The NEW ENGLAND JOURNAL of MEDICINE

Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia

T.D. Shanafelt, X.V. Wang, N.E. Kay, C.A. Hanson, S. O'Brien, J. Barrientos, D.F. Jelinek, E. Braggio, J.F. Leis, C.C. Zhang, S.E. Coutre, P.M. Barr, A.F. Cashen, A.R. Mato, A.K. Singh, M.P. Mullane, R.F. Little, H. Erba, R.M. Stone, M. Litzow, and M. Tallman

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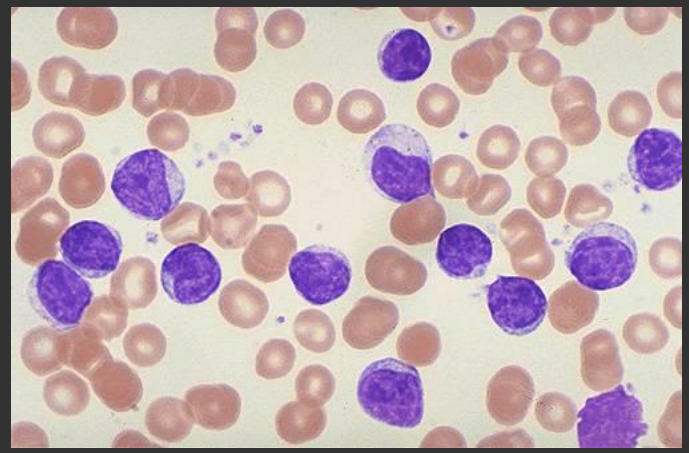
OBJECTIVES

- Discuss background information and the pathophysiology of chronic lymphocytic leukemia (CLL)
- Look at the current treatment guidelines for CLL
- Compare ibrutinib–rituximab and chemoimmunotherapy for the treatment of CLL
- Explore Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia
- Questions and answers

CHRONIC LYMPHOCYTIC LEUKEMIA

- CLL is the most common adult leukemia and accounts for up to 35% of all leukemias and 1.3% of all cancers
- Cancer starts in the lymphocytes (WBCs) in the bone marrow and then goes into the blood
- In this chronic form, cells often build up slowly so many people don't have symptoms for a few years. Over time, the cells grow and spread to other parts of the body including the lymph nodes, liver, and spleen
- There are two types of CLL



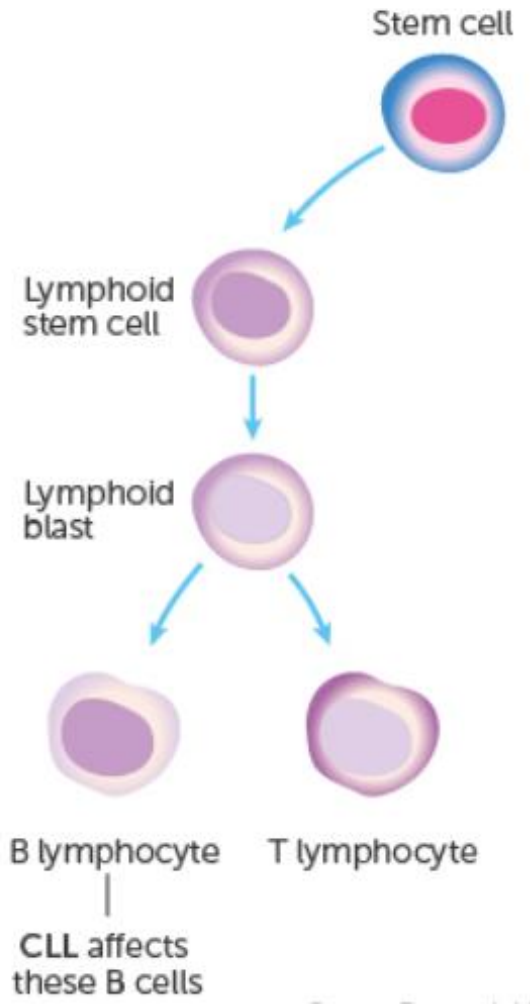
Cllbiomarkers.com. (2019). Chronic Lymphocytic Leukemia Symptoms, Survival Rate, & Staging. [online] Available at: https://www.cllbiomarkers.com/chronic-lymphocytic-leukemia/index.html [Accessed 24 Sep. 2019].
Cancer.org. (2019). What is chronic lymphocytic leukemia. [online] Available at: https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/what-is-cll.html [Accessed 24 Sep. 2019].

TYPES OF CLL

- Chronic CLL grows very slowly and it may take a long time before the patient needs treatment
- Acute CLL grows faster and is a more serious disease
- The leukemia cells from these 2 types look alike but lab tests can tell the difference between them
- The tests look for proteins called ZAP-70 and CD38. If the CLL cells have low amounts of these proteins, the leukemia tends to grow more slowly and have better long-term outcomes

Cllbiomarkers.com. (2019). Chronic Lymphocytic Leukemia Symptoms, Survival Rate, & Staging. [online] Available at: https://www.cllbiomarkers.com/chronic-lymphocytic-leukemia/index.html [Accessed 24 Sep. 2019].
Cancer.org. (2019). What is chronic lymphocytic leukemia. [online] Available at: https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/what-is-cll.html [Accessed 24 Sep. 2019].

PATHOPHYSIOLOGY



- In CLL, it's the lymphocyte white blood cells or B lymphocytes that are cancerous
- Abnormal WBCs are made in the bone marrow and can get into the bloodstream and circulate around the body
- They don't develop properly and don't provide protection from infection
- There are too many abnormal WBCs and the bone marrow can't produce healthy blood cells

Cancerresearchuk.org. (2017). About chronic lymphocytic leukemia. [online] Available at: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/about [Accessed 24 Sep. 2019].

EPIDEMIOLOGY

- The exact cause of CLL is not known
- Some risk factors are:
  - Age > 50
  - Electromagnetic radiation exposure
  - Having a first-degree relative with it
  - Being male
  - Being from North America or Europe

Cancer.org. (2019). Risk factors for chronic lymphocytic leukemia. [online] Available at: https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/causes-risks-prevention/risk-factors.html [Accessed 24 Sep.2019]
Cancerresearchuk.org. (2017). About chronic lymphocytic leukemia. [online] Available at: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/about [Accessed 24 Sep. 2019].

