Chronic leukaemias

Guide to the completion of the EBMT data collection form: Chronic_Leukaemias_v1.0

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EBMT Registry

EBMT Clinical Research & Registry Department

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Chronic leukaemias

This form must be completed for all patients whose primary disease for which the reported treatment is being given is chronic leukaemia.

No data items should be left blank unless specifically stated in the definition.

1. Date of diagnosis:

Report the date of diagnosis if this was the indication for a treatment. This is often the date on which the bone marrow aspirate and/or biopsy was performed.

(please add the instructions).

2. Classification

Select the classification that is appropriate for chronic leukaemia and check the box next to it.

Chronic myeloid leukaemia (CML) is also known as chronic myelogenous leukaemia. It's a type of cancer that starts in certain blood-forming cells of the bone marrow. In CML, a genetic change takes place in an early (immature) version of myeloid cells: the cells that make red blood cells, platelets, and most types of white blood cells (except lymphocytes). This change is related to a translocation between chromosome 9 and 22, t(9;22) which forms an abnormal gene called BCR-ABL and, which turns the cell into a CML cell. The leukaemia cells grow and divide, building up in the bone marrow and spilling over into the blood. In time, the cells can also settle in other parts of the body, including the spleen. CML is a fairly slow growing leukaemia, but it can change into a fast-growing acute leukaemia that's hard to treat. CML occurs mostly in adults, but very rarely it occurs in children, too. It belongs to the myeloproliferative neoplasms, and present initially as an indolent or chronic phase (CP), easily controlled with treatment. The natural history continues with a bi- or triphasic stage, becoming more aggressive through accelerated phase (AP) and then blast crisis (BC) or directly from CP to BC.

Chronic lymphocytic leukaemias (CLL) are malignancies of the mature lymphocyte. The normal lymphocytes can be divided into two main groups: B lymphocytes and T lymphocytes. B lymphocytes make antibodies (immunoglobulins) and T lymphocytes are cells that can kill foreign cells (e.g. virus infected cells or allogeneic transplants). The large majority of patients with, chronic lymphocytic leukaemias have a B-cell type. The T-cell types of chronic lymphocytic leukaemias are rare. General characteristics of this group of diseases are lymphocytosis (> 5 x 109 /L) and enlarged lymph nodes and spleen

Prolymphocytic leukaemia (PLL) is a type of leukaemia where the cancer cells are less mature and more atypical than in CLL and are called prolymphocytes. These are immature forms of B lymphocytes (B-PLL) or T lymphocytes (T-PLL). Both B-PLL and T-PLL tend to grow and spread faster than the usual type of CLL. PLL may develop in someone who already has CLL (in this case it tends to be more aggressive), but it can also occur in people who have never had CLL.

3. Chronic myeloid leukaemia

Chromosome Analysis

3.1. Chromosome analysis before main treatment:

(all methods including FISH):

In this section describe the results of the most recent complete chromosome analysis (performed after diagnosis but before the main treatment).

Not done or failed - the chromosome analysis has not been done or failed;

Yes, abnormal results - the chromosome analysis has been performed and at least one of the results has been found to be abnormal. In addition, indicate the number of abnormalities present in the most recent analysis with abnormal results (**number of abnormalities present**).

Yes, normal results - the chromosome analysis has been performed and all the results have been found normal;

Unknown - it is unknown whether the chromosome analysis has been done or not.

3.1.1. Date of chromosome analysis (if tested):

Indicate the date of the chromosome analysis. If the results were normal, add the date of the first test with normal results.

3.1.2. Chromosome analysis details:

See the cytogenetics form or ask the cytogenetics team and consult your physician.

If chromosome analysis was performed, indicate for each abnormality in the table whether it was Absent or Present. If cytogenetics were not evaluated, report Not evaluated.

If a chromosome abnormality was checked, but not listed as an option in the table, select Other and specify the abnormality, marking whether it was Absent or Present.

Report the chromosomal abnormalities on the total number analysed, in general it is 20 metaphasis analysed (for example a patient with 12 abnormal translocation t(9;22) is given in the report as t(9;22) [12/20] meaning 12 abnormal out of 20 analysed).

