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Nivolumab for adults with Hodgkin's lymphoma (a rapid review using the software RobotReviewer) (Review)

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[Intervention Review]

Nivolumab for adults with Hodgkin's lymphoma (a rapid review using the software RobotReviewer)

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ABSTRACT

Background

Hodgkin's lymphoma (HL) is a cancer of the lymphatic system, and involves the lymph nodes, spleen and other organs such as the liver, lung, bone or bone marrow, depending on the tumour stage. With cure rates of up to 90%, HL is one of the most curable cancers worldwide. Approximately 10% of people with HL will be refractory to initial treatment or will relapse; this is more common in people with advanced stage or bulky disease. Standard of care for these people is high-dose chemotherapy and autologous stem cell transplantation (ASCT), but only 55% of participants treated with high-dose chemotherapy and ASCT are free from treatment failure at three years, with an overall survival (OS) of about 80% at three years.

Checkpoint inhibitors that target the interaction of the programmed death (PD)-1 immune checkpoint receptor, and its ligands PD-L1 and PD-L2, have shown remarkable activity in a wide range of malignancies. Nivolumab is an anti-(PD)-1 monoclonal antibody and currently approved by the US Food and Drug Administration (FDA) for the treatment of melanoma, non-small cell lung cancer, renal cell carcinoma and, since 2016, for classical Hodgkin's lymphoma (cHL) after treatment with ASCT and brentuximab vedotin.

Objectives

To assess the benefits and harms of nivolumab in adults with HL (irrespective of stage of disease).

Search methods

We searched CENTRAL, MEDLINE, Embase, International Pharmaceutical Abstracts, conference proceedings and six study registries from January 2000 to May 2018 for prospectively planned trials evaluating nivolumab.

Selection criteria

We included prospectively planned trials evaluating nivolumab in adults with HL. We excluded trials in which less than 80% of participants had HL, unless the trial authors provided the subgroup data for these participants in the publication or after we contacted the trial authors.

Data collection and analysis

Two review authors independently extracted data and assessed potential risk of bias. We used the software RobotReviewer to extract data and compared results with our findings. As we did not identify any randomised controlled trials (RCTs) or non-RCTs, we did not meta-analyse data.

Main results

Our search found 782 potentially relevant references. From these, we included three trials without a control group, with 283 participants. In addition, we identified 14 ongoing trials evaluating nivolumab, of which two are randomised. Risk of bias of the three included studies was moderate to high. All of the participants were in relapsed stage, most of them were heavily pretreated and had received at least two previous treatments, most of them had also undergone ASCT. As we did not identify any RCTs, we could not use the software RobotReviewer to assess risk of bias. The software identified correctly that one study was not an RCT and did not extract any trial data, but extracted characteristics of the other two studies (although also not RCTs) in a sufficient way.

Two studies with 260 participants evaluated OS. After six months, OS was 100% in one study and median OS (the timepoint when only 50% of participants were alive) was not reached in the other trial after a median follow-up of 18 months (interquartile range (IQR) 15 to 22 months) (very low certainty evidence, due to observational trial design, heterogenous patient population in terms of pretreatments and various follow-up times (downgrading by 1 point)). In one study, one out of three cohorts reported quality of life. It was unclear whether there was an effect on quality of life as only a subset of participants filled out the follow-up questionnaire (very low certainty evidence). Three trials (283 participants) evaluated progression-free survival (PFS) (very low certainty evidence). Six-month PFS ranged between 60% and 86%, and median PFS ranged between 12 and 18 months. All three trials (283 participants) reported complete response rates, ranging from 12% to 29%, depending on inclusion criteria and participants' previous treatments (very low certainty evidence).

One trial (243 participants) reported drug-related grade 3 or 4 adverse events (AEs) only after a median follow-up of 18 months (IQR 15 to 22 months); these were fatigue (23%), diarrhoea (15%), infusion reactions (14%) and rash (12%). The other two trials (40 participants) reported 23% to 52% grade 3 or 4 AEs after six months' follow-up (very low certainty evidence). Only one trial (243 participants) reported drug-related serious AEs; 2% of participants developed infusion reactions and 1% pneumonitis (very low certainty evidence).

None of the studies reported treatment-related mortality.

Authors' conclusions

To date, data on OS, quality of life, PFS, response rate, or short- and long-term AEs are available from small uncontrolled trials only. The three trials included heavily pretreated participants, which had previously undergone regimens of BV or ASCT. For these participants, median OS was not reached after follow-up times of at least 16 months (more than 50% of participants with a limited life expectancy were alive at this timepoint). Only one cohort out of three only reported quality of life, with limited follow-up data so that meaningful conclusions were not possible. Serious adverse events occurred rarely. Currently, data are too sparse to make a clear statement on nivolumab for people with relapsed or refractory HL except for heavily pretreated people, which had previously undergone regimens of BV or ASCT. When interpreting these results, it is important to consider that proper RCTs should confirm these findings.

As there are 14 ongoing trials evaluating nivolumab, of which two are RCTs, it is possible that an update of this review will be published in the near future and that this update will show different results to those reported here.

PLAIN LANGUAGE SUMMARY

Nivolumab for adults with Hodgkin's lymphoma

Background

Hodgkin's lymphoma (HL) is a cancer of the lymphatic system. As part of the immune system, the lymphatic system comprises a network of lymphatic vessels, which transport lymph throughout the body. Lymph is a fluid which contains white blood cells, that tackle infection. HL occurs in children and adults, but it is more common in the third decade of life. It is one of the most curable forms of cancer and up to 90% of people will be cured; however, approximately 10% of people with HL will relapse (the cancer will return). Treatment options are chemotherapy, radiotherapy, or both, or newly developed agents, called checkpoint inhibitors that target the cancer cell directly. Nivolumab is one checkpoint inhibitor and currently approved by the US Food and Drug Administration for the treatment of various cancers and relapsed HL after treatment with stem cell transplantation and brentuximab vedotin, which is a medicine used to treat cancer. In stem cell transplantation patients receive blood building cells, so called stem cells, which replace their own when they have been destroyed along the disease or previous therapy regimens.

Review question

This systematic review evaluated the benefits and harms of nivolumab for adults with Hodgkin's lymphoma.

Study characteristics

We searched important medical databases for clinical trials assessing the benefits and harms of nivolumab in adults with HL. Two review authors independently screened, summarised and analysed the results. In addition, we tested the computer software RobotReviewer to extract data. Our search led to the inclusion of three studies involving 283 participants and 14 ongoing trials.

The evidence provided is current to May 2018.

Key results

Two studies with 260 participants evaluated survival. After six months, all participants were alive in one trial (17 participants). One trial reported quality of life for a subgroup of participants using a questionnaire but not all follow-up data were available. Although it seemed that the participants answering the questionnaire might have had a benefit, it was unclear whether this applied to all the participants. The studies also reported tumour control and tumour response, but with different results, depending on the treatment and how many previous treatments participants had received before nivolumab was given.

As nivolumab is given until the disease progresses (gets worse) or until unacceptable side effects occur, people receive the drug for a long time. Therefore, reporting of side effects is related to the time the person received the medicine, with potentially more side effects with longer usage. The most commonly reported side effects were fatigue (tiredness), diarrhoea (loose stools), infusion reactions (during or shortly after giving the medicine by a vein) and rash. Only one study reported medicine-related serious side effects. They occurred rarely (infusion reactions and lung disease). Deaths related to the medicine were not reported.

Reliability of the evidence

Due to the study design and varied type of participants with different numbers of previous treatments and various treatment options, the reliability of the evidence was low to very low.

Conclusion

This systematic review evaluated the benefits and harms of nivolumab in adults with HL.

Data on survival, quality of life, tumour response and side effects were available from small trials only. The three trials included only people different previous treatment options, very often also with a previous stem cell transplantation. In one trial, all participants were alive after six months. Quality of life data were not reported for all the included participants; moreover, data after a long period of treatment were not available for all evaluated participants, therefore meaningful conclusions were not possible. Serious side effects occurred rarely. Currently, data are too sparse to make a clear statement on nivolumab for people with relapsed or refractory HL except for those who had received several treatments before. As there are currently 14 ongoing trials evaluating nivolumab, of which two are well designed, it is possible that an update of this review will be published in the near future and that this update will show different results to those reported here.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Nivolumab compared to no other intervention for adults with Hodgkin's lymphomas

Nivolumab for adults with Hodgkin's lymphoma

Patient or population: adults with Hodgkin's lymphoma

Settings: inpatient or outpatient cancer care

Intervention: nivolumab

Comparison: none

Outcomes	Impacts	No of Participants (studies)	Quality of the evidence (GRADE)
OS follow-up: range 6-27 months	CheckMate 205 reported that median OS has not been reached after a median follow-up of 18 months. Hatake 2016 reported 100% OS after 6 months. A retrospective analysis of participants with third relapse of cHL not treated with nivolumab shows a 6-month OS of 90% and a 12 month OS of 73%.	260 (2 observational studies)	⊕⊕⊕⊕ Very low ^{a,b}
QoL follow-up: mean 7 months	Both the EQ-5D visual analogue scale (and the EORTC QLQ-C30 indicated improved QoL for those participants who filled out the forms. (EQ-5D: from 62 (standard deviation (SD) 30) at baseline (72 (90%) participants) to 80 (SD 18) at week 33 (44 (55%) participants); EORTC QLQ-C30 suggested improvement from baseline across functional, symptom and global health scores)	80 (1 observational study)	⊕⊕⊕⊕ Very low ^{a,c}
PFS follow-up: range 6 months to 23 months	2 trials reported 6-month PFS of 60-86%. In the other trial, median PFS was 12-18 months. A retrospective analysis of third relapsed people with cHL not treated with nivolumab demonstrated a 6-month PFS of 76% and a 12-month PFS of 51%.	283 (3 observational studies)	⊕⊕⊕⊕ Very low ^{a,b}
Response rate follow-up: range 6-23 months	Complete response rate was 12-29% depending on inclusion criteria and participants' previous treatments	283 (3 observational studies)	⊕⊕⊕⊕ Very low ^{a,b}
Treatment-related mortality	Not reported		—
Grade 3 or 4 AEs follow-up: range 8-23 months	1 trial reported drug-related AEs only (fatigue (23%), diarrhoea (15%), infusion reactions (14%) and rash (12%)). The other 2 trials reported 23% to 52% AEs.	283 (3 observational studies)	⊕⊕⊕⊕ Very low ^{a,b}
SAEs follow-up: range 16-23 months	2% of participants had infusion reactions and 1% pneumonitis (drug-related SAEs).	243 (1 observational study)	⊕⊕⊕⊕ Very low ^{a,b,d}

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AE: adverse event; **cHL:** classical Hodgkin's lymphoma; **CI:** confidence interval; **EORTC:** European Organisation for Research and Treatment of Cancer; **OS:** overall survival; **PFS:** progression-free survival; **QoL:** quality of life; **SAE:** serious adverse event.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aSince all included studies were uncontrolled studies, the certainty of the evidence for all outcomes started at "low" (2 points)

^bDifferent study populations with different previous therapeutic regimen and various follow-up times led to inconsistency (downgraded 1 point).

^cOnly a subset of participants was evaluated (cohort B, 80 participants, but only 44 filled out follow-up data) (downgraded by 1 point).

^dSmall number of events leads to imprecision (downgraded 1 point).

BACKGROUND

Description of the condition

Hodgkin's lymphoma (HL) is a cancer of the lymphatic system that involves the lymph nodes, spleen and other organs such as the liver, lung, bone or bone marrow, depending on the tumour stage (Lister 1989). The incidence of HL typically shows a bimodal age distribution with a first peak around the age of 30 years and a second peak after the age of 60 years. HL accounts for 10% to 15% of all lymphoma in industrialised countries, with an incidence of 2 to 3 per 100,000 inhabitants per year. It can therefore be regarded as a relatively rare disease, but is nevertheless one of the most common malignancies in young adults (Thomas 2002).

The disease usually develops in lymph nodes in the upper part of the body, mostly the latero-cervical lymph nodes, and results in painless swelling of the lymphatic tissue involved. Normally HL appears within these parts of the body, with peripheral extranodal involvement being rare. As a sign of large tumour size or spreading, 25% of people present with so-called B-symptoms, such as fever, drenching night sweats and a loss of more than 10% bodyweight (Connors 2009; Pileri 2002).

The World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues distinguishes between two types of HL: classic HL (cHL), which represents about 95% of all HL, and lymphocyte-predominant HL, which represents about 5% of all HL (Mathas 2016). The types differ in morphology, phenotype and molecular features, and therefore in clinical behaviour and presentation (Re 2005).

The Ann Arbor Classification is used for staging and distinguishes between four different tumour stages (Rosenberg 1971). Stages I to III indicate the degree of lymph node and localised extranodal organ involvement or both, and stage IV includes disseminated organ involvement, which can be found in 20% of cases. Factors associated with a poor prognosis include a large mediastinal mass, three or more involved lymph node areas, a high erythrocyte sedimentation rate, extranodal lesions, B-symptoms (weight loss greater than 10%, fever, drenching night sweats) and advanced age, but the factors considered clinically significant vary slightly between different study groups (German Hodgkin Study Group (GHSG), European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC)). HL is classified into early favourable, early unfavourable and advanced stage (Engert 2007). In Europe, the early favourable-stage group usually comprises Ann Arbor stages I and II without risk factors. The early unfavourable-stage group includes people with Ann Arbor stages I or II and one or more risk factors. Most people with stages IIB, III or IV disease are included in the advanced-stage risk group (Engert 2003).

With cure rates of up to 90%, HL is one of the most curable cancers worldwide (Engert 2010; Engert 2012; von Tresckow 2012). A combination of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) is widely accepted as the gold-standard chemotherapy regimen in people with HL (Canellos 1992; Engert 2010). People with limited-stage disease usually receive a combination of chemotherapy and involved-field radiation therapy (IF-RT) (Engert 2010; von Tresckow 2012), whereas those with advanced-stage disease usually receive an intensified regimen, such as BEACOPP (bleomycin, etoposide, doxorubicin,

cyclophosphamide, vincristine, procarbazine and prednisone) (Borchmann 2011; Engert 2012; Skoetz 2013) or ABVD. One large randomised trial showed that two cycles of ABVD followed by 20 Gy of IF-RT is sufficient for the treatment of early-favourable HL (Engert 2010). Two cycles of escalated BEACOPP (BEACOPPesc) followed by two cycles of ABVD can improve progression-free survival (PFS) in comparison to four cycles of ABVD in people with early-unfavourable HL (von Tresckow 2012).

Approximately 10% of people with HL will be refractory to initial treatment or will relapse; this is more common in people with advanced stage or bulky disease. Standard of care for these people is high-dose chemotherapy and autologous stem cell transplantation (ASCT), but only 55% of people treated with high-dose chemotherapy and ASCT have been shown to be free from treatment failure at three years, with survival rated of about 80% at three years (Rancea 2013). For people progressing after ASCT, brentuximab vedotin can improve PFS and is the preferred treatment (Younes 2012). Chen and colleagues reported an OS rate of 41% and PFS rate of 22% at five years in 102 participants who had failed haematopoietic ASCT and received brentuximab vedotin (Chen 2016). However, most participants eventually become refractory to brentuximab vedotin, with limited treatment options.

Description of the intervention

The European Medicines Agency (EMA) approved nivolumab for the treatment of people with relapsed/refractory cHL after ASCT and treatment with brentuximab vedotin in October 2016. The approval was based on an objective response rate (ORR) of 66% in a combined analysis of 95 participants with relapsed or refractory cHL who received nivolumab either in the phase II CheckMate-205 trial or the phase I CheckMate-039 trial (Ansell 2015; Younes 2016). The 12-month PFS was 54.6% and 12-month overall survival (OS) was 94.9% (Timmermann 2016).

The most common drug-related adverse events (AEs) include fatigue, infusion-related reaction, arthralgia and rash. The most common drug-related grade 3 or 4 AEs were neutropenia and increased lipase concentrations. The most common serious adverse events (SAEs) include fever and meningitis (4% or less each) (Timmermann 2016; Younes 2016).

Nivolumab is now also used in combination with other drugs to treat people with relapsed or refractory HL (Ansell 2016).

