MAYO CLINIC

CaLLing Targeted Therapies: Advancements in Chronic Lymphocytic Leukemia

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August 18th, 2020

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LEARNING OBJECTIVEs

- Review chronic lymphocytic leukemia (CLL) diagnosis and historical treatment options
- Describe the pharmacology of Bruton tyrosine kinase (BTK) inhibitors and venetoclax
- Discuss the use of targeted agents as first line therapy for CLL

Chronic Lymphocytic Leukemia

DISEASE STATISTICS

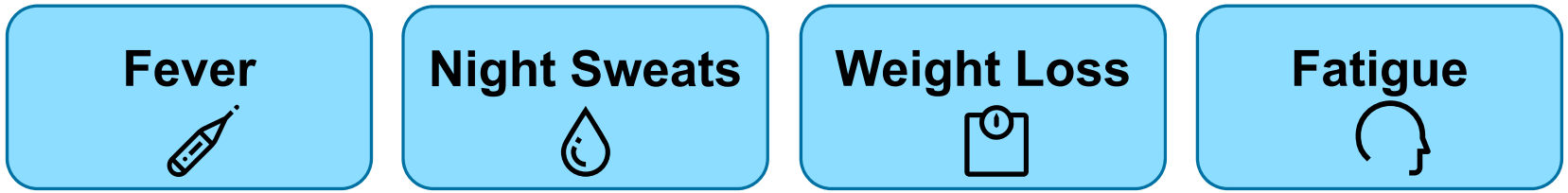
- Most common type of adult leukemia in western countries
- An estimated 21,040 new cases and 4,060 deaths in 2020
- Incidence increases with age

Am J Hematol. 2019;94:1266-87.
Cancer. 2019;125:1432-40.
NCI. SEER. Cancer Stat Facts.

Chronic Lymphocytic Leukemia

PRESENTATION & DIAGNOSIS

- Many patients with early stage disease are asymptomatic
- 5-10% of patients will present with typical B-symptoms



- Diagnosis made based on detection of lymphocytosis (B-lymphocytes > 5,000/μL of peripheral blood) with typical CLL immunophenotype sustained for three months

CLL = chronic lymphocytic leukemia

Am J Hematol. 2019;94:1266-87.
Cancer. 2019;125:1432-40.
Nature. 2018;15:510-27.

Chronic Lymphocytic Leukemia

GENETICS

- Specific genetic alterations provide biomarkers for prognostication of the clinical course and prediction of response to chemotherapy and targeted therapy

- Patients diagnosed with CLL may undergo clonal evolution during their disease course, in which they acquire new genomic alterations that impact survival outcomes

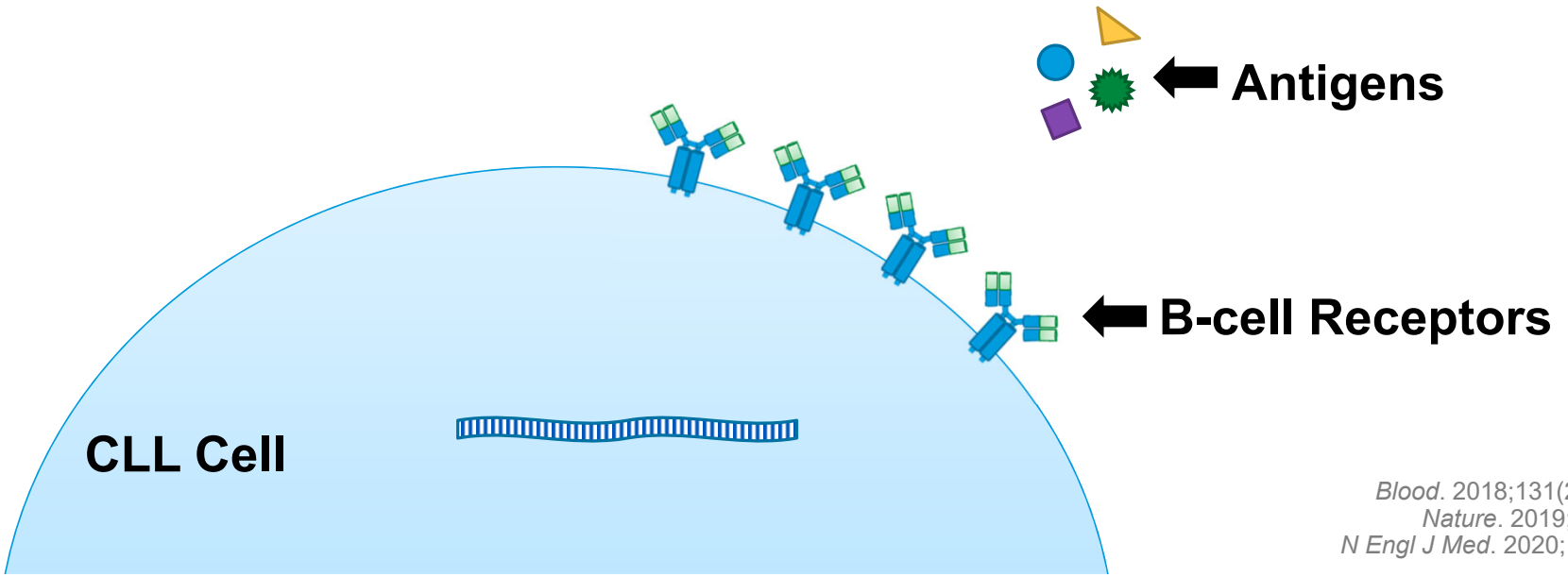
CLL = chronic lymphocytic leukemia

Blood. 2018;131(25):2745-60.
Nature. 2019;16:684-701.
N Engl J Med. 2020; 383:460-73.

Chronic Lymphocytic Leukemia

GENETICS

- Traditional chemotherapy is much less effective in patients with unmutated immunoglobulin heavy chain variable gene (IGHV-UM) and other high-risk genetic features



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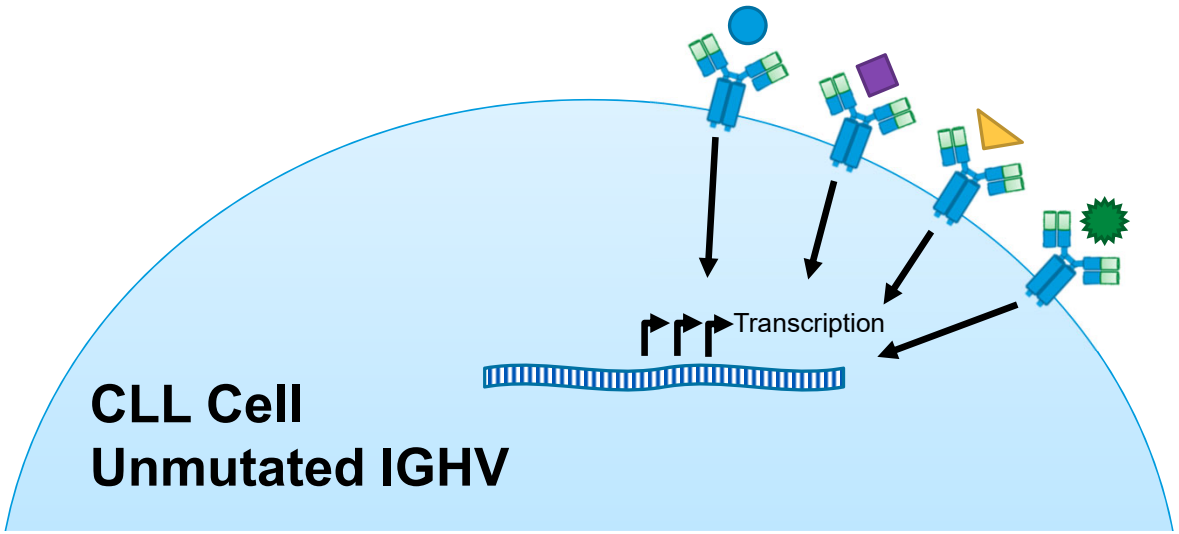

B-cell receptors respond to many antigens

⬇

Increased proliferation

Blood. 2018;131(25):2745-60.
Nature. 2019;16:684-701.
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Chronic Lymphocytic Leukemia

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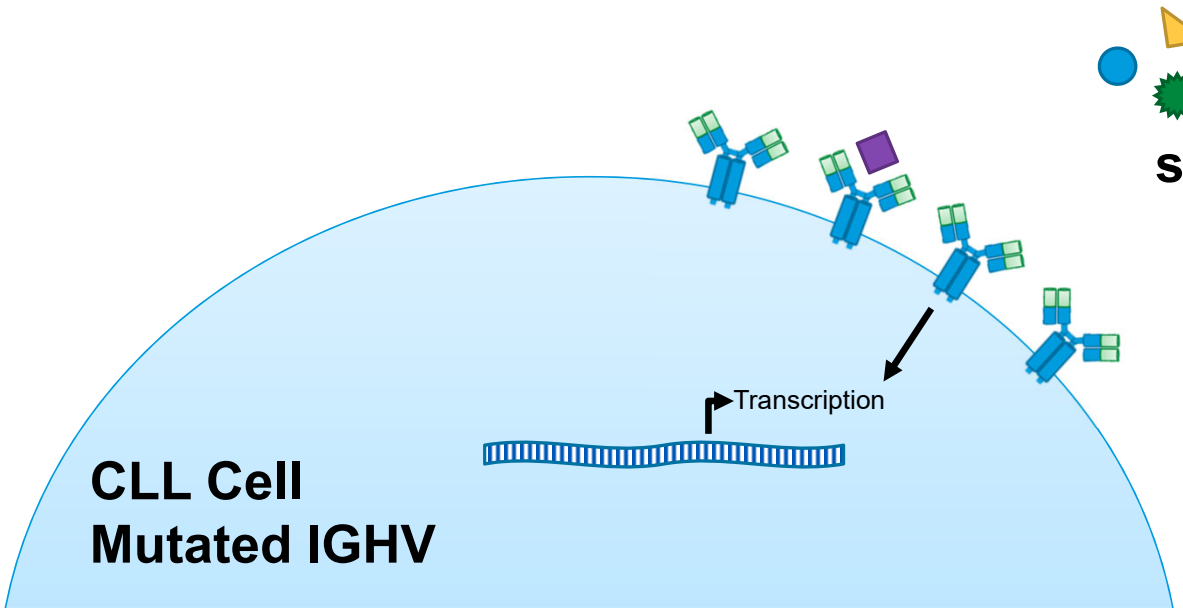


B-cell receptors bind more selectively to restricted antigens

⬇

Less active signaling

Blood. 2018;131(25):2745-60.
Nature. 2019;16:684-701.
N Engl J Med. 2020; 383:460-73.

Chronic Lymphocytic Leukemia

GENETICS

	Mutation	Frequency	5-Year Overall Survival	
Low-Risk	**Isolated del(13q14)**	55%	> 90%	• Enriched in early stages and IGHV-M • Enriched in IGHV-M
Low-Risk	**Trisomy 12**	15%	-	• No clear functional explanation • More common in SLL
High-Risk	**Del(11q) or *ATM* disruption**	10-20%	68%	• Enriched in advanced stages, bulky disease, young patients, and IGHV-UM
High-Risk	**Del(17p) or *TP53* disruption**	5-10%	35-50%	• Enriched in advanced stages and IGHV-UM • Increased genomic instability

SLL = small lymphocytic leukemia
IGHV-M = mutated immunoglobulin heavy chain variable gene
IGHV-UM = unmutated immunoglobulin heavy chain variable gene

Blood. 2018;131(25):2745-60.
Nature. 2019;16:684-701.

Chronic Lymphocytic Leukemia

TREATMENT INITIATION

- Treatment should be initiated when patients progress or present with progressive or symptomatic/active disease
  - Evidence of progressive marrow failure
  - Massive, progressive, or symptomatic splenomegaly
  - Massive, progressive, or symptomatic lymphadenopathy
  - Progressive lymphocytosis
  - Autoimmune complications
  - Symptomatic or functional extranodal involvement
  - Disease-related symptoms (B-symptoms)

Am J Hematol. 2019;94:1266-87.
Blood. 2018;131(25):2745-60.

