VIRTUAL CHALLENGING CASE CLINIC:

B-Cell Lymphomas

Chronic Lymphocytic Leukemia
Broadcast on October 13, 2021

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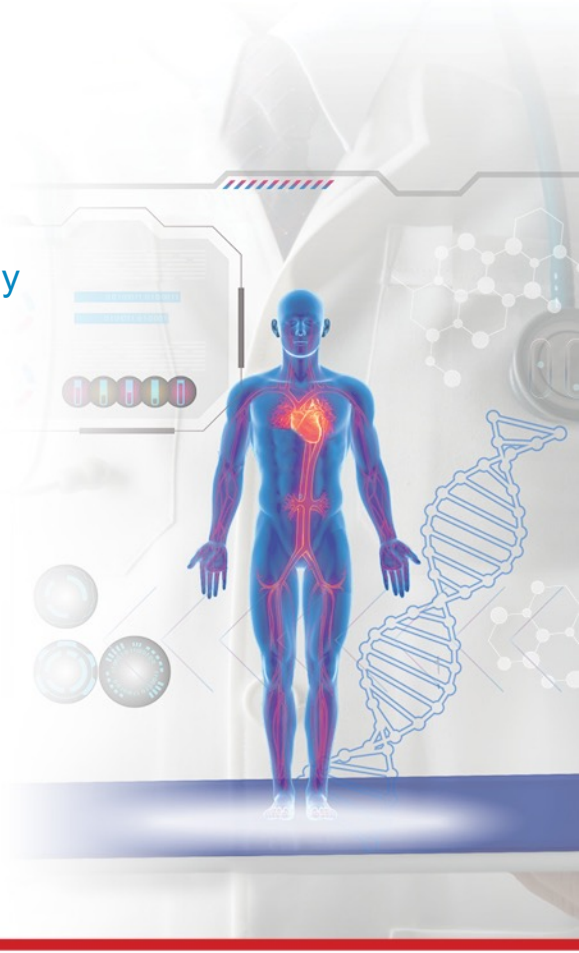

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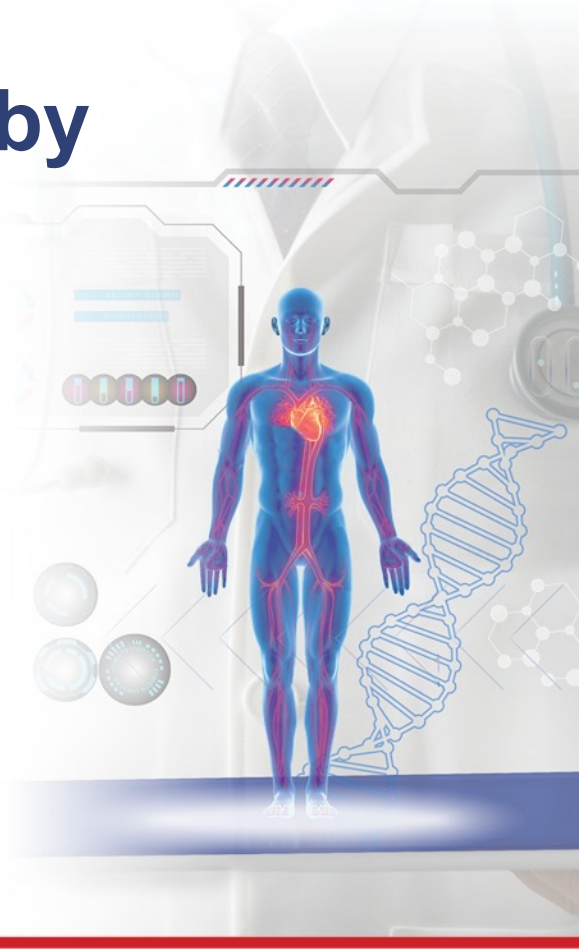

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Disclosures

John P. Leonard, MD

Consulting Fees: ADC Therapeutics, AstraZeneca, Bayer, Bristol-Myers Squibb Company, Epizyme, Kite, a Gilead Company, MEI Pharma, Miltenyi Biotec, Regeneron, Roche/Genentech, Sutro Biopharma

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Planning Committee

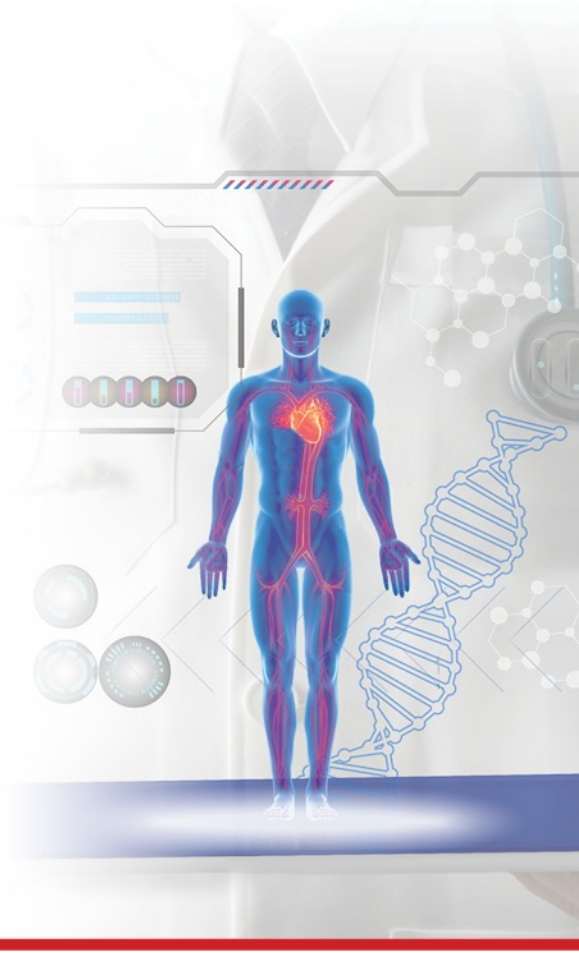
The following planning committee members have nothing to disclose:
UNMC: Brenda Ram, CMP, CHCP

Bio Ascend: Patti Bunyasaranand, MS; Dru Dace, PhD; Lucja Grajkowska, PhD; Kraig Steubing

Learning Objectives

- Evaluate best available evidence regarding treatment for patients with CLL
- Assess the implications of emerging clinical trial data regarding CLL treatment approaches
- Develop strategies to address complicated CLL cases

Patient Cases



Case 1

A 49-year-old man with HTN and stage 2 CKD presents with new lymphocytosis. Flow shows monoclonal population (CD19/20/5/23+), FISH with trisomy 12 only, also with unmutated IGHV, NOTCH1/TP53 wildtype. He is diagnosed with Rai 0 CLL and observed for 4 years. He is now 53-years old and has progressive symptomatic anemia, thrombocytopenia, and lymphadenopathy. Bone marrow biopsy shows 90% involvement by CLL, and he now requires initial therapy.

How would you choose to treat this patient?

A. Chlorambucil + obinutuzumab

B. Acalabrutinib ± obinutuzumab

C. Venetoclax monotherapy

D. Ibrutinib

E. Acalabrutinib +/- Obinutuzumab and Ibrutinib are both reasonable options

Case 2

A 64-year-old man presents with del(17p) CLL. He is observed for 1 year and requires initial therapy. He is treated with ibrutinib and has some hypertension but otherwise tolerates it well and is in PR for 4 years. Now at age 69 he has developed progressive lymphocytosis and lymphadenopathy on ibrutinib.

How would you choose to treat this patient?

A. Bendamustine + rituximab
B. Duvelisib
C. Venetoclax
D. Rituximab monotherapy
E. Acalabrutinib

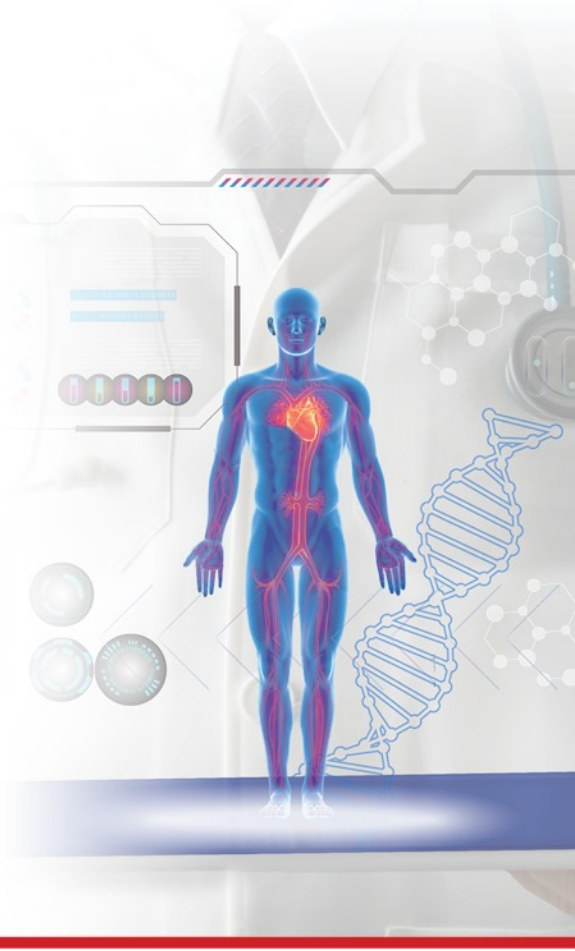
Case 3

A 74-y/o woman with atrial fibrillation on warfarin and diet-controlled type 2 diabetes presents with del(11q), unmutated IGHV CLL. After 3 years of observation, she develops progressive cytopenias and lymph node disease and is treated with 1-year of venetoclax + obinutuzumab. She achieves a PR and still has detectable MRD at the end of treatment. Six months later, she develops progressive CLL and now requires second-line therapy

How would you choose to treat this patient?

A. Acalabrutinib
B. Ibrutinib
C. Bendamustine + rituximab
D. Re-treatment with venetoclax + obinutuzumab
E. Rituximab monotherapy

CLL Background, Diagnosis, and Overview of Therapy



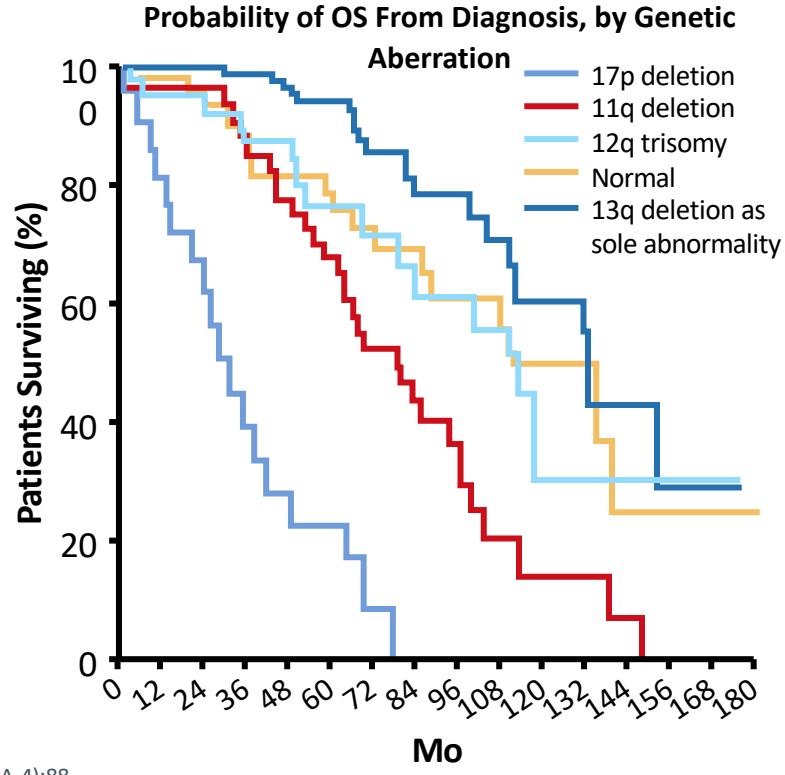
CLL/SLL: Background

- More than 21,000 estimated new cases in 2021 in the United States[1,2]
  - 7% of all NHL are CLL/SLL
- Median age at diagnosis: 70 yr[2]
- SLL and CLL considered the same B-cell malignancy[3]
  - CLL: ≥5000 clonal lymphocytes in peripheral blood
  - SLL: presence of lymphadenopathy and/or splenomegaly and <5000 clonal lymphocytes in peripheral blood
- Historical 5-yr survival: 66% (range: few mo to normal life span)[4]
  - Recent (2011-2017) 5-yr survival: 87%[2]

1. Siegel. CA Cancer J Clin. 2021;71:7. 2. SEER Cancer Stat Facts. Chronic lymphocytic leukemia.
3. Zelenetz. J Natl Compr Canc Netw. 2015;13:326. 4. Nabhan. JAMA. 2014;312:2265.

CLL: Historic Prognostic Value of FISH (Outcomes Prior to Novel Targeted Therapies)

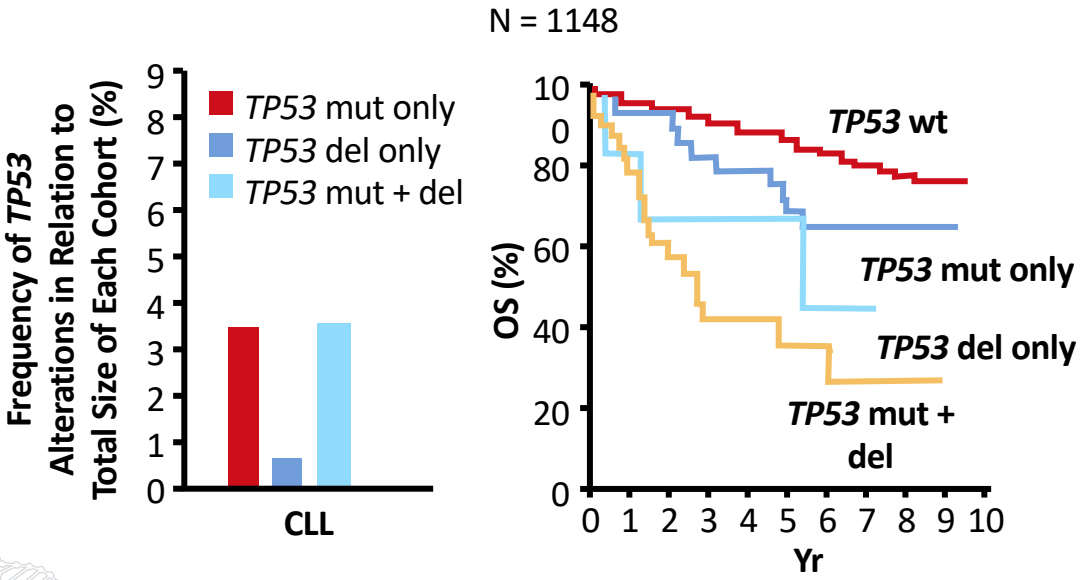
FISH Abnormalities Present in 268/325 Patients (82%)		
Lesion	**%**	**Median OS, Mo**
del(13q)	55	133
del(11q)	18	79
Trisomy 12	16	114
del(17p)	7	32
del(6q)	6	N/A
Normal	18	111



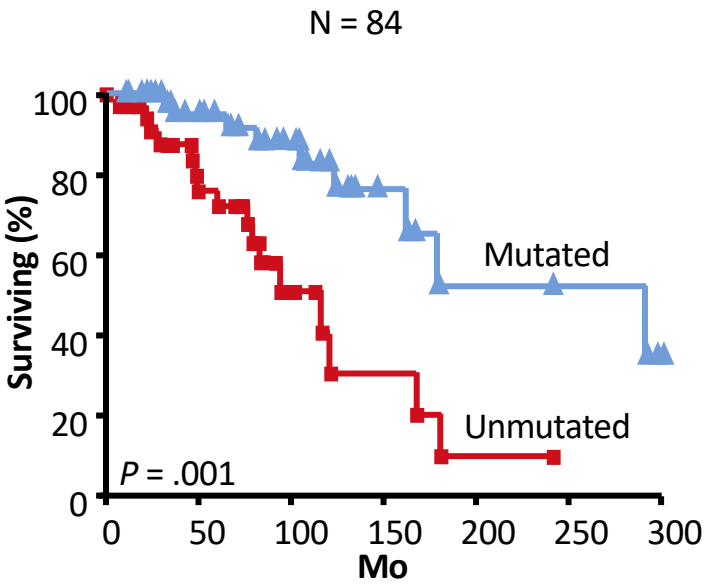
Dohner. NEJM. 2000;343:1910. Dohner. Blood. 1997;89:2516. Oscier. Haematologica. 1999;84(suppl EHA-4):88. Jarosova. Onkologie. 2001;24:60. Dewald. Br J Haematol. 2003;121:287. Sindelárová. Cancer Genet Cytogenet. 2005;160:27.