How the intervention might work

Checkpoint inhibitors that target the interaction of the programmed death (PD)-1 immune checkpoint receptor, and its ligands PD-L1 and PD-L2, have shown remarkable activity in a wide range of malignancies. Development started in solid tumours and is most advanced in malignant melanoma and lung cancer (Brahmer 2015; Hamid 2013). In cHL, malignant Hodgkin Reed-Sternberg (HRS) cells are dispersed within an extensive inflammatory/immune cell infiltrate (Küppers 2009; Mathas 2016). HRS cells frequently overexpress PD-L1 and PD-L2 due to alterations in chromosome 9p24.1 and HL tumours may thus be genetically susceptible to blockade of the PD-1 pathway (Green 2012; Roemer 2016). Nivolumab is an anti-(PD)-1 monoclonal antibody and currently approved by the US Food and Drug Administration (FDA) for the treatment of melanoma, non-small cell lung cancer, renal

cell carcinoma (Matsuki 2016), and, since 2016, cHL after treatment with ASCT and brentuximab vedotin.

Why it is important to do this review

To our knowledge, no systematic review on the effectiveness of nivolumab in people with HL has been performed. As nivolumab is now approved by the EMA and the FDA based on non-randomised data, we critically appraised all published trials and conducted this rapid review on nivolumab. If we identify controlled clinical trials in a future update, we will meta-analyse these data, which will lead to a more precise and reliable evaluation of the benefits and harms of nivolumab. In this way, we aim to overcome the limitations of individual studies, such as small sample sizes and a lack of statistical power.

For this review, we used the software RobotReviewer to extract study data (Marshall 2016; RobotReviewer 2015). For review updates including randomised controlled trials (RCT), we will use this software also to assess risk of bias. As this software has not been validated, one review author will extract all these data manually and a second review author will compare the results from the software tool and the first review author. We will resolve any discrepancies between the software results and the manually extracted data by discussion between review authors.

OBJECTIVES

To assess the benefits and harms of nivolumab in adults with HL (irrespective of stage of disease).

METHODS

Criteria for considering studies for this review

Types of studies

We searched for RCTs. As we did not identify any RCTs or quasi-RCTs (e.g. assignment to treatment by alternation or by date of birth) or cross-over trials, we included published reports of prospectively planned studies.

We included both full-text and abstract publications if sufficient information was available on study design, characteristics of participants, interventions and outcomes.

Types of participants

We included studies that evaluated adults of 18 years or more with a confirmed diagnosis of HL, with no gender or ethnicity restrictions. We considered people with all subtypes and stages of HL, undergoing first-line treatment, or having relapsed, or being refractory to previous treatment attempts. In trials that included mixed populations of participants with haematological malignancies, we would have included data from participants with HL; however, we did not identify such a trial. We excluded trials in which less than 80% of participants had HL, unless the trial authors provided the subgroup data for these participants in the publication or after we contacted the trial authors.

Types of interventions

The experimental intervention was nivolumab (with or without other drugs). If we identify RCTs in future updates of this review, the comparison of interest will be nivolumab (with or without other drugs) versus control treatment. We will conduct separate analyses

for trials that evaluate nivolumab and nivolumab combined with other drugs.

Types of outcome measures

Primary outcomes

- Overall survival (OS).
- Quality of life (QoL), if measured using reliable and valid instruments.

Secondary outcomes

- Progression-free survival (PFS):
 - * time interval from random treatment assignment onto the study to first confirmed progression, relapse or death from any cause, or to the last follow-up.
- Response rate:
 - * measured as overall response, complete response and partial response according to Cheson and colleagues (Cheson 2014).
- Treatment-related mortality (TRM).
- Overall rate of grade 3 and grade 4 adverse events (AEs), including potential relationship between intervention and adverse reactions.
- Overall rate of serious adverse events (SAEs).

Search methods for identification of studies

We adapted search strategies from the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We searched for studies in all languages to limit language bias.

Electronic searches

We searched the following databases and sources and started the search in 2000 as PD-L1 blockade for tumour control, the underlying mechanism of nivolumab, was first mentioned in 2002 (Iwai 2002).

- Databases of medical literature:
 - * Cochrane Central Register of Controlled Trials (CENTRAL; 2018 Issue 5) (Appendix 1);
 - * MEDLINE (Ovid) (2000 to 13 April 2018) (Appendix 2);
 - * Embase (2000 to October 2017) (Appendix 3);
 - * International Pharmaceutical Abstracts (2000 to October 2017) (Appendix 4).
- Conference proceedings of the annual meetings of the following societies for abstracts (2000 to May 2018, if not included in CENTRAL):
 - * American Society of Hematology;
 - * American Society of Clinical Oncology;
 - * European Hematology Association;
 - * International Symposium on Hodgkin Lymphoma.
- Databases of ongoing trials:
 - * ISRCTN: www.isrctn.com;
 - * EU clinical trials register: www.clinicaltrialsregister.eu/ctr-search/search (Appendix 5);
 - * ClinicalTrials.gov: clinicaltrials.gov/ (Appendix 6);
 - * WHO International Clinical Trials Registry Platform (ICTRP): apps.who.int/trialsearch/AdvSearch.aspx (Appendix 7);
 - * EORTC: www.eortc.be;
 - * GHSG: www.ghsg.org.

- Databases and websites of relevant institutions, such as pharmaceutical organisations, agencies and societies.

Searching other resources

- Handsearching:
 - * we checked the reference lists of all identified trials, relevant review articles and current treatment guidelines for further literature.
- Personal contacts:
 - * we contacted experts in the field, drug manufacturers and regulatory agencies to retrieve information on unpublished trials.

Data collection and analysis

Selection of studies

Two review authors independently screened the results of the search strategies for eligibility for this review by reading the abstracts using Covidence software (Covidence 2016). We coded the abstracts as either 'retrieve' or 'do not retrieve.' In the case of disagreement or if it was unclear whether we should retrieve the abstract or not, we obtained the full-text publication for further discussion. Two review authors assessed the full-text articles of selected studies. If the two review authors were unable to reach a consensus, we consulted a third review author to reach final decision (Higgins 2011a).

We documented the study selection process in a flow chart, as recommended in the PRISMA statement (Moher 2009), and showed the total numbers of retrieved references and the numbers of included and excluded studies. We listed all articles we excluded after full-text assessment and their reasons for exclusion in the [Characteristics of excluded studies](#) table.

Data extraction and management

We planned that one review author extracted data on the characteristics of included studies and a second review author compared them with the results from the software RobotReviewer (Marshall 2016; RobotReviewer 2015). However, as we identified no eligible RCTs and the software is currently designed to extract RCTs, two review authors (MG and NS) additionally extracted data independently. The two review authors resolved any discrepancies by discussion; had they not reached consensus, they planned to consult a third review author, but this was not necessary. If required, they would have contacted the authors of specific studies for supplementary information (Higgins 2011b).

We extracted the following information.

- General information: author, title, source, publication date, country, language, duplicate publications.
- Quality assessment (as specified in the [Assessment of risk of bias in included studies](#) section).
- Study characteristics: trial design, aims, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, subgroup analysis, statistical methods, power calculations, treatment cross-overs, compliance with assigned treatment, length of follow-up.
- Participant characteristics: age, gender, ethnicity, number of participants recruited/allocated/evaluated, participants lost to follow-up, additional diagnoses, stage of disease, previous

treatment (type of (multi-agent) chemotherapy (intensity of regimen, number of cycles), field and dose of radiotherapy, ASCT, brentuximab vedotin dosage and duration).

- Interventions: nivolumab dosage, duration of treatment, duration of follow-up, for RCTs: comparator (type, dosage).
- Outcomes: OS, QoL, PFS, response rate, TRM, AEs (including assessment of causality, how it was determined, relation between intervention and adverse drug reaction, method of AEs ascertainment (passive or active methods), method of measurement, how severity or seriousness was measured).

Assessment of risk of bias in included studies

Randomised controlled trials

If we identify RCTs for future updates, we will assess risk of bias with the Cochrane 'Risk of bias' tool for each RCT. Thereafter, we will use the RobotReviewer software to assess risk of bias (RobotReviewer 2015), and a second review author will compare these results with the results from the first review author. See [Differences between protocol and review](#) for a more detailed description of the 'Risk of bias' assessment we will undertake if we identify eligible RCTs in future updates.

Non-randomised prospectively planned trials (including control arm)

As reported in the [Types of studies](#) section, we would have included non-randomised studies with a control arm only if we did not identify any RCTs. However, we did not identify any non-randomised prospectively planned study with a control arm. If we identify non-randomised studies with a control arm in review updates, we will independently assess eligible studies for methodological quality and risk of bias (using the Risk Of Bias in Non-randomised Studies - of Interventions (ROBIN-I) tool) (Sterne 2016).

Uncontrolled studies

As reported in the [Types of studies](#) section, we included non-randomised studies without a control arm only as we did not identify any RCTs.

Two review authors independently assessed eligible studies for methodological quality and risk of bias (using the "risk of bias assessment criteria for observational studies" tool provided by the Childhood Cancer Group (see [Table 1](#)). The quality assessment strongly depends upon information on the design, conduct and analysis of the trial. The two review authors resolved any disagreements regarding the quality assessments by discussion, in case they would not have reached a consensus they would have consulted a third review author until final consensus.

We assessed the following domains of bias.

- Internal validity.
 - Representative study group (selection bias).
 - Complete outcome assessment/follow-up (attrition bias).
 - Outcome assessors blinded to investigated determinant (detection bias).
 - Important prognostic factors or follow-up taken adequately into account (confounding).
- External validity.

- Well-defined study group (reporting bias).
- Well-defined follow-up (reporting bias).
- Well-defined outcome (reporting bias).
- Well-defined risk estimates (analyses).

For every criterion, we made a judgement using one of three response options.

- High risk of bias.
- Low risk of bias.
- Unclear risk of bias.

Measures of treatment effect

We estimated the dichotomous outcomes of individual studies as rates by extracting the number of events and the total number of participants (overall and complete response rate, TRM, AEs).

We estimated survival data (OS, PFS) using Kaplan–Meier methods.

We measured continuous outcomes (e.g. QoL) as mean differences (MD).

In case we identify eligible RCTs in updates of this review, we will extract and report effect measures in accordance with the procedures outlines in the [Differences between protocol and review](#) section.

Unit of analysis issues

Studies with multiple treatment groups

We did not identify any eligible studies with multiple treatment groups. We described how we will proceed with such studies in review updates in the [Differences between protocol and review](#) section.

Dealing with missing data

Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* suggests a number of potential sources for missing data ([Higgins 2011a](#)), which we needed to take into account at study level, at outcome level and at summary data level. In the first instance, it is of the utmost importance to differentiate between data 'missing at random' and 'not missing at random.'

If data have been missing, we would have requested these data from the original investigators. If, after this, data were still missing, we would have to make explicit assumptions of any methods the included studies used: for example, we would have assumed that the data were missing at random or we would have assumed that missing values had a particular value, such as a poor outcome.

Assessment of heterogeneity

If we find sufficient data for meta-analysis in updates of this review, we will assess potential heterogeneity as described in [Appendix 8](#).

Assessment of reporting biases

In updates of this review where a meta-analysis is feasible, we will assess potential reporting biases in accordance with the methods described in [Appendix 8](#).

Data synthesis

We did not meta-analyse data from the included uncontrolled trials, as there might be no additional benefit in meta-analysing data without a control group. We reported results of each included trial. As data did not allow quantitative assessment, we presented outcome data individually per study (see [Characteristics of included studies](#) table). In further updates of this review we will meta-analyse data in accordance with the procedure described in [Appendix 8](#).

'Summary of findings' table

We used the GRADE approach to assess the quality of the evidence. We used GRADEpro Guideline Development Tool (GDT) software to create a 'Summary of findings' table ([GRADEpro GDT 2014](#)), as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schünemann 2011](#)). In addition, we provided an interactive 'Summary of findings' table for a better user-experience and for improved dissemination of the findings of this Cochrane Review ([Schünemann 2016](#)). We avoided use of lengthy text in the results and discussion section.

We prioritised outcomes according to their relevance to people with HL.

- OS.
- QoL.
- PFS.
- Response rates.
- TRM.
- AEs.
- SAEs.

Since all included studies were uncontrolled studies, the certainty of the evidence for all outcomes started at "low certainty" (2 points)

Subgroup analysis and investigation of heterogeneity

For future updates including meta-analyses, we will perform subgroup analyses following the procedure described in [Appendix 8](#).

Sensitivity analysis

For future updates including meta-analyses, we will perform sensitivity analyses according to the methods described in [Appendix 8](#).

RESULTS

Description of studies

Results of the search

We identified 782 potentially relevant references. At the initial screening stage, we excluded 107 duplicates and 626 reference due to a lack of conformity with the inclusion criteria. We further evaluated the remaining 49 publications either as full-text publications or, if not available, as abstract publications or study registry entry. This led to exclusion of five further trials. In addition, we identified 14 ongoing trials (18 references), which will be completed by 2021, two studies (five references) studies already reported interim results for some of the included participants ([NCT01896999](#); [NCT02572167](#)). Only two of these ongoing trials

are RCTs ([NCT03004833](#); [NCT03138499](#)). We finally included three studies (26 references) in this systematic review.

We reported the overall numbers of references screened, identified, selected, excluded and included in a PRISMA flow diagram (see [Figure 1](#)).

Figure 1. Study flow diagram.

Results of the application of RobotReviewer

Although our search did not identify any eligible RCTs, we uploaded available full-texts of the three included studies into the software RobotReviewer. The software recognised correctly that one study was not an RCT and therefore did not extract any data of this study. However, the two remaining studies were falsely labelled to be RCTs. The extraction results on both studies could not be used in the further review process. Yet some characteristics of included trials were given sufficiently. This is especially concerning the data regarding included participants and study interventions. We did not consider the 'Risk of bias' function of the software, since it was based on the criteria of the Cochrane 'Risk of bias' tool for RCTs only.

Included studies

For detailed description of the studies see the [Characteristics of included studies](#) table. Here we provided a brief overview.

Three prospectively planned, uncontrolled trials evaluated the effect and safety of nivolumab in people with HL (283 participants) ([CheckMate 039](#); [CheckMate 205](#); [Hatake 2016](#)). All of these trials included heavily pretreated participants and were published as full-texts.

Design

[CheckMate 039](#) was a phase I trial, [CheckMate 205](#) and [Hatake 2016](#) were phase II trials. Follow-up ranged between 12 months and 23 months.

Sample sizes

The smallest trial involved 17 people with HL ([Hatake 2016](#)), [CheckMate 039](#) involved 23 participants and [CheckMate 205](#) involved 243 participants.

Location

[Hatake 2016](#) was conducted in Japan and the other two trials were in several countries in US, Europe and Canada.

Participants

All trials included adults with at least one prior chemotherapy regimen.

[CheckMate 039](#) evaluated participants with relapsed or refractory HL with at least one prior chemotherapy regimen. The mean age was 35 years.

[CheckMate 205](#) included adults after failure of ASCT. It had three cohorts: cohort A had 63 people with cHL after failure of ASCT, cohort B had 80 people with cHL after failure of ASCT who received subsequent brentuximab vedotin and cohort C had 100 people with cHL after failure of ASCT who had previous or subsequent brentuximab vedotin treatment (or both). The mean age was 34 years.

[Hatake 2016](#) evaluated participants with history of treatment with ASCT, people to whom ASCT was not indicated or who refused to receive treatment with ASCT. The mean age was 63 years.

Interventions

[CheckMate 039](#): consisted of a dose escalation cohort and an expansion cohort. The dose escalation cohort (phase I trial)

received nivolumab 1 mg/kg bodyweight with escalation to 3 mg/kg. With 3 mg/kg as the final dose, the maximum tolerated dose leading to dose-limiting toxicities was not reached in this phase I trial with a preset fixed-dose escalation plan. The expansion cohort received nivolumab 3 mg/kg at week one, week four, and then every two weeks until disease progression or complete response for a maximum of two years.

[CheckMate 205](#): participants received nivolumab 3 mg/kg intravenously over 60 minutes every two weeks until disease progression, death, unacceptable toxicity, withdrawal of consent or study end (five years or more of follow-up).

[Hatake 2016](#): participants received nivolumab 3 mg/kg on day one of the treatment phase; subsequent doses were administered on day one of each 14-day cycle. Nivolumab was continued if treatment continuation criteria were met; trial was to continue until all participants discontinued treatment in the event of progressive disease, an unacceptable AE or other clinically relevant reasons, so trial participants are still under investigation.

Outcomes

The primary outcomes were:

- proportion of participants achieving an objective response;
- overall response rate;
- safety.

The secondary outcomes were:

- duration of response outcomes;
- proportion of participants who achieved response;
- PFS;
- OS;
- safety and tolerability;
- QoL;
- safety endpoints;

Conflicts of interest

Bristol-Myers Squibb funded the [CheckMate 039](#) and [CheckMate 205](#) trials and Ono Pharmaceutical Co., Ltd. funded [Hatake 2016](#), which are the pharmaceutical companies producing nivolumab.

