Pharmacotherapy Management in Chronic Lymphocytic Leukemia (CLL)

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Learning Objectives

- Describe CLL pharmaceutical treatment options and place in therapy
- Summarize new evidence-based approaches in CLL treatment
- Discuss drugs pharmacology and monitoring considerations
- Review relevant pharmacotherapy considerations for optimal patient care monitoring and adverse effect management

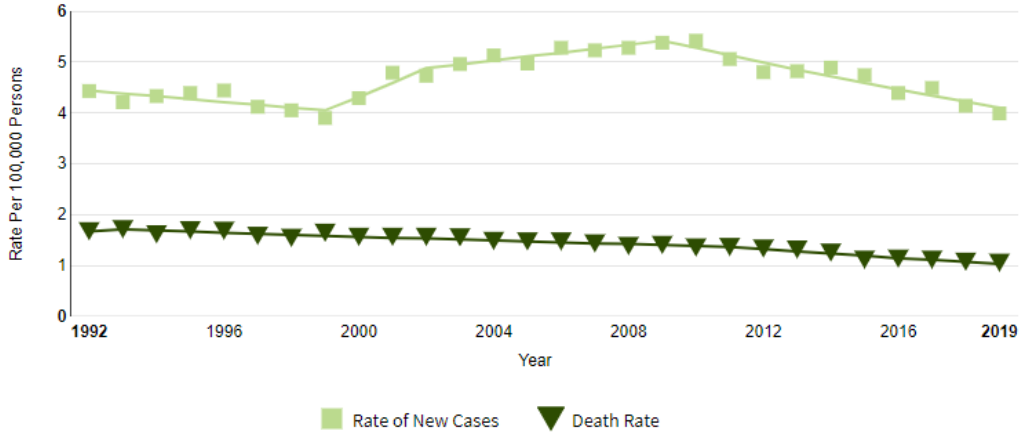
Chronic Lymphocytic Leukemia

- Chronic Lymphocytic Leukemia (CLL) is a disorder of morphologically mature but immunologically less mature lymphocytes and is manifested by progressive accumulation of these cells in the blood, bone marrow, and lymphatic tissues
- CLL and small lymphocytic lymphoma (SLL) are different manifestations of the same disease, managed similarly
- Major difference is abnormal lymphocyte location
  - CLL: found in blood, bone marrow, and lymphoid tissue
  - SLL: bulk of disease is in lymph nodes, lymphoid tissue, spleen , and bone marrow

Tsimberidou et al. J Clin Oncol 2007;25:4648-4656

Chronic Lymphocytic Leukemia

- Most prevalent adult leukemia in Western counties
- 20,160 estimated new cases in 2022
- 1.1% of all new cancer cases



Siegel et al. *CA: a cancer journal for clinicians* (2022).

Clinical Presentation

- The clinical course of this disease progresses from an indolent lymphocytosis without other evident disease to one of generalized lymphatic enlargement with concomitant pancytopenia
- Complications of pancytopenia, including hemorrhage and infection, represent a major cause of death in these patients
- Diagnosis
  - ≥5 x10^9/L monoclonal B lymphocytes in peripheral blood and B-cell clonality confirmed by flow cytometry

Anaissie et al. Ann Intern Med 129 (7): 559-66, 1998 | Tsimberidou et al. J Clin Oncol 2007;25:4648-4656

Prognostic Markers for CLL/SLL

Test	Favorable	Intermediate	Unfavorable
Interphase cytogenetics (FISH)	Del(13q) as a sole abnormality	Trisomy 12 Normal	Del(17p) Del(11q) ≥ 3 unrelated chromosomal abnormalities
DNA sequencing	TP53 – Wild type *IGHV* >2% mutation		TP53 – mutated *IGHV* ≤2% mutation
Surface markers-Flow cytometry	CD49d ≥30%		CD38 expression ≥30% ZAP-70 ≥20%

H Döhner et al. N Engl J Med 2000 Dec 28;343(26):1910-6.

FISH: Fluorescence In Situ Hybridization

Prognostic Value of FISH

- Cytogenetic abnormalities detected by FISH are present in more than 80% of patients with previously untreated CLL. The most common mutations at diagnosis are:

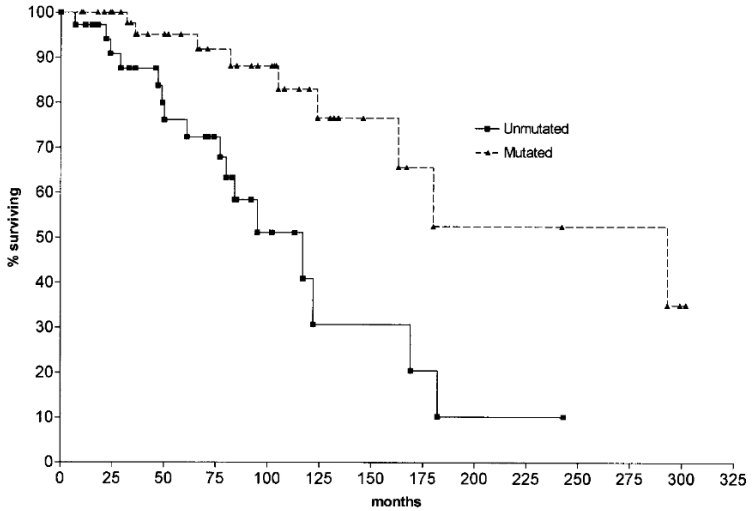
FISH Abnormalities Present in 268/325 Patients (82%)		
Lesion	**Patients (%)**	**Median OS (Mo)***
del(13q)	55	133
del(11q)	18	79
Trisomy 12	16	114
del(17p)	7	32
del(6q)	6	NR
Normal	18	111

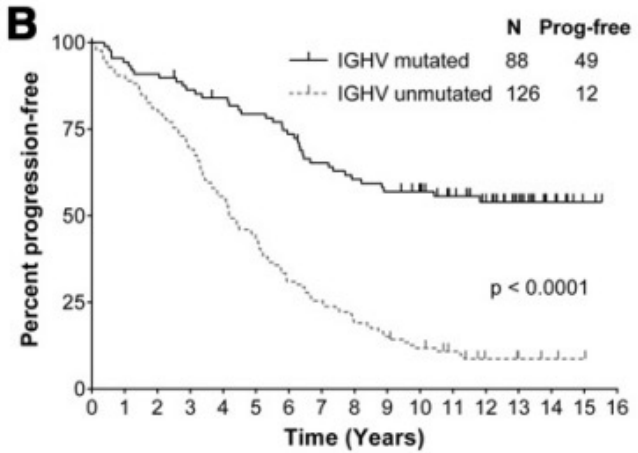
Döhner. N Engl J Med 2000 Dec 28;343(26):1910-6

*Prior to Novel Targeted Therapies

DNA Sequencing - *IGHV* Status

- *IGHV* status is necessary when considering treatment with chemo-immunotherapy
- Patients with *IGHV* mutated CLL can have long term PFS following FCR therapy (54% at 13 years)

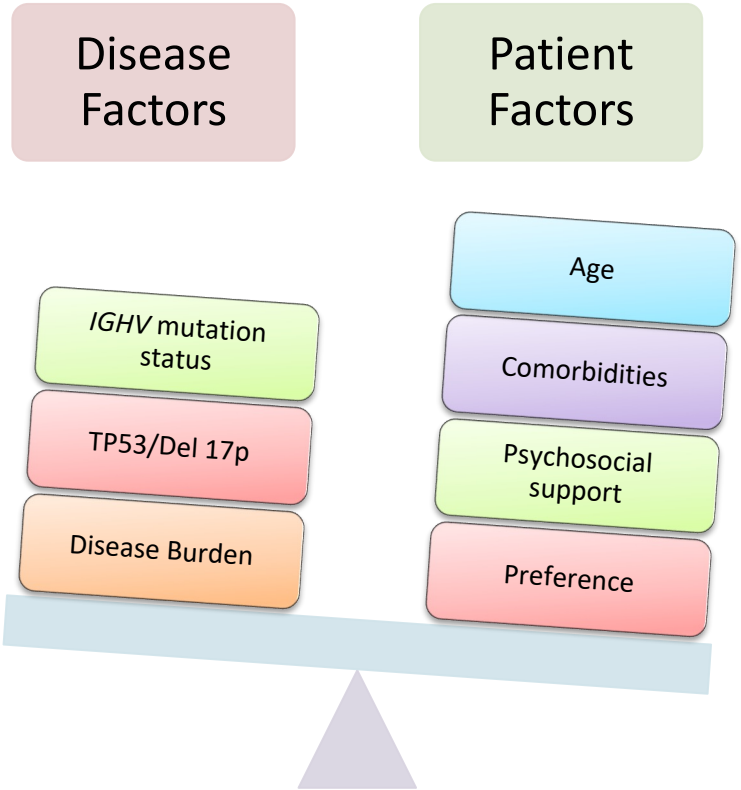




FCR: Fludarabine, Cyclophosphamide, Rituximab

Hamblin et al. Blood, Vol 94, No 6,1999: pp 1848-1854 | Thompson et al. Blood, 21 January 2016 X Volume 127, Number 3

Treatment Considerations



First-Line Therapy for CLL/SLL WITHOUT del(17p)/*TP53* Mutation

Preferred regimens

- Acalabrutinib ± Obinutuzumab (category 1)
- Venetoclax + Obinutuzumab (category 1)
- Zanubrutinib (category 1)

Other recommended regimens

- Ibrutinib (category 1)
- Bendamustine + anti-CD20 mAB
- Chlorambucil + Obinutuzumab
- Obinutuzumab
- High-dose methylprednisolone (HDMP) + rituximab or Obinutuzumab (category 2B; category 3 for patients <65 y without significant comorbidities)
- Ibrutinib + Obinutuzumab (category 2B)
- Ibrutinib + rituximab (category 2B)
- Ibrutinib + venetoclax (category 2B)

Useful in certain circumstances

(consider for *IGHV*-mutated CLL in patients <65 y without significant comorbidities)

- FCR (fludarabine, cyclophosphamide, rituximab)

Note: Zanubrutinib not FDA approved for this indication

Second or third-Line Therapy for CLL/SLL WITHOUT del(17p)/*TP53* Mutation

Preferred regimens

BTKi

- Acalabrutinib (category 1)
- Zanubrutinib

BCL-2 inhibitor

- Venetoclax + rituximab (category 1)

Other recommended regimens

- Ibrutinib (category 1)
- Venetoclax

Useful in certain circumstances

(for relapse after a period of remission if previously used as first line therapy)

- Retreatment with venetoclax + Obinutuzumab

Note: Zanubrutinib not FDA approved for this indication

First-Line Therapy for CLL/SLL WITH del(17p)/*TP53* Mutation

Preferred regimens

- Acalabrutinib ± Obinutuzumab
- Venetoclax + Obinutuzumab
- Zanubrutinib

Other recommended regimens

- Alemtuzumab ± rituximab
- HDMP + rituximab
- Ibrutinib
- Obinutuzumab
- Ibrutinib + venetoclax (category 2B)

Second-Line Therapy for CLL/SLL WITH del(17p)/*TP53* Mutation

Preferred regimens

- Acalabrutinib (category 1)
- Venetoclax + rituximab (category 1)
- Venetoclax
- Zanubrutinib

Other recommended regimens

- Ibrutinib (category 1)
- Alemtuzumab ± rituximab
- Duvelisib
- HDMP + rituximab
- Idelalisib ± rituximab
- Lenalidomide ± rituximab

Notes:

- Chemoimmunotherapy (CIT) is not recommended since del(17p)/*TP53* mutation is associated with low response rates
- Zanubrutinib not FDA approved for this indication

Key Clinical Trials in Front Line

- Ibrutinib:
  - Alliance North American Intergroup Study (A041202)
    - First line BR vs ibrutinib ± rituximab
  - E1912 study: ibrutinib vs FCR in patients ≤ 70 years
  - iLLUMINATE: ibrutinib + obinutuzumab vs chlorambucil + obinutuzumab
  - RESONATE-2: ibrutinib vs chlorambucil in older patients ≥ 65
- Acalabrutinib
  - ELEVATE-TN: Acalabrutinib + Obinutuzumab vs acalabrutinib monotherapy vs obinutuzumab and oral chlorambucil
- Zanubrutinib
  - SEQUOIA: zanubrutinib vs bendamustine + rituximab
- Venetoclax
  - CLL14 study: venetoclax + obinutuzumab vs chlorambucil + obinutuzumab

Woyach. N Engl J Med 2018; 379:2517-2528 | Shanafelt N Engl J Med 2019;381:432-43. | Moreno. Lancet Oncol. 2019;20:43. | Burger JA et al. N Engl J Med. 2015;373(25):2425-2437.Sharman. Lancet 2020; 395: 1278–91 | Shadman et al. Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR, Poster LBA5 | Al-Sawaf et al. Lancet Oncol 2020;21: 1188–200 | Al-Sawaf et al. HemaSphere: June 2022 - Volume 6 - Issue - p 49-50

