EBMT Registry

Chronic leukaemias

Guide to the completion of the EBMT data collection form:

Chronic_ Leukaemias_Core_Extended_v2.2

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EBMT Registry

EBMT Clinical Research & Registry Department

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Introduction

Please make sure you have already checked the **Introduction to the EBMT Registry Completion Guidelines** document latest version available under *Manuals and Reference Documents* section on EBMT website.

Chronic leukaemias

This form must be completed for all patients whose primary disease for which the HCT/CT treatment is given is chronic leukaemia.

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

Disease

Date of diagnosis

Report the date of diagnosis. This is often the date on which the bone marrow aspirate and/or biopsy was performed.

Classification (WHO 2022)

Select the chronic leukaemia classification. Please find a short summary below for the three classifications.

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)/Small Lymphocytic Lymphoma (SLL) are malignancies of the mature lymphocyte. CLL primarily involves the blood and bone marrow, while SLL primarily affects the lymph nodes. Despite this difference in presentation, CLL and SLL are considered to be essentially the

same disease, with similar treatment approaches and outcomes. **Richter transformation**, on the other hand, refers to the rare occurrence where CLL/SLL transforms into a more aggressive form of lymphoma, typically diffuse large B-cell lymphoma (DLBCL). This transformation can present challenges in treatment and prognosis for patients.

Prolymphocytic leukaemia (PLL) is a type of leukaemia where the cancer cells are less mature and more atypical than in CLL. These cells are called prolymphocytes. PLL tends 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. **Other chronic leukaemia** are for example Hairy Cell Leukaemia (HCL) and Splenic B-cell lymphoma/leukaemia with prominent nucleoli (SBLPN, includes B-PLL and Hairy Cell Leukaemia variant from WHO2016).

Chronic Myeloid Leukaemias (CML)

Extended dataset

Assessments at diagnosis

Status of disease (at diagnosis)

Report the CML status at diagnosis:

- Chronic phase;
- Accelerated phase or
- Blast crisis.

In order to define the answer, please use International Consensus Classification (ICC) criteria as in the table below. Select **Unknown** if this information is unavailable.

Disease status		
Chronic phase (CP)	**Accelerated phase (AP)**	**Blast crisis (BC)**
• None of the features of accelerated phase or blast crisis	• Bone marrow or peripheral blood blasts 10%-19% • Peripheral blood basophils ≥ 20% • Presence of additional clonal cytogenetic abnormality in Ph+ cells (ACA)[a]	• Bone marrow or peripheral blood blasts ≥ 20% • Extramedullary blast proliferation (myeloid sarcoma) • Presence of morphologically apparent lymphoblasts (>5%) warrants consideration of

		lymphoblastic crisis

Table 1. International Consensus Classification (ICC) criteria for Chronic Myeloid Leukaemias.

[a]Second Ph, trisomy 8, isochromosome 17q, trisomy 19, complex karyotype, or abnormalities of 3q26.2.

Haematological values (at diagnosis)

Report the values from the blood tests performed at diagnosis.

Peripheral blood

Haemoglobin (g/dL)

Report the haemoglobin in grams per deciliter (g/dL). If the haemoglobin was not tested, select **not evaluated.** If the value is not known, select **unknown**.

Platelets (10^9/L)

Report the platelets in 10^9 cells per litre (10^9/L). If the platelets were not tested, select **not evaluated.** If the value is not known, select **unknown**.

White blood cells (10^9/L)

Report the white blood cells in 10^9 cells per litre (10^9/L). If the white blood cells were not tested, select **not evaluated.** If the value is not known, select **unknown**.

Absolute basophils (10^9/L)

Report the basophils in 10^9 cells per litre (10^9/L). If the basophils were not tested, select **not evaluated.** If the value is not known, select **unknown**.

% basophils

Report the basophils as a percentage. If the basophils were not tested, select **not evaluated.** If the value is not known, select **unknown**.

Extended dataset

% blasts

Report the blasts as a percentage. If the blasts were not tested, select **not evaluated.** If the value is not known, select **unknown**.

Bone marrow

Report the findings of the bone marrow investigation at diagnosis.

% blasts

Report the blasts as a percentage. If the blasts were not tested, select **not evaluated.** If the value is not known, select **unknown**.

Precise blast count not available

If the precise blast count is not available, please indicate whether it was **below or equal to 5%**, **above 5%**, **Not evaluated**, or **Unknown**.

