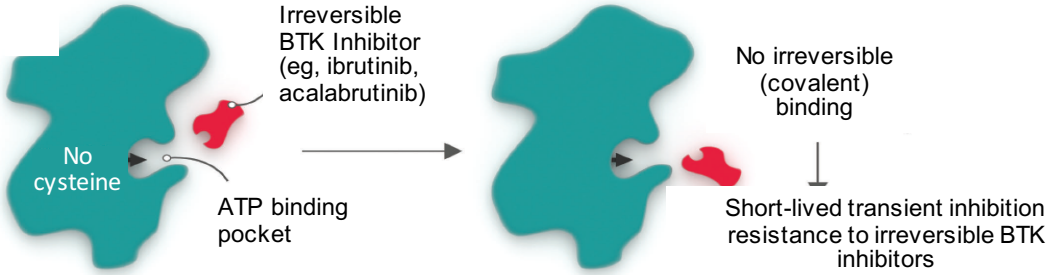
Woyach JA, et al. *Blood*. 2017;129:1270-74; Parikh SA, et al. ASH 2015. Abstract 2935; Maddocks KJ, et al. *JAMA Oncol*. 2015;1:80-7.

Resistance to BTK Inhibitors



Cys481 Mutation – Resistance to BTK

- ~80% of R/R CLL patients have the C481S mutation (has also observed in acalabrutinib). ***DO NOT use acalabrutinib for ibrutinib-refractory disease (due to the C481 mutation).***
- Reversible BTKis may mitigate resistance (e.g., vecabrutinib, GDC-0853, ARQ-531)



Adapted from Wiestner A. *Haematologica*. 2015;100:1495-507; NCCN Practice Guidelines in Oncology. CLL/SLL Guidelines. V1.2020; Byrd JC, et al. *Oncotarget*. 2018;9:13023-35; Wu J, et al. *J Hematol Oncol*. 2016;9:80; Woyach JA, et al. *N Engl J Med*. 2014;370:2286-94; Byrd JC, et al. *N Engl J Med*. 2016;374:323-32.

Selective BTK Inhibitors

- Approximately 50% of patients who discontinue ibrutinib do so because of toxicities (vs ~21% due to progression)
- Next-generation agents have thus far been associated with comparable efficacy to ibrutinib but with greater tolerability in R/R MCL
  - Studies in MCL and other B-cell malignancies (eg, CLL/SLL) are ongoing
- Compared to ibrutinib, newer agents are associated with reduction or elimination of:
    - Atrial fibrillation
    - Skin toxicity
    - Pneumonitis
    - Bleeding complications

Mato AR, et al. *Haematologica*. 2018;103:874-9.

BTK, Bruton tyrosine kinase.

BTK Inhibitors

	Ibrutinib	Acalabrutinib	Zanubrutinib (BGB-3111)	Tirabrutinib (ONO/GS-4059)
Major off-targets	EGFR, ITK, TEC	Minimal	ITK (weak)	TEC (weak)
Platelet inhibition	Yes	Minimal	Unknown	Unknown
Afib	Observed	Minimal	Unknown	Observed*
Mechanism of resistance	*BTK*/*PLCγ2* mutations	*BTK* mutations reported/TBD	TBD	TBD

*Thought to be unrelated to drug.

FDA Prescribing Information; Wu J, et al. *J Hematol Oncol*. 2016;9:80; Byrd JC, et al. *N Engl J Med*. 2016;374:323-332; Woyach JA, et al. *N Engl J Med*. 2014;370:2286-2294.

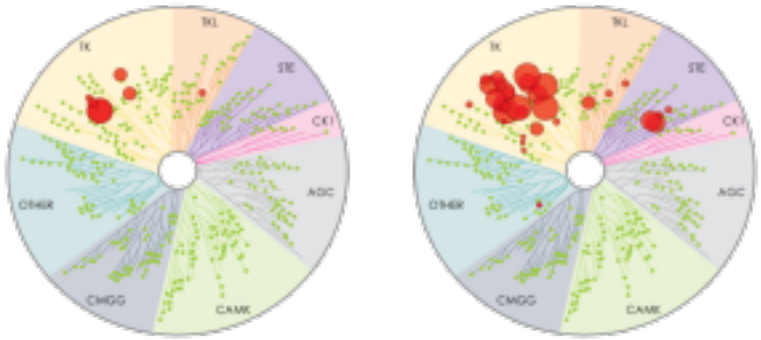
Afib, atrial fibrillation; EGFR, epidermal growth factor receptor; ITK, interleukin-2-inducible T-cell kinase; TEC, tyrosine kinase expressed in hepatocellular carcinoma.

Acalabrutinib: *Agent Overview*

- Highly selective, potent BTK inhibitor
- Designed to minimize off-target activity with minimal effects on TEC, EGFR, or ITK signaling

Kinase selectivity profiling at 1 μM

Acalabrutinib **Ibrutinib**



The size of the red circle is proportional to the degree of inhibition.

Kinase Inhibition, IC_{50} (nM)		
Kinase	**Acalabrutinib**	**Ibrutinib**
BTK	5.1	1.5
TEC	126	10
BMX	46	0.8
TXK	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
ITK	>1000	4.9
JAK3	>1000	32
BLK	>1000	0.1

Barf T, et al. *J Pharmacol Exp Ther*. 2017;363:240-52.

Acalabrutinib in Ibrutinib-intolerant R/R CLL

- Phase II study of efficacy and safety
- Entry criteria: Disease progression after discontinuing ibrutinib due to Grade 3 or 4 adverse events or persistent/recurrent Grade 2 adverse events
- 60 patients enrolled: Median age: 70; 63% male; 28% (del17p); 79% unmutated *IGHV*
- Most common adverse events causing ibrutinib discontinuation: Afib/flutter (25%); diarrhea (12%); rash (12%); arthralgias (10%)
- Median duration of ibrutinib therapy: 6 months
- Median duration of last ibrutinib to acalabrutinb initiation: 9.2 months

Rogers K. 15-ICML 2019. Abstract 029.

Acalabrutinib in Ibrutinib-intolerant R/R CLL

- ORR 72%: 5% CR; 67% PR; 5% PRL: 8% SD; PD 2%; 14% unknown or not evaluated
- At 19 months, PFS not reached; 18-month PFS 73.5%
- 21-month DOR 77.1%; median DOR not reached
- At median follow-up of 23 months, 62% remained on acalabrutinib
- Acalabrutinib discontinuation in 38% due to PD (16%), AEs (12%); and patient withdrawal, investigator decision or other (7%)
- Most common ≥3 AEs: Pneumonia (10%), neutropenia (8%), decreased lymphocyte count (7%), lymphocytosis (7%), thrombocytopenia (3%), anemia (3%)
- Bleeding in 62%, 3% with major hemorrhage; 12% hypertension

Rogers K. 15-ICML 2019. Abstract 029.

DOR, duration of response; SD, stable disease; PD, progressive disease; PRL, partial response with lymphocytosis.