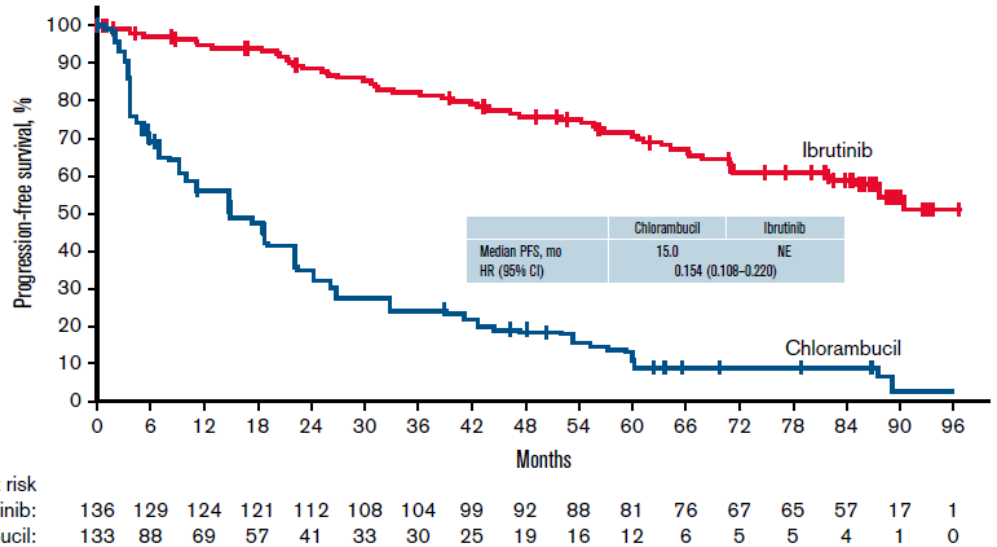
RESONATE-2 Trial

- Phase 3, randomized, multicenter, open-label
- Previously untreated CLL/SLL age ≥65 yr without del(17p) N=269
  - Ibrutinib vs chlorambucil
- Endpoints:
  - PFS, OS, ORR, improvement in hematologic parameters, patient-reported outcomes, and safety
- Results:
  - Ibrutinib resulted in higher rates of improvements in disease-related symptoms
  - Significantly more ibrutinib-treated patients with baseline anemia had sustained improvement in hemoglobin levels compared with chlorambucil

Burger JA et al. N Leukemia (2020) 34:787–798

Up to 8-year follow-up from RESONATE-2

	Ibrutinib	chlorambucil	
ORR	92%	37%	
Median PFS	NE	15 months	
PFS at 5 years	70%	12%	HR= 0.146 (95%CI, 0.098–0.218)
PFS at 7 years	59%	9%	
OS at 5 years	83%	68%	HR= 0.450 (95%CI, 0.266–0.761)
OS at 7 years	78%	--	



- PFS benefit seen across all subgroups, with and without Del (11q) and mutated vs unmutated *IGHV*

Burger JA et al. N Leukemia (2020) 34:787–798| Barr et al. Blood Adv (2022) 6 (11): 3440–3450.

ORR: overall response rate
NE: not estimable

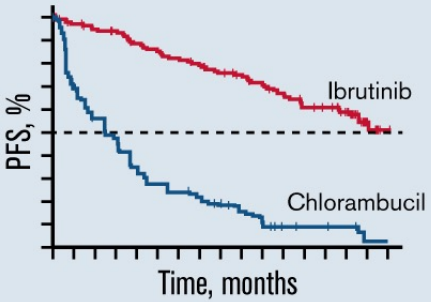
Up to 8-year follow-up from RESONATE-2

Up to 8 years of follow-up for ibrutinib treatment of CLL

Safety

- No new safety signals
- Active dose management allowed continued ibrutinib benefit

Efficacy



- Median PFS not reached up to 8 years

Patient disposition

- 42% of patients continue on ibrutinib at 8 years

Barr et al. Blood Adv (2022) 6 (11): 3440–3450.

E1912 Trial

- Phase 3 trial, randomized, multicenter, open label
- Previously untreated CLL/SLL age ≤ 70 years without del(17p) N=529
  - Ibrutinib–Rituximab or CIT for CLL (FCR)
- Endpoints:
  - Primary: PFS
  - Secondary: OS
- Results:
  - Median follow-up of 33.6 months, PFS favored ibrutinib–rituximab over CIT (89.4% vs. 72.9% at 3 years; HR, 0.35; 95%[CI], 0.22 to 0.56; P<0.001)
    - Subgroup analysis patients without *IGHV* mutation, ibrutinib–rituximab resulted in better PFS than CIT (90.7% vs. 62.5% at 3 years; HR, 0.26; 95% CI, 0.14 to 0.50)
  - OS (98.8% vs. 91.5% at 3 years; HR, 0.17; 95% CI, 0.05 to 0.54; P<0.001)

Shanafelt N Engl J Med 2019;381:432-43.

iLLUMINATE Trial

- Phase 3, randomized, multicenter, open-label
- Previously untreated CLL/SLL age ≥65 years or < 65 years with coexisting conditions N=229
  - Ibrutinib + Obinutuzumab (I+O) vs chlorambucil + Obinutuzumab (C+O)
- Endpoints:
  - PFS
- Results:
  - PFS at 30 months 79% for I+O vs 31% C+O HR=0·23 (95% CI 0·15–0·37),p<0·0001
  - Benefit seen across all high-risk groups

Moreno. Lancet Oncol. 2019;20:43.

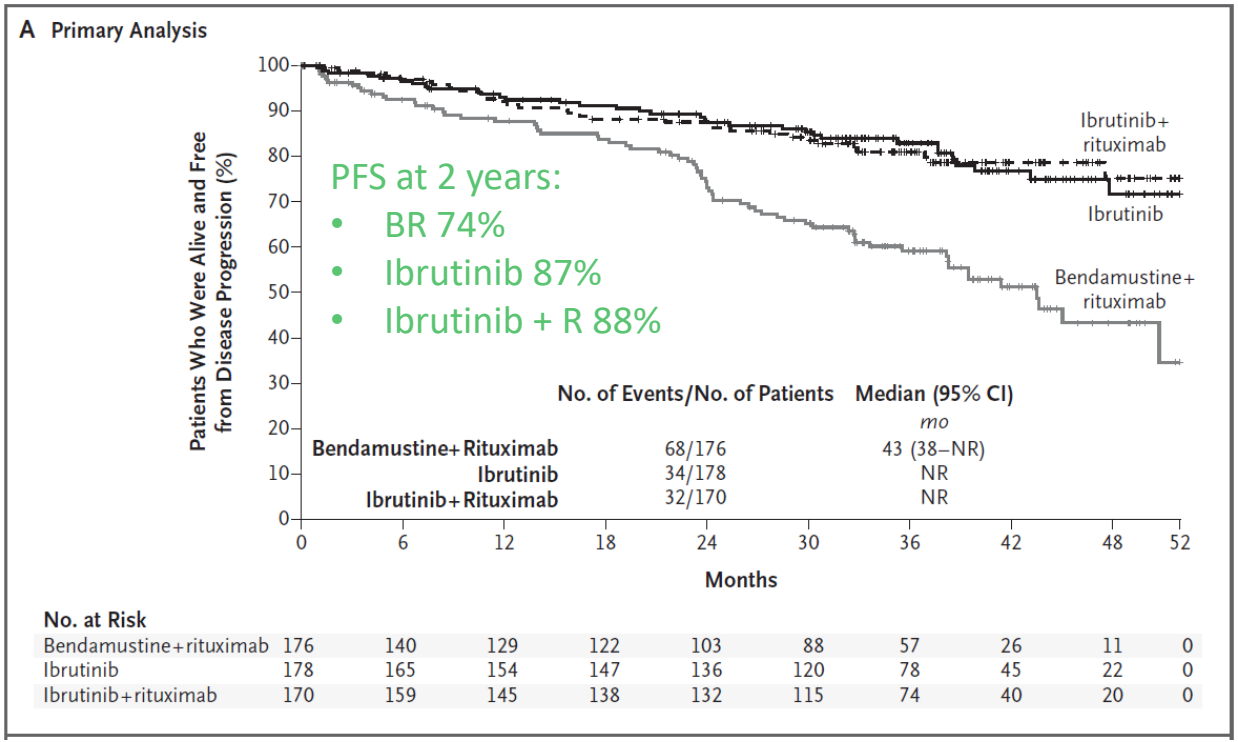
Alliance North American Intergroup Study (A041202)

- Phase 3, randomized, multicenter, open-label
- Previously untreated CLL/SLL age ≥65 years N=547
  - Ibrutinib vs Ibrutinib + rituximab vs BR
- Endpoint:
  - PFS

Woyach. NEJM. 2018;379:2517. NCT01886872.

BR: bendamustine + rituximab

Alliance North American Intergroup Study (A041202)



No significant difference between ibrutinib+R vs ibrutinib group with regard to PFS (HR, 1.00; 95% CI, 0.62 to 1.62; P = 0.49).

BR: bendamustine + rituximab

Woyach. N Engl J Med 2018;379:2517-28.

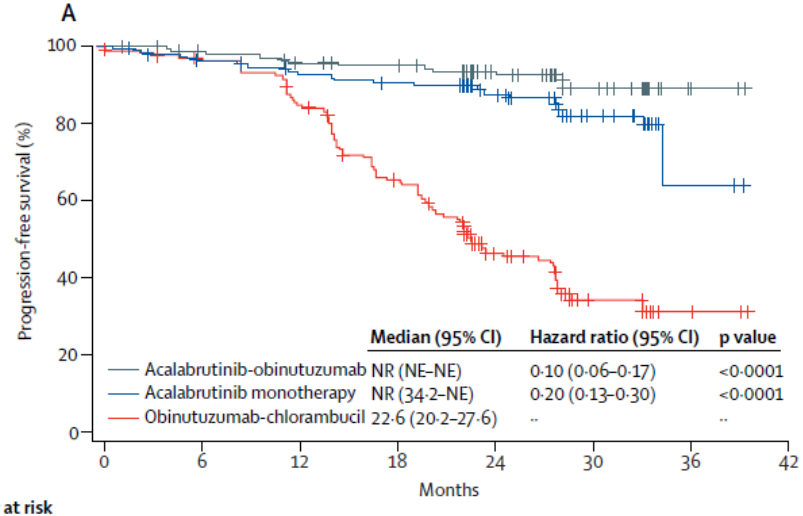
ELEVATE-TN

- Phase 3, randomized, multicenter, open-label
- Previously untreated CLL ≥65 yr or <65 yr with CIRS score >6 or CrCl 30-69 mL/min N=535
  - Acalabrutinib + Obinutuzumab vs acalabrutinib monotherapy vs obinutuzumab and oral chlorambucil
- Endpoints:
  - Primary: PFS between the two combination groups
  - Secondary: PFS between acalabrutinib vs obinutuzumab + chlorambucil, ORR by IRC and investigators, time to next treatment, OS, safety

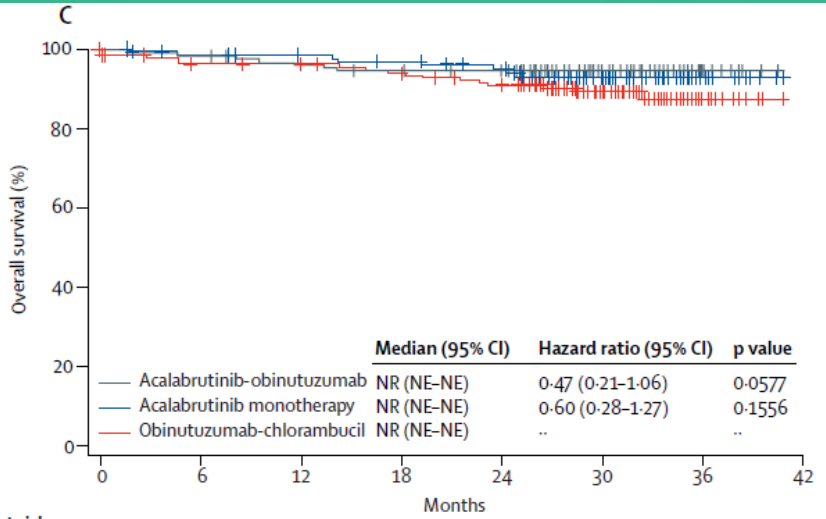
Sharman. Lancet 2020; 395: 1278–91

CIRS: Cumulative Illness Rating Scale for geriatrics score
IRC: independent review committee

