Non-Comparative, Multi-Cohort, Single Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in classical Hodgkin Lymphoma (cHL) Subjects after Failure of Autologous Stem Cell Transplant (ASCT)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas Hodgkin's disease
Study type	Interventional

Summary

ID

NL-OMON47502

Source
ToetsingOnline

Brief title
CheckMate 205

Condition

- Lymphomas Hodgkin's disease
- Lymphomas Hodgkin's disease

Synonym

(cHL), classical Hodgkin Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: autologous stem cell transplant classical Hodgkin Lymphoma, BMS-936558, nivolumab

Outcome measures

Primary outcome

The primary objective will be measured by the primary endpoint of IRRC-assessed ORR. It is defined as the number of subjects with a BOR of CR or PR, according to the 2007 IWG criteria, based on IRRC assessment, divided by the number of treated subjects. The BOR is defined as the best response designation recorded between the date of first dose and the date of initial objectively documented progression per the 2007 IWG criteria or the date of subsequent therapy, whichever occurs first. Allogeneic SCT and ASCT will be considered as subsequent anti-cancer therapy. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. For purposes of analysis, if a subject receives one dose and discontinues the study without assessment or receives subsequent therapy prior to assessment, this subject will be counted in the denominator (as non-responder).
Primary analysis will be performed separately for each cohort. (i.e. at separate time points) upon completion of a pre-specified amount of follow-up

after last patient first treatment (LPFT).

Secondary outcome

Duration of Objective Response Based on IRRC Assessment:

DOR is defined as the time from first response (CR or PR) to the date of initial objectively documented progression as determined using the 2007 IWG criteria or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR will be censored on the date of their last tumor assessment. Subjects who start subsequent therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy. This endpoint will only be evaluated in subjects with objective response of CR or PR.

Complete Remission Rate and Duration Based on IRRC Assessment:

The CR rate is defined as the number of subjects with a BOR of CR according to the 2007 IWG criteria, based on IRRC assessment, divided by the number of treated subjects. The duration of CR will only be evaluated in subjects with BOR of CR and is defined as the time from first documentation of CR (the date of first negative FDG-PET scan or the date of first documentation of no disease involvement in the bone marrow (if required), whichever occurs later) to the date of initial objectively documented progression as determined using the 2007 IWG criteria or death due to any cause, whichever occurs first. Censoring will be applied as per DOR definition.

Partial Remission Rate and Duration Based on IRRC Assessment:

The PR rate is defined as the number of subjects with a BOR of PR according to the 2007 IWG criteria, based on IRRC assessment, divided by the number of treated subjects. The duration of PR will only be evaluated in subjects with BOR of PR and is defined as the time from first documentation of PR to the date of initial objectively documented progression as determined.

Objective Response Rate and Duration Based on Investigator Assessment:

Investigator-assessed ORR and DOR are defined similarly as described for ORR and DOR per IRRC assessment above, but will be assessed per investigator.

Study description

Background summary

Cancers of the lymphatic system are called Lymphomas.There are two main types of lymphoma* Hodgkin's lymphoma (HL)
and non-Hodgkins Lymphoma. HL is the much rarer of the two, accounting for only about 1 in 5 of all lymphomas. It is characterised by the presence of ReedSternberg cells.
The majority of cells in HL tumour tissue are a mixed combination of various lymphoid cells, including regulatory Tcells and macrophages. The updated 2008 WHO classification guidelines recognise two histological types: nodular lymphocyte predominant, which accounts for about 5% of all HL cases and *classical* HL (cHL) which accounts for the remainder. In 2013, the National Cancer Institute in the US estimated that 9,290 men and women would be diagnosed with HL and 1,180 would die of HL. The prevalence of HL in the US in 2013 was estimated to be 181,928.
The treatment of limited stage cHL has improved significantly since the adoption of combined therapy, with treatment failure occurring in approximately 10% of patients. However, approximately 30% of patients presenting with newly diagnosed cHL have advanced stage disease (Stages IIB IV).
Improvements in the use of combined chemotherapy and radiotherapy in advanced stage newly diagnosed cHL have resulted in durable remission rates of approximately 60% to 80%. However, a substantial fraction of patients with cHL

