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Measurable Residual Disease Glossary of Terms

Absolute Lymphocyte Count (ALC): Measures the total number of white blood cells (WBC) that are lymphocytes in a microliter (μL) of blood. It is calculated by multiplying the WBC times the percent of lymphocytes in the differential WBC count.

Active Surveillance: Also called active observation, or most commonly “Watch and Wait.” A treatment strategy that involves regular clinical and laboratory monitoring, preventive care, and a healthy diet and lifestyle.

Bone Marrow (BM): The soft, spongy tissue inside the hollow part of long bones where blood cells are formed. Bone marrow examination may be used to diagnose CLL and may be used for MRD testing to monitor the effectiveness of treatment.

Bone Marrow Aspiration: A procedure to collect a small amount of liquid bone marrow to look for abnormal cells (e.g., cell size, shape, appearance). The sample may also be used to look for MRD.

Bone Marrow Biopsy (BMBx): A procedure to remove and examine a piece of bone marrow for cell abnormalities or scarring in the bone marrow.

Chronic Lymphocytic Leukemia (CLL): This form of leukemia progresses slowly and is characterized by an increased number of a type of clonal white blood cells known as B-lymphocytes.

Clinical Relapse: The return of signs and symptoms of a disease after a period of remission.

Clinical Trials: A type of research study that evaluates how well a drug, medical device, or treatment approach works.

Clone: A group of cells that are genetically identical and originate from a single parent cell. Leukemia cells develop from one original abnormal cell. All cancers, including CLL and SLL are thought to be clonal.

ClonoSEQ: An FDA-cleared next-generation sequencing (NGS) test used to detect measurable residual disease (MRD) in people with CLL and other blood cancers down to one in a million cells (10^{-6}).

Complete Blood Count (CBC): This is a common routine test performed on a small amount of blood. This count measures the number of each blood cell type, the size of the red blood cells, the total amount of hemoglobin, and the fraction of the blood that is made of red blood cells. It may also be called a blood count.

Complete Response (CR): Also, sometimes referred to as complete remission, it is the disappearance of all signs of cancer based on the results of standard testing. CR does not indicate a cure, only that no signs of disease can be detected by standard laboratory testing and imaging. One can have a complete response but still have detectable measurable residual disease. CR and uMRD are different and complementary ways to measure the response to therapy.

Continuous Therapy: Refers to a medical treatment that is intended to be given indefinitely until disease progression or intolerance.



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Deep Response: Indicates a significant response to a particular treatment resulting in a lasting or durable state of remission.

Durable Response: Refers to a response to a treatment that lasts for an extended period, indicating a successful outcome of the treatment on the disease.

Duration of Response (DOR): Defined as the time from onset of response to progression or death due to any reason. By definition, it is only measured in those who respond.

Flow Cytometry: A laboratory test used to evaluate individual blood or bone marrow cells that provides information about the presence or absence of certain protein markers on the cell surface. This diagnostic test may be used to identify exactly what type of cells are in the sample, including the identification of the presence and quantity of CLL cells. When flow cytometry is the method used for MRD testing, it can reliably detect one cancer cell among 10,000 normal cells (10^{-4}).

Fluorescence in Situ Hybridization (FISH) Testing: A laboratory test that helps identify abnormalities in chromosomes and genetic mutations. Under a microscope, colored lights are directed at chromosomes and genes to see if any are missing or rearranged. This test can help to assess risk, identify treatment needs, and monitor treatment effectiveness. It is not used to diagnose CLL and SLL or to measure the response to therapy.

Hematocrit (Hct): This is a blood test that is usually part of the complete blood count. It measures the proportion of blood containing red blood cells. This measurement depends on the number of red blood cells and their size. It is also sometimes referred to as packed cell volume.

Hemoglobin (Hgb): This is the iron-containing pigment in red blood cells. It carries oxygen from the lungs to the tissues in the body.

Imaging: A technique and process of visualizing organs and other structures in the body. Examples of imaging tests used in CLL and SLL include Computer Axial Tomography (CT or CAT scans), X-rays, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET scans), and ultrasonography (ultrasound).

Leukemia: A type of blood cancer characterized by large numbers of abnormal blood cells, usually white blood cells, which take over the bone marrow and are often found in the bloodstream. CLL is classified as leukemia.

Level of Detection: The lowest concentration of a target (i.e., CLL cell) that can be detected in a sample. For example, flow cytometry can detect one CLL cell in 10,000 normal cells. This level of detection is 1×10^{-4} . Next-generation sequencing can detect down to one CLL cell in one million normal cells. This level of detection is 1×10^{-6} .

Limited Duration Therapy: Also referred to as fixed duration therapy, it is a treatment that is only given for a limited and defined timeframe. For example, a medication that is expected to be given for one year and then stopped.

Lymphocytes: Blood cells that are part of the immune system which include B-lymphocytes, T-lymphocytes, and natural killer (NK) cells. CLL is a cancer of the B-lymphocytes.



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Lymphoma: This type of cancer originates in the lymphoid tissue, usually found in the lymph nodes and spleen, but also the liver, the gastrointestinal tract, and bone marrow can be involved. It results from the uncontrolled clonal production of abnormal lymphocytes. There are two main categories: Hodgkin's disease and non-Hodgkin's lymphoma (NHL). CLL is an indolent (slow-growing) B-cell non-Hodgkin's lymphoma. CLL is also classified as leukemia since it is found in both the blood and bone marrow.