ELEVATE-TN



Number at risk (number censored)														
Acalabrutinib-obinutuzumab	179 (0)	176 (3)	170 (7)	168 (7)	163 (9)	160 (11)	159 (11)	155 (13)	109 (58)	104 (63)	46 (119)	41 (124)	4 (161)	2 (163)
Acalabrutinib monotherapy	179 (0)	166 (9)	161 (11)	157 (13)	153 (14)	150 (14)	148 (15)	147 (15)	103 (56)	94 (64)	43 (112)	40 (115)	4 (149)	3 (150)
Obinutuzumab-chlorambucil	177 (0)	162 (12)	157 (15)	151 (15)	136 (16)	113 (19)	102 (20)	86 (21)	46 (49)	41 (52)	13 (72)	13 (72)	3 (81)	2 (82)



Number at risk (number censored)														
Acalabrutinib-obinutuzumab	179 (0)	178 (0)	176 (0)	173 (2)	170 (2)	168 (2)	167 (3)	165 (5)	164 (6)	122 (48)	75 (95)	47 (123)	15 (155)	3 (167)
Acalabrutinib monotherapy	179 (0)	175 (3)	173 (4)	171 (6)	169 (7)	167 (7)	166 (8)	163 (10)	159 (11)	119 (49)	77 (91)	49 (119)	19 (149)	5 (163)
Obinutuzumab-chlorambucil	177 (0)	168 (6)	165 (7)	163 (8)	163 (8)	160 (10)	158 (10)	154 (12)	150 (13)	111 (51)	70 (91)	44 (116)	17 (143)	4 (156)

PFS at 24 months:

- **Acala+obinu 93%**
- **Acala monotherapy 87%**
- **Obinu +chlorambucil 47%**

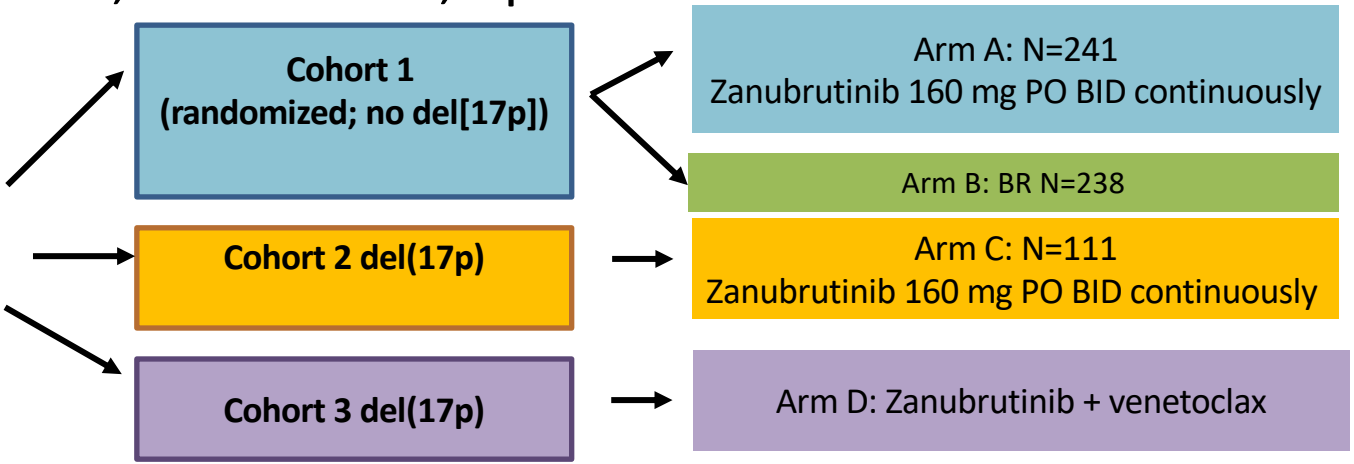
Median OS not reached and 2 year OS:

- **Acala+obinu 95 %**
- **Acala monotherapy 95 %**
- **Obinu +chlorambucil 92%**

Sharman. Lancet 2020; 395: 1278–91

SEQUOIA

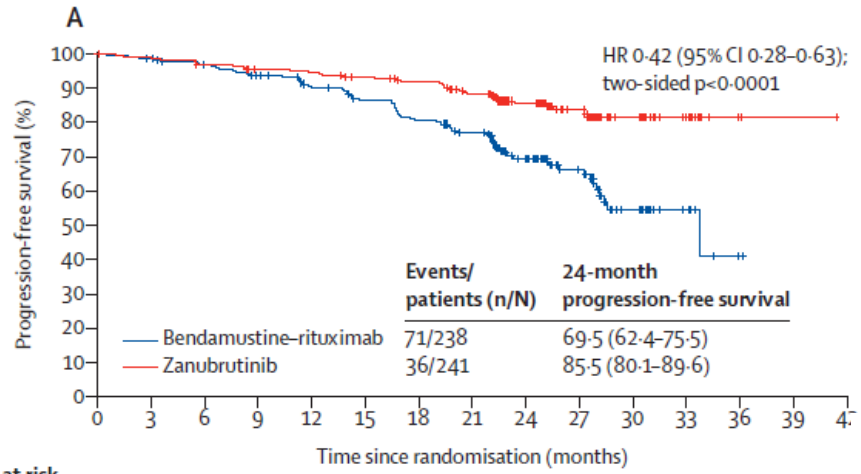
- Phase 3, randomized, multicenter, open-label



- Endpoints for cohort 1: PFS
- Endpoints for cohort 2- Arm C : ORR, OS, DoR, safety

Tam CS et al. *Lancet Oncol*. 2022;23(8):1031-1043. | Tam C et al. 63rd American Society of Hematology Annual Meeting and Exposition (ASH 2021). Abstract 396.| Brown. ASH 2020. Abstr 1306. Tam. Haematologica. 2020;[Epub] | Shadman et al. *Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR, Poster LBA5*

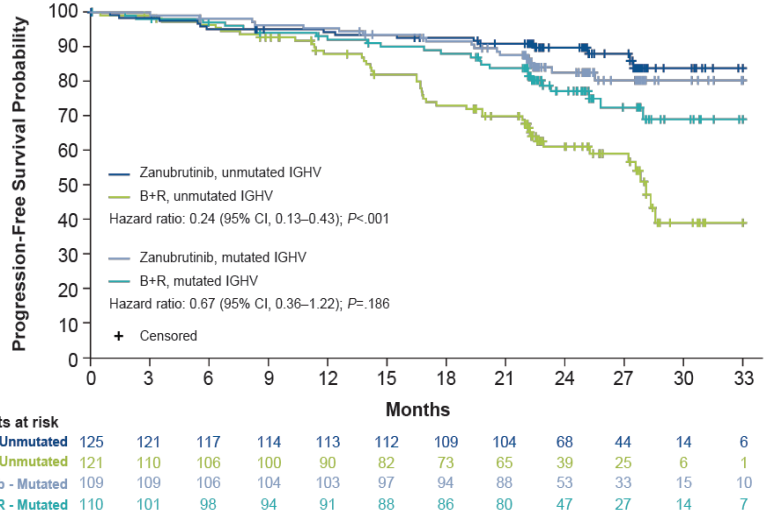
Cohort 1: PFS



Number at risk (number censored)															
Bendamustine–rituximab	238 (0)	218 (17)	210 (21)	200 (24)	187 (30)	176 (33)	164 (33)	150 (40)	89 (89)	54 (121)	20 (148)	8 (160)	1 (166)	0 (167)	.. ..
Zanubrutinib	241 (0)	237 (2)	230 (3)	224 (6)	222 (6)	214 (11)	208 (14)	195 (19)	123 (86)	79 (128)	31 (174)	17 (188)	2 (203)	1 (205)	0 (20

Zanubrutinib treatment benefit was observed for patients with unmutated *IGHV* (HR 0.24; 2-sided *P*<.0001), but not for mutated *IGHV* (HR 0.67; 2-sided *P*=.1858; **Figure 1C**)

Figure 1C. PFS by IGHV Status



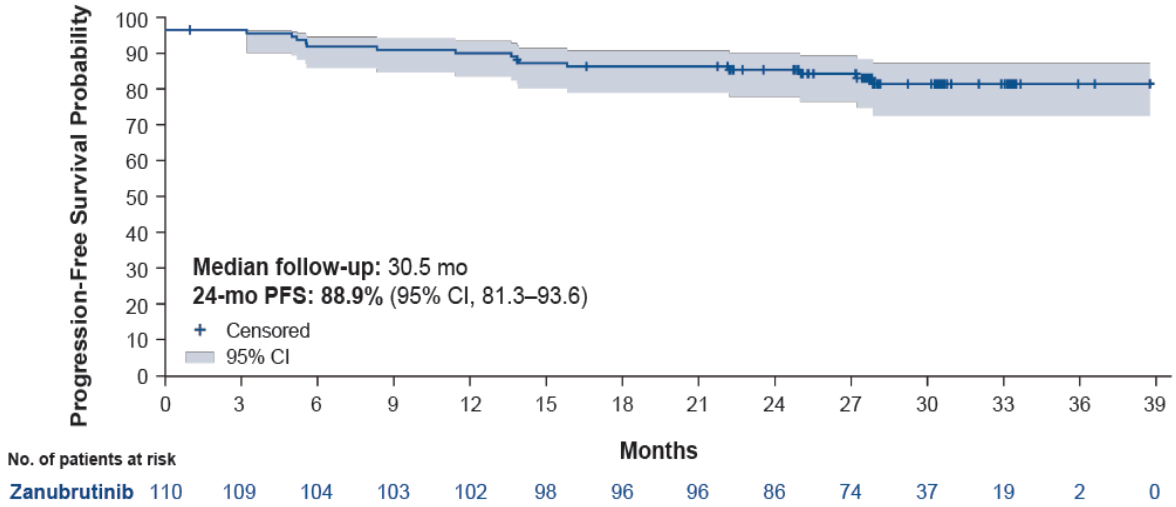
No. of patients at risk												
Zanubrutinib - Unmutated	125	121	117	114	113	112	109	104	68	44	14	6
B+R - Unmutated	121	110	106	100	90	82	73	65	39	25	6	1
Zanubrutinib - Mutated	109	109	106	104	103	97	94	88	53	33	15	10
B+R - Mutated	110	101	98	94	91	88	86	80	47	27	14	7

B+R, bendamustine + rituximab; IGHV, gene encoding the immunoglobulin heavy chain variable region; IRC, independent review committee.

Shadman et al. *Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR, 2022, Poster LBA5* | Tam CS et al. *Lancet Oncol*. 2022;23(8):1031-1043

Cohort 2: PFS

Figure 3. Cohort 2: PFS in Patients with del(17p)



del(17p), chromosome 17p deletion; PFS, progression-free survival.

ORR: 94.5%, median PFS, OS, DoR, were not reached[2]

1. Shadman et al. *Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR, 2022 Poster LBA5* | 2. Tam et al. Haematologica | 2021; 106(9)

CLL14

- Phase 3, randomized, multicenter, open-label study
- Previously untreated CLL patients ≥18 yr with CIRS score >6 and/or CrCl 30-69 mL/min N = 432
  - Ven-Obi vs Clb-Obi
- Endpoints:
  - Primary: investigator assessed PFS
  - Secondary: PFS by IRC, ORR, CR, rates of MRD response, TTNT, OS, and safety

Ven-Obi: venetoclax-obinutuzumab
Clb-Obi: Chlorambucil-Obinutuzumab
TTNT: time to next treatment

Al-Sawaf et al. Lancet Oncol 2020;21: 1188–200 | Al-Sawaf et al. HemaSphere: June 2022 - Volume 6 - Issue - p 49-50

CLL14 PFS & OS

	Ven-Obi N=216	Clb-Obi N=216	
3-year PFS	81.9%	62.6%	
5-year PFS	62.6%	27%	
Median PFS at 5 years	NR	36.4 months	HR=0.35 (95% CI 0.26-0.46), p<0.0001
5-year TTNT	72.1%	42.8%	HR=0.42, (95% CI 0.31-0.57), p<0.0001
5-year OS	81.9%	77%	HR=0.72, (95% CI 0.48-1.09), p=0.12)
4 years after treatment completion			
• uMRD $<10^{-4}$	39 (18.1%)	4 (1.9%)	
• Low MRD $\geq 10^{-4}$ and $< 10^{-2}$	27 (12.5%)	13 (6.0%)	
• High MRD ($\geq 10^{-2}$)	41 (19.0%)	24 (11.1%)	

Al-Sawaf et al. Lancet Oncol 2020;21: 1188–200 | Al-Sawaf et al. HemaSphere, 2022;6:(S3):pages 100-10

