EBMT Registry

Disease specific best response and disease status

Guide to the completion of the EBMT data collection forms

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EBMT Registry

EBMT Clinical Research & Registry Department

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Introduction

The aim of this document is to provide users with the definitions of the disease statuses and best responses. Since these definitions vary between diagnosis, the document is split into sections by diagnosis:

- Acute leukaemias;
- Chronic leukemias;
- Plasma cell neoplasms;
- MPN, MDS, MDS/MPN overlap syndromes;
- Lymphomas;
- Solid tumours;
- Bone marrow failure syndromes (BMF) including aplastic anaemia (AA);
- Autoimmune disorders;
- Haemoglobinopathies;
- Other diagnoses;
- Inborn errors.

Acute leukaemias

This section is applicable to acute myeloid leukaemias (AML), precursor lymphoid neoplasms (PLN) and other acute leukaemias.

Disease status or best response	
Complete remission (CR) is defined as meeting all of the following response criteria for at least four weeks: ● <5% leukemic blasts in the bone marrow ● No blasts with Auer rods (applies to AML only) ● No extramedullary disease (e.g., CNS, soft tissue disease)	**Not in complete remission:** In accordance with the defined criteria for complete remission (CR), a patient would not attain complete remission if they do not fulfil at least one of the complete remission criteria.

Table 1. Acute leukaemias disease status or best response.

Chronic leukaemias

The chronic leukaemias section is split into chronic myeloid leukaemia (CML) and chronic lymphocytic leukaemia (CLL), prolymphocytic leukaemia (PLL) and other chronic leukaemias.

Chronic myeloid leukaemia

Disease status or best response:

- Chronic phase (CP) and type of remission (haematological, cytogenetic, molecular);
- Accelerated phase;
- Blast crisis.

Disease status or best response		
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 2. 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.

Disease status or best response (only CP)		
Haematological remission	**Cytogenetic remission**	**Molecular remission**
Haematological remission is defined by a patient meeting all of the following: • WBC < 10 x 10^9 /L • Haemoglobin > 11.0 g/dL • Platelet Count < 450 x10^9 /L • Normal Differential (<1% precursor cells) • No palpable splenomegaly • No extramedullary disease	Cytogenetic remission is defined by: • 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	Molecular remission is defined by: • Cells with the BCR::ABL1 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.

Table 3. Definitions of haematological, cytogenetic and molecular remission for patients in chronic phase.

Chronic lymphocytic leukaemia (CLL), prolymphocytic leukaemia (PLL) and other chronic leukaemias

Disease status or best response:

- Complete Remission (CR);
- Partial Remission (PR);
- Progression;
- Stable Disease (SD);
- Relapse.

Relapse is defined as evidence of disease progression (see table. 4) in a patient who has previously achieved the criteria of a CR or PR see table. 4) for ≥6 months.

Group	Parameter	Complete Remission (CR)	Partial Remission (PR)	Stable Disease (SD)	Progressive Disease (PD)
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)*	Change of −49% to +49%	Increase ≥50% from baseline or from response
	Liver and/or spleen size†	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Change of −49% to +49%	Increase ≥50% from baseline or from response
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Change of −49% to +49%	Increase ≥50% over baseline
B	Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% over baseline	Change of −49 to +49%	Decrease of ≥50% from baseline secondary to CLL
	Haemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/dL	Decrease of ≥2 g/dL from baseline secondary to CLL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	No change in marrow infiltrate	Increase of CLL cells by ≥50% on successive biopsies

Table 4. Response evaluation according to 2018 iwCLL criteria.

*Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).
†Spleen size is considered normal if <13 cm. There is not a firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation. For the EBMT Registry, clinical (palpation) evaluation only without CT-scan (or alternate imaging), according to routine practice, is accepted.

Disease status or best response CLL	
Complete Remission (CR)	See table 4 for detailed criteria. All of the criteria have to be met. Note: ● If a patient has all CR criteria but has persistent cytopenia, the patient can be considered as a CR as an adaptation of these guidelines. ● If a patient has all criteria of a CR but bone marrow evaluation has not been performed (even with persistent cytopenia), the patient can be considered as a CR as an adaptation of these guidelines.
Partial Remission (PR)	See table 4 for detailed criteria. At least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve. Clinical (palpation) evaluation only without CT-scan (or alternate imaging), according to routine practice, is accepted.