Chronic Lymphocytic Leukemia

STAGING & PROGNOSIS

Rai Staging

	Stage	Findings	Median Survival (Years)
Low	0	Lymphocytosis	> 10
Intermediate	I	Lymphadenopathy	8
	II	Organomegaly	6
High	III	Anemia (Hgb < 11 g/dL)	1.5
	IV	Thrombocytopenia (PLT < 100,000/mcL)	1.5

Organomegaly = enlargement of spleen or liver
Hgb = hemoglobin; PLT = platelets

Binet Staging

Stage	Findings	Median Survival (Years)
A	No anemia, no thrombocytopenia, < 3 lymphoid areas enlarged	14
B	No anemia, no thrombocytopenia, ≥ 3 lymphoid areas enlarged	5
C	Anemia (Hgb < 10 g/dL) and/or PLT < 100,000/mcL	2.5

Blood. 1975;46(2):219-234.
Cancer. 1981;48(1):198-206.

Chronic Lymphocytic Leukemia

STAGING & PROGNOSIS

- CLL International Prognostic Index (IPI) is currently the most relevant prognostic score, incorporating clinical, biological, and genetic information

CLL-IPI Category	Points	Treatment Free Survival (5 year)	Potential Clinical Consequence
Low-Risk	0-1	78%	Do not treat
Intermediate-Risk	2-3	54%	Do not treat except if severely symptomatic
High-Risk	4-6	32%	Treatment indicated except if fully asymptomatic
Very High-Risk	7-10	0%	Treat with novel agents or enroll in clinical trials rather than using chemoimmunotherapy

CLL = chronic lymphocytic leukemia

Lancet Oncol. 2016;17:779-90.

Question 1

Which of the following would indicate a poorer prognosis CLL?

a) Mutated immunoglobulin heavy chain variable gene (IGHV)
b) Mutation in *TP53*
c) Isolated deletion of 13q14
d) Trisomy 12

CLL = chronic lymphocytic leukemia

Question 1

Which of the following would indicate a poorer prognosis CLL?

a) Mutated immunoglobulin heavy chain variable gene (IGHV)

b) Mutation in *TP53*

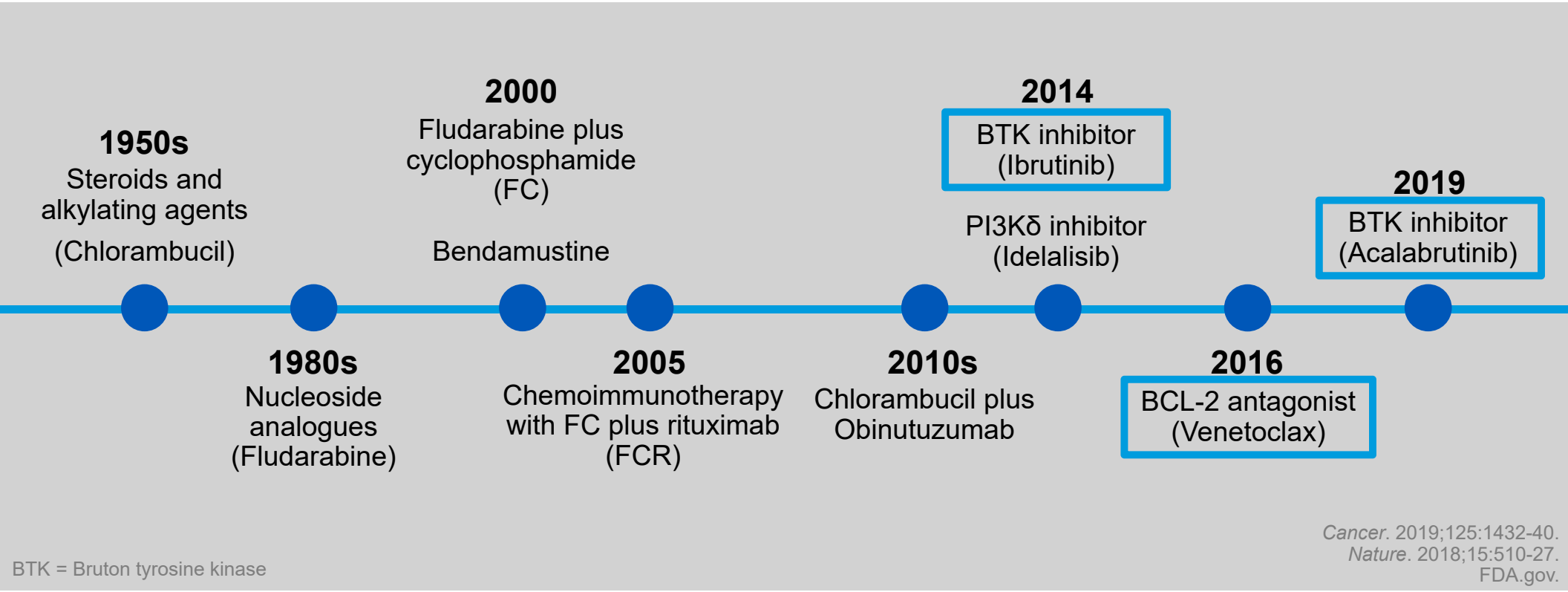
c) Isolated deletion of 13q14

d) Trisomy 12

CLL = chronic lymphocytic leukemia

Chronic Lymphocytic Leukemia

HISTORICAL APPROACH TO TREATMENT



BTK = Bruton tyrosine kinase

Cancer. 2019;125:1432-40.
Nature. 2018;15:510-27.
FDA.gov.

Targeted Therapies

Bruton Tyrosine Kinase (BTK) Inhibitors

- Ibrutinib
- Acalabrutinib

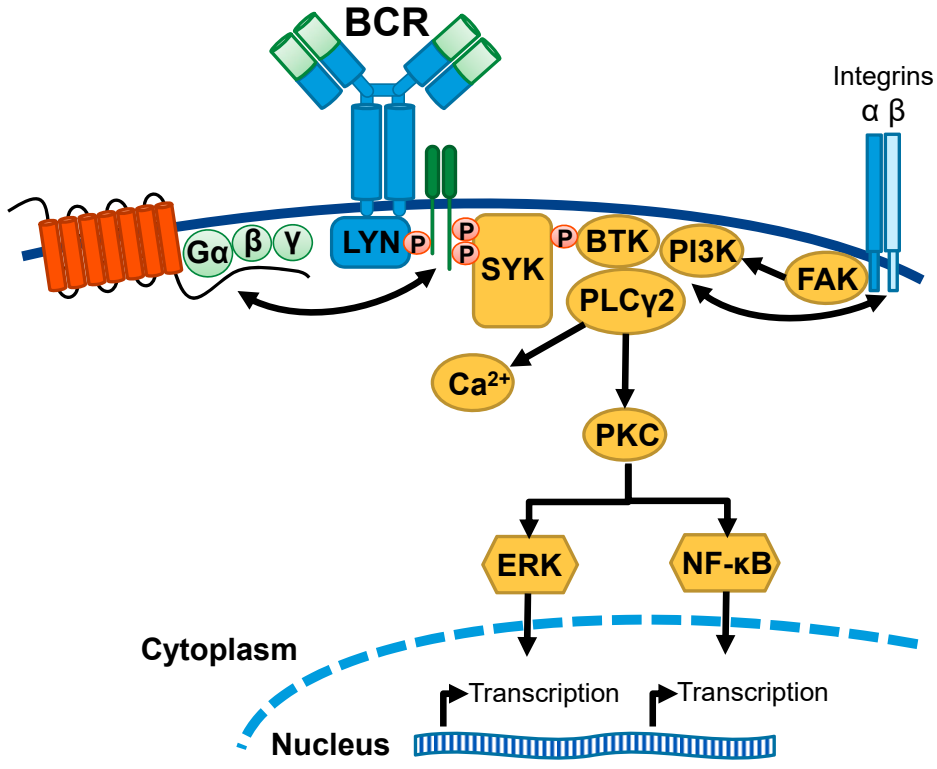
BCL-2 Antagonist

- Venetoclax

Bruton Tyrosine Kinase (BTK) Inhibitors

MECHANISM OF ACTION

- BTK is an essential component of the B-cell receptor (BCR) and cytokine receptor pathways
  - Activation contributes to survival and proliferation of malignant B-cells
- BTK regulates signaling and functioning of certain chemokine receptors
  - Affects B-cell migration and tissue homing



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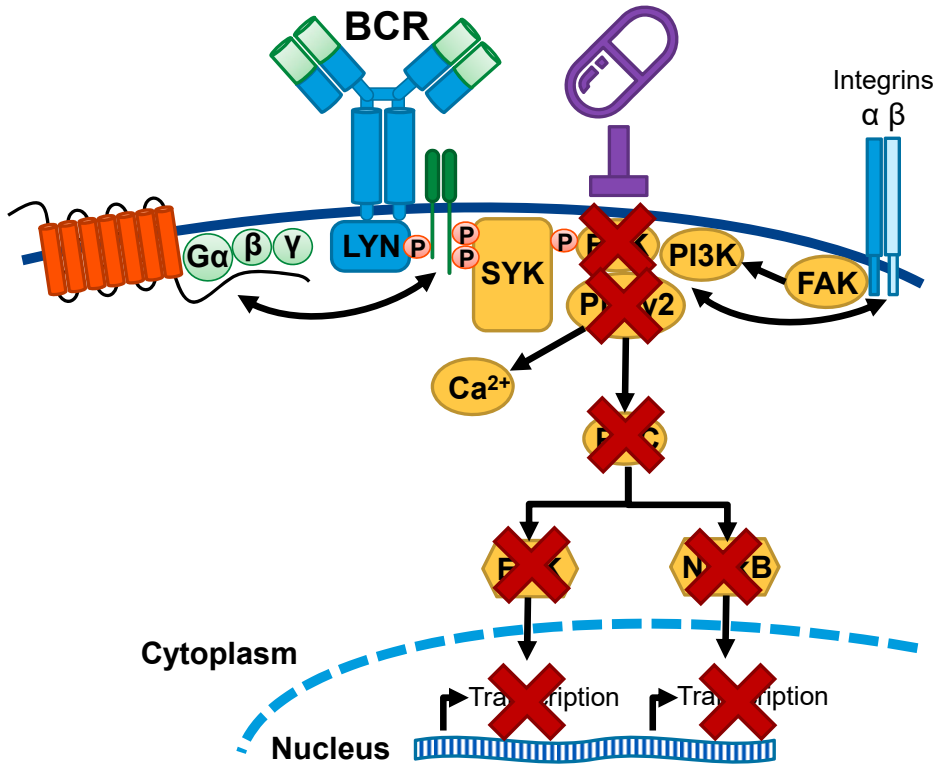
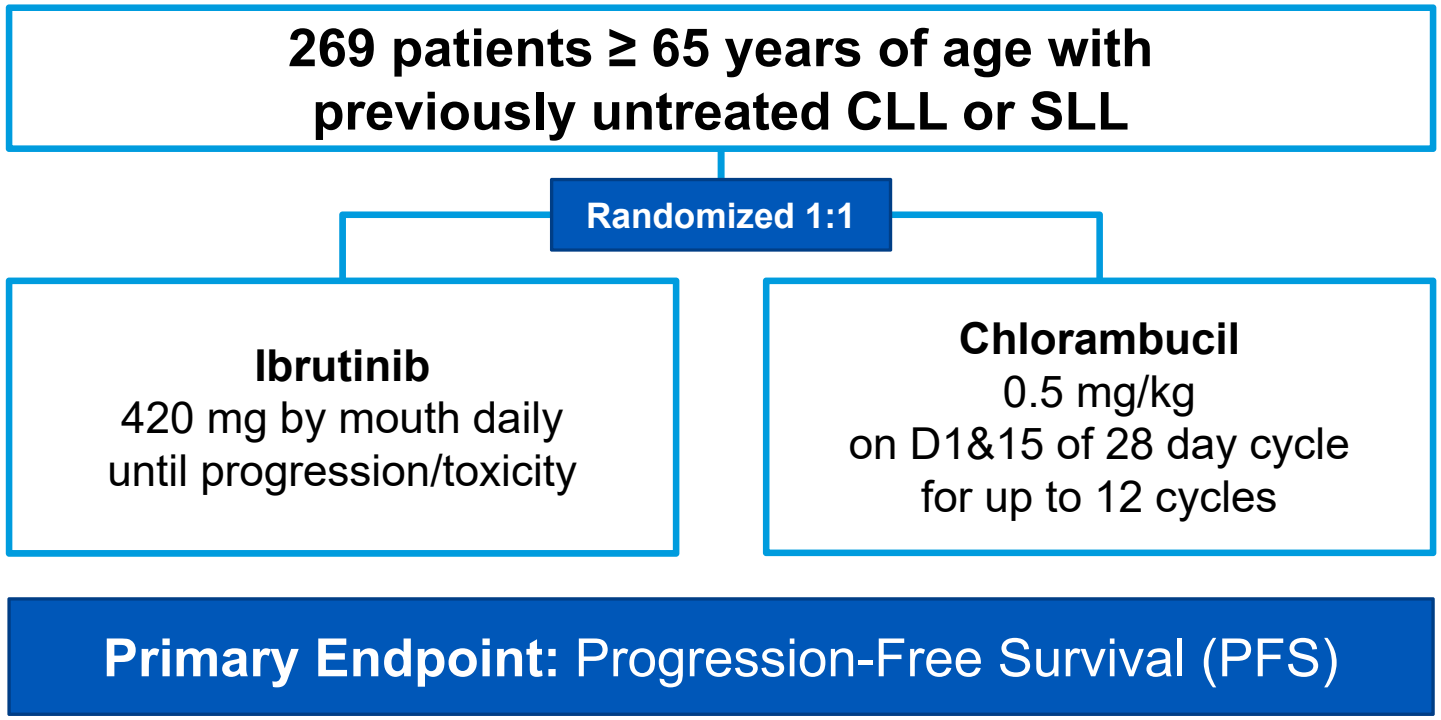