NR: not reached

Minimal Residual Disease Assessment

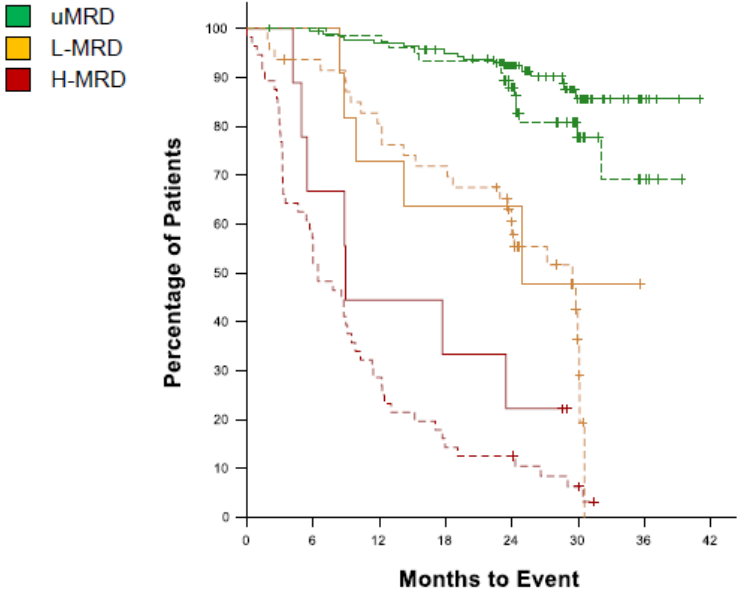
- uMRD in CLL is defined as <1 CLL cell in 10,000 leukocytes (0.01% or $<10^{-4}$)
- Methods of detection:
  - Flow cytometry (sensitivity to $10^{-4 \text{ to } -5}$)
  - Allele- specific oligonucleotide IGHV real time quantitative PCR (ASO IGH RQ-PCR) (sensitivity to 10^{-5})
  - NGS assay (sensitivity to 10^{-6})
    - August 2020: clonoSEQ NGS assay FDA-cleared to detect MRD in CLL

Moritz. Hemasphere. 2019 Aug 9;3(5):e287| https://www.ajmc.com/view/fda-clears-cloneseq-to-detect-mrd-in-chronic-lymphocytic-leukemia.

uMRD: undetectable Minimal Residual Disease

CLL14 study:

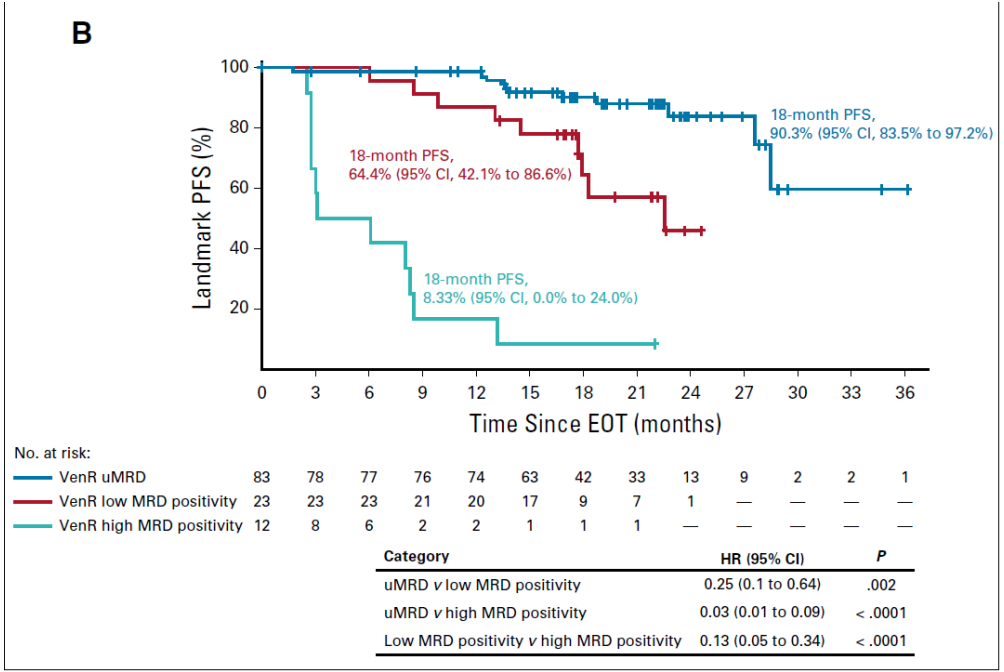
- Figure: PFS landmark analyses by MRD status in peripheral blood at EOT
- uMRD associated with longer PFS compared with low MRD or high MRD (HR 0·10, 95% CI 0·06–0·15)



Patients at risk								
VEN-OBI & uMRD	163	161	156	150	91	34	5	0
VEN-OBI & L-MRD	11	11	8	7	4	1	0	0
VEN-OBI & H-MRD	9	6	4	3	2	0	0	0
CLB-OBI & uMRD	76	76	75	71	56	18	6	0
CLB-OBI & L-MRD	47	43	37	33	23	5	0	0
CLB-OBI & H-MRD	56	32	16	8	7	3	0	0

MURANO study:

- Figure: PFS from EOT in patients in the venetoclax plus rituximab (VenR) arm who completed 2 years of venetoclax, based on MRD status at EOT
- uMRD is associated with longer PFS



- ASO-PCR MRD status is defined as uMRD (MRD level< 10-4), L-MRD (10-4≤ MRD level< 10-2), H-MRD (MRD level ≥ 10-2)

EOT: end of treatment

Al-Sawaf et al. Lancet Oncol 2020;21: 1188–200 | Kater et al. J Clin Oncol 2020 Dec 1;38(34):4042-4054.

Key Clinical Trials in Second-Line & Subsequent Therapy

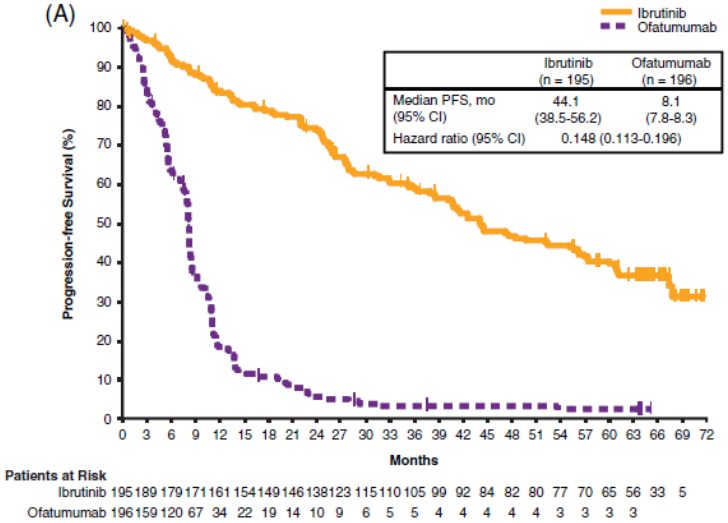
- Ibrutinib:
  - RESONATE: ibrutinib vs ofatumumab
- Acalabrutinib
  - ASCEND: acalabrutinib vs investigators choice
  - ELEVATE-RR: acalabrutinib vs ibrutinib
- Zanubrutinib
  - ALPINE: zanubrutinib vs ibrutinib
- Venetoclax
  - MURANO: venetoclax + rituximab vs BR

Byrd et al. N Engl J Med 2014;371:213-23.| Munir Am J Hematol. 2019;94:1353–1363. | Ghia P et al. J Clin Oncol. 2020:JCO1903355 | Hillmen. 62nd Annual Scientific Meeting of the British Society for Haematology, 3-5 April, 2022, Ma . PO52. |Seymour. NEJM 2018; 378:1107.

RESONATE

- Phase 3, randomized, multicenter, open-label
- R/R CLL/SLL N=391 patients
  - Ibrutinib vs ofatumumab
- Endpoints:
  - Primary: PFS
  - Secondary: OS and ORR
- Results:

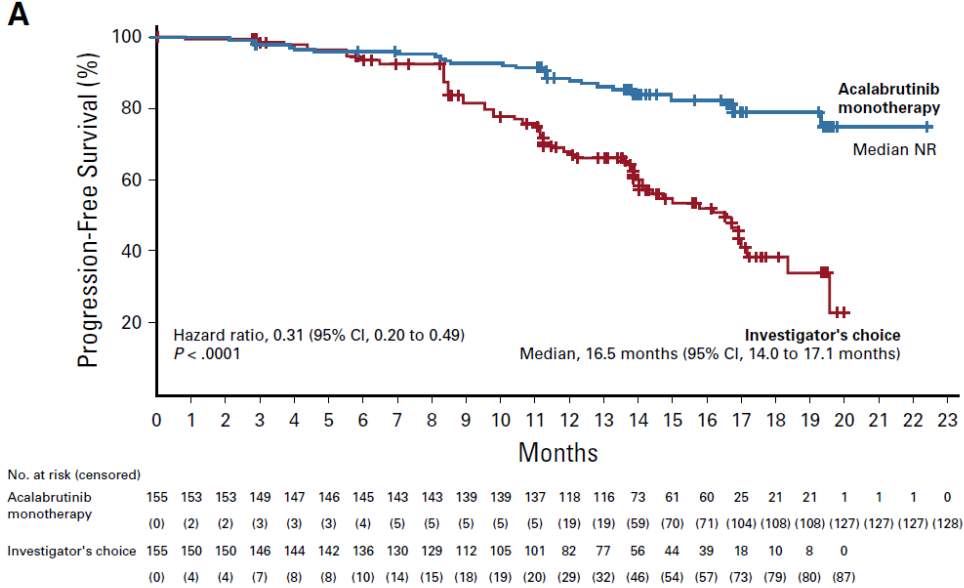
	Ibrutinib	Ofatumumab	
Median PFS	44.1 months	8.1 months	P<0.001
Median OS	67.7 months	65.1 months	HR= 0.810 (95% CI, 0.602-1.091)
ORR	42.6%	4.1%	P<0.001
PFS at 5 years	40%	3%	



Byrd et al. N Engl J Med 2014;371:213-23.| Munir Am J Hematol. 2019;94:1353–1363.

ASCEND

- Phase 3, randomized, multicenter, open-label
- R/R CLL/SLL N=310 patients
  - Acalabrutinib vs investigator's choice of therapy
    - Idelalisib + rituximab or BR
  - Primary endpoint: PFS by independent review committee
  - Results:
    - Acalabrutinib significantly prolonged PFS
      - Median follow-up of 16.1 months, median PFS acalabrutinib (not reached) vs 16.5 month investigators choice HR = 0.31 (95% CI, 0.20-0.49) p < 0.0001
    - PFS benefits seen across subgroups

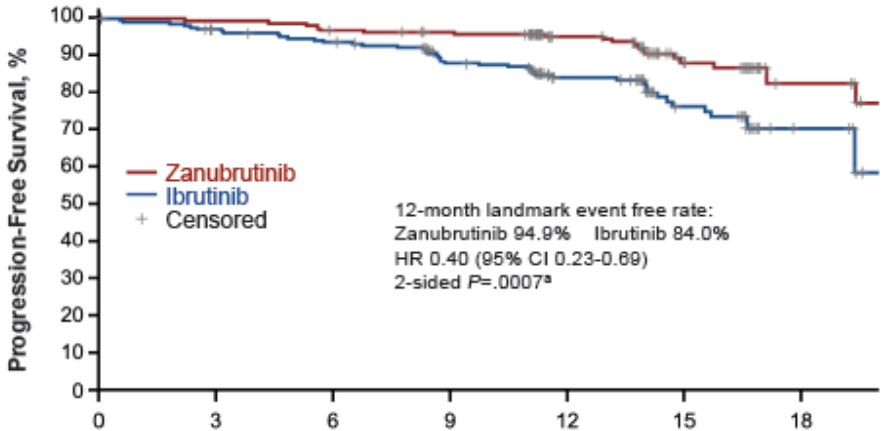


Ghia P et al. *J Clin Oncol*. 2020:JCO1903355

ALPINE

- Phase 3, randomized, multicenter, open-label
- R/R CLL/SLL N=415 patients
  - Zanubrutinib vs ibrutinib
- Primary endpoint was ORR
- The key secondary endpoint: PFS
- Results:*
  - Median follow-up time of 14 months, the investigator-assessed **12-month PFS was 94.9% for the zanubrutinib arm and 84% for the ibrutinib arm (2-sided P=.0007)**
  - Median follow-up of 15 months, **ORR was significantly higher with zanubrutinib (78.3%) versus ibrutinib (62.5%**; 2-sided P=.0006, pre-specified α=.0099)

Figure 3. PFS by Investigator Assessment



aNot 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. PFS, progression-free survival.

*Interim analysis data

Hillmen. 62nd Annual Scientific Meeting of the British Society for Haematology, 3-5 April, 2022, Ma . PO52.

