

This document describes the minimally required staging and evaluation procedures and response criteria that will be applied in all HOVON NHL studies. It is based on international working group recommendations (JCO, Vol.17, 1999, pp1244-1253 [Erratum, JCO, Vol.18, 2000, p2351]).

Response is currently assessed on the basis of clinical, radiologic, and pathologic (i.e., bone marrow) criteria. CT scans remain the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL.

Immunophenotyping of blood or bonemarrow has not been included as standard minimum requirement for the staging and restaging of lymphoma, even though it may be done standard in some centers (Hanson, Blood, Vol 94, 1999, pp 3889-3896). It may be a requirement in specific studies involving monoclonal antibodies.

Staging and restaging procedures

Only minimal requirements are specified.

A. Staging at on study before start of treatment

- History (including B symptoms)
- WHO Performance status
- Physical examination
- Laboratory tests
 - Hb, WBC, differential, platelet count, LDH
 - Calcium, creatinine, uric acid, glucose, albumin, bilirubine, ALAT
 - paraprotein by immuno-electrophoresis
 - quantitative immunoglobulins only if immuno-electrophoresis abnormal
 - Hepatitis-B in case of abnormal liver function tests
 - HIV test
- Lymph node biopsy for morphology and immunopathology
- Bone marrow biopsy (≥ 20 mm biopsy core) for histopathology
- Bone marrow aspirate for cytology
- Peripheral blood for cytology
- Imaging
 - CT thorax and abdomen including pelvis
 - US cervical region strongly recommended (Br J Hem. 88 (3) 626-8, 1994); alternative: CT cervical region
 - Consultation of ear-nose-throat specialist if indicated (i.e. complaints or gastro-intestinal lymphoma)
 - Gastroscopy if indicated (i.e. localization ENT, thyroid)
 - Lumbal puncture if indicated (i.e. localization testis, nasopharynx or brain)

B. Restaging for the evaluation of treatment

Restaging for the evaluation of treatment should be performed within 2 months after the end of treatment to assess response. Additional moments of restaging, e.g. after 3 cycles of CHOP, are specified in the study protocol.

- History (including B-symptoms)
- WHO Performance status
- Physical examination
- Laboratory tests
 - Hb, WBC, platelet count, LDH
 - Repeat previously abnormal tests
- Bone marrow biopsy (≥ 20 mm biopsy core) for histopathology if involved previously
- Bone marrow aspirate for cytology if involved previously
- Peripheral blood for cytology if involved previously
- Imaging
 - CT thorax and abdomen including pelvis
 - US of cervical region; alternative: CT cervical region
 - Assessment of other localizations only if involved previously

C. Restaging during follow up to determine remission status (until progression)

In case of CRu (see below) repeat CT 2-4 months after last CT for response evaluation.

- Physical examination
- WHO Performance status
- Laboratory tests
 - Hb, WBC, platelet count, LDH
- **Only if indicated, i.e. LDH elevation or clinical signs of progression:**
 - Bone marrow biopsy (≥ 20 mm biopsy core) for histopathology (if indicated)
 - Bone marrow aspirate for cytology (if indicated)
 - Peripheral blood for cytology (if indicated)
 - Imaging
 - CT thorax and abdomen including pelvis (if indicated)
 - US of cervical region; alternative CT of cervical region (if indicated)