are not cured* up to 10% of patients with advanced stage cHL will not achieve an initial remission, and 30% of responding patients subsequently relapse. The standard of care for patients with relapsed and refractory cHL is intensive salvage chemotherapy followed by autologous stem cell transplant (ASCT), which can produce long-term remissions in approximately 50% of patients.
Unfortunately, the remaining 50% of ASCT patients do not experience long-term disease control with an average overall survival of approximately 27 months. In particular, the prognosis remains exceedingly poor for patients who experience relapse or progressive cHL within one year after ASCT where the average survival time is approximately 1.2 years. Several small clinical studies have examined various agents in the ASCT relapsed cHL population with uniformly poor results.
Despite encouraging high response rates to a salvage drug called brentuximab vedotin (currently with conditional approval in the EMEA) long-term disease control remains challenging for classical Hodgkin Lymphoma patients as only a small proportion of patients can maintain a complete response. In addition, the tolerability of brentuximab may be of increased concern in older patients, where higher rates of anaemia and peripheral neuropathy have been reported. For the younger relatively young and otherise fit cHL population who have relapsed after ASCT, there still remains a compelling unmet need for improved salvage therapy.
The recent development of monoclonal antibodies (antibodies synthesised in a lab, made to target particular damaged cells of the body) for targeted use in cancer treatment has shown significant, documented improvements in increasing the length of overall survival in patients and also increasing the time it takes for the cancer to worsen (progression free survival, PFS) in several different cancer types.
Nivolumab, an unlicenced monoclonal antibody, is currently under development at Bristol Myers Squibb for the treatment of cancer (renal, melanoma, NSCLC and lymphoma). In an ongoing Phase I study in subjects with relapsed haematologic malignancies (CA209039), nivolumab has demonstrated preliminary activity in subjects with cHL (23 treated cHL patients). Nivolumab has been well tolerated to date, with a favourable safety profile. It has also demonstrated that used on its own as a monotherapy, can increase not only the objective tumour response rate (the amount the tumour has shrunk after receiving treatment) but also the progression free survival of patients compared to current standard of care chemotherapy.
In a healthy person the immune system (in the form of T-cells in this case) attacks any cell it recognises as abnormal or foreign. When the human body has finished attacking the abnormal cells or foreign body, the immune system sends a signal (or checkpoint) to its Tcells to switch off the attack. This signal/checkpoint or *off switch* is a protein called PDL1 (PD=Programmed Death). Since cancer cells display abnormal or foreign proteins on their surface, it is expected that the immune system should technically attack them too. However, cancer cells are also known to cover their surface with the PDL1 *off switch*. The PDL1 on cancer cells attaches itself (binds) to a protein found on the surface of the body*s attacking T-cells called PD1. When these two

proteins bind or connect, the *off switch* is activated and shuts down the Tcell. This allows the cancer cells to continue to grow undetected by the body*s immune system because the cancer cells are stopping the T-cells from performing their job (to fight foreign bodies). Nivolumab is a drug designed to bind directly to the PD1 protein on the body*s T-cell surface which effectively protects it or stops it from binding to the PDL1 switch on the surface of cancer cells. Nivolumab allows the T-cells to continue to function normally and potentially continue to fight the cancer.
This study will specifically look to answer the question as to whether nivolumab demonstrates a clinical benefit in overall tumour response rate in patietns with classical Hodgkin's Lymphoma.

Study objective

The main research question is whether or not the administration of nivolumab increases "overall response rate" (ORR) in patients with classical Hodgkin Lymphoma who have progressed or relapsed following autologous stem cell transplant (ASCT) and may or may not have received prior brentuximab treatment after their transplant.
(Overall Response Rate: The percentage of patients whose cancer shrinks or disappears after treatment as assessed using revised International Working Group criteria for Malignant Lymphoma (2007 IWG criteria).