Spleen assessment (at diagnosis)

Palpable splenomegaly

Indicate whether palpable splenomegaly at diagnosis was **Present**, **Absent**, **Not evaluated** or **Unknown**.

If present: physical examination

Indicate the size of the spleen in centimetres, measured below the costal margin as assessed by physical examination. Select **Not evaluated** if the spleen size was not assessed. If the value is unavailable, check **Unknown**.

Spleen span on ultrasound or CT scan

Indicate the maximum diameter of the spleen in centimetres assessed by ultrasound or CT scan. Select **Not evaluated** if the spleen span was not assessed. If the value is unavailable, check **Unknown**.

Chronic Myeloid Leukaemias (CML)

Chromosome Analysis

Chromosome analysis done before HCT/CT treatment

In this section describe the results of all chromosome analyses (all methods including FISH) performed after diagnosis but before the HCT/CT treatment. If there were multiple chromosome analysis tests done on different dates, the results can be registered separately along with the test date.

Indicate if chromosome analysis was done or not before the HCT/CT treatment. Check **Unknown** if it is not known whether it was performed.

Output of analysis

Indicate if the output of the chromosome analysis will be reported as **separate abnormalities** or as a **full karyotype**.

What were the results?

Normal - the chromosome analysis has been performed and the results have been found normal

Abnormal - the chromosome analysis has been performed and abnormalities have been found. In addition, indicate the total number of different abnormalities present (**number of abnormalities present**).

Failed - the chromosome analysis was done but failed

Date of chromosome analysis

Indicate the date of the chromosome analysis. If the date is unavailable, select **Unknown**.

Chromosome analysis details

Indicate for each abnormality in the table whether it was **Absent, Present, Not evaluated** or **Unknown** .

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**.

Transcribe the complete karyotype

If it is not possible to report the chromosome analysis results as per abnormalities table please enter the complete karyotype. Describe all abnormalities according to the ISCN karyotype nomenclature. This notation includes the total number of chromosomes, the sex chromosomes, and any extra, missing or mutated 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

Molecular markers analysis done before HCT/CT treatment

In this section, describe the results of all molecular marker analyses (performed at/after diagnosis but before the HCT/CT treatment). If there were multiple molecular marker analyses tests done on different dates, the results can be registered separately along with the test date.

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

Date of molecular marker analysis

Indicate the date of the molecular marker analysis. If there were multiple molecular tests done on different dates, the results can be registered separately along with the test date.

Molecular marker analysis details

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

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**.

TP53 mutation type

If TP53 mutation is present, indicate the mutation type if known. A TP53 mutation is considered a multi hit if it fulfils one of the following criteria:

- 2 or more distinct mutations of TP53 with a VAF of ≥ 10%
- 1 mutation and 1 deletion involving the TP53 locus
- 1 mutation with VAF ≥ 50%
- 1 mutation with complex karyotype

A TP53 mutation is considered single hit if either one of the following criteria is fulfilled:

- a single TP53 mutation with VAF < 50%
- loss of 17p13 involving TP53 locus without TP53 mutations

If the lab report does not specify the type, select **Unknown**.

Previous therapies

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

Previous therapy lines before the HCT/CT/GT

Indicate if the patient underwent any previous therapy lines related to chronic myeloid leukaemia before the HCT/CT/GT 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**, complete the "**Treatment non-HCT/CT/GT/IST"** form.

Chronic Lymphocytic Leukaemias (CLL)

Disease

Sub-Classification (WHO 2022)

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 lymphadenopathy and/or splenomegaly and no (or only few < $5x10^9$/L)) malignant cells in peripheral blood.

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

For Richter transformation answer the following questions:

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**. This case of "primary Richter" can occur in the following scenarios:

i. Both Richter transformation and CLL/SLL are diagnosed 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 transformation.

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

Type of Richter transformation

Report the type of Richter transformation by marking if it is:

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

Richter transformation clonally related to CLL

Report if the Richter transformation is clonally related to CLL/SLL or not.

Chromosome analysis

Chromosome analysis before HCT/CT treatment

In this section describe the results of all chromosome analyses (all methods including FISH) performed after diagnosis but before the HCT/CT treatment. If there were multiple chromosome analysis tests done on different dates, the results can be registered separately along with the test date.

Indicate if chromosome analysis was done or not before the HCT/CT treatment. Check **Unknown** if it is not known whether it was performed.

Output of analysis

Indicate if the output of the chromosome analysis will be reported as **separate abnormalities** or as a **full karyotype**.