Stable Disease (SD)	See table 4 for detailed criteria. All of the criteria have to be met.
Progression	At least 1 of the criteria of group A or group B has to be met. Sequential imaging is not warranted in CLL outside clinical trials and is not required for the EBMT Registry.

Table 5. Additional clarifications for Chronic lymphocytic leukaemias disease status classification.

Group	**Parameter**	**CR (all met)**	**PR (≥2 in A and ≥1 in B)**	**SD (all met)**	**PD (≥1 in A or B met)**
A	Lymph nodes	long-axis diameters to <1.0 cm	Decrease ≥30% in SLD	Change of − <30% to + ≤20%	Increase >20% in SLD
	Spleen†	Spleen size <13 cm	Decrease ≥50% in vertical length beyond normal from baseline	Change of −49% to +49% beyond normal from baseline	Increase ≥50% in vertical length beyond normal from baseline
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	<4 × 10^9/L	≤30 × 10^9/L and decrease ≥50% from baseline	>30 × 10^9/L or change of −49% to +49%	Increase ≥50% from baseline
	Marrow	T-PLL cells <5% of mononuclear cells	Any	Any	Any
	Any other specific site involvement*	None	Any	Any	Any
B	Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% from baseline	Change of −49% to +49%	Decrease of ≥50% from baseline
	Haemoglobin	≥11.0 g/dL (untransfused)	≥11 g/dL or increase ≥50% from baseline	<11.0 g/dL or <50% from baseline, or change <2 g/dL	Decrease of ≥2 g/dL from baseline
	Neutrophils	≥1.5 × 10^9/L	≥1.5 × 10^9/L or increase ≥50% from baseline	Change of −49% to +49%	Decrease of ≥50% from baseline

Table 6. T-PLL response evaluation according to the T-PLL consensus criteria.

SLD: sum of long-axis diameters of up to 3 target lesions
*Pleural or peritoneal effusion, skin infiltration, central nervous system involvement.
† For the EBMT Registry, clinical (palpation) evaluation only without CT-scan or alternate imaging, according to routine practice, is accepted.

Disease status: additional clarifications T-PLL	
Complete Remission (CR)	See table 6 for detailed criteria. All of the criteria have to be met, however a few exceptions are possible: ● If a patient has all CR criteria but has persistent cytopenia, the patient can be considered as being in CR as an adaptation of these guidelines. ● If a patient has all criteria of CR but bone marrow evaluation has not been performed (even with persistent cytopenia), the patient can be considered as being in CR as an adaptation of these guidelines.
Partial Remission (PR)	See table 6 for detailed criteria. At least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve. Clinical (palpation) evaluation only without CT-scan (or alternate imaging), according to routine practice, is accepted.
Stable Disease (no change, no response/loss of response)	See table 6 for detailed criteria. All of the criteria have to be met.
Relapse (untreated)	Evidence of PD in a patient who has previously achieved the criteria of a CR or PR for 6 months or more after the last dose of CLL therapy.
Progressive Disease (PD)	At least 1 of the criteria of group A or group B has to be met. Sequential imaging is not warranted in CLL outside clinical trials and is not required for the EBMT Registry. Constitutional symptoms alone do not define PD.

Table 7. Additional clarifications for T-PLL disease status classification.

Plasma cell neoplasms

Disease status or best response:

- Complete remission (CR);
- Stringent complete remission (sCR);
- Very good partial remission (VGPR);
- Partial remission (PR);
- Stable disease (no change, no response/loss of response);
- Progression;
- Relapse.

Please find below a table with the criteria for each disease status or response category for plasma cell neoplasms and a separate table with criteria for Immunoglobulin-related (AL) Amyloidosis.

