EBMT Registry

Plasma cell neoplasms (PCN)

Guide to the completion of the EBMT data collection form: PCD_incl_MM_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.

Plasma cell neoplasms (PCN)

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

PCN are a group of disorders characterised by the abnormal proliferation of plasma cells, which are a type of white blood cell responsible for producing antibodies. Diagnosis of PCN typically involves a combination of blood tests, bone marrow biopsies, imaging studies (such as X-rays or MRIs), and urine tests to detect abnormal proteins produced by the plasma cells.

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 classification of the plasma cell neoplasm according to WHO 2022[1].

Plasma cell (multiple) myeloma (PCM)

PCM (synonyms: 'Multiple Myeloma (MM)', 'Myeloma', 'myelomatosis') is a malignant lymphoproliferative disorder arising from a clonal plasma cell population. The malignant cells usually produce a monoclonal immunoglobulin readily identifiable in either the plasma (M-component) or the urine (Bence Jones' protein or urinary light chains). The most common clinical presentation in PCM is skeletal damage with lytic bone lesions and generalised osteopenia. Other features include anaemia,

hypogammaglobulinemia, renal failure and hypercalcaemia. Indicate the subtype of PCM by checking the corresponding checkbox or select 'Unknown' if this information is not available.

Heavy chain and light chain

Heavy chain and light chain is the most common PCM subtype in which the malignant plasma cells secrete a complete monoclonal immunoglobulin (M-component) which consists of both a heavy chain (IgG, IgA, IgD, IgM or IgE) and a light chain (kappa or lambda). The heavy chain is usually either IgG (c.50%) or IgA (c.20%), rarely IgD and very rarely, IgM or IgE.

Please make sure to indicate for this PCM subclassification both the heavy chain type (IgG, IgA, IgD, IgM or IgE) and the light chain type (kappa or lambda).

Light chain only

Light chain only is a PCM subtype where the malignant plasma cells only secrete a light chain component, which can be either kappa or lambda. This constitutes about 20% of all cases of PCM. The light chain can either be detected and quantitated in the serum using the Serum Free Light Chain Assay or in the urine by measuring urinary light chain excretion.

Please make sure to indicate the light chain type (kappa or lambda).

Non-secretory

Non-secretory (synonym: non-producing) is a PCM subtype in which no monoclonal protein is detected in either the serum or the urine. The diagnosis is therefore based on a tissue biopsy, usually the bone marrow. Given the sensitivity of the serum free light chain assay, this is quite rare. Do not classify as non-secretory if the serum free light chain assay has not been performed.

Heavy chain type: IgG-IgA-IgD-IgE-IgM

Please record the heavy chain type of the M component in the **heavy chain and light chain** type PCM. It should be left blank for light chain PCM and for non-secretory PCM. If the type is unknown, select the corresponding checkbox.

Please note that although there is only one M-component in almost all cases, two (for example, IgG and IgA) may rarely appear simultaneously in the serum/plasma. This is termed biclonal PCM. In these cases, the chain type of the highest value should be selected.

Light chain type: Kappa-Lambda

Please record the type of light chain (kappa or lambda) for heavy chain and light chain PCM and for light chain only PCM. It should be left blank in non-secretory PCM. If the type is unknown, select the corresponding checkbox.

Plasma cell leukaemia

Plasma cell leukaemia is a rare and aggressive form of plasma cell neoplasm characterised by the presence of a high number of malignant plasma cells in the blood. This condition is considered a variant of PCM, but it is distinguished by the significant involvement of plasma cells in the peripheral blood.

Symptoms of plasma cell leukaemia may include anaemia, fatigue, bone pain, recurrent infections, and bleeding disorders. Diagnosis typically involves blood tests, bone marrow biopsies, and imaging studies to assess the extent of the disease.

Due to its aggressive nature, plasma cell leukaemia has a poorer prognosis compared to other forms of plasma cell neoplasms.

Solitary plasmacytoma of bone

Solitary plasmacytoma of bone is a rare type of plasma cell neoplasm that involves the abnormal growth of plasma cells in a single bone or a small group of adjacent bones. Unlike PCM, which affects multiple bones and organs, solitary plasmacytoma of bone is localised and does not involve widespread disease. This condition typically presents as a single bone lesion, most commonly in the spine, pelvis, or ribs. Symptoms may include bone pain, fractures, and swelling at the site of the lesion. Diagnosis of solitary plasmacytoma of bone involves imaging studies such as X-rays, CT scans, or MRIs.

Immunoglobulin-related (AL) amyloidosis

Immunoglobulin-related (AL) amyloidosis (previously referred to as systemic AL amyloidosis), is a monoclonal plasma cell proliferative disorder. The amyloid protein is derived from abnormal plasma cells that produce monoclonal immunoglobulin light chains, which then form insoluble fibrils that deposit in tissues and disrupt normal function. These amyloid deposits can affect multiple organs, including the heart, kidneys, liver, nerves, and gastrointestinal tract, leading to a wide range of symptoms and complications.