STATISTICS ABOUT CLL

- In the US, the number of estimated new cases of both types combined in 2019 is 20,720 which makes up 1.2% of all new cancer cases
- The estimated number of deaths is 3,930 which makes up about 0.6% of all cancer deaths
- The percent surviving 5 years is 85.1%
- CLL is more common in adults, particularly white men
- The median age at diagnosis is 70 years old

Seer.cancer.gov. (2019). Cancer stat facts: CLL. [online] Available at: https://seer.cancer.gov/statfacts/html/clyl.html [Accessed 24 Sep. 2019]

HOW CLL IS DIAGNOSED

- CLL often presents without symptoms and is diagnosed incidentally through blood work
- The diagnosis of CLL requires ≥5 x 10^9/L B lymphocytes in the peripheral blood for ≥3 months
- Cloning of B cells should be confirmed by flow cytometry
- Symptoms usually develop slowly

Mayoclinic.org. (2019). Diagnosis of chronic lymphocytic leukemia. [online] Available at: https://www.mayoclinic.org/diseases-conditions/chronic-lymphocytic-leukemia/diagnosis-treatment/drc-20352433 [Accessed 24 Sep. 2019]

CLINICAL PRESENTATION

- Symptoms include:
  - Fatigue
  - Unexplained weight loss or early satiety
  - Pyrexia
  - Lymphadenopathy
  - Organomegaly
  - Hyperhidrosis & night sweats
  - Infections (especially recurring infections)
  - Abnormal bruising

Mayoclinic.org. (2019). Symptoms of chronic lymphocytic leukemia. [online] Available at: https://www.mayoclinic.org/diseases-conditions/chronic-lymphocytic-leukemia/symptoms-causes/syc-20352428 [Accessed 24 Sep. 2019]

RAI STAGING SYSTEM

- Rai staging is based on lymphocytosis. Patients must have a high number of lymphocytes in their blood and bone marrow not linked to another cause.
- For the diagnosis of CLL, the overall lymphocyte count doesn't have to be high but the patient must have at least 5,000/mm^3 monoclonal lymphocytes
- Monoclonal means that the cancer cells all came from one original cell. This causes them to have the same chemical pattern which can be seen with testing

Cancer.org. (2019). How is chronic lymphocytic leukemia staged. [online] Available at: https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/detection-diagnosis-staging/staging.html [Accessed 24 Sep.2019]

RAI STAGING SYSTEM CONT.

Rai Stage	Findings
0	Lymphocytosis; no enlargement of the lymph nodes, spleen, or liver; red blood cell and platelet counts are near normal
I	Lymphocytosis; enlarged lymph nodes; spleen and liver are not enlarged; red blood cell and platelet counts are near normal
II	Lymphocytosis; enlarged spleen (and maybe an enlarged liver); lymph nodes may or may not be enlarged; red blood cell and platelet counts are near normal
III	Lymphocytosis; lymph nodes, spleen, or liver may or may not be enlarged; red blood cell counts are low (anemia); platelet counts are near normal
IV	Lymphocytosis; enlarged lymph nodes, spleen, or liver; red blood cell counts may be low or near normal; platelet counts are low (thrombocytopenia)

Cancer.org. (2019). H
staged. [online] Avail
https://www.cancer.c
leukemia/detection-c
[Accessed 24 Sep.201

TREATMENT INITIATION

Rai Stage	General Practice
0	Not generally indicated
1/2	Possible
3/4	Yes
Active or progressive disease	Yes
Without active or progressive disease	No

Cllbiomarkers.com. (2019). Chronic Lymphocytic Leukemia Symptoms, Survival Rate, & Staging. [online] Available at: https://www.cllbiomarkers.com/chronic-lymphocytic-leukemia/index.html [Accessed 24 Sep. 2019].

ACTIVE DISEASE

- Patients with CLL may present with a markedly elevated leukocyte count
- However, leukostasis rarely occurs in patients with CLL
- The absolute lymphocyte count should not be used as the sole indicator for treatment
- Treatment is indicated when a patient develops symptomatic or progressive disease (summarized as "active disease"). Active disease should be clearly documented to initiate therapy. At least 1 of the following points of criteria should be met:

Cllbiomarkers.com. (2019). Chronic Lymphocytic Leukemia Symptoms, Survival Rate, & Staging. [online] Available at: https://www.cllbiomarkers.com/chronic-lymphocytic-leukemia/index.html [Accessed 24 Sep. 2019].

CRITERIA FOR ACTIVE DISEASE

Location	Criteria
Bone marrow	•Development or worsening of anemia and/or thrombocytopenia •Platelet counts <100 x 10^9/L may remain stable over a long period •Does not automatically require therapeutic intervention
Spleen	Spleen ≥6 cm below the left costal margin or progressive or symptomatic splenomegaly
Lymph nodes	Nodes ≥10 cm in longest diameter or progressive or symptomatic lymphadenopathy
Lymphocytes	Progressive lymphocytosis: increase ≥50% over a 2-month period, or lymphocyte doubling time (LDT) <6 months •Obtained by extrapolation of absolute lymphocyte count •Exclude factors contributing to lymphocytosis other than CLL (eg, infection, steroid administration)

Cllbiomarkers.com. (2019). Chronic Lymphocytic Leukemia Symptoms, Survival Rate, & Staging. [online] Available at: https://www.cllbiomarkers.com/chronic-lymphocytic-leukemia/index.html [Accessed 24 Sep. 2019].

CRITERIA FOR ACTIVE DISEASE CONT.

Location	Criteria
Clinical	Disease-related symptom as defined by any of the following: •Unintentional weight loss of ≥10% within the previous 6 months •Significant fatigue •Fevers ≥100.5°F or 38.0°C for ≥2 weeks without evidence of infection •Night sweats for ≥1 month without evidence of infection
Other	•Autoimmune complications, poorly responsive to steroids •Symptomatic or functional extranodal involvement

Cllbiomarkers.com. (2019). Chronic Lymphocytic Leukemia Symptoms, Survival Rate, & Staging. [online] Available at: https://www.cllbiomarkers.com/chronic-lymphocytic-leukemia/index.html [Accessed 24 Sep. 2019].

TREATMENT OF CLL

- Many people live a long time with CLL but it's generally difficult to cure
- Early treatment hasn't been shown to help people live longer
- Doctors often advise waiting until disease progression or bothersome symptoms appear
- If treatment is needed, the patient's age, overall health and prognostic factors should be taken into account

Cancer.org. (2019). Typical treatment of chronic lymphocytic leukemia. [online] Available at: https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/treating/treatment-by-risk-group.html [Accessed 24 Sep. 2019].
Cancer.gov. (2019). Drugs approved for leukemia. [online] Available at: https://www.cancer.gov/about-cancer/treatment/drugs/leukemia#7 [Accessed 24 Sep. 2019].