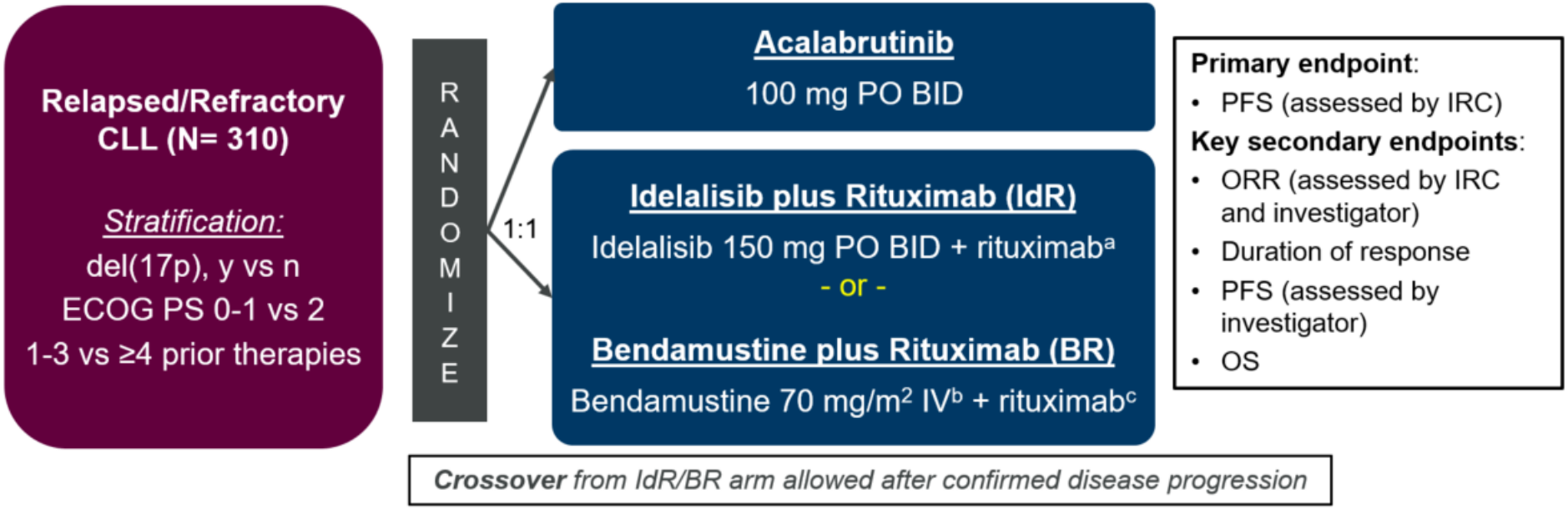
Acalabrutinib in R/R CLL

- Phase I/II multicenter trial
- Endpoints: safety, efficacy, PK/PD
- 60 patients enrolled, Phase I dose escalation (100–400 mg daily, no DLTs), Phase II dose 100 mg twice daily
  - Median age 62, median prior therapies: 3
  - 31% with del(17p), 75% with unmutated *IGHV*
- At 14.3 months, ORR 95%, 100% in del(17p)
  - No Richter's transformation, 1 patient with disease progression

Byrd JC, et al. *N Engl J Med*. 2016;374:323-32.

DLTs, dose-limiting toxicities.

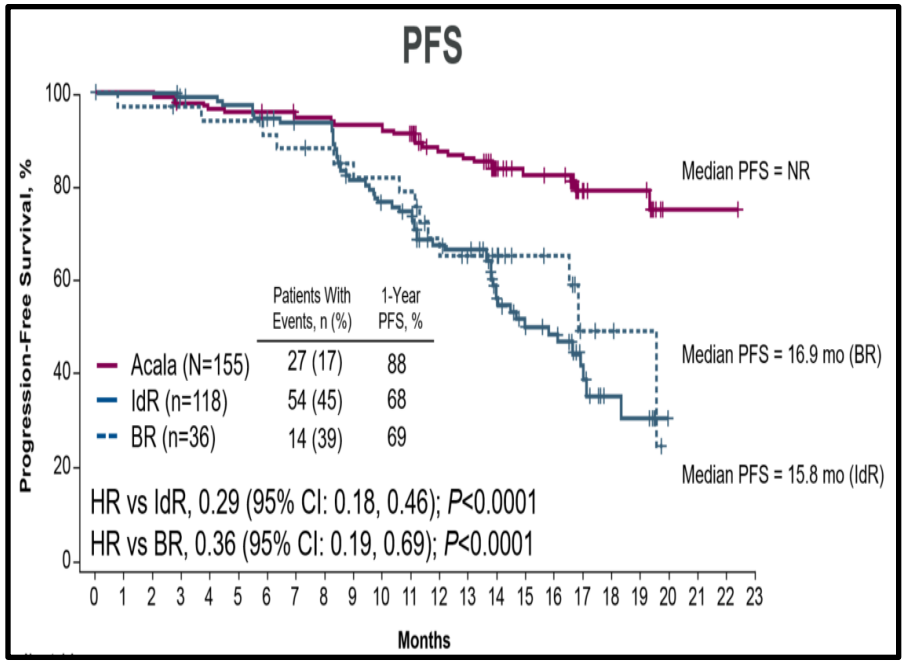
Acalabrutinib vs Investigator's Choice for Relapsed CLL (ASCEND Study)

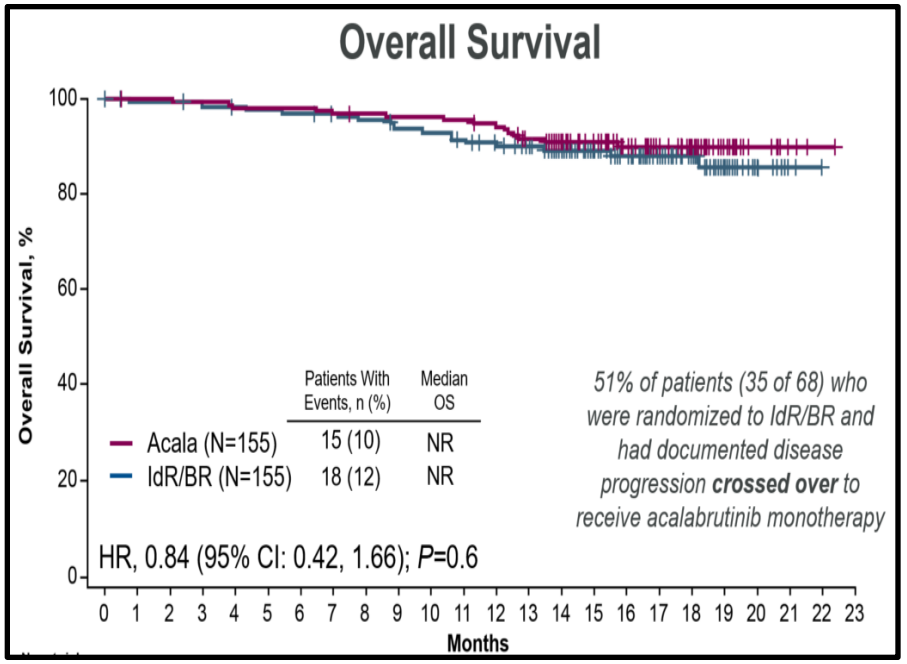


Not FDA approved for CLL as of 9/20/19

Ghia P, et al. EHA2019. Abstract LB2606.

