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Allogeneic stem cell transplantation in aggressive B-cell non-Hodgkin lymphoma and in T-cell non-Hodgkin lymphoma[1]

Extract

[1] Translation of Chapters 1 to 6 of the final report N17-02 *Allogene Stammzelltransplantation bei aggressiven B-Zell-Non-Hodgkin-Lymphomen und bei T-Zell-Non-Hodgkin-Lymphomen* (Version 1.0; Status: 26 March 2019 [German original], 19 November 2019 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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The responsibility for the contents of the report lies solely with IQWiG.

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A8 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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Key statement

Research question

This investigation comprises the following 4 research questions:

1) benefit assessment of allogeneic stem cell transplantation in adult patients with aggressive B-cell non-Hodgkin lymphoma (not including primary central nervous system [CNS] lymphomas) who did not respond to treatment with high-dose chemotherapy and autologous stem cell transplantation or have had a relapse in comparison with another treatment without curative intent (fateful course of disease) ("B-NHL/post-auto-SCT")

2) benefit assessment of allogeneic stem cell transplantation in adult patients with aggressive B-cell non-Hodgkin lymphoma (not including primary CNS lymphomas) who did not respond to treatment without stem cell transplantation or have had a relapse in comparison with high-dose chemotherapy and autologous stem cell transplantation ("B-NHL/SCT-naïve")

3) benefit assessment of allogeneic stem cell transplantation in the first-line therapy of adult patients with T-cell non-Hodgkin lymphoma (except cutaneous T-cell lymphomas) requiring systemic drug therapy in comparison with treatment with systemic drug therapy alone or in combination with high-dose chemotherapy and autologous stem cell transplantation ("T-NHL/first line") and

4) benefit assessment of allogeneic stem cell transplantation in adult patients with T-cell non-Hodgkin lymphoma (not including cutaneous T-cell lymphomas) with progression or relapse following systemic therapy in comparison with another treatment without curative intent (fateful course of disease) ("T-NHL/higher line")

each with regard to patient-relevant outcomes.

Conclusion

This benefit assessment is based on a total of 32 analysed studies on 4 research questions, which investigated allogeneic stem cell transplantation in patients with B-NHL or T-NHL at different points in the course of treatment as well as 11 studies documenting the fateful course. The searches yielded only studies with lower evidence levels. On the basis of such studies, conclusions on benefit were possible only in case of dramatic effects. Studies that would have permitted drawing conclusions on the patients' quality of life were not found for any of the comparisons. The evidence base does not reveal whether allogeneic stem cell transplantation is associated with benefits. The occurrence of graft-versus-host-disease, a specific adverse effect following allogeneic stem cell transplantation, resulted in a hint of harm of allogeneic stem cell transplantation for all research questions.

Research question 1 (B-NHL/post-auto-SCT): For the comparison of allogeneic stem cell transplantation with fateful course in patients with progressive or relapsed B-NHL following autologous stem cell transplantation, only non-comparative studies were found, from which only the outcomes of overall survival and graft-versus-host disease were considered. Studies

with usable data were found on B-NHL overall as well as on the subentities of diffuse large B-cell lymphoma and mantle-cell lymphoma. For the outcome of overall survival, no benefit or harm of allogeneic stem cell transplantation was found, either across all subgroups or for the considered subentities.

Research question 2 (B-NHL/SCT-naïve): For the comparison of allogeneic versus autologous stem cell transplantation in B-NHL, retrospective comparative cohort studies were found on the subentities of diffuse large B-cell lymphoma, follicular lymphoma grade 3, transformed lymphoma, and mantle-cell lymphoma. For these subentities, there is no hint of greater benefit or harm of allo-SCT with regard to the outcome of overall survival. With regard to the outcomes of treatment-related or non-relapse mortality, there is no hint of greater benefit or harm of allogeneic stem cell transplantation in diffuse large B-cell lymphoma. No related data were available for the other considered subentities. The outcome of disease-free survival was unusable as a patient-relevant outcome due to the operationalization used in the studies; consequently, a conclusion regarding benefit or harm was not possible. For the outcome of adverse events, only fatal adverse events were reported. This did not result in a hint of benefit or harm of allogeneic stem cell transplantation.

Research question 3 (T-NHL/first line/allo-SCT versus systemic therapy): For the comparison of allogeneic stem cell transplantation with systemic drug therapy in treatment-naïve T-NHL, 1 comparative study was found on the histological subtype of precursor T-cell lymphoblastic lymphoma. This study did not supply any usable data for the benefit assessment on mortality or morbidity outcomes. For the outcome of adverse events, only fatal adverse events were reported. This did not result in a hint of benefit or harm of allogeneic stem cell transplantation.

Research questions 3 + 4 (T-NHL/first and higher line/allo-SCT versus auto-SCT):

1) Research question 3 (T-NHL/first line): For the comparison between allogeneic and autologous stem cell transplantation in treatment-naïve T-NHL, 1 retrospective comparative cohort study on T-NHL overall was found. This study did not supply any usable data. Furthermore, the final results of 1 prematurely terminated RCT on this question are intended to be published by the authors in mid-2019.

2) Research questions 3+4 (T-NHL/first and higher line): For the comparison of allogeneic and autologous stem cell transplantation in T-NHL, 3 further retrospective comparative cohort studies on T-NHL overall and 1 retrospective comparative cohort study on the subentity of natural killer cell lymphoma were found; their populations received heterogeneous prior therapy and was therefore not unequivocally assignable to either research question 3 or 4. However, usable data were available only for T-NHL overall. This resulted in no hint of greater benefit or harm of the intervention to be assessed with regard to the outcome of overall survival. For the outcome of adverse events, only fatal adverse events were reported. This did not result in a hint of benefit or harm of allogeneic stem cell transplantation. No further outcomes were suitable for use in the benefit assessment.

3) Research question 4 (T-NHL/higher line): For the comparison of allogeneic and autologous stem cell transplantation in higher-line therapy of T-NHL, 1 retrospective comparative cohort study on T-NHL overall was found. This study did not supply any usable data.

Research question 4 (T-NHL/higher line/allo-SCT versus fateful course): For the comparison of allogeneic stem cell transplantation with fateful course in patients with T-NHL and progression following systemic therapy, only non-comparative studies were found, from which only the outcomes of overall survival and graft-versus-host disease were considered. In addition to studies presenting T-NHL across subentities, studies on the subentities of hepatosplenic lymphoma and natural killer cell lymphoma were found. No hint of benefit or harm of allogeneic stem cell transplantation with regard to overall survival was found for T-NHL overall or for either of the presented subentities.

For the time being, allogeneic stem cell transplantation is always associated with the risk of graft-versus-host disease. The benefit of allogeneic stem cell transplantation in B-NHL and T-NHL, in contrast, is generally unclear due to a lack of reliable studies.

To obtain reliable data for future use, all patients with NHL should be registered in a disease-specific registry from the date of diagnosis.

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List of abbreviations

Abbreviation	Meaning
AE	Adverse event
aGvHD	Acute graft-versus-host disease
AITL	Angioimmunoblastic T-cell lymphoma
ALCL	Anaplastic large cell lymphoma
Allo-SCT	Allogeneic haematopoietic stem cell transplantation
ALK	Anaplastic lymphoma kinase
ASBMT	American Society for Blood and Marrow Transplantation
BEAM	Carmustine, etoposide, cytarabine, melphalan
B-NHL	B-cell non-Hodgkin lymphoma
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone
CD20, CD30, CD34, CD52	Cluster of Differentiation
cGvHD	Chronic graft-versus-host disease
CLL	Chronic lymphatic leukaemia
CNS	Central nervous system
COD	Cause of death
CR	Complete remission
DFS	Disease-free survival
DLBCL	Diffuse large B-cell lymphoma
DSHNHL	Deutsche Studiengruppe hochmaligne Non-Hodgkin-Lymphome (German Study Group for Highly Malignant Non-Hodgkin Lymphomas)
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
ESMO	European Society for Medical Oncology
FL	Follicular lymphoma
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GvHD	Graft-versus-host disease
GvL	Graft-versus-lymphoma effect
HLA	Human leukocyte antigen
HSTCL	Hepatosplenic T-cell lymphoma
IPI	International prognostic index
ITT	Intention to treat
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)

Abbreviation	Meaning
MAC	Myeloablative conditioning
MCL	Mantle cell lymphoma
MZD	Marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NK cells	Natural killer cells
NMA	Non-myeloablative conditioning
NRM	Non-relapse mortality
OS	Overall survival
PBST	Peripheral blood stem cells
PD	Progressive disease
PFS	Progression-free survival
PTCL	Peripheral T-cell lymphoma
PTCL-NOS	Peripheral T-cell lymphoma, not otherwise specified
RCT	Randomized controlled trial
RIC	Reduced-intensity conditioning
SAE	Serious adverse event
SCT	Haematopoietic stem cell transplantation
SGB	Sozialgesetzbuch (Social Code Book)
SLL	Small lymphocytic lymphoma
T-LBL	T-cell lymphoblastic lymphoma
T-NHL	T-cell non-Hodgkin lymphoma
TRM	Treatment-related mortality
WHO	World Health Organization

1 Background

Definition and epidemiology of the clinical picture

Non-Hodgkin lymphomas (NHLs) are malignant diseases originating from the cells of the lymphatic system. Depending on the lymphatic cells underlying the disease, NHL is categorized into the subentities B-cell and T-cell lymphomas. This is based on the updated WHO classification of lymphoid neoplasms [1]. B-NHL and T-NHL are categorized into further subentities based on whether they stem from mature cells or immature precursor cells [1-3]. NHL is therefore a heterogeneous group which is composed of more than 60 subgroups. Some of these subgroups manifest in indolent, others in aggressive forms [4]. The therapeutic indication of this benefit assessment comprises exclusively aggressive B-NHL and aggressive T-NHL, which require systemic treatment.

The most common form of aggressive B-NHL manifests as diffuse large B-cell lymphoma (DLBCL). In addition to DLBCL, B-cell lymphoma subentities with an aggressive clinical course include the less common Burkitt or mantle cell lymphomas [4]. Unlike aggressive B-NHL, aggressive precursor T-cell lymphoblastic NHL and peripheral T-NHL (PTCL) make up only a small proportion of all diagnosed NHL cases. The most common forms are peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) and angioimmunoblastic T-cell lymphoma (AITL). Less common forms include anaplastic large cell lymphomas (ALCL) [3].

According to estimates by the Robert Koch Institute, some 8850 men and 7800 women developed NHL in Germany in 2013; the mean age of onset was 70 and 72 years, respectively [5, 6].

Stages and risk groups

Adequate patient treatment requires comprehensive diagnostics to determine the spread of disease and hence the clinical stage. Ann Arbor staging, which was originally developed for Hodgkin lymphomas, is an internationally recognized staging system for malignant lymphomas. With regard to the location and spread of lymphomas, this classification system distinguishes between 4 stages (stage I: involvement of a single lymph node region or of a single localized, extralymphatic organ or site; stage IV: diffuse or disseminated involvement of extralymphatic organs). The suffix B is added to the determined stage if general symptoms in the form of unexplained weight loss and/or unexplained fever and/or night sweat are present. If the person does not suffer from one or more of these symptoms, the suffix A is added [7]. The more recently developed Lugano classification additionally recommends performing imaging – fluorodeoxyglucose positron emission tomography or computed tomography – for staging purposes and does away with the suffixes A and B [8, 9].

No conclusions regarding the patient's prognosis can be drawn based on anatomic staging using the Ann Arbor system. The International Prognostic Index (IPI), which was designed to allow a prognosis, was developed on patients with aggressive B-NHL [7, 10]. On the basis of the factors of age, Ann Arbor tumour stage, number of involved extranodal sites, Performance

Status according to the Eastern Cooperative Oncology Group (ECOG status), and serum lactate dehydrogenase concentration, the IPI allows categorizing patients with aggressive B-NHL into 4 risk groups. The group with the lowest score has the highest survival rate. The group with the highest score, in turn, has the poorest prognosis. The IPI can also be used on patients with T-NHL, but some of its subentities have a poor prognosis, even in the group with the lowest score [11, 12].

Therapy

Initial therapy

For DLBCL, which is the most common form of aggressive B-NHL, the European Society for Medical Oncology (ESMO) recommends chemotherapy and the monoclonal antibody rituximab as standard treatment. A commonly used regimen is R-CHOP, which includes rituximab as well as cyclophosphamide, doxorubicin, vincristine, and prednisone [13]. For other subentities of aggressive B-NHL, no consistent treatment standard has been established, not even for first-line therapy [4]. According to the ESMO and NICE guidelines, these cases are usually treated the same way as DLBCL. Stem cell transplantation (SCT) is not typically used in the first-line therapy of B-NHL [4, 13].

For peripheral T-NHL, the German Study Group for Highly Malignant Non-Hodgkin Lymphomas (DSHNHL) and ESMO predominantly recommend a first-line therapy consisting of the CHOEP chemotherapy regimen (CHOP plus etoposide) for patients under 60 years of age or CHOP chemotherapy for patients above 60 years of age [14, 15]. However, autologous SCT (auto-SCT) is recommended as first-line therapy for some subentities of T-NHL due to their high relapse rates and less favourable clinical course than aggressive B-NHL [15-17]. ESMO mentions allogeneic SCT (allo-SCT) as a first-line therapy option only for the very rare subform of hepatosplenic lymphoma. A current recommendation developed by an international panel commissioned by the American Society for Blood and Marrow Transplantation (ASBMT) mentions the use of allo-SCT as first-line therapy for hepatosplenic lymphoma as well as for (disseminated) natural killer cell (NK)/T-cell lymphoma [17]. The best treatment strategy for T-NHL remains unclear [9, 15].

Treatment of relapsed or refractory NHL

For relapsed or refractory NHL following initial treatment, various treatment approaches are used depending on the subentity and therapy line. As second-line therapy of DLBCL, the ESMO guidelines suggest auto-SCT depending on patient age and health status, or even allo-SCT for patients with very poor prognoses. In case of progression or another relapse, the recommended third-line therapy is allo-SCT as well as the use of new drugs within clinical trials due to the otherwise very poor prognosis. If the patient is ineligible for allo-SCT, palliative treatment is usually the only remaining option [13].

For patients with T-NHL who have a relapse or do not achieve remission, therapeutic options are limited. Their prognosis is very poor. Peripheral T-NHL is treated with various chemotherapy regimens. In case of relapse, the international ASBMT panel recommends the use of allo-SCT for various subentities. Its use is also recommended for patients with refractory lymphoma, with the authors of the ASBMT guidelines considering it a "treatment of last resort" [17, p. 27]. There is no established treatment standard, except in relapsed or refractory $CD30^+$ ALCL, for which treatment with the antibody-drug conjugate brentuximab vedotin is recommended [15, 18].

Allogeneic stem cell transplantation

In allo-SCT, the patient receives stem cells in the form of peripheral blood stem cells or bone marrow from another, healthy person – a related or unrelated donor [19]. In auto-SCT, by contrast, the stem cells are harvested from the patient. The actual stem cell transplantation is preceded by a conditioning phase. The associated regimens are categorized by intensity into myeloablative, non-myeloablative, and reduced-intensity conditioning. Myeloablative conditioning aims to both decimate malignant cells and induce immunosuppression to ensure the establishment and growth, or engraftment, of the healthy donor graft. However, it is associated with considerable transplant-related mortality. Non-myeloablative and reduced-intensity conditioning aim to achieve a balance between transplant-related mortality and the risk of another relapse. This type of conditioning primarily aims to achieve immunosuppression [20, 21]. In addition, it makes allo-SCT an option for some patients who are ineligible for myeloablative conditioning [22].

In the context of immunosuppression, the existence of a graft-versus-tumour effect – or graft-versus-lymphoma effect (GvL) in NHL – is being debated. A potential positive GvL effect stands in contrast to the risk of graft-versus-host disease (GvHD). The latter represents a serious complication of allo-SCT and is associated with a high morbidity risk [20, 23, 24]. The extent and characteristics of GvHD are largely determined by the GvHD prophylaxis regimen as well as the compatibility between the donor's and recipient's human leukocyte antigens (HLA). The greater the HLA mismatch, the higher the risk of the patient developing GvHD [25].

2 Research question

This investigation comprises the following 4 research questions:

- benefit assessment of allogeneic stem cell transplantation in adult patients with aggressive B-cell lymphoma (not including primary CNS lymphomas) who did not respond to treatment with high-dose chemotherapy and autologous stem cell transplantation or have had a relapse in comparison with another treatment without curative intent (fateful course of disease) ("B-NHL/post-auto-SCT")
- benefit assessment of allogeneic stem cell transplantation in adult patients with aggressive B-cell lymphoma (not including primary CNS lymphomas) who did not respond to treatment without stem cell transplantation or have had a relapse in comparison with high-dose chemotherapy and autologous stem cell transplantation ("B-NHL/SCT-naïve")
- benefit assessment of allogeneic stem cell transplantation in the first-line therapy of adult patients with T-cell lymphoma (except cutaneous T-cell lymphomas) requiring systemic drug therapy in comparison with treatment with systemic drug therapy alone or in combination with high-dose chemotherapy and autologous stem cell transplantation ("T-NHL/first line") and
- benefit assessment of allogeneic stem cell transplantation in adult patients with T-cell lymphoma (not including cutaneous T-cell lymphomas) with progression or relapse following systemic therapy in comparison with another treatment without curative intent (fateful course of disease) ("T-NHL/higher line")

each with regard to patient-relevant outcomes.