INITIAL TREATMENT OF CLL

- There are many different treatment options for CLL. This includes chemotherapy, monoclonal antibodies, targeted drugs and different combinations of these

First line

- Targeted drug ibrutinib (Imbruvica)

Other Commonly Used Treatments

- Venetoclax (Venclexta) alone or with rituximab
- Bendamustine and rituximab
- High-dose prednisone and rituximab
- FCR: fludarabine, cyclophosphamide, and rituximab
- PCR: pentostatin, cyclophosphamide, and rituximab
- CVP: cyclophosphamide, vincristine, prednisone
- Chlorambucil and rituximab
- Obinutuzumab (Gazyva) alone or with rituximab
- Alemtuzumab (Campath) alone or with rituximab

Cancer.org. (2019). Typical treatment of chronic lymphocytic leukemia. [online] https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/treating/treatment-by-risk-group.html [Accessed 24 Sep. 2019].

OTHER TREATMENT OPTIONS

- Radiation or surgery
- Leukapheresis to lower blood counts quickly before chemo has a chance to work
- Stem cell transplant for high-risk patients
- Second-line treatment if the initial treatment no longer works or the disease comes back. An alternate first line option is often tried

Cancer.org. (2019). Typical treatment of chronic lymphocytic leukemia. [online] Available at: https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/treating/treatment-by-risk-group.html [Accessed 24 Sep. 2019].
Cancer.gov. (2019). Drugs approved for leukemia. [online] Available at: https://www.cancer.gov/about-cancer/treatment/drugs/leukemia#7 [Accessed 24 Sep. 2019].

- Preferred treatment for CLL
- A small-molecule, irreversible, covalent inhibitor of Bruton's tyrosine kinase which is a signaling molecule of the B-cell antigen and cytokine receptor pathway
- The recommended dose is 560 mg orally daily
- Also used for the treatment of mantle cell lymphoma, Waldenström's macroglobulinemia, Marginal zone lymphoma, and Chronic graft versus host disease

Imbruvica (Ibrutinib): First Drug Approved for the Treatment of Patients with Waldenström's Macroglobulinemia. Am Health Drug Benefits. 2016 Mar; 9(Spec Feature): 89–92.
Imbruvica.com. (2019). Prescribing information. [online] Available at:https://www.imbruvica.com/docs/librariesprovider7/default-document-library/prescribing-information.pdf [Accessed 24 Sep. 2019]

CHEMOTHERAPY

FCR

- Fludarabine: a purine analog which is an antimetabolite that mimics the structure of metabolic purines
- Cyclophosphamide: an alkylating agent more specifically a nitrogen mustard that sticks to one of the cancer cell's DNA strands
- Rituximab: a CD20 directed cytolytic antibody that interferes with the growth and spread of cancer cells

Cancerresearchuk.org. (2019) Cyclophosphamide. [online] Available at: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/drugs/cyclophosphamide [Accessed 24 Sep. 2019]
Drugs.com. (2019) Rituxan. [online] Available at: https://www.drugs.com/rituxan.html

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ORIGINAL ARTICLE

Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia

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T.D. Shanafelt, X.V. Wang, N.E. Kay, et al. Ibrutinib–rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med* 2019;381:432-43. DOI: 10.1056/NEJMoa1817073

STUDY DESIGN

- Multicenter, open label, randomized, phase 3 trial (E1912) through the National Clinical Trials Network (NCTN)
- Evaluated the efficacy and safety of treatment with ibrutinib in combination with six cycles of rituximab, as compared with fludarabine–cyclophosphamide–rituximab
- In previously untreated patients with CLL who were 70 years of age or younger

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TRIAL PARTICIPANTS

- Participants were previously untreated patients with CLL or the small lymphocytic lymphoma (SLL) subtype of CLL who were ≤ 70 years old and who would be appropriate candidates for treatment according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Working Group criteria

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INCLUSION CRITERIA

Biopsy-proven small lymphocytic leukemia or ≥5x10^9 lymphocytes (5x10^9/L) in the peripheral blood and immunophenotype (performed locally) consistent with CLL defined as:

- The predominant population of lymphocytes share both B-cell antigens [CD19, CD20 (typically dim expression), or CD23] as well as CD5 in the absence of other pan-T-cell markers
- Clonality as evidenced by κ or λ light chain restriction (typically dim immunoglobulin expression)
- Negative FISH analysis for t(11;14)(IgH/CCND1) on peripheral blood or tissue biopsy or negative immunohistochemical stains for cyclin D1 staining on involved tissue biopsy

No prior chemotherapy, BTK inhibitor therapy, or monoclonal anti-body therapy for treatment of CLL or SLL

No previous or current use of glucocorticoids for autoimmune complications that have developed since the initial diagnosis of CLL

No radiation therapy < 4 weeks before registration

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INCLUSION CRITERIA CONT.

- Not be on any other systemic immunosuppressant therapy within 28 days of the first dose of study drug
- Age ≥ 18 years and <70 years
- Eastern Cooperative Oncology Group Performance Status 0-2
- Life expectancy of ≥ 12 months
- No deletion of 17p13 on cytogenetic analysis by FISH
- No active hemolytic anemia requiring immunosuppressive therapy or other pharmacologic treatment
- No other active primary malignancy requiring treatment

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INCLUSION CRITERIA CONT.

- HIV patients are eligible meeting their own criteria
- Women must not be pregnant or breast-feeding
- Women of childbearing potential and sexually active males are advised to use an accepted and effective method of contraception or abstain from sexual intercourse for 90 days after the last dose of study drug
- Not be receiving active systemic anticoagulation with warfarin. Patients must be off warfarin therapy for at least 30 days before enrollment
- Patients must not be vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug

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INCLUSION CRITERIA CONT.

Meeting the following required initial laboratory values obtained ≤14 days before registration:

- AST or ALT: ≤ 3.0 x upper limits of normal
- Bilirubin: ≤ 2.5 x upper limits of normal (unless due to Gilbert's disease). For those with a total bilirubin >2.5 x upper limit of normal, a direct bilirubin should be performed and must be <1.5 mg/dL for Gilbert's to be diagnosed
- CrCl: >40 mL/min
- PT/INR: <1.5 x upper limits of normal
- PTT (aPTT): <1.5 x upper limits of normal

Ability to tolerate FCR based therapy

Ability to swallow capsules

Ability to adhere to the study visit schedule and other protocol requirements

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EXCLUSION CRITERIA

- Congestive heart failure
- History of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months before registration
- Recent infections requiring systemic treatment
- Cerebral vascular accident or intracranial bleed within the last 6 months
- Infection with known chronic, active hepatitis C or B
- Any known bleeding disorders
- Clinically significant hepatic impairment
- Treatment with a strong CYP3A inhibitor
- Major surgery within 4 weeks of the first dose or minor surgery within 3 days of first dose

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EXCLUSION CRITERIA CONT.