Excluded studies

After screening of titles/abstracts we excluded 561 records that did not match our inclusion criteria. We evaluated five study reports in more detail, which were finally excluded: three trials were not prospectively planned, one study evaluated people with non-HL only and one report was a case report (see [Characteristics of excluded studies](#) table).

Risk of bias in included studies

Overall, we considered potential risk of bias as high, due to the non-randomised study design, the unblinded outcome assessment and the absence of a control group. For further information, see the 'Risk of bias' sections in the [Characteristics of included studies](#) table and [Figure 2](#) ('Risk of bias' summary figure presenting all our judgements in a cross-tabulation).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Representative study group (selection bias)	Complete outcome assessment/follow-up (attrition bias)	Outcome assessors blinded to investigated determinant (detection bias)	Important prognostic factors or follow-up taken adequately into account (confounding)	Well-defined study group (reporting bias)	Well-defined follow-up (reporting bias)	Well-defined outcome (reporting bias)	Well-defined risk estimates (analyses)
CheckMate 039	?	+	?	-	-	+	+	+
CheckMate 205	?	+	-	-	-	+	+	+
Hatake 2016	?	+	-	-	-	+	+	+

Internal validity

Representative study group (selection bias)

All trials were non-randomised with no control arm. As selection bias was not assessable in this type of trial, we judged risk of selection bias as unclear. However, recurrent cHL was an inclusion criterion in all included studies.

Complete outcome assessment/follow-up (attrition bias)

We judged the risk of attrition bias to be low because the analyses reported results for all included participants.

For QoL, given for a subset of participants (cohort B) in [CheckMate 205](#), follow-up data for only 44/80 participants were available. Therefore, we judged the risk of bias for QoL to be high.

Outcome assessors blinded to investigated determinant (detection bias)

Two trials did not blind outcome assessors ([CheckMate 205](#); [Hatake 2016](#)) (potential high risk of bias) and one study had unclear blinding ([CheckMate 039](#)). For OS, lack of blinding was not an issue, therefore we judged risk of bias for OS as low.

Important prognostic factors or follow-up taken adequately into account (confounding)

All included trials reported previous treatments with ASCT and BV. [CheckMate 039](#) and [CheckMate 205](#) separately reported clinical activity results for participants in whom previous ASCT and BV failed, participants in whom BV failed who did not undergo ASCT and participants who did not receive ASCT. However, no multi-variable analyses taking into account important prognostic factors like pretreatments, participant age or the length of follow-up were reported. Therefore, we judged the risk of bias due to confounding to be high.

External validity

We considered the risk of reporting bias as high related to the criterion well-defined study groups, as all trials included heterogenous participant populations and they did not report doses for the received pretreatments.

Follow-up data, outcome reporting and the methods used for risk-estimation were well-defined, therefore we judged these criteria for all trials as low risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison Nivolumab compared to no other intervention for adults with Hodgkin's lymphomas](#)

Primary outcome: overall survival

Two studies evaluated OS. [CheckMate 205](#) reported that median OS was not reached after a median follow-up of 18 months (interquartile range (IQR) 15 to 22 months) for the overall study population, meaning that more than 50% of participants are still alive. The one-year OS was 92% (95% confidence interval (CI) 88% to 95%) for the overall study population; 93% (95% CI 82% to 98%) for cohort A (63 participants with cHL after failure of ASCT); 95% (95% CI 87% to 98%) for cohort B (80 participants with cHL after failure of ASCT and subsequent brentuximab vedotin treatment);

and 90% (95% CI 82% to 94%) for cohort C (100 participants with cHL after failure of ASCT, and previous or subsequent (or both) brentuximab vedotin treatment). [Hatake 2016](#) reported 100% OS after six months.

Overall survival in participants not treated with nivolumab

[Broeckelmann 2017](#) was a retrospective analysis of people with third or higher relapsed/refractory cHL, [CheckMate 205](#) had a median number of previous chemotherapy regimens of four and [Hatake 2016](#) had a median number of previous chemotherapy regimens of three. OS was 73.2% (95% CI 62.6 to 83.8) at 12 months for all participants. In [Broeckelmann 2017](#), participants with third relapse who underwent previous ASCT had an OS of 69.4% (95% CI 56.5% to 82.3%) at 12 months. The OS of participants who had a third relapse who did not receive ASCT was 62.5% (95% CI 29.0% to 96.0%) at 12 months. The OS at six months for both groups was 89.6% (95% CI 82.4% to 96.9%), in contrast to 100% in [Hatake 2016](#).

Primary outcome: quality of life

Only one of the three cohorts of [CheckMate 205](#) (cohort B, 80 participants with cHL after failure of ASCT and subsequent brentuximab vedotin treatment) reported QoL using the EQ-5D visual analogue scale (developed by the EuroQol Group; [Brooks 1996](#)), and the EORTC QLQ-C30 (developed by EORTC to measure QoL; [Aaronson 1993](#)). The scores increased over time with nivolumab treatment, indicating improved QoL (EQ-5D: from 62 (standard deviation (SD) 30) at baseline (72 (90%) participants) to 80 (SD 18) at week 33 (44 (55%) participants); EORTC QLQ-C30 suggested improvement from baseline across functional, symptom and global health scores). However, at week 33 only a subset of the included participants filled out the instruments.

Secondary outcome: progression-free survival

All trials reported PFS. [CheckMate 039](#) published an investigator-assessed PFS at six months of 86% (95% CI 62% to 95%). The overall PFS in [CheckMate 205](#) was 14.7 (95% CI 11.3 to 18.5). The study also reported data for the three cohorts (A: 63 participants with cHL after failure of ASCT, B: 80 participants with cHL after failure of ASCT and subsequent brentuximab vedotin treatment, C: 100 participants with cHL after failure of ASCT, and previous or subsequent (or both) brentuximab vedotin treatment). The median PFS was 18.3 months (95% CI 11.1 to 22.4) for cohort A, 14.7 months (95% CI 10.5 to 19.6) for cohort B and 11.9 months (95% CI 11.1 to 18.4) for cohort C.

[Hatake 2016](#) presented a centrally assessed PFS at six months of 60% (95% CI 31.8% to 79.7%).

Progression-free survival in participants not treated with nivolumab

The retrospective analysis of participants with third or higher relapse of cHL showed a six-month PFS of 76.3% (95% CI 66.1% to 86.4%) for all included participants ([Broeckelmann 2017](#)). The PFS at 12 months' follow-up was 50.8% (95% CI 38.9% to 62.8%). The 12-month PFS for participants with a third relapse and previous ASCT was 44.9% (95% CI 31.0% to 58.8%) and for participants with third relapse and without ASCT was 50.0% (95% CI 15.4% to 84.6%).

Secondary outcome: response rate

[CheckMate 039](#) reported a complete response rate of 17% and a partial response rate of 70% at median follow-up of 86 weeks (range 32 to 107 weeks).

In [CheckMate 205](#), the median duration of response overall was 16.6 months (95% CI 13.2 to 20.3). For cohorts A it was 20.3 months, for cohort B it was 15.9 months and for cohort C it was 14.5 months. Overall, the complete response rate was 16%, while 29% of participants received complete response in cohort A, 13% in cohort B and 12% in cohort C. There was a partial response in 53% of participants overall and 37% of participants in cohort A, 55% of participants in cohort B and 61% of participants in cohort C.

[Hatake 2016](#) reported for a centrally assessed response (one participant ineligible) a complete response rate of 25% and a partial response of 56.3% at a median follow-up of 9.8 months (range 6 to 11 months).

Secondary outcome: treatment-related mortality

None of the trials reported TRM.

Secondary outcome: overall rate of grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction

[CheckMate 039](#) reported at a median follow-up of 86 weeks (range 32 to 107 weeks) 52% of grade 3 or 4 AEs.

[CheckMate 205](#) reported drug-related AEs only after a median follow-up of 18 months (IQR 15 to 22 months). The most common drug-related AEs were fatigue (23%), diarrhoea (15%), infusion reactions (14%) and rash (12%). The most common grade 3 to grade 4 drug-related AEs for this follow-up timeframe were lipase increases (5%), neutropenia (3%) and alanine transaminase increases (3%).

[Hatake 2016](#) presented data at a median follow-up of 9.8 months (range 6 to 11 months). Four of 17 (23.5%) participants developed grade 3 or 4 AEs.

Secondary outcome: overall rate of serious adverse events

[CheckMate 205](#) reported only drug-related SAEs. About 2% of participants had infusion reactions and 1% had pneumonitis.

Adverse events in participants not treated with nivolumab

Due to data deviations, the results of the studies included in this review could not be reasonably compared with those of the retrospective analysis ([Broeckelmann 2017](#)).

DISCUSSION

Summary of main results

Although our search did not identify any eligible RCTs, we uploaded available full-texts of the three included studies into the software RobotReviewer. The software recognised correctly that one study was not an RCT and, therefore, did not extract any data of this study. However, the two remaining studies were falsely labelled to be RCTs and characteristics of included study were extracted, in a sufficient way for types of participants and types of interventions.

The following clinical findings emerged from this Cochrane Review in participants with heavily pretreated HL, for whom currently only three non-randomised, uncontrolled trials were published (283 individuals).

- Median OS was not reached (the time point when only 50% of participants were alive) in one study after 12 months of follow-up and was 100% in another trial after six months of follow-up.
- Based on the currently available research, we were unable to draw any conclusions with regard to QoL as there were insufficient data available.
- PFS was between 60% and 86% at six months, median PFS between 11.9 and 18.3 months, depending on participant population and previous treatments.
- Complete response rates ranged from 12% to 29%, depending on inclusion criteria and participant characteristics.
- None of the trials reported TRM.
- Only one trial reported SAEs, with a low number of participants experiencing SAEs. Depending on follow-up time, between 23% and 52% of participants developed grade 3 or 4 AEs. Most common were fatigue, diarrhoea, infusion reactions and rash.

When interpreting these results, it is important to consider that RCTs are needed to confirm these findings.

Overall completeness and applicability of evidence

We found three published non-randomised, uncontrolled trials evaluating nivolumab in adults with relapsed HL of whom most had received intensive therapies such as ASCT before. These trials included 283 participants who had received different therapeutic regimens before entering the trials. Therefore, the participant population might have been too small and heterogenous to generalise results. Currently, 14 trials are ongoing, of which two studies are designed as RCTs (one for participants receiving first-line treatment, one for participants with relapsed HL) ([NCT01822509](#); [NCT01896999](#); [NCT02408861](#); [NCT02572167](#); [NCT02758717](#); [NCT02927769](#); [NCT02940301](#); [NCT02973113](#); [NCT03004833](#); [NCT03016871](#); [NCT03033914](#); [NCT03057795](#); [NCT03138499](#); [NCT03161613](#)). The publication of the results of these studies will necessitate an update of this review. The conclusions of this updated review could differ from those of the present review, and may allow a better judgement about the efficacy and safety of nivolumab.

One of the primary outcomes of this review was OS, due to its clinical relevance and its importance for participants. Moreover, it is a commonly accepted measure of the benefit of cancer treatment, as well as an endpoint that is not subject to bias by the evaluator. Two studies reported that median survival was not reached after six months (100% of participants were alive) or 12 months of follow-up. Two of the three cohorts of one study reported survival rates over 94%. However, data were not reported for the third cohort within this trial.

The other primary outcome of this review, QoL, is of utmost importance for patients, especially those with several pretreatments. One of three cohorts from one study reported QoL but follow-up data were lacking, therefore an overall assessment was not possible. Detailed data for all three study cohorts might help to assess QoL sufficiently.

Quality of the evidence

All three trials were prospectively planned, non-randomised and uncontrolled trials leading to potential high risk of bias. Currently, there is no standard instrument available to assess risk of bias for this type of trials. We used the form developed by the Cochrane Childhood Cancer Group.

As we included three small observational trials only (altogether fewer than 300 participants), the certainty of evidence was low to very low for most of the outcomes (see [interactive Summary of Findings table](#) and Summary of findings table 1).

Potential biases in the review process

We tried to avoid bias by dually carrying out all relevant processes (searching, data collection, analysis). We performed a sensitive search strategy and searched all relevant data of international HL conferences and study registries to detect potential publication bias. In addition, two authors of this review (AE, BvT) are very experienced in clinical studies on HL (AE is the head of the GHSG). Therefore, we are confident that we have identified all studies relevant to the review question. We are not aware of any obvious flaws in our review process.

Agreements and disagreements with other studies or reviews

To our knowledge this is the first comprehensive systematic review focusing on nivolumab for adults with HL.

AUTHORS' CONCLUSIONS

Implications for practice

To date, data on overall survival, quality of life, progression-free survival, response rate, or short- and long-term adverse events are available from small non-randomised, uncontrolled

trials only. The three trials included heavily pretreated participants, which had previously undergone regimens of BV or ASCT. For these participants, median overall survival was not reached after follow-up times of up to 16 to 23 months, depending on pretreatment, meaning that more than 50% of these heavily pretreated participants with a limited life expectancy were alive at 16 to 23 months. Complete response rates ranged between 12% and 29%. Quality of life data were reported for one cohort out of three only, with limited follow-up data so that meaningful conclusions are not possible. Serious adverse events occurred rarely.

Currently, data are too sparse to make a clear statement on nivolumab for people with relapsed or refractory Hodgkin's lymphoma except for heavily pretreated people, which had previously undergone regimens of BV or ASCT. When interpreting these results, it is important to consider that well-designed randomised controlled trials should confirm these findings.

Implications for research

Randomised controlled trials or at least non-randomised trials with a control group are needed to confirm findings of this review. As there are 14 ongoing trials evaluating nivolumab, of which two are randomised, it is possible that an update of this review will be published in the near future. It might well be that this update will show different results than those published in this systematic review.

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NCT02572167 {published and unpublished data}

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NCT02927769 {published data only}

A phase I study of ipilimumab and nivolumab in advanced HIV-associated solid tumours with expansion cohorts in HIV-associated solid tumours and a cohort of HIV-associated classical Hodgkin's lymphoma. Ongoing study 27 August 2015; estimated primary completion date: 31 December 2020.

NCT02940301 {published data only}

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NCT02973113 {published data only}

Nivolumab with Epstein Barr virus specific T cells (EB-VSTS), relapsed/refractory EBV positive lymphoma (PREVALE). Ongoing study 16 February 2016; estimated primary completion date: 16 April 2019 (final data collection date for primary outcome).

NCT03004833 {published data only}

Nivolumab and AVD in early-stage unfavourable classical Hodgkin lymphoma (NIVAHL). Ongoing study 21 February 2017; estimated primary completion date: December 2018 (final data collection date for primary outcome).

NCT03016871 {published data only}

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NCT03033914 {published data only}

(B)VD followed by nivolumab as frontline therapy for higher risk patients with classical Hodgkin lymphoma. Ongoing study 25 January 2017; estimated primary completion date: January 2020 (final data collection date for primary outcome).

NCT03057795 {published data only}

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NCT03138499 {published data only}

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primary completion date: 29 November 2020 (final data collection date for primary outcome).

