Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2016-B-019 Nivolumab

Stand: März 2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Nivolumab

zur Behandlung von erwachsenen Patientinnen mit rezidiviertem oder refraktärem klassischem Hodgkin-Lymphom (HL)

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Grundsätzlich im Anwendungsgebiet in Betracht kommende nicht medikamentöse Behandlungen: - operative Resektion - Strahlentherapie - allogene und autologe Stammzelltransplantation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	- Allogene Stammzelltransplantation mit nicht verwandtem Spender bei Hodgkin-Lymphom bei Erwachsenen – Beschluss „Richtlinie Methoden Krankenhausbehandlung“, Beschluss 20. Dezember 2012 - Positronenemissionstomografie bei Patientinnen und Patienten mit Hodgkin-Lymphomen und aggressiven Non-Hodgkin-Lymphomen zum Interim Stadging nach bereits erfolgter Chemotherapie zur Entscheidung über die Fortführung der Therapie – Beschluss über Maßnahmen zur Qualitätssicherung – geänderter Beschluss vom 19.02.2015
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Nivolumab	- OPDIVO ist zur Behandlung des rezidivierenden oder refraktären klassischen Hodgkin-Lymphoms (cHL) bei Erwachsenen nach einer autologen Stammzelltransplantation (ASCT) und Behandlung mit Brentuximab Vedotin indiziert.
Doxorubicinhydrochlorid L01DB01 Bendalis®	- Frühstadium des Hodgkin-Lymphoms (Stadium I – II) bei schlechter Prognose - fortgeschrittenes Hodgkin-Lymphom (Stadium III – IV)
Bleomycinsulfat L01DC01 Bleomedac®	- Frühstadium des Hodgkin-Lymphoms (Stadium I – II) bei schlechter Prognose - fortgeschrittenes Hodgkin-Lymphom (Stadium III – IV)
Lomustin L01AD02 Cecenu®	- bei fortgeschrittenem Morbus Hodgkin, wenn die etablierten Chemotherapieschemata nicht mehr wirken
Vincristinsulfat L01CA02 Vincristinsulfat-Teva®	- malignen Lymphomen, einschließlich Morbus Hodgkin und Non-Hodgkin-Lymphomen
Prednison H02AB07 Prednison acis®	- Morbus Hodgkin
Cyclophosphamid L01AA01 Cyclophosphamid Trockensubstanz Baxter Onkology®	- Remissionsinduktion bei Morbus Hodgkin
Dacarbazin L01AX04	- fortgeschrittener Morbus Hodgkin

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Dacarbazin Lipomed®	
Prednisolon H02AB06 Prednisolon acis®	- Morbus Hodgkin
Vindesinsulfat L01CA03 Eldisine®	- Kombinationschemotherapie: Morbus Hodgkin nach Versagen der Standardtherapie (nicht vollständiges Ansprechen auf die Therapie bzw. Wiederauftreten der Erkrankung)
Etoposidphosphat L01CB01 Etopophos®	- Reinduktionstherapie bei Morbus Hodgkin nach Versagen von Standardtherapien (nicht vollstandiges Ansprechen auf bzw. Wiederauftreten nach Standardtherapien)
Ifosfamid L01AA06 Holoxan®	- **Morbus Hodgkin** Zur Behandlung von Patienten mit primär progredienten Verläufen und Frührezidiven des Morbus Hodgkin (Dauer der kompletten Remission kürzer als ein Jahr) nach Versagen der chemotherapeutischen bzw. radiochemotherapeutischen Primärtherapie – im Rahmen anerkannter Kombinations-Chemotherapie-Regime, wie z. B. dem MINE Protokoll.
Procarbazinhydrochlorid L01XB01 Natulan®	- Behandlung des Hodgkin-Lymphoms in der Kombinationschemotherapie - Natulan wird zur Behandlung des Hodgkin-Lymphoms bei Erwachsenen sowie bei Kindern und Jugendlichen im Alter von 2 bis 18 Jahren mit anderen Zytostatika in einem geeigneten Protokoll eingesetzt.
Vinblastinsulfat L01CA01 Vinblastinsulfat Teva®	- Morbus Hodgkin

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

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Indikation für die Recherche:

Behandlung von erwachsenen Patienten mit rezidiviertem oder refraktärem klassischem Hodgkin-Lymphom (HL) nach einer autologen Stammzelltransplantation (ASCT) und Brentuximab Vedotin

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassene Arzneimittel, siehe Tabelle „II. Zugelassene Arzneimittel im Anwendungsgebiet“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation **„**Hodgkin Lymphom**“** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 08.03.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP, WHO. Aufgrund der onkologischen Indikation wurde

zusätzlich in folgenden Datenbanken bzw. Internetseiten folgender Organisationen gesucht: CCO, ESMO, NCCN, NCI. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 199 Quellen, die anschließend in einem zweistufigen Screeningverfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 20 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

(C)HL	(classic) Hodgkin Lymphom
ASCT	autologe Stammzelltransplantation
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BCSH	British Society for Haematology
BSBMT	British Society of Blood and Marrow Transplantation
CCO	Cancer Care Ontario
CI	Confidence interval
CR	Complete remission
CRR	complete response rate
DAHTA	Deutsche Agentur für Health Technology Assessment
DHAP	dexamethasone/high-dose Ara-C/cisplatin
DOR	Duration of remission
EK	Expertenkonsens
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GKV	Gesetzliche Krankenversicherung
HDCT	high-dose chemotherapy
ICE	ifosfamide/carboplatin/etoposide
IGEV	ifosfamide/gemcitabine/vinorelbine
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
k.A.	Keine Angabe
mOS	median overall survival
NCCN	National Comprehensive Cancer Network
NCI	U.*S.* National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
PD	Progressive Disease
PEBC	Program in Evidence-Based Care
PFS	Progression free Survival
PR	Partial remission
R/R	Relapsed/Refractory
RIC	reduced-intensity conditioning
RR	Relative Risk
SD	stable disease
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic Review
TRIP	Turn Research into Practice Database
TRM	treatment-related mortality
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

G-BA, 2012 [6]: Allogene Stammzelltransplantation mit nicht-verwandtem Spender beim Hodgkin-Lymphom bei Erwachsenen. *Abschlussbericht. Beratungsverfahren gemäß § 137c SGB V (Krankenhausbehandlung).* siehe dazu auch: **IQWiG, 2010 [11]:** Allogene Stammzelltransplantation mit nicht verwandtem Spender bei der Indikation Hodgkin-Lymphom. Abschlussbericht. Auftrag N05-03F. Version 1.0. & **IQWiG, 2011 [12]:** Erratum zum Abschlussbericht[1]	[…] Bei primär refraktären oder rezidivierten Hodgkin-Lymphomen ist aber in der Regel eine Zweitlinienchemotherapie mit nachfolgender Hochdosistherapie und autologer Stammzelltransplantation die Therapie der Wahl. Patienten, die nach autologer Stammzelltransplantation ein weiteres Rezidiv erleiden, haben oftmals eine sehr ungünstige Prognose, so dass bei ihnen die Möglichkeit einer Behandlung mit allogener Stammzelltransplantation zur Kuration in Betracht gezogen werden sollte. […] […] Zusammenfassend ist festzustellen, dass aufgrund der vorliegenden Evidenz und unter Berücksichtigung der Aspekte der medizinischen Notwendigkeit Hinweise existieren, die eine Anwendung der allogenen Stammzelltransplantation mit nicht-verwandtem Spender bei Patienten mit Hodgkin-Lymphom nach Ausschöpfung der im konkreten Fall in Frage kommenden Optionen der Standardtherapie rechtfertigen. Die allogene Stammzelltransplantation mit nicht-verwandtem Spender bei Patienten und Patientinnen mit Hodkgin-Lymphom bleibt deshalb als Therapieoption für GKV-Versicherte erhalten. Bei der Einbeziehung der Patientinnen und Patienten in die Entscheidungsfindung zur Behandlung ist eine Bezugnahme auf die aktuelle Datenlage geboten und über die Risiken und Behandlungsalternativen aufzuklären.
G-BA, 2012 [8]: Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Richtlinie Methoden Krankenhausbehandlung: Allogene Stammzelltransplantation mit nicht-verwandtem Spender bei Hodgkin-Lymphom bei Erwachsenen, 2012	Nach differenzierter Abwägung entsprechend dem 2. Kapitel der Verfahrensordnung ist der Gemeinsame Bundesausschuss nach § 91 SGB V zu folgender Entscheidung gelangt: Die allogene Stammzelltransplantation mit nicht-verwandtem Spender bei Hodgkin-Lymphom bei Erwachsenen ist für eine ausreichende, zweckmäßige und wirtschaftliche Versorgung der Versicherten unter Berücksichtigung des allgemein anerkannten Standes der medizinischen Erkenntnisse (gemäß § 137c SGB V) erforderlich und bleibt damit Leistung der gesetzlichen Krankenversicherung im Rahmen einer Krankenhausbehandlung. […]
G-BA, 2013 [7]: Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a	**Anwendungsgebiet** Adcetris® wird angewendet bei der Behandlung von erwachsenen Patienten mit rezidiviertem oder refraktärem CD30+ Hodgkin-Lymphom: 1. nach einer autologen Stammzelltransplantation oder 2. nach mindestens zwei vorangegangenen Therapien, wenn eine autologe Stammzelltransplantation oder eine Kombinationschemotherapie nicht als Behandlungsoption in Frage kommt. **Ergebnis /Fazit:**