Disease status PCN (except Immunoglobulin-related (AL) Amyloidosis)	
Complete remission (CR)	Absence of detectable monoclonal immunoglobulin in serum and monoclonal light chains in the urine by immunofixation. The detection of monoclonal immunoglobulin, even at low levels which are too weak to quantitate, is not a CR. ● <5% of plasma cells in bone marrow aspirate ● Disappearance of any soft tissue plasmacytomas. ● No increase in size or number of lytic lesions if assessed (radiographic studies are not mandatory) If any of the above investigations have not been done, even if the others are indicative of a CR, the status should be registered as VGPR. Where CR has already been attained (bone marrow evaluation included) it may not be necessary to do a bone marrow evaluation again to confirm that the patient is still in CR (all other criteria confirming CR). Therefore, the patient is still in CR.
Stringent complete remission (sCR)	All of the following: ● CR as defined above ● normal free light (FLC) chain ratio ● Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Very good partial remission (VGPR)	One or more of the following: ● Serum and urine M-protein detectable by immunofixation but not on electrophoresis. ● >=90% reduction in serum M-protein plus urine M-protein level <0.1g/ per 24h. In addition, there must be no increase in size or number of lytic lesions if assessed (radiographic studies are not mandatory) If any of the above investigations have not been done, even if the others are indicative of a VGPR, the status should be registered as PR.
Partial remission (PR)	All of the following: ● >50% reduction in serum M-protein plus reduction in 24h urinary M-protein by >=90% or to <0.2g/ per 24h. ● A reduction of more than 50% in the size of soft tissue plasmacytomas if present at pre-treatment. ● No increase in size or number of lytic lesions if assessed (radiographic studies are not mandatory). In the absence of measurable serum and urine M-protein, the following criteria applies: ● A decrease in the difference between involved and uninvolved free light chain (FLC) of more than 50%. If the FLC assay cannot be measured, the following criteria apply: ● >=50% reduction in plasma cells provided baseline bone marrow plasma cell percentage was >=30% ● A reduction of more than 50% in the size of soft tissue plasmacytomas if present at pre-treatment.
Stable disease(no change, no response/loss of response)	Does not meet the criteria for CR, VGPR, PR or progressive disease (includes the old Minimal response (MR) criteria.

Progression	One or more of the following: ● Increase of 25% or more in measurable monoclonal immunoglobulin in serum and urine (absolute increase must be >=0.5g/dL). This is not applicable to light chain myelomas. ● Increase of 25% or more in urinary light chains (absolute increase must be >=0.2g/ per 24h). ● An increase of 25% or more in bone marrow plasma cells (absolute % must be >=10%). ● Increase of old/appearance of new osteolytic bone lesions on x-ray. ● Appearance of soft tissue plasmacytoma. ● Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell disorder. In the absence of measurable serum and urine M-protein, the following criteria applies: ● An increase of 25% or more in the difference between involved and uninvolved free light chain (absolute increase must be >0.01g/dL from nadir).
Relapse	Clinical relapse requires one or more of the following criteria: ● Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. ● Development of new soft tissue plasmacytomas or bone lesions. ● Increase of 50% (and at least 1 cm) in the size of existing plasmacytomas or bone lesions. ● Hypercalcemia (> 11.5 mg/dL). ● Decrease in haemoglobin of > 2 g/dL. ● Rise in serum creatinine by 2 mg/dL or more.

Table 8. Plasma cell neoplasms disease status or best response.

Disease status (Immunoglobulin-related (AL) amyloidosis)	
Complete remission (CR) 1st, 2nd, 3rd or higher	Normalisation of the free light chain (FLC) levels and ratio, negative serum and urine immunofixation.
Stringent complete remission (sCR) 1st, 2nd, 3rd or higher	Not applicable
Very good partial remission (VGPR) 1st, 2nd, 3rd or higher	Reduction in the dFLC (difference between involved FLC and uninvolved FLC) to <40 mg/L
Partial remission (PR) 1st, 2nd, 3rd or higher	A greater than 50% reduction in the dFLC
Stable disease(no change, no response/loss of response)	Less than a PR
Progression	● 50% increase in serum M protein to >0.5 g/dL or 50% increase in urine M protein to >200 mg/day (a visible peak must be present). ● Free light chain increase of 50% to >100 mg/L.
Relapse 1st, 2nd, 3rd or higher	● Any detectable monoclonal protein or abnormal free light chain ratio (light chain must double). ● Free light chain increase of 50% to >100 mg/L.
Never treated	No treatment was given.