Impact of *TP53* Aberrations and *IGHV* Mutational Status on OS (Prior to Novel Targeted Therapies)

TP53 Mutation and/or Deletion[1]



IGHV Mutation Status[2]



1. Stengel. Leukemia. 2017;31:705. 2. Hamblin. Blood. 1999;94:1848.

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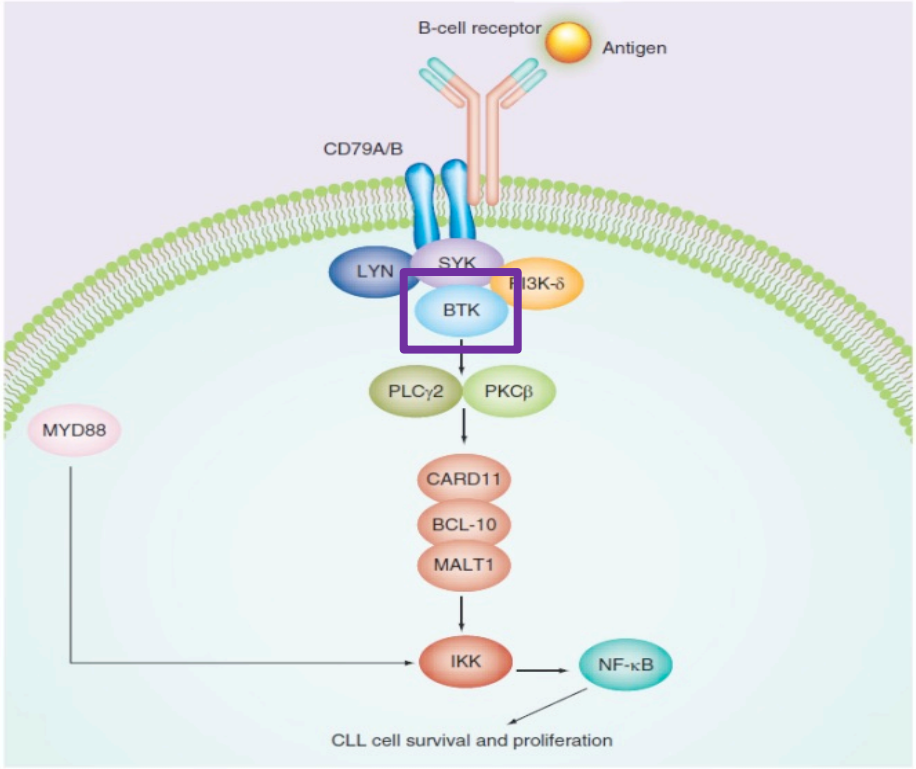
Novel Agents and Combinations for CLL/SLL

B-Cell Receptor (BCR) Signaling

- BCR: transmembrane receptor located on surface of B lymphocytes
  - Key survival molecule for normal B cells and for most B-cell malignancies
  - In CLL, BCR signaling plays key role in disease pathogenesis
- Mature B cells able to recognize an extensive array of foreign antigens via unique BCR
  - Triggers antigen-specific antibody responses
  - Promotes B-cell differentiation into plasma cells and memory B cells
- BCR stimulation occurs through signaling cascades involving activation of kinases, including SYK, BTK, and PI3K



SYK, spleen tyrosine kinase; BTK, Bruton tyrosine kinase; PI3K, phosphatidylinositol 3-kinase. Burger JA, Wiestner A. *Nat Rev Cancer*. 2018;18(3):148-167. Stevenson FK, et al. *Blood*. 2011;118(16):4313-4320.

NCCN 1L–Suggested Treatment Regimens: Standard-Risk Patients

First-Line Therapy

Frail patients with significant comorbidities OR patients aged ≥65 yrs and younger patients with significant comorbidities (CrCl <70 mL/min)

Preferred regimens

- Ibrutinib (category 1)
- Acalabrutinib ± obinutuzumab
- Venetoclax + obinutuzumab

First-Line Therapy

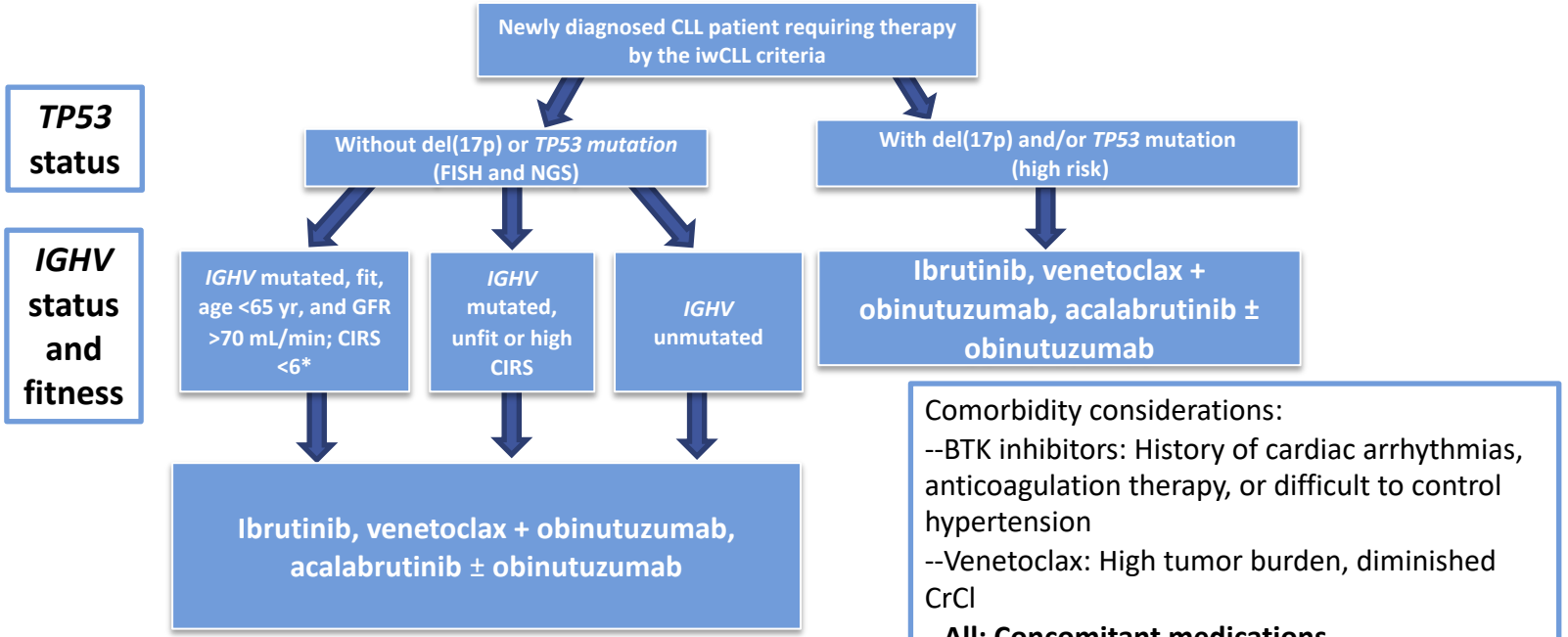
Patients aged ≤65 yrs without significant comorbidities

Preferred regimens

- Ibrutinib (category 1)
- Acalabrutinib ± obinutuzumab
- Venetoclax + obinutuzumab

NCCN Guidelines Version 4. 2020. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.

Treatment Algorithm for Newly Diagnosed CLL



Comorbidity considerations:
--BTK inhibitors: History of cardiac arrhythmias, anticoagulation therapy, or difficult to control hypertension
--Venetoclax: High tumor burden, diminished CrCl
--All: Concomitant medications

*FCR may be considered in these patients.

NCCN 1L–Suggested Treatment Regimens: Relapsed/Refractory Standard-Risk Patients

Relapsed/Refractory Therapy

Frail patients with significant comorbidities OR patients aged ≥65 yrs and younger patients with significant comorbidities (CrCl <70 mL/min)

Preferred regimens

- Acalabrutinib (category 1)
- Ibrutinib (category 1)
- Venetoclax + rituximab (category 1)
- Duvelisib
- Idelalisib + rituximab

Relapsed/Refractory Therapy

Patients aged ≤65 yrs without significant comorbidities

Preferred regimens

- Acalabrutinib (category 1)
- Ibrutinib (category 1)
- Venetoclax + rituximab (category 1)
- Duvelisib
- Idelalisib + rituximab

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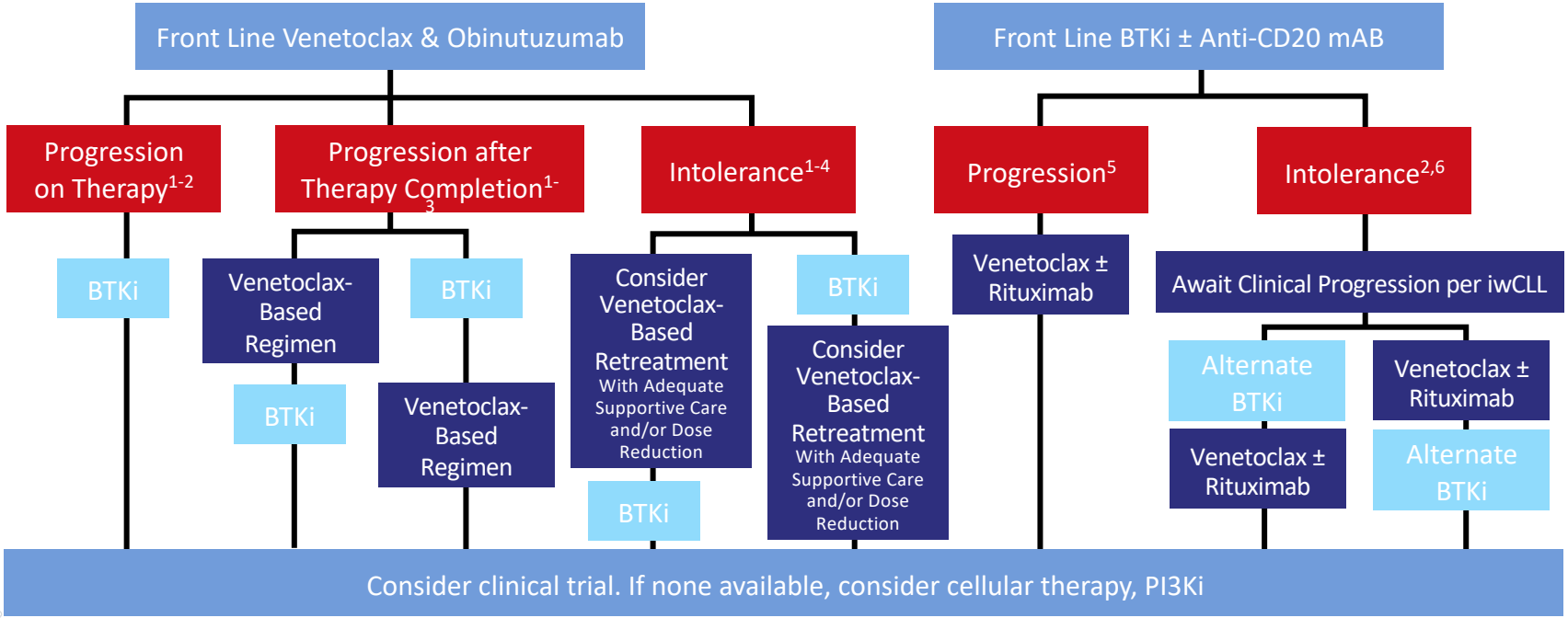
Treatment Algorithm: CT-Free Management of Relapsed/Refractory CLL



1. Harrup. ASH 2020. Abstr 3139. 2. Mato. Clin Cancer Res. 2020;26:3589. 3. Thompson. ASH 2020. Abstr 3136.
4. Kater. ASH 2020. Abstr 125. 5. Jones. Lancet Oncol. 2018;19:65. 6. Rogers. Haematologica. 2021;[Epub].

NCCN-Suggested Treatment Regimens: High-Risk Patients

First-Line Therapy

Preferred regimens

- Acalabrutinib ± obinutuzumab
- Ibrutinib
- Venetoclax + obinutuzumab

R/R Therapy

Preferred regimens

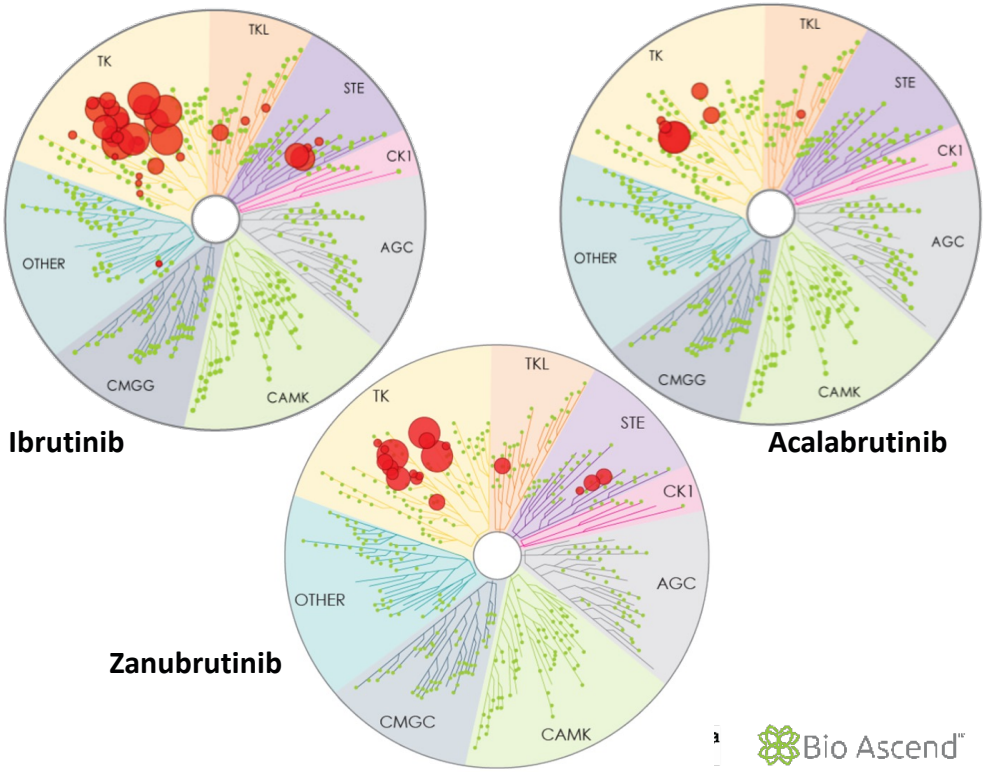
- Acalabrutinib (category 1)
- Ibrutinib (category 1)
- Venetoclax + rituximab
- Duvelisib
- Idelalisib + rituximab
- Venetoclax

NCCN Guidelines Version 4. 2020. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.

Kinase Selectivity of BTK Inhibitors in Vitro

Kinase	IC_{50}/EC_{50} (nM)		
	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	>1000	50
BMX	0.8	46	1.4
EGFR	5.3	>1000	21
ERBB4	3.4	16	6.9
JAK3	32	>1000	1377
BLK	0.1	>1000	2.5

Kinase Selectivity Profiling at 1 μmol/L (in vitro)
Larger red circles represent stronger inhibition



Kaptein. ASH 2018. Abstr 1871.