Cancer. 2019;125:1432-40.
Nature. 2018;15:510-27.

RESONATE-2: Design

IBRUTINIB vs CHLORAMBUCIL



CLL = chronic lymphocytic leukemia
SLL = small lymphocytic leukemia
D = day

N Engl J Med. 2015;373:2425-37.

RESONATE-2: Baseline Characteristics

IBRUTINIB vs CHLORAMBUCIL

Characteristic	Ibrutinib (N=136)	Chlorambucil (N=133)
Age, median (range)	73 (65-89)	72 (65-90)
Male sex, n (%)	88 (65)	81 (61)
Rai stage III or IV (high-risk), n (%)	60 (44)	62 (47)
* Unmutated *IGHV*, n (%)	58 (43)	60 (45)
* Del(11q), n (%)	29 (21)	25 (19)

* Denotes high-risk genetic alteration

N Engl J Med. 2015;373:2425-37.

Targeted Agents in the Frontline Setting

STUDY OUTCOMES SUMMARY

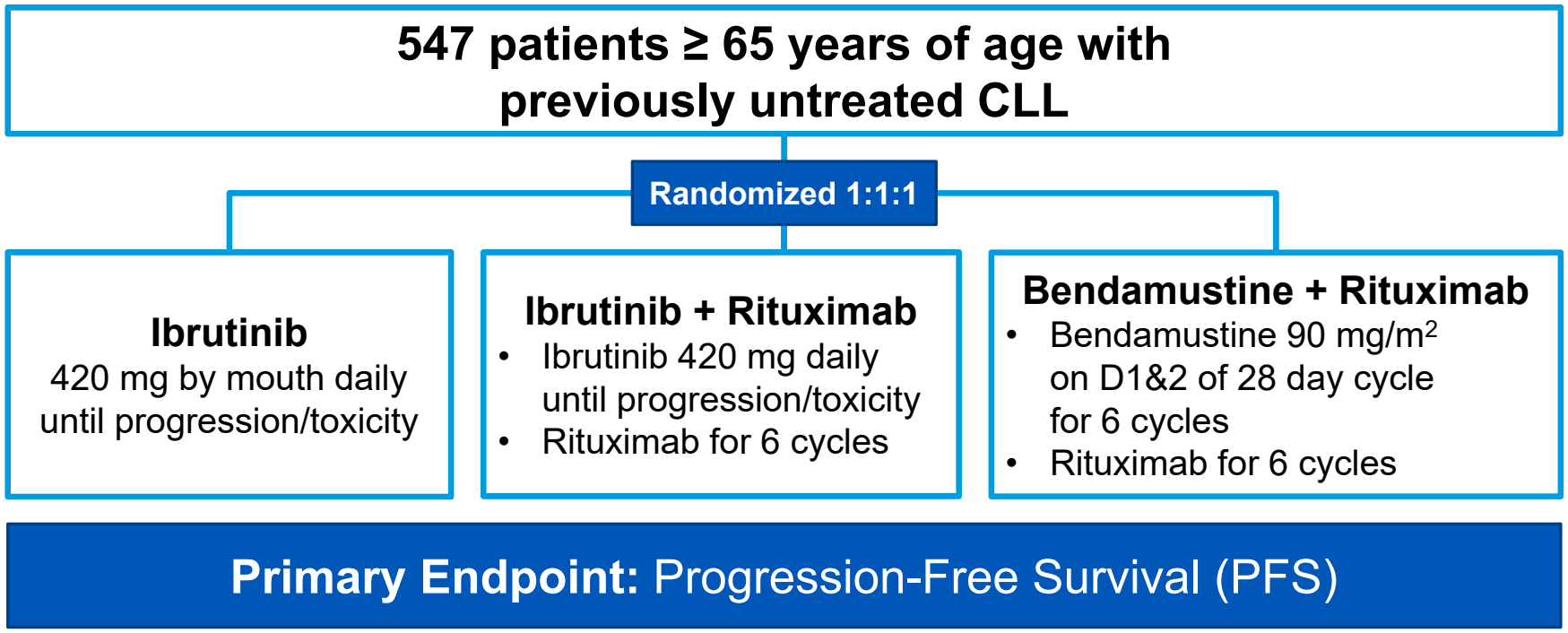
Trial	Regimen	Comparator	Follow Up	PFS	OS
RESONATE-2	Ibrutinib	Chlorambucil	5 years	**70% vs. 12%**	**83% vs. 68%**

PFS = progression free survival; OS = overall survival
Bolded denotes significant difference

Leukemia. 2020;34:787-98.

A041202: Design

IBRUTINIB +/- RITUXIMAB vs BENDAMUSTINE + RITUXIMAB



CLL = chronic lymphocytic leukemia
D = day

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

A041202: Baseline Characteristics

IBRUTINIB +/- RITUXIMAB vs BENDAMUSTINE + RITUXIMAB

Characteristic	Ibrutinib (N=182)	Ibrutinib + Rituximab (N=182)	Bendamustine + Rituximab (N=183)
Age, median (range)	71 (65-89)	71 (65-86)	70 (65-86)
Male sex, n (%)	123 (68)	125 (69)	119 (65)
Rai stage III or IV, n (%)	99 (54)	98 (54)	99 (54)
* Unmutated *IGHV*, n/tn (%)	77/122 (63)	70/115 (61)	71/123 (58)
* Del(11q), n/tn (%)	35/181 (19)	37/180 (21)	33/181 (18)
* Del(17p), n/tn (%)	9/181 (5)	11/180 (6)	14/181 (8)
* Mutated *TP35*, n/tn (%)	15/168 (9)	20/168 (12)	16/174 (9)

* Denotes high-risk genetic alteration

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

Targeted Agents in the Frontline Setting

STUDY OUTCOMES SUMMARY

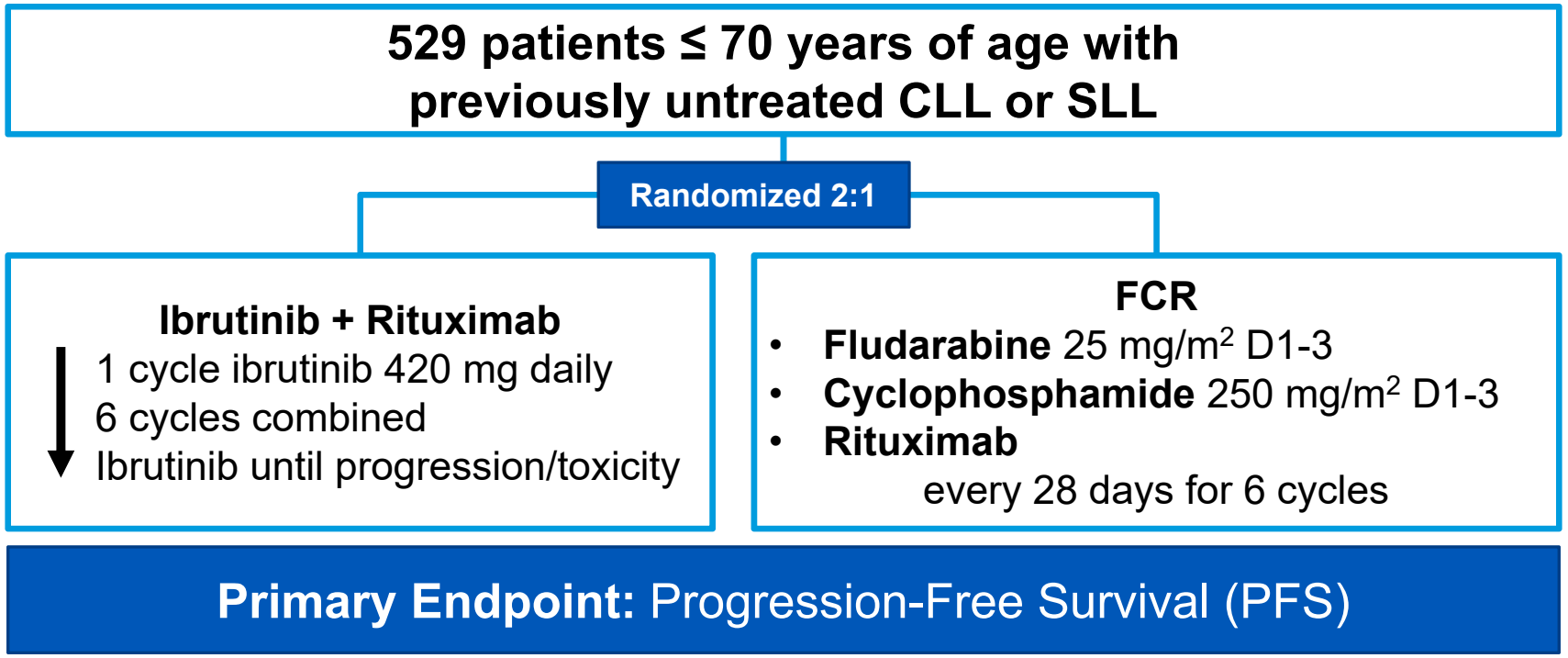
Trial	Regimen	Comparator	Follow Up	PFS	OS
RESONATE-2	Ibrutinib	Chlorambucil	5 years	**70% vs. 12%**	**83% vs. 68%**
A041202	Ibrutinib	Bendamustine + R	2 years	**87% vs. 74%**	90% vs. 95%

PFS = progression free survival; OS = overall survival; R = rituximab
Bolded denotes significant difference

Leukemia. 2020;34:787-98.
N Engl J Med. 2018;379:2517-28.