3 Methods

The following patients made up the target population of the benefit assessment, broken down by research question:

- Research question 1: Adult patients with aggressive B-NHL who failed to respond to auto-SCT treatment or have relapsed (B-NHL/post-auto-SCT)
- Research question 2: Adult patients with aggressive B-NHL who failed to respond to treatment without SCT or have relapsed (B-NHL/SCT-naïve)
- Research question 3: Adult patients with T-NHL who need systemic drug therapy in first-line therapy (T-NHL/first line)
- Research question 4: Adult patients with T-NHL with progression or relapse after systemic therapy (T-NHL/higher line)

The experimental intervention was allo-SCT. For research questions 1 and 4, the comparator intervention included all potentially available interventions without curative intent, including palliative care. For research question 2, the comparator intervention was high-dose chemotherapy with auto-SCT. For research question 3, the comparator intervention was systemic drug therapy alone or systemic drug therapy in combination with high-dose chemotherapy and auto-SCT.

The investigation considered the following patient-relevant outcomes:

- Mortality, such as
  - survival time (overall survival),
  - treatment-related mortality
- Morbidity, such as
  - disease-free survival,
- Adverse effects of therapy, such as
  - serious, life-threatening or fatal acute graft-versus host disease (GvHD) or chronic GvHD
  - serious, life-threatening, or fatal infections
  - occurrence of secondary neoplasms
  - further serious treatment-related complications, if applicable
  - serious adverse events
- Health-related quality of life, including activities of daily living and dependence on help from others

For research questions 2 and 3, comparative cohort studies (including retrospective studies and studies with historical comparison) were included in the benefit assessment. For research

questions 1 and 4, prospective and retrospective non-comparative clinical trials (e.g. 1-arm observational studies, non-comparative registry analyses) were also considered if stronger evidence was not available in sufficient quantity and/or quality. If a large number of these studies were available for each subtype, the 3 studies with the highest sample size were primarily considered. There were no restrictions regarding the study duration.

A systematic search for primary literature was conducted in the databases MEDLINE, Embase, and Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase, Cochrane Database of Systematic Reviews, and HTA Database.

The following sources of information and search techniques were additionally used: study registries, reviews of bibliographies, queries sent to study groups and professional associations, documents made available from commenting procedures, and author queries.

Relevant studies were selected by 2 reviewers independently from one another. Any discrepancies were resolved by discussion between the two reviewers. Data were extracted into standardized tables. To assess the qualitative certainty of conclusions, the risk of bias at study and outcome levels was assessed and rated as high or low. The results of the individual studies were organized according to outcomes and described.

For research questions 1 and 4, sufficiently reliable documentation of the fateful course of the disease[2] in the literature was the prerequisite for classification as a dramatic effect. In addition to comprehensive information retrieval, focused information retrieval was therefore conducted on the fateful course in the MEDLINE database. In addition, the “Similar articles” function in PubMed was used for studies which were considered potentially relevant and included.

The matches identified by the focused information retrieval in the bibliographic databases were reviewed for relevant literature by 1 reviewer, with a focus on the populations from research questions 1 and 4 and fateful course as a comparator and were then assessed in terms of their relevance. A second reviewer scrutinized the entire process, including the assessments.

To the extent that the comparative studies were comparable in terms of research questions and relevant characteristics and no meaningful heterogeneity was observed, the results from individual studies were quantitatively combined in meta-analyses.

For each outcome, a conclusion was drawn on the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: Proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the 3 scenarios. The latter was the case if no data were available or the available data did not permit classification into one of the 3 other categories. In that case, the conclusion “There is no

[2] For the purposes of this report, fateful course of disease is defined as the clinical course of disease under any treatment without curative intent.

hint of (greater) benefit or (greater) harm" was drawn. Only in case of a dramatic effect was it possible to draw conclusions on benefit on the basis of studies with lower evidence levels (retrospective comparative cohort studies, historic comparative studies, non-comparative studies).

The presentation of results on T-NHL was adapted (see Section 1.2 of the full report). A separate section was created for each comparator intervention. Sections 4.5 and 3.5 of the full report present the comparison of allo-SCT versus systemic therapy as first-line therapy. Sections 4.6 and 3.6 of the full report address the comparison of allo-SCT versus auto-SCT regardless of therapy line. Due to the varying number of prior therapy lines, some of the studies found for this comparison could not be clearly assigned to research question 3 (first line) or 4 (higher line) They were pooled to allow the studies to be considered in this benefit assessment. The section in question also discusses how unequivocally each of the studies was assignable to either research question 3 or 4. The strength of evidence was also derived, whenever possible, for each research question. Sections 4.7 and 3.7 of the full report present the comparison of allo-SCT with fateful course in higher-line therapy.

4 Results

4.1 Results of the comprehensive information retrieval

The comprehensive information retrieval identified 95 documents as relevant for this benefit assessment (see Table 1). Out of these results, 32 studies (36 documents) were analysed. This reduction was due to the methodological specifications of the report plan regarding research questions 1 and 4 (for each subtype, sufficiently reliable documentation of the fateful course of the disease as a prerequisite and consideration of a few large studies if many non-comparative studies were available per subtype [26]; also see Section 2.1.4.2 of the full report).

Out of the 32 studies, 7 non-comparative studies were analysed to answer research question 1 (B-NHL/post-auto-SCT). For research question 2 (B-NHL/SCT-naïve), 14 retrospective comparative cohort studies (15 publications) were found. For research question 3 (T-NHL/first line/allo-SCT versus systemic therapy), 1 retrospective comparative cohort study was found with data on precursor T-cell lymphoblastic lymphoma (T-LBL). To jointly answer research questions 3 and 4 (T-NHL/first line and higher line/allo-SCT versus auto-SCT), 3 retrospective comparative cohort studies and 2 retrospective observational studies which provided individual patient data and were suitable for comparison, were used. Two of these studies (1 study arm from 1 retrospectively comparative cohort study and 1 retrospective observational study) were also used for research question 4 (T-NHL/higher line/allo-SCT versus fateful course). Further, 5 additional non-comparative studies were analysed to answer this research question. Figure 1 shows an overview of the (non-)consideration of the included studies from the comprehensive and focused information retrieval (see Section 4.2) as well as on their assignment to the various research questions.

In addition, 2 ongoing studies, 1 prematurely terminated study, and 1 planned study were found. No completed studies without reported results were found.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 10 July 2018.

Table 1: Study pool of the comprehensive information retrieval on allogeneic stem cell transplantation

Study	Available documents			
	Full publication (in professional journals)	**Study registry / results report from the study registries**	**Other documents (not publicly accessible)**	**Study included in benefit assessment**
Research question 1: B-NHL/post-auto-SCT				
B-NHL all/post-auto-SCT				
Bouabdallah 2015	Yes [27]	No/no	No	No
Cabrero 2017	Yes [28]	No/no	No	No
DSHNHL-R3	Yes [29]	Yes [30] / no	Yes [31, 32]	No (supplementary presentation)
Escalon 2004	Yes [33]	No/no	No	No
Freytes 2012	Yes [34]	No/no	No	Yes
Niederwieser 2003	Yes [35]	No/no	No	No
Zoellner 2015	Yes [36]	No/no	No	No
Diffuse large B-cell lymphoma/post-auto SCT				
Avivi 2014	Yes [37]	No/no	No	No
Fenske 2016	Yes [38]	No/no	No	Yes
Rigacci 2012	Yes [39]	No/no	No	Yes
Van Kampen 2011	Yes [40]	No/no	No	Yes
Mantle cell lymphoma/post-auto-SCT				
Dietrich 2011	Yes [41]	No/no	No	No
Dietrich 2014	Yes [42]	No/no	No	Yes
Dreger 2018	Yes [43]	No/no	No	Yes
Maris 2004	Yes [44]	No/no	No	Yes
Vaughn 2015	Yes [45]	No/no	No	No
Transformed lymphoma/post-auto-SCT				
Clavert 2010	Yes [46]	No/no	No	No
Research question 2: B-NHL/SCT-naïve				
Diffuse large B-cell lymphoma/SCT-naïve				
Aksentijevich 2006	Yes [47]	No/no	No	Yes
Ghobadi 2015	Yes [48]	No/no	No	Yes
Lazarus 2010	Yes [49]	No/no	No	Yes
Robinson 2016	Yes [50]	No/no	No	Yes
Mantle-cell lymphoma/SCT-naïve				
Fenske 2014	Yes [51]	No/no	No	Yes
Ganti 2005	Yes [52]	No/no	No	Yes
Magnusson 2014	Yes [53, 54]	No/no	No	Yes
Tam 2009	Yes [55]	No/no	No	Yes
Yamasaki 2018	Yes [56]	No/no	No	Yes
Follicular lymphoma grade 3/SCT-naïve				
Klyuchnikov 2016	Yes [57]	No/no	No	Yes

(continued)

Table 1: Study pool of the comprehensive information retrieval on allogeneic stem cell transplantation (continued)

Study	Available documents			
	Full publication (in professional journals)	**Study registry / results report from the study registries**	**Other documents (not publicly accessible)**	**Study included in benefit assessment**
Transformed lymphoma/SCT-naïve				
Ban-Hoefen 2013	Yes [58]	No/no	No	Yes
Villa 2013	Yes [59]	No/no	No	Yes
Villa 2014	Yes [60]	No/no	No	Yes
Wirk 2014	Yes [61]	No/no	No	Yes
Research question 3: T-NHL/first line/allo-SCT vs. systemic therapy				
Precursor T-cell lymphoblastic lymphoma/first line/allo-SCT vs. systemic therapy				
Yang 2018	Yes [62]	No/no	No	Yes
Research questions 3+4: T-NHL/first and higher line/allo-SCT vs. auto-SCT				
T-NHL all/first and higher line/allo-SCT vs. auto-SCT				
Beitinjaneh 2015	Yes [63]	No/no	No	Yes
Busemann 2014	Yes [64]	No/no	No	Yes
Hsu 2018	Yes [65]	No/no	No	Yes
Smith 2013	Yes [66]	No/no	No	Yes
Natural killer cell lymphoma/first and higher line/allo-SCT vs. auto-SCT				
Suzuki 2006	Yes [67]	No/no		Yes
Research question 4: T-NHL/higher line/allo-SCT vs. fateful course				
T-NHL all/higher line/allo-SCT vs. fateful course				
Beitinjaneh 2015	Yes [63]	No/no	No	Yes
Corradini 2004	Yes [68]	No/no	No	No
Czajczynska 2013	Yes [69]	No/no	Yes [70]	Yes
DSHNHL-R3	Yes [29]	Yes [30] / no	Yes [31, 32]	No
Rodriguez 2001	Yes [71]	No/no	No	No
Rohlfing 2018	Yes [72]	No/no	No	Yes
Wulf 2018	Yes [73]	No/no	No	Yes
Angioimmunoblastic T-cell lymphoma/higher line/allo-SCT vs. fateful course				
Kyriakou 2009	Yes [74]	No/no	No	No (supplementary presentation)
Le Gouill 2008	Yes [75]	No/no	No	No (supplementary consideration)
Anaplastic large cell lymphoma/higher line/allo-SCT vs. fateful course				
Illidge 2015	Yes [76]	No/no	No	No
Jagasia 2004	Yes [77]	No/no	No	No

(continued)

Table 1: Study pool of the comprehensive information retrieval on allogeneic stem cell transplantation (continued)

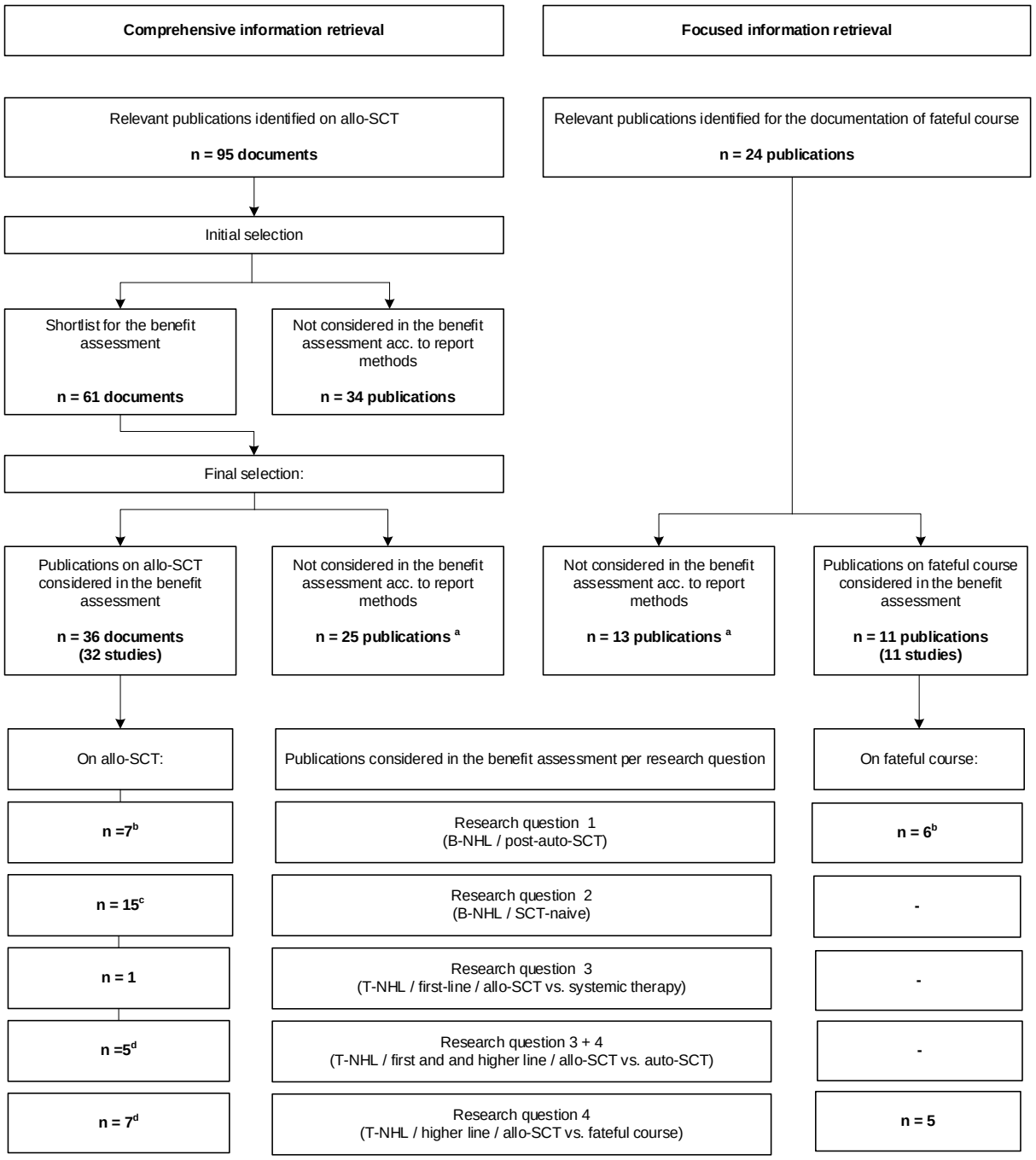
Study	Available documents			
	Full publication (in professional journals)	**Study registry / results report from the study registries**	**Other documents (not publicly accessible)**	**Study included in benefit assessment**
Precursor T-cell lymphoblastic lymphoma/higher line/allo-SCT vs. fateful course				
Broccoli 2013	Yes [78]	No/no	No	No (supplementary presentation)
Izutsu 2004	Yes [79]	No/no	No	No
Kim 2006	Yes [80]	No/no	No	No
Lazarevic 2011	Yes [81]	No/no	No	No (supplementary presentation)
Makita 2016	Yes [82]	No/no	No	No (supplementary presentation)
Hepatosplenic lymphoma/higher line/allo-SCT vs. fateful course				
Rashidi 2015	Yes [83]	No/no	No	Yes
Tanase 2015	Yes [84]	No/no	No	No
Voss 2013	Yes [85]	No/no	No	No
Natural killer cell lymphoma/higher line/allo-SCT vs. fateful course				
Ennishi 2011	Yes [86]	No/no	No	No
Izutsu 2004	Yes [79]	No/no	No	No
Kanate 2018	Yes [87]	No/no	No	No
Kim 2006	Yes [80]	No/no	No	No
Murashige 2005	Yes [88]	No/no	No	Yes
Suzuki 2006	Yes [67]	No/no	No	Yes
Initial selection: **Non-comparative studies on research questions 1 + 4 not taken into account in the benefit assessment**				
Bishop 2008	Yes [89]	No/no	No	No
Chen 2001	Yes [90]	No/no	No	No
Corradini 2007	Yes [91]	No/no	No	No
de Lavallade 2008	Yes [92]	No/no	No	No
de Lima 1997	Yes [93]	No/no	No	No
Delioukina 2012	Yes [94]	No/no	No	No
Dodero 2012	Yes [95]	No/no	No	No
Doocey 2005	Yes [96]	No/no	No	No
Glass 2004	Yes [97]	No/no	No	No
Goldberg 2012	Yes [98]	No/no	No	No
Hamadani 2008	Yes [99]	No/no	No	No
Hamadani 2009	Yes [100]	No/no	No	No
Hwang 2011	Yes [101]	No/no	No	No