Acalabrutinib vs Investigator's Choice for Relapsed CLL (ASCEND Study)





Not FDA approved for CLL as of 9/20/19

Ghia P, et al. EHA2019. Abstract LB2606.

Acalabrutinib for R/R CLL

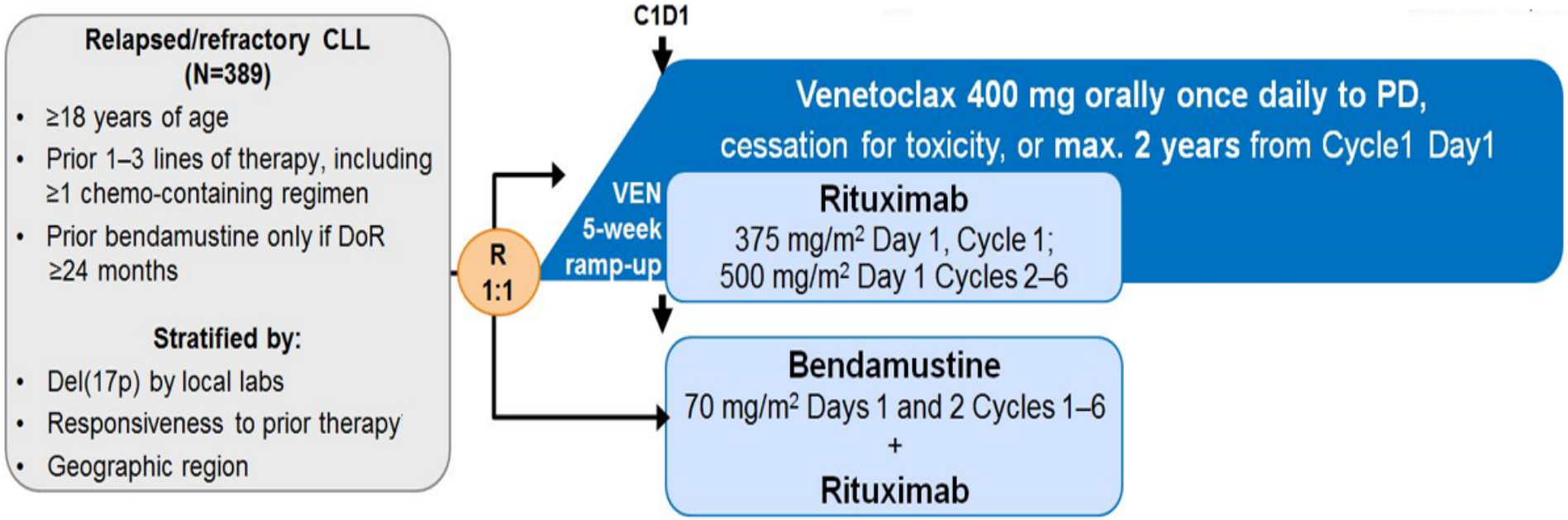
- Selective BTK inhibitor with fewer off-target effects
- **Not approved for CLL, but FDA has issued breakthrough designation for both frontline and R/R settings**
- Per NCCN guidelines, acalabrutinib is an option for patients who don't tolerate ibrutinib
- Should **NOT** be used in patients who fail ibrutinib

Off-Label Alert

Ongoing Acalabrutinib Phase III Trials

- Acalabrutinib + venetoclax ± obinutuzumab as front-line therapy
- Acalabrutinib vs ibrutinib in previously treated high-risk CLL

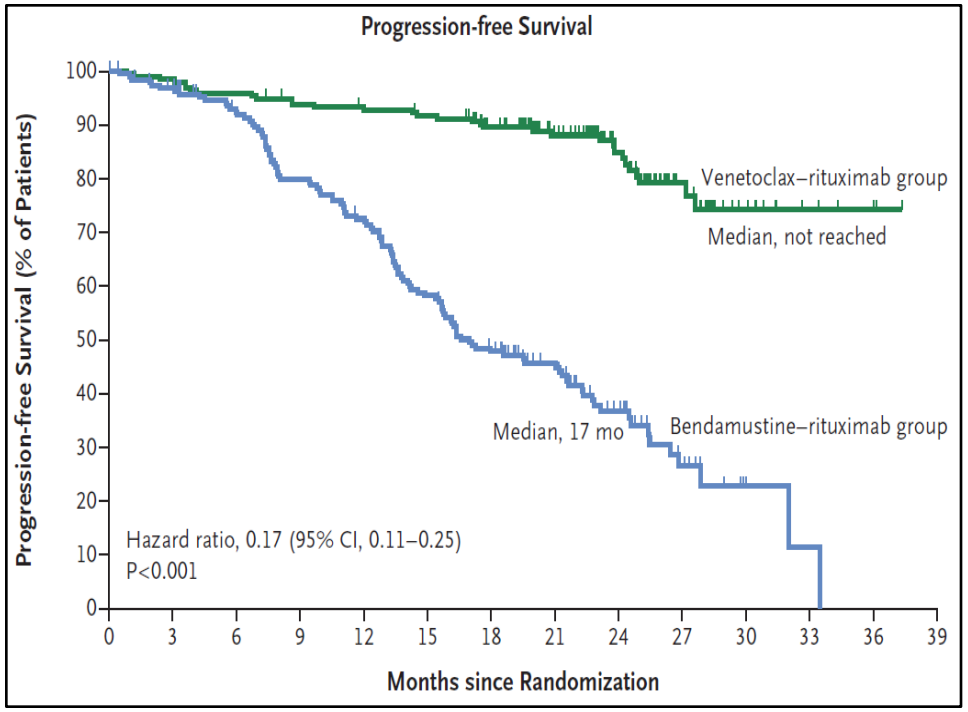
Ven-R vs BR in R/R CLL (MURANO Study)