- Other investigational agents
- Disease affecting GI function
- Prior resection of the stomach or small bowel
- Symptomatic inflammatory bowel disease
- Ulcerative colitis
- Partial or complete bowel obstruction

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TRIAL OVERSIGHT

- Designed and coordinated by the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG–ACRIN) Cancer Research Group in collaboration with the other NCTN Cooperative Groups
- The protocol was approved by the National Cancer Institute (NCI) central institutional review board and local institutional review boards
- The trial was conducted in accordance with the principles of the Declaration of Helsinki
- The trial was monitored twice annually by a standing data and safety monitoring board that included persons from both within and outside ECOG–ACRIN

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RANDOMIZATION AND TREATMENT

- After written informed consent, eligible participants underwent randomization which was stratified according to:
  - <60 years vs. 60 to 70 years
  - ECOG performance-status score (0 or 1 vs. ≥2; scores are on a 5-point scale, with higher numbers indicating greater disability)
  - Rai stage (0-II) or (III or IV)
  - The presence or absence of chromosome 11q22.3 deletion on fluorescence in situ hybridization analysis
- Patients were randomly assigned in a 2:1 ratio to receive either ibrutinib–rituximab or chemoimmunotherapy with fludarabine–cyclophosphamide-rituximab (FCR)

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TREATMENT PROTOCOL

- Ibrutinib–rituximab group: received ibrutinib (420 mg per day until disease progression or an unacceptable level of side effects occurred) and rituximab (50 mg/ m^2) of BSA on day 1 of cycle 2; 325 mg/ m^2 on day 2 of cycle 2; and 500 mg/m^2 on day 1 of cycles 3 through 7. Each cycle was 28 days
- Chemoimmunotherapy group: received 6 cycles of IV fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2) on days 1 through 3 with rituximab (50 mg/m^2 on day 1 of cycle 1; 325 mg/m^2 on day 2 of cycle 1; and 500 mg/m^2 on day 1 of cycles 2 through 6 every 28 days

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TREATMENT PROTOCOL CONT.

- Prophylaxis against *Pneumocystis jirovecii* (trimethoprim–sulfamethoxazole) and herpes zoster (valacyclovir) was given to all patients for 1 year after treatment initiation
- All patients received allopurinol (300 mg orally once daily) on days 1-14 of cycle 1. Patients treated with ibrutinib–rituximab also received allopurinol with treatment cycle 2 (the first cycle that included rituximab)

T.D. Shanafelt, X.V. Wang, N.E. Kay, et al. Ibrutinib–rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med* 2019;381:432-43. DOI: 10.1056/NEJMoa1817073

ASSESSMENTS OF SAFETY AND RESPONSE

- Bone marrow biopsies and computed tomographic (CT) scans of the chest, abdomen, and pelvis were performed at enrollment and at 12 months to assess response
- Minimal residual disease (MRD) assays were performed at the time of the 12-month response evaluation and at 24 and 36 months after randomization

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STATISTICAL ANALYSIS

- The primary end point was progression-free survival, which was defined as the time from randomization to documented CLL progression or death without documented progression
- Patients alive without documented progression had their data censored at the last disease assessment
- The trial was designed to have 80% power to detect a hazard ratio for progression or death of 0.67 or less
- Overall survival, time from randomization to death from any cause, was a secondary end point and was to be tested only if the result in the progression-free survival analysis crossed the efficacy boundary
- Patients who were alive had their data censored at the last date of contact

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STATISTICAL ANALYSIS CONT.

- Interim analyses for progression-free survival were planned to start at 24-27 months after full enrollment and annually until either the efficacy boundary was crossed or full information (203 events of progression or death) was reached
- The pre-specified boundary for the first interim analysis of progression-free survival was 2.807 on the z-statistic scale, which corresponded to a one-sided *P* value of 0.0025
- Interim analyses for overall survival were to start when the efficacy boundary for progression-free survival was crossed and to continue annually until early stopping criteria were met or full information (125 deaths) was reached

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STATISTICAL ANALYSIS CONT.

- Stratified log-rank tests were used to compare time-to-event distributions, hazard ratios were estimated with the use of stratified Cox proportional-hazards models, the frequency of response and incidence of adverse events were compared between the two groups with Fisher's exact test
- Descriptive statistics were used to summarize the characteristics of patients, time-to-event distributions were estimated with the Kaplan–Meier method
- The primary analysis was conducted in the intention-to-treat population, which included all the patients who had undergone randomization, regardless of eligibility or treatment status
- P values are two-sided, and 95% confidence intervals are presented

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Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Ibrutinib–Rituximab Group (N=354)	Chemoimmunotherapy Group (N=175)	Total (N=529)
Age			
Mean	56.7±7.5	56.7±7.2	56.7±7.4
≥60 yr — no. (%)	145 (41.0)	70 (40.0)	215 (40.6)
Sex — no. (%)			
Female	118 (33.3)	55 (31.4)	173 (32.7)
Male	236 (66.7)	120 (68.6)	356 (67.3)
Rai stage — no. (%)			
Low risk, 0	11 (3.1)	9 (5.1)	20 (3.8)
Intermediate risk, I or II	187 (52.8)	94 (53.7)	281 (53.1)
High risk, III or IV	156 (44.1)	72 (41.1)	228 (43.1)
ECOG performance-status score — no. (%)†			
0	226 (63.8)	109 (62.3)	335 (63.3)
1	119 (33.6)	63 (36.0)	182 (34.4)
2	9 (2.5)	3 (1.7)	12 (2.3)
$Beta_2$ microglobulin — mg/liter			
Mean	4.0±2.1	4.0±1.9	4.0±2.0
Median	3.6	3.4	3.6
Interquartile range	2.6–4.6	2.7–4.8	2.6–4.7
Dohner classification — no. (%)			
Chromosome 17p13 deletion‡	2 (0.6)	0	2 (0.4)
Chromosome 11q22.3 deletion	78 (22.0)	39 (22.3)	117 (22.1)
Trisomy 12	70 (19.8)	27 (15.4)	97 (18.3)
Normal	69 (19.5)	37 (21.1)	106 (20.0)
Chromosome 13q deletion	121 (34.2)	58 (33.1)	179 (33.8)
Other	14 (4.0)	14 (8.0)	28 (5.3)
IGHV mutation status — no./total no. (%)§			
Mutated	70/280 (25.0)	44/115 (38.3)	114/395 (28.9)
Unmutated	210/280 (75.0)	71/115 (61.7)	281/395 (71.1)