Staging & Remission Status Evaluation

	On Study	Evaluation of Treatment	Follow up
• History	x	x	X
• WHO performance status	x	x	X
• Physical examination	x	x	X
• Laboratory tests			
▪ Hb	x	x	X
▪ WBC	x	x	X
▪ Differential	x	o.i.	
▪ Platelet count	x	x	X
▪ Calcium	x	o.i.	
▪ Creatinine	x	o.i.	
▪ Uric acid	x	o.i.	
▪ Glucose	x	o.i.	
▪ Bilirubine	x	o.i.	
▪ ALAT	x	o.i.	
▪ Albumin	x	o.i.	
▪ Immuno-electrophoresis	x	o.i.	
▪ Quantitative immunoglobulins	o.i.	o.i.	
▪ Hepatitis-B	x		
▪ HIV test	x		
• Lymph node biopsy	x	o.i.	o.i.
• BM biopsy	x	o.i.	o.i.
• BM aspirate	x	o.i.	o.i.
• PB for cytology	x	o.i.	o.i.
• Imaging			
▪ CT thorax	x	x	o.i.
▪ CT abdomen including pelvis	x	x	o.i.
▪ US/CT cervical region	r.	r.	o.i.
▪ ENT consultation	o.i.	o.i.	o.i.
▪ Gastroscopy	o.i.	o.i.	o.i.
▪ Lumbal punction	o.i.	o.i.	o.i.

o.i. on indication

r. strongly recommended

Bone marrow evaluation

Bone marrow biopsy must be adequate (≥ 20 mm biopsy core).

A bone marrow aspirate and biopsy should always be performed at diagnosis. If positive they should be repeated to determine response. They should also be performed in case of new abnormalities in the peripheral blood.

Bone marrow biopsies should be scored as

- positive unequivocal cytologic or architectural evidence of malignancy
- negative no aggregates or only a few well-circumscribed lymphoid aggregates
- indeterminate increased number or size of aggregates without cytologic or architectural atypia

The bone marrow report should be reported not only as positive or negative for lymphoma, but the percentage of invasion and the lymphoma subtype should be indicated, the latter to describe any discordance with the nodal disease.

Measurable disease and size of disease.

Response evaluation is primarily based on bi-dimensionally measurable nodes, nodal masses or nodules in liver or spleen.

Nodes with largest diameter ≤ 1 cm are considered normal and not pathologic. The size of a single node, nodal mass or nodule is defined as the product of the two largest perpendicular diameters (PPD). Nodes of which only one dimension is specified are considered as circular for the calculation of PPD size. If after treatment a nodal mass consisting of individual confluent nodes breaks up in separate nodes the sum of the PPD of the separate nodes must be compared with the size of the pretreatment nodal mass. All nodules in liver and spleen are considered pathologic, irrespective of size.

The sum of the PPD (SPD) of a set of indicator lesions is used as a quantitative measure for response evaluation. The indicator lesions have to be chosen from the nodes and nodal masses in the following way. If the number of nodes or nodal masses before treatment is 6 or less, all these are considered as indicator lesions. If the number of nodes or nodal masses is more than 6, a minimum number of at least 6 indicator lesions have to be chosen. These nodes or nodal masses should be selected according to the following features:

- a. they should be among the largest dominant sites
- b. they should be clearly measurable in at least two perpendicular dimensions,
- c. they should be from as disparate regions of the body as possible
- d. they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

The choice of the indicator lesions should be made before start of treatment. All indicator lesions must be numbered and measured bidimensionally before start of treatment and at the evaluation times specified in the protocol. The location and size must be documented and reported in the CRF.

Assessable disease

Assessable disease are considered all abnormalities that are not bidimensionally measurable, e.g. positive bone marrow or peripheral blood.

Response criteria

Complete response (CR) requires the following:

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy
2. Normal LDH (i.e. \leq ULN). An elevated LDH detracts from a CR unless it is attributable to causes not related to NHL, f.e. hemolysis.
3.
 - All nodes and nodal masses must have reduced in size to \leq 1.0 cm in greatest transverse diameter, **or**
 - If some nodes have regressed to a size between 1.0 and 1.5 cm in greatest transverse diameter from a size over 1.5 cm, while none have a size over 1.5 cm, the SPD of the indicator lesions must have regressed by more than 75%.
4. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable and/or no longer considered enlarged on physical examination. However, no normal size can be specified, because of the difficulties in accurately evaluating splenic size. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
5. Any nodules in liver or spleen must have disappeared.
6. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site.