Secondary objectives of the study include:
-To look at the durability of the response to treatment with nivolumab i.e. the length of time that the response to treatment is maintained.
-To assess the 'complete response rate'(CRR) i.e. the percentage of patients who achieve 'complete response'. In complete response, all signs and symptoms of cancer have disappeared. However, this does not always mean the cancer has been cured.
-To assess the 'partial response rate'(PRR) i.e. the percentage of patients who achieve 'partial response'. In partial response, all signs and symptoms of cancer may have disappeared. However, this does not always mean the cancer has been cured.
-To look at the "overall response rate" (ORR), based on investigator assessments.

Exploratory Objectives
• To assess the Progression Free Survival (PFS) based on IRRC assessment
• To assess the Overall Survival (OS)
• To assess the overall safety and tolerability of nivolumab, as measured by incidence and severity of AEs, serious adverse events, and specific laboratory abnormalities
• To investigate the association between biomarkers in the peripheral blood and tumour tissue, such as PD-L1 expression, with safety and efficacy measures
• To characterise pharmacokinetics of nivolumab and explore exposure-response relationships

• To characterise the immunogenicity of nivolumab monotherapy
• To evaluate both generic health related quality of life as assessed by the EQ-5D and cancer specific quality of life as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30
• To evaluate the pharmacodynamic activity of nivolumab monotherapy in the peripheral blood and tumor tissue as measured by flow cytometry, immunohistochemistry (IHT), soluble factor analysis, and gene expression (microarray technology, quantitative reverse transcription polymerase chain reaction (RT-PCR).
• For Cohort C, to evaluate risk-benefit of discontinuation schedule of the study drug for the subjects who have persistent CR for 1 year.

Study design

This is a non-comparative, three-cohort, single-arm Phase 2 study in cHL subjects >= 18 years old who failed ASCT. Subjects may be brentuximab vedotin-naïve (Cohort A), or may have had prior brentuximab vedotin treatment as a salvage therapy after failure of ASCT (Cohort B). This cohort B is fully enrolled and now closed to recruitment. Subjects who failed ASCT and who have received prior treatment with brentuximab vedotin at any timepoint will now be included in the study (Cohort C). Approximately 270 subjects with failure after ASCT will be treated with nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks until disease progression or unacceptable toxicity. Subjects will be independently enrolled for each cohort. When one cohort completes enrolment, the other cohort will remain open until its complete accrual is reached. Primary analysis will be performed separately for each cohort. (i.e. at separate time points) upon completion of a pre-specified amount of follow-up after last patient first treatment (LPFT). All analyses will be performed separately for each cohort upon completion of follow-up for the primary endpoint in each cohort. In addition safety analyses will be performed on combined cohorts. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Each 14-day dosing period will constitute a cycle. Radiographical tumour assessments by computed tomography (CT) (preferred) or magnetic resonance imaging (MRI) will begin at screening, then at Week 9 (± 7 days) after the start of therapy and will continue every 8 weeks until week 25, then every 12 weeks for the first year of treatment. CT (preferred) or MRI will continue every 16 weeks (± 14 days) for the second year of treatment. CT (preferred) or MRI will be performed every 26 weeks (± 21 days) for the third year or beyond of treatment. [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) scan will be required in all subjects at screening and at Weeks 17 and 25 (± 7 days). Additionally, a FDG-PET scan at Week 49 (± 7 days) is required for subjects who do not have two consecutive negative FDG-PET scans after Week 1 and prior to Week 49. FDG-PET scan will also be required for confirmation of radiographic CR after initiation of the study drug at other timepoints when FDG-PET is not otherwise scheduled; this FDG-PET scan should be performed within 4 weeks of the CT scan. Tumor