3.1.3. Transcribe the complete karyotype:

If it is not possible to report the chromosome analysis results as per abnormalities table. Preferably the table above with abnormalities should be completed. If the result of the chromosome analysis is too complex, the complete karyotype should be described here. Describe all abnormalities according to the ISCN karyotype nomenclature. This notation includes the total number of chromosomes, the sex chromosomes, and any extra or missing autosomal chromosomes. For example, **47**, **XY**, **+18** indicates that the patient has 47 chromosomes, is a male, and has an extra autosomal chromosome 18.

Molecular markers analysis

3.2. Molecular markers analysis done before main treatment:

Indicate if molecular marker analysis was done or not before the treatment. Check **Unknown** if it is not known whether it was performed.

3.2.1. Date of molecular marker analysis (if tested):

Indicate the date of the molecular marker analysis.

3.2.2. Molecular marker analysis details:

If molecular marker analysis was performed, indicate for each marker in the table whether it was **Absent** or **Present**. If a molecular marker was not evaluated, report **Not evaluated**.

If a molecular marker was evaluated, but not listed as an option in the table, select **Other** and specify the marker, indicating whether it was **Absent** or **Present**.

Previous therapies

In this section provide details on previous therapies between diagnosis and the main treatment.

3.3. Previous therapy lines before the main treatment

Indicate if the patient underwent any previous therapy lines related to chronic myeloid leukaemia before the main treatment. A treatment is considered a new line of therapy when switching to a different drug (or different combination of drugs) due to toxicity or for progression or relapse of the disease. If answered **Yes**, for each treatment line answer also question 3.3.1 and -3.3.2:

3.3.1. If a Tyrosine kinase inhibitor (TKI) was given

Select the type from the listed options. If the patient received another TKI or other chemotherapy not listed in the dropdown menu, check the box **Other** and specify the chemotherapy.

Please consult the LIST OF CHEMOTHERAPY DRUGS/AGENTS AND REGIMENS on the EBMT website for drugs/regimens names.

3.3.2. Date treatment started

Report the start date of the treatment line.

Chronic lymphocytic leukaemias (CLL)

4. Sub-Classification:

Select the sub-classification that is appropriate for chronic lymphocytic leukaemia and check the box next to it:

Chronic lymphocytic leukaemia (CLL) / small lymphocytic lymphoma (SLL):

Chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) are the same in all characteristics with the exception of the percentage of malignant cells in the blood. In contrast to CLL, SLL has lymphadenopathyand/or splenomegaly and no (or only few < 5 10e9/L)) malignant cells in peripheral blood.

Richter's syndrome (also known as Richter's transformation) is when in a patient with treated or untreated Chronic Lymphocytic Leukaemia (CLL) and/or Small Lymphocytic Lymphoma (SLL) arises a rare type of non-Hodgkin lymphoma, usually diffuse large B cell lymphoma (DLBCL). The DLBCL can be either clonally related or unrelated to the underlying CLL/SLL. Sometimes Richter's transformation can lead to the development of Hodgkin lymphoma (HL) or other types of non-Hodgkin lymphoma. However, in every case the underlying disease is CLL and/or SLL. Richter's syndrome, specially DLBCL Richter's syndrome clonally related to CLL, is associated with a poor prognosis under conventional therapy.

4.1. For Richter's syndrome answer questions 4.1 - 4.1.3:

4.1.1. Transformed from a previous known CLL/SLL:

If a CLL/SLL was diagnosed previously (most cases), answer **Yes** and report the date of original CLL/SLL diagnosis.

If the patient does not have a previously known CLL/SLL diagnosis answer **No**. Different contexts can be found in such cases of "primary Richter"

i. The diagnostic of both Richter's syndrome must occur together with a and CLL /SLL are made at the same time, usually because the underlying CLL /SLL was asymptomatic.
ii. The patient develops a lymphoma and later a CLL/SLL emerges leading to retrospectively diagnosing this lymphoma as Richter's syndrome.

In both cases (transformed from previously known CLL or primary), Richter's would be the main indication diagnosis.

4.1.2. Type of Richter:

Report the type of Richter's syndrome by marking if it is:

- **Hodgkin**
- **DLBCL**
- **Other** type, please specify it in the text field.

4.1.3. Richter clonally related to CLL

Report if Richter is clonally related to CLL or not.