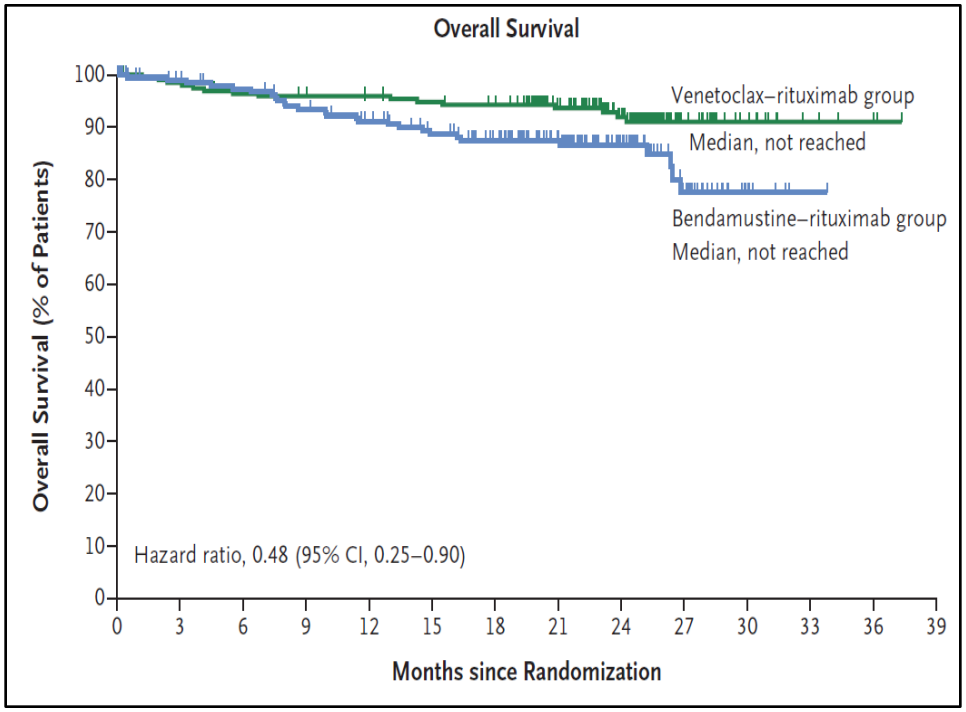


Primary Endpoint	INV-assessed PFS

Seymour JF, et al. *N Engl J Med*. 2018;378:1107-20.

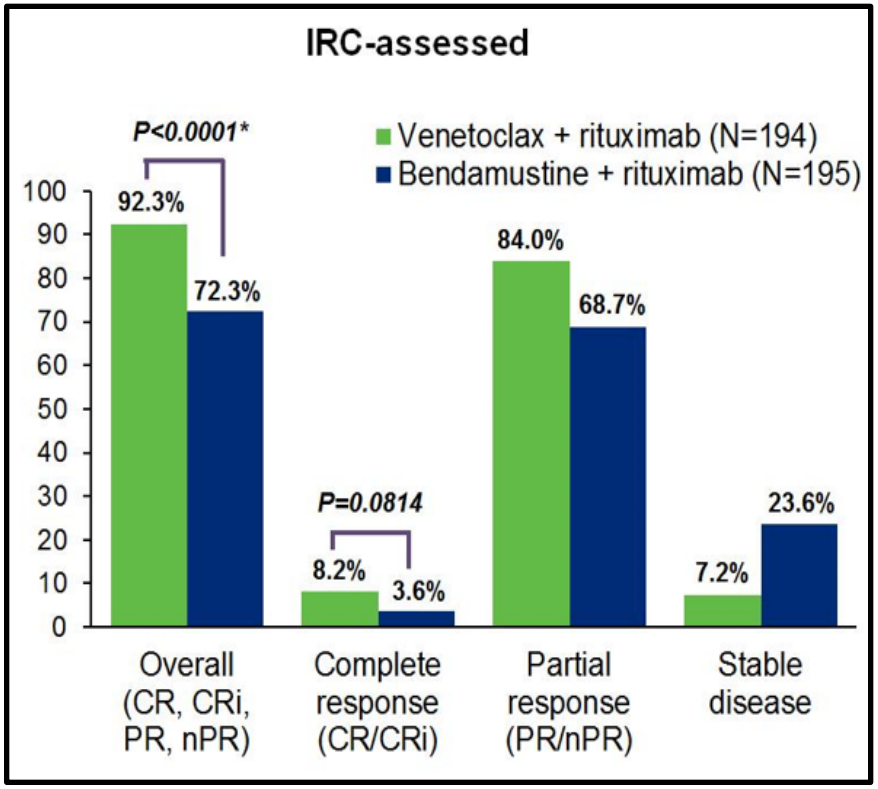
Ven-R vs BR in R/R CLL (MURANO Study)

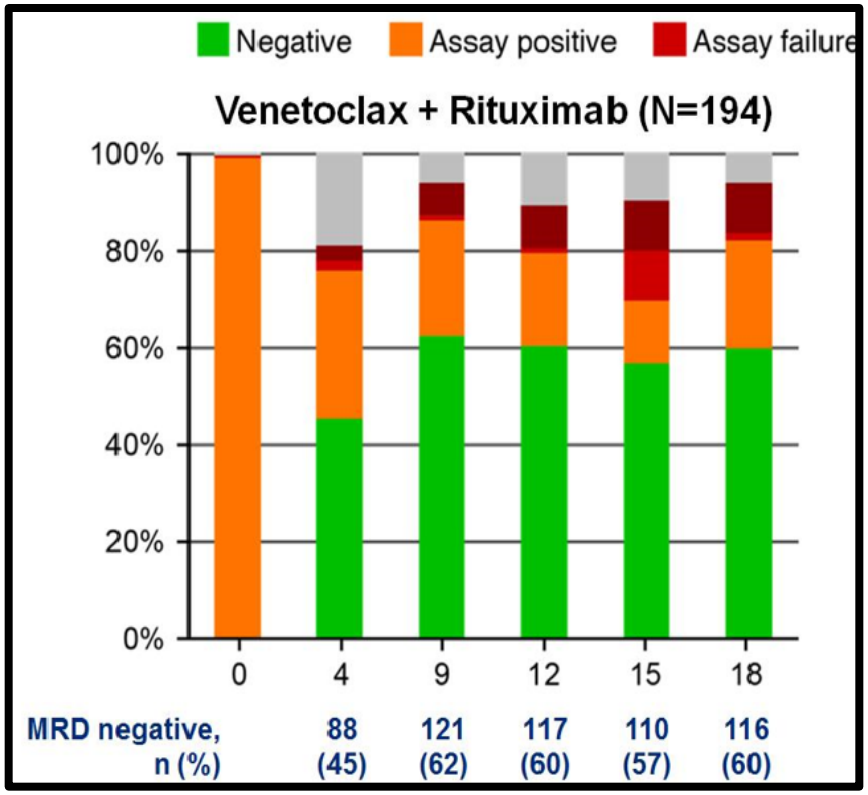




Seymour JF, et al. *N Engl J Med*. 2018;378:1107-20.

Ven-R vs BR in R/R CLL (MURANO Study)





Seymour JF, et al. *N Engl J Med*. 2018;378:1107-20.