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy/Edema, Monoclonal-protein, Skin changes)

POEMS syndrome is a rare multisystem disorder that affects multiple organs in the body. The name "POEMS" stands for Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes. This condition is caused by the abnormal growth of plasma cells in the bone marrow, leading to the overproduction of a type of protein called monoclonal gammopathy. The excessive production of this protein can cause a variety of symptoms and complications throughout the body.

Some common symptoms of POEMS syndrome include peripheral neuropathy (nerve damage in the extremities), organomegaly (enlarged organs such as the liver or spleen), endocrine abnormalities (such

as diabetes or thyroid dysfunction), skin changes (such as thickening or darkening of the skin), and the presence of monoclonal gammopathy in the blood.

Diagnosis of POEMS syndrome typically involves a combination of clinical evaluation, blood tests, imaging studies, nerve conduction studies, and bone marrow biopsy to confirm the presence of abnormal plasma cells and monoclonal gammopathy.

Mandatory major criteria	1. Polyneuropathy (typically demyelinating) 2. Monoclonal plasma cell-proliferative disorder (almost always lambda)
Other major criteria (one required)	3. Castleman disease 4. Sclerotic bone lesions 5. Vascular endothelial growth factor elevation
Minor criteria (one required)	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) 7. Extravascular volume overload (edema, pleural effusion, or ascites) 8. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) 9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid haemangiomata, plethora, acrocyanosis, flushing, white nails) 10. Papilledema 11. Thrombocytosis/polycythemia
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhoea, low vitamin B12 values

Table 1. Diagnostic criteria of POEMS syndrome.

Monoclonal immunoglobulin deposition disease

Monoclonal immunoglobulin deposition disease (MIDD) is a rare disorder characterised by the abnormal deposition of monoclonal immunoglobulin fragments in various tissues and organs of the body. This condition is closely related to other plasma cell neoplasms, such as PCM and Immunoglobulin-related (AL) amyloidosis, and is often associated with the overproduction of abnormal monoclonal immunoglobulins by plasma cells. The deposited immunoglobulin fragments can accumulate in organs such as the kidneys, heart, liver, and skin, leading to tissue damage and dysfunction.

Symptoms of MIDD can vary depending on the organs affected but may include kidney dysfunction, proteinuria (protein in the urine), edema (swelling), heart failure, liver abnormalities, and skin lesions.

Diagnosis of MIDD typically involves a combination of blood tests, urine tests, imaging studies, and tissue biopsies to confirm the presence of monoclonal immunoglobulin deposits and assess organ involvement.

Based on the type of monoclonal immunoglobulin deposits, monoclonal immunoglobulin deposition disease can be classified into three types:

- Light chain deposition disease (LCDD; approximately 80 percent of cases) – Deposits are composed of light chains only. In approximately 80 to 90 percent of LCDD, the light chains are kappa light chains.
- Heavy chain deposition disease (HCDD; approximately 10 percent of cases) – Deposits are composed of heavy chains only.
- Light and heavy chain deposition disease (LHCDD; approximately 10 percent of cases) – Deposits are composed of both light and heavy chains.

Other

If the classification of plasma cell disorder is not listed, check the box “Other” and specify it (e.g. Nemalinic myopathy should be registered under “Other”).

Note: rarely, plasmacytomas can occur on different sites simultaneously. This would be called “multiple plasmacytomas”. Bone marrow infiltration must be excluded.

Below is a table to help with the registration of the PCN diagnosis if multiple PCN have been diagnosed in the patient history:

Main diagnosis is PCM, this is the usual indication for HCT	
Plasmacytoma:	
Precedes the PCM diagnosis	The plasmacytoma is not considered the indication for the HCT and we do not require that it be registered
POEMS:	
Simultaneous to the PCM diagnosis	This would be considered as POEMS, and POEMS should be registered as indication for HCT
After HCT for PCM	POEMS, to be registered as secondary malignancy

Monoclonal immunoglobulin deposition disease:	
Precedes the PCM diagnosis Simultaneous to the PCM diagnosis	Monoclonal immunoglobulin deposition disease is considered as a diagnosis on its own. However, if it is not considered to be an indication for HCT, it does not need to be registered. If Monoclonal immunoglobulin deposition disease is considered to also be an indication for HCT, then both diagnoses should be registered as main.
After HCT for PCM	Monoclonal immunoglobulin deposition disease, to be registered as secondary malignancy
Immunoglobulin-related (AL) amyloidosis:	
Precedes the PCM diagnosis Simultaneous to the PCM diagnosis	If the patient has both diagnoses, then the indication for HCT is PCM.
After HCT for PCM	Immunoglobulin-related (AL) amyloidosis to be registered as a secondary diagnosis

Table 2. Classification of Plasma Cell Neoplasms (PCN).