E1912: Design

IBRUTINIB vs FCR



CLL = chronic lymphocytic leukemia
SLL = small lymphocytic leukemia
D = day

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

E1912 : Baseline Characteristics

IBRUTINIB vs FCR

Characteristic	Ibrutinib + Rituximab (N=354)	FCR (N=175)
Age, mean ± SD	56.7 ± 7.5	56.7 ± 7.2
Male sex, n (%)	236 (66.7)	120 (68.6)
Rai stage III or IV, n (%)	156 (44.1)	72 (41.1)
ECOG performance status of 0, n (%)	226 (63.8)	109 (62.3)
* Unmutated *IGHV*, n/tn (%)	210/280 (75.0)	75/115 (61.7)
* Del(11q), n (%)	78 (22.0)	39 (22.3)

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

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E1912	Ibrutinib + R	FCR	3 years	**89.4% vs. 72.9%**	**98.8% vs. 91.5%**

PFS = progression free survival; OS = overall survival; R = rituximab; FCR = fludarabine, cyclophosphamide, and rituximab
Bolded denotes significant difference

Leukemia. 2020;34:787-98.
N Engl J Med. 2018;379:2517-28.
N Engl J Med. 2019;381:432-43.

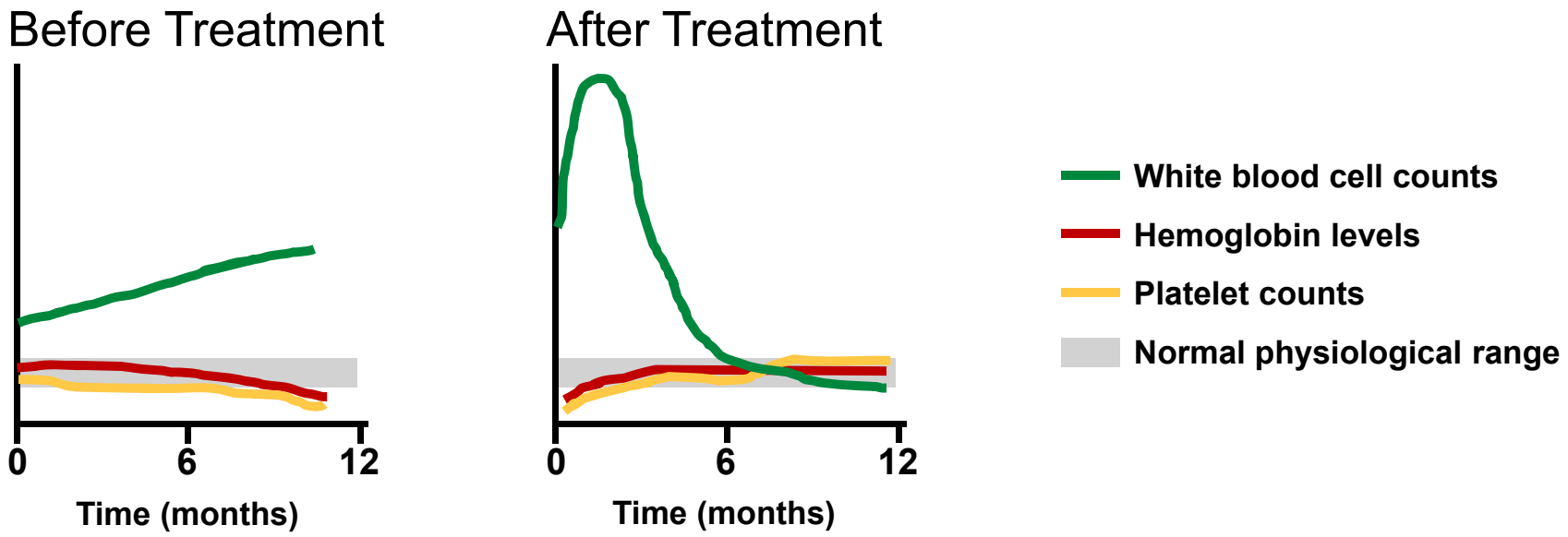
Ibrutinib is an effective frontline treatment option for CLL.

Management of patients on extended ibrutinib therapy may be complicated by adverse events.

Bruton Tyrosine Kinase (BTK) Inhibitors

IBRUTINIB: TREATMENT EFFECTS

- Following treatment initiation, leukocytosis transiently increases as a result of CLL cell redistribution



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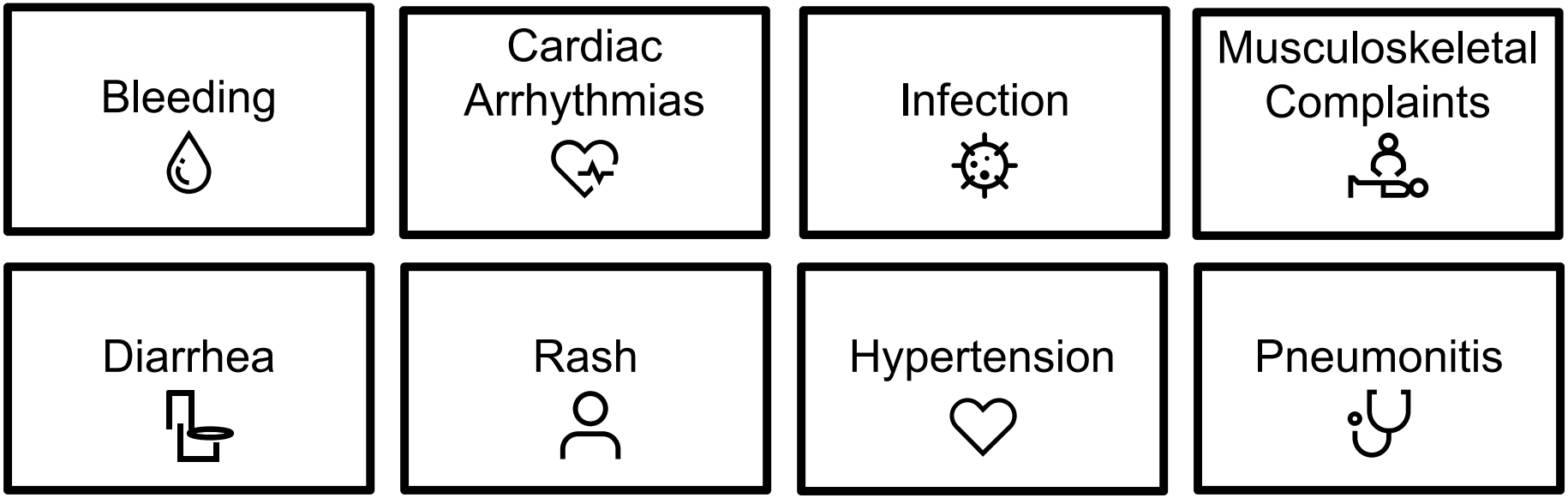
Nature. 2018;15:510-27.

Bruton Tyrosine Kinase (BTK) Inhibitors

IBRUTINIB: ADVERSE EFFECTS

- Ibrutinib causes several potentially severe off-target toxicities that may lead to treatment discontinuation



J Clin Oncol. 2020. JCO2001594.

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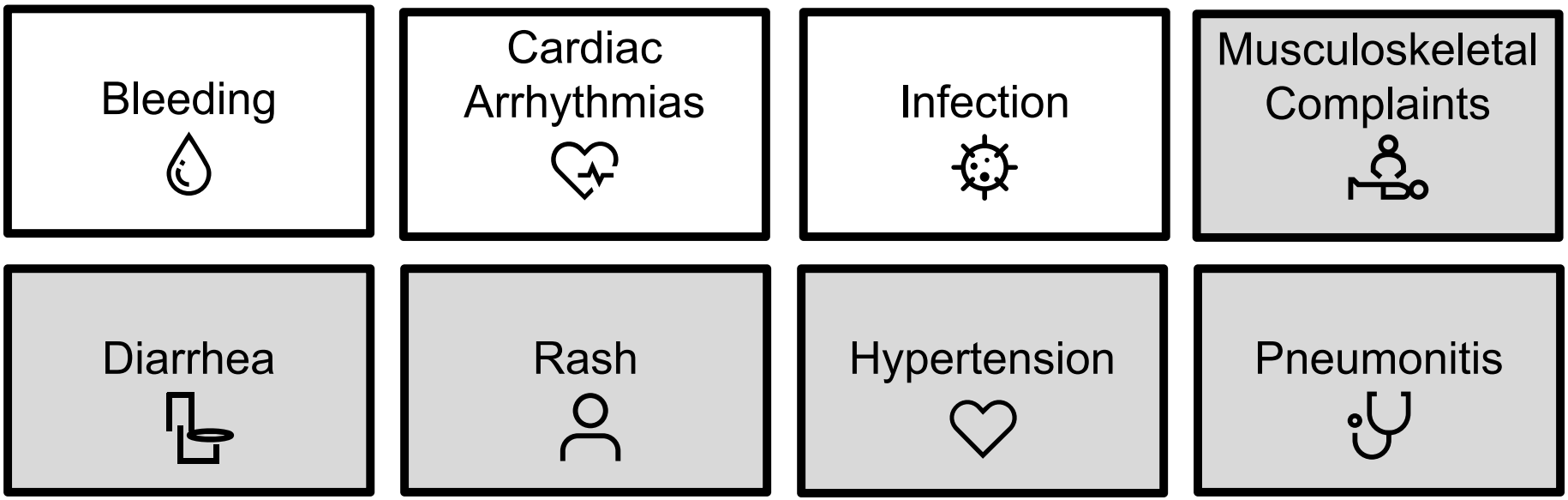

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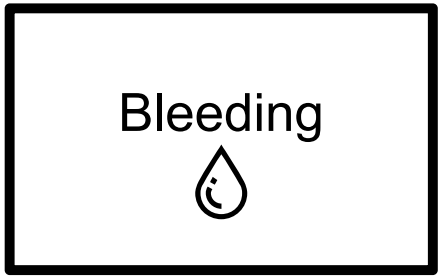


- Clinical trial data reports a risk of minor bleeding in up to 66% of patients and major bleeding in up to 6% of patients
- Risk for major bleeding is increased in patients on concurrent antiplatelet or anticoagulant agents
- BTK has a known role in platelet aggregation that is dependent upon activation of additional kinases

Blood. 2019;133(12):1298-1307.

Bruton Tyrosine Kinase (BTK) Inhibitors

IBRUTINIB: ADVERSE EFFECTS

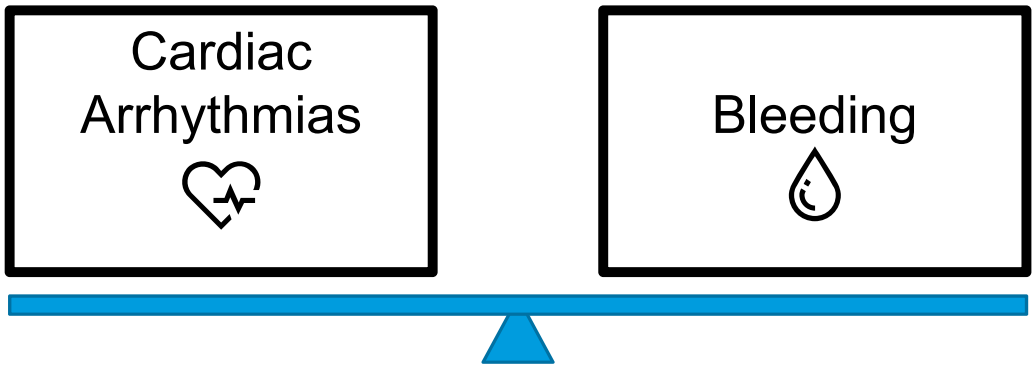
Cardiac Arrhythmias

- Atrial fibrillation is the most common ibrutinib-related cardiac arrhythmia, seen in up to 10% of treated patients
- Mechanism currently unknown

Blood. 2019;133(12):1298-1307.

Bruton Tyrosine Kinase (BTK) Inhibitors

IBRUTINIB: ADVERSE EFFECTS



- Involve hematology and cardiology teams
- Rate and/or rhythm control
  - Diltiazem and verapamil are moderate CYP3A4 inhibitors; reduce ibrutinib dose by 50% when used in combination
- Concomitant use of anticoagulation is often unavoidable

Blood. 2019;133(12):1298-1307.
Cancer Med. 2020;9:3390-9.