Table 9: response for Immunoglobulin-related (AL) amyloidosis

Number

Please report the status/response number (if it is **1st, 2nd, 3rd or higher** or if it is **Unknown)** for the following disease statuses or responses**:**

- Complete remission (CR);
- Stringent complete remission (sCR);
- Very good partial remission (VGPR);
- Partial remission (PR);
- Relapse.

Each different status/response has their own sequential count.
For example, a patient received a non-graft treatment and is in PR1 as response to this treatment. After that there is a progression, another treatment, and response to this treatment is CR1, relapse, another treatment, response CR2.
The count doesn't reflect the different disease statuses/responses (eg. in the example above it should not be PR1, CR2, CR3), but within that status/response the sequential count (so PR1, CR1, CR2).

Extended dataset: Immunoglobulin-related (AL) amyloidosis. Organ response

Please see the table below 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 10. Definitions of organ response and progression.
* Patients with progressively worsening renal function cannot be scored for NT-proBNP progression. (10)

Myeloproliferative neoplasms (MPN), Myelodysplastic neoplasms (MDS), MDS/MPN overlap syndromes

Disease status or best response:

- Complete remission (CR);
- Improvement but no CR;
- Primary refractory phase (no change);
- Relapse;
- Progression/worsening.

MPN Disease status or best response	
Complete remission (CR)	The 4 following criteria must be true: 1. Resolution of disease-related symptoms and signs including palpable hepatosplenomegaly 2. Haemoglobin (Hb) ≥ 10g/dL, platelet ≥ 100 ×10^9/L and neutrophils ≥ 1 × 10^9/L 3. <2% immature myeloid cells (<5% in splenectomized patients) 4. Normal bone marrow histology and fibrosis grade no higher than 1
Improvement but no CR	Requires one criterion in absence of progression: 1. Hb increase of 2g/dL or transfusion independence 2. Spleen reduction of 50% 3. 100% increase in platelet count and absolute platelet count of at least 50 × 10^9/L 4. 100% increase in absolute neutrophil count (ANC) and an ANC of at least 0.5 × 10^9/L
Primary refractory phase (no change)	Treatment with intent to achieve remission was given, but no remission was achieved.
Relapse	Loss of complete remission.
Progression/Worsening	Requires one of the following: 1. Progressive splenomegaly 2. Leukemic transformation (increase of peripheral blood blast percentage of at least 20%)

Table 11. MPN disease status or best response.

MDS Disease status or best response	
Complete remission (CR)	For patients with MDS with increased blasts: Complete remission was achieved if marrow blast count was below 5% and normalisation of peripheral blood counts was observed for at least 4 weeks. For patients with other types of MDS: normalisation of PB counts.
Improvement but no CR	**1) Haematological response (in patients with cytopenia)** ● If haemoglobin < 11g/dl, erythroid response (>11 g/dl); ● If platelets <100g/l, platelet response (>100 g/l); ● If neutrophils < 1g/l, neutrophil response (>1g/l); ● If >0% peripheral blasts, response when 0% peripheral blood blasts; ● If transfusion dependant (red blood cells), independence of transfusion achieved (8 weeks without transfusions); ● If transfusion dependant (platelets), independence of transfusion achieved (8 weeks without transfusions) **2) Marrow blast response (in patients with increased marrow blasts):** A decrease of 50% in marrow blasts, but still >5% marrow blasts.
Primary refractory phase (no change)	Treatment with the intent to achieve remission was given, but no remission was achieved.
Relapse	Loss of complete remission.
Progression/Worsening	More blasts in BM than before treatment.

Table 12. MDS disease status or best response.