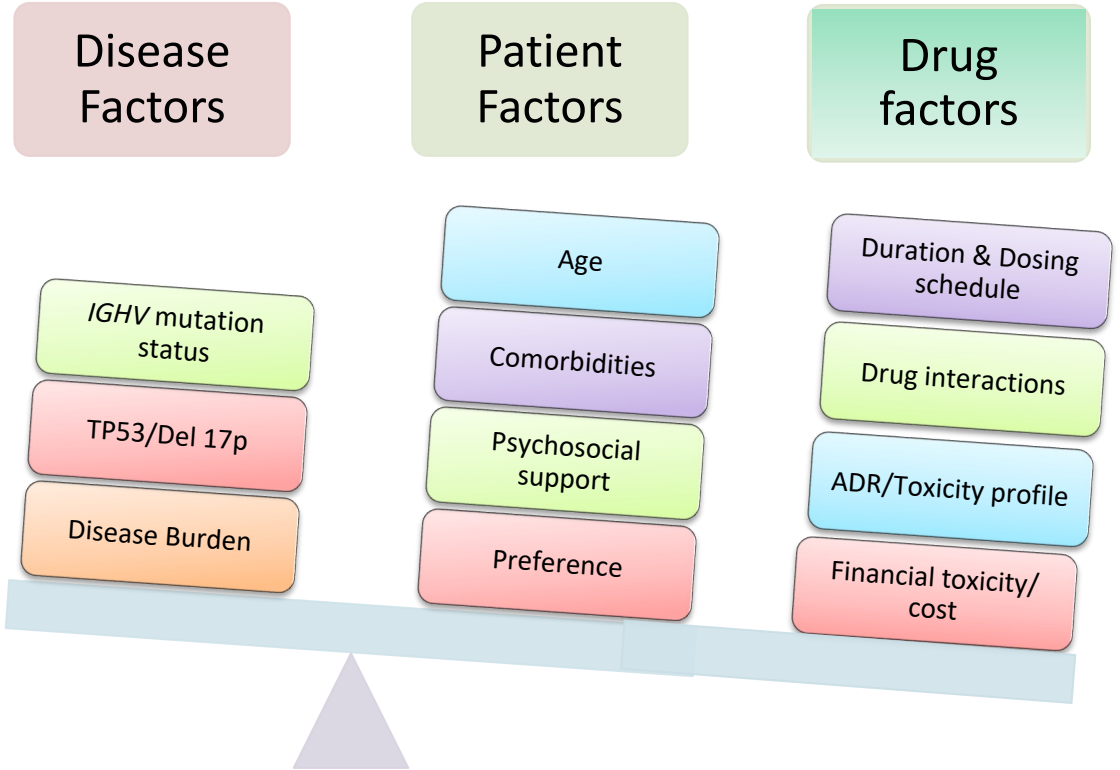
ORR: overall response rate

MURANO

- Phase 3, randomized, multicenter, open-label
- R/R CLL/SLL N=389 patients
  - Venetoclax + rituximab vs BR
- Primary endpoint: PFS by investigator
- Results:
  - Median PFS: 53.6 months for venetoclax + rituximab (95% CI: 48.4-57.0) and 17 months for BR (95% CI: 15.5-21.7)

Seymour. NEJM 2018; 378:1107. | Kater et al. *Blood* (2020) 136 (Supplement 1): 19–21

Treatment Considerations



Treatment Considerations

Continuous

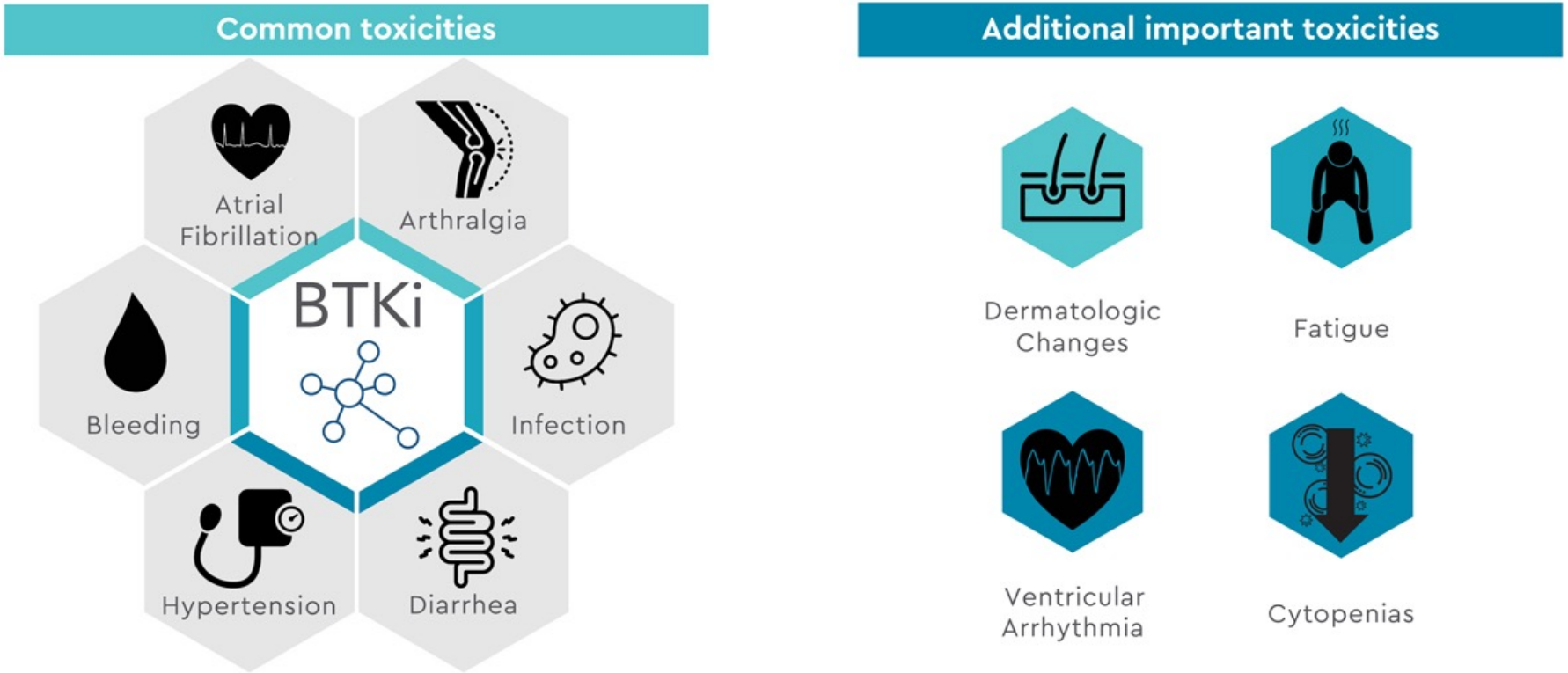
- BTK Inhibitors
  - Oral therapy
  - Cardiac risk
  - Mutation status considerations

Fixed duration*

- Venetoclax + anti-CD20 or CIT
  - Requires multiple infusion unit visits initially
  - Risk for TLS
  - Close monitoring
  - Mutation status considerations

*other options including BTKi combination in studies | CIT: chemoimmunotherapy

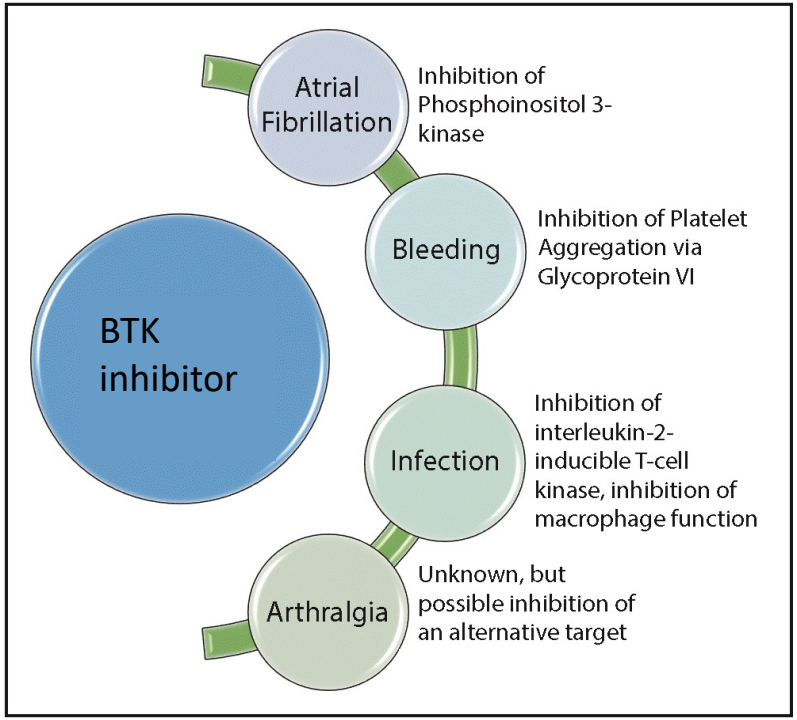
Managing Toxicities of Bruton Tyrosine Kinase Inhibitors in CLL



Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336.

BTK Inhibitor Toxicity

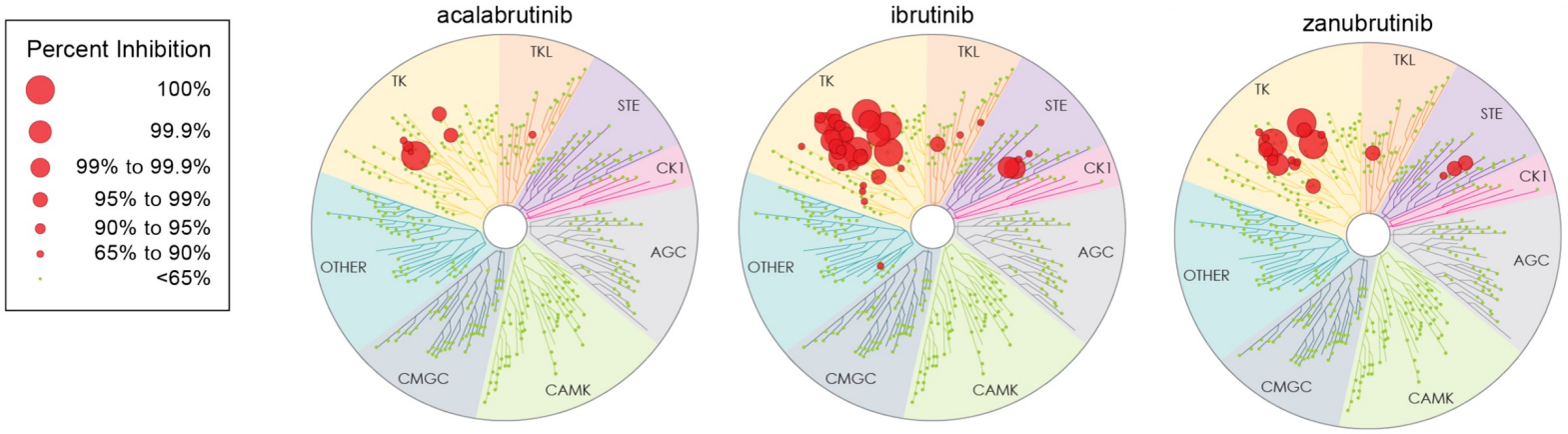
- Mediated by both on-target inhibition of BTK and variable off-target inhibition of other kinases the toxicity profile of BTKis is closely linked to their pattern of kinase binding Off target
  - TEC: bleeding, cardiotoxicity
  - EGFR: rash, diarrhea
  - ITK: infection, pneumonitis/inflammation
- Impairment of macrophages: infection



ITK: interleukin-2–inducible T-cell kinase
TEC: tyrosine-protein kinase
EGFR: endothelial growth factor receptor

Stephens.Blood (2019) 133 (12): 1298–1307. | Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336.