Bruton Tyrosine Kinase (BTK) Inhibitors

IBRUTINIB: ADVERSE EFFECTS

Infection

- Meta-analysis of clinical trials found that 56% of patients had an infectious complication and 20% developed pneumonia
- Consider holding ibrutinib for severe infections
- Reduced doses of ibrutinib are required when used in conjunction with –azole antifungals

Blood. 2019;133(12):1298-1307.

Question 2

AK is a 66 year old male with a past medical history significant for hypertension, hyperlipidemia, and type 2 diabetes. A little over a month ago, he was diagnosed with high-risk CLL and started on ibrutinib plus rituximab. At follow up, the patient is found to have new onset atrial fibrillation (CHA_2DS_2-VASc = 3), and the team suspects ibrutinib may be the cause.

Which of the following is true when considering this patient case?

a) Ibrutinib should be permanently discontinued

b) Warfarin is the anticoagulant of choice for this patient

c) Ibrutinib dose should be reduced if the patient is started on diltiazem

d) Switching to an alternative BTK inhibitor would not benefit this patient

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Bruton Tyrosine Kinase (BTK) Inhibitors

SECOND GENERATION BTK INHIBITORS

- Second generation BTK inhibitors have the same mechanism of action as ibrutinib but with reduced off-target effects

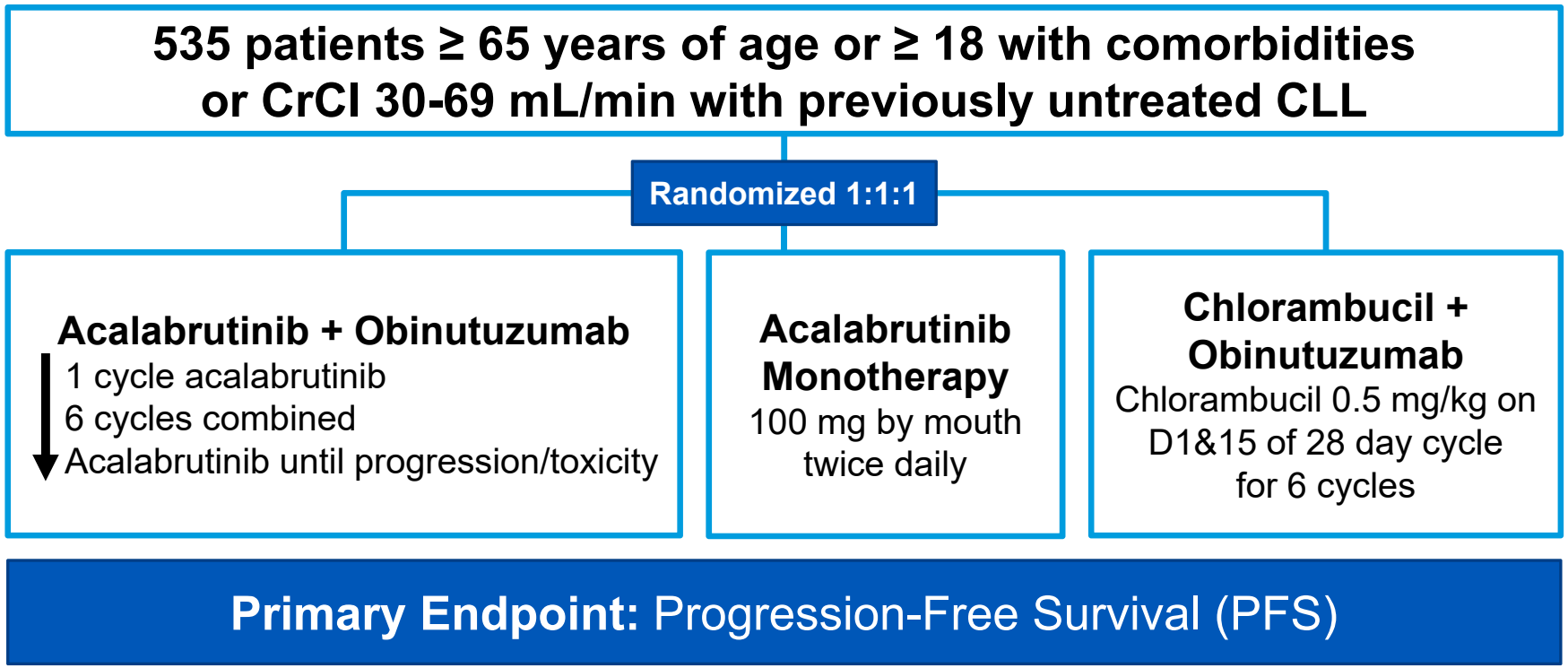
BTK Inhibitor	Approval Year	FDA Labeled Indication
Acalabrutinib	2017	Previously treated mantle cell lymphoma in adults
	2019	CLL or SLL in adults
Zanubrutinib	2019	Previously treated mantle cell lymphoma in adults
	---	Ongoing clinical trials in CLL/SLL

CLL = chronic lymphocytic leukemia
SLL = small lymphocytic leukemia

J Clin Oncol. 2020. JCO2001594.
FDA.gov

ELEVATE-TN: Design

ACALABRUTINIB +/- OBINUTUZUMAB vs CHLORAMBUCIL + OBINUTUZUMAB



CrCl = creatinine clearance
CLL = chronic lymphocytic leukemia
D = day

Lancet 2020;395:1278-91.

ELEVATE-TN : Baseline Characteristics

ACALABRUTINIB +/- OBINUTUZUMAB vs CHLORAMBUCIL + OBINUTUZUMAB

Characteristic	Acalabrutinib + Obinutuzumab (N=179)	Acalabrutinib Monotherapy (N=179)	Chlorambucil + Obinutuzumab (N=177)
Age, median (IQR)	70 (65-75)	70 (66-75)	71 (67-76)
Male sex, n (%)	111 (62)	111 (62)	106 (60)
CLL-IPI (high risk), n (%)	115 (64)	134 (75)	119 (67)
CLL-IPI (very high risk), n (%)	23 (13)	20 (11)	23 (13)
* Unmutated *IGHV*, n (%)	103 (58)	119 (67)	116 (66)
* Del(11q), n (%)	31 (17)	31 (17)	33 (19)
* Del(17p), n (%)	17 (10)	16 (9)	16 (9)
* Mutated *TP35*, n (%)	21 (12)	19 (11)	21 (12)

* Denotes high-risk genetic alteration

Lancet 2020;395:1278-91.

Targeted Agents in the Frontline Setting

STUDY OUTCOMES SUMMARY

Trial	Regimen	Comparator	Follow Up	PFS	OS
RESONATE-2	Ibrutinib	Chlorambucil	5 years	**70% vs. 12%**	**83% vs. 68%**
A041202	Ibrutinib	Bendamustine + R	2 years	**87% vs. 74%**	90% vs. 95%
E1912	Ibrutinib + R	FCR	3 years	**89.4% vs. 72.9%**	**98.8% vs. 91.5%**
ELEVATE-TN	Acalabrutinib + Obinutuzumab	Chlorambucil + Obinutuzumab	2 years	**93% vs. 47%**	95% vs. 92%

PFS = progression free survival; OS = overall survival; R = rituximab; FCR = fludarabine, cyclophosphamide, and rituximab
Bolded denotes significant difference

Leukemia. 2020;34:787-98..
N Engl J Med. 2018;379:2517-28.
N Engl J Med. 2019;381:432-43.
Lancet 2020;395:1278-91.

Adverse Effects with BTK Inhibitors

STUDY OUTCOMES SUMMARY

Trial & Regimen	Population	Follow Up	Bleeding (Grade ≥ 3)	Atrial Fibrillation (Grade ≥ 3)	Discontinuation Rate for ADE
RESONATE-2 Ibrutinib	≥ 65 years	3 years	4%	1.5%	9%
A041202 Ibrutinib	≥ 65 years	2 years	2%	9%	-
E1912 Ibrutinib + R	≤ 70 years	3 years	1%	3%	11%
ELEVATE-TN Acalabrutinib + Obinutuzumab	≥ 65 years or ≥ 18 with comorbidities	2 years	2%	3%	11% (9% with monotherapy)

R = rituximab

Real-World 25.9%

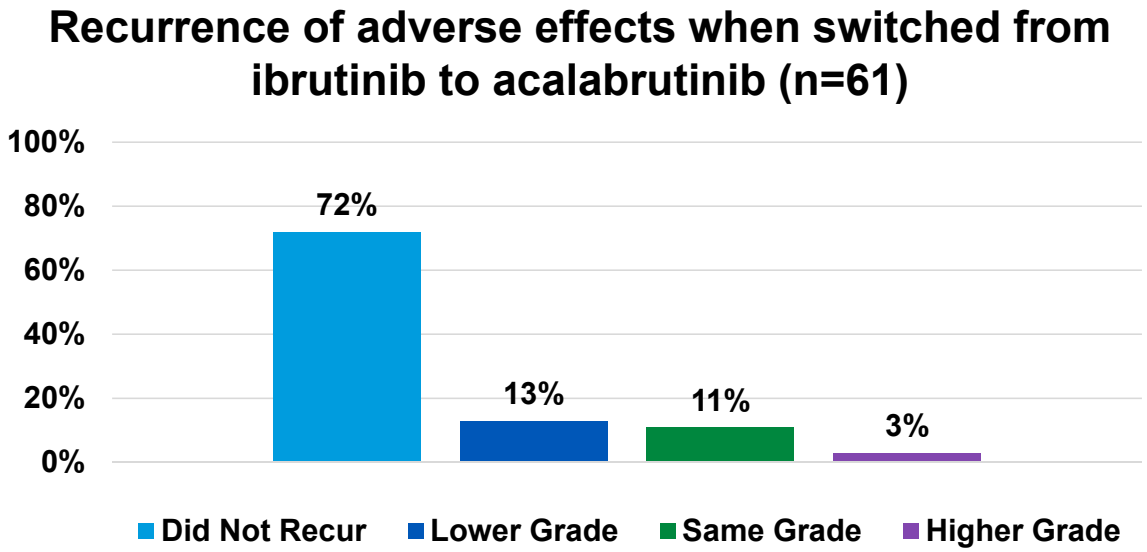
ADE = adverse drug effect

N Engl J Med. 2015;373:2425-37.
N Engl J Med. 2018;379:2517-28.
N Engl J Med. 2019;381:432-43.
Lancet 2020;395:1278-91.
Haematologica. 2018;103(5):874-9.

Bruton Tyrosine Kinase (BTK) Inhibitors

COMPARING IBRUTINIB AND ACALABRUTINIB

- Switching to acalabrutinib may be an option for patients who experience adverse effects while on ibrutinib



Blood. 2019;3(9):1553-62.

Bruton Tyrosine Kinase (BTK) Inhibitors

COMPARING IBRUTINIB AND ACALABRUTINIB

	Ibrutinib	Acalabrutinib
Standard Dose	420 mg once daily	100 mg twice daily
Dose Modifications		
Moderate CYP3A inhibitor	280 mg once daily	100 mg once daily
Voriconazole or Posaconazole	70-140 mg once daily	---
Other strong CYP3A inhibitors	Avoid concomitant use	Avoid concomitant use
Strong CYP3A inducers	Avoid concomitant use	Avoid concomitant use or increase dose to 200 mg twice daily
Other Drug Interactions	---	Avoid PPIs; take acalabrutinib two hours before H2RAs or antacids

PPIs = proton pump inhibitors
H2RAs = histamine-2 receptor antagonists

Package Insert: Ibrutinib; 2020.
Package Insert: Acalabrutinib; 2019.