MDS/MPN Disease status or best response	
Complete remission (CR)	Marrow blast count < 5% and a normalisation of peripheral blood counts was observed for at least 4 weeks.
Improvement but no CR	Bone marrow blasts decreased by ≥ 50% after pre-treatment but still > 5%. All CR criteria were abnormal before treatment.
Primary refractory phase (no change)	Treatment with intent to achieve remission was given, but no remission was achieved.
Relapse	Loss of complete remission.
Progression/Worsening	Higher blast count in the BM and/or PB than before treatment. Worsening of cytopenias (anaemia and/or thrombocytopenia). Progression from the MD- to the MP-variant of CMML.

Table 13. MDS/MPN disease status or best response.

Number

Each different status/response has their own sequential count.
For example, a patient received a non-graft treatment and is CR1 in response to this treatment, after that there is a (1st) relapse, another treatment, and response CR2.
The count doesn't reflect the different disease statuses/responses (eg. in the example above it should not be CR1, 2nd Relapse, CR3), but within that status/response the sequential count (so CR1, 1st Relapse, CR2).

Lymphomas

Disease status or best response:

- Chemorefractory relapse or pression, including primary refractory disease;
- Complete remission (CR);
- Partial remission;
- Stable disease (no change, no response/loss of response);
- Untreated relapse (from a previous CR) or progression (from a previous PR).

Disease status or best response		
Complete remission (CR)	Complete absence of disease, no signs or symptoms of the original disease.	**Confirmed** (Only applicable if the Complete Remission was evaluated by CT-scan or MRI methods.)
		Unconfirmed (Only applicable if the Complete Remission was evaluated by CT-scan or MRI methods.)
Partial response (PR) with or without prior CR	Reduction in the disease of 50% or more	
Stable disease (no change, no response/loss of response)	Less than 50% reduction in the disease burden.	
Untreated relapse from previous CR/untreated progression from previous PR	Worsening of the disease status in patients in PR or re-appearance of the lymphoma in patients in CR, such as: recurrence of disease or systemic symptoms (B-symptoms), patient remains untreated after the relapse or progression.	
Chemorefractory relapse or progression, including primary refractory disease	Does not present any of the features of any type of remission after treatment.	

Table 14. Lymphomas disease status or best response.

Solid tumours

Disease status or best response:

- Complete remission (CR);
- First partial remission;
- Partial remission (PR);
- Progressive disease;
- Relapse;
- Stable disease (no change, no response/loss of response).

Disease status or best response		
Complete remission (CR)	Disappearance of all target lesions and all non-target lesions and normalisation of tumour marker level.	**Unconfirmed** complete response with persistent scan abnormalities of unknown significance
		Confirmed CR with No abnormalities detected in scan
		Unknown if it is not known if the complete remission was confirmed, select unknown

First partial remission	The patient achieved a reduction in disease of > 30% or more for the first time ever, but did not achieve complete remission[a]	
Partial remission (PR)	The patient achieved partial remission not for the first time.	
Progressive disease (PD)	At least 20% increase in the sum of diameters of target lesions, in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).	
Relapse	Reappearance of disease in patients whose last disease status was complete remission.	**Sensitive:** patient achieves a reduction of >30% in the disease burden after treatment for this relapse.
		Resistant: patient has not achieved a reduction of more than 30% in the disease burden after treatment for this relapse.
		Unknown: if it is not known if the relapse was resistant or sensitive, select unknown.
Stable disease (no change, no response/loss of response)	Target Lesions: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum length diameters since the treatment started. Non-Target Lesions: Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits	

Table 15. Solid tumours disease status or best response.
a. As per RECIST 1.1 guidelines https://pubmed.ncbi.nlm.nih.gov/19097774/

Bone marrow failures (incl. AA)

Disease status or best response:

- Complete remission (CR);
- Partial remission (PR);
- Haematological improvement (HI); NIH partial response;
- Stable disease (no change, no response/loss of response);
- Relapse/Progression.