Extended dataset

Clinical and laboratory data (at diagnosis)

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**.

Serum creatinine (µmol/L)

To monitor kidney function, serum creatinine should be reported. Creatinine is a substance produced by the muscle which is filtered, reabsorbed and secreted by the tubular kidney. Therefore, the serum creatinine level in a patient is a good indication of renal function. Mean serum creatinine values differ between males and females (due to differences in muscle mass and, therefore, creatinine generation) as well as other factors.

Please provide the amount of creatinine present in the serum in micromol/litre (µmol/l). If the serum creatinine was not tested, select **not evaluated.** If the value is not known, select **unknown**.

Serum calcium (mmol/L)

Serum calcium levels are normally tightly controlled within a narrow range, usually 2.2 to 2.6 mmol/L. In multiple myeloma patients, these levels are often abnormally high (hypercalcemia).

Please provide the amount of calcium present in the serum in millimol/litre (mmol/l). If the serum calcium was not tested, select **not evaluated**. If the value is not known, select **unknown**.

Serum albumin (g/L)

Albumin is synthesised in the liver and serum albumin tests therefore reflect the condition of the liver. The normal range is 34 to 54 g/L.

Please provide the amount of albumin present in the serum in grams/litre (g/l). If the serum albumin was not tested, select **not evaluated**. If the value is not known, select **unknown**.

Serum β2 microglobulin (mg/L)

β2 microglobulin is one of the most important independent prognostic factors in multiple myeloma.

Please provide the amount of β2 microglobulin present in the serum in milligram/litre (mgl/l). If the serum β2 microglobulin was not tested, select **not evaluated.** If the value is not known, select **unknown**.

LDH Levels (at diagnosis)

The LDH (lactate dehydrogenase) value refers to the level of this enzyme at diagnosis and can be found in the patient's file. It is a prognostic marker with elevated values being unfavourable. In general, the normal ranges for an LDH (lactate dehydrogenase) blood test include:

People assigned male at birth: 135 – 225 international units per litre (IU/L).

People assigned female at birth: 135 – 214 international units per litre (IU/L).

Please note: the actual normal values may vary from laboratory to laboratory and from one type of testing protocol to another. Therefore, it is very important to check the reference range of the test set by the laboratory and report these as the LDH lower limit and LDH upper limit. Without the specific reference range of the laboratory, it is difficult to interpret the results.

LDH (IU/L)

Please report the LDH level reported by the laboratory in international units per litre (IU/L). If the LDH level was not tested, select **not evaluated**. If the value is not known, select **unknown**.

LDH lower limit (IU/L)

Please report the lower limit of the reference range used by the laboratory that performed the test in international units per litre (IU/L). If the LDH level was not tested, select **not evaluated**. If the lower limit is not known, select **unknown**.

LDH upper limit (IU/L)

Please report the upper limit of the reference range used by the laboratory that performed the test in international units per litre (IU/L). If the LDH level was not tested, select **not evaluated.** If the upper limit is not known, select **unknown**.

Staging (PCM only)

Staging at diagnosis

Revised ISS

Indicate Revised ISS stage (R-ISS) according to the parameters listed in table 3.

Revised ISS definitions	
Stage	**Definition**
I	I: ISS I without high risk FISH (del(17p) and/or t(4;14) and/or t(14;16)) and normal LDH
II	II: not R-ISS I or III
III	III: ISS III with high risk FISH (del(17p) and/or t(4;14) and/or t(14;16)) and/or high LDH
Unknown	The R-ISS stage is not known.

Table 3. Definitions of Revised ISS stages.

ISS

Indicate ISS stage[2] according to the parameters listed in table 4.

ISS definitions	
Stage	**Definition**
I	B2-µglob (mg/L) <3.5 and albumin (g/L) >35
II	B2-µglob (mg/L) <3.5 and albumin (g/L) <35 **or** B2-µglob (mg/:L) 3.5 ≤ 5.5 and any albumin level
III	B2-µglob (mg/L) >5.5 and any albumin level
Unknown	The ISS stage is not known.

Table 4. Definitions of ISS stages.

Extramedullary disease (EMD)

EMD is an aggressive form of PCM, characterised by the ability of a clone and/or subclone to thrive and grow independently of the bone marrow microenvironment.

Please indicate if extramedullary involvement was diagnosed or not, or mark as unknown by ticking the corresponding box.

If EMD was diagnosed, please fill out the corresponding sub questions and indicate the method of diagnosis, the location of EMD, the number of sites, and specify the organs involved.