CR/unconfirmed (CRu) includes those patients who fulfill criteria 1, 2, 4 and 5 above, but with one or more of the following features/exceptions:

1. A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the PPD size. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD size compared with the size of the original mass. The SPD size of the indicator lesions must have regressed with more than 75%.
2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

In case of apparent CRu it is recommended to perform, if possible, a cytological puncture or biopsy of a residual lymph node mass to determine the cytopathological status. It is also recommended in case of CRu to repeat CT or US of the residual lesion after 2-4 months.

Partial response (PR) requires the following:

1. \geq 50% decrease in SPD of the indicator lesions.
2. \geq 50% decrease in SPD of splenic and hepatic nodules if present and bi-dimensionally measurable at start of treatment.
3. No increase in the size of any single node, nodule, liver, or spleen by more than 25%.
4. No new sites of disease.
5. All patients who meet the criteria for CR or CRu except for an LDH $>$ ULN that is not attributable to other causes than NHL or with remaining but decreased nodules in liver or spleen, or with remaining assessable disease are classified as PR.

Stable disease (SD) is defined as less than a PR (see above) but is not progressive disease (see below).

Progressive disease (PD) requires the following

1. \geq 50% increase in the PPD-size of any at baseline identified abnormal node, nodal mass or nodule.
2. Appearance of any new lesion during or at the end of therapy.

Endpoints during follow up

Progression of disease is defined for all patients, irrespective of response on treatment. The following criteria apply:

1. $\geq 50\%$ increase from nadir in the PPD-size of any previously identified abnormal node.
2. Appearance of any new lesion.

Relapse requires the following:

1. Previous achievement of CR or CRu.
2. Progression of disease as defined above.

Note:

1. *Relapse is the same as progression of disease after CR or CRu.*
2. *An abnormal or increasing abnormal LDH, not attributable to other causes than NHL, is not sufficient evidence for the determination of progression. Imaging studies must be performed in such a case.*
3. *Note the difference between PD as response category and Progression of disease as event during or after treatment. All patients whose best response on treatment is PD, per definition also have reached the endpoint Progression of disease. But also other patients with a better response may eventually show progression of disease.*

Definitions of End Points for Clinical Trials

End Point	Response Category	Definition	Point of Measurement
Overall survival	All patients	Death from any cause	Entry onto trial
Event-free survival	All patients	Disease progression, relapse or death from any cause	Entry onto trial
Progression-free survival	All patients	Disease progression or death from NHL	Entry onto trial
Disease-free survival	CR, CRu	Time to relapse	First documentation of response
Response duration	CR, CRu, PR	Time to relapse or progression	First documentation of response
Time to next treatment	All patients	Time when new treatment is needed	Entry onto trial
Cause-specific death	All patients	Death related to NHL	Entry onto trial

Ann Arbor staging classification

Stage	Definition
I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I _E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II _E)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III _S) or by localized involvement of an extralymphatic organ or site (III _E) or both (III _{SE})
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement

B symptoms

The absence or presence of fever, night sweats, and/or unexplained loss of 10% or more of body weight in the six months preceding admission are to be denoted in all cases by the suffix letter A or B, respectively.

Extranodal involvement

Involvement of extra lymphatic tissue on one side of the diaphragm by limited direct extension from an adjacent nodal site is classified as extranodal extension and denoted by suffix letter E. The E category may also include an apparently discrete single extranodal deposit consistent with the extension from a regionally involved node. More extensive extranodal disease, f.e multiple extranodal deposits, is classified as stage IV. A single extralymphatic site as the only site of disease should be classified as I_E.

Notes

- For the purpose of defining the number of anatomical lymph node regions the following areas are considered as one region:
 - All nodes at one side of the neck are considered as in one region, i.e. consisting of the subregions supraclavicular, cervical, submandibular, occipital, preauricular and postauricular.
 - The axillary region includes the infraclavicular nodes.
 - The mediastinum is considered as one region, including the subcarinal and pericardial nodes.
- The lung-hilus is considered as a separate region. Thus involvement of both the mediastinum and a hilar localisation implies stage II disease.
- Hilar nodes should be considered lateralized and when involved on both sides constitute stage II disease.