Disease status or best response	Severe aplastic anaemia	Moderate aplastic anaemia	Genetic BMF
Complete Remission (CR)	All of the following: ● No evidence of clonal evolution, by marrow cytogenetic and flow cytometry ● Peripheral blood counts: haemoglobin >10 gr/dL, absolute neutrophils >1.0 x 10^9/L, platelets >100 x 10^9/L	All of the following: ● No evidence of clonal evolution, by marrow cytogenetic and flow cytometry ● Peripheral blood counts: haemoglobin normal for age, absolute neutrophils >1.5 x 10^9/L, platelets >150 x 10^9/L	All of the following: ● Haemoglobin higher than the inferior limit according to age, transfusion independence. For age-related reference values ● Absolute neutrophils ≥1.5 × 10^9/L up to age 18

			years, ≥1.8 × 10^9/L, in adults from 18 years ● Platelets >150 x 10^9/L, transfusion independence
Partial Remission (PR)	All of the following: ● No evidence of clonal evolution, by marrow cytogenetic and flow cytometry ● No longer meeting criteria for diagnosis of SAA ● Transfusion independence (defined as no need of any PRBC or platelet transfusion) ● Peripheral blood counts: haemoglobin >8 gr/dL, absolute neutrophils >0.5 x 10^9/L, platelets >20 x 10^9/	At least one of the following: ● No evidence of clonal evolution, by marrow cytogenetic and flow cytometry ● Transfusion independence (if previously required) doubling or normalisation of at least one cell line ● Peripheral blood counts: haemoglobin >10 gr/dL, absolute neutrophils >1.0 x 109/L, platelets >100 x 109/L	All of the following: ● Haemoglobin ≥8 <10 gr/dL, transfusion independence ● Absolute neutrophils ≥0.5 <1.0 × 10^9/L ● Platelets ≥20 <50 × 10^9/L, transfusion independence
Haematological improvement (HI); NIH partial response	No longer meeting criteria for diagnosis of SAA, in absence of CR or PR	No longer meeting criteria for diagnosis of MAA or genetic BMF, in absence of CR or PR	One or two of the following: ● Haemoglobin ≥8 <10 gr/dL, transfusion independence; or ● Absolute neutrophils ≥0.5 <1.0 × 10^9/L; or ● Platelets ≥20 <50 × 10^9/L, transfusion independence
Stable disease (no change, no response/loss of response)	Patients who have not achieved a CR, PR, HI, relapse or progression will be considered to have a stable disease.		
Relapse / Progression	Any of the following events after a haematological response (CR or PR): ● Meeting again the criteria for SAA ● Requirement of transfusion support (if not due to independent medical conditions) ● Decrease in any of the peripheral blood counts as follows: Decrease to less than 50% of the medium sustained	After a haematological response (CR or PR), once again meeting the criteria for MAA	All of the following: ● Haemoglobin <8 gr/dL or transfusion dependence ● Absolute neutrophils <0.5 × 10^9/L ● Platelets <20 × 10^9/L or transfusion dependence

	count during remission if: absolute neutrophils <1.0 x 10^9/L, platelets <50 x 10^9/L; or Or in any case if: absolute neutrophils <0.5 x 10^9/L , platelets <20 x 10^9/L The peripheral blood count decrease must be: ● Not due to any independent concomitant medical condition ● Demonstrated in at least 3 tests over a period of 2 weeks ● Not responding to re-introduction of low dose cyclosporin A		

Table 16. BMF (incl. AA) disease status or best response.

Autoimmune disorders

Disease status or best response:

- **No evidence of disease**- the patient has achieved complete absence of disease, there are no signs or symptoms of the original disease described.
- **Improved**
- **Unchanged** - Patients who have not demonstrated complete absence of disease, improvement in symptoms, or deterioration of symptoms will be classified as **Unchanged**.
- **Worse**

Haemoglobinopathies

Thalassemia best response:

- Transfusion independent;
- Transfusions required.

For clarification, transfusion independence is typically defined as going 8-12 weeks without needing transfusions, without a specific haemoglobin threshold.

Sickle cell disease best response:

- No return of sickling episodes. Patients are considered to have no return of sickling episodes when they have shown an absence of sickle cell crises.
- Return of sickling episodes. When sickle cell crises reoccur.