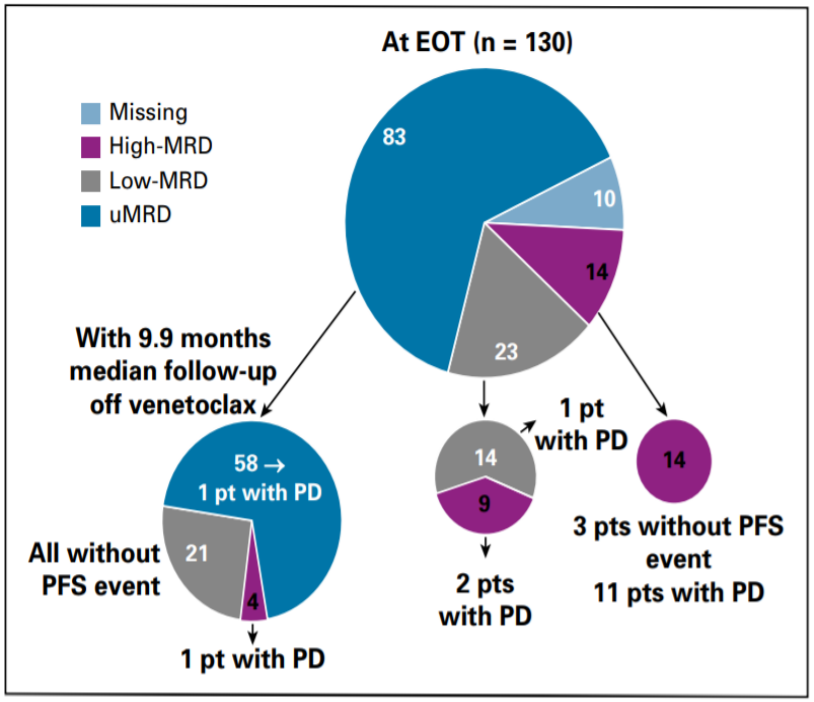
Ven-R vs BR in R/R CLL (MURANO Study)

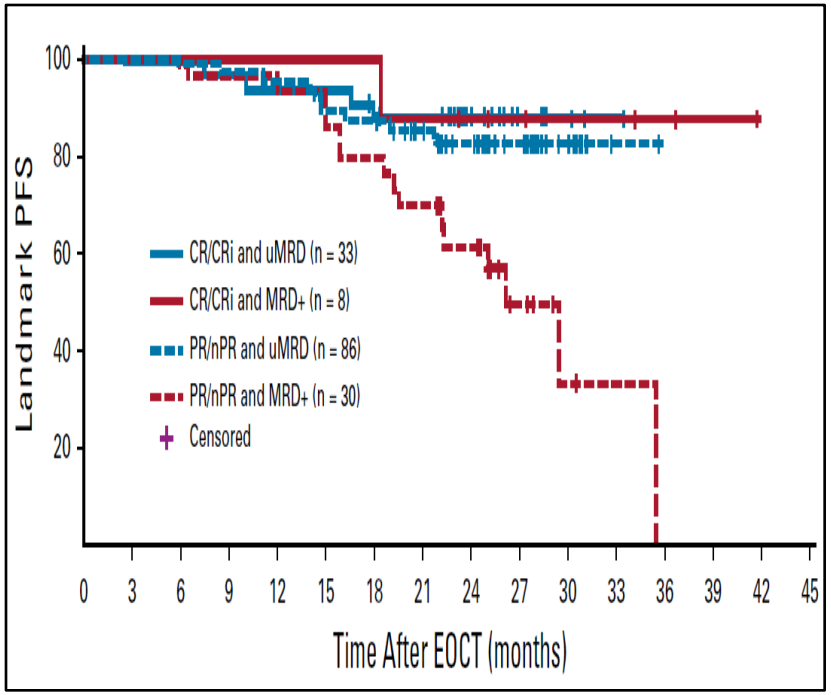
Adverse Event	Ven-R, n (%)	BR, n (%)
Grade 3 or 4 AE	159 (82%)	132 (70.2%)
Neutropenia	112 (57.7%)	73 (38.8%)
Infections	34 (17.5)	41 (21.8%)
Anemia	21 (10.8%)	26 (13.8%)
Thrombocytopenia	11 (5.7%)	19 (10.1%)

Serious Adverse Event	Ven-R, n (%)	BR, n (%)
SAEs with $\geq$ 2% incidence	90 (46.4%)	81 (43.1%)
Pneumonia	16 (8.2%)	15 (8%)
Febrile neutropenia	7 (3.6%)	16 (8.5%)
Pyrexia	5 (2.6%)	13 (6.9%)
Anemia	3 (1.5%)	5 (2.7%)
Infusion-related reaction	1 (0.5%)	6 (3.2%)
Sepsis	1 (0.5%)	4 (2.1%)
Tumor lysis syndrome	4 (2.1%)	1 (0.5%)
Hypotension	0	5 (2.7%)
Fatal adverse events	10 (5.2%)	11 (5.9%)

Seymour JF, et al. *N Engl J Med*. 2018;378:1107-20.

What Happens After Stopping Venetoclax?





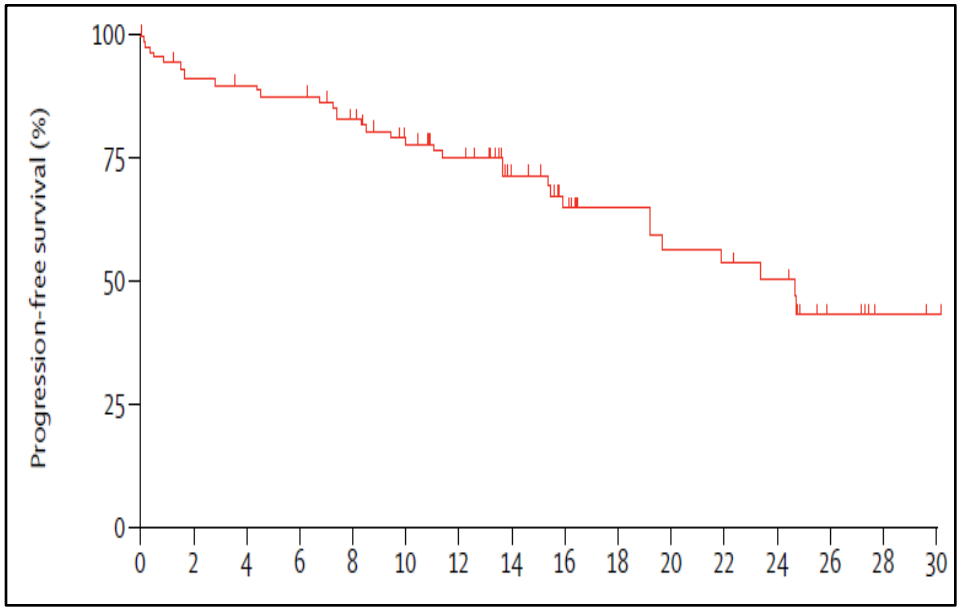
High-level MRD: $\geq 10^{-2}$
Low-level MRD: 10^{-4} to 10^{-2}
Undetectable MRD: $<10^{-4}$

Kater AP, et al. *J Clin Oncol*. 2019;37:269-77.