Chromosome analysis

Chromosome analysis done at diagnosis

In this section, describe the results of the chromosome analysis (all methods including FISH) for all PCN diagnoses.

Indicate if chromosome analysis was done or not at time of diagnosis. Check **Unknown** if it is not known whether it was performed.

Note: Chromosome analysis is very important since specific abnormalities have emerged as one of the major prognostic factors. Please complete this section as carefully as possible in each single patient.

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

Note: **'Normal' is generally not an answer option** for this question, because that would imply that the test was not performed on bone marrow plasma cells.

Date of chromosome analysis

Indicate the date of the chromosome analysis. Select **Unknown** if the date is unavailable.

Chromosome analysis method

Indicate the method used for chromosome analysis. Abnormalities can be detected by all methods, though it is almost always by FISH for PCN.

Chromosome analysis details

Indicate for each abnormality in the table whether it was **Absent, Present** or **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.**

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.

Extended dataset

Immunoglobulin-related (AL) amyloidosis

This form must be completed for all patients whose primary disease for which the HCT/CT treatment is being given is Immunoglobulin-related Amyloidosis.

Immunoglobulin-related amyloidosis, also referred to as immunoglobulin light chain (AL) amyloidosis, is a monoclonal plasma cell proliferative disorder. The amyloid protein is derived from abnormal plasma cells that produce monoclonal immunoglobulin light chains, which then form insoluble fibrils that deposit in tissues and disrupt normal function. These amyloid deposits can affect multiple organs, including the heart, kidneys, liver, nerves, and gastrointestinal tract, leading to a wide range of symptoms and complications.

Systemic presentations — The clinical presentation in AL amyloidosis depends on the number and extent of the organs affected. In some patients, only one organ is affected, whereas in others, there is extensive multi-organ involvement.

Common presentations include nephrotic syndrome. restrictive cardiomyopathy, peripheral and autonomic neuropathy, hepatomegaly with raised liver enzyme levels, macroglossia and purpura.

Evidence of underlying Plasma Cell Neoplasm

Amyloidosis may be the sole diagnosis, or it may be present in association with other plasma cell neoplasms such as PCM. All forms of systemic amyloidosis in which the fibrils are derived from monoclonal light chains are considered AL amyloidosis.

Some patients who ultimately show clinical evidence of AL amyloidosis present with what appeared to be monoclonal gammopathy of undetermined significance (MGUS). Once a diagnosis of AL amyloidosis is made, the term MGUS no longer applies.

The presence of hypercalcemia, bone pain, or lytic bone lesions are suggestive of the dual diagnoses of both PCM and amyloidosis. The diagnosis of co-existing PCM applies to patients with amyloidosis who would otherwise meet the diagnostic criteria for PCM, including an infiltrate of plasma cells constituting more than 10% of bone marrow cellularity and one or more myeloma-defining events (MDEs) such as osteolytic bone lesions.

Please indicate if there is any evidence of an underlying plasma cell neoplasm like **Monoclonal Gammopathy**, **Plasma cell (multiple) myeloma** or **Other B-cell malignancy, specify**. Please specify in the text field in English the type of B-cell malignancy.

In case of Plasma cell (multiple) myeloma

Immunoglobulins

Please record the heavy chain type (IgG, IgA, IgD, IgM or IgE) of the M component. Select **Absent** for light chain PCM and for non-secretory PCM. If the type is unknown, select the corresponding checkbox.

Please note that although there is only one M-component in almost all cases, two (for example, IgG and IgA) may rarely appear simultaneously in the serum/plasma. This is termed biclonal PCM. In these cases, the chain type of the highest value should be selected.

Light chain

Please record the type of light chain (kappa or lambda) for heavy chain and light chain PCM and for light chain only PCM. Select **Absent** for non-secretory PCM. If the type is unknown, select the corresponding checkbox.

In case of Plasma cell (multiple) myeloma

Staging at diagnosis

Revised ISS

Indicate Revised ISS stage (R-ISS) according to the parameters listed in table 5.

Revised ISS definitions	
Stage	**Definition**
I	I: ISS I without high risk FISH (del(17p) and/or t(4;14) and/or t(14;16)) and normal LDH
II	II: not R-ISS I or III
III	III: ISS III with high risk FISH (del(17p) and/or t(4;14) and/or t(14;16)) and/or high LDH
Unknown	The R-ISS stage is not known.

Table 5. Definitions of Revised ISS stages.

ISS

Indicate ISS stage[2] according to the parameters listed in table 6.

ISS definitions	
Stage	**Definition**
I	B2-µglob (mg/L) <3.5 and albumin (g/L) >35
II	B2-µglob (mg/L) <3.5 and albumin (g/L) <35 **or** B2-µglob (mg/:L) 3.5 ≤ 5.5 and any albumin level
III	B2-µglob (mg/L) >5.5 and any albumin level
Unknown	The ISS stage is not known.