T.D. Shanafelt, X.V. Wang, N.E. Kay, et al. Ibrutinib–rituximab versus chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med* 201[illegible] 10.1056/NEJMoa1817073

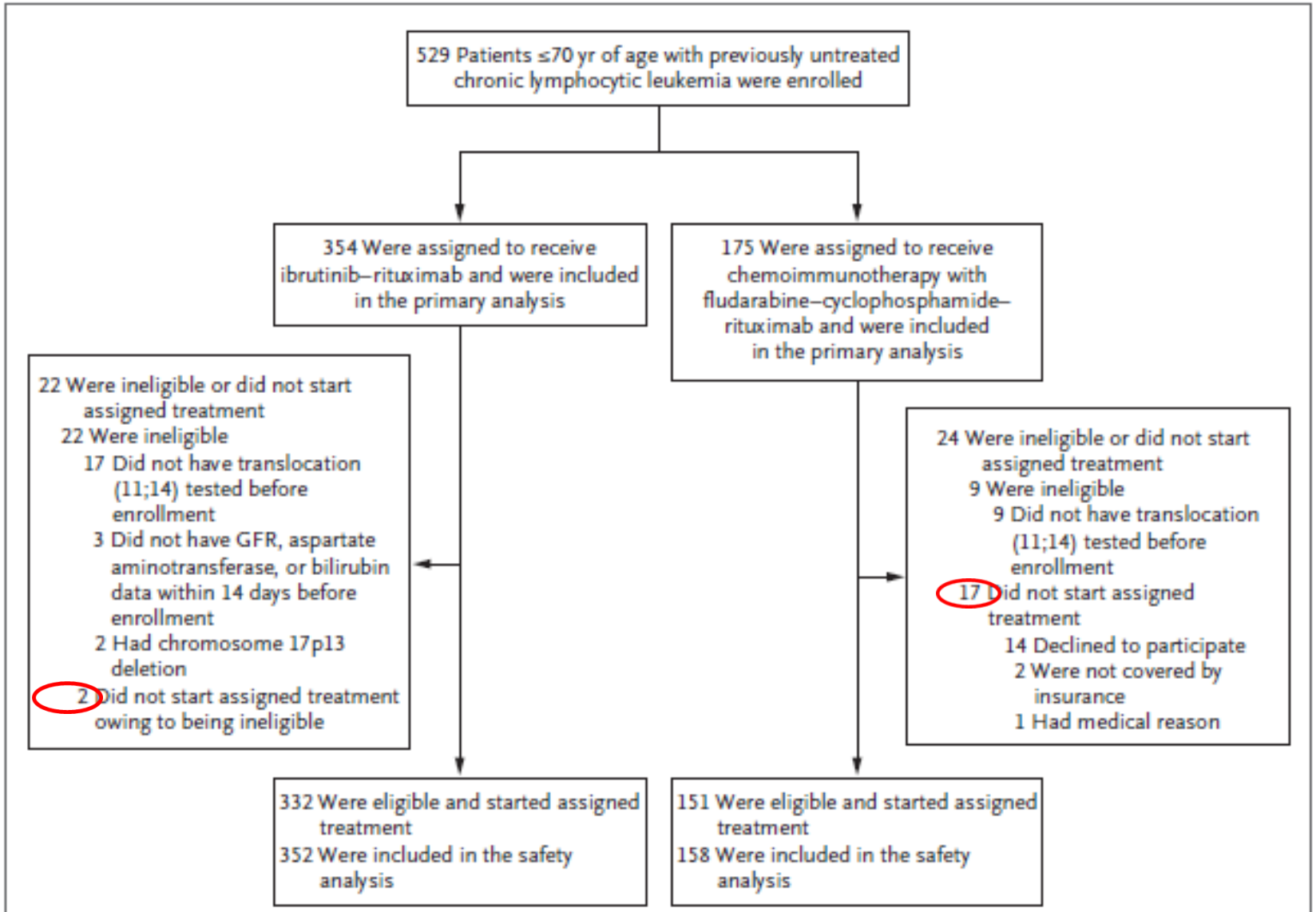
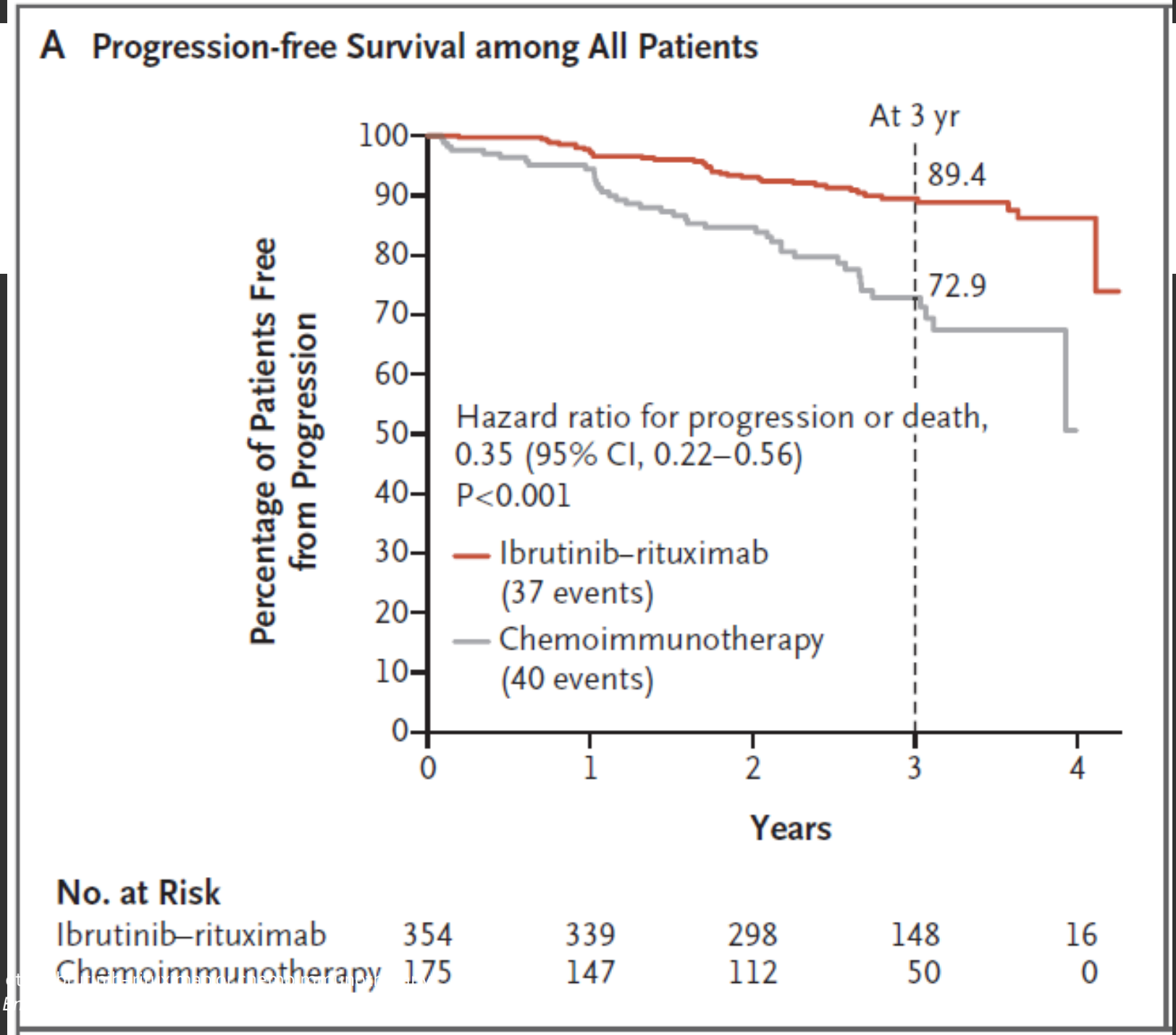