Chromosome analysis

4.2. Chromosome analysis before main treatment:

(all methods including FISH):

In this section describe the results of the most recent complete chromosome analysis (performed after diagnosis but before the main treatment).

Not done or failed - the chromosome analysis has not been done or failed;

Yes, abnormal results - the chromosome analysis has been performed and at least one of the results has been found to be abnormal. In addition, indicate the number of abnormalities present in the most recent analysis with abnormal results (**number of abnormalities present**).

Yes, normal results - the chromosome analysis has been performed and all the results have been found normal;

Unknown - it is unknown whether the chromosome analysis has been done or not.

If more than one analysis has been done since diagnosis but before treatment, indicate **Yes**, **abnormal results** if at least one analysis has been found to be abnormal. In this case, describe the results of the most recent analysis with abnormal results.

4.2.1. Date of CLL chromosome analysis (if tested):

Indicate the date of the most recent, complete chromosome analysis.

If chromosome analysis was not done, failed or unknown, leave the field blank.

4.2.2. Chromosome analysis details:

Indicate per each abnormality in the table if it was absent, present, or not evaluated in the chromosome analysis reported above. If there were other abnormalities tested that are not mentioned in the table, specify the abnormality and if it was absent or present.

4.2.3. Transcribe the complete karyotype

If it is not possible to report the chromosome analysis results based on the abnormalities listed in the Table, or if the result of the chromosome analysis is too complex, the complete karyotype should be entered here. Describe all abnormalities according to the ISCN karyotype nomenclature. This notation includes the total number of chromosomes, the sex chromosomes, and any extra or missing autosomal chromosomes. For example, **47**, **XY**, **+18** indicates that the patient has 47 chromosomes, is a male, and has an additional copy of autosomal chromosome 18.

Molecular markers analysis

4.3. Molecular markers analysis done before main treatment:

Indicate if molecular marker analysis was done or not before the treatment. Check **Unknown** if it is not known whether it was performed.

4.3.1. Date of molecular marker analysis (if tested):

Indicate the date of the molecular marker analysis.

4.3.2. IGVH mutational status:

Indicate if immunoglobulin heavy chain (IGVH) gene was found **Absent** or **Present**, or mark **Not evaluated** if it was not checked.

The mutational status of the variable region of the (IGHV) gene is a predictive biomarker of duration of response to therapy and overall survival with chemoimmunotherapy (CIT) and Venetoclax plus anti CD20 among patients with CLL. Patients with mutated IGVH have a better duration of response and survival to both immunochemotherapy and venetoclax plus anti CD20.

4.3.3. High risk subset?

Report if high risk was subset or not. Some patients, despite a mutated IGVH gene, have an unfavourable prognosis (as if their IGVH gene was unmutated) because their VDJ rearrangement results in an unfavourable stereotype. This is the "subset 2" (IGHV3-21/IGLV3-21) which corresponds to 2-3% of CLL.

Molecular marker analysis details:

If molecular analysis of TP53 gene was performed, indicate if TP53 mutations were **Absent** or **Present**. If this molecular marker was not evaluated, report **Not evaluated**.

If another marker was evaluated, select **Other** and specify the marker in the text field, indicating whether it was **Absent** or **Present**.

In this section provide details on previous therapies between diagnosis and the main treatment.

4.4. Previous therapy lines before the main treatment

Indicate if the patient underwent any previous therapy lines related to CLL or Richter's before the main treatment. If answered **Yes**, complete the table below to provide more data on each treatment line by answering questions 4.4.1-4.4.2 (see below):

Important: If a patient had Richter transformation in the course of a CLL and even if Richter transformation is the main indication of transplantation, the previous therapy lines of both CLL and Richter syndrome should be recorded indicating the indication of each line (CLL or Richter).

4.4.1. Chemo/regimen used

Select the relevant chemotherapy from the list.

Please consult the LIST OF CHEMOTHERAPY DRUGS/AGENTS AND REGIMENS on the EBMT website for drugs/regimens names

4.4.2. Treatment start date

Report the date the treatment started.

4.4.3. Treatment end date

Report the last day of the previous therapy line. If the date was unknown, select **Date unknown**.