NCT03161613 {published data only}

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

CheckMate 039

Methods	Phase I study consisting of dose escalation and expansion cohorts
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> Adults aged ≥ 18 years with cHL Histologically confirmed evidence of relapsed or refractory HL with ≥ 1 lesion > 1.5 cm (defined by the Revised Response Criteria for Malignant Lymphomas) ECOG performance-status score 0 or 1 Previous treatment with ≥ 1 chemotherapy regimen No ASCT within the last 100 days <p><u>Nivolumab cohort:</u></p> <p>Participants recruited: 23</p> <p>Mean age: 35 years (range 20 to 54)</p> <p>Gender: 12 (52%) men, 11 women</p> <p>Stage of disease:</p> <ul style="list-style-type: none"> 17 participants (74%) with ECOG status 1 Histological findings: nodular sclerosis: 22 (96%) participants; mixed cellularity 1 participant (4%) Extranodal involvement: 4 (17%) participants <p>Extent of pretreatment (number of previous systemic therapies):</p> <ul style="list-style-type: none"> 2 or 3: 8 (35%) participants 4 or 5: 7 (30%) participants ≥ 6: 8 (35%) participants

CheckMate 039 (Continued)

Interventions	<p><i>Dose escalation cohort:</i> nivolumab 1mg/kg bodyweight with escalation to 3 mg/kg. Max tolerated dose not reached.</p> <p><u>Nivolumab cohort:</u></p> <p><i>Expansion cohort:</i> nivolumab 3 mg/kg at week 1, week 4 and then every 2 weeks until disease progression or CR for a max of 2 years</p>	
Outcomes	<p>Primary outcomes:</p> <ul style="list-style-type: none">• Safety• AE profile <p>Secondary outcomes:</p> <ul style="list-style-type: none">• Efficacy• Assessment of PD-1 ligand loci integrity• Expression of encoded ligands <p>Assessment:</p> <ul style="list-style-type: none">• AEs assessed throughout the study and for 100 days after the last dose• Participants evaluated for efficacy at weeks 4, 8, 18, 24 and every 16 weeks thereafter• All participants underwent CT and FDG-PET at screening and for confirmation of a CR <p>Results:</p> <ul style="list-style-type: none">• At median follow-up: 86 weeks (range 32 to 107 weeks)• Response:<ul style="list-style-type: none">* ORR: 20 participants (87%; 95% CI 66 to 97)* CR: 4 participants (17%)* PR: 16 participants (70%)* SD: 3 participants (13%)• Investigator-assessed PFS:<ul style="list-style-type: none">* At 24 weeks: 86% (95% CI 62% to 95%)• AEs<ul style="list-style-type: none">* Any grade: 22 participants (96%)* Grade 3 or 4: 12 participants (52%)	
Notes	<p>Supported by: Bristol-Myers Squibb</p> <p>Several authors declared financial conflicts of interest, including the first and the last author.</p> <p>The original study also included people with non-Hodgkin's B- and T-cell lymphoma, as well as multiple myeloma and follicular B-cell lymphoma. The data and study results for participants with cHL were reported separately and could therefore be included in this review.</p> <p>Study also included a cohort evaluating nivolumab plus ipilimumab; this cohort included less than 80% of people with HL and no disease-specific results were reported for this cohort. Therefore, we excluded this cohort.</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Unclear risk	Histologically confirmed evidence of relapsed or refractory HL as inclusion criterion

CheckMate 039 (Continued)

Complete outcome assessment/follow-up (attrition bias)	Low risk	Quote: "All the patients who received at least one dose of nivolumab were included in the safety and efficacy analyses."
Outcome assessors blinded to investigated determinant (detection bias)	Unclear risk	Blinding NR
Important prognostic factors or follow-up taken adequately into account (confounding)	High risk	<p>Clinical activity results separately reported for:</p> <ul style="list-style-type: none"> • participants in whom previous ASCT and BV failed • participants in whom BV failed but who did not undergo ASCT before BV treatment • participants who did not receive BV <p>Follow-up not taken into account</p> <p>No multi-variable analysis reported</p>
Well-defined study group (reporting bias)	High risk	Doses of prior treatments NR
Well-defined follow-up (reporting bias)	Low risk	Quote: "The median duration of follow-up was 40 weeks (range, 0 to 75)"
Well-defined outcome (reporting bias)	Low risk	<p>All outcomes reported</p> <p>Outcomes well-defined in appendix</p>
Well-defined risk estimates (analyses)	Low risk	Use of Kaplan-Meier methods described for time-to-event outcomes

CheckMate 205

Methods	<p>Multi-centre, non-comparative multi-cohort, single-arm phase II study</p> <p>Cohorts:</p> <ul style="list-style-type: none"> • A: participants with cHL after failure of ASCT • B: participants with cHL after failure of ASCT and subsequent BV treatment • C: participants with cHL after failure of ASCT, and previous or subsequent BV (or both) treatment
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> • Aged ≥ 18 years • ECOG performance status 0 or 1 • Documented failure to achieve at least partial remission after the most recent treatment, or documented relapse (after CR), or disease progression (after PR or stable disease) <p><u>In total:</u></p> <ul style="list-style-type: none"> • Participants recruited: <ul style="list-style-type: none"> * cohort A: 63 participants * cohort B: 80 participants * cohort C: 100 participants (33 BV before ASCT; 58 BV after ASCT; 9 BV before and after ASCT) • Median age: 34 years (range 18 to 72)

CheckMate 205 (Continued)

- Stage of disease:
 - * advanced disease (stage III+) disease at study entry: 77% of participants

Cohort A:

- 63 participants
- Median age: 33 years (range 18 to 65)
- Previous lines of therapy: median: 2 (range 2 to 8)

Cohort B:

- 80 participants
- Median; overall: 37 years (range 18 to 72; IQR: 28 to 48)
 - * aged < 30 years: 27 (34%) participants
 - * aged 30-44 years: 28 (35%) participants
 - * aged 45-59 years: 18 (23%) participants
 - * aged ≥ 60 years: 7 (9%) participants
- Gender: 51 (64%) men
- Stage of disease
 - * ECOG performance status 1: 38 (48%) participants
 - * At study entry: stage I: 1 (1%) participant; stage II: 11 (14%) participants; stage III: 14 (18%) participants; stage IV: 54 (68%) participants
- Previous lines of therapy
 - * Median: 4 (range 3 to 15; IQR 4 to 7)
- Regions
 - * Europe, Canada, US

Cohort C:

- 100 participants
- Median age: 32 years (range 19 to 69 years)
- Previous lines of therapy
 - * Median: 4 (IQR 2 to 9)

Interventions	Participants received nivolumab 3 mg/kg IV over 60 minutes at every 2 weeks until disease progression, death, unacceptable toxicity, withdrawal of consent or study end (≥ 5 years of follow-up)
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> • Proportion of participants achieving an objective response (defined as % of treated participants with the best OR of CR or PR) (IRRC assessed) • Primary analysis was done when minimum follow-up of 6 months was met. <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Duration of objective response (IRRC assessed) • Proportion of participants who achieved CR or PR • Duration of CR and PR • OR (investigator assessed) • Duration of OR (investigator assessed) <p>Exploratory endpoints</p> <ul style="list-style-type: none"> • PFS (IRRC assessed) • OS • Safety and tolerability • QoL • 9p24.1 alterations • PD-1 ligand expression

CheckMate 205 (Continued)

Assessment:

- Tumour responses assessed by CT or MRI at baseline and at weeks 9, 17, 25, 37 and 49 during first year, and then every 16 weeks until week 97, continuing every 26 weeks beyond week 97
- F-FDG-PET done at baseline and at weeks 17 and 25. F-FDG-PET done at week 49 in participants who did not have 2 consecutive negative scans to this time point
- QoL assessed every 2 cycles for first 17 cycles, then every 6 cycles with the EQ-5D questionnaire and the EORTC QLQ-C30
- On-treatment local laboratory assessments done within 72 hours before dosing
- Toxicity assessments done continuously during treatment phase. During the safety follow-up phase, AEs assessed at follow-up visits 35 days from last dose and 80 days from last dose. Toxicity assessments done continuously during treatment phase. During safety follow-up phase, AEs assessed at follow-up visits 35 days from last dose and 80 days from last dose

Results:

In total:

- Median follow-up (at database lock December 2016)
 - * Cohort A: 19 months (min: 1; max: 25)
 - * Cohort B: 23 months (min: 2; max: 27)
 - * Cohort C: 16 months (min: 1; max: 20)
- ORR
 - * Cohort A: 65%
 - * Cohort B: 68%
 - * Cohort C: 73%
- CR
 - * Cohort A: 29%
 - * Cohort B: 13%
 - * Cohort C: 12%
- Median DOR
 - * Cohort A: 20 months (95% CI 13 to 20)
 - * Cohort B: 16 months (95% CI 8 to 20)
 - * Cohort C: 15 months (95% CI 9 to 17)
- Median PFS
 - * Cohort A: 18.3 months (95% CI 11.1 to 22.4) (for participants with CR, PR and SD: ≥ 17 months)
 - * Cohort B: 14.7 months (95% CI 10.5 to 19.6) (for participants with CR, PR and SD: ≥ 15 months)
 - * Cohort C: 11.9 months (95% CI 11.1 to 18.4) (for participants with CR, PR and SD: ≥ 9 months)
- Median OS not reached in any cohort
- Most common drug-related AEs:
 - * Fatigue: 23%
 - * Diarrhoea: 15%
 - * Infusion reactions: 14%
 - * Rash: 12%
- Grade 3-4 drug-related AEs in $\geq 3\%$ of participants
 - * Lipase increases: 5%
 - * Alanine aminotransferase increases: 3%
 - * Neutropenia: 3%
- Drug-related serious AEs:
 - * Infusion reactions: 2%
 - * Pneumonitis: 1%

Cohort A:

At median follow-up: 14 months (range 1 to 20)

CheckMate 205 (Continued)

- Response:
 - * ORR: 43 participants (68%)
 - * CR: 14 participants (22%)
 - * PR: 29 participants (46%)
 - * SD: 13 participants (21%)
- Median DOR: NR; range 1-16
- Treatment-related AEs
 - * Any grade: 47 (75%) participants
 - * Grade 3 to 4: 7 (11%) participants

Cohort B:

At median follow-up: 8.9 months (range 1.9 to 11.7)

- IRRC assessed response (80 participants):
 - * ORR: 53 (66.3%; 95% CI 54.8 to 76.4) participants
 - * CR: 7 (8.8%) participants
 - * PR: 46 (57.5%) participants
 - * SD: 18 (23%) participants
- Investigator assessed response (80 participants):
 - * ORR: 58 (72.5%; 95% CI 61.4 to 81.9) participants
 - * CR: 22 (27.5%) participants
 - * PR: 36 (45%) participants
 - * SD: 18 (23%) participants
- Median time to first OR (IRRC assessed): 21 months
- Median duration of OR (IRRC assessed): 7.8 months (95% CI 6.6 to not reached)
- Median duration of OR (investigator assessed): 9.1 months (95% CI not available)
- Median duration of CR (investigator assessed): 8.7 months (95% CI not available)
- Median duration of PR (investigator assessed): 7.8 months (95% CI 6.7 to 7.8)
- PFS (IRRC assessed):
 - * At 6 months: 76.9% (95% CI 64.9 to 85.3)
 - * At 12 months: 23 progressions reported
 - * Median PFS at 12 months: 10.0 months (95% CI 8.41 to not reached)
- OS (IRRC assessed)
 - * 98.7% (91.0 to 99.8)
 - * At 12 months: 1 death reported
- All-cause AEs: 79 (99%) participants
 - * Grade 1 or 2 events: 46 (58%) participants
 - * Grade 3 events: 26 (33%) participants
 - * Grade 4 events: 6 (8%) participants
 - * Death from multi-organ failure: 1 (1%) participant
- SAEs of any cause reported in 20 (25%) participants
- Participant-reported outcomes:
 - * EQ-5D visual analogue scale score increased over time with nivolumab treatment: from 62 (SD 30) at baseline (72 (90%) participants) to 80 (SD 18) at week 33 (44 participants) (least squares mean change from baseline of week 33: 19.1 (standard error 3.1))
 - * EORTC QLQ-C30 suggested improvement from baseline across functional, symptom and global health scores (least squares mean change from baseline of week 33: 7.6 (standard error 2.3))

At median follow-up: 15 months (range 2 to 19)

- Response:
 - * ORR: 54 (68%; 95% CI 56 to 78) participants
 - * CR: 6 (8%; 95% CI 3 to 16) participants
 - * PR: 48 (60%; 95% CI 48 to 71) participants
 - * SD: 17 (21%) participants

CheckMate 205 (Continued)

- Median DOR: 13 (range 0 to 14)
- IRRC assessed PFS
 - * Median: 14.8 months (95% CI 11.3 to NA)
 - * 12-months PFS: 54% (95% CI 40.9 to 66.4)
- 12-months OS: 94.9% (median OS not reached)
- Treatment-related AEs
 - * Any grade: 73 (91%) participants
 - * Grade 3 to 4: 24 (30%) participants

Cohort C:

At median follow-up: 8.8 months

- IRRC assessed response:
 - * ORR: 73 (73%, 95% CI 63.2 to 81.4) participants
 - * CR: 17 (17%, 95% CI 10.2 to 25.8) participants
 - * PR: 56 (56%, 95% CI 45.7 to 65.9) participants
- PFS:
 - * 6-month PFS rate per IRRC: 76.6% (95% CI 66.3 to 84.2)
 - * Median: 11.2 months (95% CI 8.5 to NA)
- DOR:
 - * Median: 7.0 months (95% CI 6.7 to NA)
- Time to response:
 - * Median: 2.1 months (range 0.8 to 6.5)
- OS
 - * Median 6 months OS: 93.9% (95% CI 86.9% to 97.2%)
- Drug-related AEs (between first dose and after 30 days of the last dose): 68% of participants; primarily fatigue, diarrhoea, infusion reaction
- Grade 3 to 4 drug-related AEs: 19% of participants

Notes

Other study cohorts included:

- BV-naïve participants after failure of ASCT
- Participants after failure of ASCT who received BV at any time prior to receiving study drug
- Participants with newly diagnosed advanced-stage cHL

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Unclear risk	Recurrent cHL after failure of ASCT and subsequent BV as inclusion criterion
Complete outcome assessment/follow-up (attrition bias)	Low risk	Quote: "All patients who received at least one dose of nivolumab were included in the clinical activity and safety analyses." "80 patients were recruited and enrolled into the trial, all of whom were given treatment and included in the analyses."
Outcome assessors blinded to investigated determinant (detection bias)	High risk	Blinding NR
Important prognostic factors or follow-up taken adequately into account (confounding)	High risk	Clinical activity results separately reported for <ul style="list-style-type: none"> • participants who were BV-naïve • participants who received BV after ASCT • participants who received BV before or after (or both) ASCT

CheckMate 205 (Continued)

		Follow-up not taken into account
		No multi-variable analysis reported
Well-defined study group (reporting bias)	High risk	Doses of prior treatments NR
Well-defined follow-up (reporting bias)	Low risk	Quote: "median follow-up of 8.9 months (IQR 7.8 – 9.9)"
Well-defined outcome (reporting bias)	Low risk	All outcomes reported Statistical methods well-defined
Well-defined risk estimates (analyses)	Low risk	Use of Kaplan-Meier methods including median values and 95% CIs for time-to-event outcomes well defined

Hatake 2016

Methods	Non-randomised, open-label, multi-centre phase II study <ul style="list-style-type: none"> Conducted in 7 sites in Japan Study started on 18 March 2015; data cut-off for the analyses: 16 March 2016 Median duration of follow-up: 9.8 months (range 6.0 to 11.1)
Participants	Eligibility criteria <ul style="list-style-type: none"> Participants aged ≥ 20 years Histopathological diagnosis of cHL People with history of treatment with ASCT, people to whom ASCT was not indicated, people who refused to receive treatment with ASCT Detectable lesion on FDG-PET and ≥ 1 lesion with a longest diameter of ≥ 15 mm on CT or MRI ECOG performance status 0 or 1 Participants enrolled (17 in safety analysis set) Median age: 63 years (range: 29 to 83) Gender: 13 (76.5%) men Stage of disease <ul style="list-style-type: none"> 9 participants (52.9%) with ECOG status 1 Disease subtype: nodular sclerosis: 8 (47.1%) participants; lymphocyte rich: 0 (0%) participants; mixed cellularity: 6 (35.3%) participants; lymphocyte depleted: 2 (11.8%) participants Disease stage at study enrolment: stage II: 4 (23.5%) participants; stage III: 5 (29.4%) participants; stage IV: 8 (47.1%) participants Extent of pretreatment <ul style="list-style-type: none"> Median number of prior chemotherapy regimens: 3 (range 2 to 5) Prior BV: 17 (100%) participants Prior ASCT: 5 (29.4%) participants Prior radiotherapy: 9 (52.9) participants
Interventions	Participants received their first dose of nivolumab 3 mg/kg on day 1 of treatment phase; subsequent doses were to be administered on day 1 of each 14-day cycle nivolumab was continued if treatment

Hatake 2016 (Continued)

continuation criteria were met; trial was to continue until all participants discontinued treatment in the event of progressive disease, an unacceptable AE or other clinically relevant reasons.