Figure 1. Enrollment, Randomization, and Follow-up.

All 529 patients who had been enrolled in the trial were included in the intention-to-treat analysis. Of the 529 patients who underwent randomization, 31 (5.9%) were determined to have not met the eligibility criteria and were excluded from the analysis of eligible patients who started assigned therapy (see the Supplementary Appendix). The safety analysis included 510 patients who started the assigned protocol therapy. GFR denotes glomerular filtration rate.

T.D. Shanafelt, X.V. Wang, N.E. Kay, et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Engl J Med 2019;381:432-43. DOI: 10.1056/NEJMoa1817073



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for chronic lymphocytic leukemia. *N E*
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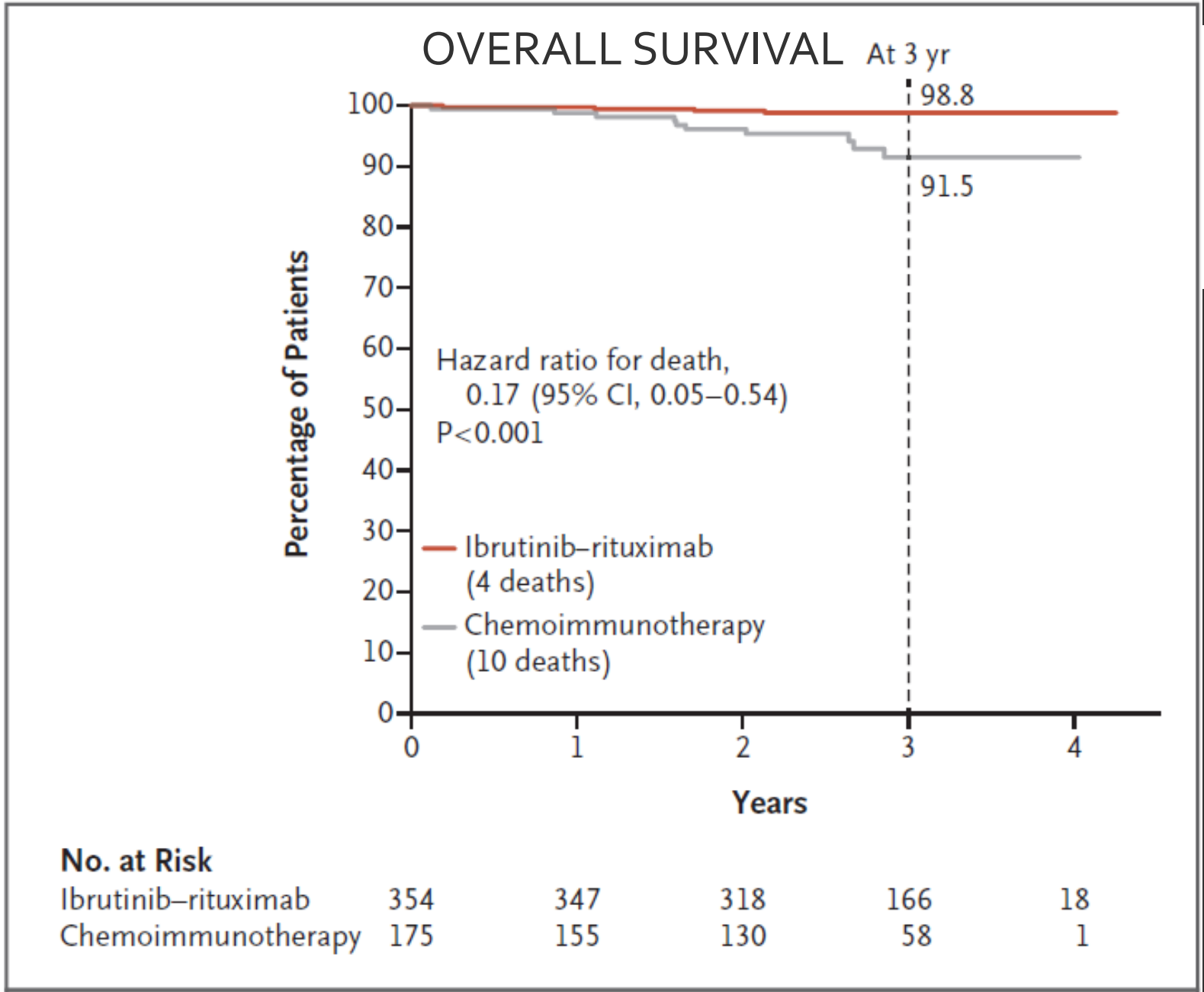
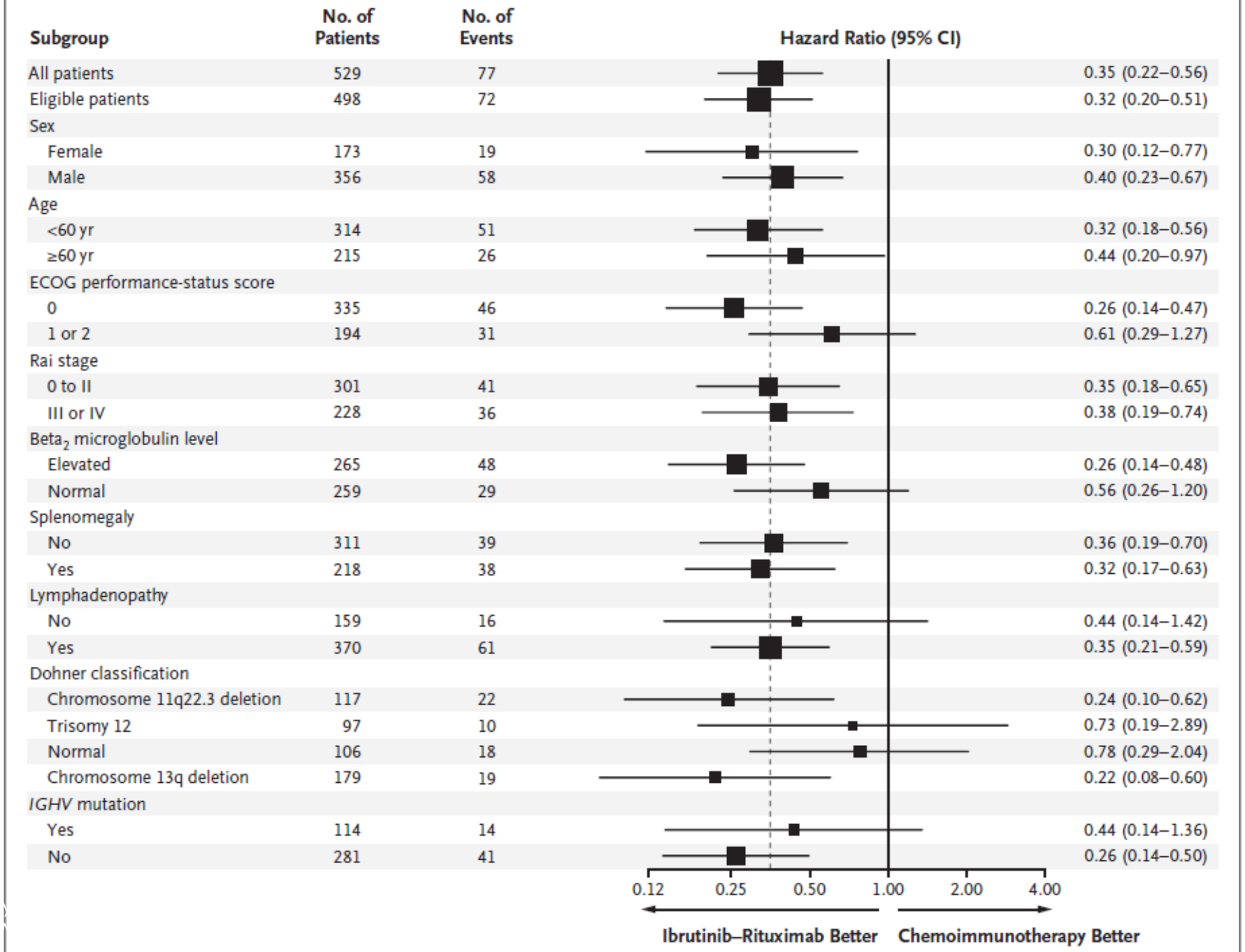