4.4.4. Reason for treatment withdrawal (*) (**)

- **Planned withdrawal**
- **Toxicity**
- **Progression or insufficient response**
- **Other reason**
- **Unknown**

(*) Today, CLL is treated with two main types of approach in terms of treatment duration.

On the one hand, there are fixed-duration treatments in which treatment is interrupted either because the regimen defines a fixed duration from the start or because a sufficient level of response has been obtained. In such situations withdrawal can be either planned as per protocol or unplanned because of toxicity, progression or insufficient response or other reasons.

On the other hand, CLL have been more and more treated since 2015 with continuous duration treatments delivered in theory until progression or intolerance. In such situation most withdrawal is unplanned (as per protocol) and are related to either toxicity, or insufficient response or progression or other reasons

In general:

- Immunochemotherapies are fixed-duration treatments.

- BTK inhibitors (Ibrutinib, acalabrutinib, zanubrutinib, etc.) alone or in combination with anti-CD20 agents are continuous treatments. (Some protocols are evaluating the possibility of a fixed duration.)

- BCL2 inhibitors (Venetoclax) as monotherapy are continuous treatments.

- BCL2 inhibitors in combination with anti-CD20 agents are fixed-duration treatments.

- Combinations of BCL2 and BTK inhibitors are fixed-duration treatments.

(**) It is extremely relevant to collect and report the reason of withdrawal I the perspective to correctly describe the treatment pedigree of transplanted CLL patients. In some situation more than one reason do exist. Both should be reported.

5. Prolymphocytic (PLL) and Other Chronic Leukaemias

5.1. Sub-Classification: Prolymphocytic (PLL) and others chronic leukaemias:

Select the sub-classification that is appropriate for prolymphocytic and other chronic leukaemias by checking the box next to it. If the sub-classification is not listed, check the box **Other chronic leukaemia** and specify it in the text field.

For Prolymphocytic Leukaemia (PLL), indicate if it is:

- PLL; B-cell
- PLL; T-cell

PLL T-cell (or T-PLL) stands for T-cell prolymphocytic leukaemia and is characterised by high and rapidly growing peripheral counts of monoclonal T-cells with a characteristic CD4+ immunophenotype in the absence of lymph nodes and cutaneous lesions. It is a very rare leukaemia. The disease is mostly insensitive to chemotherapy and the prognosis is unfavourable within a few years. The diagnosis is made on morphologic characteristics, immunophenotype and cytogenetics.

PLL B-cell (or B-PLL) stands for B-cell prolymphocytic leukaemia and is also a very rare leukaemia. The disease is mostly insensitive to chemotherapy and the prognosis is unfavourable within a few years. The diagnosis is made on morphologic characteristics and on immunophenotype. Sometimes the discrimination between CLL and B-cell PLL may be difficult.

Hairy cell leukaemia (HCL) is always of B-cell origin. The morphology and the immunophenotype is very characteristic but most of the patients are not leukaemic but pancytopenic (low haemoglobin, low leukocyte count, low platelet count) which makes the diagnosis not always easy. Usually, the patients do not present with enlarged lymph nodes, but they do have a large spleen. Most of the patients have a ‘dry tap’ at diagnosis, which means that you cannot find a result (laboratory form) of the bone marrow aspirate, in this case check the bone marrow biopsy. Long remissions can be obtained with conventional treatment. The disease is rare and candidates for transplantation are even more unique.

Hairy cell leukaemia variant (atypic), also referred to as atypical hairy cell leukaemia or atypical HCL. The cells in Atypical HCL are more “punk” than “hairy” in morphology and they differ also in immunophenotype. The disease is very rare and the clinical course is much more unfavourable than the true HCL.

Chromosome analysis

Complete this section only for T-PLL

5.2. Chromosome analysis done before main treatment:

(all methods including FISH):

In this section describe the results of complete chromosome analysis (performed either at diagnosis or during disease course).

Not done or failed - the chromosome analysis has not been done or failed;

Yes, abnormal results - the chromosome analysis has been performed and at least one of the results has been found to be abnormal. In addition, indicate the number of abnormalities present in the most recent analysis with abnormal results (**number of abnormalities present**).

Yes, normal results - the chromosome analysis has been performed and all the results have been found normal;

Unknown - it is unknown whether the chromosome analysis has been done or not.