Venetoclax After Ibrutinib Failure

- Relapsed/refractory after prior ibrutinib
- *TP53*
  - deletion: 47%
  - mutation: 33%
- Relapsed: 31%; Refractory: 68%
- Time on ibrutinib: 20 months (range, 1–61)

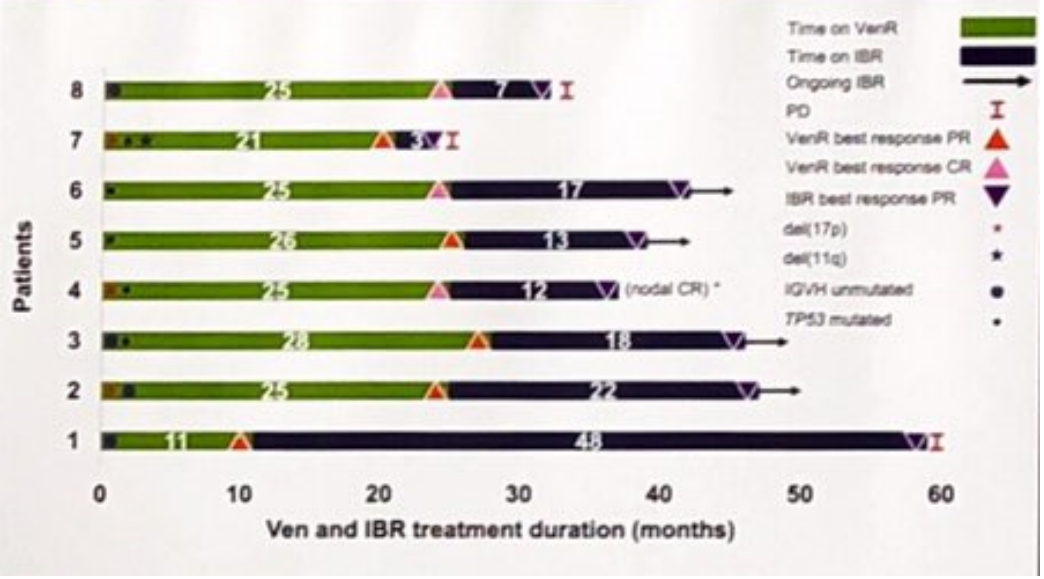
	All patients (n=91)
Overall response	59 (65%, 53-74)
Complete response or complete response with incomplete bone marrow recovery	8 (9%)
Nodular partial response	3 (3%)
Partial response	48 (52%)
Stable disease	22 (24%)
Disease progression	5 (5%)
Discontinued before response assessment	6 (7%)



Median follow-up: 14 months (8–18)

Jones JA, et al. *Lancet Oncol*. 2017;19:65-75.

Ibrutinib After Venetoclax Failure



Stay tuned: Real-World Experience (RWE) Collaboration @ ASH '19

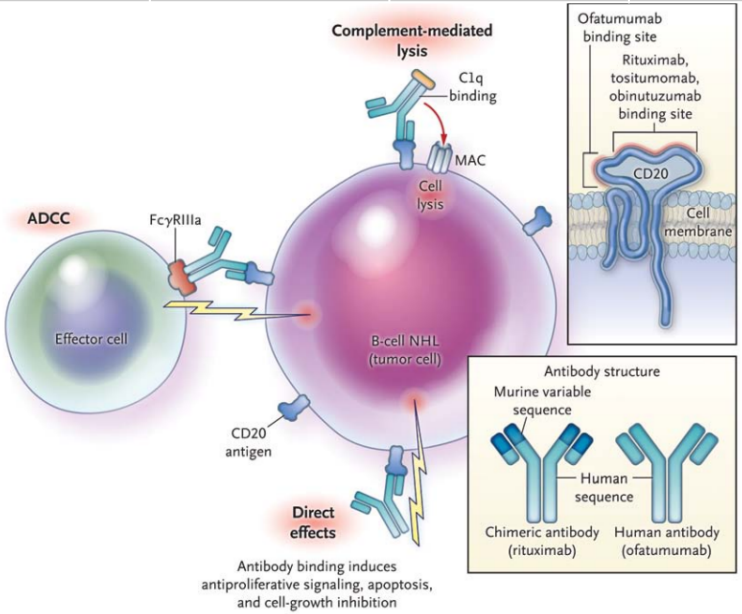
Greil R, et al. EHA 2019. Abstract PS1161.

Novel Agents for the R/R Setting

	Ibrutinib	Venetoclax	Idelalisib/Duvelisib
Target	BTK	BCL-2	PI3K delta/ delta + gamma
Dose	420 mg po daily	Ramp-up → 400 mg po daily	150 mg po BID (idelalisib) 25 mg po BID (duvelisib)
Anti-CD20 Ab	No major benefit Faster "response"	Recommended R/R label	Yes for idelalisib
Major side effect (concern)	Bleeding (anticoagulation)	TLS (initially)	Colitis (diarrhea) Infections (FDA alert)
Other side effects	• Body pain • Fatigue • Hypertension • Afib	• Neutropenia	• Pneumonitis • Transaminitis (idelalisib) • PJP • CMV
Duration	Indefinite	Fixed	Indefinite

Anti-CD20 Antibodies

		Type	Direct effect	CDCC	ADCC
Rituximab	Chimeric	I	↑	↑↑↑↑	↑↑
Ofatumumab	Humanized	I	↑	↑↑↑↑	↑↑
Obinutuzumab	Humanized	II	↑↑↑↑	↑	↑↑↑



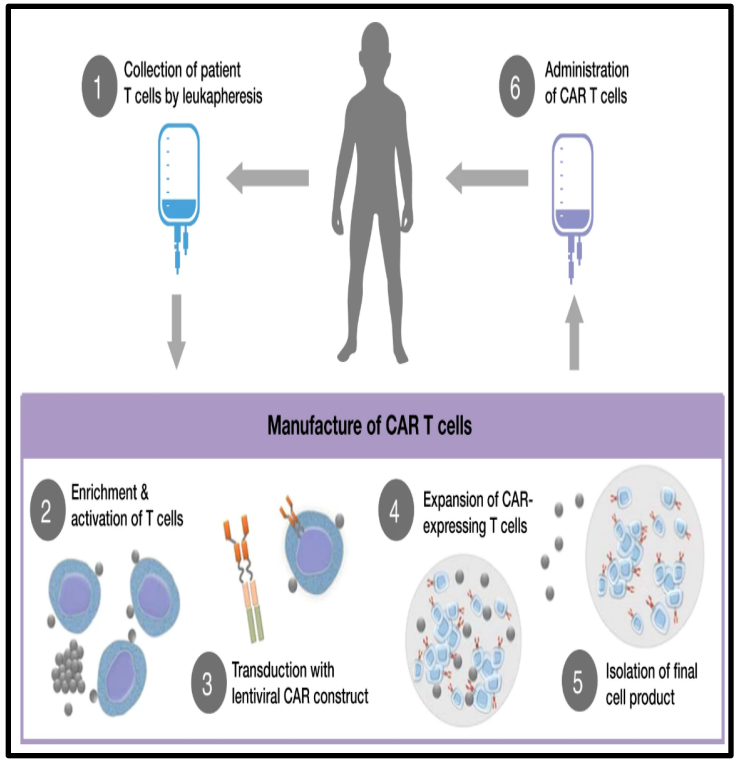
Maloney DG. *N Engl J Med*. 2012;366:2008-16.