SGB V – Brentuximabvedotin siehe dazu auch: **G-BA, 2013 [9]:** Zusammenfassende Dokumentation über die Änderung der Arzneimittel - Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Brentuximabvedotin.	a) Behandlung rezidivierter/refraktärer CD30+ Hodgkin-Lymphome nach einer autologen Stammzelltransplantation: Für erwachsene Patienten mit rezidiviertem oder refraktärem CD30+ Hodgkin-Lymphom, die mindestens eine ASCT als Vortherapie ihrer Erkrankung erhalten haben, liegt ein Zusatznut-zen vor, ist aber nicht quantifizierbar, weil die wissenschaftliche Datenlage dies zum derzeitigen Zeitpunkt nicht zulässt. *Evidenzbasis*: Studie SG035-0003. Bei dieser Studie handelt es sich um eine einarmige, multizentrische offene Studie der Phase II. b) Behandlung rezidivierter/refraktärer CD30+ Hodgkin-Lymphome nach mind. 2 vorangegangenen Therapien, wenn eine autologe Stammzelltransplantation/Kombinationschemotherapie nicht als Behandlungsoption in Frage kommt (ASCT-naive Patienten): Für erwachsene Patienten mit rezidiviertem oder refraktärem CD30+ Hodgkin-Lymphom, die mindestens eine ASCT als Vortherapie ihrer Erkrankung erhalten haben, liegt ein nicht quantifizierbarer Zusatznutzen vor. *Evidenzbasis*: Aggregierte Fallserie ASCT-naiver Patienten

[1] *Der Review von Messer et al. 2014 [15]: Unrelated and alternative donor allogeneic stem cell transplant in patients with relapsed or refractory Hodgkin lymphoma: a systematic review war Bestandteil des IQWiG Berichts.*

Cochrane Reviews

Es wurde ein Cochrane Review identifiziert, welcher durch den aktuelleren systematischen Review von Rancea et al. 2014 (siehe unten) abgedeckt wird.

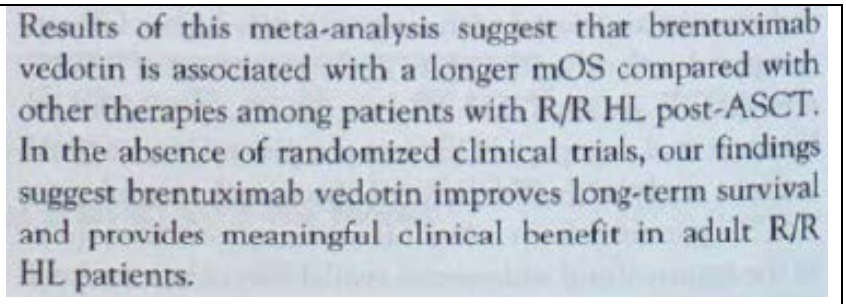
Systematische Reviews

Bonthapally V et al. 2015 [1]: Bentuximab vedotin in relapsed / refractory Hodgkin lymphoma post-autologous transplant: meta-analysis versus historical data	1. Fragestellung Evaluation oft he antitumor acivity of Bentuximab vedotin versus historical values in patients with relapsed/refractory HL post-autologous stem cell transplantation (ASCT)
	2. Methodik Population: Patients with relapsed / refractory HL post-ASCT. Intervention: A wide range of drug treatment regimens were utiliued: Gemcitabine-based regimens were the most common (14 studies), The remaining 3 studies evaluated immunotherapy, unspecified salvage chemotherapy and/or radiation therapy, second SCT, or palliation and RIC-allogeneic SCT. Komparator: Bentuximab vedotin Endpunkt: CR rate Suchzeitraum (Aktualität der Recherche): Systematische Literaturrecherche bis 2013. Anzahl eingeschlossene Studien/Patienten (Gesamt): 17 studies of chemotherapy with 827 patients. 8 Phase 2, two phase 1/2 and one phase 1, two investigator initiated clinical trials, and four retrospective studies identified.

	Treatment history: median numerb of prior regimens ranged from +2 to 5 and prios ASCT used varied condsiderably across the studies ranging from 55% tp 100%. Qualitätsbewertung der Studien: Assessed by two independent researchers (no specific tool described). Sensitivityanalyses conducted. Random effects model used (due to heterogeneity).
	3. Ergebnisdarstellung Pooled Overall CR rate: Overall CR rate across the 17 studies was 11,1% (95%KI: 7-17,6) and statistical significant lower than the reported CR rate for Bentuximab vedotin (33,3%; 95%KI: 25,3-43,9; p<0,0001) Individual CR rates across the 17 studies ranged from 0% to 38,5%. Sensitivitätsanalysen: In the sensitivity analyses, estimated overall CR rates were 13.6% (95% CI 8.7, 21.4) when only HL trials that reported a CR rate of >0% were included (13 studies; $n = 696$ response-evaluable patients[30,31,34,35,37–42,44–46]), 9.0% (95% CI 4.9, 16.6) when only HL trials were included where CR was measured using the same criteria as used in the SG035-0003 study (12 studies; $n = 562$ response-evaluable patients[30–36,38,39,42,45,46]), and 11.2% (95% CI 6.0, 20.8) when only trials reporting a CR rate of >0% using the same criteria as the SG035-0003 study were included (9 studies; $n = 473$ response-evaluable patients[30,31,34,35,38,39,42,45,46]). All estimates were significantly lower than the reported CR rate for brentuximab vedotin observed in the SG035-0003 trial ($p = 0.0009$, $p = 0.0001$, and $p = 0.0016$, respectively).
	4. Fazit der Autoren In conclusion, there is a large variability in the reported outcomes for patients with R/R HL across a spectrum of available treatments. Controlling for this variation as far as possible, the results of this meta-analysis suggest that the antitumor activity of brentuximab vedotin may exceed that of other therapies used to treat patients with R/R HL following ASCT. Given the known association between CR and long-term benefit[47], and considering the 40.5 month median OS reported from the recent 3-year follow-up of SG035-0003[20], it seems that brentuximab vedotin can provide meaningful long-term clinical benefit in R/R HL; however, future studies, particularly comparative trials, will be needed to confirm these results.