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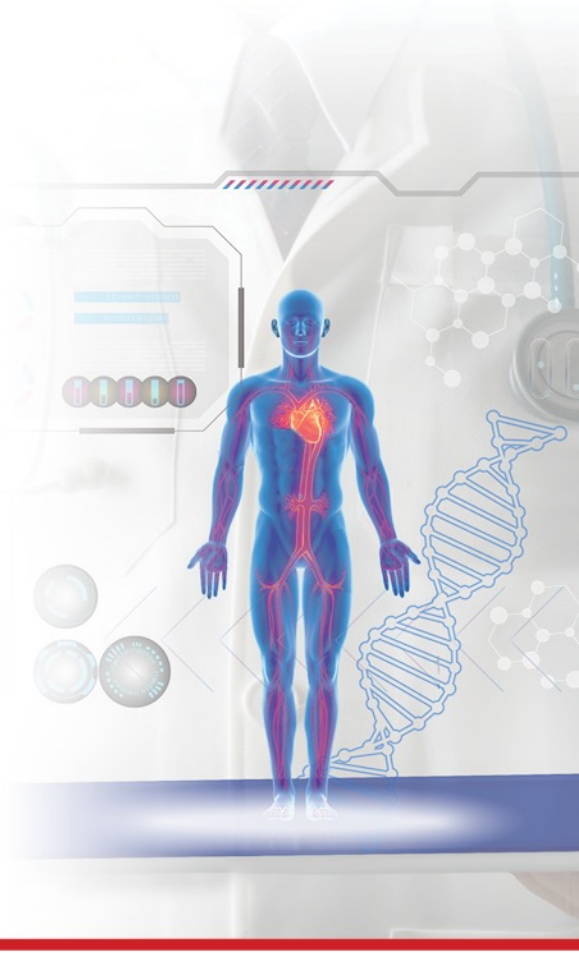
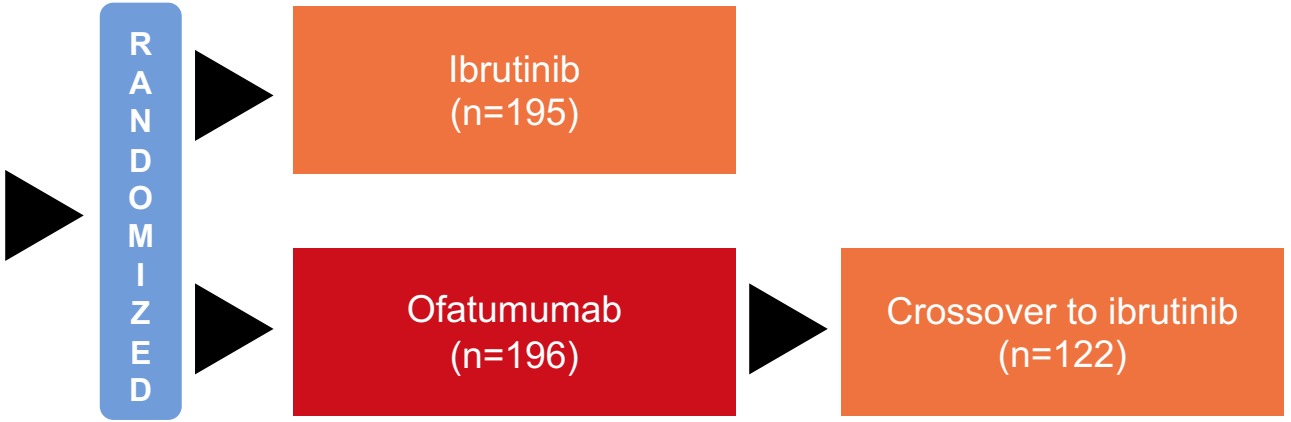
Currently Available BTK Inhibitor-Based Strategies: Phase 3 Studies — Ibrutinib



RESONATE Trial: Ibrutinib vs Ofatumumab in Previously Treated CLL/SLL

- Phase 3, open-label, multicenter trial
- Patients with CLL or SLL who had received ≥1 prior therapy (N=391)
- ≥70 yrs old
- ECOG <2



Primary endpoint: Duration of PFS

Secondary endpoints: Duration of OS and ORR

ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Byrd JC, et al. *N Engl J Med*. 2014;371:213-223.

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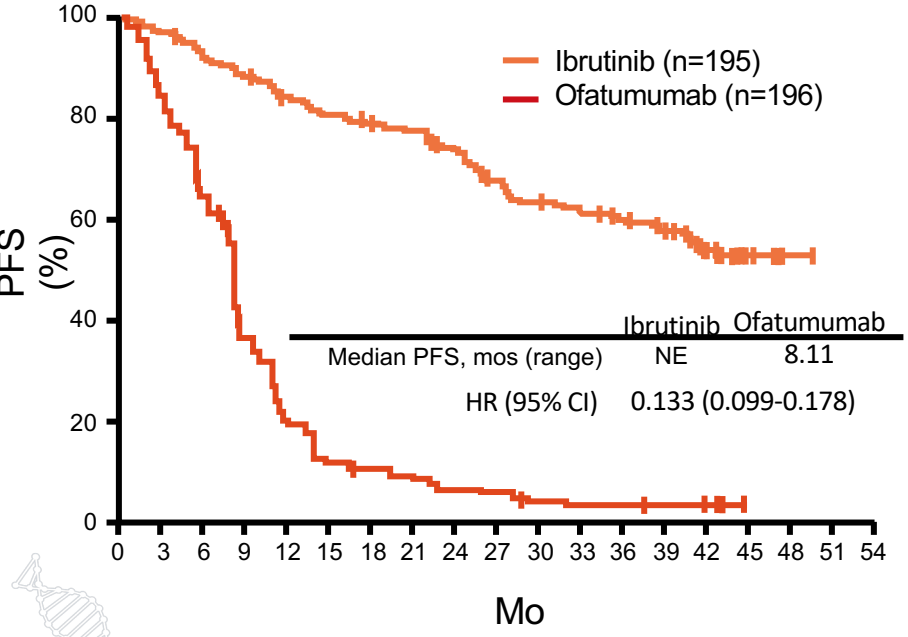
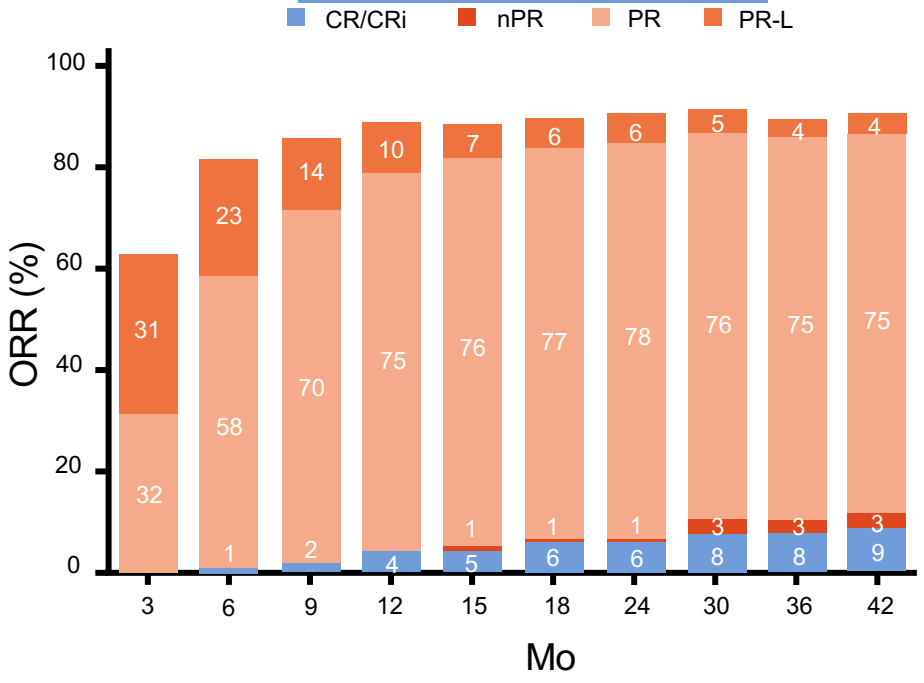
RESONATE Trial: Long-Term Follow-Up

Long-Term PFS



Best Response



Byrd JC, et al. *Blood*. 2019;133:2031-2042.

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RESONATE-2 Trial: Ibrutinib vs Chlorambucil in Treatment-Naïve Older Patients With CLL/SLL

- Phase 3, randomized, international, open-label trial
- Patients ≥65 yrs old with treatment-naïve CLL/SLL (N=269)
- ECOG ≤2
- No del(17p)

RANDOMIZED 1:1

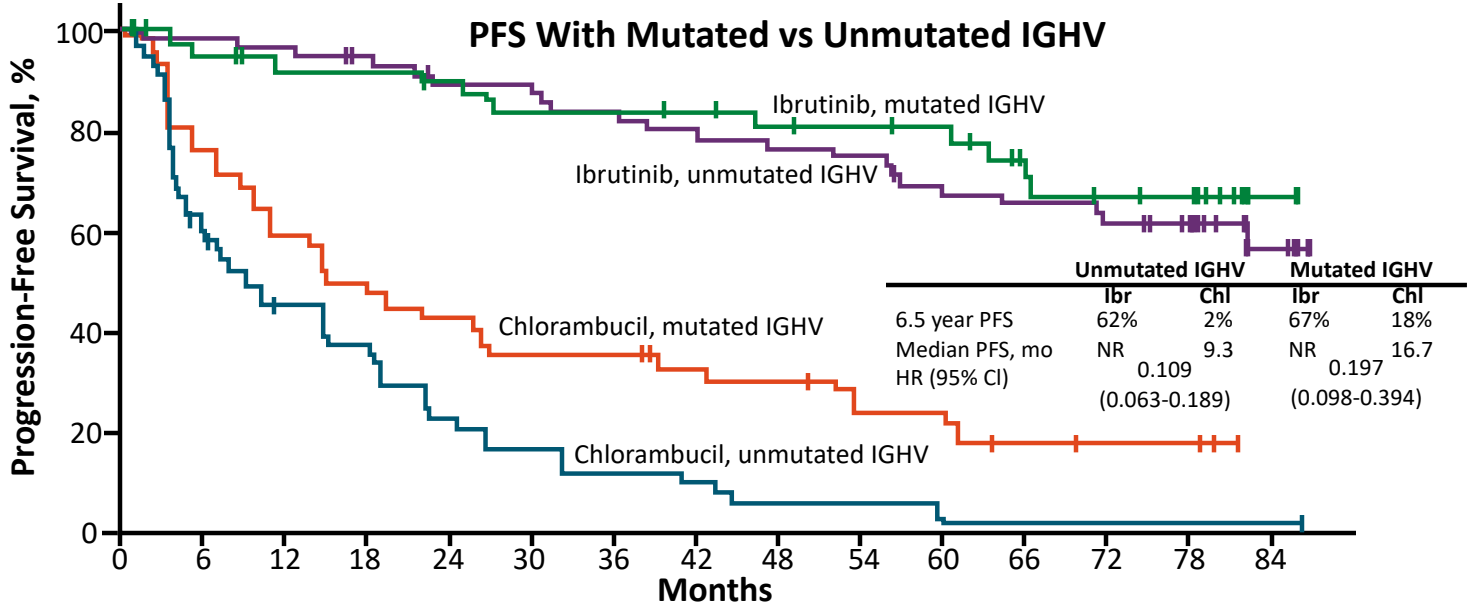
- Ibrutinib (n=136)
- Chlorambucil (n=133) → Following confirmation of PD, patients randomized to chlorambucil eligible to cross over to second-line treatment with ibrutinib (investigator's choice)

Primary endpoint: Duration of PFS

Secondary endpoints: OS, ORR, rate of sustained improvement in hematologic variables, safety

Burger JA, et al. *N Engl J Med*. 2015;373:2425-2437.

RESONATE-2: 7-Year Follow-Up – PFS Mutated vs Unmutated IGHV



Patients at Risk

Ibrutinib, mutated IGHV:	40	37	34	34	32	30	30	29	27	26	25	20	17	16	4
Ibrutinib, unmutated IGHV:	58	58	56	53	49	48	46	43	42	41	36	35	32	26	8
Chlorambucil, mutated IGHV:	42	42	25	21	18	15	15	12	11	8	8	5	4	4	
Chlorambucil, unmutated IGHV:	60	60	23	19	11	8	6	5	3	3	2	1	1	1	1

Barr. ASCO 2021. Abstr 7523.

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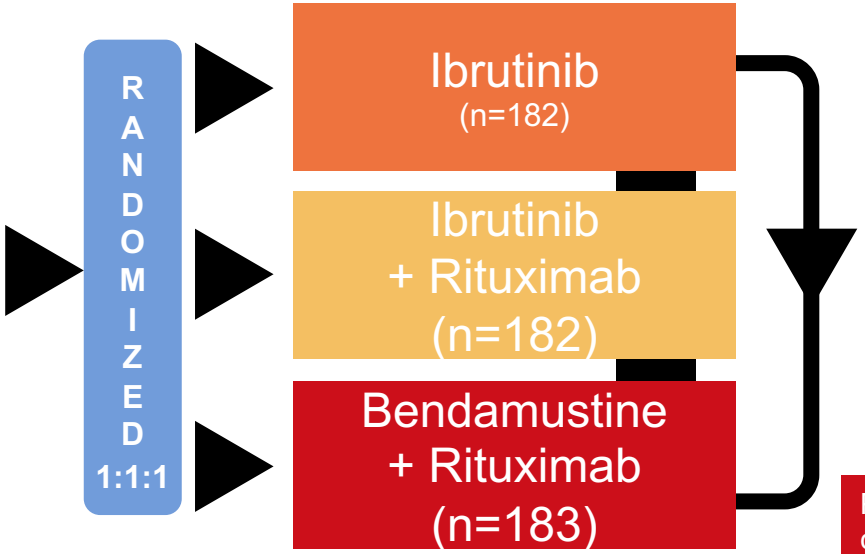
ALLIANCE Trial A041202: Ibrutinib +/- Rituximab vs Bendamustine + Rituximab in Untreated CLL

- Phase 3, randomized
- Patients with untreated CLL meeting iwCLL 2008 criteria for treatment initiation (N=547)
- ≥65 yrs old
- ECOG PS 0-2
- Patients had
  - CrCl 40 mL/min
  - Bilirubin ≤1.5 x ULN
  - No need for warfarin treatment



Patients in this arm with PD could cross over to ibrutinib within 1 year after progression

Primary endpoint: PFS

Secondary endpoints: OS, CR, MRD

Woyach JA, et al. *N Engl J Med.* 2018;379:2517-2528.

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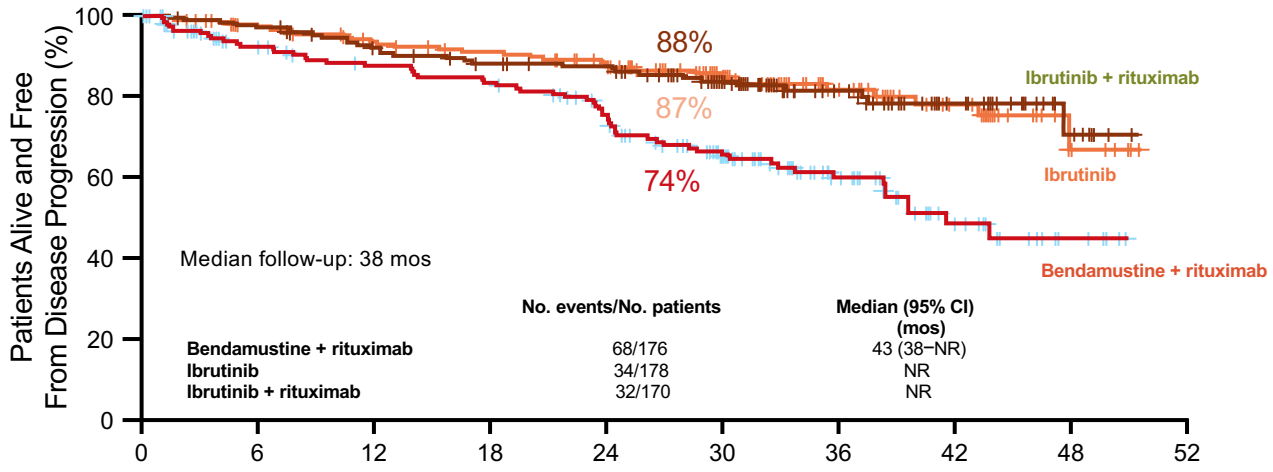
ALLIANCE Trial A041202: Results

PFS



Bendamustine + rituximab
Ibrutinib
Ibrutinib + rituximab

Woyach JA, et al. *N Engl J Med.* 2018;379:2517-2528.