Table 6. Definitions of ISS stages.

Assessments at diagnosis

Tested at diagnosis

Diagnostic criteria for systemic AL Amyloidosis

The diagnosis of systemic AL amyloidosis by IMWG diagnostic criteria requires all of the following:

- Presence of an amyloid-related systemic syndrome (e.g. renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement)
- Positive amyloid staining by Congo red in any tissue (e.g. fat aspirate, bone marrow, or organ biopsy
- Evidence that amyloid is light-chain-related established by direct examination of the amyloid using mass spectrometry-based proteomic analysis, or immunoelectron microscopy, and
- Evidence of a monoclonal plasma cell proliferative disorder (serum or urine monoclonal protein, abnormal free light-chain ratio, or clonal plasma cells in the bone marrow)

Methods used for diagnosis

Mass spectrometry is the method of choice as immunohistochemistry and immunofluorescence have a higher risk of false positive and false negative results. However, this test is not widely available, and appropriate tissue samples need to be sent to referral centres. If available, immunoelectron microscopy is an alternative to mass spectrometry.

Please specify for each of the following methods whether the results are aligned with the patient's AL amyloidosis diagnosis.

Positive immunohistochemistry

Immunohistochemical staining (e.g. for kappa and lambda light chains, transthyretin, and serum amyloid A component) of the amyloid can determine the type of amyloidosis. However, immunohistochemical staining should only be done in centres with expertise with the antibodies as false negatives and false positives are common.

Indicate whether the light-chain type was confirmed as the causative protein by immunohistochemistry by selecting **Yes**. If it was not the causative protein, select **No**. Select **Unknown** if this information is not known.

Mass spectrometry

Laser microdissection with mass spectrometry (MS) combines tissue sampling by laser microdissection and tandem mass spectrometry-based proteomic analysis. This technique can identify all types of amyloidosis, including rare subtypes, with excellent specificity.

Indicate whether mass spectrometry was used to diagnose AL amyloidosis. Select **Yes** if it was used, **No** if it was not used or **Unknown** if this information is not known.

Immunoelectron microscopy

Immunoelectron microscopy combines immunohistochemistry and electron microscopy to confirm amyloid deposition and identify the protein within the amyloid fibrils.

Indicate whether immunoelectron microscopy was used to diagnose AL amyloidosis. Select **Yes** if it was used, **No** if it was not used or **Unknown** if this information is not known.

Proteomic analysis

Indicate whether proteomic analysis was used to diagnose AL amyloidosis. Select **Yes** if it was used, **No** if it was not used or **Unknown** if this information is not known.

Clinical and laboratory data

Total urinary protein excretion (mg/24 h)

The detection of proteins excreted in the urine has been extensively used to assess kidney disease. Total urinary protein excretion in the normal adult should be less than 150 mg/day. Higher rates of protein

excretion (proteinuria) identifies patients with kidney damage and those at risk for worsening kidney disease and increased cardiovascular morbidity.

Please provide the amount of total urinary protein excretion in milligrams per 24 hours (mg/24h). If it was not investigated, select **not evaluated.** If the value is not known, select **unknown**.

eGFR

Estimated Glomerular Filtration Rate (eGFR) is used to determine if there is a kidney disease and in which stage it is. A very low number may indicate kidney failure, which requires dialysis or a kidney transplant. eGFR is measured in millilitres of cleansed blood per minute per body surface (mL/min/1.73m^2).

Please provide the eGFR as listed on the lab report. If eGFR was not tested, select **not evaluated**. If the value is not known, select **unknown**.

Serum alkaline phosphatase (IU/L)

A decrease in the alkaline phosphatase value represents the primary measure of hepatic response. In patients who have hepatic involvement, the alkaline phosphatase abnormality should decrease by 50%. In other words, if the institutional normal value is 100 U/L, and the patient's alkaline phosphatase value is 200 U/L, it must decrease below 150 U/L to be considered a hepatic response. Progression is defined as an increase of greater than 50% above the lowest recorded value. If the institutional normal value for alkaline phosphatase is 100 U/L, and the patient's alkaline phosphatase value is 160 U/L, then a value of 240 U/L is required to reflect progressive disease. Right-sided heart failure can produce modest changes in alkaline phosphatase concentration. Recognition of this phenomenon is necessary when interpreting outcomes.

Please provide the amount of alkaline phosphatase present in the serum in international units/litre (IU/l). If the serum alkaline phosphatase was not tested, select not evaluated. If the value is not known, select unknown.