Targeted Therapies

Bruton Tyrosine Kinase (BTK) Inhibitors

- Ibrutinib
- Acalabrutinib

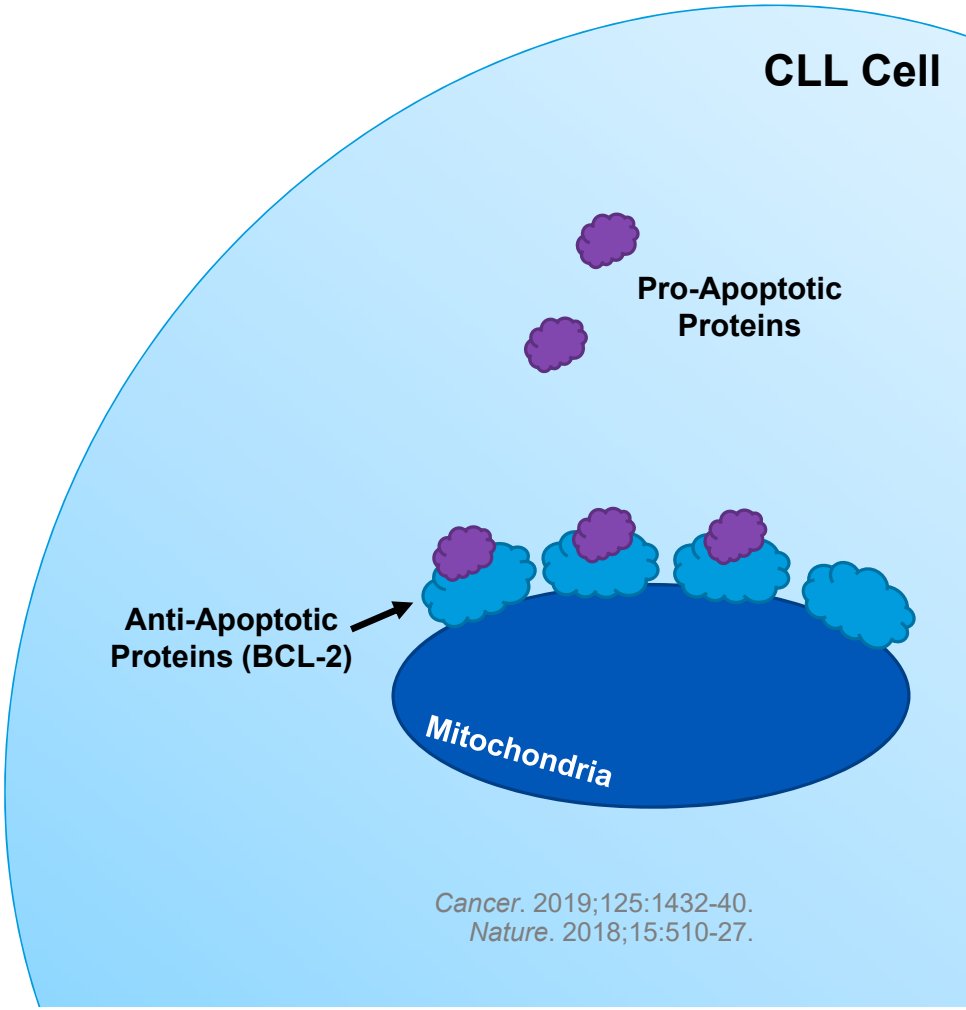
BCL-2 Antagonist

- Venetoclax

Venetoclax

MECHANISM OF ACTION

- The B-cell lymphoma 2 (BCL-2) protein is overexpressed in CLL
  - Promotes survival of CLL cells by inhibiting pro-apoptotic proteins



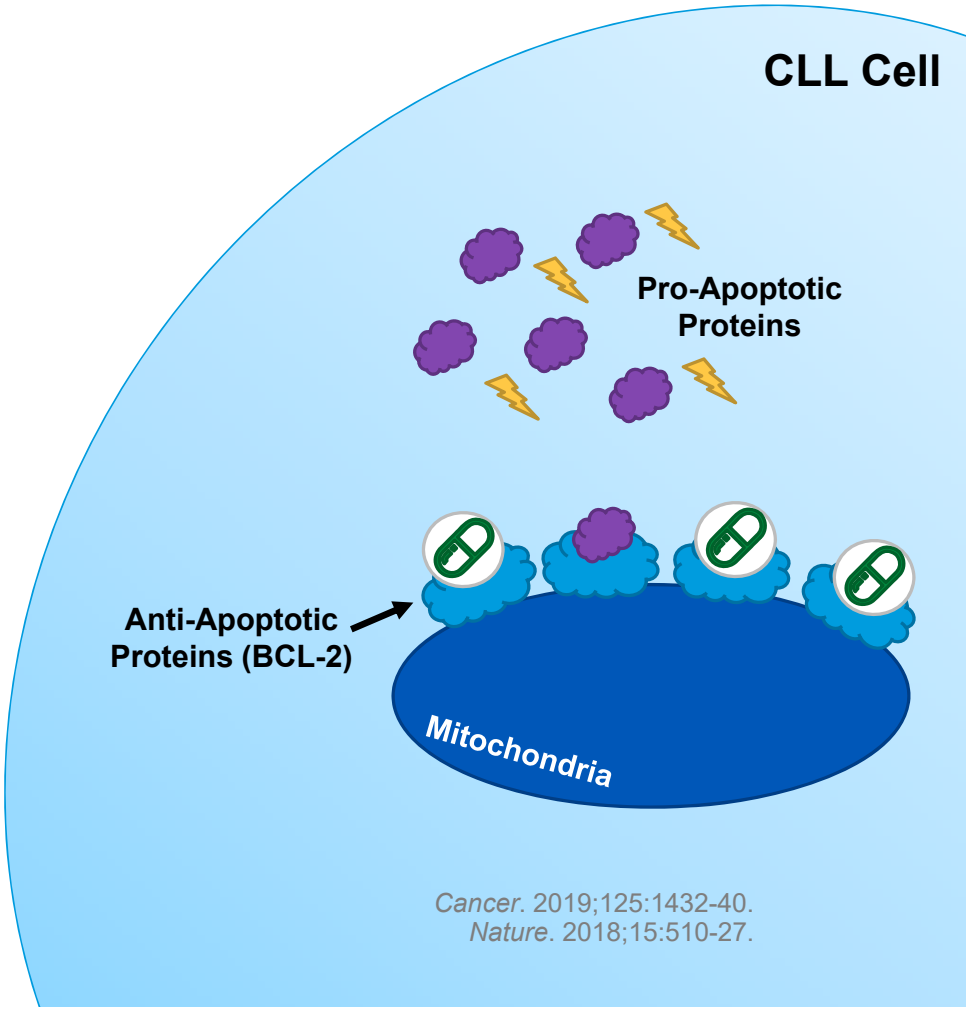
CLL = chronic lymphocytic leukemia

Cancer. 2019;125:1432-40.
Nature. 2018;15:510-27.

Venetoclax

MECHANISM OF ACTION

- The B-cell lymphoma 2 (BCL-2) protein is overexpressed in CLL
  - Promotes survival of CLL cells by inhibiting pro-apoptotic proteins
- Venetoclax antagonizes BCL-2
  - Activates proapoptotic proteins and restores the apoptotic process
- Direct cytotoxic activity can result in tumor lysis syndrome



CLL = chronic lymphocytic leukemia

Cancer. 2019;125:1432-40.
Nature. 2018;15:510-27.

Venetoclax

TUMOR LYSIS SYNDROME

- Tumor lysis syndrome occurs when tumor cells release their contents into the bloodstream
  - Hyperuricemia
  - Hyperkalemia
  - Hyperphosphatemia
  - Hypocalcemia
- May progress to AKI, cardiac arrhythmias, seizures, and death

TLS Risk	Tumor Burden
Low	All lymph nodes < 5 cm **AND** ALC < 25 x 10^9/L
Medium	Any lymph nodes 5-10 cm **OR** ALC ≥ 25 x 10^9/L
High	Any lymph nodes ≥ 10 cm **OR** ALC ≥ 25 x 10^9/L **AND** any lymph node ≥ 5 cm

AKI = acute kidney injury
ALC = absolute lymphocyte count
TLS = tumor lysis syndrome

Package Insert: Venetoclax; 2019.

Venetoclax

DOSING AND INTERACTIONS

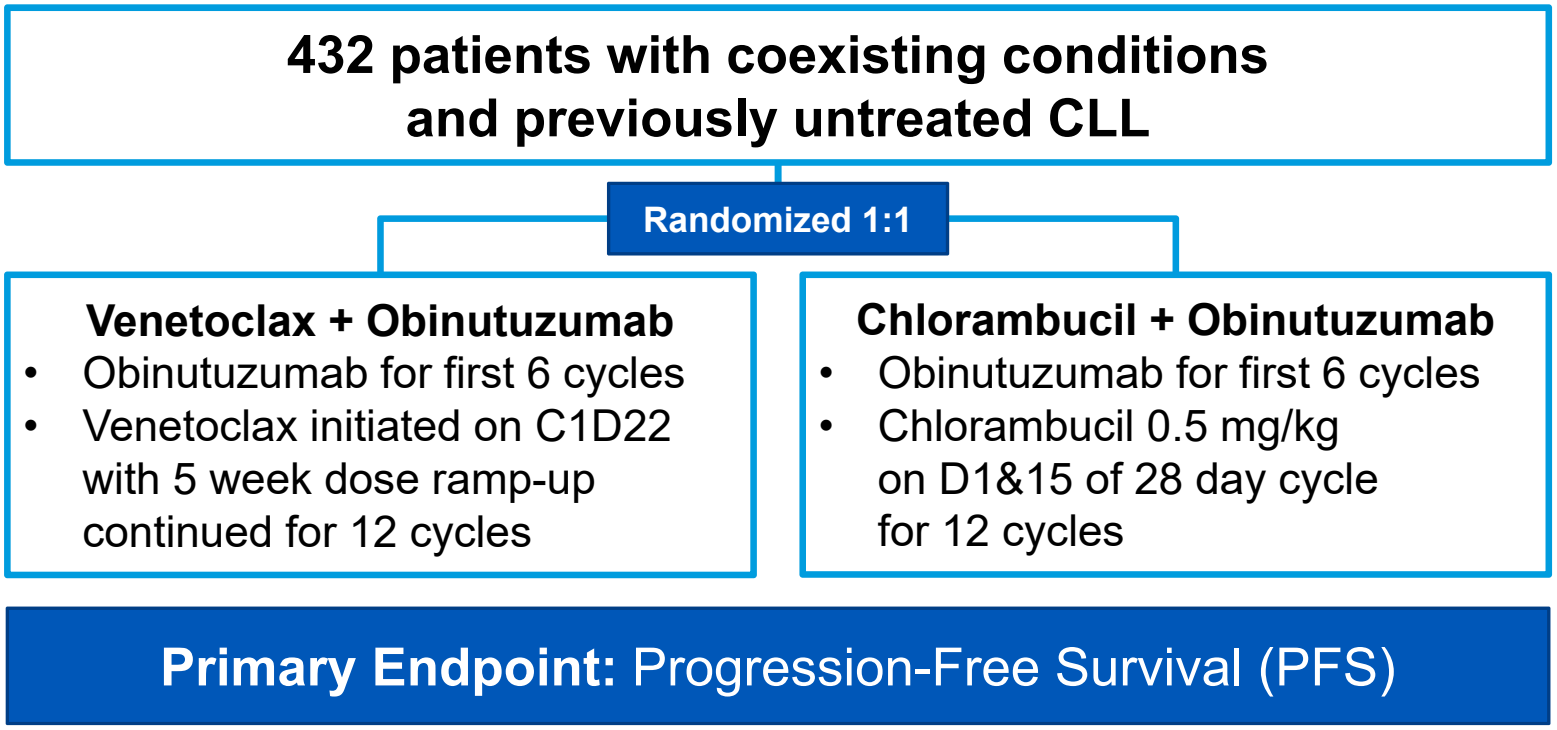
VENETOCLAX					
Dose Schedule	Week 1: 20 mg daily	Week 2: 50 mg daily	Week 3: 100 mg daily	Week 4: 200 mg daily	Week 5 and beyond: 400 mg daily

DRUG INTERACTIONS	
CYP3A inducers	Avoid concomitant use; may reduce the efficacy of venetoclax
Strong CYP3A inhibitors	Avoid at initiation and during ramp-up phase due to increased risk of tumor lysis syndrome; reduce venetoclax dose by at least 75% after ramp-up
Moderate CYP3A inhibitors	Reduce venetoclax dose by at least 50%
P-glycoprotein inhibitors	Reduce venetoclax dose by at least 50%
P-glycoprotein substrates	Avoid concomitant use, as venetoclax may increase toxicities of these substrates, or separate dosing by at least 6 hours
Warfarin	Venetoclax may increase warfarin concentration, increasing bleed risk

Package Insert: Venetoclax; 2019.