If more than one analysis has been done since diagnosis but before treatment, indicate **Yes**, **abnormal results** if at least one analysis has been found to be abnormal. In this case, describe the results of the first and last analysis with abnormal results.

5.2.1. Date of T-PLL chromosome analysis (if tested):

Indicate the date of the most recent, complete chromosome analysis.

If chromosome analysis was not done, failed or unknown, leave the field blank.

5.2.2. Chromosome analysis details:

Indicate per each abnormality in the table if it was absent, present, or not evaluated in the chromosome analysis reported above. If there were other abnormalities tested that are not mentioned in the table, specify the abnormality and if it was absent or present.

5.2.3. Transcribe the complete karyotype

If it is not possible to report the chromosome analysis results based on the abnormalities listed in the Table, or if the result of the chromosome analysis is too complex, the complete karyotype should be entered here. Describe all abnormalities according to the ISCN karyotype nomenclature. This notation includes the total number of chromosomes, the sex chromosomes, and any extra or missing autosomal chromosomes. For example, **47**, **XY**, **+18** indicates that the patient has 47 chromosomes, is a male, and has an additional copy of autosomal chromosome 18.

Immunophenotyping

Complete this section only for T-cell PLL.

5.3. Immunophenotype of T-cells at diagnosis:

Note: Terminal desoxynucleotidyl transferase (TdT) must be negative.

Report here if the immunophenotype of T-cells was evaluated at diagnosis (answer **Yes and proceed to 5.2.1.**), not evaluated (answer **No**) or it is **Unknown**.

5.3.1. Indicate if phenotypes CD4+ and CD8+ were **Absent**, **Present** or **Not evaluated**.

5.4. Lymphocyte count at diagnosis:

Report the lymphocyte count for T-cell PLL at diagnosis (number x 10 9 cells/L) or mark if it was **Not evaluated** or it is **Unknown**.

5.5. Was mantle cell lymphoma excluded at diagnosis:

- If the answer is **No**
- if the answer is **Yes** - specify what method was used:
    - FISH on t(11;14)(q23;q11)
    - Cyclin D1 expression
    - Both
    - Other

Disease status at HCT/CT/IST

Chronic Myelogenous Leukaemias (CML) - Status at treatment

1. Status

Report Chronic Myelogenous Leukaemias (CML) status at treatment by choosing the corresponding check box:

- Chronic phase (CP)
- Accelerated phase
- Blast crisis

In order to define the answer, please use WHO criteria or explanation below.

Chronic phase (CP): none of the features of accelerated phase or blast crisis.

Accelerated phase: any of the following:

- Blasts 10-19% in peripheral blood and/or nucleated bone marrow cells
- Peripheral blood basophiles >=20%
- Persistent thrombocytopenia (<100 x 109/L) unrelated to therapy
- Persistent thrombocytosis (>1000 x 109/L) unresponsive to standard therapy
- Increasing spleen size and increasing WBC count unresponsive to standard therapy
- Cytogenetic evidence of clonal evolution

Blast Crisis: any one of the following symptoms:

- Blasts >=20% in peripheral blood or nucleated bone marrow cells
- Extramedullary blast proliferation
- Large foci or clusters of blasts in the bone marrow biopsy

1.1. Number

For all disease statuses, report the response number by choosing one of the following check boxes:

- 1st;
- 2nd;
- 3rd or higher;
- Unknown.

Note: if a patient presents at diagnosis in accelerated phase or blast crisis, you must assume that prior to the presentation there has been a period of chronic phase which went undetected. Therefore, when a patient presenting in accelerated phase or blast crisis is restored (by whatever means) to chronic phase, this must be CP2.

1.2. Haematological remission:

All of the following:

- WBC < 10 x 109 /L
- Haemoglobin > 11.0 g/dL
- Platelet Count < 500 x 109 /L
- Normal Differential (<1% precursor cells)
- No palpable splenomegaly
- No extramedullary disease

If answered Chronic phase (CP) in the question 1, report if haematological remission achieved (answer **Yes**), or not achieved (answer **No**). Answer **Not evaluated** if it was not evaluated or **Unknown** if it cannot be verified if it was evaluated or not.