Figure 1. Kinome profiling at a single dose of 1 µM (KINOMEscan, Eurofins DiscoverX)

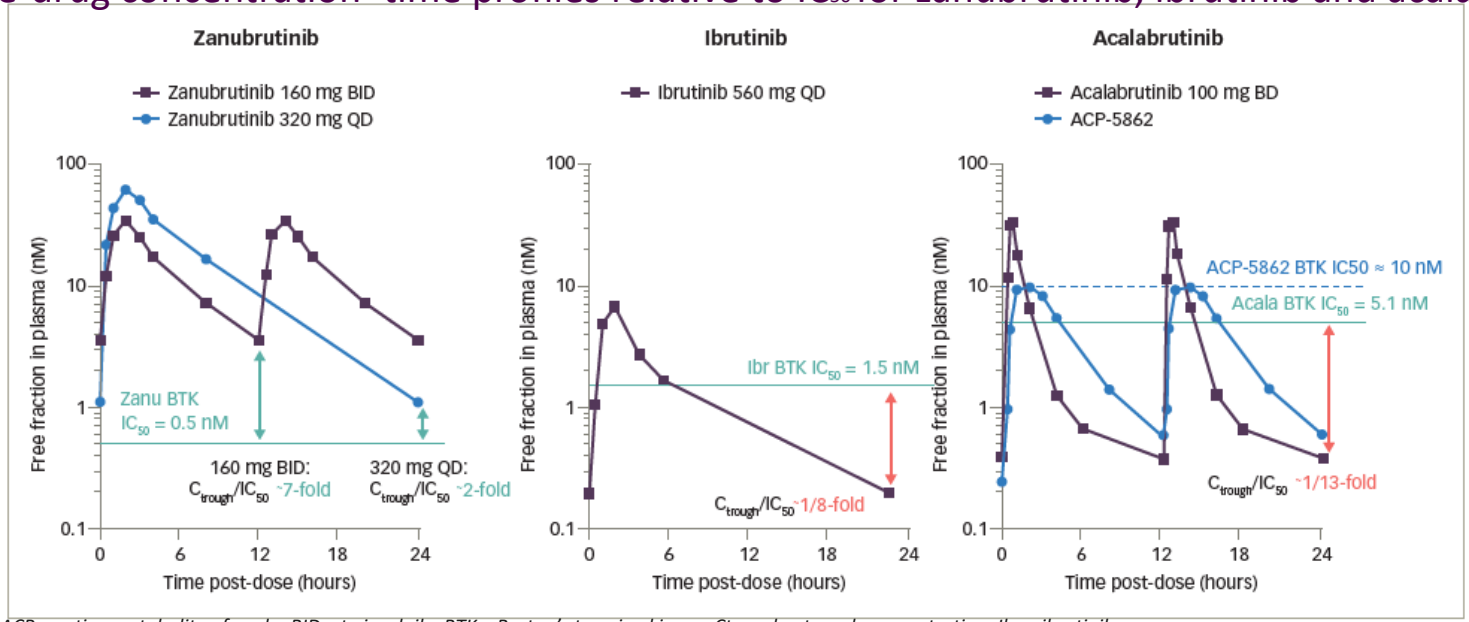


Target	IC_{50}/EC_{50} (nM)		
	Acalabrutinib	**Ibrutinib**	**Zanubrutinib**
BTK	5.1 ± 1.0	1.5 ± 1.0	0.5 ± 0.0
TEC	126 ± 11	10 ± 12	44 ± 19
EGFR	>1000	5.3 ± 1.3	21 ± 1
ITK	>1000	4.9 ± 1.2	50 ± 5

Kaptein et al. Blood (2018) 132 (Supplement 1): 1871.

Pharmacology

Figure: Free-drug concentration–time profiles relative to IC_{50} for zanubrutinib, ibrutinib and acalabrutinib



Acala = acalabrutinib; ACP = active metabolite of acala; BID = twice daily; BTK = Bruton's tyrosine kinase; Ctrough = trough concentration; Ibr = ibrutinib; IC50 = concentration for 50% inhibition; QD = once daily; Zanu = zanubrutinib.

Tam et al.Expert Rev Clin Pharmacol. 2021;14:1329–44.

Table 1. Approved dose regimens and key clinical pharmacology properties of zanubrutinib relative to those of ibrutinib and acalabrutinib (Table view)

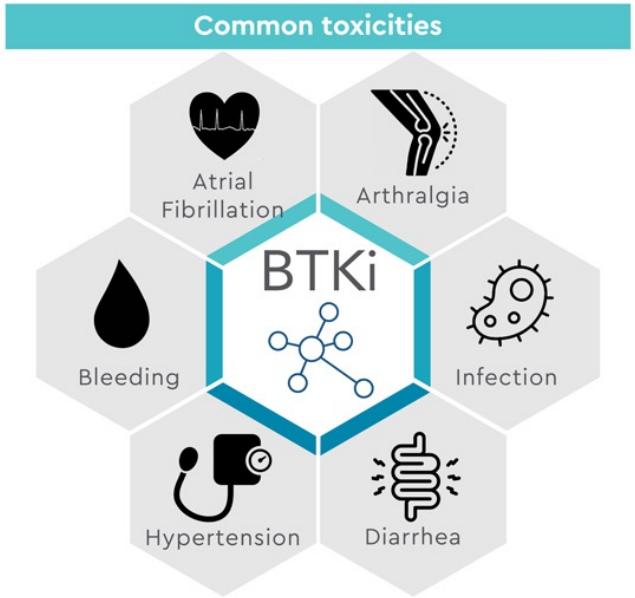
	Zanubrutinib	Ibrutinib	Acalabrutinib
Approved indications	MCL, WM*	MCL, CLL, and WM. MZL chronic graft versus host disease (cGVHD)	MCL, CLL
FDA approved dose	160 mg BID or 320 mg QD	420 or 560 mg QD	100 mg BID
IC_{50} against BTK (nM) [24]	0.5	1.5	5.1
Potency of major active metabolite against BTK	NA	~15-fold less potent compared to the parent molecule [15]	~2-fold less potent compared to the parent molecule [24]
Half-life (hr)	~2 to 4	~4 to 6	~0.6 to 2.8
Plasma protein binding (%)	~94%	97.3% – 97.7% [15]	97.4% – 97.5% [57]
$AUC_{0\text{-}24hr}$ (CV%) ng·hr/mL	160 mg BID: 2295 (37%) 320 mg QD: 2180 (41%)	420 mg QD: 707–1159 (50%-72%) 560 mg QD: 865–978 (69%-82%)	100 mg BID: 1843- (38%) −1850 (72%) [29]
fu. $AUC_{0\text{-}24hr}$ (nM·hr)	160 mg BID: 278 320 mg QD: 267	420 mg QD: 37–60 560 mg QD: 46–51	100 mg BID: 103
Plasma exposure of major active metabolite	NA	1- to 2.8-fold higher than parent AUC [15]	2- to 3-fold higher than parent AUC [57]
Median BTK occupancy in PBMC at trough	320 mg QD:100% 160 mg BID: 100%	420 mg to 820 mg QD: >90% [30,33]	100 mg BID: ≥95% [32]
Median BTK occupancy in lymph node at trough	320 mg QD: 94% 160 mg BID: 100%	420 mg QD: >90% [16]	200 mg QD: 90% 100 mg BID: 95.8% [34]
Pgp and brain penetration	Weak P-gp substrate Brain penetration data in patients available	Not a P-gp substrate Brain penetration data in patients available	P-gp substrate Likely limited brain penetration
Major enzyme involved	CYP3A	CYP3A	CYP3A

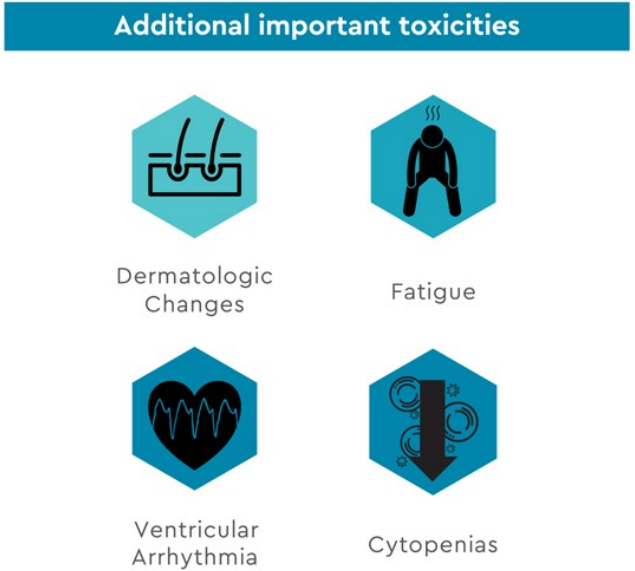
Tam et al.Expert Rev Clin Pharmacol. 2021;14:1329–44.

BTK Inhibitors Class Considerations

Lymphocytosis

Drug interactions





Burger N engl j med 383;5 nejm.org July 30, 2020 | Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336.

Lymphocytosis

- Can occur upon initiation of therapy with BTKi
  - Due to inhibition of kinase involved in B-cell migration and homing
  - Asymptomatic, typically resolves during the first months of therapy (although it can persist for more than 12 months)
  - Not a sign of resistance or a suboptimal response

Burger N engl j med 383;5 nejm.org July 30, 2020

Atrial Fibrillation

- The prevalence of AF associated with ibrutinib → greatest in the first 3 months on therapy (median time of onset 2.8 months) and late events (onset at month 18 or later) ~1% of patients
- Acalabrutinib and zanubrutinib have a lower rate of AF compared to ibrutinib
- Conditions that have been associated with increased risk of AF while on therapy:
  - Older age, male sex, history of hypertension, history of coronary artery disease, diabetes, and history of valvular heart disease

AF: atrial fibrillation

Burger N engl j med 383;5 nejm.org July 30, 2020| Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2 | Shanafelt Leukemia & lymphoma 58.7 (2017): 1630-1639. | Bhat et al. *Blood* blood.2022016953. | Hillmen. 62nd Annual Scientific Meeting of the British Society for Haematology, 3-5 April, 2022, Ma . PO52.

ELEVATE-RR

AEs >10%, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
AF	24 (9.0)	12 (4.5)	**41 (15.6)**	9 (3.4)

NOTE. Data are reported as No. (%). Adverse events are reported as individual MedDRA preferred terms. **Higher incidences are shown in bold text for terms with statistical differences.**

A

Events	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Atrial fibrillation[b]	25 (9.4)[c]	13 (4.9)	42 (16.0)	10 (3.8)
Events/100 person-months	0.366	0.155	0.721	0.124
Age 75 years or older	8 (32.0)	6 (46.2)	11 (26.2)	4 (40.0)
Patients with a history of atrial fibrillation	10 (40.0)	6 (46.2)	5 (11.9)	2 (20.0)
Patients with risk factors[d]	23 (92.0)	12 (92.3)	32 (76.2)	8 (80.0)
Hypertension	15 (60.0)	6 (46.2)	23 (54.8)	6 (60.0)
Diabetes mellitus[e]	10 (40.0)	5 (38.5)	4 (9.5)	2 (20.0)
Myocardial infarction/ischemia	3 (12.0)	3 (23.1)	4 (9.5)	0
Cardiac disease[f]	2 (8.0)	2 (15.4)	5 (11.9)	2 (20.0)
Time to atrial fibrillation onset, median (range), months	28.8 (0.4-52.0)	22.3 (0.4-45.1)	16.0 (0.5-48.3)	4.8 (0.5-28.2)

Byrd et al. J Clin Oncol 2021

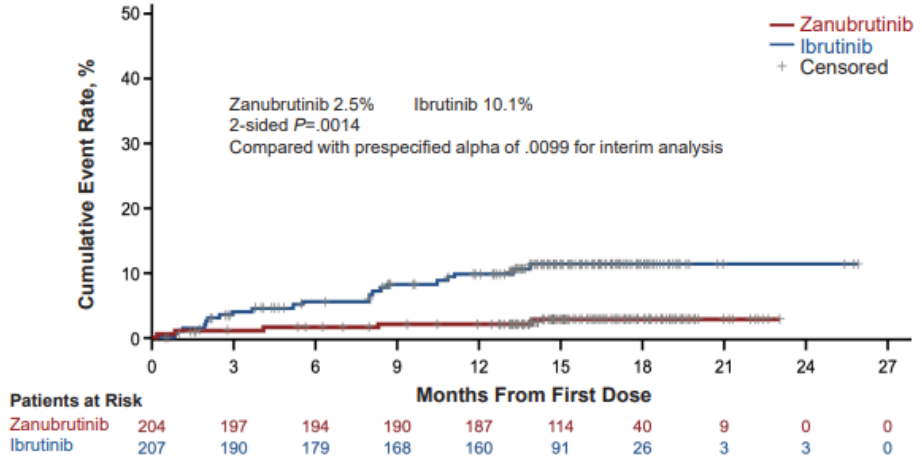
ALPINE

Table 4. Additional AEs of Special Interest

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

[a]Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 (3.4%) patients. [b]Includes hemorrhages that were serious or grade ≥3 or CNS hemorrhages of all grades. [c]Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased. AE, adverse events.

Figure 5. Atrial Fibrillation/Flutter



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Atrial Fibrillation Management

- Baseline clinical risk assessment of cardiovascular risk factors before initiating therapy
- Pre-existing AF is not an absolute contraindication to therapy
- New AF:
  - Withholding therapy does not result in higher resolution rates of atrial fibrillation, but may compromise PFS and OS
    - If uncontrollable arrhythmias develop consider switching to alternate therapy
  - Interdisciplinary risk–benefit assessment
    - CHA2DS2-VASc 0-1, most clinicians favor continuing BTKi therapy; ≥2, consider temporary drug hold until AF control or discontinuation

Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. | Burger N engl j med 383;5 nejm.org July 30, 2020| Shanafelt Leukemia & lymphoma 58.7 (2017): 1630-1639.