Obinutuzumab in CLL

- First line with chlorambucil in the elderly, without del(17p) or *TP53*
- First line with venetoclax, all ages, all comorbidities, without del(17p) or *TP53*
- Monotherapy
  - First line in patients without del(17p) or *TP53*
  - First line in patients with del(17p) or *TP53*

CAR-T for CLL

- Experimental
- Long-term remissions ~30–35%
- Best predictor of response: MRD neg after treatment
- Registration studies are currently ongoing
- Recommend before alloSCT, if available



Allogeneic SCT for High-risk CLL

- Reduced intensity/ nonmyeloablative allogeneic transplant

Author	Shadman	Kramer	Sorror	Dreger	Brown	Khouri	Khouri	Michallet
Year	**2019**	**2017**	**2008**	**2013**	**2013**	**2011**	**2017**	**2013**
N	55	90	82	90	76	86	26	40
Conditioning	Flu-TBI-R	variable	Flu-TBI	FC ± ATG	Flu-Bu	FCR	BFR	FCR
Follow-up (yr)	3	10	5	6	5	5	3	3
OS	**54**	**51**	**50**	**58**	**63**	**51**	**82**	**55**
PFS	**45**	**34**	**39**	**38**	**43**	**36**	**63**	**46**
NRM	**38 (<12)***	**20**	**23**	**23**	**16**	**17**	**8**	**27**
aGVHD	20	?	16-23	14	17	7	4	23
Extensive cGVHD	66	?	49-53	55	48	56	45	29

50
40
20-25

*In patients without comorbidities.

Side Effects and Management

Ibrutinib
Safety

Adverse Effect	Incidence
Afib[1,2]	~5x increase with ibrutinib
	3.3 events per 100 person-yrs RR 3.9 vs comparator (*P* < 0.0001)
Bleeding[3,4]	61% (53% Grade 1/2)
	55% (all grade 1/2)
Hypertension[1]	12% all grade (*median time to onset:* 5.9 months)
Pneumonitis[5]	Not yet defined
Skin (rash)[6]	27%
Hair/Nail changes[7]	67% nail, 26% hair
Diarrhea[1]	39% all grades (*median time to onset:* ~21 days; ~117 days for Grade ≥3)
Lymphocytosis[1]	CLL: 66% all grades (*median time to onset:* ~4 weeks) MCL: 33% all grades (*median time to onset:* first few weeks)

[1]Pharmacyclics/Janssen Biotech (2019). Imbruvica (ibrutinib) prescribing information; [2]Leong DP, et al. *Blood*. 2016;128:138-40; [3]Byrd JC, et al. *Blood*. 2015;125:2497-506; [4]Lipsky AH, et al. *Haematologica*. 2015;100:1571-8; [5]Mato AR, et al. *Blood*. 2016;127:1064-7; [6]Byrd JC, et al. *N Engl J Med*. 2013;369:32-42; [7]Bitar C, et al. *JAMA Dermatol*. 2016;152:698-701.

Ibrutinib AEs Grade ≥3 Over Time

Adverse Event	0-6 months	6-12 months	1-2 years	2-3 years	3-4 years	4-5 years
Hypertension	1%	7%	7%	20%	18%	25%
Pneumonia	6%	3%	9%	7%	12%	7%
Neutropenia	7%	3%	2%	2%	3%	3%
Thrombocytopenia	3%	<1%	2%	2%	1%	0
Atrial fibrillation	1%	<1%	2%	1%	6%	4%
Diarrhea	2%	<1%	2%	1%	3%	3%
BLEEDING				Cumulative rate 8%		Cumulative rate 9%
Sepsis	<1%	<1%	4%	0	3%	3%
Fatigue	1%	<1%	1%	0	3%	0
Decreased lymphocyte count	0	0	1%	6%	5%	4%
Hyperglycemia	1.5%	0	1%	4%	6%	0

Coutre SE. *Blood*. 2019;133:2737-8.

Acalabrutinib Safety

Adverse Event	All Grades	Grades 1–2	Grades 3–4
	Number of patients (%)		
Headache	26 (43)	26 (43)	0
Diarrhea	24 (39)	23 (38)	1 (2)
Increased weight	16 (26)	15 (25)	1 (2)
Pyrexia	14 (23)	12 (20)	2 (3)
Upper resp. tract infection	14 (23)	14 (23)	0
Fatigue	13 (21)	11 (18)	2 (3)
Peripheral edema	13 (21)	13 (21)	0
Hypertension	12 (20)	8 (13)	4 (7)
Nausea	12 (20)	12 (20)	0
Contusion	11 (18)	11 (18)	0
Arthralgia	10 (16)	9 (15)	1 (2)
Petechiae	10 (16)	10 (16)	0
Decreased weight	10 (16)	10 (16)	0

Byrd JC, et al. *N Engl J Med.* 2016;374:323-332.

Special Considerations for BTK Inhibitor AE Management

Toxicity	Ibrutinib	Acalabrutinib
Infections	≥ Gr 3: 24%	≥ Gr 3: 18%
• Cases of progressive multifocal leukoencephalopathy (PML), pneumocystis jirovecii pneumonia (ibrutinib), and infections due to hepatitis B reactivation (acalabrutinib) have occurred • Monitor and evaluate patients for fever and infections; treat appropriately		
Lymphocytosis	33%	32%
• Presents during the first few weeks of therapy and typically resolves by 2 months		
Second Primary Malignancies	9%	11%
• Most common malignancy seen is skin cancer • Advise protection from sun exposure and encourage routine cancer screening		
Headache	13%	39%
• Usually observed early in therapy and typically resolves over 1–2 months • Generally well managed with analgesics such as acetaminophen and caffeine supplements		

FDA Prescribing Information; Rogers B, Khan N. *J Adv Pract Oncol*. 2017;8:97-111;
NCCN Practice Guidelines in Oncology. CLL/SLL Guidelines. V1.2020.

Special Considerations for BTK Inhibitor AE Management

Toxicity	Ibrutinib	Acalabrutinib
Hemorrhage/Bleeding	44% ≥ Gr 3: 3%	50% ≥ Gr 3: 2%
• Increased risk of bleeding on concomitant anticoagulant therapy or antiplatelet therapy • Consider risk/benefit of withholding for 3–7 days pre- and post-surgery		
Afib/flutter	5%–7.7%	3%
• Periodically monitor for cardiac arrhythmias and obtain ECG for those who develop symptoms (palpitations, lightheadedness, syncope, chest pain) or new-onset dyspnea • Manage cardiac arrhythmias and manage as appropriate		
Hypertension	12%	NR
• Monitor for new/uncontrolled hypertension • Initiate antihypertensives as needed		

Rogers B, Khan N. *J Adv Pract Oncol*. 2017;8:97-111; NCCN Practice Guidelines in Oncology. CLL/SLL Guidelines. V1.2020.

Unique AEs with Venetoclax: Tumor Lysis Syndrome

- Venetoclax therapy can cause rapid reduction in tumor and pose a risk for TLS at initiation and during ramp-up phase
- Changes in blood chemistries consistent with TLS (requiring prompt management) can occur as early as 6–8 hours after first dose and at each dose increase
- Risk increases in those with comorbidities (eg, reduced renal function) and increased tumor burden
- Concomitant use with P-gp inhibitors or strong/moderate CYP3A inhibitors increases risk of TLS and requires dose adjustment
- ***Best managed if anticipated and prophylaxis is started prior to treatment***

AbbVie/Genentech (2019). Venclexta (venetoclax tablets) prescribing information.