(continued)

Table 1: Study pool of the comprehensive information retrieval on allogeneic stem cell transplantation Table 1: Study pool of the comprehensive information retrieval on allogeneic stem cell transplantation (continued)

Study	**Available documents**			
	Full publication (in professional journals)	**Study registry / results report from the study registries**	**Other documents (not publicly accessible)**	**Study included in benefit assessment**
Jacobsen 2011	Yes [102]	No/no	No	No
Kahl 2002	Yes [103]	No/no	No	No
Kanakry 2013	Yes [104]	No/no	No	No
Kim 2014	Yes [105]	No/no	No	No
Kim 2013	Yes [106]	No/no	No	No
Link 2016	Yes [107]	No/no	No	No
Ram 2011	Yes [108]	No/no	No	No
Rezvani 2015	Yes [109]	No/no	No	No
Schmitt 2014	Yes [110]	No/no	No	No
Shustov 2010	Yes [111]	No/no	No	No
Tanimoto 2003	Yes [112]	No/no	No	No
Thomson 2009	Yes [113]	No/no	No	No
Tse 2014	Yes [114]	No/no	No	No
Urbano-Ispizua 2015	Yes [115]	No/no	No	No
Van den Neste 2017	Yes [116]	No/no	No	No
Wulf 2005	Yes [117]	No/no	No	No
Yamazaki 2017	Yes [118]	No/no	No	No
Yang 2015	Yes [119]	No/no	No	No
Yokoyama 2010	Yes [120]	No/no	No	No
Yoon 2017	Yes [121]	No/no	No	No
Zain 2011	Yes [122]	No/no	No	No

allo: allogeneic; auto: autologous; B-NHL: B-cell non-Hodgkin lymphoma; SCT: stem cell transplant; SCT-naïve: patients who have not received a prior stem cell transplant; T-NHL: T-cell non-Hodgkin lymphoma; vs.: versus



a. Some publications could be allocated to multiple research questions and/or different sub-entities.
b. The publication Dietrich 2014 contained data on both allo-SCT and fateful course.
c. Two publications (Magnusson 2014 and Laudi 2006) were allocated to the study Magnusson 2014.
d. The publications Beitinjaneh 2015 and Suzuki 2006 could be used for both research questions 3 and 4.

Figure 1: Presentation of the (non-)consideration of the included studies and matching to the various research questions

4.2 Results of the focused information retrieval

The focused information retrieval identified 24 non-comparative studies (24 documents) as relevant for the documentation of fateful course of the disease for research questions 1 and 4

(see Table 2). In accordance with the reporting methodology, 11 of these studies were used in the assessment (see Sections 4.1 and 2.1.4.2 of the full report as well as Figure 1).

The search strategy for MEDLINE is found in the appendix. The most recent search was conducted on 12 July 2018.

Table 2: Study pool from the focused information retrieval on fateful course

Study	**Available documents**		
	Full publication (in professional journals)	**Study registry / results report from the study registries**	**Study included in benefit assessment**
Research question 1: B-NHL/post-auto-SCT			
B-NHL all/post-auto-SCT			
Kuittinen 2005	Yes [123]	No/no	Yes
Smeland 2016	Yes [124]	No/no	Yes
Vose 2013	Yes [125]	No/no	No
Diffuse large B-cell lymphoma/post-auto SCT			
Calvo-Villas 2010	Yes [126]	No/no	Yes
Hunter 2017	Yes [127]	No/no	No
Kewalramani 2003	Yes [128]	No/no	No
Kewalramani 2006	Yes [129]	No/no	No
Nagle 2013	Yes [130]	No/no	Yes
Song 2003	Yes [131]	No/no	No
Tsirigotis 2010	Yes [132]	No/no	No
Van den Neste 2017	Yes [116]	No/no	Yes
Mantle cell lymphoma/post-auto-SCT			
Dietrich 2011	Yes [41]	No/no	No
Dietrich 2014	Yes [42]	No/no	Yes
Transformed lymphoma/post-auto-SCT			
Vose 2013	Yes [125]	No/no	No
Research question 4: T-NHL/higher line/allo-SCT vs. fateful course			
T-NHL all/higher line/allo-SCT vs. fateful course			
Biasoli 2015	Yes [133]	No/no	No
Briski 2015	Yes [134]	No/no	No
Ellin 2014	Yes [135]	No/no	No
Kewalramani 2006	Yes [129]	No/no	No
Rohlfing 2018	Yes [72]	No/no	No
Song 2003	Yes [131]	No/no	No
Zhang 2018	Yes [136]	No/no	Yes

(continued)

Table 2: Study pool from the focused information retrieval on fateful course (continued)

Study	Available documents		
	Full publication (in professional journals)	**Study registry / results report from the study registries**	**Study included in benefit assessment**
Peripheral T-cell lymphoma, not otherwise specified/higher line/allo-SCT vs. fateful course			
Chihara 2017	Yes [137]	No/no	No
Angioimmunoblastic T-cell lymphoma/higher line/allo-SCT vs. fateful course			
Chihara 2017	Yes [137]	No/no	No
Hepatosplenic lymphoma/higher line/allo-SCT vs. fateful course			
Falchook 2009	Yes [138]	No/no	Yes
Weidmann 2000	Yes [139]	No/no	Yes
Natural killer cell lymphoma/higher line/allo-SCT vs. fateful course			
Kim 2009	Yes [140]	No/no	Yes
Zhou 2014	Yes [141]	No/no	Yes
Enteropathy-associated T-cell lymphoma/higher line/allo-SCT vs. fateful course			
Raderer 2012	Yes [142]	No/no	No
allo: allogeneic; auto: autologous; B-NHL: B-cell non-Hodgkin lymphoma; SCT: stem cell transplantation; T-NHL: T-cell non-Hodgkin lymphoma; vs.: versus			

4.3 Research question 1: B-NHL/post-auto-SCT

4.3.1 Characteristics of the studies included in the evaluation

For the assessment of allo-SCT, all studies were included in which at least 80% of patients received high-dose chemotherapy with subsequent autologous haematopoietic stem cell transplantation (auto-SCT) in a prior therapy line[3] – regardless of the timing of auto-SCT within the course of therapy. Not all studies included as relevant for the research question were also used in the benefit assessment. An overview of primary studies which were included, but not presented, is provided in Section 3.1.4 of the full report.

Overall, 3 studies which jointly considered various histological subtypes of B-NHL were taken into account (Freytes 2012 [34] on allo-SCT, Kuittinen 2005 [123] and Smeland 2016 [124] on fateful course). All 3 studies included patients with aggressive forms of B-NHL as well as patients with subentities which were nor unequivocally characterized as aggressive or indolent. Since this share of patients was considered comparable to the study on allo-SCT as well as the two studies on fateful course, they were considered in this benefit assessment. For 1 additional study which supplied data on the use of allo-SCT for exclusively aggressive subtypes of B-NHL (DSHNHL-R3 [29]), no suitable study on fateful course was found. Since the patient population

[3] The therapeutic component of the intervention always includes high-dose therapy preceding autologous haematopoietic stem cell transplantation. Below, auto-SCT is therefore to be understood as the combination of high-dose chemotherapy with subsequent stem cell transplantation (to prevent bone marrow aplasia).

exactly matched the patient population of this research question, the study was presented as supplementary information in Section 3.3.3 of the full report.

Further, 6 studies on diffuse large B-cell lymphomas (DLBCL) (Fenske 2016 [38], Rigacci 2012 [39], and Van Kampen 2011 [40] on allo-SCT, Calvo-Villas 2010 [126], Nagle 2013 [130], and Van den Neste 2017 [143] on fateful course) and 3 further studies on mantle-cell lymphoma (MCL) (Dietrich 2014 [42] on allo-SCT and fateful course; Dreger 2018 [43] and Maris 2004 [44] on allo-SCT) were considered.

B-NHL overall

Study on allo-SCT

Freytes 2012 [34] is a retrospective, non-comparative registry analysis of the CIBMTR registry, which contains data from 69 centres worldwide. The study analysed results of 263 patients with B-NHL relapse following auto-SCT who then received reduced-intensity or non-myeloablative allo-SCT between 1996 and 2006. Only patients with DLBCL, MCL, or follicular lymphoma (FL) were included. Patients with planned tandem auto-allo transplant as well as patients who were in their first complete remission at the time of allo-SCT were excluded from the study.

Studies on fateful course

Kuittinen 2005 [123] was used to document the fateful course of the disease for the benefit assessment. The retrospective, non-comparative registry analysis reported results from 6 Finnish centres. These centres predominantly treated patients with DLBCL, but also patients with FL or MCL. Since fewer than 20% of patients had T-cell NHL, it was possible to use the study to provide information on the fateful course of B-NHL. Other subentities, such as LBL and BL, made up 5% of cases. Between 1991 and 2000, auto-SCT was performed on 353 patients. By 2001, progression or relapse following auto-SCT had occurred in 115 of these patients, who were then analysed within the study. Out of this group, 107 patients (93%) underwent no further transplantation.

The population-based study Smeland 2016 [124] compiled data on adult patients treated with auto-SCT for NHL in Norway between 1987 and 2008. At the beginning of this period, all auto-SCT procedures were performed at a hospital in Oslo. At a later time, 4 additional centres provided this treatment and compiled patient data, so that all auto-SCT procedures performed on patients in Norway were included. In this patient population as well, DLBCL was the most common subentity of NHL, followed by PTCL at 16%, transformed lymphomas at 15%, FL at 13%, and MCL at 12%. In 288 patients (50%), the relapse occurred after auto-SCT, and 254 (88%) of these patients underwent no further transplantation. This is the patient population relevant for this benefit assessment with regard to fateful course.

Diffuse large B-cell lymphoma

Studies on allo-SCT

Fenske 2016 [38] is a retrospective, non-comparative registry analysis for the time period 2000 to 2012. The analysis used data on allo-SCT from 503 patients and 133 centres worldwide. It included adult patients with relapsed or refractory DLBCL following auto-SCT. It excluded patients who received stem cells from a syngeneic or haploidentical donor as well as patients with a T-cell depleted stem cell transplant. Also excluded were patients with DLBCL who received prior auto-SCT or subsequent allo-SCT for another indication or in whom tandem auto-allo stem cell transplantation was planned.

Rigacci 2012 [39] is a retrospective and non-comparative study. It reported data from 48 centres of the Italian bone marrow transplant registry for the period 1995 through 2008. Out of 884 patients with DLBCL who relapsed or were refractory after auto-SCT, 165 later received an allogeneic stem cell transplant and were included in the study. The authors did not report any further inclusion or exclusion criteria.

Results from the European EBMT database were reported by Van Kampen 2011 [40]. The retrospective, non-comparative registry analysis includes data from 65 centres for the time period 1997 through 2006. The reported inclusion criteria were a primary diagnosis of DLBCL, relapse after auto-SCT, and allo-SCT with HLA-identical sibling donor or HLA-matched unrelated donor. The authors did not list any exclusion criteria. In total, data on 101 patients are available.

In all 3 studies on allo-SCT for the treatment of DLBCL, most patients received non-myeloablative or reduced-intensity chemotherapy regimens (63% to 75% of allo-SCT), whereas myeloablative conditioning regimens were administered less commonly (25% to 37%). For Van Kampen 2011, the reported median follow-up of patients with myeloablative conditioning (MAC) was 63 months, much longer than the median follow-up for patients with reduced-intensity conditioning (RIC), at 44 months. Fenske 2016 and Rigacci 2012 reported median follow-up periods for the total patient population. These were 55 months and 39 months, respectively.

Studies on fateful course

Calvo-Villas 2010 [126] was used to document the fateful course of disease in DLBCL. This retrospective, non-comparative observational study supplies data from 28 Spanish centres. In the observation period from 1993 to 2007, 82 adult patients with progression or relapse following auto-SCT were treated, and 62 of these patients (76%) underwent no further transplantation. Included were only patients who had achieved at least partial remission after prior auto-SCT and who were between 18 and 70 years of age.

The retrospective, non-comparative observational study Nagle 2013 [130] was used for the fateful course of disease as well. This monocentric study was conducted in the United States. At the centre, a total of 225 adult patients were treated with auto-SCT for relapsed or primary

refractory DLBCL between 2005 and 2011. Included were only patients with progressive disease following auto-SCT who had received rituximab as a component of their first-line therapy. The study comprised 56 patients, of whom 50 patients (89%) underwent no further transplantation. Patients whose relapse had not been pathologically confirmed or who exhibited indolent lymphoma were excluded from the study.

Van den Neste 2017 [143] reported results on a subgroup of participants of the multicentre CORAL RCT. Between 2003 and 2008, this study randomized patients with $CD20^+$ B-NHL to 2 different rituximab-containing chemotherapy regimens (both with subsequent auto-SCT). Van den Neste 2017 is a retrospective, non-comparative observational study in which 75 patients with progressive disease were combined from both study arms of the original study after receiving auto-SCT. Out of this group, 57 patients (76%) underwent no further transplantation. Van den Neste 2017 did not list any explicit inclusion or exclusion criteria. The original exclusion criteria of the CORAL RCT listed, among other things, CNS involvement and inadequate organ function [144].

Mantle-cell lymphoma

Study on allo-SCT and fateful course

The retrospective registry analysis Dietrich 2014 [42] included data on allo-SCT as well as fateful course. It reported results from 82 European centres in which adult patients with MCL received auto-SCT between 2000 and 2009. Out of 1054 patients with disease progression or relapse following auto-SCT, the patient and treatment characteristics required by the authors were available for 360 patients. Out of this group, 80 patients underwent allogeneic transplantation. For conditioning, 71% of patients with allo-SCT received a reduced-intensity regimen, and 29%, a myeloablative regimen. Treatment without allo-SCT was received by 280 patients, 7 of whom underwent repeat auto-SCT. This group represented the comparator group with fateful course.

Studies on allo-SCT

The retrospective analysis of the EBMT registry by Dreger 2018 [43] included adult patients with MCL who received both allo-SCT between 2013 and 2016 and, at an earlier time, the tyrosine kinase inhibitor ibrutinib. No further inclusion and exclusion criteria were listed. Results were reported on 22 patients with relapsed or refractory MCL. The study also investigated patients with chronic lymphatic leukaemia (CLL), who are not presented in this benefit assessment.

The Maris 2004 study [44] with a prospective, but not comparative, design presented results from 7 American centres from 2000 through 2003. As a primary study on allo-SCT, the study was used in the benefit assessment. Included were patients who were either older than 50 years or ineligible for myeloablative conditioning regimens due to comorbidities. All patients therefore received non-myeloablative conditioning regimens. In total, results on 33 patients

were reported, of whom 14 patients met the inclusion criteria of this benefit assessment. The remaining patients did not meet the criterion of prior auto-SCT.

4.3.2 Overview of assessment-relevant outcomes

For research question 1, overall survival (OS) is the central patient-relevant outcome. Therefore, only OS and potential harm were used as assessment-relevant outcomes. Studies from the comprehensive or focused information retrieval were not used for the assessment if they did not report results on the central patient-relevant outcome. Since presentation in the form of the "matrix of patient-relevant outcomes" therefore offers no additional information, no such table was generated.

4.3.3 Assessment of the risk of bias at study and outcome levels

The risk of bias at study level is seen as high for all studies. Therefore, all reported outcomes are considered potentially highly biased at study level as well. The risk of bias at outcome level was not assessed in detail.

4.3.4 Results on patient-relevant outcomes

4.3.4.1 Results on overall survival

All 1-arm observational studies and non-comparative registry analyses used in the benefit assessment reported results on overall survival. Due to these studies' very low qualitative certainty of results, a conclusion on benefit can be drawn only if the patient populations exhibit a dramatic difference in overall survival.

The median survival after allo-SCT is 8 months in Freyes 2012, which jointly considered the various histological subtypes. The 3-year survival rate was 32%, and 5-year survival, 27%. In comparison, Kuittinen 2005 and Smeland 2016 reported a median survival of between 8 and 12 months for fateful course. The 4-year survival of the total patient population in Kuittinen 2005, in which a small percentage of 7% underwent another transplantation, was 21%. In Smeland 2016, after 5 years, 30% of the overall patient population was still alive, including 34 patients (12%) who underwent another transplantation. Out of these patients, 24 survived for at least 2.5 years.