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ECOG-1912 Trial: Ibrutinib + Rituximab vs FCR Chemoimmunotherapy for CLL

- Phase 3, randomized, open-label trial
- Treatment-naive CLL (N=529)
- ≤70 yrs
- ECOG 0-2
- CrCl >40 mL/min
- FCR eligible
- No del(17p) by FISH

RANDOMIZED 2:1

Ibrutinib + Rituximab (n=354)

Ibrutinib maintenance until PD

Fludarabine + Cyclophosphamide + Rituximab (n=175)

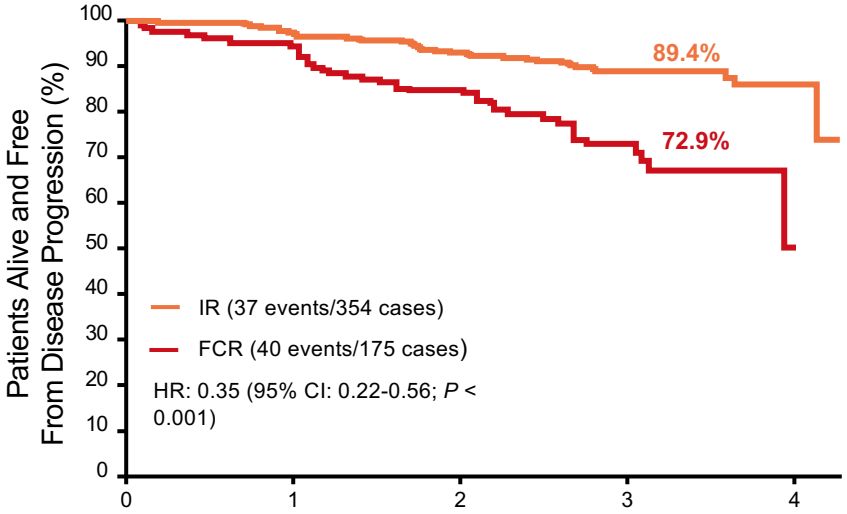
Primary endpoint: PFS

Secondary endpoints: OS, safety

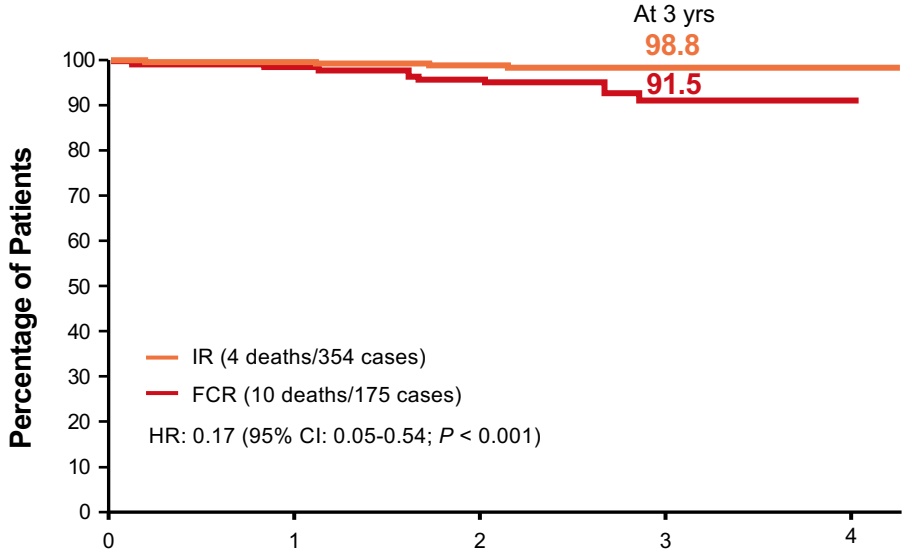
Shanafelt TD, et al. *N Engl J Med*. 2019;381:432-443.

ECOG-1912 Trial: Results

PFS Among All Patients



OS (ITT Population)



ITT, intent-to-treat.

Shanafelt TD, et al. *N Engl J Med*. 2019;381:432-443.

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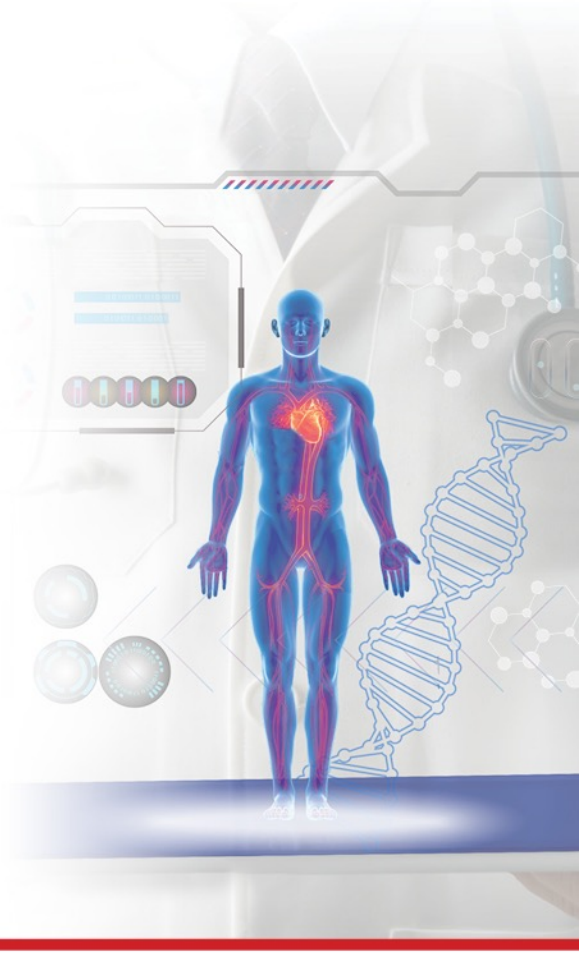
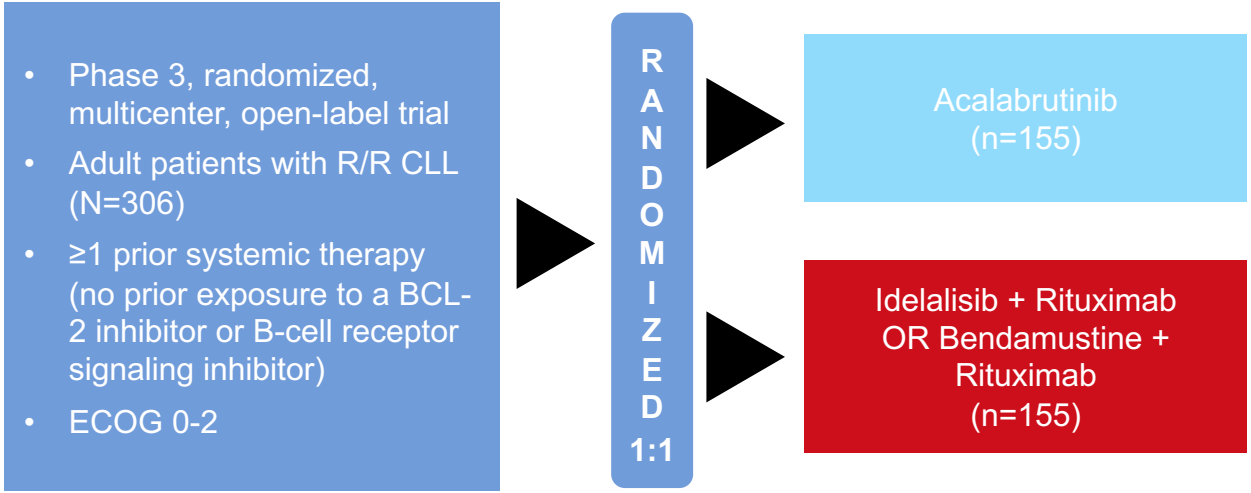
Currently Available BTK Inhibitor-Based Strategies: Phase 3 Studies — Acalabrutinib



ASCEND Trial: Acalabrutinib vs Rituximab + Idelalisib or Bendamustine in R/R CLL



Primary endpoint: PFS per IRC

Secondary endpoints: ORR, DoR, PFS per investigator, OS

Ghia P, et al. EHA 2019. [Abstract LB2606].

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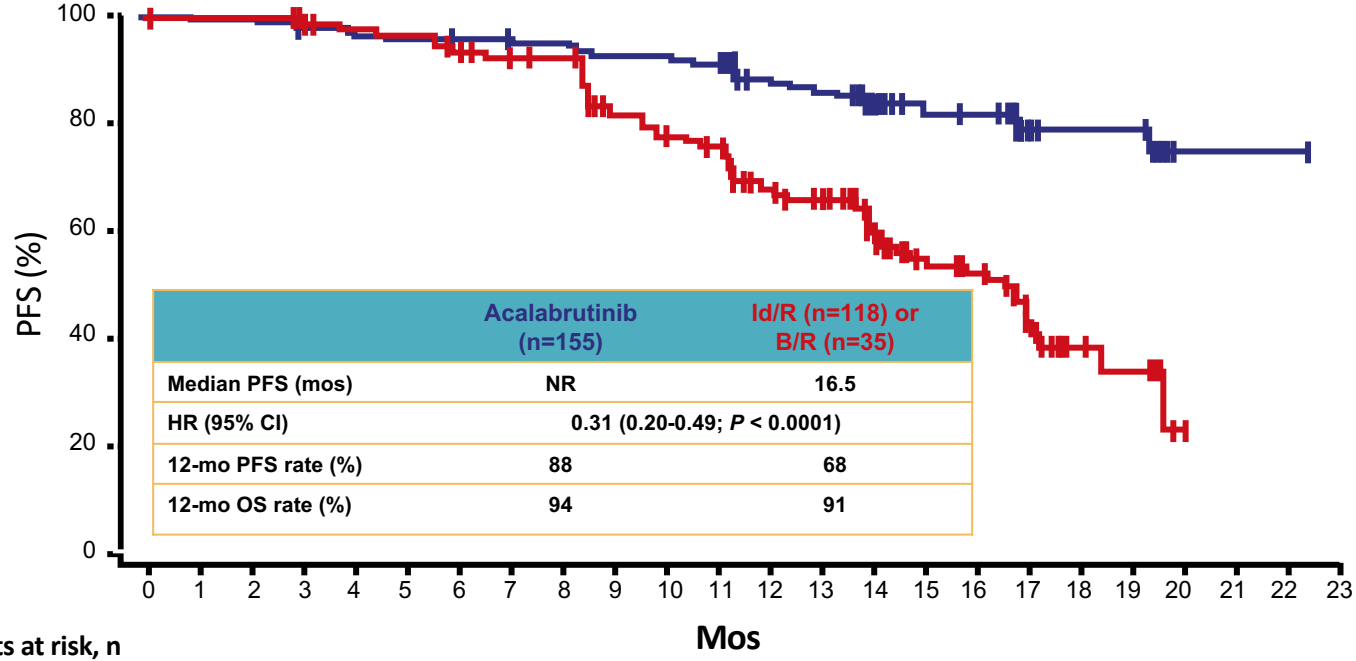
ASCEND Trial: PFS (IRC Review)



	Acalabrutinib (n=155)	Id/R (n=118) or B/R (n=35)
Median PFS (mos)	NR	16.5
HR (95% CI)	0.31 (0.20-0.49; *P* < 0.0001)	
12-mo PFS rate (%)	88	68
12-mo OS rate (%)	94	91

23% of patients randomly assigned to rituximab/idelalisib or rituximab/bendamustine crossed over to receive subsequent treatment with acalabrutinib

Patients at risk, n

Acalabrutinib	155	153	153	149	147	146	145	143	143	139	139	137	118	116	73	61	60	25	21	21	1	1	1	0
Id/R or B/R	155	150	150	146	144	142	136	130	129	112	105	101	82	77	56	44	39	18	10	8	0			

Ghia P, et al. EHA 2019. [Abstract LB2606].

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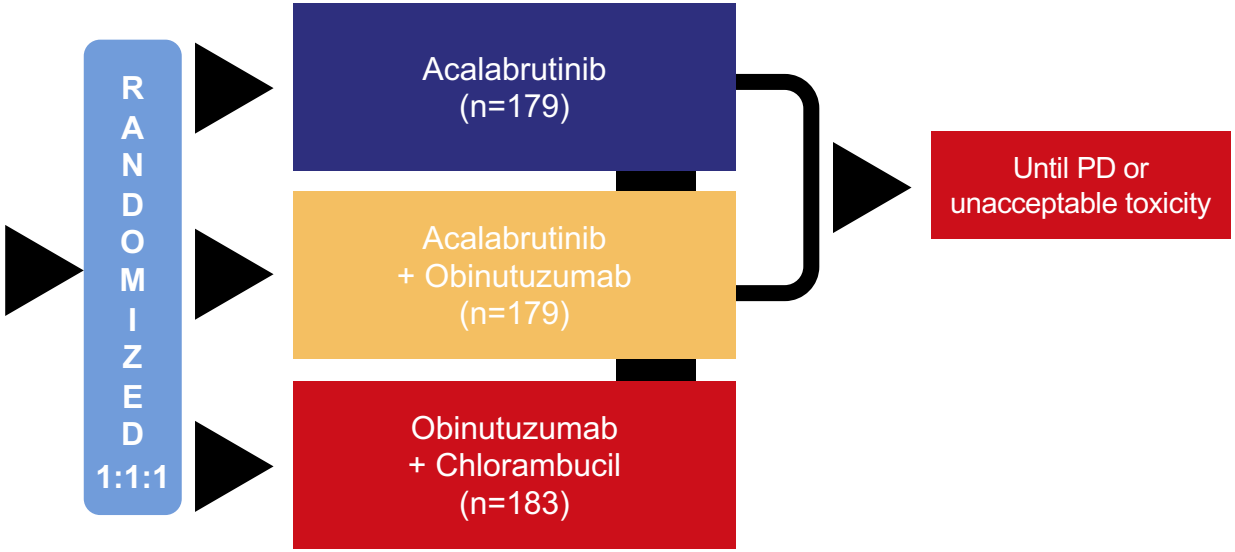
ELEVATE-TN Trial: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naïve CLL

- Phase 3, randomized, multicenter, open-label trial
- Treatment-naïve patients with CLL (N=535)
- ≥65 yrs, or <65 with CIRS score >6 and CrCl <70 mL/min
- Patients stratified by del(17p) status, ECOG ≤1 vs 2, geographic region



Primary endpoint: PFS per IRC (acalabrutinib/obinutuzumab vs chlorambucil/obinutuzumab)

Secondary endpoints: PFS of acalabrutinib monotherapy vs obinutuzumab/chlorambucil, ORR, TTNT, OS, safety

Sharman JP, et al. *Lancet.* 2020;395:1278-1291.

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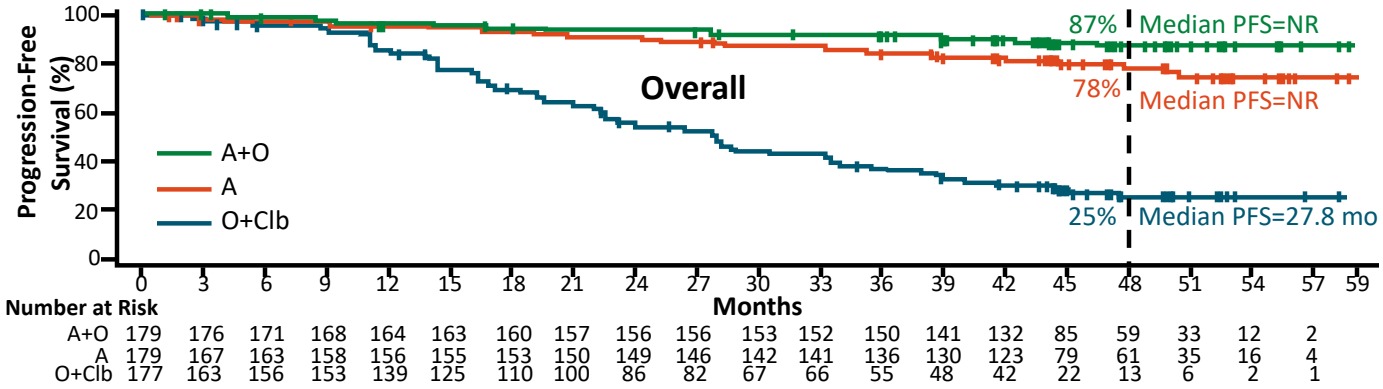
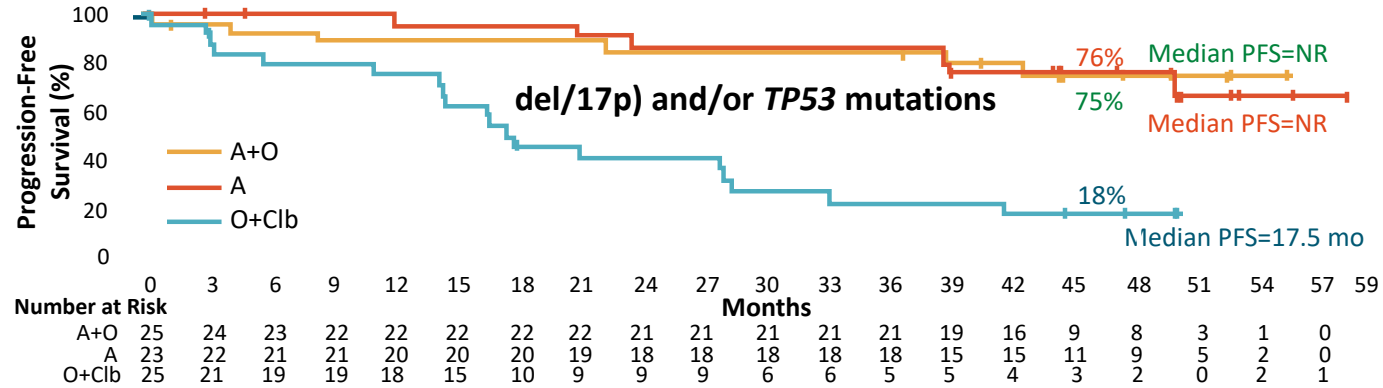
ELEVATE-TN Trial: PFS 4-year Follow-Up

A+O vs O+Clb
HR: 0.10 (95% CI: 0.07-0.17)
P <.0001
A vs O+Clb
HR: 0.19 (95% CI: 0.13-0.28)
P <.0001
A+O vs A
HR: 0.56 (95% CI: 0.32-0.95)
P=.0296



A+O vs O+Clb
HR: 0.17 (95% CI: 0.07-0.42)
P <.0001
A vs O+Clb
HR: 0.18 (95% CI: 0.07-0.46)
P <.0001



Sharman. ASCO 2021. Abstr 7509.