Outcomes
Primary endpoint:

- ORR assessed by a central review committee

Secondary endpoints:

- Investigator-assessed ORR
- CR rate
- PR rate
- DOR
- Time to response
- PFS
- OS
- Disappearance rate of B symptoms
- Median time to disappearance of B symptoms
- Occurrence rate of B symptoms
- Rate of change in the sum of the products of the greatest diameters of the target lesion
- Max rate of change in the sum of the products of the greatest diameters of the target lesion
- Safety endpoints

Assessment

- During treatment, CT or MRI in cycles 4, 8, 12, 18, 24, 32, 40, 48 and 61, and every 13 cycles thereafter
- FDG-PET on day 15 in cycles 8, 12 and 24

Results
At median follow-up of 5.1 months

- Response (1 participant ineligible)
 - * ORR: 75% (12 participants; 95% CI 47.6 to 92.7)
 - * CR: 4 participants
 - * PR: 8 participants
- AE
 - * observed in all 17 participants
 - * Grade 3 or 4 in 2 participants: lymphopenia (1 participant); anaemia, hyponatraemia, interstitial pneumonia (1 participant)

At median follow-up of 9.8 months (range 6 to 11)

- Centrally assessed response (1 participant ineligible)
 - * ORR: 81.3% (13 participants; 95% CI 54.5 to 96.0)
 - * CR: 4 (25%) participants
 - * PR: 9 (56.3%) participants
 - * SD 1 (6.3%) participants
- Investigator-assessed response (1 participant ineligible)
 - * ORR: 62.5% (95% CI 35.4 to 84.8) participants
 - * CR: 3 (18.8%) participants
 - * PR: 7 (43.8%) participants
 - * SD 3 (18.8%) participants
- Centrally-assessed PFS:
 - * 6-months PFS: 60% (95% CI 31.8 to 79.7)
 - * Median: NR (range 0.0 to 11.0)
- OS
 - * At 6 months: 100%

Hatake 2016 (Continued)

- AE
 - * AE: Observed in all 17 participants
 - * Grade 3 or 4 AE: 4 participants (anaemia, lymphopenia, thrombocytopenia, pyrexia, hepatic function abnormal, pneumonia, hyponatraemia, fulminant type 1 diabetes mellitus, interstitial lung disease and rash) (each occurred in 1 participant)

Notes Funded by Ono Pharmaceutical Co., Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Unclear risk	Histopathological diagnosis of cHL as eligibility criterion
Complete outcome assessment/follow-up (attrition bias)	Low risk	17 participants enrolled; 17 participants included in safety analysis and 16 participants included in efficacy analysis
Outcome assessors blinded to investigated determinant (detection bias)	High risk	Open-label design
Important prognostic factors or follow-up taken adequately into account (confounding)	High risk	Prior treatments assessed, including prior BV, prior ASCT and prior radiotherapy Length of follow-up not taken into account No multi-variable analysis described
Well-defined study group (reporting bias)	High risk	Doses of prior treatments NR
Well-defined follow-up (reporting bias)	Low risk	Quote: "The median (range) duration of treatment and follow-up were 7.0 (1.4–10.6) months and 9.8 (6.0–11.1) months, respectively."
Well-defined outcome (reporting bias)	Low risk	All outcomes reported Statistical methods well-defined
Well-defined risk estimates (analyses)	Low risk	Using the Clopper-Pearson methods for 95% CI for response rates and the Kaplan-Meier method for time-to-event outcomes was well described.

AE: adverse events; ASCT: autologous stem cell transplantation; BV: brentuximab vedotin; cHL: classical Hodgkin's lymphoma; CI: confidence interval; CR: complete response; CS: clinical stage; CT: computed tomography; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; esc: escalated; FDG: fluorodeoxy-D-glucose; HL: Hodgkin's lymphoma; IF-RT: involved-field radiotherapy; IN-RT: involved-node radiotherapy; IQR: interquartile range; IRR: immune-related response criteria; IV: intravenous; IGEV: ifosfamide, gemcitabine and vinorelbine; max: maximum; min: minimum; MRI: magnetic resonance imaging; MT: magnetisation transfer; NA: not applicable/available; NFT: no further treatment; NR: not reported; OR: overall response; ORR: objective response rate; OS: overall survival; PBSC: peripheral blood stem cell; PD: programmed death; PET: positron emission tomography; PFS: progression-free survival; PR: partial response; QoL: quality of life; SAE: serious adverse events; SD: standard deviation; VEBEP: vinblastine, etoposide, bleomycin, epirubicin, prednisone; WHO: World Health Organization.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Armand 2016	Adults with non-Hodgkin's lymphoma as study population
Falchi 2016	Retrospective study
Herbaux 2015	Retrospective study
Merryman 2017	Retrospective study
Yared 2016	Case report

Characteristics of ongoing studies [ordered by study ID]

NCT01822509

Trial name or title	Ipilimumab or nivolumab in treating adults with relapsed hematologic malignancies after donor stem cell transplant
Methods	Phase I study <ul style="list-style-type: none"> Single group assignment, open label, treatment
Participants	Eligibility criteria <ul style="list-style-type: none"> Histologically or cytologically confirmed haematological malignancy The following malignancies will be considered eligible if progressive or persistent: CLL, NHL, HL, MM, acute leukaemia (AML, ALL), MDS, MPN, CML Life expectancy > 3 months Must have undergone allogeneic HSCT (regardless of stem cell source) Must have baseline donor T-cell chimerism $\geq 20\%$ ECOG performance status ≤ 2 Total bilirubin $\leq 1.5 \times$ institutional ULN (unless due to Gilbert's disease or disease-related haemolysis, then $\leq 3.0 \times$ ULN) AST/ALT $\leq 3.0 \times$ institutional ULN Creatinine $\leq 1.5 \times$ institutional ULN Prednisone dose ≤ 5 mg/day and off all other systemic immunosuppressive medications for ≥ 4 weeks prior to study entry Ability to understand and the willingness to sign a written informed consent document
Interventions	Arm A: ipilimumab Arm B: nivolumab
Outcomes	(Current) primary outcome: <ul style="list-style-type: none"> Incidence of AEs as assessed by NCI CTCAE version 4.0 (Phase Ib) (Current) secondary outcomes: <ul style="list-style-type: none"> Clinical response <ul style="list-style-type: none"> * Complete, partial, and best OR, stable and progressive disease. OS PFS
Starting date	9 April 2013; planned primary completion date: 31 December 2018

NCT01822509 (Continued)

Contact information	Principal Investigator: Matthew Davids, Dana-Farber Cancer Institute
Notes	Study supported by: National Cancer Institute (NCI) (Study Sponsor)

NCT01896999

Trial name or title	Brentuximab vedotin and nivolumab with or without ipilimumab in treating adults with relapsed or refractory Hodgkin's Lymphoma
Methods	<p>Randomised phase I/II trial</p> <p>Phase I study consisting of dose escalation followed by a phase II study</p> <p>Recruitment period</p> <ul style="list-style-type: none"> Start date: 24 January 2014 Preliminary safety and response data for the participants treated with brentuximab vedotin and nivolumab (arms D and E): 20 July 2016 <p>"Patients will be randomised into 1 of 2 arms"</p>
Participants	<p>Eligibility criteria (phase I)</p> <ul style="list-style-type: none"> Participants aged ≥ 18 years Adults with biopsy-confirmed relapsed or refractory HL ECOG performance status 0-2 Participants must have relapsed after first-line chemotherapy; may have relapsed after autologous or allogenic SCT, or have primary refractory disease Participants may have received prior brentuximab vedotin, but not within 6 months prior to registration <p><u>Interim results for 2 cohorts:</u></p> <p><u>20 July 2016:</u></p> <ul style="list-style-type: none"> Arm D (non-randomised): 3 participants; arm E: 7 participants (1 ineligible) <p>Mean age: 46 years (range 25 to 53)</p> <p>Gender: 6 men</p> <p>Stage of disease</p> <ul style="list-style-type: none"> Prior SCT: 5 autologous, allogenic <p>Extent of pretreatment</p> <ul style="list-style-type: none"> Median number of prior therapies: 3 Prior treatment with brentuximab vedotin <p><u>3 October 2017</u></p> <ul style="list-style-type: none"> 19 participants (1 ineligible) <p>Mean age: 44 years (range 21 to 70)</p> <p>Gender: 9 men</p> <p>Extent of pretreatment</p>

NCT01896999 (Continued)

- Median number of prior therapies: 3
- Prior treatment with brentuximab vedotin: 4 participants
- Prior SCT: 8 participants

Brentuximab vedotin, ipilimumab, nivolumab-cohort

- Not reported

Interventions	<p>Arm 1:</p> <ul style="list-style-type: none"> • Brentuximab vedotin IV over 90 minutes and nivolumab IV over 30 minutes on day 1. Treatment of brentuximab vedotin repeats every 21 days for up to 16 courses and treatment of nivolumab repeats every 21 days for up to 34 courses in the absence of disease progression or unacceptable toxicity. <p>Arm 2:</p> <ul style="list-style-type: none"> • Brentuximab vedotin IV over 90 minutes on day 1 of courses 1-16, nivolumab IV over 30 on day 1 of courses 1-34, and ipilimumab IV over 30 minutes on day 1 of courses 1, 5, 9 and 13 and then every 12 weeks for up to 8 doses. Courses repeat every 21 days in the absence of disease progression or unacceptable toxicity.
Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> • CRR (phase II) • MTD of each combination <p>Secondary outcome:</p> <ul style="list-style-type: none"> • CRR (phase I) • DOR (phase I and II) • ORR (phase II) • OS (phase I and II) • PRR (phase I) • PFS (phase I and II)
Starting date	13 July 2013; estimated primary completion date: not reported; interim results for some of the cohorts already reported
Contact information	Principal Investigator: Catherine Diefenbach, ECOG-ACRIN Cancer Research Group
Notes	Funding not reported; several authors declared financial conflicts of interest

NCT02408861

Trial name or title	Nivolumab and ipilimumab in treating adults with HIV associated relapsed or refractory classical Hodgkin's lymphoma or solid tumours that are metastatic or cannot be removed by surgery
Methods	<p>Phase I</p> <ul style="list-style-type: none"> • Single group assignment, open label, treatment
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Participants must have histologically confirmed solid tumour malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective; participants with uncontrolled Kaposi's sarcoma are permitted.

NCT02408861 (Continued)

- For participants in the 24 participant solid tumour cohort, only those histologies not known to respond to single agent nivolumab (such as pancreas, prostate and MSS colorectal cancer) will be excluded.
- For participants in the relapsed refractory HIV-cHL expansion cohort, participants must have histologically confirmed, relapsed/refractory (defined as relapsed/refractory to ≥ 1 lines of therapy) HIV-associated cHL.
- HIV-1 infection, as documented by any federally approved, licensed HIV rapid test performed in conjunction with screening (or enzyme linked immunosorbent assay, test kit, and confirmed by Western blot or other approved test); alternatively, this documentation may include a record demonstrating that another physician has documented the participant's HIV status based on either: approved diagnostic tests or the referring physician's written record that HIV infection was documented, with supporting information on the participant's relevant medical history or current management (or both) of HIV infection.
- Participants must have measurable disease, defined as ≥ 1 lesion that can be accurately measured in ≥ 1 dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan, MRI or calipers by clinical examination; scans must have been performed within 4 weeks prior to registration. Note: for participants with Kaposi's sarcoma, the following apply: ≥ 5 measurable cutaneous Kaposi's sarcoma lesions or any number of lesions with systemic unresectable disease with no previous local radiation, surgical or intralesional cytotoxic therapy that would prevent response assessment.
- Prior therapy for metastatic disease permitted; ≥ 4 weeks must have elapsed since prior chemotherapy or biological therapy, 6 weeks if the regimen included carmustine (BCNU) or mitomycin C; radiotherapy must be completed ≥ 4 weeks prior to registration.
- ECOG performance status ≤ 1 (Karnofsky $\geq 70\%$)
- HIV plasma HIV-1 RNA below detected limit obtained by Food and Drug Administration (FDA)-approved assays (limit of detection: 75) within 4 weeks prior to registration.
- CD4 counts:
 - * for Stratum 1: CD4+ cell count > 200 cells/mm³ obtained within 2 weeks prior to enrolment at any US laboratory that has a clinical laboratory improvement amendments certification or its equivalent;
 - * for Stratum 2: CD4 cell count 100-200 cells/mm³ obtained within 2 weeks prior to enrolment at any US laboratory that has a clinical laboratory improvement amendments certification or its equivalent
 - * expansion cohort: CD4 cell count for this cohort will be specified once Stratum 1 and Stratum 2 have completed enrolment
 - * solid tumour expansion cohort: CD4+ cell count > 200 cells/mm³ obtained within 2 weeks prior to enrolment at any US laboratory that has a clinical laboratory improvement amendments certification or its equivalent
 - * cHL cohort: CD4 cell count ≥ 100 cells/mm³.
- WOCBP and men must agree to use adequate contraception (hormonal or barrier method of contraception; abstinence) prior to study entry and for the duration of study participation.
- Participants MUST receive appropriate care and treatment for HIV infection, including antiretroviral medications when clinically indicated, and should be under the care of a physician experienced in HIV management; participants will be eligible regardless of antiretroviral medication (including no antiretroviral medication) provided there is no intention to initiate therapy or the regimen has been stable for ≥ 4 weeks with no intention to change the regimen within 12 weeks following enrolment.
- Participants who have hepatitis C (both reactive anti-HCV antibody and detectable HCV RNA) and hepatitis B (HBsA positive and anti-HBc-total positive), may be enrolled, provided total bilirubin is $\leq 1.5 \times$ institutional ULN, and AST and ALT must be $\leq 3 \times$ institutional ULN, and HBV DNA < 100 IU/mL (if hepatitis B positive) within 2 weeks prior to enrolment.
- Ability to understand and to sign a written informed consent document.
- Criteria for Solid Tumour Expansion and Lymphoma Cohorts: inclusion and exclusion criteria for this cohort are the same as above, with the following rule for CD4 count based on tolerability in phase I; if, participants with lymphocyte T CD4 count 100-200/mm³ (Stratum 2) are shown to tolerate treatment in the phase I dose de-escalation portion at the same dose level as those with

NCT02408861 (Continued)

CD4 counts $> 200/\text{mm}^3$ (Stratum 1), participants in the expansion cohort with CD4 counts $\geq 100/\text{mm}^3$ are permitted; otherwise, the expansion is open to all participants from solid tumours except those whose tumours are known not to respond to nivolumab (pancreas, prostate and MSS colon cancer); for the relapsed refractory HIV-cHL cohort, participants with CD4 count $\geq 100/\text{mm}^3$ are permitted.

Interventions	<p>Arm A: nivolumab</p> <p>Arm B: ipilimumab</p> <p>Participants receive nivolumab IV over 60 minutes on day 1. Participants in dose level 2 also receive ipilimumab IV over 90 minutes on day 1 of every third course of nivolumab, and participants in dose level -2 also receive ipilimumab IV over 90 minutes on day 1 of every sixth course of nivolumab. Courses repeat every 14 days for up to 46 courses of nivolumab (with ipilimumab if receiving dose level 2 or -2) in the absence of disease progression or unacceptable toxicity.</p>
Outcomes	<p>Current primary outcomes:</p> <ul style="list-style-type: none"> • MTD of nivolumab defined as the starting dose level at which 0/6 or 1/6 participants experience DLT with the next higher dose having $\geq 2/3$ or 2/6 participants encountering DLT. • Change in HIV viral load • Change in HIV viral load from prestudy to end of study will be examined using a non-parametric Wilcoxon signed-rank test. • Change in immune status • Change in immune status from prestudy to end of study • Descriptive statistics will be generated to evaluate the effects of single-agent nivolumab, and the combination of ipilimumab and nivolumab, on immune function (HI) viral load, CD4 and CD8 cells). • ORR
Starting date	27 August 2015; estimated primary completion date: 31 December 2020
Contact information	Principal Investigator: Lakshmi Rajdev AIDS Malignancy Consortium
Notes	Study supported by (Study Sponsor): National Cancer Institute (NCI)

NCT02572167

Trial name or title	A study of brentuximab vedotin combined with nivolumab for relapsed or refractory Hodgkin's lymphoma
Methods	<p>Phase I/II study</p> <p>Study start date: October 2015; estimated completion date 2020</p> <p>Study location: US</p>
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> • Participants aged ≥ 18 years • Relapsed of refractory HL following failure of standard first-line chemotherapy for the treatment of cHL • ECOG status 0 or 1 • Previously untreated with brentuximab vedotin, immune-oncology agents, or received an allogenic- or autologous-SCT • No documented history of a cerebral vascular event

NCT02572167 (Continued)

- No history of another invasive malignancy that has not been in remission for ≥ 3 years
- No history of progressive multi-focal leukoencephalopathy

Participants enrolled:

Interim analysis:

Participants enrolled to this date: 62

Median age: 36 years

Gender: 52% women

Stage of disease

- Primary refractory disease: 45%

Interventions	Brentuximab vedotin 1.8 mg/kg by IV infusion for up to 4 cycles + nivolumab 3 mg/kg by IV infusion for up to 4 cycles
Outcomes	<p>Primary outcomes:</p> <ul style="list-style-type: none"> • Incidence of AEs • CRR <p>Secondary outcomes</p> <ul style="list-style-type: none"> • ORR • Duration of CR • Duration of OR • PFS post-ASCT <p>Assessment:</p> <ul style="list-style-type: none"> • Investigator assessment of lymphoma response and progression per Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) <p>Interim results:</p> <ul style="list-style-type: none"> • AE <ul style="list-style-type: none"> * Infusion-related reactions: 41%; Grade 3: < 5% * Excluding infusion-related reactions, potential immune-related AEs: 72% of participants • Response <ul style="list-style-type: none"> * ORR: 85% * CR: 64% * SD: 4 participants (7%)
Starting date	Study start date: October 2015; estimated study completion date: October 2020
Contact information	Study director: Faith Galderisi, DO, Seattle Genetics, Inc.
Notes	<p>Study sponsor: Seattle Genetics, Inc.</p> <p>Collaborator: Bristol-Myers Squibb</p>

NCT02758717

Trial name or title	Phase II, multi-center trial of nivolumab and brentuximab vedotin in individuals with untreated Hodgkin lymphoma over the age of 60 years or unable to receive standard adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy
Methods	<p>Phase II</p> <ul style="list-style-type: none"> • Single group assignment, open label, treatment
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • cHL determined by local haematopathology review • 1 of the following: <ul style="list-style-type: none"> * Age $\geq$ 60 years * Age < 60 years but unsuitable for standard chemotherapy because of a cardiac ejection fraction of < 50%, a pulmonary diffusion capacity < 80%, or a creatinine clearance $\geq$ 30 and < 60 mL/minute, or refused standard chemotherapy despite efforts to convince them otherwise • Requirement for systemic chemotherapy: all stages except IA (not bulky disease), if involved field is considered radiotherapy curative • Previously untreated with either chemotherapy, radiotherapy, or either brentuximab vedotin or nivolumab, or another check point inhibitor • ECOG performance status 0, 1 or 2 • WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to registration <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Any of the following: <ul style="list-style-type: none"> * pregnant women * nursing women * men or women of childbearing potential who are unwilling to employ adequate contraception • Comorbid systemic illnesses or other severe concurrent disease which, in the judgement of the investigator, would make the person inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens. • Active, known or suspected autoimmune disease; note: people are permitted to enrol if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger. • Use of systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications $\leq$ 14 days of registration. Note: inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. • Immunocompromised people, people with known history of testing positive for HIV or known AIDS and currently receiving antiretroviral therapy, people with history of known or suspected autoimmune disease, active HBsAg positive, active hepatitis C (if antibody positive then polymerase chain reaction positive) indicating acute or chronic infection, or history of interstitial lung disease, or both. • Allergy to brentuximab vedotin or nivolumab, or both • Receiving any other investigational agent that would be considered as a treatment for the primary neoplasm. • Have had prior chemotherapy or radiotherapy for HL • Have received either of the study drugs • Aged < 60 years who are considered candidates for standard chemotherapy • Other active malignancy $\leq$ 2 years prior to registration, unless treated with curative intent; exceptions: non-melanotic skin cancer or carcinoma-in-situ of the cervix; Note: if there is a history or prior malignancy, they must not be receiving other specific treatment for their cancer
Interventions	Arm A: brentuximab vedotin, nivolumab

NCT02758717 (Continued)

Participants receive brentuximab vedotin IV over 30 minutes and nivolumab IV over 60 minutes on day 1. Treatment repeats every 21 days for 7 courses and 6-8 weeks in course 8 in the absence of disease progression or unacceptable toxicity

Outcomes	<p>Primary objective:</p> <ul style="list-style-type: none"> To determine the efficacy based on CMR rate of brentuximab vedotin/nivolumab in people with previously untreated HL at ≥ 60 years of age, or people considered unsuitable for standard chemotherapy because of a low cardiac ejection fraction ($< 50\%$) or impaired pulmonary or renal function. <p>Secondary objective:</p> <ul style="list-style-type: none"> ORR (CMR + partial metabolic response). Safety and tolerability of the regimen DOR PFS OS <p>Tertiary objective:</p> <ul style="list-style-type: none"> T-cell/cytokine: peripheral blood specimens will be used to assess T-cell activation and cytokine upregulation as measures of treatment effect. Biomarkers: intratumoural cell populations, genetic variability, serum cytokines and T-cell activation will be evaluated to identify potential biomarkers that correlate with response to therapy.
Starting date	13 May 2016; estimated primary completion date: 13 November 2019
Contact information	Principal investigator: Bruce Cheson, Academic and Community Cancer Research United
Notes	Study sponsor: Academic and Community Cancer Research United; Collaborator: National Cancer Institute (NCI)

NCT02927769

Trial name or title	A phase I study of ipilimumab and nivolumab in advanced HIV-associated solid tumours with expansion cohorts in HIV-associated solid tumours and a cohort of HIV-associated classical Hodgkin's lymphoma
Methods	<p>Phase I study</p> <ul style="list-style-type: none"> Single group assignment, open label, treatment Location countries: Australia, US
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Participants aged ≥ 19 years Men or women Participants must have histologically confirmed solid tumour malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective; participants with uncontrolled Kaposi's sarcoma are permitted (Kaposi's sarcoma must be increasing despite HAART and HIV suppression for ≥ 2 months, or stable Kaposi's sarcoma despite HAART for ≥ 3 months). HIV-1 infection, as documented by any federally approved, licensed HIV rapid test performed in conjunction with screening Measurable disease

NCT02927769 (Continued)

- Prior therapy for metastatic disease permitted; ≥ 4 weeks must have elapsed since prior chemotherapy or biological therapy, 6 weeks if the regimen included carmustine (BCNU) or mitomycin C; radiotherapy must be completed ≥ 4 weeks prior to registration.
- ECOG performance status ≤ 1 (Karnofsky $\geq 70\%$)
- HIV plasma HIV-1 RNA below detected limit obtained by FDA-approved assays (limit of detection: 75) within 4 weeks prior to registration
- Participants must be purified protein derivative negative
- Participants MUST receive appropriate care and treatment for HIV infection
- Participants who have hepatitis C (both reactive anti-HCV antibody and detectable HCV RNA) and hepatitis B (HBsAg positive and anti-HBc-total positive), may be enrolled, provided total bilirubin is $\leq 1.5 \times$ institutional ULN, and AST and ALT must be $\leq 3 \times$ institutional ULN, and HBV DNA < 100 IU/mL (if hepatitis B positive) within 2 weeks prior to enrolment.

Exclusion criteria

- Participants who have received any other investigational agents within the 4 weeks prior to enrolment; concurrent radiotherapy is not permitted, except palliative (limited-field) radiotherapy, if all of the following criteria are met: repeat imaging demonstrates no new sites of bone metastases; the lesion being considered for palliative radiation is not a target lesion.
- Participants with known brain metastases or leptomeningeal metastases must be excluded unless they qualify for enrolment as described below because of poor prognosis and concerns regarding progressive neurological dysfunction that would confound the evaluation of neurological and other AEs; participants with brain metastases are permitted if metastases have been treated and there is no MRI evidence of progression for ≥ 4 weeks after treatment is complete and within 4 weeks prior to the first dose of nivolumab administration.
- Participants should be excluded if they have had prior treatment with an anti-PD-1, anti-programmed cell death ligand 1 (PD-L1), anti-programmed cell death ligand 2 (PD-L2), anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways; prior immune-modulating therapy including vaccines may be eligible; prior or immune events must be evaluated and the risk for new events which may represent continued subclinical disease or a new process at previously damaged site or immune potentiation (e.g. ipilimumab followed by interleukin-2 causing bowel perforation, ipilimumab followed by indoleamine 2,3-dioxygenase inhibitor resulting in clinical hypophysitis).
- The participant has not recovered to baseline or CTCAE $\leq$ grade 1 from toxicity due to all prior therapies except $\leq$ grade 2 alopecia, neuropathy and other non-clinically significant AEs.
- The participant has a primary brain tumour
- Participant has $\geq$ grade 2 diarrhoea (participants with grade 1 diarrhoea are eligible provided stool for ova/parasites and stool cryptosporidium studies are negative).
- Opportunistic infection within the last 3 months
- Participants with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded.
- Participants who have had evidence of *Clostridium (C) difficile* infection, active or acute diverticulitis, intra-abdominal abscess, intra-abdominal abscess, gastrointestinal obstruction and abdominal carcinomatosis, which are known risk factors for bowel perforation, should be evaluated for the potential need for additional treatment before coming on study.

Interventions	<p>Arm A: nivolumab, ipilimumab</p> <p>Participants receive nivolumab IV over 60 minutes on day 1. Participants in dose level 2 also receive ipilimumab IV over 90 minutes on day 1 of every third course of nivolumab, and participants in dose level -2 also receive ipilimumab IV over 90 minutes on day 1 of every sixth course of nivolumab. Courses repeat every 14 days for up to 46 courses of nivolumab (with ipilimumab if receiving dose level 2 or -2) in the absence of disease progression or unacceptable toxicity.</p>
Outcomes	<p>Primary objective:</p> <ul style="list-style-type: none"> • safety and feasibility of ipilimumab and nivolumab

NCT02927769 (Continued)

Secondary objectives:

- Effects of single agent nivolumab, and the combination of ipilimumab and nivolumab, on immune function (HIV viral load in plasma using conventional assay, CD4+ and CD8+ cells)
- ORR

Starting date	27 August 2015; estimated primary completion date: 31 December 2020
Contact information	Principal investigator: Lakshmi Rajdev, AIDS Malignancy Consortium
Notes	Study sponsor: National Cancer Institute (NCI)

NCT02940301

Trial name or title	Ibrutinib and nivolumab in treating adults with relapsed or refractory classical Hodgkin's lymphoma
Methods	Phase II study, single group assignment, open label, treatment
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> • Adults with histologically confirmed cHL that is relapsed or refractory after ≥ 1 prior therapy are eligible • Adults with lymphocyte predominant HL are eligible • Prior treatments: participants must have had ≥ 1 prior therapy • Adults with previous autologous transplant are permitted • Adults who are eligible and willing to undergo autologous transplant should not be enrolled on this trial • Prior allogeneic transplant is NOT permitted • Prior treatment with Bruton's tyrosine kinase inhibitors is NOT permitted • Prior treatment with nivolumab is permitted • Presence of radiographically measurable disease (defined as the presence of a ≥ 1.0 cm lesion, as measured in the longest dimension by CT scan or PET/CT scan or MRI scan) • ECOG performance status ≤ 2 • People with HIV are not permitted to enrol • People with history of hepatitis B or C infection are not permitted to enrol; to enrol participants must have no evidence of hepatitis B or C surface antigen and negative HBc antibody; people previously immunised for hepatitis B who are hepatitis B surface Ab positive, but surface Ag and core Ab negative are eligible • Non-pregnant and non-nursing; pregnant and nursing women may not be enrolled; women and men of reproductive potential must agree to use acceptable forms of contraception during the study • Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty • Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorisation to use protected health information (in accordance with national and local subject privacy regulations) <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer or other cancer from which the person has been disease free for ≥ 2 years or which will not limit survival to < 2 years

NCT02940301 (Continued)

	<ul style="list-style-type: none"> • A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the person's safety, interfere with the absorption or metabolism of ibrutinib, or put the study outcomes at undue risk • Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure or myocardial infarction within 6 months of screening, or any class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification • CNS involvement by lymphoma • Major surgery within 4 weeks before first dose of study drug • History of stroke or intracranial haemorrhage within 6 months before the first dose of study drug
Interventions	<p>Arm A: experimental: treatment (ibrutinib, nivolumab)</p> <p>Participants receive ibrutinib orally once daily on days 1-21 and nivolumab IV continuously over 60 minutes on day 1</p> <p>Treatment with nivolumab repeats every 21 days for up to 16 courses and treatment with ibrutinib continues in the absence of disease progression or unacceptable toxicity</p>
Outcomes	<p>Current primary outcomes</p> <ul style="list-style-type: none"> • Proportion of participants in CR <p>Current secondary outcomes</p> <ul style="list-style-type: none"> • DOR • Incidence of AEs measured by CTCAE version 4.03 • ORR • PFS
Starting date	20 December 2016; estimated primary completion date: 31 May 2019 (final data collection date for primary outcome)
Contact information	Principal investigator: Lapo Alinari Ohio State University Comprehensive Cancer Center
Notes	Study Sponsor: Ohio State University Comprehensive Cancer Center

NCT02973113

Trial name or title	Nivolumab with Epstein Barr virus specific T cells (EB-VSTS), relapsed/refractory EBV positive lymphoma (PREVALE)
Methods	Phase I, single-group assignment, open label, treatment
Participants	<p>Eligibility criteria</p> <p>Procurement inclusion</p> <ul style="list-style-type: none"> • Any individual, regardless of age^a or sex, with measurable EBV-positive Hodgkin's or non-Hodgkin's lymphoma (regardless of the histological subtype)^b or EBV (associated)-T/NK- or B-cell lymphoproliferative disease. ^aThe first 3 participants enrolled will be adults. People < 18 years of age are eligible if those first 3 participants do not experience DLT considered to be primarily related to the EB-VST or nivolumab. ^bPeople with relapsed or refractory lymphoma who failed or are ineligible for an autologous haematopoietic cell transplantation are also eligible for this study. • EBV-positive tumour (can be pending) • Weighs ≥ 12 kg • Informed consent explained to, understood by and signed by participant/guardian. Participant/guardian given a copy of informed consent.

Nivolumab for adults with Hodgkin's lymphoma (a rapid review using the software RobotReviewer) (Review)

NCT02973113 (Continued)

- Life expectancy > 6 weeks.

Treatment inclusion

- Any person, regardless of age^a or sex, with measurable EBV-positive Hodgkin's or non-Hodgkin's lymphoma (regardless of the histological subtype)^{ab} or EBV (associated)-T/NK- or B-cell lymphoproliferative disease. ^aThe first 3 participants enrolled will be adults. People < 18 years of age are eligible if those first 3 participants do not experience DLT considered to be primarily related to the EB-VST or nivolumab. ^bAdults with relapsed or refractory lymphoma who failed or are ineligible for an autologous hematopoietic cell transplantation are also eligible for this study.

And

- People with HL in second relapse or first relapse and refractory to ≥ 2 lines of salvage chemotherapy including brentuximab vedotin or primary refractory disease after ≥ 2 lines therapy or
- People with NHL in first relapse or refractory to ≥ 1 salvage chemotherapy (or both) or with primary refractory disease after ≥ 2 lines of therapy or in second or subsequent relapse or
- T/NK- or B-lymphoproliferative disease in first relapse or refractory to ≥ 1 salvage chemotherapy (or both) or with primary refractory disease after ≥ 2 lines of therapy or in second or subsequent relapse
- EBV-positive tumour
- People with life expectancy > 6 weeks
- People should have been off other investigational therapy for 4 weeks prior to entry in this study
- People with a Karnofsky/Lansky score of > 60
- Sexually active participants must be willing to utilise 1 of the more effective contraceptive methods during the study and for 6 months after the study is concluded. The male partner should use condoms.
- Informed consent explained to, understood and signed by participant/guardian. Participant/guardian given a copy of informed consent

Exclusion criteria

Procurement exclusion

- Active infection with HIV, HTLV, HBV, HCV (can be pending at this time)
- History of solid organ transplant

Treatment exclusion

- Pregnant or lactating due to unknown effects of this therapy on a fetus or lactation
- Severe active intercurrent infection.
- Current use of systemic corticosteroids > 0.5 mg/kg/day
- Currently receiving any investigational agents or radiotherapy within 4 weeks prior to entering the study
- People with CNS involvement

Interventions	<p>EB-VST cells + PD1 inhibitor nivolumab 3 mg/kg (maximum dose: 240 mg) every 2 weeks for total 4 doses and repeat 1 day prior to each EB-VST infusion</p> <p>EB-VST- $1 \times 10^8/\text{m}^2$ at days +1 and +15. PD1 inhibitor nivolumab 3 mg/kg (maximum dose: 240 mg) every 2 weeks for total 4 doses and repeat a day prior to each EB-VST infusion</p> <p>Can receive up to 3 additional infusions of EB-VSTs with a single dose of nivolumab at 6-12 week intervals starting ≥ 6 weeks after the second infusion if stable disease or a partial response at week 8 evaluation</p>
Outcomes	<p>Current primary outcome</p> <ul style="list-style-type: none"> Number of dose-limiting toxicities

NCT02973113 (Continued)

For the purpose of this study, dose-limiting-toxicity will be defined as any of the below listed items considered to be primarily related to the EB-VST infusion or nivolumab