The median survival following allo-SCT in patients with DLBCL was reported as 14 months (Rigacci 2012), 16 months (Fenske 2016), and 32 months (Van Kampen 2011). Among the studies on fateful course, Van den Neste 2017 revealed a median survival of 8 months without another transplantation. Nagle 2013 provided no information on the subpopulation without further transplantation. However, at 7.2 months, the 6 patients who received a second (allogeneic) SCT had a lower reported median survival than the total patient population. The 1-year, 3-year, and 5-year survival rates in the studies on allo-SCT are 54%, 37%, and 34% in Fenske 2016 and 55%, 42%, and 39% in Rigacci 2012, respectively. For the patient population of Van Kampen 2011, 1-year and 3-year survival rates of 64.7% and 52.2%, respectively, were reported. This is contrasted by the results on fateful course in Calvo-Villas 2010, at a 3-year

survival rate of 31.1% for the subpopulation without further transplantation (at a 39% survival rate for the total population). The Van den Neste 2017 study showed very similar values at 1 year (1-year survival of 31.2% in the subpopulation without transplantation and 39.1% in the total patient population). In Nagle 2013, 19% of the total population reached the 3-year mark.

In Diedrich 2014, the median survival time of patients with MCT who received allo-SCT was 17 months. The 2-year and 5-year survival rates were 46% and 34%, respectively. In Dreger 2018 and Maris 2004, median survival could not be calculated since fewer than 50% of all patients, 22 and 14 patients, respectively, died within the median follow-up period. However, Dreger 2018 reported a 1-year survival rate of 86%. These results are contrasted by the Dietrich 2014 study with a median survival time of 15 months for fateful course. In this study, the 2-year and 5-year survival rates were 37% and 16%, respectively.

The difference in overall survival between patient populations who received allo-SCT and patient populations who did not receive allo-SCT cannot be considered dramatic, thus resulting in no hint of benefit of allo-SCT.

4.3.4.2 Results on acute and chronic GvHD

Results on acute and chronic GvHD were reported in all studies used to answer research question 1, except for Dreger 2018 and Dietrich 2014 on MCL. The operationalization of aGvHD differed between studies and included grades I to IV in some studies and grades II to IV or grades III to IV in others. Similarly, cGvHD was operationalized differently between studies and comprised all events in some studies, but only extensive cGvHD in others. Since this adverse event is specific and can only occur following allo-SCT, the onset of GvHD is considered a hint of harm of allo-SCT.

No other adverse effects of therapy were reported in the studies on fateful course. Since it was impossible to draw a comparison, any data available in the studies on allo-SCT were not presented.

4.4 Research question 2: B-NHL/SCT-naïve

4.4.1 Characteristics of the studies included in the evaluation

For research question 2, all studies were used which both reported a comparison between allogeneic SCT and autologous SCT and included a population of at least 80% of patients without prior haematopoietic stem cell transplant, whether from their own or donor stem cells (SCT naïve). Overall, 14 studies were found for research question 2. All of them were retrospective, comparative cohort studies on various histological subentities of B-NHL. Most studies did not report any criteria used to determine whether patients received allogeneic or autologous SCT. In all studies, the patients who received auto-SCT were of a higher median age than the patients receiving allogeneic transplants. None of the studies reported how many patients had secondary central nervous system involvement. The time until disease progression during the period from prior therapy to SCT was not reported by any of the studies either.

Diffuse large B-cell lymphoma

Aksentijevich 2006 [47] was conducted in a transplantation centre in the United States. Within the observation period of 1985 through 2001, 183 patients with DLBCL were included. No further differentiation of patients by DLBCL subtypes was reported. Excluded were patients with transformation from indolent lymphoma to DLBCL as well as patients with composite lymphoma, in whom indolent lymphoma was confirmed alongside DLBCL. Patients under the age of 60 years with a matching sibling donor preferentially received allo-SCT, regardless of the characteristics of the disease. In total, 45 patients received allo-SCT with MAC. Autologous transplantations were received by 138 patients. In this group, 57% of patients received ciclosporin and interferon alpha to induce auto-GvHD. This was done to investigate the influence of a potential GvL effect in auto-SCT. Only rudimentary results on induced GvHD in the auto-group were reported.

The monocentric cohort study Ghobadi 2015 [48], which was conducted in the United States, included patients with DLBCL and either primary induction failure or relapse within one year. Out of the 42 patients with allo-SCT, the majority (67%) received transplants between 1997 and 2003, and the remainder, between 2004 and 2010. In contrast, the majority of the 79 patients with auto-SCT (62%) received the transplant during the later time period from 2004 to 2010. The authors did not report the median follow-up period. Similarly, no information was provided on the percentages of patients receiving myeloablative, non-myeloablative, or reduced-intensity conditioning for allo-SCT. However, it was noted that the percentage of patients receiving MAC prior to allo-SCT was greater than the percentage of patients receiving RIC/non-myeloablative conditioning [NMA].

Lazarus 2010 [49] represents an analysis of the CIBMTR registry from 17 countries from 1995 to 2003. Included were patients with DLBCL who received MAC allo-SCT using a matching sibling donor or auto-SCT. Patients who received allo-SCT with RIC, T-cell depletion, or auto-SCT prior to allo-SCT were excluded. The analysis included 79 patients with allo-SCT and 837 patients with auto-SCT. At a median of 81 months, the population of survivors who underwent allo-SCT was followed up for longer than the population of survivors who underwent auto-SCT, at a median of 60 months.

Robinson 2016 [50] is another retrospective registry analysis: It reported results on SCT in patients who were diagnosed with DLBCL and registered in the EBMT between 2002 and 2009. Under the term DLBCL, the authors pooled centroblastic and immunoblastic large-cell lymphomas, primary mediastinal large B-cell lymphoma, intravascular B-cell lymphoma as well as primary effusion lymphoma. Included were patients with relapse or refractory disease. Patients with planned tandem transplantation or cases where umbilical cord blood was used as the source of stem cells were excluded. The presentation of patient characteristics and the analysis of patients with allogeneic transplants was stratified by conditioning regimen into a MAC group and a RIC group. In the largest study included on this research question on DLBCL, data on 132 patients with MAC allo-SCT, 98 with RIC allo-SCT, and 3980 with auto-SCT were collected. The follow-up time of surviving patients in the two allo groups differed from that of

the auto group: Patients with MAC or RIC allo-SCT had a median follow-up of 36 months and 34 months, respectively, while patients with auto-SCT had a followed-up of 18 months.

Follicular lymphoma grade 3

Klyuchnikov 2016 [57], a retrospective analysis of the CIBMTR registry, included patients with grade 3 follicular lymphoma (FL III) according to the WHO classification. It included 61 patients with initial allogeneic SCT and 136 patients with initial autologous STC who had relapsed or were refractory between 2000 and 2012. The allo-SCT group included only patients with reduced-intensity regimens (NMA or RIC) and an HLA match of at least 7 out of 8. Excluded were patients with T-cell-depleted or CD34-selected stem cells. Patients with follicular lymphoma (FL) transformation to DLBCL were excluded as well.

Transformed lymphoma

Four comparative studies on transformed lymphoma met the inclusion criteria. In these studies, transformation was virtually exclusively to DLBCL, except in 2 patients, who experienced transformation to BL or BL-like lymphoma.

Ban-Hoefen 2013 [58] reported on patients registered in the NHL database of the NCCN (National Comprehensive Cancer Network) who received SCT for the treatment of transformed NHL between 2000 and 2011 (18 patients with allo-SCT, 50 with auto-SCT). Included were all patients with transformed lymphoma, regardless of the histology of the originally diagnosed indolent lymphoma. The transformed lymphoma developed from an FL in most cases (86%) and less commonly from marginal zone lymphoma (MZL) (11%) or small lymphocytic lymphoma (SLL) (3%). Patients with FL IIIB were excluded. The number of therapies after transformation and before SCT varied within the patient population and between the two interventions: For patients with allo-SCT, a median of 2 prior therapies for transformed lymphoma was reported, for patients with auto-SCT, a median of 1. Intervention characteristics, such as intensity of the conditioning regimen or stem cell source, were not reported in the publication.

The retrospective comparative cohort study Villa 2013 [59] was conducted in 14 transplantation centres. Within the observation period from 2001 to 2010, 22 patients received an allogeneic transplant (with MAC in > 95% of cases), and 97 patients received auto-SCT. The first diagnosed indolent lymphoma was FL grade 1 through 3a. The type and number of therapies for indolent FL varied and included both chemotherapy and radiotherapy. In the patient population with allo-SCT, 9% of patients received auto-SCT. Patients who received allo-SCT after auto-SCT due to transformed lymphoma therapy were not included in the study, however. Results are available not only on patients treated with SCT, but also on 53 patients treated with rituximab and chemotherapy without SCT. Since this comparison for B-NHL does not correspond to the report's research question, it is not presented below.

Villa 2014 [60] also reported the results of a retrospective Canadian cohort study. Unlike Villa 2013, this study considered only non-follicular lymphoma (MLC, chronic lymphocytic

leukaemia, lymphoplasmocytic lymphomas as well as SLL) with transformation to aggressive B-NHL. In the observation period from 1996 to 2013, 12 patients received an allogeneic transplant; a classic conditioning regimen was used in all cases. In 4 patients (33%), the donor was an HLA-incompatible family donor. Auto-SCT was received by 22 patients.

In the retrospective cohort study by Wirk 2014 [61], 141 patients with FL-transformed DLBLC were included. The analysis included patients registered in the CIBMTR registry between 1990 and 2009. Allo-SCT was received by 33 patients (20 with MAC, 11 with RIC; no information on conditioning type available for 2 patients) and auto-SCT by 108 patients. Patients who had previously received SCT for treating FL were excluded from the study.

Mantle-cell lymphoma

Fenske 2014 [51] reported the results on patients with MCL who were registered in the CIBMTR registry between 1996 and 2007. Patients with allo-SCT and auto-SCT were each categorized into 2 groups: The "early SCT" cohort comprised 50 patients with RIC allo-SCT and 249 patients with auto-SCT who were in their first partial or complete remission and had received no more than 2 chemotherapy lines. The "late SCT" cohort comprised all remaining patients: 88 patients with RIC allo-SCT and 132 with auto-SCT. Patients with classic conditioning prior to allo-SCT, T-cell depletion, non-matching donor, or syngenetic donor were excluded. Patients who did not respond to chemotherapy were excluded for both interventions.

The monocentric, retrospective study Ganti 2005 [52] was conducted in the United States. Between 1988 and 2003, 17 patients with MCL received allo-SCT and 80 patients, auto-SCT. All patients with allo-SCT received a myeloablative conditioning regimen and stem cells from matching sibling donors. The authors did not list any explicit inclusion or exclusion criteria.

Magnusson 2014 [54] described the results from a transplantation centre in the United States as well. The transplantations were performed between 1999 and 2010. Results from this centre for an earlier but overlapping time period (1994 through 2003) were reported by Laudi 2006 [53]. The benefit assessment primarily used the results of the more current publication since it additionally comprised a larger patient population (28 patients with allo-SCT, 38 patients with auto-SCT). From among the patients with allogeneic transplant, 13 patients received MAC and 15, RIC. The study also included patients who received a transplant harvested from umbilical cord blood. The share of stem cell transplants obtained in this manner is 36%. In the allo group, 7% of patients had blastoid MCL, in the auto group, 15% of patients. The median follow-up for the patient population with allo-SCT was 80 months, for those with auto-SCT, only 42 months.

Tam 2009 [55] reported results on SCT performed at a US centre in patients with MCL between 1990 and 2007. Up to the year 1997, patients with relapsed or primary refractory MCL received an autologous transplant; from 1997 onwards, they alternatively received a non-myeloablative allogeneic transplantation if an HLA-compatible donor was available. Up to the year 2004, auto-SCT was performed up to an age of 70 years; from 2004 onwards, patients up to the age of 75 years received auto-SCT. Allo-SCT was administered to patients up to an age of 65 years.

In the study, 35 patients received an allogeneic transplant. The study's authors reported results on patients with auto-SCT in 2 patient populations: "early auto-SCT" performed to consolidate the first complete or partial remission and "late auto-SCT", which, like allo-SCT, was performed in relapsed or primary refractory MCL. For this research question, the results of the 36 patients with late auto-SCT are presented. The share of patients with blastoid variant MCL was 3% in the allo group (1 patient) and 6% in the late auto group (2 patients).

The retrospective Japanese registry study Yamasaki 2018 [56] reported results on patients with MCL who received auto or allo SCT between 2004 and 2014 and had a relapse or were refractory after rituximab-containing chemotherapy. Not included were patients who received SCT only to consolidate the first-line therapy. Out of 162 patients, 111 underwent autologous transplantation and 51, allogeneic transplantation. In the allo-SCT group, conditioning was conducted with a reduced-intensity regimen in most cases (46 patients). Stem cells from a matching sibling or unrelated donor were given to 21 patients. The remaining 30 patients in the allo-SCT group, in contrast, received stem cells from an HLA-incompatible donor.

4.4.2 Overview of assessment-relevant outcomes

For the benefit assessment, data on patient-relevant outcomes were extracted from 12 studies. Data from 1 study were presented only as supplementary information. Table 3 presents an overview of the available data on patient-relevant outcomes from the included studies.

Table 3: Matrix of patient-relevant outcomes (research question 2: B-NHL/SCT-naïve)

Study	Outcomes												
	Mortality			Morbidity		Adverse effects of therapy						Health-related quality of life	
	Overall survival	Treatment-related mortality	Non-relapse mortality	Disease-free survival	Relapse/progression	GvHD	Infections	Secondary neoplasms	Other complications	SAE	Fatal AE	Activities of daily living	Dependence on help from others
Diffuse large B-cell lymphoma													
Aksentijevich 2006	●	○	-	○	○	●	-	-	-	-	-	-	-
Ghobadi 2015	●	-	○	○	○	-	-	-	-	-	-	-	-
Lazarus 2010	●	●	-	○	○	●	-[a]	○	-[a]	-	●	-	-
Robinson 2016	●	-	●	○	○	-	-	-	-	-	-	-	-
Follicular lymphoma III°													
Klyuchnikov 2016	●	-	○	○	○	●	-[a]	○	-[a]	-	●	-	-
Transformed lymphoma													
Ban-Hoefen 2013	○	○	-	-	-	-	-[a]	○	-[a]	-	●	-	-
Villa 2013	●	○	-	○	-	●	-	-	-	-	-	-	-
Villa 2014	○	○	○	○	-	●	-	-	-	-	-	-	-
Wirk 2014	○	-	○	○	○	●	-	-	-	-	-	-	-
Mantle-cell lymphoma													
Fenske 2014	●	-	○	○	○	-	-[a]	○	-[a]	-	●	-	-
Ganti 2005	○	-	-	○	○	-	-	-	-	-	-	-	-
Magnusson 2014	○	○	-	○	○	●	-	-	-	-	-	-	-
Tam 2009	○	○	-	○	-	●	-	-	-	-	-	-	-
Yamasaki 2018	○	-	○	○	○	●	-	-	-	-	-	-	-

(continued)

Table 3: Matrix of patient-relevant outcomes (research question 2: B-NHL/SCT-naïve) (continued)

● Data were reported and used in the benefit assessment.
○ Data were reported but not used in the benefit assessment (particularly due to an uneven distribution of prognostic factors between intervention groups).
- No data were reported (no further information) / The outcome was not surveyed.
a: The subset of fatal events is considered under the outcome of fatal AEs.
AE: adverse event ; B-NHL: B-cell non-Hodgkin lymphoma; GvHD: graft-versus-host disease; SAE: serious adverse event; SCT-naïve: patients who have not yet received a stem cell transplantation

4.4.3 Assessment of the risk of bias at study and outcome levels

Fourteen retrospective, comparative cohort studies were found for research question 2. Systematic bias is possible due to the study design; therefore, the risk of bias at study level is generally rated as high. Patients who received allo-SCT differed from patients with auto-SCT with regard to prognostic factors. No summary assessment of the risk of bias at study level was performed for studies where these factors were not adequately considered in the analysis for any reported outcome. Results from those studies are provided as supplementary information (Ban-Hoefen 2013, Villa 2014, and Wirk 2014 on transformed lymphoma as well as Ganti 2005, Magnusson 2014, Tam 2009, and Yamasaki 2018 on MCL). An exception are results on adverse effects of therapy, which are considered from all studies. For the studies in which potentially biasing factors were adequately considered and for which a summary assessment of the risk of bias at study level was therefore generated, the high risk of bias at study level translated into a high risk of bias at outcome level. Additional factors, such as lack of blinding of outcome data collection, lack of intention to treat (ITT) analysis, potential reporting bias, and differences in follow-up periods, further increased the risk of bias at outcome level. Some outcomes from these studies, for which the consideration of prognostic factors was considered inadequate, are presented as supplementary information but not used for assessing the benefit.

4.4.4 Results on patient-relevant outcomes

For the benefit assessment, 14 studies were used to compare treatment with allo-SCT versus treatment with auto-SCT in SCT-naïve patients with B-NHL. Four of these studies included patients with DLBCL (Aksentijevich 2006, Ghobadi 2015, Lazarus 2010, Robinson 2016), 1 study, patients with FL III (Klyuchnikov 2016), 4 studies, patients with transformed lymphoma (Ban-Hoefen 2013, Villa 2013, Villa 2014, Wirk 2014), and 5 studies, patients with MCL (Fenske 2014, Ganti 2005, Magnusson 2014, Tam 2009, Yamasaki 2018). From these studies, data on mortality (overall survival, treatment-related mortality, and non-relapse mortality) as well as potential harm of SCT (GvHD, fatal adverse events [AEs]) were considered.