CYP3A4:cytochrome P 3A4

Atrial Fibrillation Management

- Consider beta-blockade, often preferred as the first choice over CYP3A4 inhibitors (eg, verapamil and diltiazem) or P-glycoprotein substrates (amiodarone), which interact with BTKis
- Anticoagulation strategies:
  - Apixaban
  - Enoxaparin (at regular doses in patients with a platelet count >50,000/µL)
  - Avoid combination with vitamin K antagonists

Burger N engl j med 383;5 nejm.org July 30, 2020| Shanafelt Leukemia & lymphoma 58.7 (2017): 1630-1639.

Atrial Fibrillation Management

Ibrutinib

Adverse Reaction	Occurrence	Dose Modification for CLL/SLL After Recovery Starting Dose = 420 mg
Grade 3 cardiac arrhythmia	First	Restart at 280 mg daily
	Second	Discontinue therapy

Acalabrutinib

Adverse Reaction	Occurrence	Dosage Modification (Starting dose = 100 mg approximately every 12 hours)
Grade 3 or greater non-hematologic toxicities	First and second	Interrupt acalabrutinib. Once toxicity has resolved to Grade 1 or baseline level, acalabrutinib may be resumed at 100 mg approximately every 12 hours

Imbruvica [package insert]. Sunnyvale, CA. Pharmacyclics LLC 2022 | CALQUENCE [package insert]. Wilmington, DE AstraZeneca Pharmaceuticals LP 2022

Ventricular Arrhythmia

- Ventricular arrhythmias – reported with ibrutinib and acalabrutinib
  - Longer term follow up → Cases of ventricular arrhythmias and sudden cardiac death have emerged
  - Rare but serious
- Obtain a detailed cardiac history and baseline electrocardiogram for all patients; reserve echocardiogram for patients with significant cardiac history or risk factors
- Instruct patients to remain vigilant for potential early warning signs of ventricular arrhythmia and immediately investigate incident lightheadedness, palpitations, or syncope

Burger N engl j med 383;5 nejm.org July 30, 2020| Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2 | Shanafelt Leukemia & lymphoma 58.7 (2017): 1630-1639. | Bhat et al. *Blood* blood.2022016953.

Hypertension

- Prevalence of HTN (any grade) increases over time (11% year 1, 15% year 2; 20% year 3 in a pooled ibrutinib analysis)
- Optimize and control patient's HTN prior to initiating BTKi therapy
- Development of new onset hypertension while a patient is on BTKi does not warrant therapy discontinuation, unless medically necessary

HTN: hypertension

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Hypertension

- New onset HTN: patients should be appropriately managed with antihypertensive medications
  - Consider drug-drug interactions when initiating treatment with supportive care medications as ibrutinib, acalabrutinib, and zanubrutinib are metabolized primarily by CYP3A4

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Bleeding

- Increased risk of bleeding due to the BTK inhibition and other related TEC family kinases, which play an important role in platelet aggregation, adhesion and activation
- Ibrutinib is associated with predominantly minor bleeding (grade ≤2), ecchymoses and petechiae
  - Major bleeding (grade ≥3), necessitating transfusion or hospitalization occurs less frequently, in 2% to 9% of patients
- ELEVATE-RR
  - Acalabrutnib bleeding events were less frequent 38.0% vs ibrutinib 51.3% and rates of major bleeding were comparable
- ALPINE
  - Zanubrutinib bleeding events were comparable to ibrutinib in the study

Byrd et al. J Clin Oncol 2021 | Burger N engl j med 383;5 nejm.org July 30, 2020| Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2 | Hillmen. 62nd Annual Scientific Meeting of the British Society for Haematology, 3-5 April, 2022, Ma . PO52.

Bleeding

- Caution when using concurrent anticoagulation therapy
- Consider non-warfarin anticoagulation
- Apixaban and rivaroxaban may be preferred due to minimal drug interactions
- Note in clinical studies for acalabrutinib and ibrutinib, patients on warfarin therapy were excluded vs warfarin use was not excluded in zanubrutinib studies

Byrd et al. J Clin Oncol 2021 | Burger N engl j med 383;5 nejm.org July 30, 2020| Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2

Bleeding

- Hold BTKi for 3 days before and after minor surgical procedures and for 7 days before and after major surgical procedures
- For minor bleeding, holding BTKi results in the resolution of bleeding tendency in 2 to 3 days
- For severe bleeds, provide platelet transfusions as appropriate to overcome clinical bleeding, regardless of platelet count
- Patient counseling: abstain from over-the-counter supplements that may exacerbate bleeding risk, such as **vitamin E or fish oil, ginger and turmeric**

Burger N engl j med 383;5 nejm.org July 30, 2020| Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2 | Natural Medicines database

Diarrhea

- Early in the treatment course ~ first 6 months; it is self-limiting and can be managed
- Manage with supportive care, antimotility agents, and nighttime dosing of drug (in the case of ibrutinib) to mitigate symptoms
- Consider temporary drug holds in the case of grade ≥3 diarrhea

Stephens. Blood 133.12 (2019): 1298-1307. | Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2

Table 3. Frequency of adverse events in landmark studies of currently approved BTKis

Adverse events	Ibrutinib		Acalabrutinib	
	RESONATE2[5]	RESONATE[83,84]	ELEVATE-TN[10]	ASCEND[12]
	TN n = 135	RR n = 195	TN n = 179	RR n = 154
	f/u = 18.4 mo	f/u = 19 mo	f/u = 28.3 mo	f/u = 22 mo
Diarrhea				
All grades	57 (42)	105 (54)	62 (35)	30 (20)
Grade ≥3	5 (4)	9 (5)	1 (0.6)	3 (2)

f/u, follow-up; NR, not reported in original publication; RR, relapsed or refractory; TN, treatment-naive.
*Reported numbers reflect 16.1-month follow-up.[85]

ELEVATE-RR AEs >15%, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	92 (34.6)	3 (1.1)	**121 (46)**	**13 (4.9)**

NOTE. Data are reported as No. (%). Adverse events are reported as individual MedDRA preferred terms. **Higher incidences are shown in bold text for terms with statistical differences.**

ALPINE first interim analysis n (%)	Zanubrutinib (n=204)	Ibrutinib (n=207)
Diarrhea	34 (16.7)	40 (19.3)

Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2 | Byrd et al. J Clin Oncol 2021 | Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2 | Hillmen. 62nd Annual Scientific Meeting of the British Society for Haematology, 3-5 April, 2022, Ma . PO52.

Infection

- Patients receiving BTKis are immunocompromised and are at risk of infectious complications despite receiving effective therapy
- Infection (of any grade) occurs in >50% of patients on BTKis particularly during the early period after starting treatment, and R/R patients are at greater risk
- Of all infectious complications, pneumonia was the most common, observed in an integrated analysis of landmark ibrutinib studies in 12% of patients (grade ≥3 infection)
- Opportunistic infections, including Aspergillus fumigatus and PJP, have been reported
- Monitor for fungal infection

Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2

PJP: Pneumocystis Jirovecii Pneumonia

Table 3. Frequency of adverse events in landmark studies of currently approved BTKis

Adverse events	Ibrutinib		Acalabrutinib	
	RESONATE2[5]	RESONATE[83,84]	ELEVATE-TN[10]	ASCEND[12]
	TN n = 135	RR n = 195	TN n = 179	RR n = 154
	f/u = 18.4 mo	f/u = 19 mo	f/u = 28.3 mo	f/u = 22 mo
Infection				
All grades	NR	NR	116 (65)	97 (63)
Grade ≥3	21 (23)	59 (30)	25 (14)	30 (20)

ELEVATE-RR AEs >10%, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Pneumonia	47 (17.7)	28 (10.5)	43 (16.3)	23 (8.7)
URTI	71 (26.7)	5 (1.9)	65 (24.7)	1 (0.4)

ALPINE first interim analysis n (%)	Zanubrutinib (n=204)		Ibrutinib (n=207)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infection	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)

Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2 | Byrd et al. J Clin Oncol 2021 | Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2 | Hillmen. 6
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Infection – Management

- Acute infection hold vs continue BTKi → Regardless of approach, pharmacotherapy can be reinitiated after the start of clinical improvement when deemed appropriate by the caring provider
- In the case of severe infection → Hold BTKi until a definitive diagnosis is determined and restart after the start of clinical improvement, except in the case of fungal infections
- Consider PJP and VZV prophylaxis depending on risk factor
  - High risk factors (R/R or heavily pretreated patients) or patients with a prior history of infection
- Screen for and treat HBV infections
- Provide clinically indicated vaccinations (eg, against influenza and pneumococcus) of patients before treatment initiation
- Caution with drug interactions → Triazoles and fluoroquinolones increase drug levels
- Consider COVID-19 prophylaxis

VZV: Varicella zoster virus
HBV: Hepatitis B virus

Hwang JP, et al. J Clin Oncol 38:1-20, 2020 | Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2

Fatigue

- Commonly reported symptom seen early during BTKi therapy and is usually self-limited
  - Up to 36% of patients on ibrutinib (in a pooled analysis, up to 3% grade 3) and in 28% to 34% of patients on acalabrutinib (up to 2% grade 3)
- Avoid dosage reductions for fatigue early in the course of therapy
- If observed later in the course → search for potential causes of fatigue; consider drug holiday or dosage reduction only when severe and truly drug related

ELEVATE-RR AEs >10%, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	54 (20.3)	**9 (3.4)**	44 (16.7)	0

NOTE. Data are reported as No. (%). Adverse events are reported as individual MedDRA preferred terms. **Higher incidences are shown in bold text for terms with statistical differences.**

Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2 | Byrd et al. J Clin Oncol 2021

Arthralgia-Myalgia

- Arthralgia and myalgia are seen in 11% to 36% of patients on ibrutinib, with higher rates compared with comparators in a pooled analysis
- Arthralgias were associated with 42% of ibrutinib discontinuations in real-world data
- Rule out other causes of arthralgia
- Grade 1-2 → observation and supportive care vs grade ≥3 consider hold and/or dose reduce
- Adjunctively treat with pharmacotherapy, approaches include
  - Magnesium supplementation and quinine-containing tonic water
  - Severe arthralgias → short-course steroids and anti-inflammatory agents

ELEVATE-RR AEs >15%, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Arthralgia	42 (15.8)	0	**60 (22.8)**	2 (0.8)

Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2 | Byrd et al. J Clin Oncol 2021

NOTE. Data are reported as No. (%). Adverse events are reported as individual MedDRA preferred terms. **Higher incidences are shown in bold text for terms with statistical differences.**

Headaches

- Acalabrutinib
  - Acalabrutinib-associated headaches reported up to 70% and are generally observed early in therapy (weeks 1-3), they subside over time typically within the first two months of treatment
  - Headaches pose concerns with patient compliance
  - Consider analgesics such as acetaminophen and caffeine supplements for management

Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2 | Byrd et al. J Clin Oncol 2021

Dermatologic

- Skin manifestations of BTKi therapy
  1. Nonpalpable asymptomatic petechial rash thought to result from -induced platelet dysfunction
  2. Palpable rash that is often pruritic, associated with EGFR inhibition and infiltration of inflammatory cells→ **responsive to corticosteroids or dose holds**
  3. Erythema nodosum → **responsive to corticosteroids or dose holds**
  4. Textural changes in hair and nails
     a. Brittle fingernails or toenails with the formation of vertical nail ridges in two-thirds of patients treated with ibrutinib
     b. Appear **gradually** - median reported **onset of 9 months**, and do not represent a dose-limiting toxicity
     c. Treat with biotin supplementation and the application of nail oil

Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2

Cytopenias

- CLL is associated with AICs which occur in ~4% to 10% of patients
  - Autoimmune hemolytic anemia is most common (~7%) > Immune thrombocytopenia (<1% to 2%)>>>Pure red cell aplasia occurring less frequently
- Management:
  - Short-course corticosteroids or anti-CD20 monoclonal antibody treatment and then resume treatment with BTKis
- Other cytopenias including neutropenia
  - Unless higher grade, rarely necessitate dose interruption or discontinuation, provide growth factor support

Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. 2

AICs: autoimmune cytopenias

Cytopenias

- Drug related cytopenias

ELEVATE-RR AEs >15%, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia	56 (21.1)	52 (19.5)	65 (24.7)	60 (22.8)
Thrombocytopenia	40 (15.0)	26 (9.8)	35 (13.3)	18 (6.8)

ALPINE first interim analysis n (%)	Zanubrutinib (n=204)		Ibrutinib (n=207)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia	58 (28.4)	38(18.6)	45(21.7)	31(15)
Thrombocytopenia	19(9.3)	7(3.4)	26(12.6)	7(3.4)

Hillmen. 62nd Annual Scientific Meeting of the British Society for Haematology, 3-5 April, 2022, Ma . PO52.