- CTCAE grade 3-4 diarrhoea needing steroids for > 1 week or needing hospitalisation for > 1 week
- Pancreatitis of any grade needing hospitalisation,
- Pneumonitis needing hospitalisation for > 1 week or needing home oxygen despite appropriate treatment for 1 week.
- Hepatitis $\geq$ grade 3 not resolving in 2 weeks after discontinuation of therapy
- Stomatitis/mucositis needing TPN
- Musculoskeletal symptoms affecting activities of daily living for > 2 weeks after discontinuation of therapy

Current secondary outcomes

- Duration of OR
- Changes in EB-VST levels in the peripheral blood over time
- Changes of EB-VSTs continuing at detectable levels over time

Starting date	16 February 12016; estimated primary completion date: 16 April 2019 (final data collection date for primary outcome)
Contact information	Principal investigator: Ravi Pingali, MD, Baylor College of Medicine
Notes	Study sponsor: Baylor College of Medicine

NCT03004833

Trial name or title	Nivolumab and AVD in early-stage unfavourable classical Hodgkin lymphoma (NIVAHL)
Methods	Phase II, randomised, parallel assignment, open label, treatment
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> • Histologically confirmed cHL • First diagnosis, no previous treatment • Aged: 18-60 years • Stage I, IIA with risk factors a-d, IIB with risk factors confirmed by central review <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Composite lymphoma or nodular lymphocyte-predominant HL • History of other malignancy $\leq$ 5 years • Prior chemotherapy or radiotherapy • Concurrent disease precluding protocol treatment • Pregnancy, lactation • Non-compliance
Interventions	<p>Arm A:</p> <ul style="list-style-type: none"> • 4 cycles of nivolumab plus AVD followed by IF-RT (30 Gy) <p>Arm B:</p> <ul style="list-style-type: none"> • 4 cycles of nivolumab, followed by 2 cycles of nivolumab plus AVD, followed by 2 cycles of AVD followed by IF-RT (30 Gy)

NCT03004833 (Continued)

Outcomes	<p>Current primary outcome:</p> <ul style="list-style-type: none"> Complete remission rate <p>Current secondary outcomes:</p> <ul style="list-style-type: none"> Treatment-related morbidity PFS OS
Starting date	21 February 2017; estimated primary completion date: December 2018 (final data collection date for primary outcome)
Contact information	Principal investigator: Professor Andreas Engert
Notes	Study sponsor: University of Cologne

NCT03016871

Trial name or title	Nivolumab, ifosfamide, carboplatin, and etoposide as second-line therapy in treating adults with refractory or relapsed Hodgkin lymphoma
Methods	Phase II, single-group assignment, open label, treatment
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> Participants must have histologically documented or cytologically confirmed HL; confirmation must include CD30 expression Participants must be either refractory to or relapsed after only induction therapy; participants who do not achieve CR after induction therapy are considered primary refractory and are allowed to enter study. Participants must have measurable disease > 1.5 cm evidenced by CT scan of the neck/chest/abdomen/pelvis or CT/PET scans Life expectancy > 3 months ECOG 0-2 Documented informed consent/assent of the participant or legally responsible guardian Women is either postmenopausal, surgically sterilised or willing to use and acceptable method of contraception (i.e. a hormonal contraceptive, intrauterine device, diaphragm with spermicide, condom with spermicide or abstinence) for the duration of the study; WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to the start of nivolumab Men who are sexually active with WOCBP must use any contraceptive method with a failure rate < 1% per year; men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product; women who are not of childbearing potential (i.e. who are postmenopausal or surgically sterile) as well as azospermic men do not require contraception Person must be either refractory to or relapsed after 1 line of therapy Prior radiotherapy is allowed <p>Exclusion criteria</p> <ul style="list-style-type: none"> Prior exposure to PD-1 or PD-L1 inhibitors is not allowed Must not have had second-line chemotherapy for HL Unwilling or unable to participate in all required study evaluations and procedures

NCT03016871 (Continued)

- Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form and authorisation to use protected health information (in accordance with national and local subject privacy regulations)
- Pregnant women are excluded from this study; breastfeeding should be discontinued
- Active with HCV or HBV, people who are positive for HBc antibody or HBsAg must have a negative polymerase chain reaction result before enrolment, people who are PCR positive will be excluded; people who have an undetectable HIV viral load with CD (cluster of differentiation) 4 $\geq$ 300 and are on HAART medication are allowed; people with previously treated hepatitis C are also allowed; as there is potential for hepatic toxicity with nivolumab or nivolumab/ipilimumab combinations, drugs with a predisposition to hepatotoxicity should be used with caution in people treated with nivolumab-containing regimen
- History of allergy or adverse drug reaction to study components

Interventions	<p>Participants receive nivolumab IV over 30 minutes on day 1. Courses repeat every 14 days for up to 6 weeks in the absence of disease progression or unacceptable toxicity</p> <p>Participants with CR or PR receive nivolumab for an additional 6 weeks</p> <p>Participants with SD or PD after 6-week nivolumab treatment or participants with PR, SD or PD after 12-week nivolumab treatment receive nivolumab IV over 30 minutes on day 1, etoposide IV on days 1-3, ifosfamide IV continuously over 24 hours on day 2, and carboplatin IV on day 2. Treatment repeats every 21 days for up to 2 courses in the absence of disease progression or unacceptable toxicity</p>
Outcomes	<p>Current primary outcomes:</p> <ul style="list-style-type: none"> • CR rate ASCT assessed by Lugano criteria • Incidence of AEs assessed by National Cancer Institute (NCI) CTCAE version 4.03 <p>Current secondary outcomes:</p> <ul style="list-style-type: none"> • Non-relapse mortality • ORR • OS of haematopoietic cell transplant • OS • PFS • PFS of HCT • Relapse/progression event <p>Current other outcome:</p> <ul style="list-style-type: none"> • Role of PDL (PD-ligand) 1/L2, CD (cluster of differentiation) 68 on lymphoma specimens
Starting date	8 May 2017; estimated primary completion date: 24 April 2019 (final data collection date for primary outcome)
Contact information	Principal investigator: Robert Chen, MD, City of Hope Medical Center
Notes	Study sponsor: City of Hope Medical Center

NCT03033914

Trial name or title	(B)VD followed by nivolumab as frontline therapy for higher risk patients with classical Hodgkin lymphoma
Methods	Phase I, non-randomised, parallel assignment, open label, treatment

NCT03033914 (Continued)

Cohort A will include adults < 60 years of age with advanced stage (Stage III or IV) cHL who are at higher risk for relapse due to baseline IPS of 3-7 or positive PET scan after 2 cycles of ABVD ("PET-2 positive").

Cohort B will include adults ≥ 60 years of age with HL (any stage) and receive AVD

Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> Cohort A overview: adults aged < 60 years with untreated Stage III or IV cHL will be eligible for cohort A. In phase I, People may enrol onto cohort A if they have a baseline IPS ≥3 OR if their PET scan after 2 cycles of ABVD is positive (Deauville 4 or 5). Participants enrolled based upon IPS score may enrol at any time during the first 2 cycles of ABVD. Participants enrolled based upon PET-2 positivity may enrol only after the PET scan is obtained. In phase II, only people with PET-2 positivity will be eligible. Cohort B overview: people aged ≥ 60 years with untreated cHL (regardless of stage) will be eligible for cohort B. <p>The following eligibility criteria apply to both cohort A and B except when stated otherwise.</p> <ul style="list-style-type: none"> Histological diagnosis of cHL FDG-avid disease by FDG-PET/CT Ann Arbor Stage III or IV disease (Cohort A only). WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to the start of study drug. Women who undergo fertility preservation within 2 weeks of beginning chemotherapy are expected to have false-positive pregnancy tests and therefore testing may be waived for these women. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to the start of study drug. Women must not be breast-feeding. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion. Age ≥ 18 years <p>Exclusion criteria</p> <ul style="list-style-type: none"> People with active brain metastases or leptomeningeal metastases. People with nodular lymphocyte-predominant HL Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the person to receive protocol therapy, or interfere with the interpretation of study results. Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer; superficial bladder cancer; or carcinoma in situ of the prostate, cervix or breast.
Interventions	<p>High-risk advanced-stage HL</p> <ul style="list-style-type: none"> The study will employ a 3+3 design and include 3 treatment cohorts. In each cohort, participants will receive 6 cycles of A(B)VD and 8 doses of nivolumab. In dose level 1, participants will receive nivolumab plus AVD during cycle 6 only followed by 6 additional doses of nivolumab. In subsequent dose levels, nivolumab will be combined with increasing numbers of cycles of AVD. Based upon safety data from another study with nivolumab, we will no longer need to evaluate dose level 2. If we determine that dose level 1 is safe, the next group of participants will enrol onto dose level 3. <p>Older people with HL</p> <ul style="list-style-type: none"> The study will employ a 3+3 design and include 3 treatment cohorts. In each cohort, participants will receive 6 cycles of AVD and 12 doses of nivolumab. In this cohort, participants will receive nivolumab plus AVD during cycles 5 and 6 only, followed by 8 additional doses of nivolumab. In subsequent cohorts, nivolumab will be combined with increasing numbers of cycles of AVD. Based upon safety data from another study with nivolumab, we will no longer need to evaluate dose

NCT03033914 (Continued)

level 2. If we determine that dose level 1 is safe, the next group of participants will enrol onto dose level 3.

Outcomes	Current primary outcome <ul style="list-style-type: none"> Number of participants who have dose limiting toxicity
Starting date	25 January 2017; estimated primary completion date: January 2020 (final data collection date for primary outcome)
Contact information	Principal investigator: Alison Moskowitz, MD, Memorial Sloan Kettering Cancer Center
Notes	Study sponsor: Memorial Sloan Kettering Cancer Center

NCT03057795

Trial name or title	Nivolumab and brentuximab vedotin after stem cell transplant in treating patients with relapsed or refractory high-risk classical Hodgkin lymphoma
Methods	Phase II, single group assignment, open label, treatment
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> Documented informed consent Agreement to allow the use of archival tissue from pre-ASCT tumour biopsies ECOG performance status ≤ 2 Histologically confirmed diagnosis of cHL (excluding nodular lymphocyte predominant HL) according to the WHO classification, with haematopathology review at the participating institution Have high-risk relapsed or refractory HL, defined as: primary refractory disease to front-line therapy; relapse within 1 year of completing front-line therapy; extranodal involvement at the time of pre-ASCT relapse; B symptoms at pre-ASCT relapse; > 1 type of pre-ASCT salvage therapy required Planning to receive or have received ACST per institutional standards as part of standard of care; pre-ASCT participants may consent but will not be eligible to begin treatment until after ASCT, and must fulfill all inclusion and exclusion criteria; post-ASCT participants must initiate day 1 of protocol therapy within 30-60 days post stem cell reinfusion; consult study principal investigator for exceptions to these time frames Recovery from ASCT toxicity as defined as outpatient status, able to drink, eat normally and do not need IV hydration prior to day 1 of therapy Achieved at least stable disease to salvage treatment determined by PET/CT using 2014 Lugano Classification prior to ASCT Brentuximab vedotin naive or had at least stable disease by Lugano Classification to prior brentuximab vedotin treatment WOCBP only: negative urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. WOCBP: use 2 effective methods of contraception (hormonal or barrier method) or be surgically sterile, or abstain from heterosexual activity for the course of the study through 7 months post last dose of nivolumab. WOCBP defined as not being surgically sterilised or have not been free from menses for > 1 year. Male: use 2 effective methods of contraception (barrier method) or abstain from heterosexual activity with the first dose of study therapy through 7 months post last dose of nivolumab. <p>Exclusion criteria</p>

NCT03057795 (Continued)

	<ul style="list-style-type: none"> Post-ASCT anti-lymphoma or investigational therapy; immediate post-ASCT consolidative radiotherapy is allowed as long as it occurs prior to initiation of study therapy; baseline imaging and pulmonary function tests must be performed after completion of radiation Previous allogeneic transplant Refractory to prior brentuximab vedotin (i.e. progression while on treatment) Refractory to prior anti-PD-1/PD-L1 agent History of prior $\geq$ grade 3 hypersensitivity to either brentuximab vedotin or nivolumab History of another primary malignancy that has not been in remission for $\geq$ 3 years; exceptions include: basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. Women who are pregnant or lactating
Interventions	<p>Beginning 30-60 days post-ASCT, participants receive brentuximab vedotin IV over 30 minutes and nivolumab IV over 60 minutes on day 1.</p> <p>Treatment repeats every 21 days for up to 8 courses in the absence of disease progression or unacceptable toxicity.</p>
Outcomes	<p>Current primary outcomes:</p> <ul style="list-style-type: none"> PFS <p>Current secondary outcomes:</p> <ul style="list-style-type: none"> Cumulative incidence of non-relapse mortality defined as the time from the first dose of study treatment to non-disease-related death Cumulative incidence of relapse/progression defined as the time from the first dose of study treatment to disease relapse/progression Incidence of toxicities evaluated according to NCI CTCAE version 4.03 OS OR rate
Starting date	3 May 2017; estimated primary completion date: April 2019 (final data collection date for primary outcome)
Contact information	Principal investigator: Alex Herrera, MD, City of Hope Medical Center
Notes	Study sponsor: City of Hope Medical Center

NCT03138499

Trial name or title	A study of nivolumab plus brentuximab vedotin versus brentuximab vedotin alone in patients with advanced stage classical Hodgkin lymphoma, who are relapsed/ refractory or who are not eligible for autologous stem cell transplant (CheckMate 812)
Methods	Phase III, randomised, parallel assignment, open label, treatment
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> ECOG performance status 0 or 1 Participants must have a pathological diagnosis of cHL who are relapsed or refractory with 1 of the following: ASCT ineligible people; people after failure of ASCT (must have $\geq$ 1 lesion that is $>$ 15 mm in the longest diameter and avid by FDG-PET scan) <p>Exclusion criteria</p> <ul style="list-style-type: none"> Known CNS lymphoma

NCT03138499 (Continued)

	<ul style="list-style-type: none"> Participants with nodular lymphocyte-predominant HL Participants with known history of pancreatitis or progressive multi-focal leukoencephalopathy
Interventions	<p>Arm A</p> <ul style="list-style-type: none"> Nivolumab plus brentuximab vedotin <p>Arm B</p> <ul style="list-style-type: none"> Brentuximab vedotin alone
Outcomes	<p>Current primary outcome</p> <ul style="list-style-type: none"> PFS <p>Current secondary outcomes</p> <ul style="list-style-type: none"> CRR ORR DOR Duration of complete response OS PFS
Starting date	16 May 2017; estimated primary completion date: 29 November 2020 (final data collection date for primary outcome)
Contact information	Study director: Bristol-Myers Squibb
Notes	Study sponsor: Bristol-Myers Squibb

NCT03161613

Trial name or title	Study to assess the safety of nivolumab in the treatment of metastatic melanoma, lung cancer, renal cancer, squamous cell carcinoma of the head and neck, and chronic Hodgkin's lymphoma in adults in Mexico
Methods	Observational study, prospective
Participants	<p>Eligibility criteria</p> <ul style="list-style-type: none"> Adults > 18 years of age who have a confirmed diagnosis of advanced or metastatic melanoma and is indicated for the treatment of advanced (unresectable or metastatic) melanoma; metastatic non-small cell lung cancer; metastatic RCC; recurrent or metastatic SCCHN; or cHL in Mexico. Participants who completed the following lines of therapy: first-line platinum treatment for metastatic SqNSCLC or non-SqNSCLC; 1 first-line treatment for metastatic RCC; first-line platinum therapy for SCCHN; or brentuximab vedotin for the treatment of cHL. Adults who present with brain metastases are allowed, if asymptomatic, do not have oedema, and are not receiving corticosteroids or radiation. Participants have received ≥ 1 dose of nivolumab <p>Exclusion criteria</p> <ul style="list-style-type: none"> Exclusion criteria at the discretion of the physician Physician should use his or her clinical judgement and international recommendations when determining eligibility. Participant will be excluded if he or she does not want to start or continue treatment.