4.4.4.1 Results on overall survival

Out of the studies used for the assessment, 7 reported results on overall survival. The 4 studies on DLBCL were not combined in a meta-analysis. Due to the studies' very low qualitative certainty of results, a conclusion on benefit can be drawn only in case of a dramatic effect. However, the results were not on the scale of a dramatic effect. Consequently, there is no hint of greater benefit or harm of allo-SCT for the outcome of overall survival.

4.4.4.2 Results on treatment-related and non-relapse mortality

Results on treatment-related mortality (TRM) used for the benefit assessment were reported in 1 study on DLBCL (Lazarus 2010). It defined TRMs as deaths within 28 days after SCT or deaths without lymphoma progression. Results on non-relapse mortality (NRM) came from 1 study on DLBCL (Robinson 2016) as well. Two further studies also reported effect measures regarding NRM, one of them done in patients with DLBCL (Ghobadi 2015) and the other in patients with FL III (Klyuchnikov 2016). Unlike for overall survival, the adjustment was inadequate or no information on adjustment was available for this outcome; consequently, these results are presented as supplementary information.

However, the results on TRM and NRM in DLBCL are not on the scale of a dramatic effect. Consequently, there is no hint of greater benefit or harm of allo-SCT in DBLCL for the outcomes of TRM and NRM. No usable data were available for further histological subentities.

4.4.4.3 Results on disease-free survival

Most of the included studies used the operationalization of PFS for disease-free survival, while 3 studies used the operationalizations of EFS or DFS. However, a specific operationalization of all 3 outcomes with information on the diagnosis of progression, the event, or the disease was not reported by any of the included studies. Hence, it cannot be concluded that reliable evidence of relapse was available; consequently, the data were not relevant for the conclusion and were presented as supplementary information.

4.4.4.4 Results on acute and chronic GvHD

Results on acute and chronic GvHD were reported in 9 studies and on all subentities presented in this research question. The occurrence of both acute and chronic GvHD greatly varied between patient populations. However, this was in part due to the studies' different operationalizations (inclusion of all events regardless of severity versus exclusion of mild forms; different analysis time points). Three studies also reported the number of deaths due to GvHD. In summary, the occurrence of GvHD was considered a hint of harm of allo-SCT for all presented subentities.

4.4.4.5 Results on secondary neoplasms

No suitable data were available for the outcome of secondary neoplasms.

4.4.4.6 Results on adverse effects

Results on adverse events were reported in 4 studies. The presented analyses are exclusively on fatal AEs. In all studies, more fatal AEs occurred in the group of patients who received an allogeneic transplant. Given the differences in patient characteristics, which largely suggest a less favourable prognosis, and lack of a dramatic difference in the occurrence of fatal AEs, there is still no hint of greater harm of allo-SCT.

4.4.4.7 Results on health-related quality of life

No usable results on the outcome of health-related quality of life were found in the included studies.

4.5 Research question 3: T-NHL/first line/allo-SCT vs. systemic therapy

For the comparison of allo-SCT with systemic drug therapy as first-line therapy in patients with T-LBL, 1 comparative study was found. No suitable comparative studies were found on other histological subtypes.

4.5.1 Characteristics of the study included in the evaluation

For the comparison of allogeneic SCT with chemotherapy, the retrospective, comparative cohort study Yang 2018 [62] was found. This study included only patients with lymphoblastic lymphomas (LBL). Since these were largely LBL of the T-cell line (87% of patients), the study was placed in the T-NHL category. It reported results on patients treated in a Chinese centre between 2006 and 2016 who responded to induction chemotherapy for the treatment of LBL with partial or complete remission and subsequently received allo-SCT or chemotherapy. Patients who did not achieve at least partial remission were excluded. Out of 39 patients, 22 received chemotherapy, and 17, allo-SCT. Patients were not allocated to interventions based on prognostic factors (such as age or relapse status following induction therapy): The decision for allo-SCT was taken on the basis of donor availability as well as the patient's willingness to undergo SCT. Although the percentage of patients under 18 years of age is unclear (median age of 26 years, range of 15 to 61 years), the results are considered to adequately translate to adult patients; therefore, the study was included in this benefit assessment.

4.5.2 Overview of assessment-relevant outcomes

Data from the Yang 2018 study were used for the benefit assessment. An overview of the available data on patient-relevant outcomes is shown in Table 4.

Table 4: Matrix of patient-relevant outcomes (research question 3: T-LBL/first line/allo-SCT vs. chemotherapy)

Study	Outcomes												
	Mortality			Morbidity		Adverse effects of therapy						Health-related quality of life	
	Overall survival	Treatment-related mortality	Non-relapse mortality	Disease-free survival	Relapse/progression	GvHD	Infections	Secondary neoplasms	Other complications	SAE	Fatal AE	Activities of daily living	Dependence on help from others
Yang 2018	○	-	○	○	○	●	-[a]	-	-	-	●	-	-

● Data were reported and used in the benefit assessment.
○ Data were reported but not used in the benefit assessment.
- No data were reported (no further information) / The outcome was not surveyed.
a: The subset of fatal events is considered under the outcome of fatal AEs.
AE: adverse event; allo: allogeneic; GvHD: graft-versus-host disease; SAE: serious adverse event; SCT: stem cell transplantation; T-LBL: precursor T-cell lymphoblastic lymphoma; vs.: versus

4.5.3 Assessment of the risk of bias at study and outcome levels

Due to the study design (retrospective comparative study), the risk of bias at study level for the Yang 2018 study is rated as high. Since it is unclear whether a) the groups were comparable, b) prognostic factors were adequately taken into account, and c) the intervention groups were followed up for the same period of time, the risk of bias at study level was not rated overall. The results are presented as supplementary information, except for the results on adverse effects of therapy, which were analysed.

4.5.4 Results on patient-relevant outcomes

Yang 2018 does not report any results on patient-relevant outcomes which are suitable for the benefit assessment, except for results on adverse effects of therapy, which are presented below.

4.5.4.1 Results on overall survival

For the outcome of overall survival, no suitable data are available. The results of the only study identified on this research question, Yang 2018, are presented as supplementary information in Section 3.5.3 of the full report.

4.5.4.2 Results on treatment-related and non-relapse mortality

For the outcome of treatment-related and non-relapse mortality, no suitable data are available. The results of the only study identified on this research question, Yang 2018, are presented as supplementary information in Section 3.5.3 of the full report.

4.5.4.3 Results on disease-free survival

For the outcome of disease-free survival, no suitable data are available. The results of the only study identified on this research question, Yang 2018, are presented as supplementary information in Section 3.5.3 of the full report.

4.5.4.4 Results on acute and chronic GvHD

One study reported the occurrence of acute and extensive chronic GvHD as well as one death due to chronic GvHD. The occurrence of GvHD was considered a hint of harm of allo-SCT.

4.5.4.5 Results on fatal adverse events

Results on fatal adverse events were reported in 1 study. There was no dramatic difference in the occurrence of fatal AEs. Consequently, on the basis of this study, there was no hint of greater harm of allo-SCT.

4.5.4.6 Results on health-related quality of life

No data are reported for the outcome of health-related quality of life.

4.6 Research questions 3+4: T-NHL/first and higher line/allo-SCT vs. auto-SCT

As part of the comprehensive information retrieval, several comparative studies were found on the comparison of allo-SCT and auto-SCT in patients with T-NHL. Due to the varying numbers of prior therapy lines within the respective patient population, some of the studies were not unequivocally assignable to either research question 3 (first line) or 4 (higher line). In order to nevertheless permit consideration of the studies in this benefit assessment, the identified comparative studies were presented jointly in this section – regardless of line of therapy. The section also discusses how unequivocally each of the studies was assignable either to research question 3 or 4. The strength of evidence was also derived for each research question, if possible. It must be noted that for the comparison of allo-SCT and auto-SCT in first-line therapy of T-NHL, the final results of 1 prematurely terminated RCT (AATT study [145]), whose patient population unequivocally fits research question 3, have not yet been published. The authors have indicated that they intend to publish this in mid-2019.

4.6.1 Characteristics of the studies included in the evaluation

For the comparison of allogeneic and autologous SCT, 5 retrospective studies were found, of which 3 were comparative cohort studies and 2 were observational studies reporting individual patient data which were suitable for making comparative calculations. Most of the studies did not report any criteria for the use of allo-SCT or auto-SCT. Out of the 5 included studies,

4 studies combined different histological subentities of T-NHL, while 1 study reported results only on NK cell lymphomas.

The monocentric, retrospective cohort study Beitinjaneh 2015 [63] covered the period from 1990 to 2009. Included were patients with nodal T-NHL (except anaplastic lymphoma kinase [ALK]-positive ALCL) as well as patients with extranodal T-NHL (except primary cutaneous T-NHL). The authors categorized the study population into 2 groups, which are reported separately: The first group comprises patients in their first complete remission, with primary induction failure or with partial response to salvage therapy. In this group, 11 patients received MAC-allo-SCT or RIC-allo-SCT, and 47 patients, auto-SCT. Patients with allo-SCT or auto-SCT had a median follow-up of 45 months or 35 months, respectively. This subgroup unequivocally fit research question 3. The second group comprises patients who had a recurrence and therefore unequivocally fit research question 4. From this group, 41 patients received MAC-allo-SCT or RIC-allo-SCT, and 35 patients, auto-SCT. For relapsed patients, the median follow-up period was not reported. The most common histological subentity in both patient populations is PTCL-NOS.

Busemann 2014 [64] reported individual patient data on all patients who received SCT at a German centre between 1996 and 2013. In this study, patients were considered jointly, regardless of prior treatment status (first line or higher line therapy); therefore, it was not a clear fit for either research question 3 or 4. The most common histological subentity was PTCL-NOS. In total, 14 patients received allogeneic SCT, and 6 patients, autologous SCT. Allo-SCT was used whenever possible, as it was preferred over auto-SCT. Among the patients with auto-SCT, 3 did not qualify for allo-SCT, 2 received auto-SCT before introduction of allo-SCT at the centre, and 1 patient was treated following the SMILE protocol. Half the patients undergoing allo-SCT received a myeloablative conditioning regimen, while the other half received a reduced-intensity regimen. In the allo group, 71% of patients also received alemtuzumab, an antibody against the surface antigen CD52.

The retrospective cohort study Hsu 2018 [65] reported results on patients who received SCT for T-NHL (PTCL-NOS, ALCL, AITL, ENKL, and rare subentities) in 15 Taiwanese centres between 2009 and 2014. Included were all patients with SCT, regardless of therapy line. The study therefore did not unequivocally fit research either question 3 or 4. The authors did not report any inclusion or exclusion criteria. The decision for auto-SCT or allo-SCT was made by the treating physician based on prognostic factors such as refractory or relapsed disease, patients' health condition, or histological subtype of T-NHL. Auto-SCT was performed in 90 patients, and allo-SCT, in 41 patients. In the auto-SCT group, most patients (91%) received BEAM or similar regimens; in the allo-SCT group, patients received myeloablative (68%) or reduced-intensity (32%) conditioning regimens. In both auto-SCT and allo-SCT, all stem cells were harvested from peripheral blood.

The retrospective cohort study Smith 2013 [66] is the largest included study comparing allo-SCT and auto-SCT in T-NHL. Between 1996 and 2006, 126 patients received an allogeneic

transplant and 115 patients an autologous transplant in 72 and 67 US centres, respectively. In this study, patients were considered jointly, regardless of prior treatment status (first line or higher line therapy); therefore, it was not a clear fit for either research question 3 or 4. Included were only patients with T-NHL up to an age of 60 years who received their first SCT. Precursor T-cell neoplasms and primary cutaneous T-NHL were excluded. Also excluded were patients undergoing allo-SCT with stem cells harvested from umbilical cord blood, with a syngeneic stem cell donor, or with a related, but HLA-incompatible donor. Patients with allo-SCT were conditioned with myeloablative (59%) or non-myeloablative/reduced-intensity (45%) regimens. In 5% of patients, no information was reported on the conditioning regimen. In 16% of patients, stem cells were harvested from an HLA-incompatible donor. GvHD prophylaxis involved particularly methotrexate and/or ciclosporin. In 11% of patients, the stem cell material was subjected to T-cell depletion. Over the considered study period, the percentage of patients receiving allo-SCT continuously rose, while the share of patients with auto-SCT decreased.

The observational study Suzuki 2006 [67] reported individual patient data on patients with NK neoplasms. Out of the 40 patients who underwent transplantation in Japan between 1994 and 1998, 33% of the allo group and 4% of the auto group were under the age of 18. The research question of the benefit assessment covers adult patients only; therefore, one inclusion criterion was not met. Since the authors reported individual patient data, however, it was possible to use the results of 10 patients in the allo group and 24 patients in the auto group to make comparative calculations. The data were not a clear fit for either research question 3 or 4 since no information was available on the number of prior therapies. All stem cells for allo-SCT were harvested from HLA-compatible sibling donors. Patients underwent myeloablative conditioning and received methotrexate in combination with ciclosporin or tacrolimus for GvHD prophylaxis. The authors did not report any intervention characteristics of auto-SCT. In addition to patients undergoing SCT, a population of 188 patients who received only chemotherapy was presented. While this is a relevant comparison with allo-SCT in terms of the research question, not all important basic characteristics were reported on this patient population; therefore, the comparability of groups cannot be evaluated. For this reason, this cohort with chemotherapy is not presented.

4.6.2 Overview of assessment-relevant outcomes

Data for the benefit assessment were obtained from 2 studies. Results from 3 further studies were presented only as supplementary information. Table 5 shows an overview of the available data on patient-relevant outcomes.

Table 5: Matrix of patient-relevant outcomes (research questions 3 + 4: T-NHL/first and higher line/allo-SCT vs. auto-SCT)

Study	Outcomes												
	Mortality			Morbidity		Adverse effects of therapy						Health-related quality of life	
	Overall survival	Treatment-related mortality	Non-relapse mortality	Disease-free survival	Relapse/progression	GvHD	Infections	Secondary neoplasms	Other complications	SAE	Fatal AE	Activities of daily living	Dependence on help from others
Research question 3: T-NHL overall, first line													
Beitinjaneh 2015	○	-	-	○	-	-	-	-	-	-	-	-	-
Research questions 3 + 4: T-NHL overall, first and higher line													
Busemann 2014	○	-	○	-	-	●	-	-	-[a]	-[a]	●	-	-
Hsu 2018	○	-	○	○	-	●[b]	-	-	-	-	-	-	-
Smith 2013	●	○	○	○	○	●	-[a]	-	-[a]	-[a]	●	-	-
Research question 4: T-NHL overall, higher line													
Beitinjaneh 2015	○	-	○	○	-	-	-	-	-	-	-	-	-
Research questions 3+4: Natural killer cell lymphoma, first and higher line													
Suzuki 2006	○	-	-	-	-	-	-	-	-	-	-	-	-

● Data were reported and used in the benefit assessment.

○ Data were reported but not used in the benefit assessment (particularly due to an uneven distribution of prognostic factors between intervention groups).

- No data were reported (no further information) / The outcome was not surveyed.

a: The subset of fatal events is considered under the outcome of fatal AEs.
b: The study reported only fatal events.

AE: adverse event; allo: allogeneic; auto: autologous; GvHD: graft-versus-host disease; SAE: serious adverse event; SCT: stem cell transplantation; T-NHL: T-cell non-Hodgkin lymphoma; vs.: versus

4.6.3 Assessment of the risk of bias at study and outcome levels

Due to the study design (retrospective comparative study), the risk of bias at study level is rated as high. Out of 5 included studies, only 1 study (Smith 2013) adequately considered prognostic factors. The risk of bias at study level was further evaluated for this study only. The results of the other studies, which did not adequately consider prognostic factors, are provided as supplementary information (Beitinjaneh 2015, Busemann 2014, Hsu 2018, Suzuki 2006). An exception are results on adverse effects of therapy which are considered from all studies. For

Smith 2013, in which potentially biasing factors were adequately considered and for which the risk of bias at study level was therefore assessed overall, the high risk of bias at study level translates into a high risk of bias at outcome level. Furthermore, the outcome data collection was not blinded, the ITT principle was inadequately implemented, and it remains unclear whether there was reporting bias. For Smith 2013, the risk of bias is therefore also high at outcome level.

4.6.4 Results on patient-relevant outcomes

One study (Smith 2013) reported overall survival results which were suitable for the benefit assessment. In addition, data on GvHD and fatal adverse events were used from Busemann 2014 and Smith 2013. Hsu 2018 also reported GvHD-related fatal events. Hence, all available results are from studies which cannot be unequivocally assigned to either research question 3 or 4.

4.6.4.1 Results on overall survival

Research question 3

For the comparison of allo-SCT and auto-SCT as first-line therapy in patients with T-NHL, no studies with suitable data on overall survival were found. The results of the only study found on this research question, Beitinjaneh 2015, are presented as supplementary information in Section 3.6.3 of the full report.