	Acalabrutinib	Ibrutinib	Zanubrutinib
Dose	**100 mg PO BID**	420 mg PO daily	160 mg PO BID or 320 mg PO daily
Lymphocytosis	Yes		
Antimicrobial prophylaxis	Consider PJP and VZV in patients at increased risk for infections. Monitor for fungal infections		
Hepatic impairment	Avoid in patients with severe impairment	Reduce dose in mild and moderate, avoid in severe impairment	Reduce dose in patients with severe impairment
CYP3A4 inhibitors	Strong: Avoid with concomitant use Moderate: Reduce dose to 100 mg PO daily	See next slide	Strong: Reduce dose to 80 mg once daily Moderate: Reduce dose to 80 mg BID
CYP3A4 inducers	Avoid with concomitant strong CYP3A4 inducers. If unavoidable, increase dose to 200 mg PO BID	Avoid with concomitant strong CYP3A4 inducers	Avoid concomitant use of moderate or strong CYP3A4 inducers
Antacids	**Capsule formulation** • **Avoid concomitant PPIs** • **Take acalabrutinib 2 hours before taking a H2-RA** • **Separate dosing by at least 2 hours with antacids**	NA	

CALQUENCE [package insert]. AstraZeneca Pharmaceuticals LP Wilmington, DE; 2019 | Tam et al. haematologica | 2021; 106(9)
Imbruvica [package insert]. Sunnyvale, CA. Pharmacyclics LLC 2020 |

PJP: Pneumocystis Jiroveci Pneumonia
VZV: Varicella zoster virus

Ibrutinib Dose Adjustment

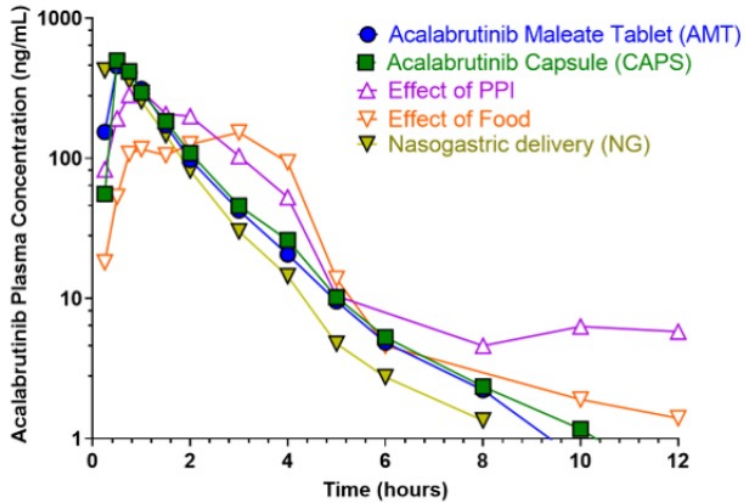
Coadministered Drug	Recommended ibrutinib dosage
Moderate CYP3A inhibitor	280 mg once daily
• Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily
• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole intravenously 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	70 mg once daily
Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short term (such as anti-infectives for seven days or less), interrupt ibrutinib

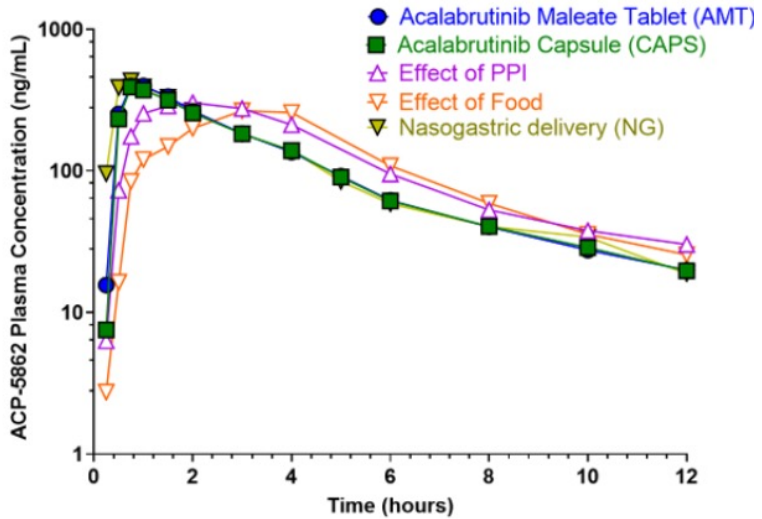
Imbruvica [package insert]. Sunnyvale, CA. Pharmacyclics LLC 2020

Acalabrutinib Formulation

- New Acalabrutinib Formulation Enables Co-administration with Proton-Pump Inhibitors (PPI) and Dosing in Patients Unable to Swallow Capsules (ELEVATE-PLUS)

Figure 1: PK Profiles of Acalabrutinib and its Major Pharmacologically Active Metabolite, ACP-5862, Across 3 Clinical Trials





Sharma (ELEVATE-PLUS) [abstract]. Blood. 2021;138 (supplement 1). Abs 4365.

Note: Arithmetic mean is shown in the figures.

Venetoclax Considerations

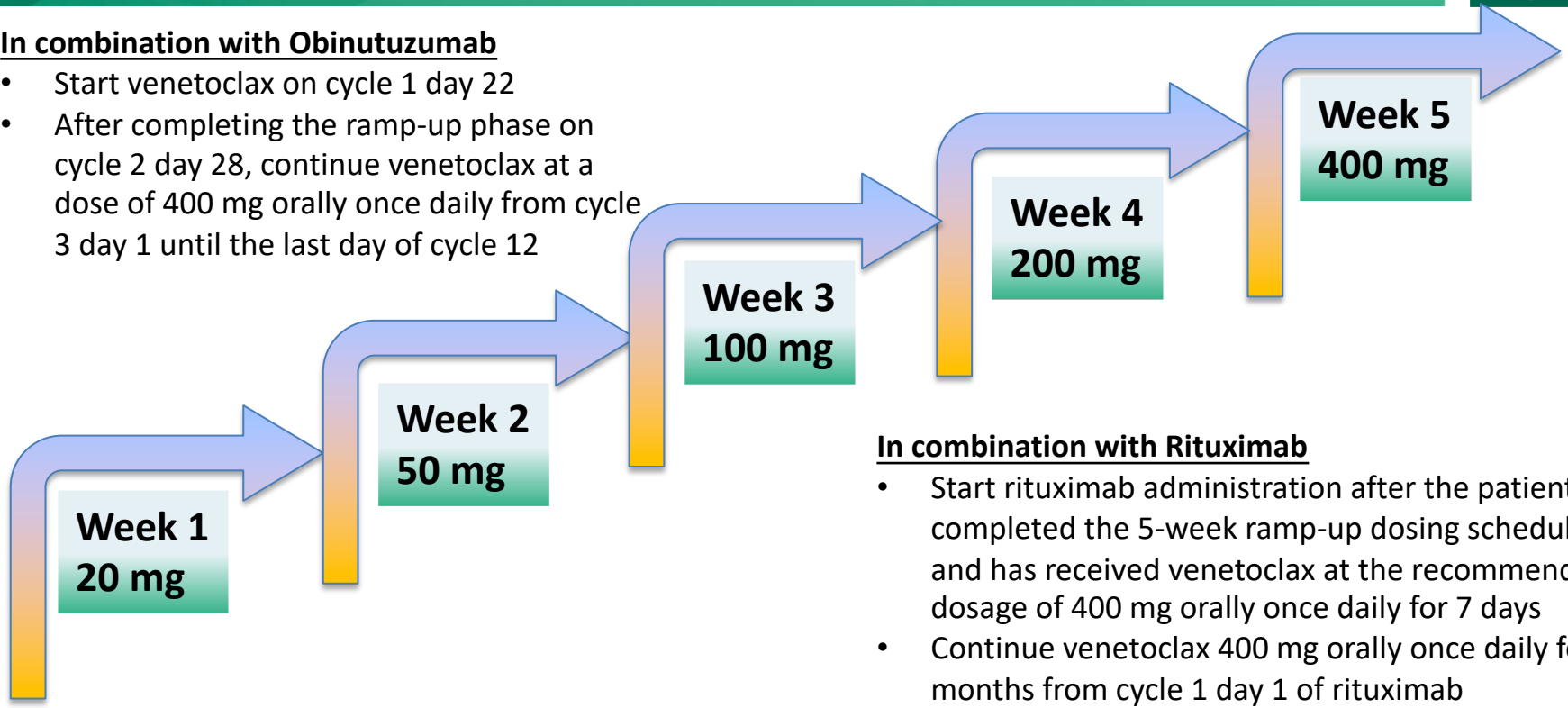
- Tumor Lysis Syndrome (TLS)
  - Dosing ramp-up and obinutuzumab lead in
- Neutropenia
  - Dose interruptions or reductions – refer to PI
- Infectious complications
- Immunization: no live attenuated vaccines prior to, during, or after treatment with venetoclax until B-cell recovery
- Caution with drug interactions

Al-Sawaf et al. Lancet Oncol 2020;21: 1188–200 Venclexta [package insert]. North Chicago, IL. AbbVie Inc 2022

Venetoclax Ramp-up Dosing

In combination with Obinutuzumab

- Start venetoclax on cycle 1 day 22
- After completing the ramp-up phase on cycle 2 day 28, continue venetoclax at a dose of 400 mg orally once daily from cycle 3 day 1 until the last day of cycle 12



In combination with Rituximab

- Start rituximab administration after the patient has completed the 5-week ramp-up dosing schedule and has received venetoclax at the recommended dosage of 400 mg orally once daily for 7 days
- Continue venetoclax 400 mg orally once daily for 24 months from cycle 1 day 1 of rituximab

Venclexta [package insert]. North Chicago, IL. AbbVie Inc 2022

TLS Risk	Tumor Burden	Prophylaxis, monitoring, and management*
Low	All LN < 5 cm AND ALC <25 x 10^9/L	**Outpatient:** • Oral hydration (1.5 to 2 L) and allopurinol • First dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • Subsequent ramp-up doses: Pre-dose
Medium	LN ≥5 cm and <10 cm OR ALC: ≥25 x 10^9/L	**Outpatient:** • Oral hydration (1.5 to 2 L) and (IV PRN), and allopurinol • First dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • Subsequent ramp-up doses: Pre-dose • First dose of 20 mg and 50 mg: Consider hospitalization for patients with CLcr <80ml/min; see below for monitoring in Hospital
High	LN ≥10 cm OR LN ≥5 cm AND ALC ≥25 x 10^9/L	**In hospital:** • Oral hydration (1.5 to 2 L) and IV (150 to 200 mL/hr as tolerated) and allopurinol; consider rasburicase if baseline uric acid is elevated • First dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12, and 24 hours **Outpatient:** • Subsequent ramp-up doses: Pre-dose, 6 to 8 hours, 24 hours

*Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time. For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.
Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation

Venclexta [package insert]. North Chicago, IL. AbbVie Inc 2022

ALC = absolute lymphocyte count; CLcr = creatinine clearance; LN = lymph node

Venetoclax Considerations

	Venetoclax
AEs ≥20%	• Neutropenia, thrombocytopenia, anemia, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, and edema
Antimicrobial prophylaxis	• Consider fluoroquinolones and fungal prophylaxis during neutropenia
CYP3A4 inhibitors P-glycoprotein inhibitor	• Avoid concomitant use of moderate or strong CYP3A4 inhibitors **at initiation and during ramp-up (contraindicated)**. If unavoidable after the ramp-up venetoclax dose modification is required • Reduce dose by at least 50% when used with a moderate CYP3A4 or P-glycoprotein inhibitor • Resume the venetoclax dosage that was used prior to concomitant use of a strong or moderate CYP3A inhibitor or a P-gp **inhibitor 2 to 3 days after discontinuation of the inhibitor**
CYP3A4 inducers	• Avoid with concomitant strong and moderate CYP3A4 inducer
Concomitant therapy considerations	• Increase INR monitoring if used with warfarin • Avoid use with P-glycoprotein substrates (as venetoclax increases their level), **if unavoidable then separate by 6 hours**

Venclexta [package insert]. North Chicago, IL. AbbVie Inc 2022

Importance of Adverse Events Management

- Adherence and discontinuation rate
  - Toxicity with ibrutinib can lead to discontinuation in up to 20% in trials, higher in real-world experience up to 42%
- AEs affecting quality of life
  - Musculoskeletal pain, headaches, diarrhea, fatigue
- Life-threatening
  - Arrhythmias, bleeding, hypertension, infections, TLS

Byrd. ASCO 2021. Abstr 7500. Mato. Haematologica. 2018;103:874. Dickerson. Blood. 2019;134:1919.

Conclusion

- Cytogenetics and molecular markers play a role in treatment choice
- Choice of treatment is disease and patient-specific. It requires considerations of pros/cons with each therapy
- For almost all patients, targeted therapies are preferred with few exceptions
- Choice of targeted therapies is determined by patient preference, comorbidities, and safety considerations
- Given the efficacy of agents used in the treatment of CLL, appropriate management of BTKi toxicities and venetoclax based therapies is critical

Pharmacotherapy Management in Chronic Lymphocytic Leukemia (CLL)

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