What were the results?

Normal - the chromosome analysis has been performed and the results have been found normal

Abnormal - the chromosome analysis has been performed and abnormalities have been found. In addition, indicate the total number of different abnormalities present (**number of abnormalities present**).

Failed - the chromosome analysis was done but failed

Date of chromosome analysis

Indicate the date of the chromosome analysis. If the date is unavailable, select **Unknown**.

Chromosome analysis details

Indicate for each abnormality in the table whether it was **Absent**, **Present**, **Not evaluated** or **Unknown .**

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**.

Transcribe the complete karyotype

If it is not possible to report the chromosome analysis results as per the abnormalities table please enter the complete karyotype. Describe all abnormalities according to the ISCN karyotype nomenclature. This notation includes the total number of chromosomes, the sex chromosomes, and any extra, missing or mutated 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

Molecular markers analysis done before HCT/CT treatment

In this section, describe the results of all molecular marker analyses (performed at/after diagnosis but before the HCT/CT treatment). If there were multiple molecular marker analyses tests done on different dates, the results can be registered separately along with the test date.

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

Date of molecular marker analysis

Indicate the date of the molecular marker analysis. If there were multiple molecular tests done on different dates, the results can be registered separately along with the test date. If the date is unavailable, select **Unknown**.

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 (IGVH) 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.

High risk subset?

In case of an IGVH mutation, report if the mutation was high risk 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 "subset 2" (IGHV3-21/IGLV3-21) which is found in 2-3% of CLL patients.

Molecular marker analysis details

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

TP53 mutation type

If TP53 mutation is present, indicate the mutation type if known. A TP53 mutation is considered a multi hit if it fulfils one of the following criteria

- 2 or more distinct mutations of TP53 with a VAF of ≥ 10%
- 1 mutation and 1 deletion involving the TP53 locus
- 1 mutation with VAF ≥ 50%
- 1 mutation with complex karyotype

A TP53 mutation is considered single hit if either one of the following criteria is fulfilled:

- a single TP53 mutation with VAF < 50%
- loss of 17p13 involving TP53 locus without TP53 mutations

If the lab report does not specify the type, select **Unknown**.

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

Previous therapies between diagnosis and HCT/CT

Previous therapy lines before the HCT/CT

Indicate if the patient underwent any previous therapy lines related to CLL/SLL or Richter transformation before the (HCT/CT) treatment. If answered **Yes**, complete the **Treatment non-HCT/CT/GT/IST** form. If this information is not available, mark **Unknown**.

Important: If a patient had Richter transformation in the course of a CLL/SLL and even if Richter transformation is the main indication of transplantation, the previous therapy lines of both CLL/SLL and Richter transformation should be registered.

Extended dataset

Answer the questions below for treated patients only:

Purine analogue-refractory?

Purine analogue-containing regimens are regimens that contain one of the following drugs: Fludarabine, Clofarabine, Cladribine, Azathioprine, Mercaptopurine, Thioguanine, Nelarabine or Pentostatin. Refractory is defined as a non-response or relapse within 6 months after completion of the purine analogue-containing chemotherapy.

Indicate whether the patient was considered to be purine analogue-refractory (**No**, **Yes**, **No purine analogue-containing chemotherapy treatment**, **Unknown**).

Resistance to a BTK inhibitor?

Resistance to BTK inhibitors can either be primary or secondary. Primary resistance is a failure to respond to BTK inhibitor treatment upfront. Secondary (acquired) resistance is a relapse after initial response. Currently available BTK inhibitors are: Ibrutinib, Acalabrutinib, Zanubrutinib, Pirtobrutinib and ONO-4059.

Please indicate whether the patient was resistant to a BTK inhibitor (**Absent**, **Present**, **No BTK inhibitor treatment**, **Unknown**).

If resistance was present please answer the following questions on the resistance mechanism:

Has any testing on the resistance mechanism been performed?

Were tests done to check if mutations that can impact the effectiveness of BTK inhibitor binding were present (**No**, **Yes**, **Unknown**)?

What was tested and what was the result?

Select all the tests performed on the resistance mechanism and indicate the result for each test.

Indicate if structural changes to the BTK inhibitor were tested. If tested, indicate whether the changes were present or absent. Structural changes to the BTK protein can be caused, for example, by one or more of the following mutations: C481, T316A, L528W, V416L, A428D, M437R, T474I.