	5. Hinweise • Indirekte Vergleiche • Hohe Variabilität zwischen den Studien hinsichtlich CR rates, treatment history (heterogeneity)
Bonthapally V et al. 2015 [2]: Bentuximab vedotin compared with other therapies in relapsed / refractory Hodgkin lymphoma post-autologous transplant: median overall survival meta-analysis	1. Fragestellung Comparison of the median overall survival (mOS) of BV reported in the pivotal phase 2 study with published results of other therapies fort he treatment of relapsed/refractory (R/R) HL post-autologous stem cell transplantation (ASCT)
	2. Methodik Population: Patients with relapsed / refractory HL post-ASCT. Intervention: Chemotherapy included single sequential or multi-agent treatments, and the agent used varied, including: gemcitabine (N=3), bendamustine (N=3), Vinorelbine (N=4, and pegylated liposomal doxorubicin (N=2). The remaining 11 studies reported outcomes for other therapies including radiation therapy, immunotherapies and mixed treatments such as radiation therapy in combination wth salvage therapy. Komparator: Bentuximab vedotin Endpunkt*:* OS Suchzeitraum (Aktualität der Recherche): Systematische Literaturrecherche 2013 - 2014. Additional / Update to the review Benthapally 2015a. Using the same search strategy. Anzahl eingeschlossene Studien/Patienten (Gesamt): 41 studies including the BV study with in total of 2619 patients. One phase ½, 11 phase 2 studies, 8 prospective cohort studies, 21 retrospective studies. Treatment history: median numerb of prior regimens ranged from ≤2 to 5 and prios ASCT used varied condsiderably across the studies ranging from 52% tp 100%. Qualitätsbewertung der Studien: Assessed by two independent researchers (no specific tool described). Sensitivityanalyses conducted.
	3. Ergebnisdarstellung mOS Overall mOS across the 40 studies was 26,4 months (95%KI: 23,5-28,5). This was significantly lower than the mOS of 40,5 months (95%KI: 30,8-NA; p<0,0001) for patients receiving Bentuximab vedotin in the pivotal phase 2 trials. The estimated mOS for chemotherapy, allo-SCT, and other treatment regimens was 23 months (95%KI: 21-28,1), 27,9 months (95%KI: 23,9-30,2) and 23,9 months (95%KI: 21-28), respectively. Bentuximab vedotin-treated patients experienced significantly lower mOS compared with patients on chemotherapies, allo-SCT, and other treatments as demonstrated by differences in mOS of 17,7

	months (95%KI: 10,6-24,7; p<0.0001), 12,5 months (95%KI: 8,2-16,9;p<0,0001), and 15,2 months (95%KI: 4,9-25,5;p=0,0037), respectively. <u>Sensitivitätsanalysen:</u> The sensitivity meta-analysis, which included only those studies that reported a 100% prior-ASCT rate, showed a significant difference between the reported mOS of 40.5 months in the brentuximab vedotin trial and the estimated mOS across the 11 pooled studies of 28.1 months (95% CI 23.9–34.5; $p < 0.0001$). The results The estimated mOS for chemotherapy, allo-SCT, and other treatment regimens in the sensitivity meta-analysis was 21.1 months (95% CI 17.0–28.1), 31.1 months (95% CI 23.9–62.1), and 34.1 months (95% CI 29.5–41.5), respectively. Brentuximab vedotin-treated patients experienced significantly longer mOS compared with patients on chemotherapies, and other treatment regimens as demonstrated by differences in mOS of 19.0 months (95% CI 12.9–25.1; $p < 0.0001$), and 6.8 months (95% CI 1.2–12.5; $p = 0.0018$), respectively. The median difference in mOS estimated from the censored quantile regression method between patients receiving brentuximab vedotin and allo-SCT was not reported as the assumption of monotonicity for quantile difference was not met; however, the raw numeric difference of 9.4 months was not statistically significant ($p > 0.05$). The sensitivity meta-analysis, which grouped studies using a relaxed classification for chemotherapy, further demonstrated that brentuximab vedotin-treated patients experienced a significantly longer mOS compared with patients on chemotherapies. The estimated mOS for the broad chemotherapies group was 22.2 months (95% CI 21.0–27.5). The difference in mOS between brentuximab vedotin and broad chemotherapies was 17.3 months (95% CI 9.9–24.7; $p < 0.0001$) (Figure 4).
	4. Fazit der Autoren

	
Rahemtulla A et al. 2015 [18]: Hodgkin's lymphoma (relapsed or refractory): autologous stem cell therapy	1. Fragestellung High-dose chemotherapy and autologous stem cell transplant is the current standard of care for patients with refractory or relapsed Hodgkin's lymphoma.We have focused this overview on the evidence base for this intervention.
	2. Methodik Population: Patients with primary refractory or first-relapse histologically confirmed Hodgkin's lymphoma. Intervention/Komparator: See results section Endpunkte: Mortality (overall survival); disease progression/recurrence (progression-free survival); response rate (overall response rate, complete response rate, partial response rate); quality of life; adverse effects (e.g., treatment-related mortality). Suchzeitraum (Aktualität der Recherche): The literature search was carried out in September 2014. Anzahl eingeschlossene Studien/Patienten (Gesamt): 1 systematic review was included. *Further information on SR:* The systematic review identified and meta-analysed two open-label RCTs evaluating high-dose chemotherapy (BEAM) plus autologous stem cell transplantation compared with conventional chemotherapy (mini-BEAM in one RCT, and Dexa-BEAM in the other RCT) in people with primary refractory or first-relapse Hodgkin's lymphoma. The median follow-up was 34 months in one RCT, and 83 months in the other RCT (ranges were not reported). Both studies were stopped before reaching final trial size. In one RCT, participants refused randomisation and demanded treatment with autologous stem cell transplantation. In the other RCT, the scientific committee stopped the study early due to "low accrual of patients". Blinding in both RCTs was unclear. However, the authors of the review stated that "trials evaluating stem cell transplantation are usually not blinded". Qualitätsbewertung der Studien: GRADE evaluation
	3. Ergebnisdarstellung **What are the effects of high-dose chemotherapy plus autologous stem cell therapy for relapsed or refractory Hodgkin's lymphoma?** High-dose chemotherapy plus autologous stem cell therapy versus chemotherapy alone:

We found one systematic review, which identified three open-label RCTs. Comparators assessed in the systematic review were conventional chemotherapy alone, and additional sequential high-dose chemotherapy followed by autologous stem cell therapy. Here, based on BMJ Clinical Evidence reporting criteria, results are presented for two RCTs, which evaluated high-dose chemotherapy plus autologous stem cell therapy versus hemotherapy alone.

Mortality: High-dose chemotherapy plus autologous stem cell therapy compared with conventional chemotherapy alone We don't know whether high-dose chemotherapy plus autologous stem cell transplantation is more effective than conventional chemotherapy at improving overall survival in people with primary refractory or first-relapse Hodgkin's lymphoma *(low-quality evidence).*

Disease progression/recourrence: High-dose chemotherapy plus autologous stem cell therapy compared with conventional chemotherapy alone Highdose chemotherapy plus autologous stem cell therapy may be more effective than conventional chemotherapy at improving progression-free survival in people with primary refractory or first-relapse Hodgkin's lymphoma *(low quality evidence).*

Response Rate: High-dose chemotherapy plus autologous stem cell therapy compared with conventional chemotherapy alone Highdose chemotherapy plus autologous stem cell therapy may be more effective than conventional chemotherapy at improving complete response rate in people with primary refractory or first-relapse Hodgkin's lymphoma *(low quality evidence).*

QoL: No data

Adverse events:

Ref (type)	Population	Outcome, interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] Systematic review	People with primary refractory or first-relapse Hodgkin's lymphoma	**Treatment-related mortality , length of follow-up unclear** 3/81 (4%) with high-dose chemotherapy plus autologous stem-cell transplantation 5/76 (7%) with conventional chemotherapy 157 people (2 open-label RCTs) in this analysis	RR 0.61 95% CI 0.16 to 2.22 P = 0.45	⟷	Not significant
[23] Systematic review	117 people with primary refractory or first-relapse Hodgkin's lymphoma Data from 1 RCT	**Serious adverse effects** 51/61 (84%) with high-dose chemotherapy plus autologous stem-cell transplantation 49/56 (88%) with conventional chemotherapy Open-label RCT Serious adverse effects (WHO grade 3 and 4 toxicity) included infection, oral (mucositis), gastrointestinal, pulmonary or respiratory tract, cardiac, neurological, hepatic, and renal	Significance not assessed		

4. Fazit der Autoren

High-dose therapy and autologous stem cell transplant is the

	standard of care for patients with refractory or relapsed Hodgkin's lymphoma. Approximately 50% of these patients are cured after autologous stem cell transplantation; however, most patients with unfavourable risk factors progress after transplantation. For these patients, novel agents have been entered into clinical practice. Brentuximab vedotin induces durable objective responses and results in tumour regression for most patients with relapsed or refractory Hodgkin's lymphoma post autologous stem cell transplantation. Furthermore, a recent phase 3 study showed that early consolidation with brentuximab vedotin after autologous stem cell transplantation improved progression-free survival in patients with Hodgkin's lymphoma with risk factors for relapse or with progression after transplantation. Allogeneic stem cell transplantation, especially with reduced intensity conditioning regimens, is another option after failure of autologous stem cell transplantation in eligible patients with relapsed or refractory Hodgkin's lymphoma, offering a 25% probability of 5-year overall survival.
Rancea M et al. 2014 [20]: High-dose chemotherapy followed by autologous stem cell transplantationfor patients with relapsed or refractory Hodgkin lymphoma: A systematicreview with meta-analysis. <u>Siehe auch:</u> *Rancea M et al. 2013 [19]:* *High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma*	1. Fragestellung This systematic review with meta-analysis was conducted to evaluate the effect of HDCT plus ASCT onoverall onoverall survival compared to chemotherapy without stem celltransplantation.
	2. Methodik <u>Population</u>: Adult patientswith a relapsed Hodgkin lymphoma or a primary refrac-tory disease after first-line treatment for HL <u>Intervention</u>: HDCTfollowed by ASCT <u>Komparator</u>: Any HDCT without ASCT, conventional chemotherapy without ASCT, and different HDCT regimens followed by ASCT wouldhave been possible. Other treatment approaches, such asradiotherapy or combined-modality treatments compared toHDCT plus ASCT would also have been considered rele-vant, but no RCTs were found regarding these topics. <u>Endpunkte</u>*:* OS (primary endpoint), PFS, response rates (overall response rate, complete response rate (CRR), and partial response rate), treatment-related mortality (TRM), adverse events and quality of life. <u>Suchzeitraum (Aktualität der Recherche):</u> Bis 2013 <u>Anzahl eingeschlossene Studien/Patienten (Gesamt):</u> 3 RCTsreported in 14 publications were eligible for this systematic review. A total amountof 398 patients treated from 1993 to 2006 were assessed. <u>Qualitätsbewertung der Studien:</u> According tot he Cochrane Handbook for Systematic Reviews of Interventions. Overall, we judged the risk of bias of the included trialsas moderate.
	3. Ergebnisdarstellung **High-dose chemotherapy followed by autologousstem cell**

	transplantation versus conventionalchemotherapy *OS:* The available evidence from two trials assessing OS in157 patients was not sufficiently powered to show a statisti-cally significant difference between HDCT plus ASCT andconventional chemotherapy without ASCT *PFS:* PFS was statistically significantly improved in patients who were treatedwith HDCT plus ASCT compared to those treated withconventional chemotherapy (HR 0.55; 95% CI 0.35–0.86, *P* = .009). At three years, the event-free survival was 53% inthe HDCT + ASCT arm compared to 10% in the conventionalchemotherapy arm (based on the BNLI trial) *Response rates:* Complete response rates were 32% higher in patients afterHDCT plus ASCT than in patients treated with conventionalchemotherapy (RR 1.32; 95% CI 1.07–1.64, P = .01). Theoverall response rate was also superior in the HDCT plusASCT group, but this effect was not statistically significant (RR 1.15; 95% CI 0.99–1.34, P = .076). *Treatment related mortality:* We are therefore not able to make a validconclusion on TRM for relapsed or refractory patients withHL. The pooled estimates were not significant between thetreatment arms. *Adverse events:* Only one trial reported data and results were not stat. significant. **Additional sequential high-dose chemotherapyversus high-dose chemotherapy before autologous stemcell transplantation** Only 1 study evaluated this scenario. The trial (241 patients) showed an statistically significant increase in infections and 5% more treatment-related mortalities following sequential HDCT plus HDCT and ASCT compared to HDCT plus ASCT, without differences in the efficacy endpoints overall survival or progression-free survival.
	4. Fazit der Autoren *Actual and future research needs more evidence from ran-domised controlled trials with larger patient populations, longfollow-up and the assessment of OS as a primary endpoint. Additionally, research should concentrate on the optimal sal-vage regimen. To the best of our knowledge, this is the firstsystematic review with meta-analysis assessing HDCT followed by ASCT in patients with relapsed or refractory HL.Our analysis showed that patients benefit from this treat-ment strategy regarding PFS and also have a positive trendregarding overall survival. Intensifying the chemotherapy regimens, however, does not improve patient-related out-comes, but increases toxicities and is therefore not feasible.*

Hintringer K et al. 2012 [10]: Brentuximab (Adcetris®) for the treatment of relapsed Hodgkin's lymphoma (HL) or relapsed systemic anaplastic large cell lymphoma (sALCL) siehe auch: *CADTH 2013 [3]:* *Brentuximab Vedotin (Adcetris) for Hodgkin Lymphoma (→basiert auf selber Phase 2 Studie)*	1. Fragestellung To review the efficacy and safety of Bentuximab Vedotin for the treatment of relapsed Hodgkin's lymphoma (HL) or relapsed systemic anaplastic large cell lymphoma (sALCL)
	2. Methodik Population: patients with relapsed or refractory HL *or relapsed sALCL (nicht relevant)* Intervention: Bentruximab Vedotin Komparator: no control group → single arm study Endpunkte*:* ORR, CR, PR, SD, PD, DOR, PFS, OS Suchzeitraum (Aktualität der Recherche): bis 2012. Anzahl eingeschlossene Studien/Patienten (Gesamt): Two phase II singlearm trials. Only one study for HL! *Inclusion criteria oft he study:* Patients with relapsed or refractory HL who have received ASCT at least 12 weeks (3 months) before first dose of brentuximab and completed any prior treatment with radiation, chemotherapy, biologics and/or other investigational agents at least 4 weeks prior to first dose of SGN-35; must have completed any prior immunotherapy (e.g., rituximab) or radioisotopic therapy at least 12 weeks prior first dose of SGN-35 in the absence of clear disease progression; Histologically-documented CD30-positive disease; Age ≥18 years OR ≥12 years enrolled at US sites - ECOG performance status 0 or 1 Qualitätsbewertung der Studien: k.A.
	3. Ergebnisdarstellung • 75% of patients had an objective response (complete or partial remission) with a median duration of 6.7 months. • Notably, 34% of patients achieved complete remission with a median duration of 20.5 months. • No deaths occurred within 30 days of the last dose of brentuximab vedotin; 25 (25%) patients experienced serious adverse events (SAE); 21 (21%) patients discontinued treatment due to AEs; 56 (55%) patients had a grade 3 or 4 treatment-emergent adverse event. • The most common adverse event leading to treatment discontinuation (12 patients) and dose reduction (10 patients) was peripheral neuropathy; overall 56 patients developed neuropathy. • Other SAEs included hyperglycaemia, gastrointestinal haemorrhage, grade 3-4 pneumonitis and pulmonary embolism.
	4. Fazit der Autoren: k.A.