Figure 3. Overall Survival (Intention-to-Treat Population).

T.D. Shanafelt, X.V. Wang, N.E. Kay et al. Figure 3. Ibrutinib–Rituximab versus Chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med* 2019;381:432-43. DOI: 10.1056/NEJMoa1817073

C Subgroup Analysis



Subgroup	No. of Patients	No. of Events	Hazard Ratio (95% CI)
All patients	529	77	0.35 (0.22–0.56)
Eligible patients	498	72	0.32 (0.20–0.51)
Sex			
Female	173	19	0.30 (0.12–0.77)
Male	356	58	0.40 (0.23–0.67)
Age			
<60 yr	314	51	0.32 (0.18–0.56)
≥60 yr	215	26	0.44 (0.20–0.97)
ECOG performance-status score			
0	335	46	0.26 (0.14–0.47)
1 or 2	194	31	0.61 (0.29–1.27)
Rai stage			
0 to II	301	41	0.35 (0.18–0.65)
III or IV	228	36	0.38 (0.19–0.74)
$Beta_2$ microglobulin level			
Elevated	265	48	0.26 (0.14–0.48)
Normal	259	29	0.56 (0.26–1.20)
Splenomegaly			
No	311	39	0.36 (0.19–0.70)
Yes	218	38	0.32 (0.17–0.63)
Lymphadenopathy			
No	159	16	0.44 (0.14–1.42)
Yes	370	61	0.35 (0.21–0.59)
Dohner classification			
Chromosome 11q22.3 deletion	117	22	0.24 (0.10–0.62)
Trisomy 12	97	10	0.73 (0.19–2.89)
Normal	106	18	0.78 (0.29–2.04)
Chromosome 13q deletion	179	19	0.22 (0.08–0.60)
IGHV mutation			
Yes	114	14	0.44 (0.14–1.36)
No	281	41	0.26 (0.14–0.50)

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SAFETY

Table 2. Adverse Events of Grade 3 or Higher Reported in More Than 2% of Patients in Either Group.*

Event	Ibrutinib–Rituximab Group (N=352)			Chemoimmunotherapy Group (N=158)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
	number of patients (percent)					
Hematologic event						
Anemia	17 (4.8)	0	0	17 (10.8)	6 (3.8)	0
Hemolysis	2 (0.6)	0	0	3 (1.9)	1 (0.6)	0
Leukocytosis	61 (17.3)	1 (0.3)	0	12 (7.6)	0	0
Lymphocyte count decreased	10 (2.8)	0	0	43 (27.2)	32 (20.3)	0
Lymphocyte count increased	77 (21.9)	0	0	12 (7.6)	0	0
Neutropenia	38 (10.8)	52 (14.8)	0	35 (22.2)	36 (22.8)	0
Platelet count decreased	9 (2.6)	6 (1.7)	0	16 (10.1)	8 (5.1)	0
White-cell count decreased	7 (2.0)	1 (0.3)	0	35 (22.2)	23 (14.6)	0
Nonhematologic event						
Infection†	28 (8.0)	4 (1.1)	1 (0.3)	9 (5.7)	5 (3.2)	1 (0.6)
Febrile neutropenia	8 (2.3)	0	0	21 (13.3)	4 (2.5)	0
Alanine aminotransferase increased	6 (1.7)	2 (0.6)	0	1 (0.6)	0	0
Aspartate aminotransferase increased	9 (2.6)	0	0	2 (1.3)	0	0
Hyperglycemia	12 (3.4)	2 (0.6)	0	8 (5.1)	0	0
Hyponatremia	11 (3.1)	0	0	3 (1.9)	0	0
Atrial fibrillation	9 (2.6)	2 (0.6)	0	1 (0.6)	1 (0.6)	0
Arthralgia	17 (4.8)	0	0	2 (1.3)	0	0
Hypertension	65 (18.5)	1 (0.3)	0	13 (8.2)	0	0
Fatigue	7 (2.0)	0	0	4 (2.5)	0	0
Maculopapular rash	11 (3.1)	0	0	8 (5.1)	0	0
Diarrhea	15 (4.3)	0	0	2 (1.3)	0	0
Any event, according to worst grade	204 (58.0)	75 (21.3)	3 (0.9)	57 (36.1)	67 (42.4)	2 (1.3)