1.3. Cytogenetic remission:

0% t(9;22) positive metaphases together with haematological remission

A minimum of 20 analysable metaphases must be assessed for appropriate evaluation of a cytogenetic remission. Remission should be confirmed with repeated cytogenetic analysis within 4 to 12 weeks

Note: A patient in cytogenetic remission must be in haematological remission but could still present a molecular relapse. This is because the cytogenetic technique has a higher resolution than haematological measurements but lower resolution than molecular methods

If answered Chronic phase (CP) in the question 1, report if cytogenetic remission achieved (answer **Yes**), or not achieved (answer **No**). Answer **Not evaluated** if it was not evaluated or **Unknown** if it cannot be verified if it was evaluated or not.

1.4. Molecular remission:

Cells with the BCR/ABL fusion protein are not detectable, in the peripheral blood and /or the bone marrow, by an assay with a sensitivity to allow detection of one t(9;22) positive cell in 105 to 106 RT-PCR cells. The result should be confirmed by two consecutive tests done at least 4 weeks apart.

Note: A patient in molecular remission must also be in cytogenetic and haematological remission. This is because molecular techniques have a higher resolution than both haematological and cytogenetic measurements.

If answered Chronic phase (CP) in the question 1, report if molecular remission achieved (answer **Yes**), or not achieved (answer **No**). Answer **Not evaluated** if it was not evaluated or **Unknown** if it cannot be verified if it was evaluated or not.

Chronic Lymphocytic Leukaemias (CLL) - Status at treatment

1. Status

Report Chronic Lymphocytic Leukaemias (CLL) status at treatment by choosing the corresponding check box:

- **Complete remission (CR)**: Absence of clonal lymphocytes in the peripheral blood and absence of significant lymphadenopathy (e.g. lymph nodes greater than 1,5 cm in diameter) and absence of hepatomegaly or splenomegaly and absence of constitutional symptoms.
- **Partial remission (PR)**: To define a PR, at least one of the following parameters needs to be documented for a minimal duration of 2 months
  - A decrease in the number of blood lymphocytes by below 50% or more from the value prior to therapy;
  - A decrease in lymph node size by below 50% or more in the sum products of up to 6 lymph nodes, or in one lymph node diameter if only a single lymph node was present prior to therapy, without increase in any lymph node, and no new enlarged lymph node;
  - A decrease in the size of the liver and/or spleen by 50% or more as defined by CT scan, palpation, or ultrasound.
  - The blood count should show one of the following results if abnormal prior to therapy: Polymorphonuclear leukocytes at 1,500/µL or more or 50% improvement over baseline without G-CSF support; platelet counts greater than 100,000/µL or 50% improvement over baseline; haemoglobin greater than 11.0 g/dL or 50% improvement over baseline without transfusions or erythropoietin support.
- **Stable disease (SD)**: Patients who have not achieved a CR or a PR, and who have not exhibited progression, will be considered to have no change (which is equivalent to a non-response).
- **Relapse (untreated)**:
- **Progressive disease (PD)**: Progressive disease is defined by at least one of the following:
  - Lymphadenopathy: progression of lymphadenopathy occurs, if one of the following events is observed:
    - Appearance of any new lesion such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates.
    - An increase by 50% or more in greatest determined diameter of any previous site.

        - An increase of 50% or more in the sum of the product of diameters of multiple nodes.
    - An increase in the liver or spleen size by 50% or more or the de novo appearance of hepatomegaly or splenomegaly
    - An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B-cells per µL.
    - Transformation to a more aggressive histology (e.g. Richter's syndrome).
    - Occurrence of cytopenia (neutropenia, anaemia or thrombocytopenia) attributable to CLL.
- **Never treated;**
- **Unknown.**

1.1. Minimal residual disease (MRD) at initiation of treatment: (by FACS or PCR)

If answered Complete remission (CR) in the previous question. Report if MRD tested by FACS or PCR was found **Negative**, **Positive** or if it was **Not evaluated**.

Prolymphocytic (PLL) and Other Chronic Leukaemias Status at treatment

2. Status

Report Prolymphocytic (PLL) and Other Chronic Leukaemias status at treatment by choosing the corresponding check box:

- **Complete remission (CR);**
- **Partial remission (PR);**
- **Stable disease (SD);**
- **Relapse (untreated);**
- **Progressive disease (PD);**
- **Never treated;**
- **Unknown.**