Molecular Relapse: The return, or detection of measurable residual disease following a period of remission, without the presence of signs and symptoms. This indicates the disease is returning but is not otherwise detectable. People experiencing molecular relapse may not need treatment until symptoms return.

Measurable Residual Disease (MRD): Sometimes referred to as Minimal Residual Disease. This test measures the amount of cancer cells in a person's body using a sample of blood or bone marrow. The test is looking for any small amount of cancer cells that remain in the body after treatment that cannot be found by routine blood and bone marrow tests. These remaining cancer cells can start to grow and multiply, causing a relapse of the disease. MRD testing may be used to detect early signs of returning disease, or in clinical trials to measure the response to new therapies that are being studied. MRD status is usually the most sensitive way to measure the depth of response to treatment.

MRD Detectable: Sometimes referred to as MRD positive. This is a test result that indicates there are still detectable cancer cells remaining in the body. When cancerous cells are found in the test sample, the person is said to be MRD detectable.

MRD Undetectable: Sometimes referred to as uMRD or MRD negative. When no cancer cells are found in the sample of blood or bone marrow that is tested, the person is said to have undetectable MRD (uMRD). Undetectable MRD status is considered to be a very deep state of remission, but undetectable does not mean there are no cancer cells in the body, only that the number of cells is too low to detect. MRD undetectable does not equate to a cure. Also, one can be MRD undetectable and only be in partial remission.

Next-Generation Sequencing (NGS): A testing technique that refers to a number of different sequencing technologies that can rapidly examine sections of DNA. Cancer cells in the body have a unique DNA sequence from healthy DNA cells. NGS can detect these abnormalities (also called mutations) that are commonly associated with CLL. Based on the DNA of cells in a sample, NGS testing is sensitive enough to detect down to one CLL cell in one million normal cells in a sample of blood or bone marrow. This level of detection is 1×10^{-6} .

Overall Response Rate (ORR): This is the proportion of people who have a partial or complete response to therapy.

Overall Survival (OS): The length of time that spans from the start of a treatment or diagnosis until death. In clinical trial. OS is often used to measure the overall impact of the treatment on the person's lifespan. This usually is the most important outcome of any therapy.

Partial Response (PR): Also referred to as partial remission. It refers to a decreased amount of cancer in the body after treatment. PR occurs when there has been significant improvement in a disease following treatment, but some evidence of the disease is still present. In clinical trials, there are precise



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definitions of what qualifies as a PR (i.e., a 50% reduction in lymph node size and a 50% decrease in peripheral blood lymphocyte count).

Peripheral Blood: Refers to the blood that circulates through the body. Blood drawn from a vein in your arm for laboratory testing is an example of peripheral blood.

Personalized Medicine: An approach to healthcare that takes into consideration the unique characteristics of a person's disease and genetic features to select the treatment option that is most likely to provide the best outcome for that individual.

Platelets: The smallest type of blood cell whose sticky surface helps the blood to clot and stop bleeding. They are also called thrombocytes.

Polymerase Chain Reaction (PCR): This laboratory test can be used to detect and measure MRD. It uses a technique to increase trace amounts of specific pieces of genetic material, either DNA or RNA, to make them easier to detect and count. As a result, genetic abnormalities can be found even when a very small number of cancer cells remain. With PCR, it is possible to identify one cancer cell among 100,000 cells to one million normal cells.

Progression Free Survival (PFS): The length of time during and after the treatment of a disease that a person lives without the disease growing or spreading. In clinical trials, PFS is often used to measure the effectiveness of the treatment being studied.

Progressive Disease: Cancer that is worsening or growing. In CLL, this might mean that the absolute lymphocyte count (ALC) is increasing and/or the lymph nodes and/or spleen are enlarging.

Red Blood Cell (RBC): The most numerous type of blood cell circulating within the human body that contain hemoglobin, a protein that carries oxygen from the lungs to all the tissues in the body.

Reticulocytes: These are immature red blood cells that are normally found in the bone marrow. They should be present in the bloodstream only in very low numbers.

Remission: Remission refers to the reduction or disappearance of the signs and symptoms of a disease.

Small Lymphocytic Lymphoma (SLL): This is a slow-growing type of lymphoma in which too many clonal white blood cells or lymphocytes are found in the lymph nodes, causing them to become enlarged. When 5,000 or more of these clonal lymphocytes are also found in each microliter (μL) of blood, the disease is called chronic lymphocytic leukemia. The cells involved are identical to CLL.

Stable Disease: Disease that is not getting worse or getting better.

Time to Next Treatment (TTNT): The duration of time that occurs between the completion of one course of treatment and the start of the next treatment. It is often used in clinical trials as a measure of treatment effectiveness. Longer TTNT may suggest a more sustained response to the initial treatment.

White Blood Cell (WBC): There are several types of white blood cells circulating within the human body. These include granulocytes (i.e., neutrophils, eosinophils, and basophils), lymphocytes, and monocytes. White blood cells are responsible for fighting disease and infection by attacking and killing germs. They are also called leukocytes.