Research questions 3 + 4

For the outcome of OS, a pooled consideration of peripheral T-cell lymphomas (PTCL) in Smith 2013 showed no significant difference between allo-SCT and auto-SCT. On the basis of this study, which, given the heterogeneous prior therapy of the patient population, was not unequivocally assignable to either research question 3 or 4, there is no hint of greater benefit or harm of allo-SCT for the outcome of overall survival.

No conclusion can be drawn on the benefit or harm of allo-SCT for various histological subgroups of T-NHL. For PTCL-NOS, no significant difference was reported for the comparison of allo-SCT versus auto-SCT. However, the model adjustment is unclear; therefore, it cannot be assessed whether prognostically relevant factors were in fact adequately taken into account. The results on the histological subtypes are therefore provided as supplementary information in Section 3.6.3 of the full report.

Research question 4

For the comparison of allo-SCT and auto-SCT as higher-line therapy in patients with T-NHL, no studies with suitable data on overall survival were found. The results of the only study identified on this research question, Beitinjaneh 2015, are presented as supplementary information in Section 3.6.3 of the full report.

4.6.4.2 Results on treatment-related and non-relapse mortality

For the outcomes of TRM and NRM, no usable data were reported for any research question.

Smith 2013 reported results on TRM organized by histological subtype in the form of non-adjusted event rates, which were therefore not used in the benefit assessment. Results on NRM were reported as well, but they are also non-adjusted event rates (for ALCL and AITL) or results from models in which the consideration of prognostic factors was unclear (PTCL-NOS) or inadequate (total population of PTCL). All of these data were presented as supplementary information in Section 3.6.3 of the full report.

4.6.4.3 Results on disease-free survival

For the outcome of PFS, no usable data were reported on any research question.

The data from Smith 2013 could not be used either, despite the adequate consideration of prognostic factors. For the presentation of disease-free survival, Smith 2013 used the operationalization of PFS. However, the authors did not operationalize this outcome (diagnosis of progression, event, or disease). It is therefore impossible to conclude that relapse was reliably confirmed; consequently, the data were not relevant for the conclusion. All available data are presented as supplementary information in Section 3.6.3 of the full report.

4.6.4.4 Results on acute and chronic GvHD

Research question 3

For the comparison of allo-SCT and auto-SCT as first-line therapy in patients with T-NHL, no studies with data on acute or chronic GvHD were found.

Research questions 3 + 4

Results on acute and chronic GvHD were reported in Busemann 2014 and Smith 2013, whose patient populations was not be unequivocally assignable to either research question 3 or 4. Hsu 2018 reported only the number of fatal events, but not the total number of occurred events. GvHD is a specific AE of allo-SCT and therefore exclusively occurs in the group of patients treated with allo-SCT. Since neither acute nor chronic GvHD occurs under the comparator treatment, a hint of harm of allo-SCT was derived on the basis of these studies, which, given the heterogeneous prior treatment of the patient population, was not unequivocally assignable to either research question 3 or 4.

Research question 4

For the comparison of allo-SCT and auto-SCT in patients with T-NHL as higher-line therapy, no studies with data on acute or chronic GvHD were found.

4.6.4.5 Results on fatal adverse events

Research question 3

For the comparison of allo-SCT and auto-SCT as first-line therapy for patients with T-NHL, no studies with data on fatal adverse events were found.

Research questions 3 + 4

Results on fatal adverse events were reported in 2 studies with heterogeneous prior treatment of the patient population. There was no dramatic difference in the occurrence of fatal AEs. On the basis of these studies, which, given the heterogeneous prior therapy of the patient population, were not unequivocally assignable to either research question 3 or 4, there is consequently no hint of greater harm of allo-SCT.

Research question 4

For the comparison of allo-SCT and auto-SCT as higher-line therapy in patients with T-NHL, no studies with data on fatal adverse events were found.

4.6.4.6 Results on health-related quality of life

No study reported data on health-related quality of life.

4.7 Research question 4: T-NHL/higher line/allo-SCT vs. fateful course

For the comparison of allo-SCT with fateful course in patients receiving higher-line therapy for T-NHL, no comparative study was found. To ensure that no dramatic curative effect is overlooked in this regard, non-comparative studies were also reviewed for this research question and are presented below.

4.7.1 Characteristics of the studies included in the evaluation

For the comparison of allo-SCT with a fateful course in patients receiving higher-line therapy for T-NHL, 4 studies reporting results on allo-SCT across subentities and 1 suitable study on fateful course were used. In addition, for the histological subtypes of hepatosplenic lymphoma and NK-cell lymphoma, suitable studies were found on both allo-SCT and fateful course; these are also presented below.

Five further studies on allo-SCT for which no comparator data were available on fateful course were presented as supplementary information in Section 3.7.3 of the full report (Kyriakou 2009 and Le Gouill 2008 on angioimmunoblastic T-cell lymphoma; Broccoli 2013, Lazarevic 2011, and Makita 2016 on precursor T-cell lymphoblastic lymphoma).

T-NHL overall

For the assessment in patients with any subentity of T-NHL, 4 studies on allo-SCT (Beitinjaneh 2015 [63], Czajczynska 2013 [69], Rohlfing 2018 [72], and Wulf 2018 [73]) and 1 study on fateful course (Zhang 2018 [136]) were used.

Studies on allo-SCT

Beitinjaneh 2015 was already characterized in Section 4.6.1 since this publication reports on a comparison between allo-SCT and auto-SCT. The study arm of 35 patients with relapse who received allo-SCT was used for research question 4 as well. Results on overall survival were further reported separately for patients with chemosensitive and chemorefractory relapse.

The non-comparative observational study Czajczynska 2013 is a retrospective analysis of 24 patients with various subentities of T-NHL who received allo-SCT at a centre in Kiel between 2005 and 2010. The majority of patients had been prepared for SCT with myeloablative conditioning; only 2 out of 24 patients received RIC. The median age of the patient population was 53 years; it included a small percentage (8%) of children. The majority of patients received a transplant from an unrelated donor (58% HLA-compatible; 21% HLA-incompatible). To supplement the results provided in the publication, the authors of the study supplied long-term data.

The study Rohlfing 2018 includes patients with various subentities of T-NHL – except ALK-positive ALCL – who were treated at Heidelberg University Medical Centre between 2001 and 2014. Out of 142 treated patients, 91 were refractory or had a relapse. This was followed by treatment with allo-SCT in 31 patients, auto-SCT in 7 patients, and salvage therapy without SCT in 51 patients. The study therefore supplies data on the survival of patients treated with allo-SCT and on fateful course. According to the authors, however, the latter group of patients did not qualify for SCT, which means that the groups are not comparable (see Chapter 5 for a more detailed discussion). Therefore, only the study arm of allo-SCT is considered in the benefit assessment below. The patient population of the allo-SCT group comprised mostly patients with chemosensitive relapse (77%).

The non-comparative observational study Wulf 2018 is a retrospective analysis of 84 patients with various subentities of T-NHL who received allo-SCT at 4 German DSHNHL centres between 2003 and 2013. Fifteen of these patients also participated in the DSHNHL-R3 study. Since these 15 patients made up 65% of the T-NHL population of the DSHNHL-R3 study, resulting in considerable overlap, only the data presented in Wulf 2018, offering a larger patient population and more recent data collection period, were used. In this study, all patients had been prepared for SCT using myeloablative conditioning. The median age of the patient population was 50 years. The majority of patients received a transplant from an unrelated donor (53% HLA-compatible; 11% HLA-incompatible). A transplant from an HLA-compatible sibling donor was received by 26%.

Studies on fateful course

In the retrospective, non-comparative observational study Zhang 2018, adult patients with chemoresistant, primary refractory T-NHL were included at 1 centre in the United States between 1988 and 2016. Zhang 2018 included a greater percentage of patients with ALK-positive ALCL than the studies on allo-SCT. As first-line therapy, the majority of patients received a CHOP or CHOEP regimen. Salvage therapy comprised various regimens, including

non-systemic therapies for some patients. Out of 93 included patients, 15 received auto-SCT and 20 allo-SCT, with 1 patient receiving both therapies. The results reported in Zhang 2018, both for the total patient population and for the population of 58 patients without SCT, are presented for fateful course.

Hepatosplenic lymphoma

For the assessment regarding the rare subentity of hepatosplenic lymphoma in higher-line therapy, 1 study on allo-SCT (Rashidi 2015 [83]) and 2 studies on fateful course (Falchook 2009 [138], Weidmann 2000 [139]) were used. For all 3 publications, individual patient data were available; therefore, only patients who met the inclusion criteria were included in this benefit assessment.

Study on allo-SCT

The non-comparative study Rashidi 2015 is a retrospective analysis of cases published worldwide. On the basis of a PubMed search, the authors found 24 publications from 1996 through 2015 which reported on a total of 54 patients with hepatosplenic lymphoma receiving allo-SCT. This analysis included 49 of these patients. The other 5 were children.

Studies on fateful course

Like Rashidi 2015, the non-comparative study Weidmann 2000 retrospectively analysed published cases. This study used 29 publications from 1986 to 1999 but did not report its search strategy. The study reported on 45 patients, of whom 31 met this benefit assessment's inclusion criteria for the documentation of fateful course. The remaining patients were either children (n = 6), patients without available results (n = 3), or patients who received SCT in the course of therapy (1 with auto-SCT, 4 with allo-SCT).

Falchook 2009 was used as well to document fateful course. This was a retrospective, non-comparative observational study conducted within one centre. Within the observation period of 1997 through 2007, 15 adult patients with hepatosplenic lymphoma were treated at this centre, 11 of them without SCT[4].

The relevant patient populations of all 3 studies consisted largely of young men. In all patient populations, the predominant phenotype was hepatosplenic gamma-delta T-cell lymphoma. The majority of patients also exhibited hepatomegaly and/or splenomegaly. Depending on the study, they were reported separately (Falchook 2009 and Weidmann 2000) or combined as hepatosplenomegaly (Rashidi 2015). In Rashidi 2015, patients received a median of 2 treatments prior to allo-SCT. In Falchook 2009 and Weidmann 2000, patients received a median of 3 and 1 therapies, respectively.

[4] Two out of 4 patients with SCT in Falchook 2009 are also included in the study Rashidi 2015. However, the 4 patients with allo-SCT who are cited in Weidmann 2000 are not part of the dataset in Rashidi 2015.

The disease status of the patient populations was not directly comparable. Rashidi 2015 reported the disease status of patients prior to allo-SCT. Out of the patient population relevant for the report, 41% of patients were in complete remission at that time, while 39% were in partial remission. Falchook 2009 and Weidmann 2000, in contrast, reported the response to all administered therapies. To optimize comparability, this report therefore considered the best status achieved over the course of therapy for these studies. In Falchook 2009, 27% of patients achieved complete remission, and 9%, partial remission over the course of therapy. In Weidmann 2000, these figures were much lower, at 16% and 3%, respectively. Regardless of the different measurement time points, it stands to reason that the patient population with allo-SCT had an advantage in terms of disease status over the patient populations used to document the fateful course.

In Rashidi 2015, both myeloablative conditioning (51%) and reduced-intensity conditioning (24%) were used (unknown regimen: 24%). The stem cells were predominantly harvested from HLA-compatible sibling or unrelated donors. In one-third of transplantations, the source of stem cells was unknown. The studies used to document the fateful course mostly involved chemotherapy regimens – particularly the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

Natural killer cell lymphoma

For the assessment of the subentity of NK cell lymphomas, 2 studies on allo-SCT (Murashige 2005 [88] and Suzuki 2006 [67]) and 2 studies on fateful course (Kim 2009 [140] and Zhou 2014 [141]) were used.

Studies on allo-SCT

The non-comparative observational study Murashige 2005 is a retrospective analysis of 28 patients with NK cell lymphomas who received allo-SCT in Japan between 1990 and 2003. The majority of patients had been prepared for SCT with myeloablative conditioning; only 5 out of 28 patients received RIC. At 52 years, the latter group had a considerably higher median age than patients with MAC at a median age of 35 years. HLA-incompatible transplants from a related or unrelated donor were received by 18% of patients.

The study Suzuki 2006 has already been characterized in Section 4.6.1. Since patient data were reported individually in this study, the results were suitable for comparing allo-SCT with auto-SCT for research question 3 as well as research question 4. Only the 10 patients with allo-SCT were included in the assessment of research question 4.

Studies on fateful course

Kim 2009 was used to assess the fateful course of NK cell lymphomas. This prospective observational study reported the results of 32 patients with extranodal NK cell lymphoma. In the observation period from 1996 to 2002, adult patients with an ECOG status of 0 to 3 were treated at 1 centre in South Korea if they had at least 1 measurable lesion and if any previous or accompanying malignant tumours were ruled out.

The retrospective observational study Zhou 2014 included 17 patients with pathologically confirmed NK cell lymphoma which had relapsed or was refractory. The authors did not list any further inclusion or exclusion criteria. Individual patient data were reported. Between 2011 and 2012, patients at 1 Chinese centre were treated with multiple cycles of a chemotherapy regimen (consisting of gemcitabine, pegaspargase, cisplatin, and dexamethasone). The cycle was repeated after 21 days.

4.7.2 Overview of assessment-relevant outcomes

Like for research question 1, OS is the central patient-relevant outcome for research question 4. Therefore, only OS and potential harm are used as assessment-relevant outcomes. For this research question, no table was generated in the form of a "matrix of patient-relevant outcomes", since it would not provide any additional information.

4.7.3 Assessment of the risk of bias at study and outcome levels

Due to the study design, the risk of bias at study level is seen as high for all studies. No separate assessment of the risk of bias at outcome level was generated. Due to the high risk of bias at study level, all reported outcomes must be considered potentially highly biased as well.

4.7.4 Results on patient-relevant outcomes

4.7.4.1 Results on overall survival

T-NHL overall

Beitinjaneh 2015 reports the median survival separately for chemosensitive and chemo-refractory patients, with a median survival of 6 and 4 months, respectively, as well as a pooled 4-year survival rate of 36%. In the patient population of Czajczynska 2013, the majority (79%) of which was in complete or partial remission at the time of allo-SCT, median survival was 66.7 months. The survival rates after 1, 3, and 5 years were 62.5%, 50.0%, and 50.0%, respectively. In Rohlfing 2018, most patients (77%) were chemosensitive. The median survival was not reached, and the 5-year survival rate was reported as 52%. In Wulf 2018, more than half of the patients were in complete or partial remission at the time of transplantation. The total population reached a median survival of 13 months. The 1-year, 3-year, and 5-year survival rates were 52.5%, 38.2%, and 38.2%, respectively. In comparison with these studies with allo-SCT, Zhang reports a median survival of 5.3 months for chemoresistant patients not receiving SCT as well as 1-year and 3-year survival rates of 29% and 13%, respectively. Although the survival rates of patients with allogeneic transplantation are higher than those of the comparator population, the unequal distribution of disease status between the patient populations alone may potentially explain a large part of the difference in overall survival. In addition, further confounders cannot be ruled out in this comparison of different patient populations; overall, this results in no hint of benefit of allo-SCT for this outcome.

Hepatosplenic lymphoma

In the Rashidi 2015 study on allo-SCT, the 1-year and 3-year survival rates for hepatosplenic lymphoma were 74.5% and 54.8%, respectively. The 1-year survival rates in the studies on fateful course, Falchook 2009 and Weidmann 2000, were only 18.2% and 27.6%, respectively. After 3 years, only 15.8% of patients were still alive in Weidmann 2000. In Falchook 2009, 1 patient was censored after 11 months. The last patient in this study died after 25 months. Similarly, with 68 months versus 8 months, median survival exhibited a large difference between the included non-comparative studies (Rashidi 2015 versus Falchook 2009/Weidmann 2000) in favour of allo-SCT in comparison with fateful course.

When interpreting this difference, at least the following potential confounders must be considered:

- One aspect that may affect results is **disease status**, which was more favourable in the patients receiving allo-SCT than in those of the comparator population. While 80% of patients in the Rashidi 2015 study were in complete or partial remission prior to undergoing allo-SCT, only 36% achieved remission over the course of therapy in Falchook 2009, and only 19% in Weidmann 2000. The results for the very small subpopulations highlight the influence of this confounder: While the survival of the overall population differs by a factor of 8, this factor changes when only the subpopulations are considered. The subpopulations without remission, for instance, differ only by a factor of 3 to 4, and subpopulations with complete or partial remission, by a factor of 2 to 4 (see Tables 113 and 114 of the original report).
- Further, the included data differed in terms of the **time period** in which they were published. While the data used in Rashidi 2015 were published between 1996 and 2015, the data analysed in Weidmann 2000 were published almost exclusively before this period (1986 to 1999). Over this period of time, new and improved therapies may have been developed, which may explain the difference.
- The **definition of overall survival** differed between patient populations as well. In Rashidi 2015, overall survival was measured, for the vast majority of patients, from the time allo-SCT was administered, and only for one fifth of patients, it was measured starting at the time of induction therapy. In the Weidmann 2000 study, in contrast, overall survival was defined – to the extent it could be determined for individual patients – from the time of diagnosis.

