Clinical Decision Making in CLL: Efficacy Assessments

Learning Objectives

Understand the types of efficacy assessments used in clinical trials and routine practice

Identify how assessments aid in clinical decision making based on the type of CLL therapy administered

Efficacy Assessments Differ Between Routine Practice and Clinical Trials

Diagnostic test[1]	Routine practice	Clinical trial
History, physical examination	Always	Always
CBC and differential count	Always	Always
Marrow aspirate and biopsy	At cytopenia of uncertain cause	At CR or cytopenia of uncertain cause
Ultrasound of the abdomen*	Consider if previously abnormal	Not generally indicated
Assessment of MRD	Not generally indicated	Indicated based on study design and regimen studied[2] (BCL-2i or combinational therapies)[3]
CT scans of chest, abdomen, and pelvis	Not generally indicated	Recommended if previously abnormal and otherwise with a CR or PR

Timing of assessment

- For **fixed-duration** therapies, the assessment should be performed at least **2 months after completion of therapy**[1,3]
- For **continuous** therapies, the assessment should be performed at least **2 months after** patients achieve their **maximum response**[1,3†]

*Used in some countries to monitor lymphadenopathy and organomegaly. †Maximum response: treatment phase in which no additional improvement is seen during at least 2 months of therapy.[1]
CBC, complete blood count; CR, complete response; CT, computed tomography; MRD, minimal residual disease; PR, partial response.
1. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 2. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 3. Del Giudice I, et al. *Cancers (Basel).* 2024;16(11):2049.

A Comprehensive Efficacy Assessment in CLL Extends Beyond Overall Survival

Overall survival

OS is considered the **gold standard** of CLL clinical trials, but should be coupled with other clinical endpoints[1-4]

- OS can be confounded by patient factors, including physical fitness, age, and comorbidities since it includes noncancer deaths

FDA and EMA consider OS as a standard endpoint, but focus on the overall clinical benefit of the drug and consider emerging, relevant endpoints[3,4]

Well-rounded assessment would consider multiple clinical trial endpoints in addition to OS[1-3,5]

PFS	EFS/DFS	ORR
DOR	MRD	TTNT
TTR	Symptomatic progression	CBR

Advantage: surrogate endpoints are tied to **clinical response** and therefore can be assessed earlier than survival

Disadvantage: endpoints do not always correlate with survival

CBR, clinical benefit rate; CLL, chronic lymphocytic leukemia; DFS, disease-free survival; DOR, duration of response; EFS, event-free survival; EMA, European Medicines Agency; FDA, US Food and Drug Administration; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS progression-free survival; TTNT, time to next treatment; TTR, time to response.

1. Hallek M, et al. *Blood*. 2018;131(25):2745-2760. 2. Delgado A, Guddati AK. *Am J Cancer Res.* 2021;11(4):1121-1131. 3. FDA. Accessed August 29, 2025. https://www.fda.gov/media/71195/download. 4. Kordecka A, et al. *Value Health*. 2019;22(8):884-890. 5. Weber HJ, et al. *Pharm Stat*. 2024;23(1):91-106.

Treatment Endpoints Typically Used in CLL Clinical Trials[1-4]

Endpoint		Definition	Advantage	Disadvantage
OS	Overall survival	Time between the first treatment day and death from any cause	• Gold standard primary clinical endpoint • Easily and precisely measured	• May be affected by study arm crossover • Requires longer follow-up • Includes noncancer deaths
PFS	Progression-free survival	Time between the first treatment day and the first sign of disease progression or death from any cause	• Includes stable disease measurement • Assessed earlier compared with survival studies	• Subject to assessment bias • Definitions vary across studies • May not correlate with survival • Includes noncancer deaths
EFS/ DFS	Event-free/ disease-free survival	Time between first treatment until disease recurrence or death from any cause	• Assessed earlier compared with survival studies • EFS used to assess highly toxic treatment and DFS used to assess adjunctive and curative therapies	• Subject to assessment bias • Definitions vary across studies • May not correlate with survival • Includes noncancer deaths
ORR	Overall response rate	Proportion of patients who respond to therapy (CR/PR)	• Attributable to drug not natural history • Assessed earlier compared with survival studies	• Definitions vary across studies • May not correlate with survival • Subject to assessment bias
DOR	Duration of response	Time from the start of response to disease progression or death in patients who achieve CR or PR	• Assessed earlier compared with survival studies	• May not correlate with survival • Subject to assessment bias

References and footnotes in the slide notes.