CLL14: Design

VENETOCLAX + OBINUTUZUMAB vs CHLORAMBUCIL + OBINUTUZUMAB



CLL = chronic lymphocytic leukemia
D = day

N Engl J Med. 2019;380(23):2225-36.

CLL14: Baseline Characteristics

VENETOCLAX + OBINUTUZUMAB vs CHLORAMBUCIL + OBINUTUZUMAB

Characteristic	Venetoclax + Obinutuzumab (N=216)	Chlorambucil + Obinutuzumab (N=216)
Age ≥ 75 years, n (%)	72 (33.3)	78 (36.1)
Male sex, n (%)	146 (67.6)	143 (66.2)
High TLS risk category, n (%)	48 (22.2)	43 (19.9)
* Unmutated *IGHV*, n/tn (%)	121/200 (60.5)	123/208 (59.1)
* Del(11q), n/tn (%)	36/200 (18.0)	38/193 (19.7)
* Del(17p), n/tn (%)	17/200 (8.5)	14/193 (7.3)
* Mutated *TP35*, n/tn (%)	19/171 (11.1)	13/157 (8.3)

* Denotes high-risk genetic alteration

N Engl J Med. 2019;380(23):2225-36.

Targeted Agents in the Frontline Setting

STUDY OUTCOMES SUMMARY

Trial	Regimen	Comparator	Follow Up	PFS	OS
RESONATE-2	Ibrutinib	Chlorambucil	5 years	**70% vs. 12%**	**83% vs. 68%**
A041202	Ibrutinib	Bendamustine + R	2 years	**87% vs. 74%**	90% vs. 95%
E1912	Ibrutinib + R	FCR	3 years	**89.4% vs. 72.9%**	**98.8% vs. 91.5%**
ELEVATE-TN	Acalabrutinib + Obinutuzumab	Chlorambucil + Obinutuzumab	2 years	**93% vs. 47%**	95% vs. 92%
CLL14	Venetoclax + Obinutuzumab	Chlorambucil + Obinutuzumab	2 years	**88.2% vs 64.1%**	91.8% vs. 93.3%

PFS = progression free survival; OS = overall survival; R = rituximab; FCR = fludarabine, cyclophosphamide, and rituximab
Bolded denotes significant difference

Leukemia. 2020;34:787-98.
N Engl J Med. 2018;379:2517-28.
N Engl J Med. 2019;381:432-43.
Lancet 2020;395:1278-91.
N Engl J Med. 2019;380(23):2225-36.

Question 3

Which of the following is true about venetoclax use in patients with CLL?

a) Venetoclax binds to and inhibits the B-cell receptor signaling pathway

b) The dose of venetoclax is increased each day until the maximum dose is reached

c) Venetoclax and obinutuzumab significantly improved overall survival in the CLL14 trial

d) Venetoclax has direct cytotoxic activity that may result in tumor lysis syndrome

Question 3

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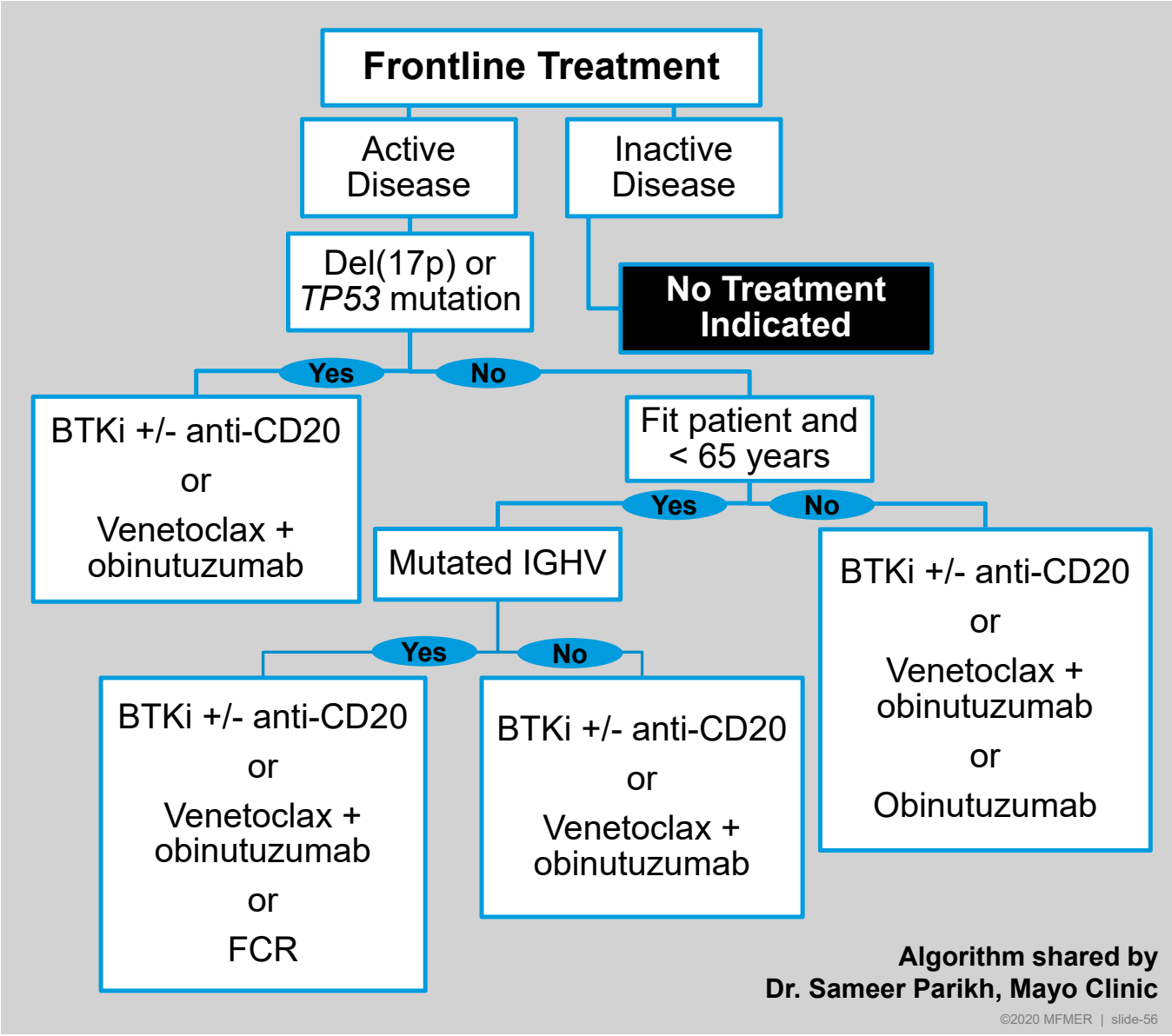
FRONTLINE TREATMENT ALGORITHM

How are targeted therapies used in practice?

FRONTLINE TREATMENT ALGORITHM



BTKi = Bruton tyrosine kinase inhibitor
IGHV = immunoglobulin heavy chain variable gene
FCR = fludarabine, cyclophosphamide, and rituximab

Summary

- Targeted therapies are revolutionizing treatment of chronic lymphocytic leukemia
  - New treatment options and combination therapies are currently under investigation

- While convenient and effective compared to chemoimmunotherapy, targeted therapies are accompanied with unique adverse effects that require careful management

- Targeted therapies are often preferred frontline treatment options, especially in patients with deletions in 17p, mutated *TP53,* or other high-risk genetic features

QUESTIONS & ANSWERS

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Chronic Lymphocytic Leukemia

DEFINITIONS OF RESPONSE

	Parameter	Complete Remission	Partial Remission	Progressive Disease	Stable Disease
A	Lymph nodes	None ≥ 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%	Change of -49% to +49%
A	Liver and/or spleen size	Spleen < 3 cm; liver normal	Decrease ≥ 50%	Increase ≥ 50%	Change of -49% to +49%
A	Constitutional symptoms	None	Any	Any	Any
A	Circulating lymphocyte count	Normal	Decrease ≥ 50%	Increase ≥ 50%	Change of -49% to +49%
B	Platelet Count	≥ 100,000/mcL	≥ 100,000/mcL or ≥ 50% over BL	Decrease ≥ 50%	Change of -49% to +49%
B	Hemoglobin	≥ 11 g/dL	≥ 11 g/dL or ≥ 50% over BL	Decrease of ≥ 2 g/dL from BL	Increase < 11 g/dL or < 50% over BL, or decrease < 2 g/dL
B	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥ 50% on successive biopsies	No change in marrow infiltrate

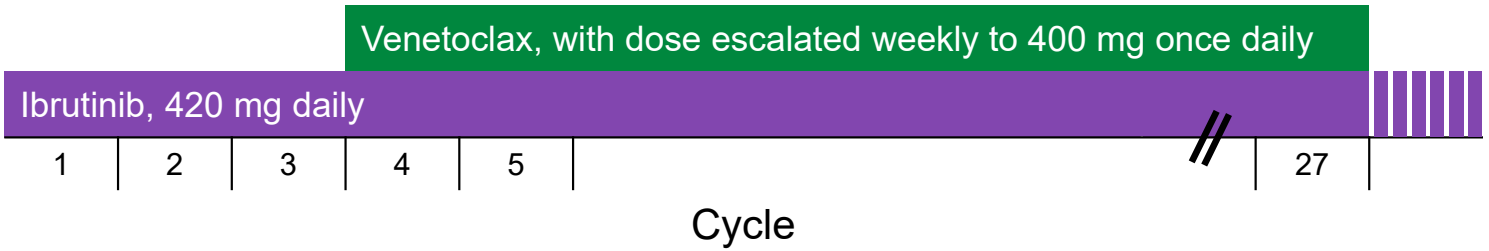
Am J Hematol. 2019;94:1266-87.

Jain et al. Phase II: Design

IBRUTINIB + VENETOCLAX IN UNTREATED CLL

80 patients with at least one high-risk genetic feature or who were ≥ 65 years of age with previously untreated CLL

Ibrutinib + Venetoclax



Primary Endpoint: Best Response (CR or CRi)

CLL = chronic lymphocytic leukemia
CR = complete remission
CRi = complete remission with incomplete count recovery

N Engl J Med. 2019;380(22):2095-103.