Serum bilirubin (mg/dL)

Please provide the amount of bilirubin present in the serum in milligrams/decilitre (mg/dl). If the serum bilirubin was not tested, select **not evaluated.** If the value is not known, select **unknown**.

Cardiac laboratory data

Cardiac biomarkers NT-proBNP and troponin have prognostic significance in systemic disease but can also be used in combination with clinical assessment to screen for the presence of cardiac involvement.

Serum NT-pro-BNP (ng/L)

N-terminal pro b-type natriuretic peptide (NT-pro-BNP) is a protein that's an "ingredient" for making the Brain natriuretic peptide (BNP) hormone. Like BNP, the heart makes larger amounts of NT-proBNP when it has to work harder to pump blood.

It's normal to have some BNP and NT-proBNP in the bloodstream, but higher than normal levels may be a sign of heart failure. Normal levels are less than 125 ng/L for people under 75 years old and less than 450 ng/L for people over age 75. NT-proBNP levels over 900 ng/L may be a sign of heart failure.

Please provide the amount of NT-pro-BNP in the serum in nanogram/litre. If the serum NT-pro-BNP was not tested, select **not evaluated**. If the value is not known, select **unknown**.

Serum BNP (ng/L)

Brain natriuretic peptide (BNP) 'tells' the blood vessels to open wider and the kidneys to get rid of water and salt through urine. This helps reduce the workload on the heart by lowering blood pressure and reducing the amount of blood the heart has to pump.

Please provide the amount of BNP in the serum in nanogram/litre. If the BNP was not tested, select **not evaluated**. If the value is not known, select **unknown**.

Serum c-Troponin T (µg/L)

Troponin T is a protein that is found in the cells of the heart muscle.

Normally, troponin levels in blood are so low that only the most sensitive types of tests can measure them. But if the heart muscle is damaged, troponin leaks into the bloodstream, and the troponin blood levels will rise. The more damage there is to the heart, the more troponin is released into the blood.

Please provide the amount of Troponin T in the serum in microgram/litre. If the serum cardiac Troponin T was not tested, select **not evaluated**. If the value is not known, select **unknown**.

Troponin lower limit (µg/L)

Please report the lower limit of the reference range used by the laboratory that performed the test in international units per litre (IU/L). If the LDH level was not tested, select **not evaluated**. If the lower limit is not known, select **unknown**.

Troponin upper limit (µgL)

Please report the upper limit of the reference range used by the laboratory that performed the test in international units per litre (IU/L). If the LDH level was not tested, select **not evaluated.** If the upper limit is not known, select **unknown**.

Bone marrow investigations

BM aspirate % plasmacytosis

The bone marrow (BM) aspirate % plasmacytosis represents the percentage of plasma cells of the total number of nucleated cells in cytologic bone marrow smears.

Please report the percentage of plasmacytosis in the bone marrow aspirate. If it was not tested, select **not evaluated**. If it is not known, select **unknown**.

BM trephine % plasmacytosis

'Trephine' means a special technique for bone marrow biopsy.

Please report the percentage of plasmacytosis in the bone marrow trephine. If it was not tested, select **not evaluated**. If it is not known, select **unknown**.

Immunoglobulins

Monoclonal Ig in serum (paraprotein) (g/L)

Monoclonal immunoglobulins (Ig) are secreted by an abnormally expanded clone of plasma cells. A frequently used synonym for monoclonal Ig is M-component, paraprotein, or monoclonal protein. Be sure to give the value of the monoclonal Ig. For example, the total IgG in a patient might be 53 g/L, but of this only 48 g might be monoclonal and the remaining 5 g polyclonal. In this situation, the correct value to report is 48.

Please report the value in grams per litre (g/L).

Immunofixation of serum

An immunofixation blood test is used to identify immunoglobulins in blood. A normal (**negative**) result means that the blood sample had normal types of immunoglobulins. The level of one immunoglobulin was not higher than any other. In case of abnormal (**positive**) results there were abnormal types of immunoglobulins found. If the immunofixation blood test was not done, select **not evaluated**. If the test result is not known, select **unknown**.

Free light chains in serum

A free light chains test measures the level of free light chains in the blood. Light chains are proteins made by plasma cells. Light chains usually link up with other proteins called heavy chains. Together, the light and heavy chains make immunoglobulins. Normally, plasma cells will make a small amount of extra light chains

that don't bind with heavy chains. Instead, they are put into the bloodstream. These unlinked chains are known as free light chains. There are two types of light chains: kappa and lambda light chains.

Kappa light chains (mg/L)

Please report the amount of kappa light chains found in the serum in milligram/litres. If the test was not done, select **not evaluated**. If the test result is not known, select **unknown**.

Lambda light chains (mg/L)

Please report the amount of lambda light chains found in the serum in milligram/litres. If the test was not done, select **not evaluated**. If the test result is not known, select **unknown**.