Leitlinien

Collins GP et al. 2014	Fragestellung: The objective of this guideline is to aid clinicians in deciding which

[4]: Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma.	patients with primary refractory or relapsed Hodgkin lymphoma (HL) should receive salvage therapy with a view to autologous stem cell transplantation (ASCT); what response is adequate to allow ASCT and how to determine this; what is the role of radiotherapy in patient management; and what is the best management of patients unsuitable for autologous transplantation.
	Methodik The production of these guidelines involved the following steps: 1. Establishment of a working group comprising experts in the field followed by literature review to 1 Feb 2013 including Medline, Pubmed and the Cochrane reviews database, using 1970 as a start date 2. The GRADE nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. Development of key recommendations was based on best available evidence. Due to the paucity of randomized studies the majority of recommendations are based on literature review and a consensus of expert opinion. 3. Initial review of the manuscript was performed by the British Committee for Standards in Haematology (BCSH) Haem-Onc Task Force, and the British Society of Blood and Marrow Transplantation (BSBMT) executive committee. 4. Final Review by the sounding board of the British Society for Haematology (BSH).
	Empfehlungen *Salvage chemotherapy* • The choice of a first line salvage regimen in patients eligible for ASCT should be based on patient factors and familiarity of the treatment centre with the regimen **(LoE: 2C)** • Regimens containing stem cell toxic agents (such as carmustine and melphalan) should be avoided if possible until stem cells have been successfully collected and cryopreserved if ASCT is planned **(LoE: 1B)** • There is currently no evidence to support intensive sequential induction/consolidation strategies prior to ASCT **(LoE: 1B)** • Consider switching to an alternative non-cross-resistant salvage regimen if there are residual FDG-avid lesions after first line salvage treatment and the intent is to proceed to ASCT **(LoE: 2B)** • In patients not eligible for ASCT, combined modality therapy should be considered, especially in early stage relapse and in patients who have not received prior radiotherapy or who have relapsed outside of the initial radiotherapy field **(LoE: 2B)** • In patients unlikely to tolerate the toxicities associated with more

	intensive regimens, palliation with either a single agent or with a multi-agent oral regimen with or without intravenous vinblastine should be considered **(LoE: 2C)** • Early consideration of involvement of palliative care services is recommended, particularly in those not eligible for high dose therapy **(LoE: 1C)** *Autologous stem cell transplantation* • ASCT is the standard treatment for patients with relapsed disease who achieve an adequate response to salvage therapy **(LoE: 1A)** • ASCT is also the standard treatment for patients with primary resistant disease who achieve an adequate response to salvage therapy **(LoE: 1B)** • ASCT is not recommended in those failing to achieve an adequate response **(LoE: 1B)** • An adequate response to salvage therapy is currently defined as a PR by conventional CT criteria **(LoE: 2B)** • Choice of conditioning regimen should be based on familiarity of the treatment centre with the regimen **(LoE: 2C)** • Current evidence does not support the use of maintenance cytotoxic therapies post-ASCT **(LoE: 1C)** • Tandem ASCT cannot currently be recommended outside of clinical trials **(LoE: 1C)** *Allogeneic haematopoietic stem cell transplantation (HSCT)* • Allogeneic transplantation using a reduced intensity conditioning regimen is the treatment of choice for younger patients with a suitable donor and chemo-sensitive disease following failure of ASCT **(LoE: 2B)** • An appropriately HLA-matched unrelated donor should be considered when there is no HLA-matched sibling **(LoE: 2B)** • A second autologous transplant is a reasonable clinical option in selected patients with late relapse following ASCT **(LoE: 2C)** • Investigation of the use of allogeneic transplantation earlier in the treatment pathway should be performed in the context of prospective clinical trials, but may be justified in selected patients who have required multiple lines of therapy to achieve a response **(LoE: 2C)** *Radiotherapy:* • The use of radiotherapy should be given serious consideration in cases of local relapse or relapse at sites where local disease is dominating the clinical picture. The use of involved site techniques is recommended to minimize toxicity to normal tissues (for example, lung fields) if subsequent high dose consolidation therapy is planned **(LoE: 2B)** • Salvage radiotherapy alone may be considered a reasonable

<table>
<tr><td></td><td>treatment option in selected patients not eligible for ASCT, especially for older patients with relapsed HL who lack B symptoms, have a good performance status, and have limited stage disease at relapse (LoE: 2B)
• In the rare event of late relapse >5 years after primary therapy occurring at a localized site without B symptoms, treatment with standard-dose chemotherapy and involved field radiation alone may be appropriate (LoE: 2B)
• Peri-transplant (ASCT) radiotherapy should be considered in patients that have a dominant site of local relapse at an initially involved site (these are usually patients who have had bulky disease with residual abnormalities following salvage chemotherapy and ASCT) (LoE: 2C)</td></tr>
<tr><td rowspan="2">Leitlinienprogramm Onkologie, 2013 [14]:

Hodgkin Lymphom; Diagnostik, Therapie und Nachsorge von erwachsenen Patienten.</td><td>Fragestellung
Das primäre Ziel der vorliegenden S3-Leitlinie ist es, die Diagnostik, Therapie und Nachsorge von Patienten mit einem Hodgkin Lymphom zu standardisieren und zu optimieren, um sowohl bei der Ersterkrankung als auch im Rezidiv ein individuell adaptiertes, qualitätsgesichertes Therapiekonzept zu gewährleisten.</td></tr>
<tr><td>Methodik

Für die detaillierte Methodik der Erstellung, Verbreitung und Implementierung dieser Leitlinie existiert ein Leitlinienreport zu dieser Leitlinie: http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html

Evidenzgraduierung mit GRADE

<table>
<tr><th>GRADE</th><th>Beschreibung</th><th>Symbol</th></tr>
<tr><td>Hohe Qualität</td><td>Es ist sehr unwahrscheinlich, dass weitere Forschung das Vertrauen in den Behandlungseffekt verändert</td><td>⊕⊕⊕⊕</td></tr>
<tr><td>Moderate Qualität</td><td>Weitere Forschung wird sich vermutlich erheblich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Möglicherweise ändert sich der Behandlungseffekt.</td><td>⊕⊕⊕⊖</td></tr>
<tr><td>Niedrige Qualität</td><td>Weitere Forschung wird sich sehr wahrscheinlich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Wahrscheinlich ändert sich der Behandlungseffekt.</td><td>⊕⊕⊖⊖</td></tr>
<tr><td>Sehr niedrige Qualität</td><td>Der beobachtete Behandlungseffekt ist mit sehr großer Unsicherheit behaftet.</td><td>⊕⊖⊖⊖</td></tr>
</table>
<table>
<tr><th>Empfehlungsgrad</th><th>Beschreibung</th><th>Syntax</th></tr>
<tr><td>A</td><td>Starke Empfehlung</td><td>soll</td></tr>
<tr><td>B</td><td>Empfehlung</td><td>sollte</td></tr>
<tr><td>0</td><td>Empfehlung offen</td><td>kann</td></tr>
</table>

Die OL-Methodik sieht eine Vergabe von Empfehlungsgraden durch die LL-Autoren im Rahmen eines formalen Konsensusverfahrens vor. Dementsprechend wurde ein durch das OL, vertreten durch Herrn Dr.</td></tr>
</table>