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BTK Inhibitors in CLL: Conclusions

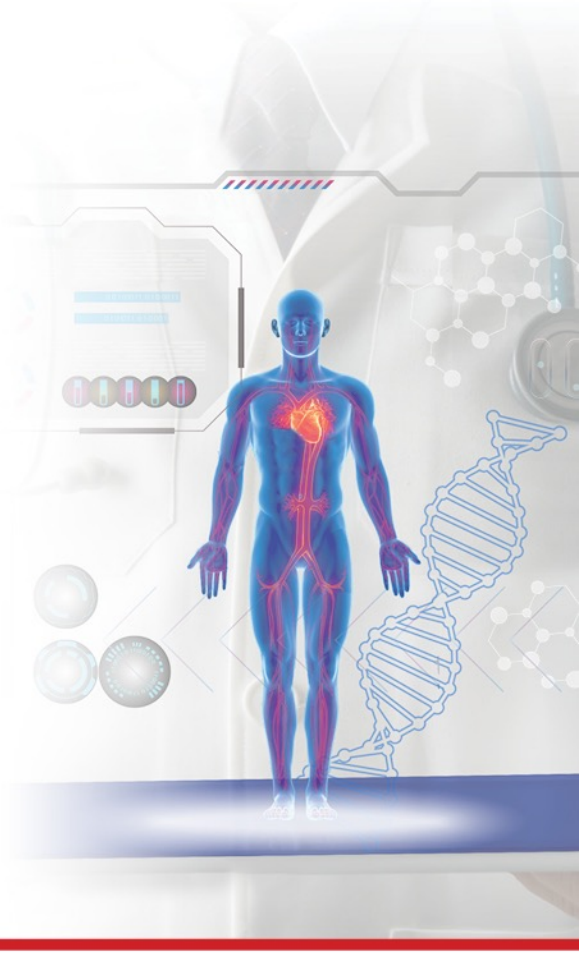
01 BTK has central role in BCR pathway and is an important therapeutic target in treatment of B-cell malignancies

02 BTK inhibitors, alone or in combination with anti-CD20 agents, have expanded the treatment landscape for patients with CLL/SLL in both frontline and R/R settings

03 In phase 3 clinical trials, ibrutinib has demonstrated favorable efficacy and safety as a chemotherapy-free treatment option for patients with previously untreated or R/R CLL/SLL, including those with high-risk disease

04 In phase 3 clinical trials, acalabrutinib has demonstrated favorable efficacy and safety as front-line treatment of patients with previously untreated or R/R CLL/SLL, including combination therapy with CD20 therapy

BCL-2 Inhibitor-Based Regimens for Patients with CLL



CLL14: First-line Obinutuzumab + Venetoclax or Chlorambucil in CLL With Coexisting Medical Conditions

- International, open-label, randomized phase III trial

Patients with previously untreated CLL and coexisting medical conditions (CIRS >6 and/or CrCl <70 mL/min) (N = 432)

Venetoclax PO 5-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 1000 mg Days 1, 8, 15 of cycle 1, then 1000 mg Day 1 of cycles 2-6 (n = 216)

Chlorambucil PO 0.5 mg/kg Days 1, 15 of cycles 1-12 + **Obinutuzumab** IV 1000 mg Days 1, 8, 15 of cycle 1, then 1000 mg Day 1 in cycles 2-6 (n = 216)

Total 28-day cycles

- Venetoclax: 12
- Chlorambucil: 12
- Obinutuzumab: 6

- Primary endpoint: investigator-assessed PFS in ITT
- Secondary endpoints: IRC-assessed PFS, ORR, MRD negativity, OS, safety

Al-Sawaf. Lancet Oncol. 2020;21:1188.

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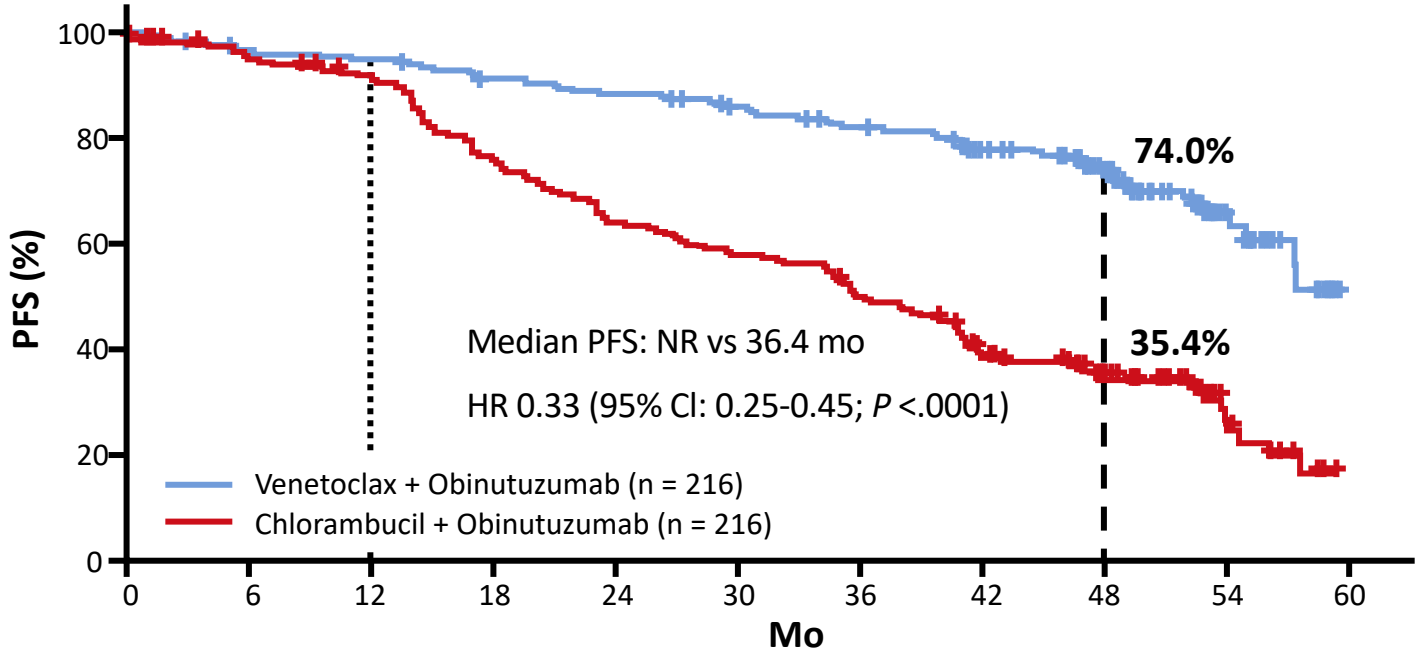
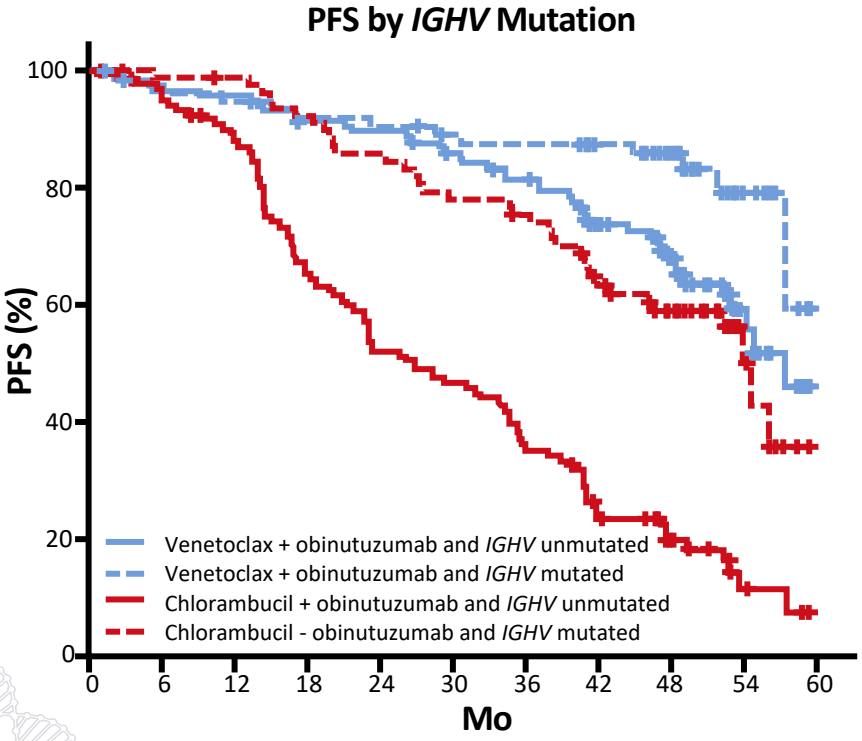
CLL14: PFS With 4-Yr Follow-up

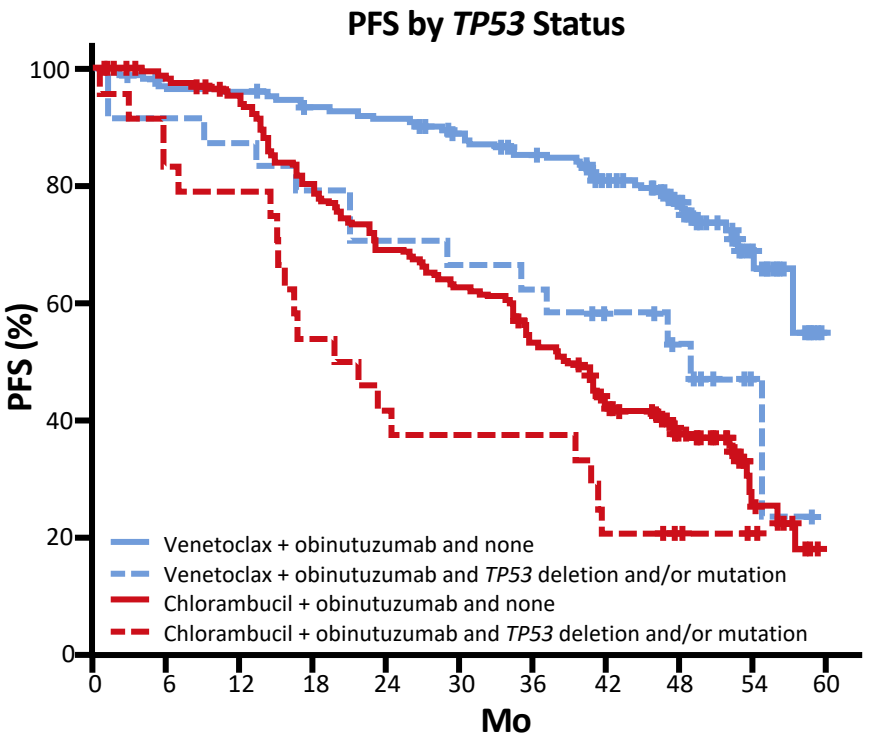


Median follow-up: 52.4 months

Al-Sawaf. EHA 2021. Abstr S146.

CLL14: PFS by *IGHV* Mutation and *TP53* Status





Al-Sawaf. EHA 2021. Abstr S146.

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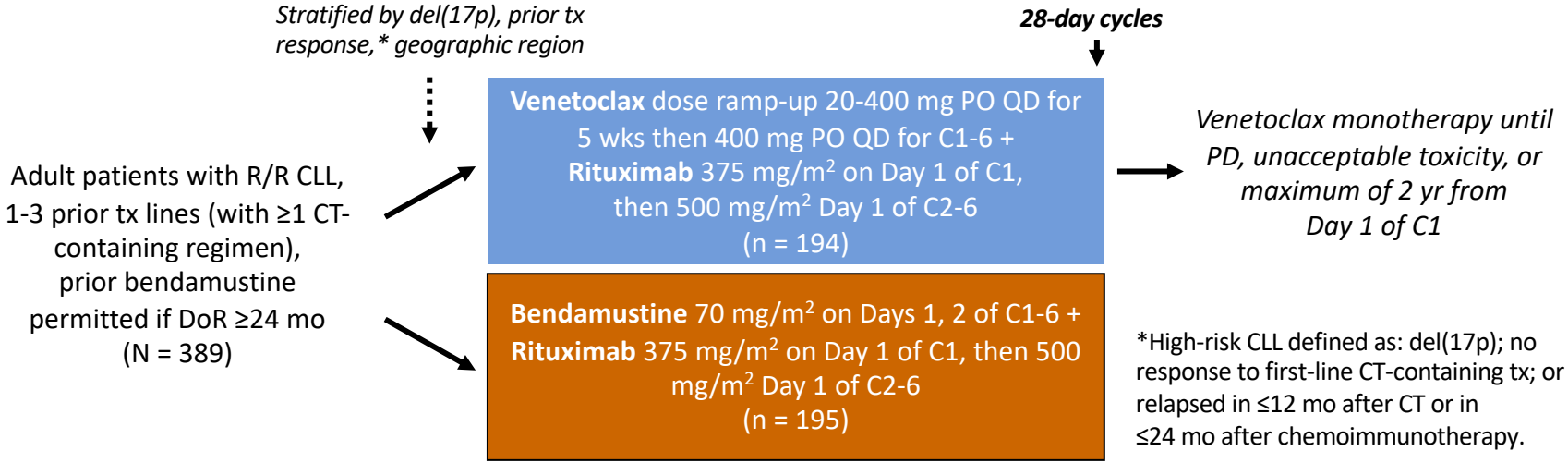
MURANO: Venetoclax + Rituximab vs BR in Previously Treated CLL/SLL

- Multicenter, randomized, open-label phase III trial



- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: IRC-assessed PFS and MRD negativity, IRC-assessed CR → ORR → OS (hierarchical testing), safety

Seymour. NEJM 2018; 378:1107. NCT02005471.

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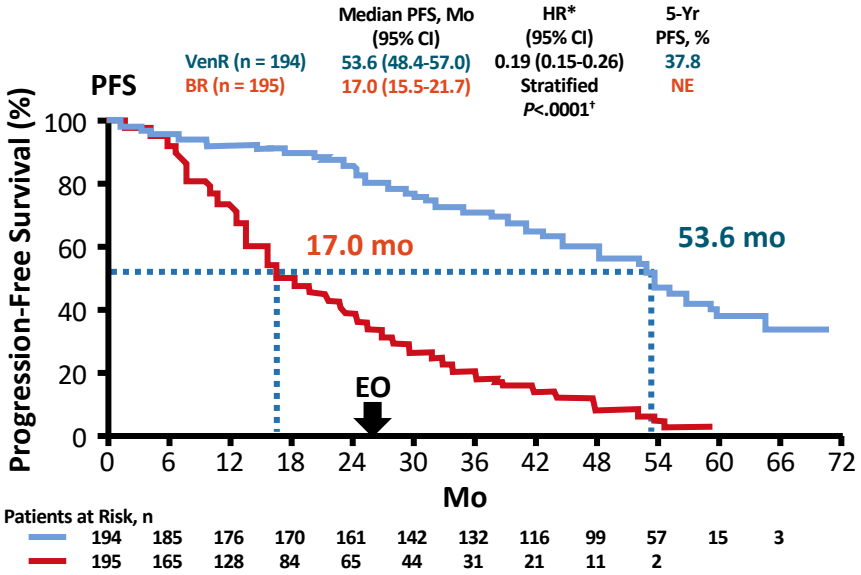
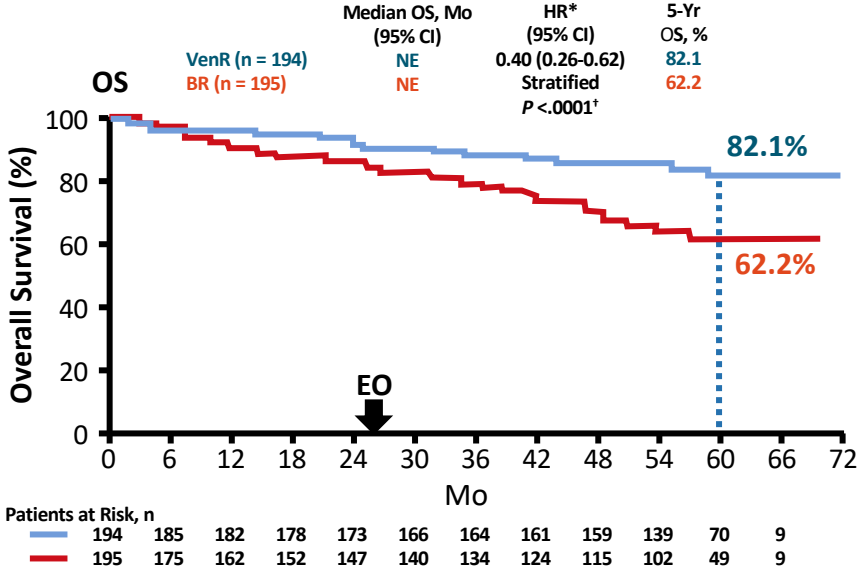
5-Yr Analysis of the MURANO Study: PFS and OS





*Unstratified HR = 0.21 †*P* values are descriptive ‡Unstratified HR = 0.042

- This report included:
  - Outcomes with a median follow-up of 59 mo (range: 0-71.5)
  - Outcomes of patients off-therapy based on MRD status at EOT
  - MRD kinetics and MRD status of patients who received VenR retreatment

Kater. ASH 2020. Abstr 125.