  At first glance, the different definitions suggest that the patients with allo-SCT live even longer than those without SCT since their calculation does not include the time from diagnosis or induction to allo-SCT. On the other hand, the different definitions in combination with the study design (retrospective analyses of already treated patients) suggest potential **immortal time bias**. This bias may be present if, due to the study design, there is a time period during which the event cannot occur [146]. This problem arises when comparing Rashidi 2015 with Falchook 2009 and Weidmann 2000. While the

patient populations on fateful course were analysed from the time of diagnosis, i.e. early deaths were recorded, the patients in Rashidi 2015 had to have survived until the administration of allo-SCT to be considered in the analysis. Unlike in Falchook 2009 and Weidmann 2000, given the definition as per the study design, no deaths could have occurred between the time of diagnosis and allo-SCT in the Rashidi 2015 study. Therefore, the selection made in Rashidi 2015 overlaps with the next bias.

- **Selection bias** is present if a sample was not selected randomly. This type of bias likely exists in this comparison as well. After potential alternatives are weighed, allo-SCT is typically proposed only to patients whose health status is considered adequate. In case of numerous comorbidities, patients tend to be advised against allo-SCT.
- **Publication bias** cannot be ruled out either – particularly regarding the experimental intervention of allo-SCT. It is to be expected that centres are more likely to publish cases with very long survival after allo-SCT than cases where survival is as long with allo-SCT as it is with conventional salvage therapy. Hence, the result of the summary of published cases in Rashidi 2015 is potentially subject to systematic bias in this regard as well.

In consideration of the above aspects, the patient populations differ too greatly, and the sum of confounders is too considerable to confidently attribute the large difference in overall survival between the patient populations with and without allo-SCT to allo-SCT alone. Consequently, for the subentity of hepatosplenic lymphoma, there is no hint of benefit of allo-SCT with regard to the outcome of overall survival.

Natural killer cell lymphoma

No dramatic difference between patient populations with and without allo-SCT was observed as regards median survival in patients with NK cell lymphoma. For this subentity, there is consequently no hint of benefit of allo-SCT for this outcome.

4.7.4.2 Results on acute and chronic GvHD

In the included studies on fateful course, additional patient-relevant outcomes were operationalized differently. They were either not suitable for a comparison across subentities or not reported, which was the case for hepatosplenic lymphoma and NK cell lymphoma. Given the lack of comparability, the data available from studies on allo-SCT were therefore not presented. An exception was acute and chronic GvHD.

Data across subentities are available from Czajczynska 2013. More than half of patients had acute GvHD (grade I: 29%; grade II: 21%; grade III: 0%; grade IV: 4%). Patients with limited or extensive chronic GvHD each made up 15% of the population.

According to Rashidi 2015, in hepatosplenic lymphoma, acute and chronic GvHD occurred in 50% and 43% of patients, respectively, but they affected only 30 out of 49 patients. GvHD was not differentiated by severity.

For NK cell lymphoma, data from 1 study are available as well. Patients with severe aGvHD or extensive cGvHD made up 14% and 11% of the population, respectively.

In consideration of the fact that these adverse effects of treatment can occur only in the group of patients with allogeneic transplants, these results were rated as a hint of harm of allo-SCT, both for T-NHL overall and for the subentities of hepatosplenic lymphoma and NK cell lymphoma.

4.8 Evidence map

Table 6 shows the evidence map regarding patient-relevant outcomes.

Table 6: Evidence map regarding patient-relevant outcomes

Outcome / Subentity[a]	Mortality			Mor-bidi-ty	Adverse effects of therapy							Health-related quality of life	
	Overall survival	Treatment-related mortality	Non-relapse mortality	Disease-free survival	aGvHD	cGvHD	Infections	Secondary neoplasms	Other complications	SAE	Fatal AE	Activities of daily living	Dependence on the help of others
Research question 1: B-NHL/post-auto-SZT – non-comparative studies on allo-SCT vs. fateful course													
B-NHL overall	(⇔)	-[b]	-[b]	-[b]	⇓	⇓	-	-	-	-	-	-[b]	-[b]
Diffuse large B-cell lymphoma	(⇔)	-[b]	-[b]	-[b]	⇓	⇓	-	-	-	-	-	-[b]	-[b]
Mantle-cell lymphoma	(⇔)	-[b]	-[b]	-[b]	⇓	⇓	-	-	-	-	-	-[b]	-[b]
Transformed lymphoma	No (usable) data reported												
Follicular lymphoma grade 3	No (usable) data reported												
Precursor B-cell lymphoblastic lymphoma	No (usable) data reported												
T-cell rich B-cell lymphoma	No (usable) data reported												
Primary effusion lymphoma	No (usable) data reported												
Intravascular B-cell lymphoma	No (usable) data reported												
Primary mediastinal B-cell lymphoma	No (usable) data reported												
Burkitt lymphoma	No (usable) data reported												
Aggressive marginal zone lymphoma	No (usable) data reported												

(continued)

Table 6: Evidence map regarding patient-relevant outcomes (continued)

Outcome / Subentity[a]	Mortality			Mor-bidi-ty	Adverse effects of therapy							Health-related quality of life	
	Overall survival	Treatment-related mortality	Non-relapse mortality	Disease-free survival	aGvHD	cGvHD	Infections	Secondary neoplasms	Other complications	SAE	Fatal AE	Activities of daily living	Dependence on third-party help
Research question 2: B-NHL / SCT-naïve – comparative studies on allo-SCT vs. auto-SCT													
Diffuse large B-cell lymphoma	(⇔)	(⇔)	(⇔)	-	⇓	⇓	-[c]	-	-[c]	-	(⇔)	-	-
Mantle-cell lymphoma	(⇔)	-	-	-	⇓	⇓	-[c]	-	-[c]	-	(⇔)	-	-
Transformed lymphoma	(⇔)	-	-	-	⇓	⇓	-[c]	-	-[c]	-	(⇔)	-	-
Follicular lymphoma grade 3	(⇔)	-	-	-	⇓	⇓	-[c]	-	-[c]	-	(⇔)	-	-
Precursor B-cell lymphoblastic lymphoma	No (usable) data reported												
T-cell rich B-cell lymphoma	No (usable) data reported												
Primary effusion lymphoma	No (usable) data reported												
Intravascular B-cell lymphoma	No (usable) data reported												
Primary mediastinal B-cell lymphoma	No (usable) data reported												
Burkitt lymphoma	No (usable) data reported												
Aggressive marginal zone lymphoma	No (usable) data reported												

(continued)

Table 6: Evidence map regarding patient-relevant outcomes (continued)

Outcome / Subentity[a]	Mortality			Mor-bidi-ty	Adverse effects of therapy							Health-related quality of life	
	Overall survival	Treatment-related mortality	Non-relapse mortality	Disease-free survival	aGvHD	cGvHD	Infections	Secondary neoplasms	Other complications	SAE	Fatal AE	Activities of daily living	Dependence on help from others
Research question 3: T-NHL/first line – comparative studies on allo-SCT vs. systemic therapy													
Precursor T-cell lymphoblastic lymphoma	-	-	-	-	⇓	⇓	-	-	-	-	(⇔)	-	-
T-NHL overall	No (usable) data reported												
Natural killer cell lymphoma	No (usable) data reported												
Hepatosplenic lymphoma	No (usable) data reported												
Peripheral T-cell lymphoma, not further specified	No (usable) data reported												
Angioimmunoblastic T-cell lymphoma	No (usable) data reported												
Anaplastic large cell lymphoma	No (usable) data reported												
Subcutaneous panniculitis-like peripheral T-cell lymphoma	No (usable) data reported												
Aggressive T/natural killer cell lymphoma	No (usable) data reported												

(continued)

Table 6: Evidence map regarding patient-relevant outcomes (continued)

Outcome / Subentity[a]	Mortality			Mor-bidi-ty	Adverse effects of therapy							Health-related quality of life	
	Overall survival	Treatment-related mortality	Non-relapse mortality	Disease-free survival	aGvHD	cGvHD	Infections	Secondary neoplasms	Other complications	SAE	Fatal AE	Activities of daily living	Dependence on the help of others
Research questions 3+4: T-NHL/first and higher line – comparative studies on allo-SCT vs. auto-SCT													
T-NHL overall, first line[d]	-	-	-	-	-	-	-	-	-	-	-	-	-
T-NHL overall, first and higher line	(⇔)	-	-	-	⇘	⇘	-[c]	-	-[c]	-[c]	(⇔)	-	-
T-NHL overall, higher line	-	-	-	-	-	-	-	-	-	-	-	-	-
Natural killer cell lymphoma, first and higher line	-	-	-	-	-	-	-	-	-	-	-	-	-
Hepatosplenic lymphoma	No (usable) data reported												
Peripheral T-cell lymphoma, not further specified	No (usable) data reported												
Angioimmunoblastic T-cell lymphoma	No (usable) data reported												
Anaplastic large cell lymphoma	No (usable) data reported												
Precursor lymphoblastic T-cell lymphoma	No (usable) data reported												
Subcutaneous panniculitis-like peripheral T-cell lymphoma	No (usable) data reported												
Aggressive T/natural killer cell lymphoma	No (usable) data reported												

(continued)

Table 6: Evidence map regarding patient-relevant outcomes (continued)

Outcome / Subentity[a]	Mortality			Mor-bidi-ty	Adverse effects of therapy							Health-related quality of life	
	Overall survival	Treatment-related mortality	Non-relapse mortality	Disease-free survival	aGvHD	cGvHD	Infections	Secondary neoplasms	Other complications	SAE	Fatal AE	Activities of daily living	Dependence on the help of others
Research question 4: T-NHL/higher line – non-comparative studies on allo-SCT vs. fateful course													
T-NHL overall	(⇔)	-[b]	-[b]	-[b]	⇓	⇓	-	-	-	-	-	-[b]	-[b]
Natural killer cell lymphoma	(⇔)	-[b]	-[b]	-[b]	⇓	⇓	-	-	-	-	-	-[b]	-[b]
Hepatosplenic lymphoma	(⇔)	-[b]	-[b]	-[b]	⇓	⇓	-	-	-	-	-	-[b]	-[b]
Peripheral T-cell lymphoma, not further specified	No (usable) data reported												
Angioimmunoblastic T-cell lymphoma	No (usable) data reported												
Anaplastic large cell lymphoma	No (usable) data reported												
Precursor lymphoblastic T-cell lymphoma	No (usable) data reported												
Subcutaneous panniculitis-like peripheral T-cell lymphoma	No (usable) data reported												
Aggressive T/natural killer cell lymphoma	No (usable) data reported												

(continued)

Table 6: Evidence map regarding patient-relevant outcomes (continued)

↘: Hint of harm
⇔: no hint, indication, or proof, no dramatic difference
-: No (usable) data reported
a: Subentities were defined in accordance with the DSHNHL 2003-R3 study [147].
b: Outcome was not considered.
c: The subset of fatal events is considered under the outcome of fatal AEs.
d: On this research question, the final results of 1 prematurely terminated study are not yet available, but the authors have signalled that they intend to publish in mid-2019.

aGvHD: acute graft-versus-host disease; allo: allogeneic; auto: autologous; B-NHL: B-cell non-Hodgkin lymphoma; cGvHD: chronic graft-versus-host disease; DSHNHL: Deutsche Studiengruppe Hochmaligne Non-Hodgkin Lymphome (German Study Group for Highly Malignant Non-Hodgkin Lymphoma); SAE: serious adverse event; SCT: stem cell transplant; SCT-naïve: patients who have not received prior stem cell transplant; T-NHL: T-cell non-Hodgkin lymphoma; AE: adverse event; vs.: versus

5 Classification of the assessment result

Patients with aggressive B-cell or T-cell non-Hodgkin lymphomas can be categorized into two groups by course of disease and treatment: One group are patients for whom treatment with an intent to cure appears promising. This treatment may include systemic drug therapy or chemotherapy in combination with autologous stem cell transplantation. The other group are patients for whom these treatments have been exhausted and no cure can be achieved any longer by these means. The remaining option is palliative care.

The question whether allogeneic stem cell transplantation may be of benefit applies to both groups.

Allogeneic stem cell transplantation is a treatment with curative intent. However, it can be associated with grave adverse events ranging from host-versus-graft disease, which occurs only in allogeneic stem cell transplantation and can be associated with considerable reduction of the quality of life in serious cases, all the way to treatment-related mortality.

For patients considered to have a chance of cure with either standard therapies or allogeneic stem cell transplantation, the evidence base did not reveal whether allogeneic stem cell transplantation would be an alternative associated with benefits.

In patients for whom all chances of a cure using standard therapies have been exhausted, allogeneic stem cell transplantation represents the last potential curative option. Physicians can offer them only palliative care, but no other chance of cure. For these patients as well, the data available for this report fail to clarify whether allogeneic stem cell transplantation is associated with benefits.

In the commenting procedure, this result was criticized. In terms of the disease course of patients who did not undergo allogeneic stem cell transplantation, the data were questioned. They were said to considerably deviate from the clinical experience of the commenting parties, according to whom patients had little chance of surviving for even 1 more year. In contrast, about one-third of patients who underwent allogeneic stem cell transplantation were said to survive for 5 years and longer. According to the commenting parties, this was a dramatic difference.

Even after reviewing the data once more, it was not possible to resolve the discrepancy between clinical experience and the data found on the disease course in patients who did not undergo allogeneic stem cell transplantation in the palliative situation.

The argument regarding a dramatic difference does not stand up to scrutiny if confounders such as severity of disease or age are considered. For instance, comparator groups typically used from the literature to document the course of disease without allogeneic stem cell transplantation are comprised of patients who were too ill, too weak, or too old to undergo allogeneic stem cell transplantation. Using these patients in the comparison is not appropriate.

The less favourable initial conditions alone considerably minimize their chance of survival. The recommendation to interpret such comparisons with caution can be found in the literature as well. Reasonably unbiased conclusions on differences can be drawn only if the comparator group consists exclusively of patients who were eligible for allogeneic stem cell transplantation. It is currently unclear whether one-third of these patients would not survive for 5 years even without allogeneic stem cell transplantation.

Consequently, it remains true that allogeneic stem cell transplantation offers the only curative treatment option once all other options have been exhausted. It also remains true that depending on the lymphoma type, long-term survival with this therapy is about 30%. However, the data available for this report do not show to what extent the treatment is of benefit, particularly in view of the considerable treatment-related harm, when compared with patients who do not undergo allogeneic stem cell transplantation in a similar initial situation.

To draw a robust conclusion in this regard, it is therefore imperative for long-term data of all patients with non-Hodgkin lymphoma from the time of diagnosis, regardless of the therapies performed, to be compiled in a disease-specific registry or for existing registries to be correspondingly restructured. In a few years, this will make it possible to perform diagnosis-specific analyses, which in turn will allow drawing conclusions about the benefit and harm of allogeneic stem cell transplantation. On the basis of these robust data, long-term survival after allo-SCT can then be compared to empirical data on fateful course. Finally, such data would permit comparisons with newly developed therapies. Particularly in view of the developments in CAR T-cell therapy, this seems useful.

Below, individual aspects will be discussed in detail.

Heterogeneity of NHL

NHL is a heterogeneous group consisting of numerous subentities. As commissioned, several research questions were examined, 2 on NHL of the B-cell line and 2 on the T-cell line. Particularly for research questions 2 and 3, the analyses were to be broken down by subentity. It should be noted that some subentities are very rare, particularly in cases where the lymphatic cells from which the NHL originates are T-cells. Consequently, for many subentities, no studies with usable data or no studies at all were found. In addition, even the patient populations of the individual subentities are not always homogeneous: One subentity can include various subforms. For example, in an included study on DLBCL [50], the authors report combining centroblastic and immunoblastic large-cell lymphomas, primary mediastinal large B-cell lymphoma, intravascular B-cell lymphoma as well as primary effusion lymphoma under this subentity. No related details can be found in the other studies on DLBCL. Further, only 2 studies on mantle-cell lymphoma [54, 55] report the percentage of cases with the blastoid variant, which exhibits a more aggressive clinical course than the non-blastoid form. Even for histologically clearly defined NHL subentities which exhibit differentiation on a molecular level, different responses to various therapies are being discussed [148]. It therefore remains unclear whether some subforms of a subentity may benefit more from allo-SCT than others.

Evidence base

Conducting an evaluation of allo-SCT in aggressive B-NHL and T-NHL exclusively on the basis of RCTs seemed virtually impossible, in part due to the above-mentioned heterogeneity of NHL and the low incidence of some subentities. For research questions 1 and 4, this situation was aggravated by the lack of alternative procedures with curative intent. This benefit assessment therefore considered both RCTs and studies with lower evidence levels. Although prospective interventional and cohort studies with comparisons relevant for the comparison are generally feasible, none were found, except for 1 RCT for which no usable results are available to date. The available evidence allowed drawing conclusions on benefit only on the basis of a dramatic effect (comparative cohort studies) or dramatic difference (non-comparative studies).