Treatment Endpoints Typically Used in CLL Clinical Trials (cont'd)[1-6]

Endpoint		Definition	Advantage	Disadvantage
TTNT	Time to next treatment	Time between the first treatment day and when the patient starts a new therapy	• Encompasses disease progression, treatment toxicity, and death • Meaningful endpoint for long-term malignancies • Assessed earlier compared with survival studies	• Requires further validation before serving as a stand-alone marker to assess treatment efficacy • May not correlate with survival
MRD	Minimal residual disease	<1 CLL cell per 10,000 leukocytes in blood or marrow	• Strong prognostic factor for fixed-duration therapies • Assessed earlier compared with survival studies	• Not applicable to continuous therapies
TTR	Time to response	Time from the start of treatment to onset of PR or CR	• Supplements ORR by providing insight regarding how quickly response occurred	• Subject to assessment bias • May not correlate with survival • Requires context with other endpoints (eg, ORR, PFS)
Symptomatic progression*		Measurement of CLL-related symptoms for disease progression	• Direct measurement of clinical benefit rather than surrogate endpoint • Assessed earlier compared with survival studies	• Subject to assessment bias • Lack of validated tools • Definitions may vary across studies • Symptoms related to cancer and not drug toxicity
CBR	Clinical benefit rate	CR, PR, or at least 6 months of SD	• Used when disease stabilization is meaningful • Assessed earlier compared with survival studies	• Inconsistent definitions for clinical benefit • May not correlate with survival

*Time to symptom progression is a similar measure to symptomatic progression, defined as time from the start of treatment to onset of CLL-related symptoms.

References and footnotes in the slide notes.

Many Treatment Endpoints Entail Defining Response With CLL Treatment

Group A parameters assess the lymphoid tumor load and constitutional symptoms, whereas group B assesses the hematopoietic system[1]

	Parameter	CR	PR	SD	PD
	iwCLL 2018 criteria	*All criteria must be met*	*At least 2 from group A and 1 from group B need to improve if previously abnormal**	*All criteria must be met†*	*At least 1 criterion from group A or group B must be met*
GROUP A	**Lymph nodes**	<1.5 cm in longest dimension	Decrease ≥50% from BL‡	Change from −49% to +49%	Increase ≥50% from BL or response
GROUP A	**Liver/spleen size§**	Spleen size <13 cm Liver size normal	Decrease ≥50% from BL	Change from −49% to +49%	Increase ≥50% from BL or response
GROUP A	**Constitutional symptoms**	None	Any	Any	Any
GROUP A	**Circulating lymphocyte count**	Normal	Decrease ≥50% from BL	Change from −49% to +49%	Increase ≥50% over BL
GROUP B	**Platelet count**	≥100 X 10^9/L	≥100 X 10^9/L or increase ≥50% from BL	Change from −49% to +49%	Decrease ≥50% over BL secondary to CLL
GROUP B	**Hemoglobin**	≥11 g/dL‖	≥11 g/dL or increase ≥50% from BL	Increase <11.0 g/dL or <50% over BL or decrease <2 g/dL	Decrease of ≥2 g/dL from BL secondary to CLL
GROUP B	**Marrow**	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells or of B-lymphoid nodules, or not done	No change in marrow infiltrate	Increase of CLL cells by ≥50% on successive biopsies

*If only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve. †Constitutional symptoms alone do not define PD. ‡Sum of 6 or fewer lymph nodes. §Spleen size is considered normal if <13 cm. No international consensus for normal liver size. ‖Untransfused and without erythropoietin.

BL, baseline; CR, complete response; CLL, chronic lymphocytic leukemia; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PD, progressive disease; PR, partial response; SD, stable disease.

1. Hallek M, et al. *Blood.* 2018;131(25):2745-2760.

PR-L: An Additional Response Category to Consider With Certain Therapies

Parameter	CR	PR	SD	PD

Patients with **PR-L** meet all criteria for PR, but persistent lymphocytosis remains[1]

PR-L* accounts for therapies such as **BTKi** that can induce lymphocytosis as a sign of a response to therapy (not a sign of disease progression)[1,2]

- Inhibiting the BTK pathway can mobilize CLL cells from the lymph nodes and spleen into the peripheral blood, resulting in transiently elevated lymphocyte count

Scientific literature accepts PR-L* as meeting criteria for a PR[1-3]

- PR-L has been used in multiple clinical trials and drug approval agencies (eg, FDA, EMA) consider emerging, relevant endpoints[1,2,4,5]

*PR-L has not been defined in iwCLL 2018. BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; EMA, European Medicines Agency; FDA, US Food and Drug Administration; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

1. Narang J, et al. *J Clin Oncol.* 2021;39(15 suppl):e19502. 2. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 3. Cheson B. et al. *J Clin Oncol*. 2012;30(23):2820-2822. 4. FDA. Accessed August 29, 2025. https://www.fda.gov/media/71195/download. 5. Kordecka A, et al. *Value Health*. 2019;22(8):884-890.

Overcome Assessment Bias: Independent Review Committee vs Investigator Review

Endpoints such as **PFS, EFS/DFS, and ORR** require **interpretation of response,** which may introduce **assessment bias**, including[1,2]:

- Measurement precision of disease symptoms
- Reader perception of imaging and image quality
- Inherent disease characteristics
- Manifestation of treatment effect
- Underlying patient conditions

IRC review is used to minimize assessment bias for clinical trials and drug approvals[1-3]

- The IRC provides an independent verification of clinical trial endpoints by physicians not involved in the treatment of the patient and may be blinded to certain components of the study (eg, treatment arm)

IRC vs investigator review[1,3]

- Many oncology studies have demonstrated consistency between investigator review and IRC outcomes[1]
- Errors can be introduced for both investigator review and IRC[1,3]
  - Investigators may be aware of more patient information and have more process errors compared with IRC[1]
  - Errors can be introduced in the transfer of materials to the IRC[3]

DFS, disease-free survival; EFS, event-free survival; IRC, independent review committee; ORR, overall response rate; PFS, progression-free survival.