BCL-2 Inhibitor: Venetoclax

Dose	Ramp up for first 5 weeks and then 400 mg daily (ramp-up to reduce risk of tumor lysis syndrome)
Dosage Form	Tablets: 10 mg, 50 mg, 100 mg
Most common adverse events (>20%)	Neutropenia, diarrhea, upper respiratory track infection, thrombocytopenia, musculoskeletal pain, edema, fatigue, cough, and nausea
Drug Interactions	Strong or moderate CYP3A inhibitors, P-gp inhibitors
Resistance	GLy101Val

AbbVie/Genentech (2019). Venclexta (venetoclax tablets) prescribing information;
Thangavadivel S, Byrd JC. *Cancer Discov*. 2019:9:320-2.

TLS Prophylaxis Based on Tumor Burden

Tumor Burden	Prophylaxis	Blood Chemistry Monitoring
Low All LN <5 cm and ALC <25 x 10^9/L	• Oral hydration (1.5–2 L) • Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6–8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose
Medium Any LN 5 cm to <10 cm or ALC ≥25 x 10^9/L	• Oral hydration (1.5–2 L) and consider additional intravenous • Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6–8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalization for patients with ClCr <80 mL/min
High Any LN ≥10 cm or ALC ≥25x10^9/L and any LN ≥5 cm	• Oral hydration (1.5–2 L) and intravenous (150–200 mL/hour as tolerated) • Allopurinol (consider rasburicase if baseline uric acid is elevated)	In hospital • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12, 24 hours Outpatient • For subsequent ramp-up doses: Pre-dose, 6–8 hours, 24 hours

AbbVie/Genentech (2019). Venclexta (venetoclax tablets) prescribing information.

Safety Summary for Use of PI3K Inhibitors in CLL

Idelalisib

- Monitor for GI events, hepatotoxicity, pneumonitis, intestinal perforation
  - Interrupt, consider steroids, then reduce or discontinue agent
- Potential for infections, including opportunistic infections such as CMV and PJP

Duvelisib

- Monitor hepatic function and blood counts
- Advise patients of potential risk to a fetus and to use effective contraception
- Monitor for GI events, hepatotoxicity, pneumonitis, intestinal perforation
  - Interrupt, consider steroids, then reduce or discontinue agent

Gilead Sciences (2018). Zydelig (idelalisib) capsules prescribing information; Verastem (2018). Copiktra (duvelisib) capsules prescribing information; Hallek M, et al. *Blood*. 2018;131:2745-60.

Case Study 1

- 72-year-old male diagnosed 5 years ago with Stage I CLL with del(13q), *IGHV* mutated, no *TP53* abnormality
- Widower, lives alone, PMH remarkable for hypertension
- Slowly increasing lymphocyte count and decreasing platelets, now with ALC 117K and Plts in 80K-90K range for the past few months
- New mild fatigue and upper body night sweats
- What additional testing does he need?
- What are his treatment options?

Case Study 1

- Repeat prognostic work-up reveals del(13q) and new trisomy 12, TP53 continues to be negative
- CT reveals ongoing adenopathy, slightly larger, no concern for transformation
- Splits time between home and Florida, does not want to commit to a clinical trial or coordinate IV therapy while in Florida
- Opts for ibrutinib

Frail with significant comorbidity OR Age ≥65 y and younger patients with significant comorbidities
Preferred first-line regimens:
• **Ibrutinib** • **Venetoclax + obinutuzumab**
Other recommended regimens:
• Bendamustine + CD20 monoclonal antibody (not recommended for frail patients) • Chlorambucil + anti-CD20 monoclonal antibody • **High-dose methylprednisolone + rituximab** • **Ibrutinib + obinutuzumab** • **Onibutuzumab** • Chlorambucil • **Rituximab**

NCCN Practice Guidelines in Oncology. CLL/SLL Guidelines. V1.2020.

Case Study 1

- Initial lymphocytosis, mild diarrhea and nausea, improves with ondansetron and OTC anti-diarrheals, good adherence
- CBC normalizes, 75% reduction in adenopathy
- Remains on ibrutinib
- Year 3, phones from Florida reporting hospitalization for Afib and worsening hypertension
- Next steps?

Case Study 1

- Ibrutinib held
- Requires cardioversion for Afib, now on 3 anti-hypertensives for BP control
- Responding to ibrutinib but experiencing late toxicities
- Discussion of remaining on BTK therapy with acalabrutinib vs changing drug classes
- Patient motivated to remain on oral-only options

Case Study 1

- Decision made to continue BTK therapy with acalabrutinib
- Tolerates well, with no significant toxicities, no worsening of hypertension or return of Afib
- Remains on acalabrutinib

Case Study 2

- 60-year-old female with del(17p) CLL, *IGHV* unmutated, no PMH
- On initial therapy of ibrutinib x 4 years
- Presents with progressive disease; lymphocytosis, new palpable adenopathy
- What testing does she need?
  - Repeat FISH?
  - Do you need to know *TP53* status?
  - Imaging to rule out transformation?
- What are her treatment options?

Case Study 2

- Referral to transplant center
- Venetoclax ± rituximab and PI3K therapy discussed
- Patient chooses venetoclax + rituximab

Relapsed/Refractory del(17p)
Preferred regimens:
• **Acalabrutinib** • **Ibrutinib** • **Venetoclax + rituximab** • **Duvelisib** • **Idelalisib + rituximab** • **Venetoclax**
Other recommended regimens
• **Acalabrutinib** • **Alemtuzumab +/- rituximab** • **HDMP + rituximab** • **Idelalisib** • **Lenolidomide +/- rituximab** • **Ofatumumab**

NCCN Practice Guidelines in Oncology. CLL/SLL Guidelines. V1.2020.

Case Study 2

- Meets criteria for medium TLS risk
- Allopurinol started
- Arrives for 24-hour TLS labs post 50 mg dosing
- K 5.7, Creat 2.1, Uric acid 10
- Admitted for TLS management, recovers fully
- Tolerates remaining ramp-up doses without lab abnormalities

Medium **Any LN 5 cm to <10 cm or ALC ≥25 x 10^9/L**	• **Oral hydration (1.5–2 L) and consider additional intravenous allopurinol**	**Outpatient** • **For first dose of 20 mg and 50 mg: Pre-dose, 6–8 hours, 24 hours** • **For subsequent ramp-up doses: Pre-dose** • **For first dose of 20 mg and 50 mg: Consider hospitalization for patients with ClCr <80 mL/min**

AbbVie/Genentech (2019). Venclexta (venetoclax tablets) prescribing information.

Case Study 2

- What is the role of transplant in CLL in the age of novel agents?
  - Timing
  - Toxicity
- Where does CAR-T fit in?

Conclusions

- Novel agents have improved response rates and overall survival for all-risk CLL patients
- Side-effect identification and management is critical and challenging with oral therapies
- Patient education and shared decision making are more important than ever
- Oncology APPs and pharmacists play a key role in successful outcomes for patients with CLL

Q&A

Improving Outcomes for Patients With Chronic Lymphocytic Leukemia

Thank you for joining us!

Please complete your evaluation.