	Follmann, moderierter, mehrteiliger Gruppenprozess durchgeführt. Sofern für eine spezifische Fragestellung bei der 1. Konsensuskonferenz konsentiert wurde, dass keine systematische Literaturrecherche durchgeführt werden soll, ist die Empfehlung zusätzlich mit dem Hinweis „Expertenkonsens (EK)“ gekennzeichnet.
	Rezidivtherapie **Transplantation** • Patienten bis 60 Jahre ohne schwere Begleiterkrankungen **sollen** bei Rezidiv oder Progress eines Hodgkin Lymphoms eine Hochdosischemotherapie mit autologer Stammzelltransplantation erhalten. (Empfehlungsgrad: A / GRADE: ⊕⊕⊕⊖) • Patienten über 60 Jahre in gutem körperlichem Zustand und ohne schwere Begleiterkrankungen **können** bei Rezidiv oder Progress eines Hodgkin Lymphoms eine Hochdosischemotherapie mit autologer Stammzelltransplantation erhalten. (Empfehlungsgrad: EK) • Patienten mit Progress nach Salvage-Therapie **können** vor Hochdosischemotherapie eine alternative Salvage-Therapie mit nicht-kreuzresistenten Substanzen erhalten, z.B. IGEV nach DHAP. (Empfehlungsgrad: EK) • Als eine mögliche Alternative **kann** bei Progress nach Salvage-Therapie eine Therapie mit Brentuximab Vedotin durchgeführt werden. (Empfehlungsgrad: EK) • Patienten mit spätem Rezidiv (mindestens ein Jahr) nach autologer Transplantation **können** mit einer zweiten autologen Transplantation behandelt werden. (Empfehlungsgrad: EK) **Salvage-Therapie vor Hochdosischemotherapie bei einer autologen Transplantation** • Patienten **sollen** vor der Hochdosistherapie bei einer autologen Transplantation eine Salvage-Therapie erhalten. (Empfehlungsgrad A / GRADE: ⊕⊕⊕⊖) • Als Salvage-Therapie-Schema **sollten** Patienten vor der Hochdosistherapie zwei Zyklen zeitintensiviertes DHAP erhalten. (Empfehlungsgrad: B / GRADE: ⊕⊕⊖⊖) • Patienten **können** vor der Hochdosistherapie statt DHAP eine Salvage-Therapie mit einem alternativen Schema erhalten, z.B. IGEV. (Empfehlungsgrad: 0 / GRADE: ⊕⊕⊖⊖) • Patienten **sollen** zwischen Salvage- und Hochdosistherapie keine zwischengeschaltete sequentielle Hochdosistherapie erhalten sondern zeitnah mit der myeloablativen Hochdosischemotherapie behandelt und transplantiert werden. (Empfehlungsgrad A / GRADE: ⊕⊕⊕⊕) • Patienten **sollen**, wenn sie durch die Salvage-Therapie mindestens eine Krankheitsstabilisierung erreichen, zeitnah

	transplantiert werden. (Empfehlungsgrad A / GRADE: ⊕⊕⊕⊕) **Allogene Transplantation im Rezidiv** • Patienten mit rezidiviertem oder refraktärem Hodgkin Lymphom **sollen** nicht mit einer myeloablativen Konditionierung allogen transplantiert werden. (Empfehlungsgrad: A / GRADE: ⊕⊕⊖⊖) • Patienten mit rezidiviertem, chemosensitivem Hodgkin Lymphom **können**, wenn sie bereits autolog transplantiert wurden oder nicht autolog transplantiert werden können und in gutem Allgemeinzustand sind, mit einer dosisreduzierten Konditionierung gefolgt von einer allogenen Stammzelltransplantation behandelt werden. Es empfiehlt sich für diese Patienten ganz besonders der Einschluss in klinische Studien. (Empfehlungsgrad: 0 / GRADE: ⊕⊖⊖⊖) • Patienten mit rezidiviertem Hodgkin Lymphom, bei denen eine allogene Stammzelltransplantation durchgeführt werden soll und bei denen kein verwandter Spender vorliegt, **können** auch mit nicht verwandtem Spender transplantiert werden. (Empfehlungsgrad: 0 / GRADE: ⊕⊖⊖⊖) **Alternativtherapie zur Transplantation** • Ausgewählte Patienten mit lokalisiertem Spätrezidiv ohne B-Symptome und in gutem Allgemeinzustand **können** alternativ zur autologen Transplantation mit Bestrahlung behandelt werden. (Empfehlungsgrad: 0 / GRADE: ⊕⊕⊖⊖) • Patienten mit Rezidiv nach zwei Zyklen Chemotherapie und Bestrahlung im frühen Stadium und Patienten mit Rezidiv nach alleiniger Bestrahlung **können** alternativ mit intensiver, konventioneller Chemotherapie (z.B. BEACOPP eskaliert für Patienten unter 60) und ggf. Bestrahlung von Resten behandelt werden. (Empfehlungsgrad: 0 / GRADE: ⊕⊕⊖⊖) • Patienten, die nicht für eine Transplantation in Frage kommen, **sollen** mit einer palliativen Antikörpertherapie mit Brentuximab Vedotin, Chemotherapie oder Bestrahlung behandelt werden. Dies gilt insbesondere für mehrfach rezidivierte Patienten. Es empfiehlt sich für dieses Patientenkollektiv ganz besonders der Einschluss in klinische Studien. (Empfehlungsgrad: A / GRADE: ⊕⊕⊖⊖)
ESMO, 2014 [5]: Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.	Fragestellung: k.A.
	Methodik Levels of evidence and grades of recommendation have been applied using the system shown below. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

Table 6. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [38].

No further information on methodology given.

relapsed disease

- For most patients with refractory or relapsed HL, the treatment of choice consists of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) **[II, A]**
- High-risk patients may benefit from tandem ASCT **[III, B]**
- Salvage regimens such as dexamethasone/high-dose Ara-C/cisplatin (DHAP), ifosfamide/gemcitabine/vinorelbine (IGEV) or ifosfamide/carboplatin/etoposide (ICE) are given to reduce the tumour burden and mobilise stem cells before high-dose chemotherapy and ASCT **[II–III, A]**
- A subset of low-risk patients relapsing after primary treatment with two cycles of chemotherapy followed by RT can be successfully salvaged with a second, more intensive conventional chemotherapy such as BEACOPP escalated **[IV, B–C]**
- In some patients with localised late relapse, salvage RT alone appears to be sufficient **[IV, B–C]**

	• The use of the antibody-drug conjugate brentuximab vedotin represents an option in patients failing ASCT. After a pivotal phase II study including 102 HL patients with relapse after ASCT had revealed an overall response rate (ORR) of 75% with singleagent brentuximab vedotin, the drug was recently approved for the treatment of such patients **[III, B]** • Reduced-intensity conditioning allogeneic stem cell transplantation (RIC-aSCT) can be considered in young, chemosensitive patients in good general condition who relapse after high-dose chemotherapy and ASCT **[III, C]** • In patients with multiple relapses who have no other treatment options, acceptable remission rates, satisfying quality of life and prolonged survival can be achieved by palliative singleagent chemotherapy with gemcitabine or bendamustine and/or regional RT. As brentuximab vedotin has also been approved for the treatment of HL patients with disease recurrence after at least two lines of treatment who are not candidates for high-dose chemotherapy followed by ASCT, its use can also be considered in this patient group. **[Keine Angabe des LoE]**
NCCN, 2015 [16]: Hodgkin Lymphoma.	Fragestellung The guideline discusses the clinical management of patients with CHL.
	Methodik Methodenreport beschreibt systematische Evidenzaufbereitung (basierend auf aktueller Literaturrecherche bis 2014) mit Konsensusprozessen - Repräsentativität der Gremien unklar - ob formalisierte Konsensusverfahren angewendet werden ist unklar. Eigenes Graduierungssystem **NCCN Categories of Evidence and Consensus** **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. **All recommendations are category 2A unless otherwise noted.**
	Empfehlungen:

	NCCN Recommendations for Refractory Disease Individualized treatment is recommended since there are no data to support a superior outcome with any of the treatment modalities. Histologic confirmation with biopsy is recommended before initiating treatment for refractory disease. Although further cytoreduction and HDT/ASCR (with ISRT if not previously given) are often appropriate, occasional clinical circumstances may warrant the use of ISRT or systemic therapy with or without ISRT. Conventional-dose second-line systemic therapy may precede HDT/ASCR. ISRT is recommended when the sites of relapse have not been previously irradiated. In radiation-naïve patients, TLI may be an appropriate component of HDT/ASCR.[193] Second-line systemic therapy followed by response assessment with PET is recommended for all patients. Patients with a Deauville score of 1 to 3 should be treated with HDT/ASCR with or without ISRT or observation with or without ISRT, if HDT/ASCR is contraindicated. Additional second-line therapy (ISRT or second-line systemic therapy with or without ISRT) is recommended for patients with a Deauville score of 4 or 5. Alternatively, those with a Deauville score of 4 can be treated with HDT/ASCR with or without ISRT. Among patients with relapsed or refractory disease, those with a CR to second-line therapy prior to HDT/ASCR have better outcomes following HDT/ASCR compared to those with resistant disease.[160,161] Everolimus and brentuximab vedotin are included as options for second-line systemic therapy for patients with relapsed or refractory CHL.[187,191] Bendamustine and lenalidomide are included as options for third-line therapy for patients with relapsed or refractory CHL.[185,186] The use of brentuximab vedotin as consolidation therapy following HDT/ASCR was evaluated in the AETHERA trial. In this trial, 329 patients who were at high risk of progression (patients with disease refractory to front-line therapy, relapsed disease <12 months after frontline therapy, and relapsed disease ≥12 months after frontline therapy with extranodal disease) were randomized (following HDT/ASCR) to brentuximab vedotin (n = 165) or placebo (n = 164).[194] Patients were required to have obtained a CR, PR, or stable disease to second-line therapy prior to ASCT. The interim analysis (after a median follow-up of 30 months) showed that early consolidation with brentuximab vedotin following HDT/ASCR was associated with improved PFS and the survival benefit was demonstrated across all risk groups. The median PFS was 42·9 months in the brentuximab vedotin group and 24·1 months in the placebo group. The estimated 2-year PFS rates were 65% and 45%, respectively, for the brentuximab vedotin and placebo arms (*P* = .0013). At the time of this interim analysis, there was no statistically significant difference in OS between the two groups (HR 1.15; *P*=·6204). Brentuximab vedotin was also well tolerated. Peripheral sensory neuropathy (36%), upper

	respiratory tract infection (25%), neutropenia (24%) and fatigue (21%) were the most common adverse events. Based on the results of this study, the panel has included maintenance therapy with brentuximab vedotin (for one year) following HDT/ASCR for patients with primary refractory disease or for those with disease relapse less than 12 months following primary treatment. However, the value of this approach in patients who have received prior treatment with brentuximab vedotin is not known. Allogeneic HSCT with myeloablative conditioning has been associated with lower relapse rate in patients with relapsed or refractory disease; however, TRM was >50%. Allogeneic HSCT with reduced-intensity conditioning has been reported to have decreased rates of TRM.[195,196] However, this approach remains investigational. The panel has included allogeneic HSCT with a category 3 recommendation for patients with refractory or relapsed disease. *NCCN Recommendations for Relapsed Disease* While second-line systemic therapy is an appropriate treatment for any patient with relapsed disease, regardless of the length of initial remission,[197] some studies have also suggested that it may not be essential before proceeding to HDT/ASCR for patients with minimal residual disease at relapse.[198] In selected patients with long disease-free intervals and other favorable features, the selection of second-line therapy should be individualized. Suspected relapse should be confirmed with biopsy. Observation (with short-interval follow-up with PET/CT) is appropriate if biopsy is negative. Restaging is recommended for patients with positive biopsy. Second-line systemic therapy with or without ISRT or HDT/ASCR is the preferred treatment option for patients with stage IA to IIA disease who were initially treated with chemotherapy alone and experienced failure at the initial sites. RT alone (conventional or extended field treatment) may be appropriate for selected patients. All other patients experiencing disease relapse after initial treatment with chemotherapy or combined modality therapy should be treated with second line systemic therapy. Restaging after completion of treatment is recommended for all patients. Additional treatment options (based on the score on interim PET scan) are as described for patients with refractory disease.
Kouroukis CT et al. 2012 [13]: Stem Cell Transplantation in Lymphoma: Recommendations	Fragestellung What is the role of stem cell transplantation in the treatment of the various lymphomas?
	Methodik Systematische Literaturrecherche bis 2011. Ein- und Ausschlusskriterien definiert. *Assessment of Quality:* For systematic reviews that would be used as the evidence base for our recommendations, the AMSTAR tool would

	be used to assess quality. For Clinical Practice Guidelines, the AGREE 2 instrument would be used, but only if adaptation of the recommendations was being considered. Any meta-analysis would be assessed for quality using similar criteria as used for RCTs, where appropriate. RCTs would be assessed for quality by examining the following seven criteria: the method of randomization, reporting of blinding, the power and sample size calculation, length of follow-up, reporting details of the statistical analysis, reporting on withdrawals to treatment and other losses to follow-up, and reporting on the sources of funding for the research. Comparative, but non-randomized, evidence would be assessed according to full reporting of the patient selection criteria, the interventions each patient received and of all relevant outcomes. The Collaborative Projects produce Standards, Evidence-based Series, and Special Reports, developed by Expert Panels or Working Groups that are convened by Cancer Care Ontario. The groups work together with the Program in Evidence-Based Care (PEBC) to gather and examine evidence on specific topics relevant to providing quality cancer care in Ontario. The PEBC has a formal and standardized process to ensure the currency of each document (please see the PEBC Assessment & Review Protocol for more information).
	Empfehlungen: • Autologous stem cell transplantation (ASCT) is the recommended treatment option for chemo-sensitive patients with HL who are refractory to or who have relapsed after primary chemotherapy. Patients with stable disease following salvage chemotherapy could also remain eligible for autologous stem cell transplantation. Patients with progressive disease despite salvage chemotherapy should not be offered autologous stem cell transplantation outside the context of a clinical trial. *Evidenzbasis*: This Recommendation was brought forward from the 2009 Recommendation Report.1 As none of the more-recent evidence included in this report refutes this earlier recommendation, the Expert Panel continues to endorse it. • Allogeneic stem cell transplantation is an option for chemo-sensitive patients with refractory or relapsed HL if they have a syngeneic (identical twin) donor, following autologous stem cell transplantation failure, or alternatively in patients in whom sufficient numbers of autologous stem cells cannot be collected. *Evidenzbasis:* This Recommendation was brought forward from the 2009 Recommendation Report. As none of the more-recent evidence included in this report refutes this earlier recommendation, the Expert Panel continues to endorse it. One retrospective cohort study detected an overall survival difference,

<table>
<tr><td></td><td>and this was in favour of reduced-intensity conditioning compared with myeloablative conditioning followed by allogeneic SCT.</td></tr>
<tr><td rowspan="2">Perales MA et al. 2015 [17]:

Role of Cytotoxic Therapy with Hematopoietic Cell Transplantation in the Treatment of Hodgkin Lymphoma: Guidelines from the American Society for Blood and Marrow Transplantation</td><td>Fragestellung
The goals of this review are to assemble and critically evaluate all evidence regarding the role of hematopoietic cell transplantation (HCT) in the therapy of patients with Hodgkin lymphoma (HL), make treatment recommendations based on the available evidence, and identify areas of needed research.</td></tr>
<tr><td>Methodik

Systematische Literaturrecherche bis 2014

Experts in the treatment of HL were invited to join the independent expert panel that examined the literature and provided subsequent treatment recommendations based on the available evidence.

A standardized grading system that includes grading the levels of evidence was used to grade the studies included in this review and the treatment recommendations, as recommended by the ASBMT Steering Committee for evidence-based reviews. Studies were also evaluated based on study design, sample size, patient selection criteria, duration of follow-up, and treatment plan.