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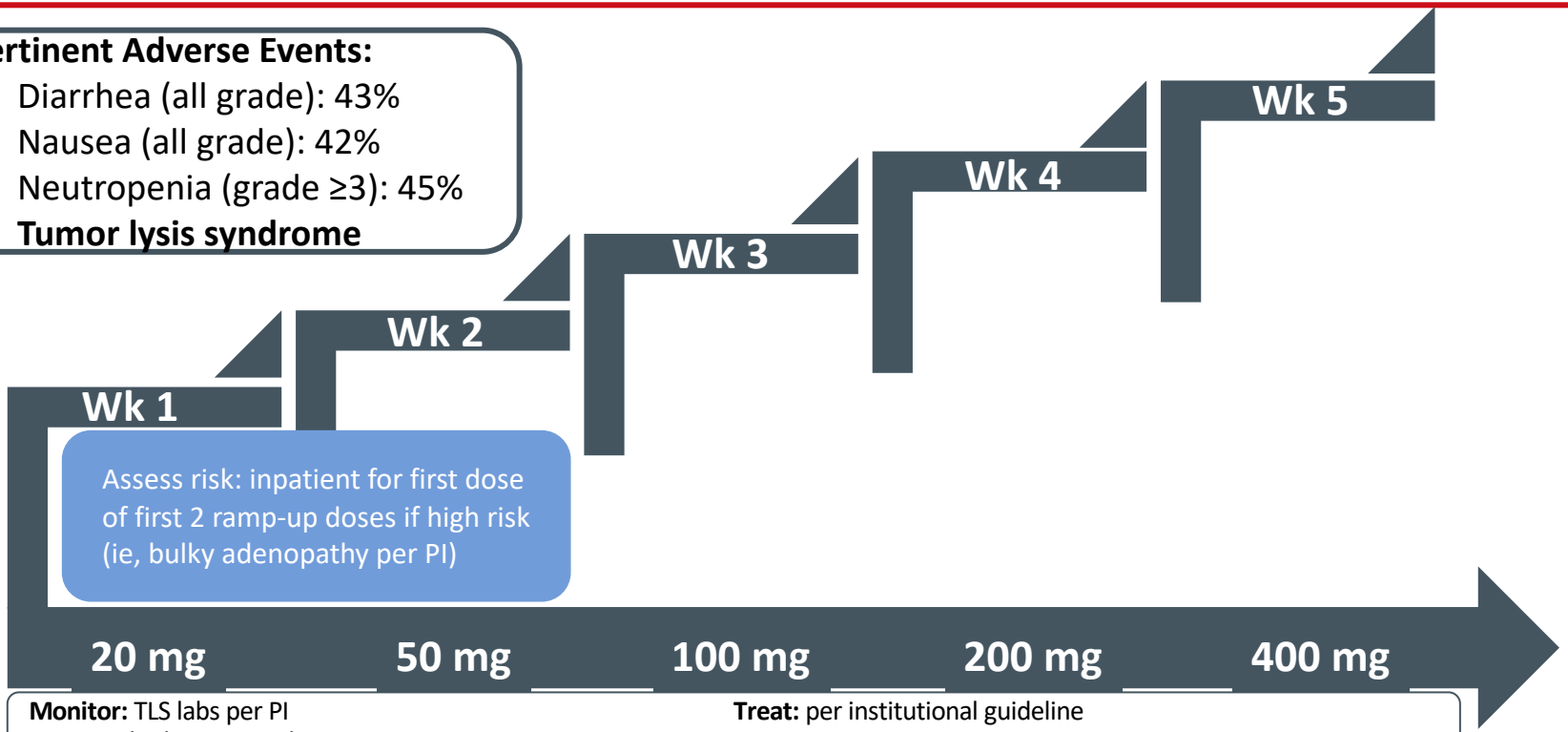
Venetoclax: Adverse Events and Management

Pertinent Adverse Events:

- Diarrhea (all grade): 43%
- Nausea (all grade): 42%
- Neutropenia (grade ≥3): 45%
- **Tumor lysis syndrome**



Monitor: TLS labs per PI
Prevent: hydration, antihyperuricemic agents

Treat: per institutional guideline

Venetoclax PI.

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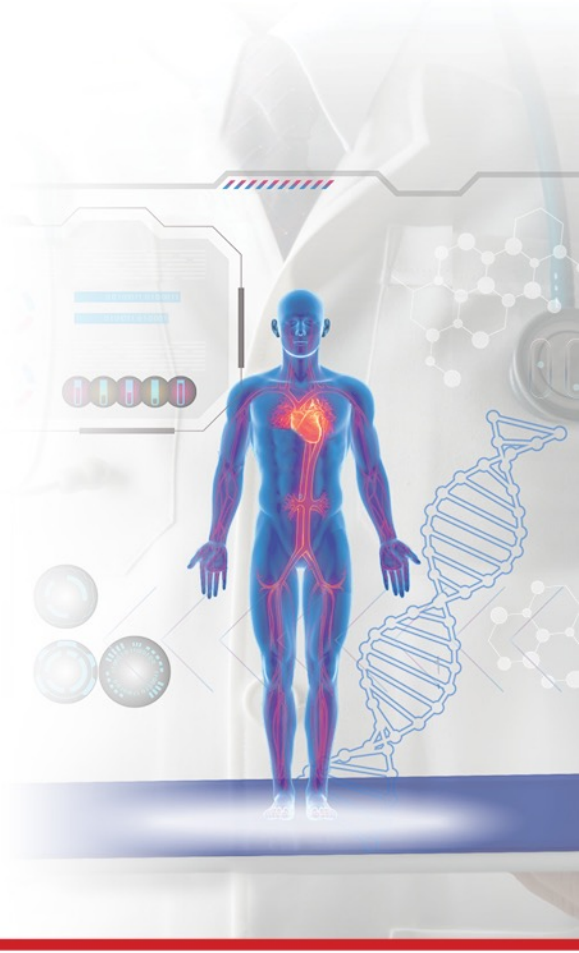
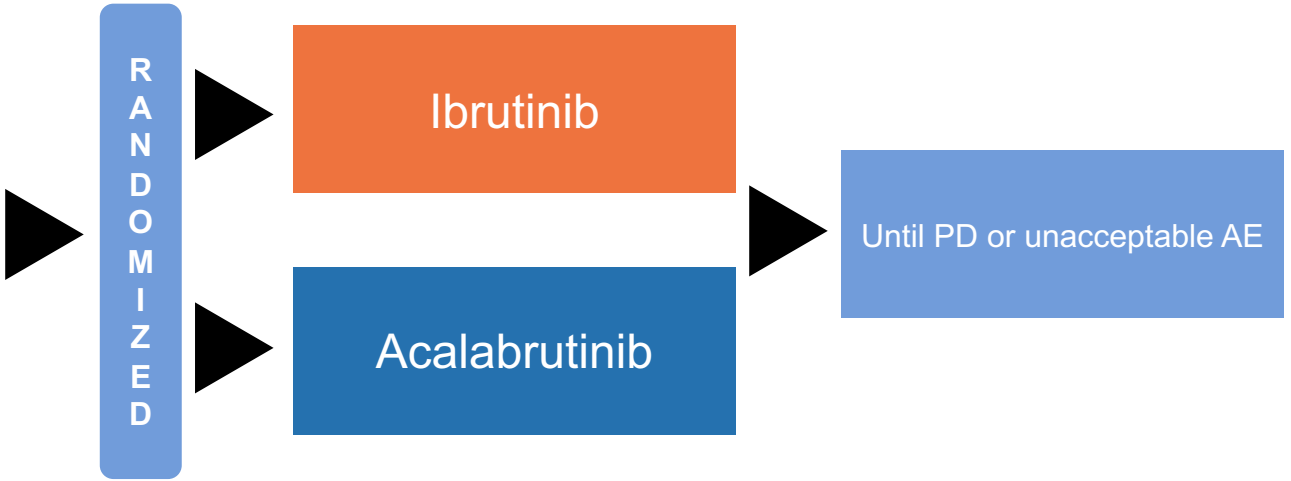
Future Directions and Emerging Data



ELEVATE R/R Trial: Ibrutinib vs Acalabrutinib in Patients With High-Risk R/R CLL

- Ongoing phase 3, randomized, multicenter, open-label, noninferiority trial
- Patients with del(17p) or del(11q) CLL with active disease (N=533)
- ≥1 previous line of treatment
- ECOG 0-2

Status:
Active, not recruiting



Primary endpoint: PFS

Secondary endpoints: OS, incidence of treatment-emergent AEs, atrial fibrillation, Richter's transformation

Clinicaltrials.gov. NCT02477696.

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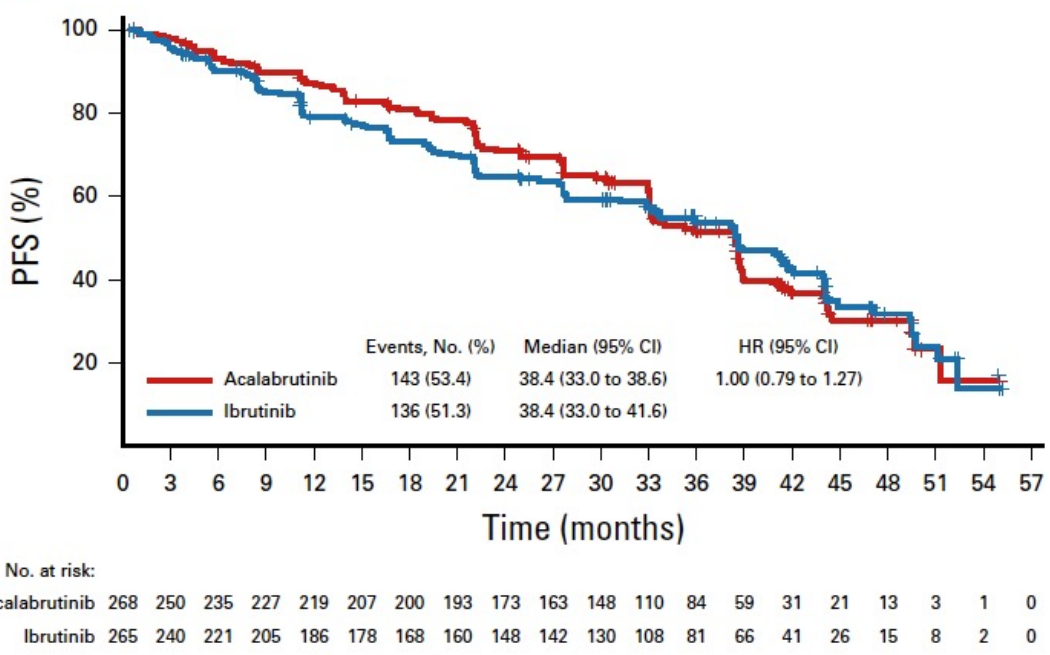
ELEVATE R/R Trial: Ibrutinib vs Acalabrutinib in Patients With High-Risk R/R CLL



Byrd J. et al. JCO 2021

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ELEVATE-RR: AEs of Clinical Interest

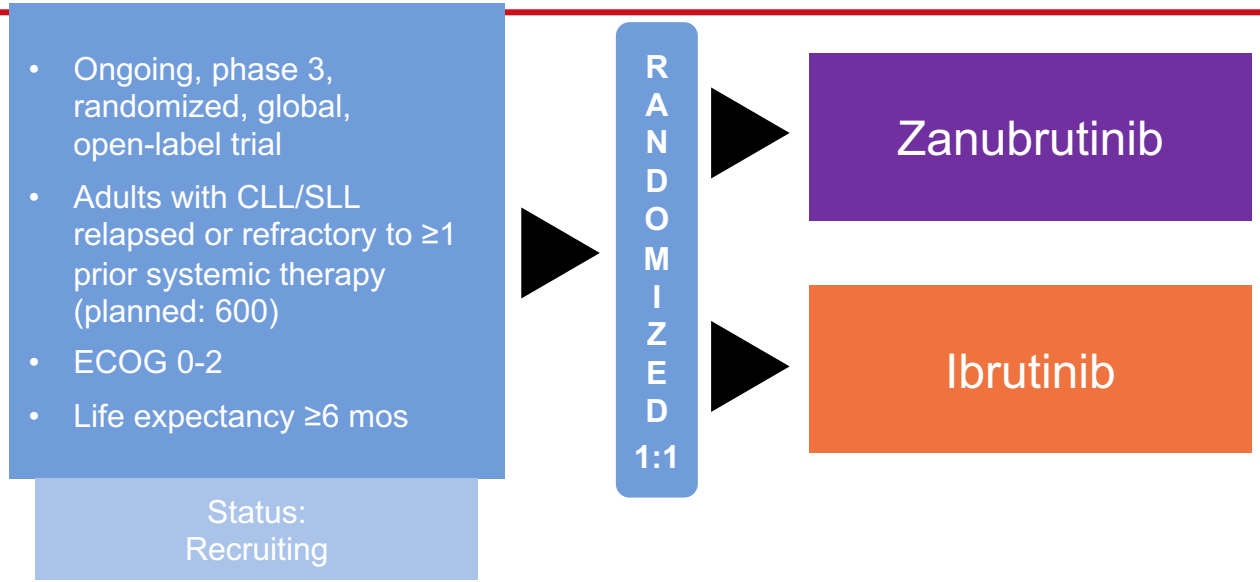
AE, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
▪ Atrial fibrillation/flutter	25 (9.4)	13 (4.9)	**42 (16.0)***	10 (3.8)
▪ Ventricular arrhythmias	0	0	3 (1.1)	1 (0.4)
Bleeding events	101 (38.0)	10 (3.8)	**135 (51.3)**	12 (4.6)
▪ Major bleeding events	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Hypertension	25 (9.4)	11 (4.1)	**61 (23.2)**	**24 (9.1)**
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)
ILD/pneumonitis	7 (2.6)	1 (0.4)	**17 (6.5)**	2 (0.8)
SPMs, excluding NMSC	24 (9.0)	16 (6.0)	20 (7.6)	14 (5.3)

*Bolded numbers statistically significantly higher vs the comparator (P <.05).

- Most common grade ≥3 infections: pneumonia (acalabrutinib vs ibrutinib, 10.5% vs 8.7%), sepsis (1.5% vs 2.7%), and urinary tract infections (1.1% vs 2.3%)

Byrd. ASCO 2021. Abstr 7500.

ALPINE Trial: Zanubrutinib vs Ibrutinib in R/R CLL/SLL



Primary endpoint: ORR (up to 36 mos)

Secondary endpoints: PFS, DoR, OS, TTF, safety

Clinicaltrials.gov. NCT03734016.

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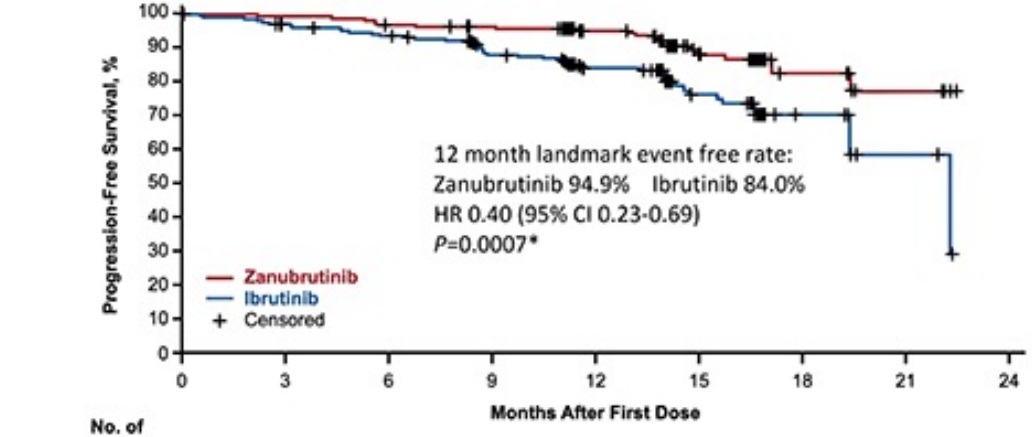
ALPINE Trial: Zanubrutinib vs Ibrutinib in R/R CLL/SLL

ORR	zanubrutinib	ibrutinib
overall	78.3%	62.5%
del11q	83.6%	69.1%
del17p	83.3%	53.8%

Figure. PFS by Investigator Assessment



*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached.
Median PFS follow-up was 14.0 months for both zanubrutinib and ibrutinib arms by reverse KM method.