Indicate if structural changes to the proteins downstream of BTK were tested. If tested, indicate whether the changes were present or absent. Examples of proteins downstream of BTK where structural changes can occur: PLCG2 and CARD11.

If another mechanism of resistance was tested please select **Other** and specify what was tested in the text field.

Resistance to a BCL2 inhibitor?

Resistance to BCL2 inhibitors can either be primary or secondary. Primary resistance is a failure to respond to BCL2 inhibitor treatment upfront. Secondary (acquired) resistance is a relapse after initial response. Currently available BCL2 inhibitors are Venetoclax, GDC-0199, SPC2996 and BGB-11417.

Please indicate whether the patient was resistant to a BCL2 inhibitor (**Absent**, **Present**, **No BCL2 inhibitor treatment**, **Unknown**).

If resistance was present please answer the following questions on the resistance mechanism:

Has any testing on the resistance mechanism been performed?

Were tests done to check if mutations that can impact the effectiveness of BCL2 inhibitor binding were present (**No**, **Yes**, **Unknown**)?

What was tested and what was the result?

Select all the tests performed on the resistance mechanism and indicate the result for each test.

Indicate if structural changes to the BCL2 inhibitor were tested. If tested, indicate whether the changes were present or absent. Structural changes to the BCL2 protein can be caused, for example, by one or more of the following mutations: Phe101Cys, Phe101Leu, Phe104Leu, Gly101Val, Asp103Tyr.

Indicate if structural changes to the proteins downstream of BCL2 were tested. If tested, indicate whether the changes were present or absent. Examples of proteins downstream of BTK where structural changes can occur: BCL-XL and MCL-1.

If another mechanism of resistance was tested please select **Other** and specify what was tested in the text field.

Prolymphocytic (PLL) and Other Chronic Leukaemias

Disease

Sub-Classification (WHO 2022): 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.

T-Prolymphocytic leukaemia (T-PLL) is a very rare leukaemia characterised by high and rapidly growing peripheral counts of monoclonal T-cells with a CD4+ immunophenotype. T-PLL is often widespread at diagnosis and involves the peripheral blood (PB), bone marrow (BM), lymph nodes, liver, spleen, and skin. The disease is mostly insensitive to chemotherapy and the prognosis is unfavourable. The diagnosis is made on morphologic characteristics, immunophenotype and cytogenetics.

Hairy cell leukaemia (HCL) is always of B-cell origin. It is characterised by the presence of abnormal B-cells with hair-like projections on their surface, giving them a "hairy" appearance under a microscope. Most patients are not leukaemic but pancytopenic (low haemoglobin, low leukocyte count, low platelet count) which can make the diagnosis difficult. Usually, the patients do not present with enlarged lymph nodes, but they do have a large spleen. Long remissions can be obtained with conventional treatment. The disease is rare and candidates for transplantation are even more unique.

Splenic B-cell lymphoma/leukaemia with prominent nucleoli (SBLPN) is a new entity in the WHO 2022 classification that replaces the previous terms “hairy-cell leukaemia variant” and “CD5-negative B-prolymphocytic leukaemia (B-PLL)” . It is characterised by the presence of prominent nucleoli. Diagnosis typically involves a combination of blood tests, imaging studies (such as CT scans or MRI), and bone marrow biopsy to confirm the presence of abnormal B-cells with prominent nucleoli.

Chromosome analysis

Complete this section only for T-PLL

Chromosome analysis done before HCT/CT treatment

In this section, describe the results of all chromosome analyses (all methods including FISH) performed at/after diagnosis but before the HCT/CT treatment. If there were multiple chromosome analysis tests done on different dates, the results can be registered separately along with the test date.

Indicate if chromosome analysis was done or not before the HCT/CT treatment. Check **Unknown** if it is not known whether it was performed.

Output of analysis

Indicate if the output of the chromosome analysis will be reported as **separate abnormalities** or as a **full karyotype**.

What were the results?

Normal - the chromosome analysis has been performed and the results have been found normal

Abnormal - the chromosome analysis has been performed and abnormalities have been found. In addition, indicate the total number of different abnormalities present (**number of abnormalities present**).

Failed - the chromosome analysis was done but failed

Date of T-PLL chromosome analysis

Indicate the date of the chromosome analysis.

Chromosome analysis details

Indicate for each abnormality in the table whether it was **Absent**, **Present**, **Not evaluated** or **Unknown** .

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**.