Immunofixation of urine

Urine immunofixation is a test that looks for abnormal proteins in urine. In particular, it looks for an abnormal protein known as monoclonal protein. Select **negative** if no monoclonal proteins were found in the urine. Select **positive** if monoclonal proteins were found in the urine. If the immunofixation of the urine was not tested, select **not evaluated.** If the test result is not known, select **unknown**.

Monoclonal light chains in urine (g/24h)

If immunofixation of urine was **positive** please report the amount of monoclonal light chains found in the urine in grams per 24 hours (g/24h). If the amount of monoclonal light chains in the urine was not tested, select **not evaluated.** If the value is not known, select **unknown**.

Bone imaging

Please indicate for each of the imaging techniques (X-ray, CT, MRI, PET-CT) whether the results were normal or if bone lesions were found. If a technique was not used, select **not evaluated**. If it is not known whether the technique was used, select **unknown.**

SERUM AMYLOID P SCINTIGRAPHY

Was serum Amyloid P Scintigraphy performed?

Serum amyloid P component is a normal plasma protein and a universal non-fibrillar constituent of amyloid deposits. Radiolabelled serum amyloid P component scintigraphy is a non-invasive and quantitative method for imaging amyloid deposits in vivo, which produces diagnostic images in most patients with systemic amyloidosis, and can be used repeatedly to monitor the course of the disease.

Please indicate whether serum amyloid P scintigraphy was performed and if yes, please report the involvement for each of the listed organs. If serum amyloid P scintigraphy was not carried out, please select **not evaluated.** If it is not known whether it was performed, select **unknown.**

Organ involvement

Please indicate the involvement as assessed by serum amyloid P scintigraphy of each of the following organs: heart, liver, spleen, and kidneys. If the organ was not investigated, select **not evaluated.** If it is not known whether the organ was investigated via serum amyloid P scintigraphy, select **unknown.**

Organ involvement untreated

For treatment purposes, organ involvement by amyloidosis is defined by consensus criteria created in 2005 at the 10th International Symposium on Amyloid and Amyloidosis and revised in 2011.

For the completion of the form, the organs in question need to be assessed by the treating physician, using clinical examination and different laboratory methods , and the physician's decision on organ involvement needs to be documented in the patient file.

Please report here the organ status of the patient prior to any treatment.

The categories are: Kidneys, Heart, Gastrointestinal tract, Liver, Peripheral nerves, Autonomic nerves, Skin, and Bone Marrow.

Dominant organ(s) involved

Most patients have more than 1 organ involved, however one organ is often leading regarding clinical symptoms.

Please indicate which organ(s) is(are) leading regarding the clinical symptoms and thus considered the dominant organ(s) involved.

Additional organ(s) involvement

All other involved organs should be listed. It is not necessary to make a biopsy of all organs to diagnose involvement by amyloidosis.

Please indicate for each organ if they are involved in addition to the dominant organ(s) involved.

No involvement

Please select this option if there are no clinical symptoms or typical lab values that this organ is involved.

Unknown

If it is not known whether the organ is involved or not, select unknown.

Not evaluated
Select this option in case the organ was not evaluated.

Biopsy done

Indicate for each organ that was involved (as dominant or additional organ) or not involved, if a biopsy was done or not. If this information is not available, please select **Unknown**.

Organ-specific data untreated

Liver

Liver span in ultrasound or CT scan (cm craniocaudal diameter)

Please report the craniocaudal diameter of the liver in centimetres as assessed on ultrasound or CT scan. If the liver span was not investigated, select **not evaluated.** If it is not known whether this was evaluated, select **unknown.**

Heart

NYHA class

Please report the New York Heart Association (NYHA) class according to the following criteria:

Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III: patients with marked limitation of activity; they are comfortable only at rest.
Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

If this information is not available, please select **Unknown**.

Left ventricular ejection fraction (%)

Left ventricular ejection fraction (LVEF) is the most commonly reported clinical metric of global left ventricular systolic function. It is an important tool in the diagnosis and monitoring of heart failure and certain types of cardiomyopathies. An ejection fraction of less than 40 percent may be present in these conditions.

Please report the LVEF in percentage. If the LVEF was not investigated, select **not evaluated**. If it is not known whether the LVEF was assessed, select **unknown**.

Echocardiogram consistent with amyloidosis

Please report whether the echocardiogram results were consistent with amyloidosis. If the test was not done, select **not evaluated**. If the test result is not known, select **unknown**.

Cardiac MRI consistent with amyloidosis

Please report whether the cardiac MRI results were consistent with amyloidosis. If the test was not done, select **not evaluated**. If the test result is not known, select **unknown**.

Gastrointestinal

Weight loss

Loss of weight more or less despite adequate nutrition, mostly combined with loss of appetite.