Jain et al. Phase II: Baseline Characteristics

IBRUTINIB + VENETOCLAX IN UNTREATED CLL

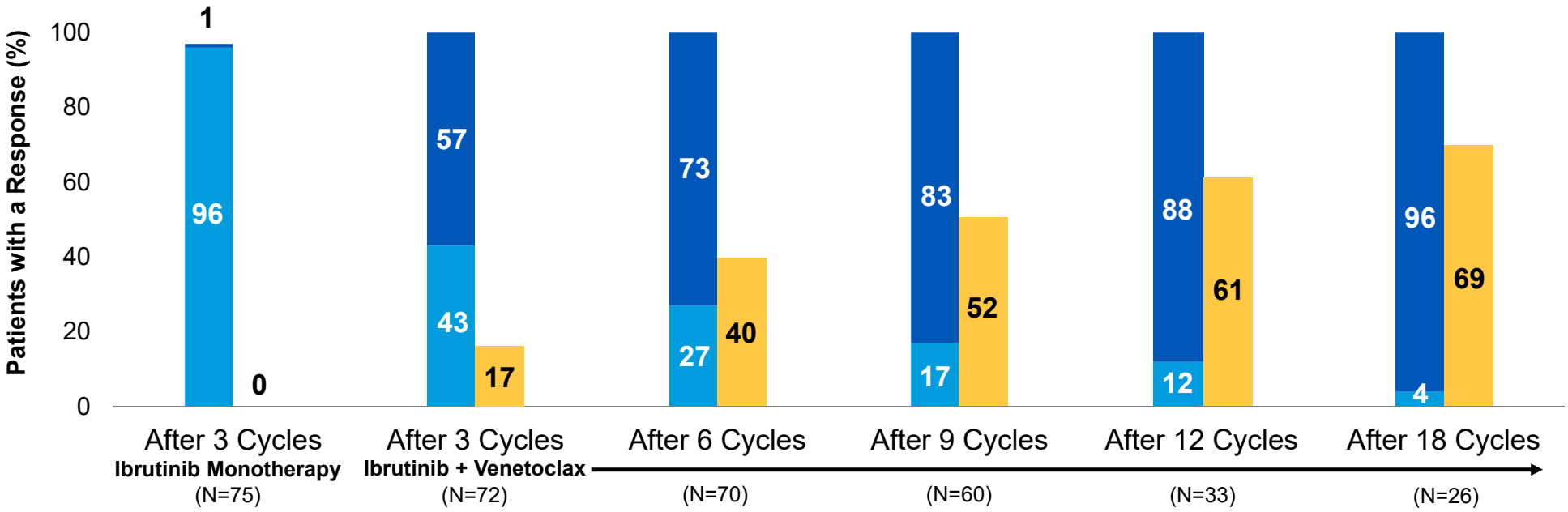
Characteristic	Ibrutinib + Venetoclax (N=80)
Age, median (range)	65 (26-83)
Age ≥ 65 years, n (%)	43 (54)
Male sex, n (%)	57 (71)
* Unmutated *IGHV*, n/tn (%)	63/76 (83)
* Del(11q), n (%)	20 (25)
* Del(17p), n (%)	14 (18)
* Mutated *TP35*, n/tn (%)	11/79 (14)

* Denotes high-risk genetic alteration

N Engl J Med. 2019;380(22):2095-103.

Jain et al. Phase II: Outcomes

IBRUTINIB + VENETOCLAX IN UNTREATED CLL



- Complete remission with or without normal blood count recovery (CR or CRi)
- Partial remission (PR)
- Undetectable minimal residual disease (MRD) in bone marrow

N Engl J Med. 2019;380(22):2095-103.

Jain et al. Phase II: Key Takeaways

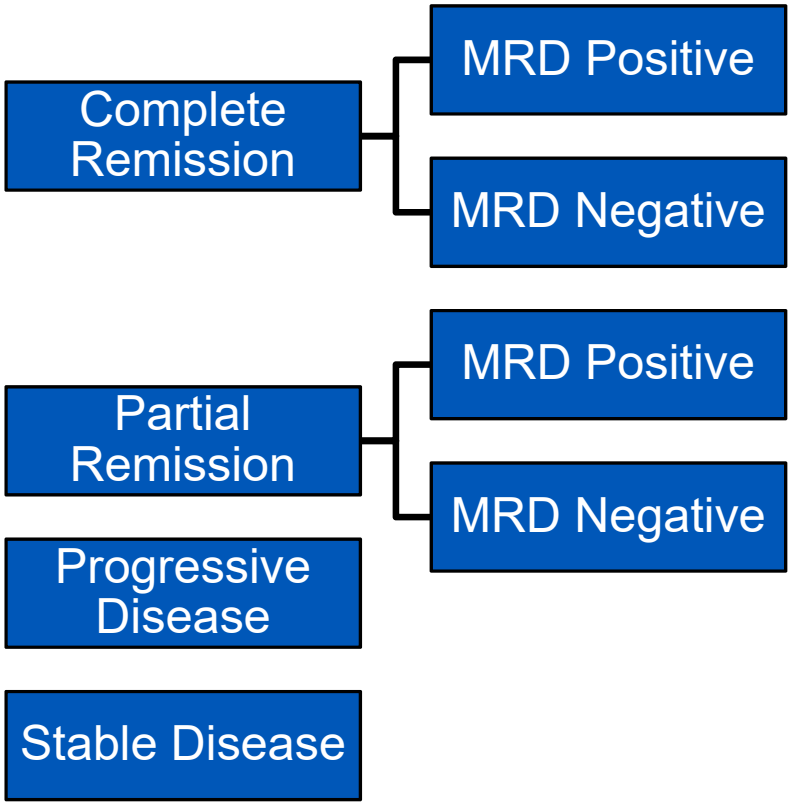
IBRUTINIB+VENETOCLAX IN UNTREATED CLL

- After 12 cycles, 88% of patients were in complete remission or complete remission with incomplete count recovery, and 61% were in remission with undetectable MRD
  - Substantially better than what is reported in the literature for ibrutinib or venetoclax monotherapy or chemoimmunotherapy
  - Saw benefit across all genetic subgroups
- No new safety concerns were noted in the study
- This combination is not yet approved for use
- Additional combination studies in the frontline setting currently recruiting

N Engl J Med. 2019;380(22):2095-103.

Chronic Lymphocytic Leukemia

ASSESSING TREATMENT OUTCOMES

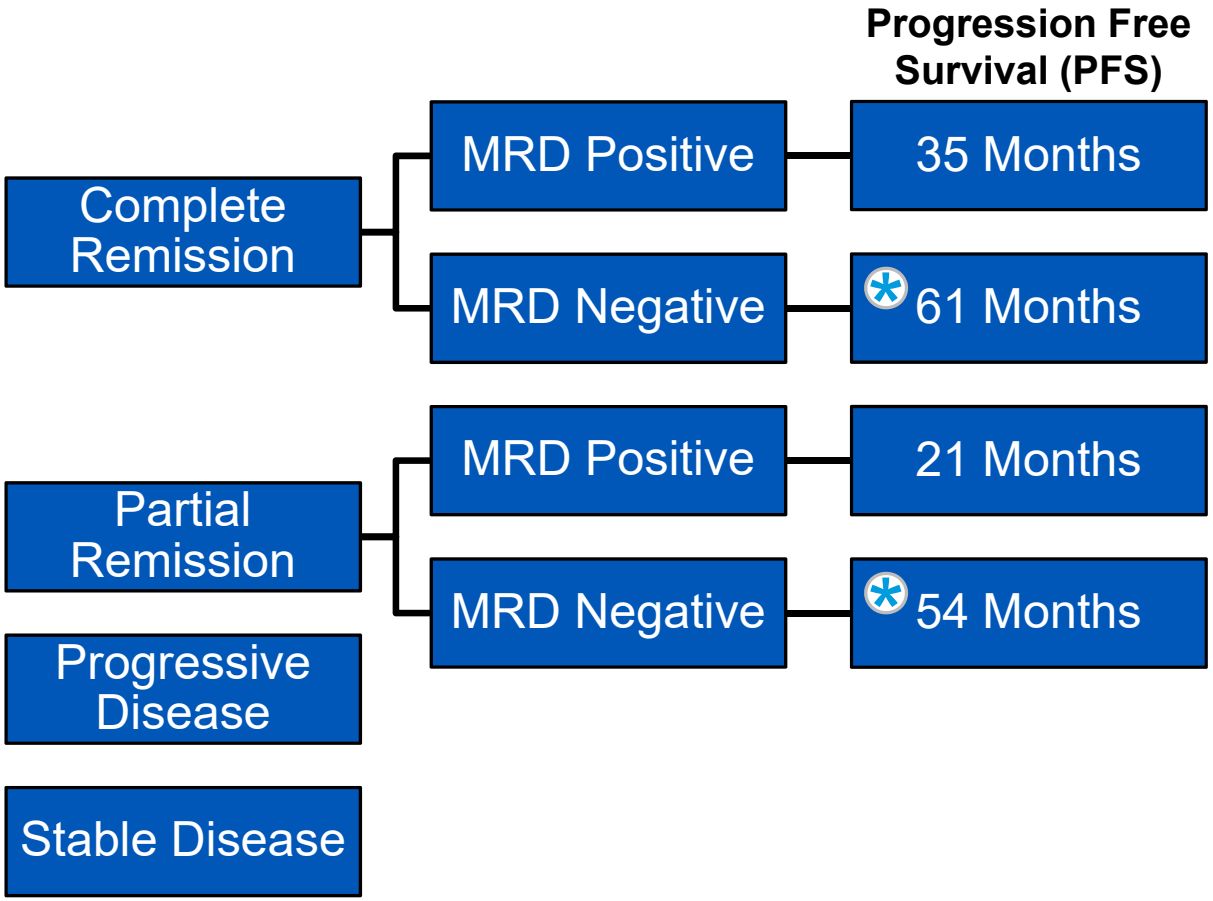


- Minimal residual disease (MRD) is assessed using sensitive multicolor flow cytometry, PCR, or next-generation sequencing
  - Definition: < 1 CLL cell detectable per 10,000 leukocytes
- Therapies that eradicate MRD usually result in improved long-term clinical outcomes

Am J Hematol. 2019;94:1266-87.
Blood. 2019;134(22):1951-9.

Chronic Lymphocytic Leukemia

ASSESSING TREATMENT OUTCOMES

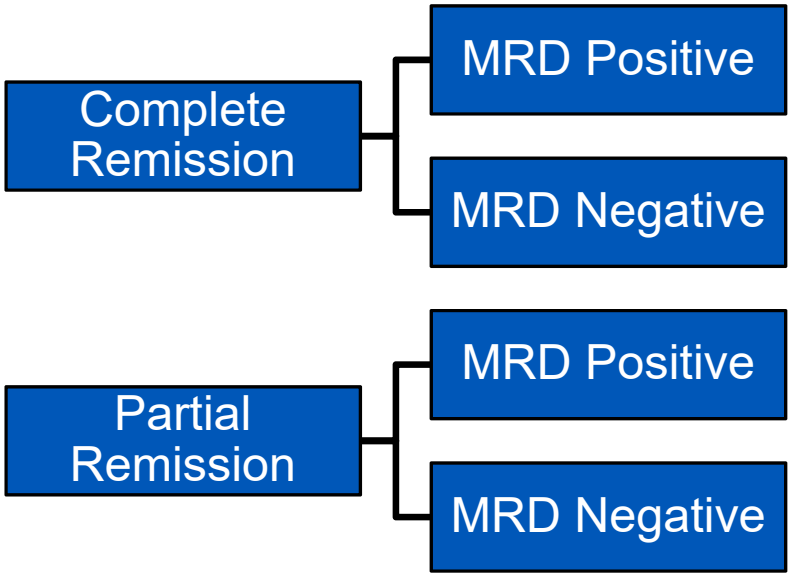


* Median PFS did not differ significantly between MRD-negative CR and MRD-negative PR

J Clin Oncol. 2016;34:3758-65.

Chronic Lymphocytic Leukemia

ASSESSING TREATMENT OUTCOMES



- MRD negativity correlates with both progression free survival and overall survival
- Greatest impact of MRD negativity in patients receiving frontline treatment
  - 10-year PFS of 65% vs 10%
  - 10-year OS of 70% vs 30%

Blood. 2016;128(24):2770-3.

Bruton Tyrosine Kinase (BTK) Inhibitors

IBRUTINIB: ADVERSE EFFECTS

Musculoskeletal Complaints

- In clinical trials ~20% of patients developed arthralgias
- In a retrospective, real-world analysis, arthralgia was the most common toxicity leading to treatment discontinuation
- Acetaminophen or short pulses of prednisone are preferred to treatment with NSAIDs

Blood. 2019;133(12):1298-1307.

Bruton Tyrosine Kinase (BTK) Inhibitors

IBRUTINIB: ADVERSE EFFECTS

Diarrhea

- Common
- Often self-limited
- Treat with loperamide as needed

Rash

- Typically low grade, but may be bothersome
- Often self-limited
- Treat with topical steroids or oral antihistamines as needed

Hypertension

- Reported in up to 20% of patients
- Incidence remains stable over time
- Ibrutinib-related HTN associated with increased MACE
- Monitor and treat hypertension

Pneumonitis

- Rare but life-threatening
- Treat with systemic corticosteroids through resolution
- Permanently discontinue ibrutinib

Blood. 2019;133(12):1298-307.
Blood. 2019;134(22):1919-28.