1. Ford RR, et al. *Leuk Lymphoma.* 2017;58(6):1332-1340. 2. Ford RW, et al. *Eur J Cancer.* 2009;45(2):268-74. 3. FDA. Accessed August 29, 2025. https://www.fda.gov/media/71195/download

Incorporating Diverse Endpoints Helps Capture the Spectrum of CLL Disease

Are OS and PFS enough to encompass disease complexities?

- OS and PFS have long been regarded as the clinical standards for treatment effectiveness in CLL[1,2]
- However, OS and PFS can take a while to measure in an indolent disease like CLL[1,2]
- Both can be confounded by non–disease-related deaths, which is common in an elderly population over a prolonged period of time[1,2]

Complementary endpoint: TTNT

- TTNT serves as a surrogate marker for duration of clinical benefit[1]
- Encompasses treatment effectiveness and a patient's overall experience[1]

Complementary endpoint: MRD

- Measuring detectable vs undetectable MRD, which has been shown to correlate with OS and PFS specifically for fixed-duration therapies[3,4]

CLL, chronic lymphocytic leukemia; PFS, progression-free survival; OS, overall survival; MRD, minimal residual disease; TTNT, time to next treatment.

1. Molica S. *Expert Rev Hematol.* 2023;16(11):803-806. 2. Delgado A, Guddati AK. *Am J Cancer Res.* 2021;11(4):1121-1131. 3. Del Giudice I, et al. *Cancers (Basel).* 2024;16(11):2049. 4. Benintende G, et al. *Front Oncol.* 2023;13:1112616.

MRD Assessment Can Be Applied to Specific CLL Therapies

Role of MRD assessment

Fixed-duration therapies

- uMRD is a **strong prognostic factor** for fixed-duration therapies[1-3]
- uMRD has been **correlated with improved PFS and OS** with fixed-duration therapies[1-3]
- MRD assessment may detect durable remission when **combining** fixed-duration therapy with continuous therapy, but further investigation is needed[3-5]

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Continuous therapies

- uMRD is **not correlated with improved outcomes** in patients treated with continuous BTKi monotherapy[2]
  - Prolonged PFS was observed for patients, irrespective of MRD status
- Thus, MRD is not a recommended endpoint for continuous therapies[2,4]

MRD assessment is not part of routine practice but likely will be increasingly used to determine a definitive response to therapy specifically for fixed-duration regimens and combination therapies[2-5]

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; MRD, minimal residual disease; OS, overall survival; PFS progression-free survival; uMRD, undetected minimal residual disease.

1. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 2. Del Giudice I, et al. *Cancers (Basel).* 2024;16(11):2049. 3. Benintende G, et al. *Front Oncol.* 2023;13:1112616. 4. Soumerai JD, et al. *Blood Adv.* 2025;9(5):1213-1229. 5. Hallek M, et al. *Am J Hematol.* 2021;96(12):1679-1705.

Consider the Following Questions to Optimize Efficacy Assessments

How do I optimize assessment of patients on continuous and fixed-duration therapy?

What efficacy measure(s) are most appropriate? How can I limit assessment bias?

If receiving fixed-duration therapy, how might an MRD assessment add value?

How can I best measure my patient's durability of treatment efficacy? Would TTNT provide important additional information?

If the patient is being treated with a BTKi and experiences lymphocytosis, should PR-L be considered?

How should imaging be incorporated into CLL response evaluation?

How might the patient's comorbidities and concomitant medications impact the efficacy assessment?

For symptomatic progression, how can you differentiate between a symptom and drug toxicity?

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; MRD, minimal residual disease; PR-L, partial response with lymphocytosis; TTNT, time to next treatment.

Key Takeaways

- The type and timing of efficacy assessments depend on the setting and treatment being administered[1]
- While OS remains the gold standard, additional endpoints can aid in providing a well-rounded efficacy assessment[1-3]
- Surrogate endpoints can provide information to help guide treatment decisions over a more tractable time frame[2,3]
- Clinical trials include multiple endpoints to provide a well-rounded assessment, which facilitates interpretation of outcomes and translation to routine clinical practice[1-4]

OS, overall survival.

1. Hallek M, et al. *Blood.* 2018;131(25):2745-2760. 2. Delgado A, Guddati AK. *Am J Cancer Res.* 2021;11(4):1121-1131. 3. FDA. Accessed August 29, 2025. https://www.fda.gov/media/71195/download 4. Ford RR, et al. *Leuk Lymphoma.* 2017;58(6):1332-1340.