Please indicate whether weight loss was present or not. If it is not investigated, select **not evaluated**. If it is not known whether weight loss was present or not, select **unknown**.

Malabsorption

Patients with GI involvement often have diarrhoea which leads to a reduced absorption of some components of food, e.g. vitamins, calcium, fat, iron.

Please indicate whether malabsorption was present or not. If it is not investigated, select **not evaluated**. If it is not known whether malabsorption was present or not, select **unknown**.

GI bleeding

GI bleeding is a feared complication of GI involvement. It can occur spontaneously or often after colonoscopy (and perforation) and other interventions.

Please indicate whether GI bleeding occurred or not. If it is not investigated, select **not evaluated**. If it is not known whether GI bleeding occurred or not, select **unknown**.

Other evidence of gastrointestinal involvement

Please describe other symptoms present that point to gastrointestinal involvement (e.g. gastric ulcer) in the text box in English.

Peripheral neuropathy

Peripheral neuropathy happens when the nerves that are located outside of the brain and spinal cord (peripheral nerves) are damaged. This condition often causes weakness, numbness and pain, usually in the hands and feet. It also can affect other areas and body functions including digestion and urination.

Neurological exam

Please indicate whether the results of the neurological exam were normal or abnormal. If the neurological exam was not done, select not evaluated. If the test result is not known, select unknown.

Neuropathy confirmed on nerve conduction studies

A nerve conduction velocity (NCV) test measures how fast an electrical impulse moves through the nerve. NCV can identify nerve damage. This test is also called a nerve conduction study.

Please report whether the NCV test confirmed neuropathy. If the test was not done, select not evaluated. If the test result is not known, select unknown.

Autonomic neuropathy

Orthostatic hypotension

Orthostatic hypotension consists of symptoms of dizziness, faintness or light-headedness which appear only on standing, and which are caused by low blood pressure.

Please indicate whether orthostatic hypotension was present or not. If it is not investigated, select **not evaluated**. If it is not known whether orthostatic hypotension was present or not, select **unknown**.

Intractable diarrhoea

This is a severe diarrhoea unresponsive to conventional treatment leading to hypoproteinemia by severe protein losing enteropathy.

Please indicate whether intractable diarrhoea was present or not. If it is not investigated, select **not evaluated**. If it is not known whether intractable diarrhoea was present or not, select **unknown**.

Other sites

Clinical evidence for involvement of other sites

Please report any clinical evidence for involvement of other sites than listed above in the text box in English. For example: Faktor X deficiency, arthropathy, skin involvement.

Plasma cell neoplasms (PCN)

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 PCN 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.

Immunoglobulin-related (AL) amyloidosis

Organ response to therapy given before the HCT/CT given

Please see table 7 for definitions of organ response and progression.

Organ	Response	Progression
Heart	• NT-proBNP response (>30% and >300 ng/L decrease in patients with baseline NT-proBNP ≥650 ng/L) or • NYHA class response (≥2 class decrease in subjects with baseline NYHA class 3 or 4).	• NT-proBNP progression (>30% and >300 ng/L increase)* or • cTn progression (≥33% increase) or • ejection fraction progression (≥10% decrease)
Kidney	• ≥30% decrease (at least 0.5 g/day) of 24-hr urine protein (urine protein must be > 0.5 g/day pretreatment) • Creatinine and creatinine clearance must not worsen by 25% over baseline	• ≥25% decrease in eGFR
Liver	• 50% decrease in abnormal alkaline phosphatase value • Decrease in liver size radiographically at least 2 cm	• 50% increase of alkaline phosphatase above the lowest value
Peripheral nervous system	• Improvement in electromyogram nerve conduction velocity	• Progressive neuropathy by electromyography or nerve conduction velocity

Table 7. Definitions of organ response and progression.

* Patients with progressively worsening renal function cannot be scored for NT-proBNP progression.(3)

Bibliography

1. Alaggio, R., Amador, C., Anagnostopoulos, I. et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 36, 1720–1748 (2022). https://doi.org/10.1038/s41375-022-01620-2
2. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, Richardson P, Caltagirone S, Lahuerta JJ, Facon T, Bringhen S, Gay F, Attal M, Passera R, Spencer A, Offidani M, Kumar S, Musto P, Lonial S, Petrucci MT, Orlowski RZ, Zamagni E, Morgan G, Dimopoulos MA, Durie BG, Anderson KC, Sonneveld P, San Miguel J, Cavo M, Rajkumar SV, Moreau P. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015 Sep 10;33(26):2863-9. doi: 10.1200/JCO.2015.61.2267. Epub 2015 Aug 3. PMID: 26240224; PMCID: PMC4846284.
3. Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia 2012; 26:2317.