Hillmen P. Presented at EHA 2021. Abstract LB1900

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ALPINE Trial: Zanubrutinib vs Ibrutinib in R/R CLL/SLL

AE of Special Interest in Safety Analysis Population, n (%)	Zanubrutinib (n = 204)		Ibrutinib (n = 207)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter	5 (2.5)	2 (1.0)	21 (10.1)	4 (1.9)
Hemorrhage ▪ Major hemorrhage*	73 (35.8) 6 (2.9)	6 (2.9) 6 (2.9)	75 (36.2) 8 (3.9)	6 (2.9) 6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies ▪ Skin cancers	17 (8.3) 7 (3.4)	10 (4.9) 3 (1.5)	13 (6.3) 10 (4.8)	4 (1.9) 2 (1.0)

*Includes serious or grade ≥3 hemorrhage or any-grade CNS hemorrhage.

SEQUOIA Trial: Zanubrutinib vs Bendamustine + Rituximab in Treatment-Naïve CLL/SLL

- Ongoing, phase 3, randomized, global, open-label trial
- Adults with previously untreated CLL/SLL (planned: 600)
- Unsuitable for treatment with FCR
- ECOG 0-2
- Life expectancy ≥6 mos

Status: Recruiting

RANDOMIZED

Cohort 1
Zanubrutinib 160 mg
OR Bendamustine + Rituximab

Cohort 2
Zanubrutinib

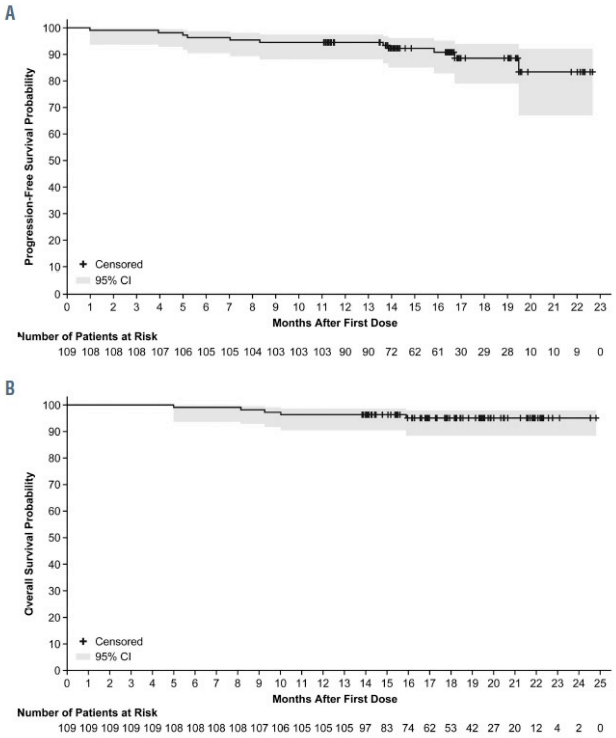
Cohort 3
Zanubrutinib + Venetoclax

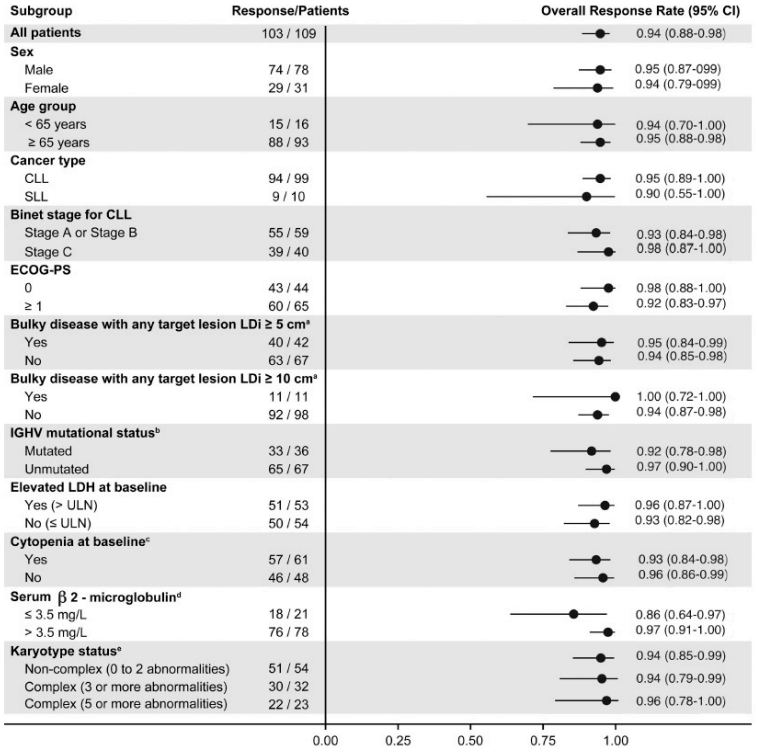
Primary endpoint: PFS (Cohort 1)

Secondary endpoints: ORR, OS, DoR

Clinicaltrials.gov. NCT03336333.

SEQUOIA Trial: Del17P Cohort





Tam CSL, et al. Hematologica 2020

PFS appears to be preserved in patients with unmutated IGHV and complex karyotype

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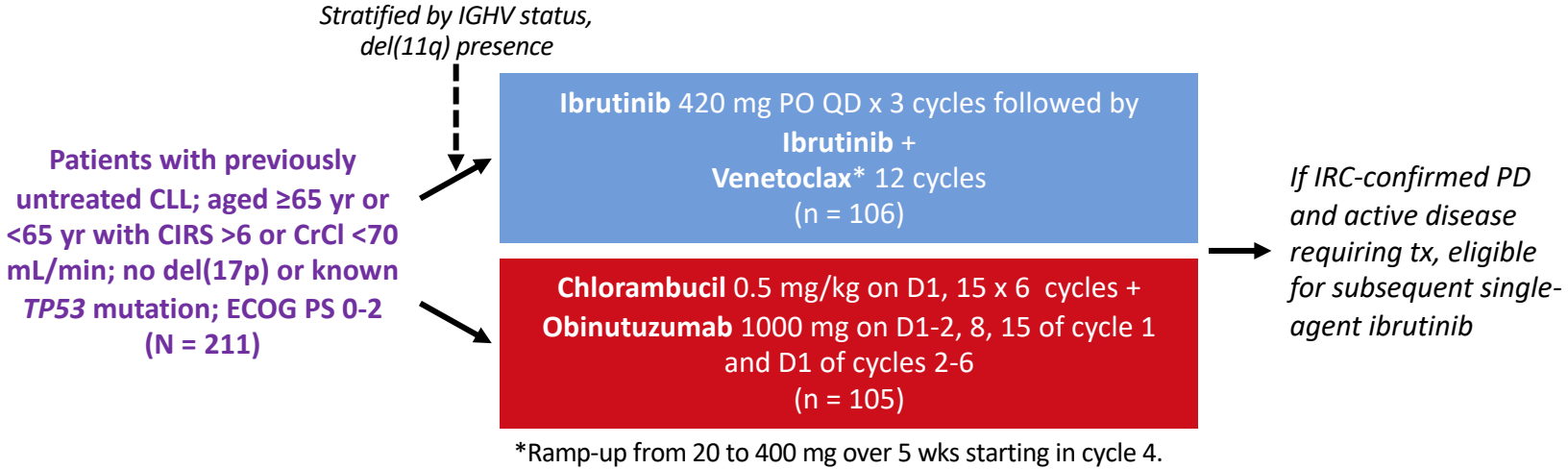
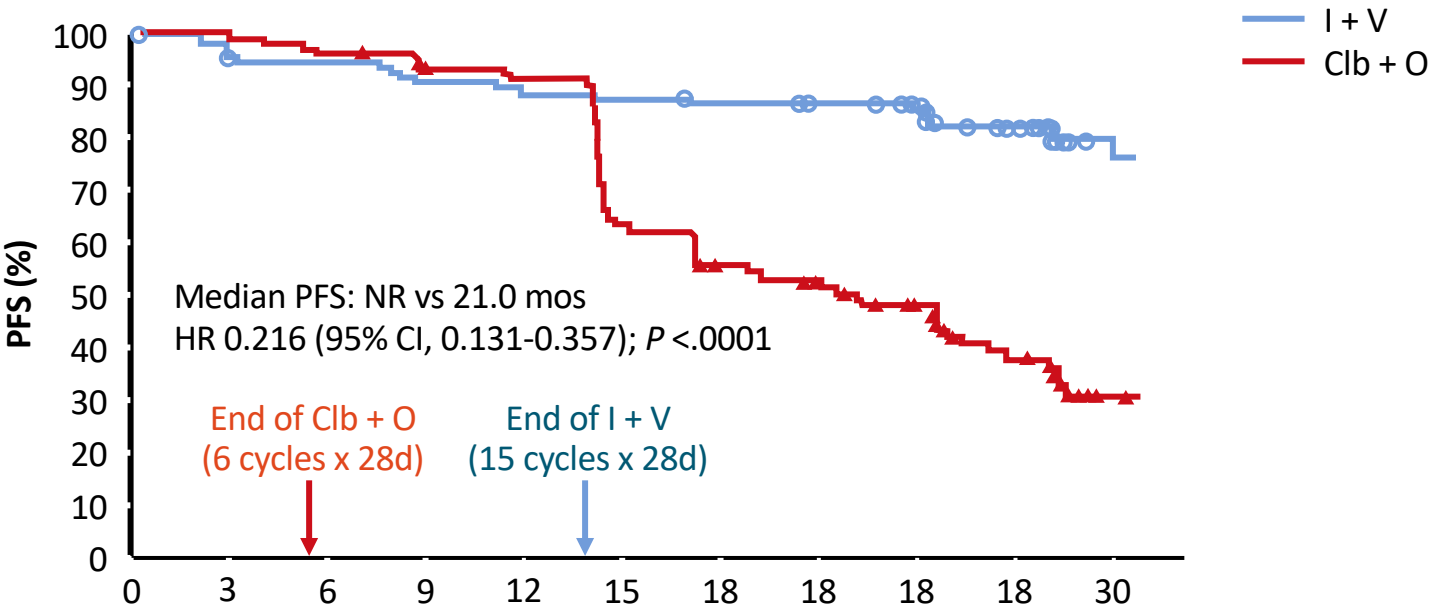
GLOW: Fixed-Duration Ibrutinib + Venetoclax vs Chlorambucil + Obinutuzumab in Frontline CLL



*Ramp-up from 20 to 400 mg over 5 wks starting in cycle 4.

- **Primary endpoint:** PFS per IRC
  - 71 PFS events to detect effect size with HR of 0.5 (80% power, 2-sided $\alpha = 0.05$)
- **Key secondary endpoints:** uMRD in BM, CR rate per IRC, ORR per IRC, OS, safety

GLOW: PFS by IRC



Patients at risk

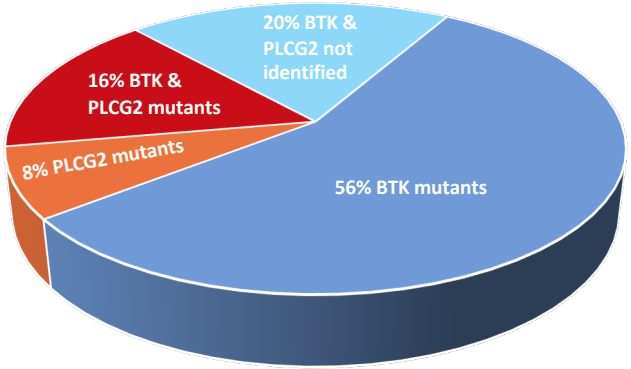
I + V	106	98	98	94	92	91	89	87	71	59	20
Clb + O	105	104	101	95	93	63	54	47	36	25	6

Median Follow-up: 27.7 months

Kater. EHA 2021. Abstr LB1902.

Pirtobrutinib (LOXO-305): Selective Noncovalent BTK Inhibitor

Acquired Resistance to Ibrutinib in Patients With Progressive CLL[1]



- *BTK* C481 mutations are principal reason for progressive CLL after treatment with covalent BTK inhibitors[2]
- *BTK* C481 mutations impair target inhibition by covalent BTK inhibitors[2]

1. Lampson. Expert Rev Hematol. 2018;11:185. 2. Mato. Lancet. 2021;397:892.
3. Mato. ASH 2020. Abstr 542.

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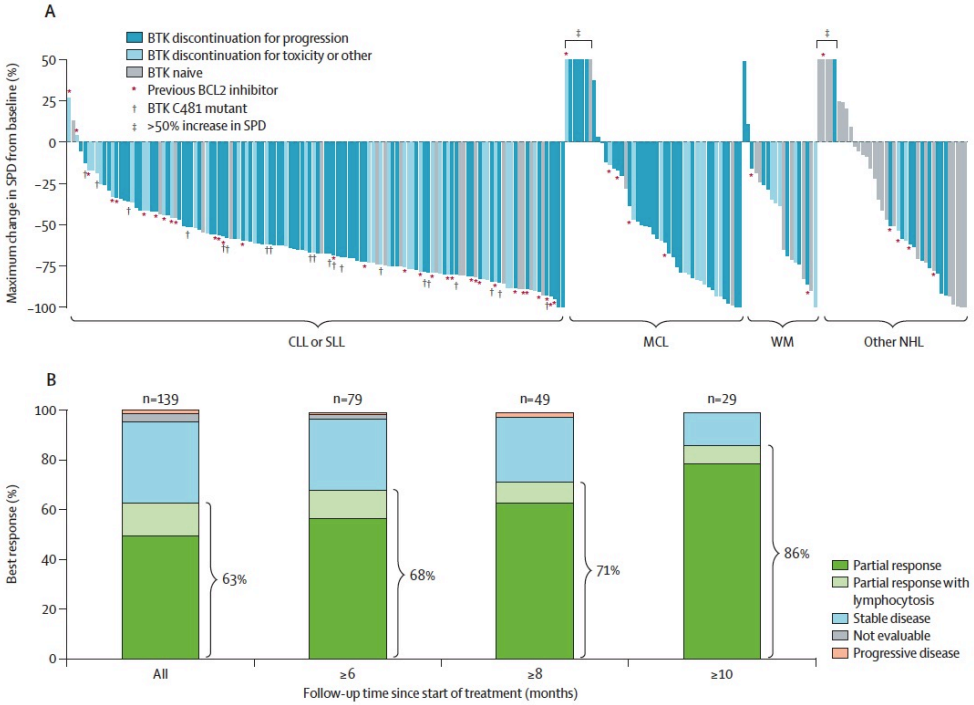
BRUIN: Pirtobrutinib

- Primary endpoints: MTD and recommended phase 2 dose
- Secondary endpoints: safety, PK, ORR



Mato. Lancet 2021

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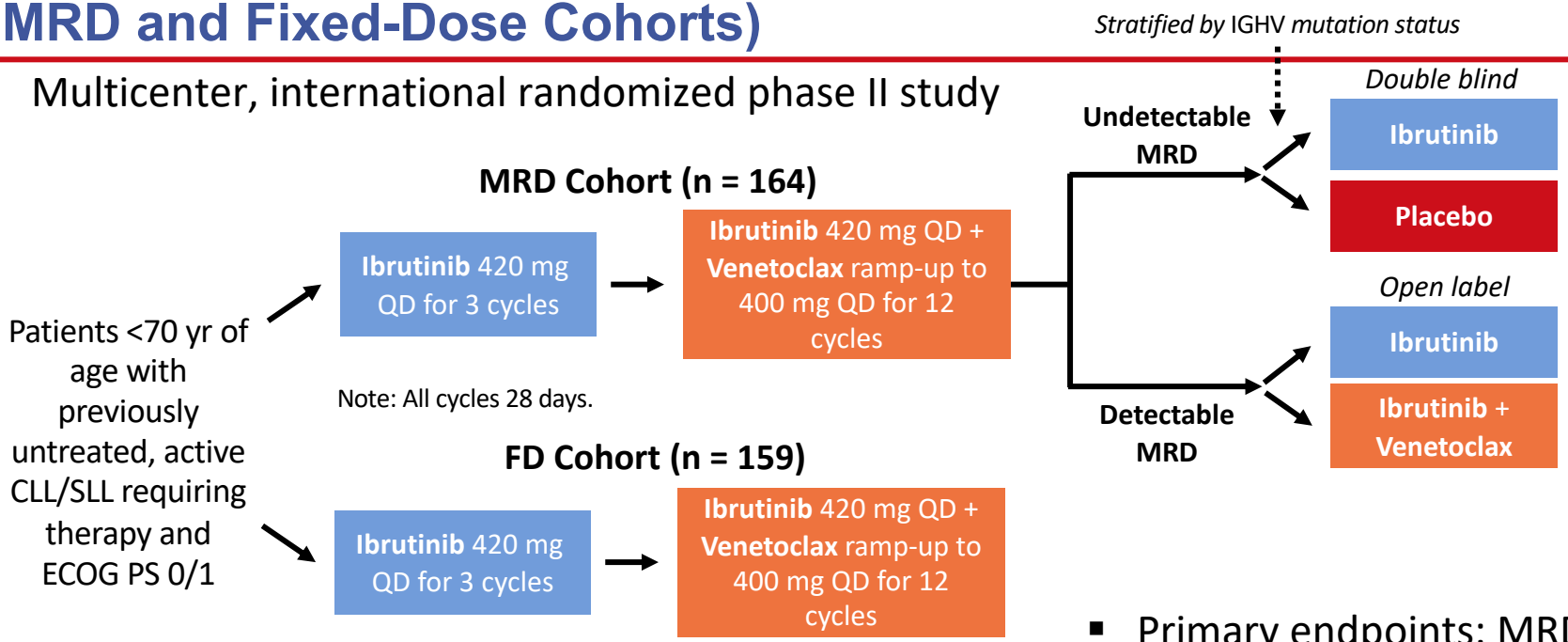
Phase II CAPTIVATE: First-line Ibrutinib + Venetoclax in CLL (MRD and Fixed-Dose Cohorts)

- Multicenter, international randomized phase II study



- Primary endpoints: MRD negativity, DFS, CR rate

- Results from MRD cohort: uMRD in >2/3 of patients who received 12 cycles of ibrutinib/venetoclax[1]; FD results presented at ASCO 2021[2]
  - PB: 75%; BM: 68%
  - 30-mo PFS: ≥95%, regardless of subsequent MRD-guided randomized tx

1. Wierda. ASH 2020. Abstr 123. 2. Ghia. ASCO 2021. Abstr 7501.

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CAPTIVATE—Fixed-Duration Cohort: Efficacy Outcomes From Primary Analysis

Outcome	Patients Without del(17p) (n = 136)	All Patients (N = 159)
CR/CRi, n (%)	76 (56)	88 (55)
Durable CR/CRi,* n/N (%)	66/76 (87)	78/88 (89)
ORR, n (%)	130 (96)	153 (96)
uMRD,† n (%)		
▪ PB	104 (76)	122 (77)
▪ BM	84 (62)	95 (60)
24-mo rate, % (95% CI)		
▪ PFS	96 (91-98)	95 (90-97)
▪ OS	98 (93-99)	98 (94-99)

*Defined as progression free ≥12 cycles after achieving first CR.
†uMRD rates in MRD cohort (n = 164): PB: 75%, BM: 68%.