Despite the consideration of studies with lower evidence levels, data were available for only few subentities. For the comparison of allo-SCT with systemic therapy in the first-line therapy of T-NHL (research question 3), for instance, only 1 study was found whose patient population had a rare subform – precursor T-cell lymphoblastic lymphoma. The biology of this subform considerably differs from that of other (mature) forms of T-NHL. Therefore, results are not transferable. For other comparisons and research questions as well, evidence was found only for some subentities.

Conclusions on benefit on the basis of dramatic differences (research questions 1 and 4)

For research questions 1 (B-NHL/post-auto-SCT/allo-SCT versus fateful course) and 4 (T-NHL/higher line/ allo-SCT versus fateful course), only non-comparative studies were found, but not all of them could be used for the benefit assessment due to relevant differences, for instance in patient characteristics between studies on allo-SCT and fateful course. For some subentities, such as FL III, it was not possible to reliably document the fateful course. It must also be noted that in none of the studies found on fateful course, patients received exclusively pain medication. Since such studies were also not expected to exist, however, the studies used were considered the only available evidence. Even in studies reporting results on patients with and without allo-SCT, which could have potentially been used to extract comparative data, the data on fateful course were not suitable for the benefit assessment. This is due to the fact that patients who do not receive allo-SCT in a higher-line therapy are typically ineligible for this treatment. For instance, in Rohlfing 2018 [72], the study authors explicitly point out that the patient population without SCT was negatively selected on the basis of poor performance status or advanced age and was ineligible for allo-SCT. Hence, this population considerably differed in central prognostic factors from the population receiving allo-SCT. In the results section on hepatosplenic lymphoma, various confounders have already been discussed, and the influence of disease status alone on overall survival has been discussed as an example (see Section 4.7.4.1). The derivation of evidence on the basis of non-comparative or retrospective comparative studies is associated with considerable problems due to these confounders and additional influencing factors, such as heterogeneity of the study population (e.g. different subforms, different type, and number of prior therapies), heterogeneity of the intervention (e.g. myeloablative or non-myeloablative conditioning, HLA compatibility of the donor), low

sample sizes due to low incidence of some subforms, and the associated limited options for adjustment. Particularly the inclusion of 1-arm observational studies, which are essentially simple aggregate statistics of published cases, can be justified only in cases where, firstly, very large treatment effects are conceivable, and secondly, the extreme rarity of a disease impedes higher-quality studies. After all, even major treatment successes found in 1-arm studies may simply be overestimates. Lasch et al. 2017 [149] have demonstrated this fact on the example of the rare disease of Fanconi anaemia, for which 1 RCT showed that major treatment success was possible even under placebo treatment.

Supplementary consideration of outcomes (research questions 2 and 3)

Auto-SCT is often preferred over allo-SCT; as a result, patients with allo-SCT generally have received more prior therapy than patients with auto-SCT. This was also true for the comparative studies regarding research questions 2 and 3. In addition, the patients in the different intervention groups also differed in terms of further prognostic factors. For example, patients eligible for auto-SCT often have comorbidities which would make them ineligible for allo-SCT. Conversely, in rare cases, a patient with NHL-associated symptoms may be eligible for allo-SCT, but not for auto-SCT. The data on numerous outcomes in the comparative studies were used only for supplementary consideration since the patient populations were not comparable and the statistical analysis failed to consider this sufficiently or at all. However, adjusting for all relevant factors was virtually impossible in some studies due to the low patient numbers alone; therefore, even results from studies which reported individual patient data could not be used for the report. For the outcome of progression-free survival, it was impossible to conclude that relapse was reliably confirmed based on the information reported in the studies. The data were nevertheless included as supplementary information since, despite their deficiencies, they represent the only available evidence for the comparison between allo-SCT and auto-SCT in aggressive B-NHL and T-NHL.

Supplementary consideration of data on allo-SCT without data on fateful course (research questions 1 and 4)

For research question 1, one RCT conducted in German centres was found (DSHNHL-R3); the Institute received separate data from the authors on its relevant subpopulation. This subpopulation – which is to be analysed as a quasi-prospective, non-comparative observational study – as well as its subentities exactly match the inclusion criteria of the report. However, no studies on fateful course were found whose populations would have been comparable with the subpopulation of the DSHNHL-R3 study [29]. Therefore, consideration in the benefit assessment was impossible. The data were presented as supplementary information.

Regarding research question 4, for the subentities AITL and T-LBL, studies on allo-SCT are provided as supplementary information although no comparator data on fateful course were available.

GvHD and GvL effect

A hint of harm of allo-SCT was derived for all research questions. This assessment is based on the occurrence of both acute and chronic GvHD in all studies used on allo-SCT. This is an adverse effect specific to allo-SCT, which cannot occur under the comparator treatment. Currently available prophylactic measures cannot yet fully prevent this adverse effect; for the time being, allo-SCT is therefore always associated with a risk of GvHD.

However, the same cells that lead to GvHD are also considered the triggers of a (potential) graft-versus-lymphoma (GvL) effect: The lymphocytes which newly form after allo-SCT are supposed to recognize and destroy remaining lymphoma cells and thus reduce the risk of relapse [20, 23]. However, this effect cannot be directly proven, and consequently, the included studies did not supply any data in this regard. It is unclear to what extent patient-relevant outcomes such as overall survival or progression-free survival are influenced by the GvL effect. Assuming a favourable influence of the GvL effect, one would expect this to translate into longer overall survival or longer progression-free survival. Yet, on the basis of the available data with a low evidence level, none of the research questions showed a benefit of allo-SCT.

No therapeutic equivalence

The fact that no dramatic effect on overall survival in favour of or to the disadvantage of allo-SCT was shown for any of the histological subtypes cannot conversely be interpreted as an indication or hint of therapeutic equivalence. Potential treatment effects in either direction may have been obscured by confounders.

6 Conclusion

This benefit assessment is based on a total of 32 analysed studies on 4 research questions, which investigated allogeneic stem cell transplantation in patients with B-NHL or T-NHL at different points in the course of treatment as well as 11 studies documenting the fateful course. The searches yielded only studies with lower evidence levels. On the basis of such studies, conclusions on benefit were possible only in case of dramatic effects. Studies that would have permitted drawing conclusions on the patients' quality of life were not found for any of the comparisons. The evidence base does not reveal whether allogeneic stem cell transplantation is associated with benefits. The occurrence of graft-versus-host-disease, a specific adverse effect following allogeneic stem cell transplantation, resulted in a hint of harm of allogeneic stem cell transplantation for all research questions.

Research question 1: B-NHL / post-auto-SCT

For the comparison of allogeneic stem cell transplantation with fateful course in patients with progressive or relapsed B-NHL following autologous stem cell transplantation, only non-comparative studies were found, from which only the outcomes of overall survival and graft-versus-host disease were considered. Studies with usable data were found on B-NHL overall as well as on the subentities of diffuse large B-cell lymphoma and mantle-cell lymphoma. For the outcome of overall survival, no benefit or harm of allogeneic stem cell transplantation was found, either across all subgroups or for the considered subentities.

Research question 2: B-NHL/SCT-naïve

For the comparison of allogeneic versus autologous stem cell transplantation in B-NHL, retrospective comparative cohort studies were found on the subentities of diffuse large B-cell lymphoma, follicular lymphoma grade 3, transformed lymphoma, and mantle-cell lymphoma. For these subentities, there is no hint of greater benefit or harm of allo-SCT with regard to the outcome of overall survival. With regard to the outcomes of treatment-related or non-relapse mortality, there is no hint of greater benefit or harm of allogeneic stem cell transplantation in diffuse large B-cell lymphoma. No related data were available for the other considered subentities. The outcome of disease-free survival was unusable as a patient-relevant outcome due to the operationalization used in the studies; consequently, a conclusion regarding benefit or harm was not possible. For the outcome of adverse events, only fatal adverse events were reported. This did not result in a hint of benefit or harm of allogeneic stem cell transplantation.

Research question 3: T-NHL/first line/allo-SCT versus systemic therapy

For the comparison of allogeneic stem cell transplantation with systemic drug therapy in treatment-naïve T-NHL, 1 comparative study was found on the histological subtype of precursor T-cell lymphoblastic lymphoma. This study did not supply any usable data for the benefit assessment on mortality or morbidity outcomes. For the outcome of adverse events, only fatal adverse events were reported. This did not result in a hint of benefit or harm of allogeneic stem cell transplantation.

Research questions 3 + 4: T-NHL/first and higher line/allo-SCT versus auto-SCT

Research question 3: T-NHL/first line

For the comparison between allogeneic and autologous stem cell transplantation in treatment-naïve T-NHL, 1 retrospective comparative cohort study on T-NHL overall was found. This study did not supply any usable data. Furthermore, the final results of 1 prematurely terminated RCT on this question are intended to be published by the authors in mid-2019.

Research questions 3+4: T-NHL/first and higher line

For the comparison of allogeneic and autologous stem cell transplantation in T-NHL, 3 further retrospective comparative cohort studies on T-NHL overall and 1 retrospective comparative cohort study on the subentity of natural killer cell lymphoma were found; their populations received heterogeneous prior therapy and was therefore not unequivocally assignable to either research question 3 or 4. However, usable data were available only for T-NHL overall. This resulted in no hint of greater benefit or harm of the intervention to be assessed with regard to the outcome of overall survival. For the outcome of adverse events, only fatal adverse events were reported. This did not result in a hint of benefit or harm of allogeneic stem cell transplantation. No further outcomes were suitable for use in the benefit assessment.

Research question 4: T-NHL/higher line

For the comparison of allogeneic and autologous stem cell transplantation in higher-line therapy of T-NHL, 1 retrospective comparative cohort study on T-NHL overall was found. This study did not supply any usable data.

Research question 4: T-NHL/higher line/allo-SCT versus fateful course

For the comparison of allogeneic stem cell transplantation with fateful course in patients with T-NHL and progression following systemic therapy, only non-comparative studies were found, from which only the outcomes of overall survival and graft-versus-host disease were considered. In addition to studies presenting T-NHL across subentities, studies on the subentities of hepatosplenic lymphoma and natural killer cell lymphoma were found. No hint of benefit or harm of allogeneic stem cell transplantation with regard to overall survival was found for T-NHL overall or for either of the presented subentities.

For the time being, allogeneic stem cell transplantation is always associated with the risk of graft-versus-host disease. The benefit of allogeneic stem cell transplantation in B-NHL and T-NHL, in contrast, is generally unclear due to a lack of reliable studies.

To obtain reliable data for future use, all patients with NHL should be registered in a disease-specific registry from the date of diagnosis.

7 References for English extract

Please see full final report for full reference list.

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The full report (German version) is published under
https://www.iqwig.de/en/projects-results/projects/non-drug-interventions/n-projekte/n17-02-allogeneic-stem-cell-transplantation-in-aggressive-b-cell-non-hodgkin-lymphoma-and-in-t-cell-non-hodgkin-lymphoma.7810.html

Appendix A – Search strategies

A.1 – Searches in bibliographic databases

A.1.1 Search strategies in bibliographic databases for comprehensive information retrieval

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to June Week 5 2018
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 09, 2018
- Ovid MEDLINE(R) Daily Update July 09, 2018
- Ovid MEDLINE(R) Epub Ahead of Print July 09, 2018

#	**Searches**
1	exp Lymphoma, Non-Hodgkin/
2	(lymphoma* adj3 (mantle-cell or follicular* or b-cell or t-cell or non-hodgkin* or large cell or lymphoblastic* or burkitt* or aggressive*)).ti,ab.
3	or/1-2
4	exp *Stem Cell Transplantation/
5	Transplantation, Homologous/
6	((allogen?ic* or hematopoietic* or haematopoietic*) adj5 (cell transplant* or HCT or SCT)).ab,ti.
7	(allogen?ic* transplant* or allogen?ic bone marrow transplant*).ti,ab.
8	or/4-7
9	3 and 8
10	exp Animals/ not Humans/
11	9 not 10
12	11 not (comment or editorial).pt.

2. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#1	Search lymphoma*[tiab] AND (mantle-cell[tiab] OR follicular*[tiab] OR b-cell[tiab] OR t-cell[tiab] OR non-hodgkin*[tiab] OR large cell[tiab] OR lymphoblastic*[tiab] OR burkitt*[tiab] OR aggressive*[tiab])
#2	Search (allogeneic*[tiab] OR allogenic*[tiab] OR hematopoietic*[tiab] OR haematopoietic*[tiab]) AND (cell transplantation*[tiab] OR HCT[tiab] OR SCT[tiab])
#3	Search allogeneic* transplant*[tiab] OR allogeneic bone marrow transplant*[tiab] OR allogenic* transplant*[tiab] OR allogenic bone marrow transplant*[tiab]
#4	Search #1 AND (#2 OR #3)
#5	Search #4 not medline[sb]

3. Embase

Search interface: Ovid

- Embase 1974 to 2018 July 09

#	Searches
1	exp *Nonhodgkin Lymphoma/
2	exp B Cell Lymphoma/
3	(lymphoma* adj3 (mantle-cell or follicular* or b-cell or t-cell or non-hodgkin* or large cell or lymphoblastic* or burkitt* or aggressive*)).ti,ab.
4	or/1-3
5	exp *Hematopoietic Stem Cell Transplantation/
6	exp Allogeneic Stem Cell Transplantation/
7	((allogen?ic* or hematopoietic* or haematopoietic*) adj5 (cell transplant* or HCT or SCT)).ab,ti.
8	(allogen?ic* transplant* or allogen?ic bone marrow transplant*).ti,ab.
9	or/5-8
10	4 and 9
11	10 not MEDLINE*.cr.
12	11 not (exp animal/ not exp humans/)

#	Searches
13	12 not (Conference Abstract or Conference Review).pt.
14	13 not Editorial.pt.

4. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 7 of 12, July 2018
- Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018

ID	Search
#1	MeSH descriptor: [Lymphoma, Non-Hodgkin] explode all trees
#2	(lymphoma* near/3 (mantle-cell or follicular* or b-cell or t-cell or non-hodgkin* or large cell or lymphoblastic* or burkitt* or aggressive*)):ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Stem Cell Transplantation] explode all trees
#5	MeSH descriptor: [Transplantation, Homologous] this term only
#6	((allogeneic* or allogenic* or hematopoietic* or haematopoietic*) near/5 (cell transplant* or HCT or SCT)):ab,ti
#7	(allogeneic* transplant* or allogeneic bone marrow transplant or *allogenic* transplant* or allogenic bone marrow transplant*):ti,ab
#8	#4 or #5 or #6 or #7
#9	#3 and #8 in Cochrane Reviews (Reviews and Protocols) and Trials

5. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

- HTA

Line	Search
1	MeSH DESCRIPTOR Lymphoma, Non-Hodgkin EXPLODE ALL TREES
2	((lymphoma* AND (mantle-cell OR follicular* OR b-cell OR t-cell OR non-hodgkin* OR large cell OR lymphoblastic* OR burkitt* OR aggressive*)))
3	#1 OR #2
4	MeSH DESCRIPTOR Stem Cell Transplantation EXPLODE ALL TREES
5	MeSH DESCRIPTOR Transplantation, Homologous EXPLODE ALL TREES
6	((allogeneic* OR allogenic* OR hematopoietic* OR haematopoietic*) AND (cell transplant* OR HCT OR SCT))

Line	Search
7	(allogeneic* transplant* OR allogeneic bone marrow transplant* OR allogenic* transplant* OR allogenic bone marrow transplant*)
8	#4 OR #5 OR #6 OR #7
9	* IN HTA
10	#3 AND #8 AND #9

A.1.2 Search strategies in bibliographic databases for focused information retrieval (fateful course of disease)

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to July Week 1 2018
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 11, 2018
- Ovid MEDLINE(R) Daily Update July 11, 2018
- Ovid MEDLINE(R) Epub Ahead of Print July 11, 2018

#	Searches
1	exp *Lymphoma, Non-Hodgkin/ mo,su,th [Mortality,Surgery,Therapy]
2	((non-Hodgkin* or large b-cell or null cell or mantle cell or t-cell) adj lymphom*).ti,ab.
3	or/1-2
4	(second-line or third-line or "after first-line").ti,ab.
5	((post or after or follow*) adj2 (autoSCT or auto-SCT or ASCT or autologous)).ti,ab.
6	4 or 5
7	Recurrence/
8	((post or after or following) adj1 (relapse* or progression)).ti,ab.
9	7 or 8
10	and/3,6,9
11	10 not exp Animals/ not Humans/
12	11 not (comment or editorial).pt.

A.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategy
(allogeneic OR allogenic OR hematopoietic OR haematopoietic) AND transplantation AND (mantle-cell OR follicular OR b-cell OR t-cell OR non-hodgkin OR large cell OR lymphoblastic OR aggressive OR burkitt) AND lymphoma

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Search strategy
(allogeneic OR allogenic OR hematopoietic OR haematopoietic) AND transplantation AND Lymphoma

3. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/
- Type of search: Standard Search

Search strategy
allogeneic AND transplantation AND Lymphoma OR allogenic AND transplantation AND Lymphoma OR hematopoietic AND transplantation AND Lymphoma OR haematopoietic AND transplantation AND Lymphoma