- There was a lower incidence of grade 3-4 neutropenia and infection complications in IR
- There was a higher incidence of grade 3-4 hypertension and cardiac toxic effects in the IR
- Afib occurred in 7.4% of IR patients and 3.2% of chemo patients
- The 10 deaths in the chemo group- cause was CLL or therapy related as a majority
- The 4 deaths in the IR group- cause was CLL in a minority of patients

CONCLUSION

- In patients 70 years or younger who had previously untreated CLL or SLL, ibrutinib–rituximab treatment was superior to chemoimmunotherapy with FCR with respect to progression-free survival and overall survival
- The risk of progression or death was 65% lower and the risk of death was 83% lower with IR than with chemo
- There were similar rates of adverse events of grade 3 or higher in the two groups
- The long-term follow-up for survival will be important
- Atrial fibrillation during ibrutinib therapy should be noted along with risk factors
- The benefit of combining ibrutinib with rituximab is unclear
- Although promising in effectiveness, the price and potential for long term effects and resistance is something to take note of

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ANALYSIS AND RELEVANCE

- Strengths: A larger sample size, appropriate age group, and relevant to current oncology practice
- Weaknesses: A 2:1 ratio of patients, increased bias in open-label study, the expensive cost potential with Ibrutinib
- Clinical implication: An improvement in the way CLL is treated. Patients have a higher chance of progression-free survival and overall survival

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ADVERSE EVENTS AND COST

- Similar AE profile
- Cost for Ibrutinib- 560 mg oral tablet: $12,613 for 28 tablets
- Cost for FCR: $38,000 per year

Nerdwallet.com. (2016). How much does chemotherapy cost. [online] Available at:https://www.nerdwallet.com/blog/health/how-much-does-chemotherapy-cost/ [Accessed 25 Sep. 2019]
Schmier J, Ogden K, Nickman N, et al. Costs of providing infusion therapy for rheumatoid arthritis in a hospital-based infusion center setting. *Clin Ther*.2017;39:1600–1617

QUESTIONS?

Questions.https://www.parliament.nz/media/4552/question-mark-istock.jpg. 2019.

SUPPLEMENTARY INFORMATION

CRITERIA FOR TREATMENT AS DEFINED BY IWCLL 2008 GUIDELINES

- At least one of the following criteria:
  - Evidence of progressive marrow failure as manifested by the development of worsening anemia (Hg < 11 g/dl) and/or thrombocytopenia (Platelets < 100 x 10^9/L) that was not attributable to autoimmune hemolytic anemia or thrombocytopenia)
  - Symptomatic or progressive lymphadenopathy, splenomegaly, or hepatomegaly
  - Constitutional symptoms attributable to CLL, which include one or more of the following disease-related symptoms: weight loss ≥ 10% within the previous 6 months, grade 2 or 3 fatigue attributed to CLL, fevers >100.5° F for 2 weeks without evidence of infection, or clinically significant night sweats without evidence of infection
  - Progressive lymphocytosis (not due to the effects of corticosteroids) with an increase of >50% over a two--month period or an anticipated doubling time of less than six months

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ELIGIBILITY CRITERIA FOR PATIENTS WITH HIV INFECTION

- CD_4-positive cell count: ≥ Lower limit of institutional normal
- Viral load: <10,000 copies HIV RNA/mL (if not on anti-HIV therapy) OR <50 copies HIV RNA/mL (if on anti-HIV therapy)
- No evidence of hepatitis B or C
- No history of AIDS-defining condition

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CAUSES OF DEATH IN IBRUTINIB-RITUXIMAB GROUP

Ibrutinib-Rituximab	On study at time of death	Cause of Death	Baseline Characteristics					Savage therapy received
			Disease stage	11q deletion	Baseline CrCL	IGHV status	Baseline mutations on sequencing	
Patient 1	No	Progressive CLL	III	Yes	96.5	UM	TP53: p.P151S[1]	Rituximab
Patient 2	No	Metastatic lung cancer	IV	No	108.7	UM		Ibrutinib and Rituximab[4]
Patient 3	Yes (last dose before hospitalization and death)	Other cause: acute respiratory failure due to infection	II	No	91.2	M		None.
Patient 4	Yes	Unknown	IV	No	90.6	M		None.

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CAUSE OF DEATH IN FCR GROUP

FCR	On study at time of death	Cause of Death	Baseline Characteristics					Savage therapy received
			Disease stage	11q deletion	Baseline CrCL	IGHV status	Baseline mutations on sequencing	
Patient 1	No	Progressive CLL	II	No	91.2	M	No mutation	1.Bendamustine+Rituximab, 2.Rituximab, 3.Venetoclax
Patient 2	Yes	Infection, septic shock	IV	No	94.8			None
Patient 3	No	AML	I	Yes	90.6	UM		None
Patient 4	No	Progressive CLL and infection	II	No	94.5	UM	NOTCH1[2]: p.P2514Rfs4* TBL1XR1: p.V307L	None
Patient 5	No	Progressive CLL	II	No	94.8	UM	ATM: p.K2756* ATM: p.K2317* EGR2[3]: p.E356K	1.Ibrutinib, 2.Methylprednisolone + rituximab 3.Venetoclax 4.Methylprednisolone + Rituximab 5. CHOP
Patient 6	No	AML	II	Yes	94.5	UM		FCR
Patient 7	No	Metastatic colon cancer	II	Yes	95.1	UM		1. Folfox plus Avastin for colon cancer 2. Folfiri and Avastin for colon cancer
Patient 8	No	Drug overdose	III	Yes	92.5	UM		None
Patient 9	No	Lung cancer	I	Yes	95.8	UM		None (lung wedge resection)
Patient 10	No	Progressive CLL	IV	No	97.9	UM	DDX3X[4]: IVS2+2T>C SAMHD1: p.L431F SAMHD1: p.T138A	1. Rituximab 2. Bendamustine (1 cycle)