Ghia. ASCO 2021. Abstr 7501.

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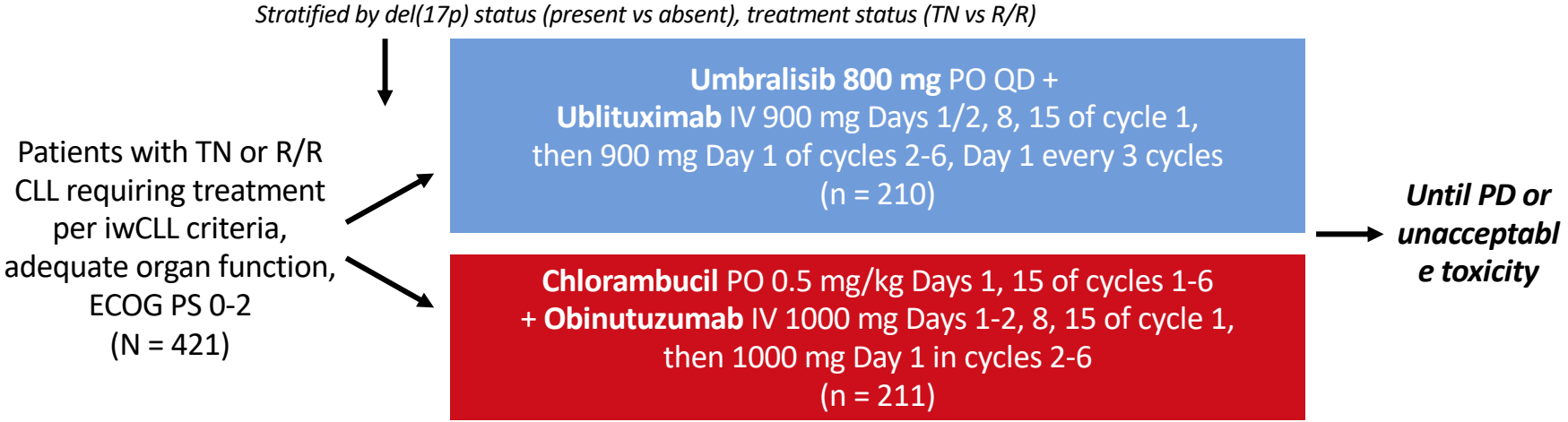
UNITY-CLL: Study Design

- Open-label, multicenter, randomized phase III trial*



*The umbralisib/ublituximab regimen is currently under FDA review for patients with CLL.

- Primary endpoint: IRC-assessed PFS
- Secondary endpoints: IRC-assessed ORR, CR, and DoR, uMRD (central), safety

Gribben. ASH 2020. Abstr 543. NCT02612311.

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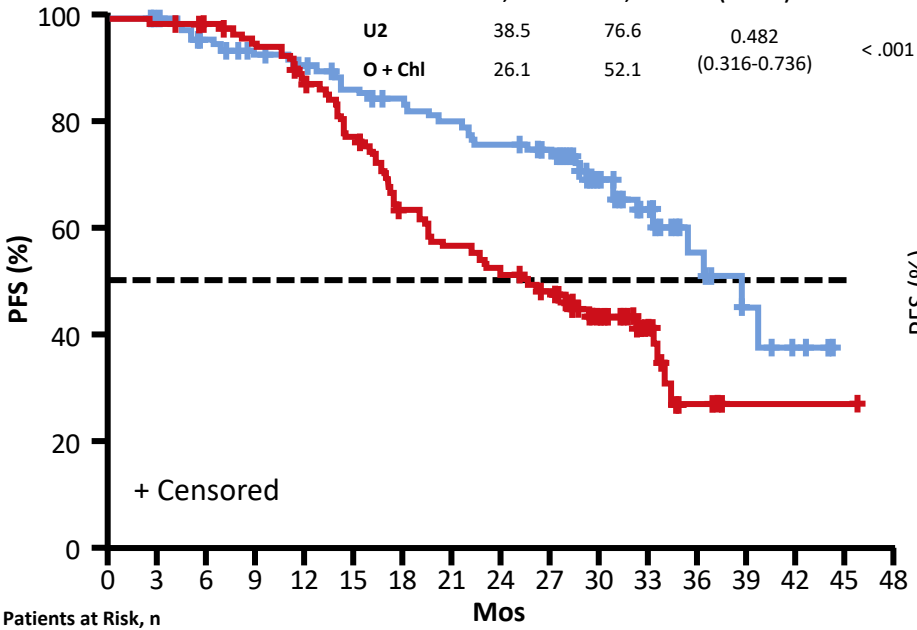
UNITY-CLL: IRC-Assessed PFS in TN and R/R Patients

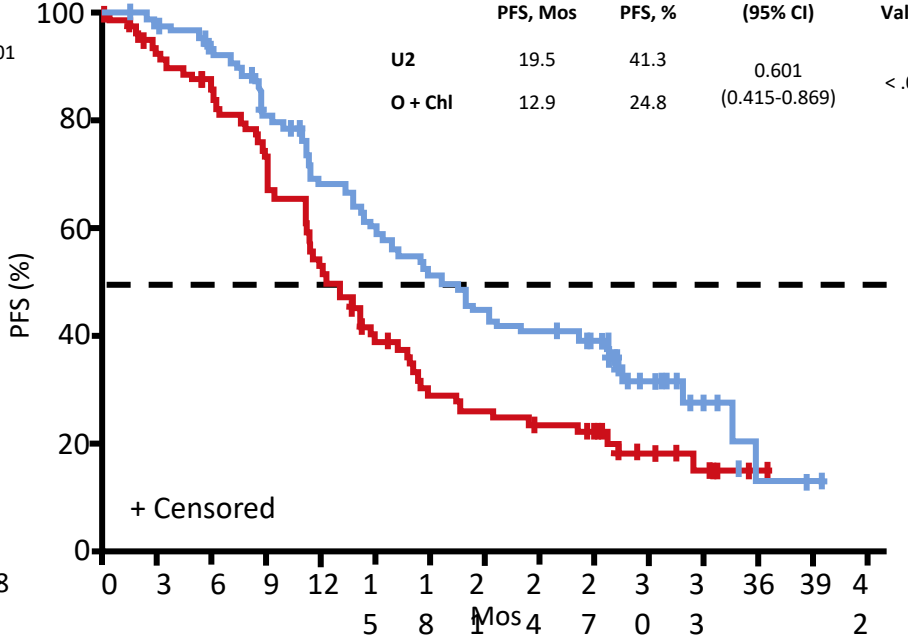
TN Pts	Median PFS, Mos	2-Yr PFS, %	HR (95% CI)	*P* Value
U2	38.5	76.6	0.482 (0.316-0.736)	< .001
O + Chl	26.1	52.1		



Patients at Risk, n

U2	119	106	100	94	90	84	79	76	72	68	39	25	12	6	3	0
O + Chl	121	109	106	100	90	80	64	57	52	46	27	14	4	1	1	1	0

R/R Pts	Median PFS, Mos	2-Yr PFS, %	HR (95% CI)	*P* Value
U2	19.5	41.3	0.601 (0.415-0.869)	< .01
O + Chl	12.9	24.8		



	91	87	80	66	53	47	40	35	32	28	13	6	2	1	0
	90	76	68	57	42	30	22	20	17	15	8	5	1	0	

Gribben. ASH 2020. Abstr 543.

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Select Ongoing Phase 3 Clinical Trials of BTK Inhibitors in CLL

Clinical Trial	Study Design	Population	Estimated Enrollment	Treatment Arms	Status
Ibrutinib Studies					
UK FLAIR Trial	Phase 3, randomized	Newly diagnosed, aged 18-75 yrs	1516	Ibrutinib vs ibrutinib + rituximab vs ibrutinib + venetoclax vs FCR	Recruiting
CLL13 (NCT02950051)	Phase 3, randomized	Newly diagnosed	926	FCR or BR vs venetoclax + rituximab vs venetoclax + obinutuzumab vs venetoclax + ibrutinib + obinutuzumab	Active, not recruiting
EA9161 (NCT03701282)	Phase 3, randomized, open label	Aged 18-69 yrs	720	Ibrutinib + obinutuzumab vs ibrutinib + obinutuzumab + venetoclax	Recruiting
A041702 (NCT03737981)	Phase 3, randomized, open label	Untreated, aged ≥70 yrs	454	Ibrutinib + obinutuzumab vs ibrutinib + obinutuzumab + venetoclax	Recruiting
CLL17	Phase 3, randomized	Untreated, aged ≥18 yrs	897	Ibrutinib vs ibrutinib + venetoclax vs obinutuzumab + venetoclax	Recruiting
Acalabrutinib Studies					
ACE-CL-311 (NCT03836261) ClinicalTrials.gov.	Phase 3, randomized, global, open label	Aged ≥18 yrs	780	Acalabrutinib + venetoclax vs acalabrutinib + venetoclax + obinutuzumab vs standard chemotherapy	Recruiting
MAJIC	Phase 3, randomized, global, open label	Newly diagnosed, aged ≥18 yrs	600	MRD-guided acalabrutinib + venetoclax vs MRD-guided venetoclax + obinutuzumab	Coming Soon

Picking a BTK vs BCL2 Inhibition Strategy

BTK Inhibitor[1-4]

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

BCL2 Inhibitor[4,5]

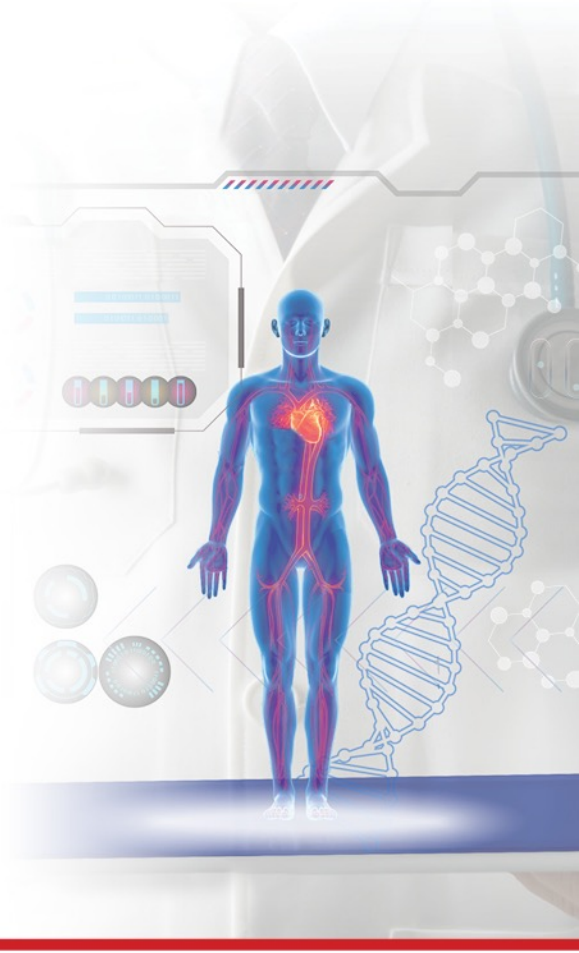
- Cumbersome initiation
- Fixed duration
- Risk for TLS requires monitoring
- GFR sensitivity
- Question if best for high-risk patients

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

Conclusions

- Novel targeted agents are eclipsing chemoimmunotherapy both in patients with newly diagnosed and relapsed CLL
- Initial therapy options include acalabrutinib ± obinutuzumab, ibrutinib, and venetoclax + obinutuzumab
- Therapy options for relapsed CLL include acalabrutinib, ibrutinib, venetoclax + rituximab, duvelisib, and idelalisib + rituximab
- Ongoing investigation is exploring novel agents and multitargeted combination regimens with the goal of MRD eradication

Patient Cases and Post-Assessment



Case 1, revisited

A 55-year-old man with HTN and stage 2 CKD presents with new lymphocytosis. Flow shows monoclonal population (CD19/20/5/23+), FISH with trisomy 12 only, also with unmutated *IGHV*, *NOTCH1/TP53* wildtype. He is diagnosed with Rai 0 CLL and observed for 4 years. He is now 59-years old and has progressive symptomatic anemia, thrombocytopenia, and lymphadenopathy. Bone marrow biopsy shows 90% involvement by CLL, and he now requires initial therapy.

How would you choose to treat this patient?

A. Chlorambucil + obinutuzumab

B. Acalabrutinib ± obinutuzumab → PFS advantage over Chlorambucil + obinutuzumab in the ELEVATE-CLL TN trial

C. Venetoclax monotherapy

D. Ibrutinib → OS advantage over FCR in the ECOG 1912 trial, particularly for IGHV unmutated patients

E. Acalabrutinib +/- Obinutuzumab and Ibrutinib are both reasonable options

Case 2, revisited

A 69-year-old man presents with del(17p) CLL. He is observed for 1 year and requires initial therapy. He is treated with ibrutinib and has some hypertension but otherwise tolerates it well and is in PR for 4 years. Now at age 74 he has developed progressive lymphocytosis and lymphadenopathy on ibrutinib.

How would you choose to treat this patient?

A. Bendamustine + rituximab → CIT is ineffective in del(17p) CLL

B. Duvelisib → Little data post BTKi

C. Venetoclax → Would expect a 65% ORR and 2 yr mPFS for this approach

D. Rituximab monotherapy → Does not provide durable benefit in CLL

E. Acalabrutinib → Common resistance mechanisms with ibrutinib

Case 3, revisited

A 74-y/o woman with atrial fibrillation on warfarin and diet-controlled type 2 diabetes presents with del(11q), unmutated *IGHV* CLL. After 3 years of observation, she develops progressive cytopenias and lymph node disease and is treated with 1-year of venetoclax + obinutuzumab. She achieves a PR and still has detectable MRD at the end of treatment. Six months later, she develops progressive CLL and now requires second-line therapy.

How would you choose to treat this patient?

A. Acalabrutinib → According to ELEVATE R-R trial, acala is comparably efficacious but with less CV toxicity than ibrutinib

B. Ibrutinib

C. Bendamustine + rituximab → Patient has higher risk molecular features and would not be expected to have durable benefit with BR; BR was inferior to acalabrutinib in ASCEND trial

D. Re-treatment with venetoclax + obinutuzumab → Given the short initial remission this is unlikely to provide durable remission

E. Rituximab monotherapy → Ineffective as a single agent in CLL

Thank You!

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Next presentation: Wednesday, November 10, 2021
Diffuse Large B-cell Lymphoma
Grzegorz Nowakowski, MD