<u>LoE</u>:
<table><tr><td>1++</td><td>High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias</td></tr><tr><td>1+</td><td>Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td></tr><tr><td>1–</td><td>High-quality systematic reviews of case-control or cohort studies.</td></tr><tr><td>2++</td><td>High quality case-control or cohort studies with a very low risk of confounding, bias, or chance, and a high probability that the relationship is causal</td></tr><tr><td>2+</td><td>Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal</td></tr><tr><td>2–</td><td>Case-control or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal</td></tr><tr><td>3</td><td>Nonanalytic studies (eg, case reports, case series)</td></tr><tr><td>4</td><td>Expert opinion</td></tr></table>
<u>Grades of recommendation</u>
<table><tr><td>A</td><td>At least 1 meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of</td></tr></table></td></tr>
</table>

	results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++.
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+.

Empfehlungen:

Recommendation	Grade of Recommendation	Highest Level of Evidence
ASCT should not be offered as first-line therapy for advanced disease	A	1+
ASCT should be offered as first-line therapy for patients who fail to achieve CR	B	2++
ASCT should be offered as salvage therapy over nontransplantation (except localized disease, where IFRT may be considered, or patients with low-stage disease and late relapse, where chemotherapy may be considered)	A	1+
ASCT should be offered to pediatric patients with primary refractory disease or high-risk relapse who respond to salvage therapy	B	2++
Several salvage chemotherapy regimens may be considered before ASCT in adult patients	B	2++
Several salvage chemotherapy regimens may be considered before ASCT in pediatric patients	B	2++
BEAM or CBV are the most common conditioning regimens for ASCT in standard-risk patients	B	2++
IFRT should be considered in patients with bulky disease not previously irradiated	C	2+
Tandem ASCT is not routinely recommended in standard-risk patients	C	2+
Maintenance therapy with brentuximab vedotin post-ASCT is recommended in high-risk patients*	A	1+
Chemosensitive disease and negative functional imaging are associated with improved outcome	B	2++

Recommendation	Grade of Recommendation	Highest Level of Evidence
Allo-HCT should be used instead of conventional therapy for relapse after ASCT	B	2++
RIC is the recommended regimen intensity	B	2++
All donor sources can be considered	A	1+
DLI can be given for relapse or progressive disease (limited data for mixed donor chimerism)	B	2++
There are limited data for tandem ASCT/Allo-HCT	D	4
Allo-HCT is preferred over ASCT as second HCT (except in late relapse)	C	2+

	Recommendation	Grade of Recommendation	Highest Level of Evidence
Should ASCT be offered as first-line therapy for advanced disease?	No	A	1+
Should ASCT be offered as first-line therapy for patients who fail to achieve a CR?	Yes	B	2++
Should ASCT or nontransplantation be offered as salvage therapy?	ASCT	A	1+

	Recommendation	Grade of Recommendation	Highest Level of Evidence
What are common regimens of salvage therapy before ASCT in adult patients?	ICE, ESHAP, or GDP*	B	2++
What are common regimens of salvage therapy before ASCT in pediatric patients?	GV, IV	B	2++
What is the recommended conditioning regimen for ASCT?	BEAM, CBV, Bu/Cy (±Et), Bu/Mel, or TLI/chemotherapy	B	2++
Is there a role for tandem ASCT?	Not in standard-risk patients	C	2+
What is the role of IFRT and when should it be performed?	Recommended in bulky disease previously not irradiated, post-ASCT in most centers	C	2+
Should maintenance therapy be given after ASCT?	Yes†	A	1+
What is the role of comorbidities in outcomes?	Paucity of data	—	—
Should ASCT be offered to pediatric patients?	Yes	B	2++

	Recommendation	Grade of Recommendation	Highest Level of Evidence
Should allo-HCT be used instead of conventional therapy for patients who relapse after ASCT?	Yes	B	2++
What is the recommended regimen intensity?	RIC	B	2++
Is there a preferred donor source?	No	A	1+
When should DLI be given?	Progressive disease/ relapsed	B	2++
	Incomplete donor chimerism	D	3
What is the role of comorbidities in outcomes?	Paucity of data	—	—

	Recommendation	Grade of Recommendation	Highest Level of Evidence
Should allo-HCT be performed instead of ASCT as first SCT?	No	C	2+
Should allo-HCT be performed instead of ASCT as second SCT in most patients?	Yes	C	2+
Should second ASCT be considered for patients who relapse after ASCT?	Not within 1 year	C	2+
Is there a role for tandem ASCT-allo-HCT?	No	D	4

Primärstudien

Da ausreichend Literatur aus aggregierter Evidenz vorliegt, wurde eine Suche nach Primärstudien nicht in Auftrag gegeben.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) am 08.03.2016

#	Suchfrage
#1	MeSH descriptor: [Hodgkin Disease] explode all trees
#2	MeSH descriptor: [Reed-Sternberg Cells] explode all trees
#3	Hodgkin*:ti,ab,kw and disease or lymphoma or granuloma:ti,ab,kw (Word variations have been searched)
#4	reed sternberg cell*:ti,ab,kw (Word variations have been searched)
#5	#1 or #2 or #3 or #4 Publication Year from 2011 to 2016

SR, HTAs in Medline (PubMed) am 08.03.2016

#	Suchfrage
#1	Search (("hodgkin disease"[MeSH Terms]) OR "reed sternberg cells"[MeSH Terms])
#2	Search ((hodgkin*[Title/Abstract]) AND (disease*[Title/Abstract] OR lymphoma*[Title/Abstract] OR granuloma*[Title/Abstract]))
#3	Search (((reed[Title/Abstract] AND sternberg[Title/Abstract] AND cell[Title/Abstract])) OR ("reed sternberg cell"[Title/Abstract] OR "reed-sternberg cell"[Title/Abstract]))
#4	Search (#1 OR #2 OR #3)
#5	Search (("recurrence"[MeSH Terms]) OR "neoplasm recurrence, local"[MeSH Terms])
#6	Search ((((classic*[Title/Abstract] OR relap*[Title/Abstract] OR recurren*[Title/Abstract] OR recurring[Title/Abstract] OR refractory[Title/Abstract] OR recrudesc*[Title/Abstract] OR resisten*[Title/Abstract] OR resistance[Title/Abstract])))
#7	Search (salvage therapy[MeSH Terms] OR salvage therap*[Title/Abstract])
#8	Search (((((((2nd[Title/Abstract]) OR second[Title/Abstract]) OR 3rd[Title/Abstract]) OR third[Title/Abstract]) OR 4th[Title/Abstract]) OR fourth[Title/Abstract]))
#9	Search line[Title/Abstract]
#10	Search (#8 AND #9)
#11	Search (#5 OR #6 OR #7 OR #10)
#12	Search (#4 AND #11)
#13	Search (#12 AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]))
#14	Search (#12 AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-

	analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))))
#15	Search (#13 OR #14) Filters: published in the last 5 years
#16	Search (#15 NOT "The Cochrane database of systematic reviews"[Journal])

Leitlinien in Medline (PubMed) am 08.03.2016

#	Suchfrage
#1	Search (("hodgkin disease"[MeSH Terms]) OR "reed sternberg cells"[MeSH Terms])
#2	Search ((hodgkin*[Title/Abstract]) AND (disease*[Title/Abstract] OR lymphoma*[Title/Abstract] OR granuloma*[Title/Abstract]))
#3	Search (((reed[Title/Abstract] AND sternberg[Title/Abstract] AND cell[Title/Abstract])) OR ("reed sternberg cell"[Title/Abstract] OR "reed-sternberg cell"[Title/Abstract]))
#4	Search (#1 OR #2 OR #3)
#5	Search (#4 AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title]))) Filters: published in the last 5 years

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