Transcribe the complete karyotype

If it is not possible to report the chromosome analysis results as per the abnormalities table please enter the complete karyotype.Describe all abnormalities according to the ISCN karyotype nomenclature. This notation includes the total number of chromosomes, the sex chromosomes, and any extra, missing or mutated 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-PLL.

Immunophenotype of T-cells at diagnosis

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

Indicate if phenotypes CD4+ and CD8+ were **Absent**, **Present** or **Not evaluated**. Mark **Unknown** if this information is unavailable.

Lymphocyte count at diagnosis

Report the lymphocyte count (x10^9/L) for T-PLL at diagnosis or mark if it was **Not evaluated** or **Unknown**.

Was mantle cell lymphoma excluded at diagnosis?

Indicate whether mantle cell lymphoma was excluded or not. If yes, please specify the methods used by checking all that apply. Mark **Unknown** if this information is unavailable.

Extended dataset

PREVIOUS THERAPIES (between diagnosis and HCT/CT)

Previous therapy lines before the HCT/CT/GT

Indicate if the patient underwent any previous therapy lines related to Prolymphocytic (PLL) before the HCT/CT/GT 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, complete the "Treatment non-HCT/CT/GT/IST" form.

Answer the following questions for treated patients only.

Purine analogue-refractory?

Purine analogue-containing regimens are regimens that contain one of the following drugs: Fludarabine, Clofarabine, Cladribine, Azathioprine, Mercaptopurine, Thioguanine, Nelarabine or Pentostatin. Refractory is defined as a non-response or relapse within 6 months after completion of the purine analogue-containing chemotherapy.

Indicate whether the patient was considered to be purine analogue-refractory (**No**, **Yes**, **No purine analogue-containing chemotherapy treatment**, **Unknown**).

Resistance to a BTK inhibitor?

Resistance to BTK inhibitors can either be primary or secondary. Primary resistance is a failure to respond to BTK inhibitor treatment upfront. Secondary (acquired) resistance is a relapse after initial response. Currently available BTK inhibitors are: Ibrutinib, Acalabrutinib, Zanubrutinib, Pirtobrutinib and ONO-4059.

Please indicate whether the patient was resistant to a BTK inhibitor (**Absent**, **Present**, **No BTK inhibitor treatment**, **Unknown**).

If resistance was present please answer the following questions on the resistance mechanism:

Has any testing on the resistance mechanism been performed?

Were tests done to check if mutations that can impact the effectiveness of BTK inhibitor binding were present (**No**, **Yes**, **Unknown**)?

What was tested and what was the result?

Select all the tests performed on the resistance mechanism and indicate the result for each test.

Indicate if structural changes to the BTK inhibitor were tested. If tested, indicate whether the changes were present or absent. Structural changes to the BTK protein can be caused, for example, by one or more of the following mutations: C481, T316A, L528W, V416L, A428D, M437R, T474I.

Indicate if structural changes to the proteins downstream of BTK were tested. If tested, indicate whether the changes were present or absent. Examples of proteins downstream of BTK where structural changes can occur: PLCG2 and CARD11.

If another mechanism of resistance was tested please select **Other** and specify what was tested in the text field.

Resistance to a BCL2 inhibitor?

Resistance to BCL2 inhibitors can either be primary or secondary. Primary resistance is a failure to respond to BCL2 inhibitor treatment upfront. Secondary (acquired) resistance is a relapse after initial response. Currently available BCL2 inhibitors are Venetoclax, GDC-0199, SPC2996 and BGB-11417.

Please indicate whether the patient was resistant to a BCL2 inhibitor (**Absent**, **Present**, **No BCL2 inhibitor treatment**, **Unknown**).

If resistance was present please answer the following questions on the resistance mechanism:

Has any testing on the resistance mechanism been performed?

Were tests done to check if mutations that can impact the effectiveness of BCL2 inhibitor binding were present (**No**, **Yes**, **Unknown**)?

What was tested and what was the result?

Select all the tests performed on the resistance mechanism and indicate the result for each test.

Indicate if structural changes to the BCL2 inhibitor were tested. If tested, indicate whether the changes were present or absent. Structural changes to the BCL2 protein can be caused, for example, by one or more of the following mutations: Phe101Cys, Phe101Leu, Phe104Leu, Gly101Val, Asp103Tyr.

Indicate if structural changes to the proteins downstream of BCL2 were tested. If tested, indicate whether the changes were present or absent. Examples of proteins downstream of BTK where structural changes can occur: BCL-XL and MCL-1.

If another mechanism of resistance was tested please select **Other** and specify what was tested in the text field.