NCT03161613 (Continued)

Interventions	Other: non-interventional
Outcomes	<p>Current primary outcomes:</p> <ul style="list-style-type: none"> Incidence of people who report on-study AEs incidence of people who report on-study SAEs <p>Current secondary outcomes:</p> <ul style="list-style-type: none"> Distribution of on-study AEs Distribution of on-study SAEs Distribution of drug-related AEs Distribution of drug-related SAEs Distribution of AEs leading to discontinuation Distribution of SAEs leading to discontinuation Distribution of age in participants Distribution of gender in participants Distribution of tumour history in participants
Starting date	17 July 2017; estimated primary completion date: 1 April 2019 (final data collection date for primary outcome)
Contact information	Study director: Bristol-Myers Squibb
Notes	Study sponsor: Bristol-Myers Squibb

ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; AE: adverse event; ALL: acute lymphoblastic leukaemia; ALT: alanine aminotransferase; AML: acute myeloid leukaemia; ANC: absolute neutrophil count; ASCT: autologous stem cell transplantation; AST: aspartate aminotransferase; AVD: adriamycin, vinblastine, dacarbazine; BCNU: bis-chloroethylnitrosourea; CHL: classical Hodgkin's lymphoma; CLL: chronic lymphocytic leukaemia; CML: chronic myeloid leukaemia; CMR: complete metabolic remission; CNS: central nervous system; CR: complete response; CRR: complete response rate; CS: clinical staging; CT: computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; DLT: dose-limiting toxicity; DOR: duration of response; EB-VST: Epstein Barr virus specific T cells; EBV: Epstein Barr virus; ECOG: Eastern Cooperative Oncology Group; FDA: Food and Drug Administration; FDG: fluorodeoxy-D-glucose; HAART: highly active antiretroviral therapy; HBc: hepatitis B core; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; hCG: human chorionic gonadotropin; HCV: hepatitis C virus; HL: Hodgkin's lymphoma; HSCT: haematopoietic stem cell transplantation; HTLV: human T-lymphotropic virus; IF-RT: involved-field radiotherapy; IPS: international prognostic score; IV: intravenous; LVEF: left ventricular ejection fraction; MDS: myelodysplastic syndrome; MM: multiple myeloma; MPN: myeloproliferative neoplasms; MRI: magnetic resonance imaging; MSS: microsatellite stable; MTD: maximum tolerated dose; N/A: not available; NCI CTCAE v 3.0: National Cancer Institute, Common Terminology Criteria for Adverse Events Version 3.0; NHL: non-Hodgkin's lymphoma; OR: overall response; ORR: objective response rate; OS: overall survival; PD: programmed death; PET: positron emission tomography; PFS: progression-free survival; PRR: partial response rate; RCC: renal cell carcinoma; RNA: ribonucleic acid; SAE: serious adverse event; SC: subcutaneous; SCCN: squamous cell carcinoma of the head and neck; SCT: stem cell transplantation; SqNSCLC: squamous non-small-cell lung carcinoma; TPN: total parenteral nutrition; ULN: upper limit of normal; WHO: World Health Organization; WOCBP: women of childbearing potential.

ADDITIONAL TABLES

Table 1. Risk of bias assessment criteria for observational studies

Heading	Internal validity	External validity
Study group	<p>Selection bias (<u>representative</u>: yes/no)</p> <ul style="list-style-type: none"> if the described study group consisted of > 80% of the Hodgkin's lymphoma participants treated with nivolumab in the original cohort 	<p>Reporting bias (<u>well defined</u>: yes/no)</p> <ul style="list-style-type: none"> if the mean/median or range of the cumulative nivolumab dose was mentioned <p>and</p>

Table 1. Risk of bias assessment criteria for observational studies (Continued)

	or <ul style="list-style-type: none"> if it was a random sample with respect to the cancer treatment and important prognostic factors 	<ul style="list-style-type: none"> when it was described what prior treatment (including the received doses) was given
Follow-up	Attrition bias (<u>adequate</u> : yes/no) <ul style="list-style-type: none"> if the outcome was assessed for > 90% of the study group of interest (++) or <ul style="list-style-type: none"> if the outcome was assessed for 60-90% of the study group of interest (+) 	Reporting bias (<u>well defined</u> : yes/no) <ul style="list-style-type: none"> if the length of follow-up was mentioned
Outcome	Detection bias (<u>blind</u> : yes/no) <ul style="list-style-type: none"> if the outcome assessors were blinded to the investigated determinant 	Reporting bias (<u>well defined</u> : yes/no) <ul style="list-style-type: none"> if the outcome definition was objective and precise, and the method of detection was provided
Risk estimation	Confounding (<u>adjustment for other factors</u> : yes/no) <ul style="list-style-type: none"> if important prognostic factors (i.e. age, gender, cotreatment) or follow-up were taken adequately into account 	Analyses (<u>well defined</u> : yes/no) <ul style="list-style-type: none"> if a risk ratio, odds ratio, attributable risk, linear or logistic regression model, mean difference or Chi² was calculated

APPENDICES

Appendix 1. CENTRAL search strategy

ID Search

#1 MeSH descriptor: [Lymphoma] this term only

#2 MeSH descriptor: [Hodgkin Disease] explode all trees

#3 Germinoblastom*

#4 Reticulolymphosarcom*

#5 Hodgkin*

#6 (malignan* near/2 lymphogranulom*) or (malignan* near/2 granulom*)

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 nivolumab*

#9 opdivo*

#10 nivo*

#11 (BMS-936558 or MDX-1106 or ONO-4538 or BMS936558 or MDX1106 or ONO4538)

#12 (Anti-PD-1 or Anti-PD1)

#13 ("death 1 (PD-1)" near/3 checkpoint-inhibitor*)

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#14 #8 or #9 or #10 or #11 or #12 or #13

#15 #7 and #14

Appendix 2. MEDLINE (via Ovid) search strategy

#	Searches
1	*LYMPHOMA/
2	exp HODGKIN DISEASE/
3	Germinoblastom\$.tw,kf,ot.
4	Reticulolymphosarcom\$.tw,kf,ot.
5	Hodgkin\$.tw,kf,ot.
6	(malignan\$ adj2 (lymphogranulom\$ or granulom\$)).tw,kf,ot.
7	or/1-6
8	nivolumab*.tw,kf,ot,nm.
9	Opdivo*.tw,kf,ot.
10	nivo*.tw,kf,ot.
11	(BMS-936558 or MDX-1106 or ONO-4538 or BMS936558 or MDX1106 or ONO4538).tw,kf,ot.
12	(Anti-PD-1 or Anti-PD1).tw,kf,ot.
13	("death 1 (PD-1)" adj3 checkpoint-inhibitor*).tw,kf,ot.
14	or/8-13
15	7 and 14

Appendix 3. Embase (via EBSCO) search strategy

No.	Query
#1	'lymphoma'/mj
#2	'hodgkin disease'/exp
#3	germinoblastom*
#4	reticulolymphosarcom*
#5	hodgkin*:ti,ab,de

(Continued)

#6	hodgkin*:tt
#7	(malignan* NEAR/2 (lymphogranulom* OR granulom*)):ti,ab,de
#8	(malignan* NEAR/2 (lymphogranulom* OR granulom*)):tt
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#11	nivolumab*
#12	opdivo*
#13	nivo*
#14	'bms 936558' OR 'mdx 1106' OR 'ono 4538' OR bms936558 OR mdx1106 OR ono4538
#15	'anti pd 1' OR 'anti pd1'
#16	'death 1 (pd-1)' NEAR/3 'checkpoint inhibitor*'
#17	#11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	#9 AND #17

Appendix 4. International Pharmaceutical Abstracts (via EBSCO) search strategy

#	Query
S1	Germinoblastom*
S2	Reticulolymphosarcom*
S3	Hodgkin* OR (SU Lymphoma)
S4	(malignan* N2 (lymphogranulom* or granulom*))
S5	S1 OR S2 OR S3 OR S4
S6	nivolumab*
S7	opdivo*
S8	nivo*
S9	BMS-936558 OR MDX-1106 OR ONO-4538 OR BMS936558 OR MDX1106 OR ONO4538
S10	Anti-PD-1 OR Anti-PD1
S11	"death 1 (PD-1)" N3 checkpoint-inhibitor*
S12	S6 OR S7 OR S8 OR S9 OR S10 OR S11

(Continued)

S13

S5 AND S12

Appendix 5. EU Clinical Trials Register search strategy

hodgkin in the condition

AND nivolumab in the intervention

Appendix 6. ClinicalTrials.gov search strategy

Conditions: Hodgkin OR Lymphom

Interventions: nivolumab OR BMS-936558 OR MDX-1106 OR ONO-4538 OR Opdivo

Appendix 7. WHO ICTRP search strategy

hodgkin in the condition

AND nivolumab in the intervention

Appendix 8. Assessment of heterogeneity and risk of bias

Assessment of risk of bias in included studies

Randomised controlled trials

As we identified neither randomised controlled trials (RCTs) nor non-RCTs with a control group, we could not use the Cochrane 'Risk of bias' tool or Risk Of Bias in Non-randomised Studies - of Interventions (ROBIN-I) for risk of bias assessment. We used the "risk of bias assessment criteria for observational studies" tool provided by the Childhood Cancer Group to assess risk of bias for prospectively planned studies without a control arm (see [Table 1](#)).

If we identify RCTs for future updates, we will assess risk of bias with the Cochrane 'Risk of bias' tool for each RCT. Thereafter, we will use the RobotReviewer software to assess risk of bias ([RobotReviewer 2015](#)), and a second review author will compare these results with the results from the first review author. Both review authors will resolve any discrepancies between the results from the first review author and the software by discussion. We will use the following criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)).

- Sequence generation.
- Allocation concealment.
- Blinding (participants, personnel, outcome assessors).
- Incomplete outcome data.
- Selective outcome reporting.
- Other sources of bias.

For every criterion, we will make a judgement using one of three categories.

- 'Low risk:' if the criterion was adequately fulfilled in the study (i.e. the study was at a low risk of bias for the given criterion).
- 'High risk:' if the criterion was not fulfilled in the study (i.e. the study was at high risk of bias for the given criterion).
- 'Unclear risk:' if the study report did not provide sufficient information to allow for a judgement of 'low risk' or 'high risk,' or if the risk of bias was unknown for one of the criteria listed above.

In case we identify non-randomised studies with a control arm in review updates, we will independently assess eligible studies for methodological quality and risk of bias (using the ROBIN-I tool) ([Sterne 2016](#)). The quality assessment strongly depends upon information on the design, conduct and analysis of the trial. The two review authors will resolve any disagreements regarding the quality assessments by consulting a third review author until they reach a consensus.

We will assess the following domains of bias.

- Bias due to confounding.
- Bias in selection of participants into the study.
- Bias in classification of interventions.
- Bias due to deviations from intended interventions.

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- Bias due to missing data.
- Bias in measurement of outcomes.
- Bias in selection of the reported result.

For every criterion, we will make a judgement using one of five response options.

- Yes.
- Probably yes.
- Probably no.
- No.
- No information.

Non-randomised prospectively planned trials (including control arm)

As reported in the [Types of studies](#) section, we would have included non-randomised studies with a control arm only if we did not identify any RCTs. However, we did not identify any non-randomised prospectively planned study with a control arm. In case we identify non-randomised studies with a control arm for review updates, we will independently assess eligible studies for methodological quality and risk of bias (using the ROBIN-I tool) ([Sterne 2016](#)).

Uncontrolled studies

As reported in the [Types of studies](#) section, we included non-randomised studies without a control arm only as we did not identify any RCTs. We added the following criteria to assess potential risk of bias, as the ROBIN-I tool works for controlled trials only.

Two review authors independently assessed eligible studies for methodological quality and risk of bias (using the "risk of bias assessment criteria for observational studies" tool provided by the Childhood Cancer Group (see [Table 1](#)). The quality assessment strongly depends upon information on the design, conduct and analysis of the trial. The two review authors resolved any disagreements regarding the quality assessments by discussion, in case they would not have reached a consensus they would have consulted a third review author until final consensus.

We assessed the following domains of bias.

- Internal validity.
 - Representative study group (selection bias).
 - Complete outcome assessment/follow-up (attrition bias).
 - Outcome assessors blinded to investigated determinant (detection bias).
 - Important prognostic factors or follow-up taken adequately into account (confounding).
- External validity.
 - Well-defined study group (reporting bias).
 - Well-defined follow-up (reporting bias).
 - Well-defined outcome (reporting bias).
 - Well-defined risk estimates (analyses).

For every criterion, we made a judgement using one of three response options.

- High risk of bias.
- Low risk of bias.
- Unclear risk of bias.

Measures of treatment effect

For RCTs, we would have extracted dichotomous outcomes from both study arms and reported them as risk ratios (RR) with 95% confidence intervals (CIs) ([Deeks 2011](#)).

For updates identifying RCTs, we will extract and report hazard ratios (HR). If HRs are unavailable, we will estimate the HR by using the available data as described by [Parmar 1998](#) and [Tierney 2007](#).

For review updates identifying RCTs, we will extract and report the mean or mean change from baseline, standard deviation and total number of participants in both the experimental and control arms. If the same scale is used to measure effect, we will perform analyses using the mean difference (MD) with 95% CIs. If the included studies used different scales to measure effect, we will use standardised mean differences with 95% CIs.

Unit of analysis

Studies with multiple treatment groups

As recommended in Section 16.5.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), for review updates identifying studies with multiple treatment groups, we will combine arms as long as they can be regarded as subtypes of the same intervention. When arms cannot be pooled this way, we will compare each arm with the common comparator separately. For pair-wise meta-analysis, we will split the 'shared' group into two or more groups with smaller sample size, and include two or more (reasonably independent) comparisons. For this purpose, for dichotomous outcomes, both the number of events and the total number of participants will be divided up, and for continuous outcomes, the total number of participants will be divided up with unchanged means and standard deviations.

Assessment of heterogeneity

In case of meta-analyses, we would have assessed heterogeneity of treatment effects between trials using a χ^2 test with a significance level at P value < 0.1 . For future updates containing meta-analyses we will use the I^2 statistic to quantify possible heterogeneity (I^2 statistic value $> 30\%$ to signify moderate heterogeneity, I^2 statistic $> 75\%$ to signify considerable heterogeneity) (Deeks 2011). If heterogeneity is above 80%, and we identify a cause for the heterogeneity, we will explore potential causes through sensitivity and subgroup analyses. If we cannot find a reason for heterogeneity, we will not perform a meta-analysis, but will comment on results from all studies and presented these in tables.

Assessment of reporting biases

In review updates including meta-analyses involving at least 10 trials, we intend to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test (Sterne 2011). We will consider a P value of less than 0.1 as significant for this test.

Data synthesis

For review updates if the clinical and methodological characteristics of individual studies with a control group are sufficiently homogeneous, we will pool the data in a meta-analysis. We will perform analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We will use Review Manager 5 (RevMan 5) software for analyses (Review Manager 2014). One review author will enter the data into the software, and a second review author will check the data for accuracy. As we expect some heterogeneity in trial design, we will use a random-effects model.

We will not conduct meta-analyses by including both RCTs and non-RCTs. In case meta-analysis is feasible for non-randomised but controlled trials, we will only analyse outcomes with adjusted effect estimates if these are adjusted for as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2011).

Subgroup analysis and investigation of heterogeneity

For future updates including meta-analyses, we will perform subgroup analyses of the following characteristics.

- Age.
- Stage of disease (first-line treatment versus relapsed and refractory disease, early versus advanced stage).
- Type of previous therapy (autologous stem cell transplantation, brentuximab vedotin).
- Duration of follow-up.

We will use the tests for interaction to test for differences between subgroup results.

Sensitivity analysis

For future updates including meta-analyses, we will perform sensitivity analyses for the following.

- Quality components.
- Preliminary results versus mature results.

CONTRIBUTIONS OF AUTHORS

MG: developed and wrote the review.

MD: trial selection and data extraction.

GG: provided methodological expertise.

IM: designed the search strategy.

PD: provided methodological expertise.

JPG: provided content expertise.

AE: provided clinical expertise and content input.

BvT: provided clinical expertise.

NS: developed and wrote the review and provided methodological expertise.

DECLARATIONS OF INTEREST

MG: none known.

MD: none known.

GG: none known.

IM: none known.

PD: none known.

JPG: none known.

AE: none known.

BvT: received travel grants, scientific grants, personal fees and non-financial support from Novartis; travel grants, scientific grants, personal fees and non-financial support from Takeda; personal fees from Amgen; personal fees from Celgene; scientific grants and personal fees from MSD; and a travel grant from Bristol-Myers Squibb.

NS: none known.

SOURCES OF SUPPORT

Internal sources

- Cochrane Haematological Malignancies, Department of Internal Medicine, University Hospital of Cologne, Germany.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we specified the full methods for the assessment and analyses of randomised controlled trials (RCTs) and non-RCTs. Further we gave a detailed description of the methods we would have applied to meta-analyse data. However, as we identified neither RCTs nor non-RCTs we were not able to assess such studies nor to undertake a meta-analysis. Therefore we moved respective methods to the appendix.

NOTES

Some passages in this protocol, especially in the [Methods](#) section, are from the standard template of the CHMG.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal [*therapeutic use]; Antineoplastic Agents [*therapeutic use]; Hodgkin Disease [*drug therapy] [pathology]; Nivolumab; Software

MeSH check words

Adult; Humans