assessments will follow the above schedule until disease progression is documented or until the subject initiates a preparative regimen for allogeneic SCT or ASCT, whichever occurs earlier. If the subject discontinues treatment prior to disease progression, tumour assessment will continue in the follow-up phase. If the subject discontinues study therapy by proceeding to allogeneic SCT or ASCT, they will not undergo IRRC radiographic assessments described here, but will be followed with a specific schedule. Nivolumab will be administered until unacceptable toxicity or disease progression which is defined by relapsed disease (after complete remission achieved during the study) or progressive disease (after Partial Response, Stable Disease attained during the study) according to the 2007 IWG criteria. An IRRC will also be utilised. In Cohort C, subjects who have persistent CR for one year will discontinue the study drug and continue in the follow-up (FU)/Observational phase of the study. These patients will be closely observed for up to two years from the date of last dose of study drug. Re-initiation of study therapy is allowed should these subjects relapse according to the 2007 IWG criteria during these two years. They will follow the original treatment schedule and assessments. The primary endpoint of this study is objective response rate (ORR) based on IRRC assessments, using the 2007 IWG criteria. Secondary endpoints include DOR, as well as complete and partial remission rates and durations based on IRRC assessments.Primary analysis will be performed separately for each cohort. (i.e. at separate time points) upon completion of a pre-specified amount of follow-up after last patient first treatment (LPFT). Additional survival analysis will be conducted for up to 5 years beyond analysis of the primary endpoint. Cohort C will provide an extended assessment of the benefit-risk for this study drug in advanced stage cHL patients in a larger patient population. Approximately 100 subjects recruited from Cohort C will assist in the identification and characterisation of less common safety events as well as further confirmation of the activity initially observed in Cohort B. Importantly, Cohort C will also provide initial data concerning whether discontinuation of nivolumab monotherapy is safe in patients who have remained in CR for one year on nivolumab. All currently ongoing nivolumab Phase 2 and Phase 3 studies for solid tumour and hematologic malignancies permit treatment until disease progression or unacceptable toxicity. Because nivolumab is generally tolerable, some patients who have achieved CR may remain on study therapy indefinitely unless disease progression occurs. Therefore, it will be critical to answer whether these patients can safely stop treatment at some point in order to avoid unnecessary exposure to study drug, and can experience similar benefit. To address this scientific question, a discontinuation schedule will be examined in Cohort C. Subjects who have persistent CR for one year on study drug will discontinue the study drug. If 15 to 20% of the subjects from Cohort C achieve CR and maintain their CR for one year, the discontinuation schedule will be assessed on approximately 30 - 40 subjects. To ensure that patients can safely discontinue study therapy, regular follow-up observational visits will be conducted after treatment discontinuation for up to two years. Furthermore, re-initiation of study therapy will be permitted for those patients relapsing within two years of study drug discontinuation. This

discontinuation schedule will provide important information as to whether the patients who have attained good disease control can safely discontinue study drug without increasing risk of relapse. In addition, plasma samples will be collected in cohort C subjects for, but not limited to, the determination of Minimal Residual Disease (MRD).

Intervention

The medical intervention will be BMS-936558 (nivolumab) supplied by the Sponsor company. BMS-936558 will be administered
as a 60-minute IV infusion on Treatment Day 1. A treatment cycle is determined as 2 weeks for BMS-936558.

Study burden and risks

Nivolumab may cause one or more of the side effects listed below. This information is based on data from cancer subjects in other clinical trials of nivolumab. In addition, there may be side effects that are not yet known that may occur. Patients will be advised to tell the doctor or nurse right away about any possible side effects they are experiencing. The research team are experienced in dealing with this participant group.
The most common side effects of nivolumab are:
• Fatigue and Rash.
Less common side effects of nivolumab include:
• Abdominal pain
• Alkaline phosphatase increased: lab test result associated with liver or bone abnormalities
• ALT increased: lab test result associated with abnormal liver function
• Amylase increased: lab test result associated with pancreas inflammation
• AST increased: lab test result associated with abnormal liver function
• Chills
• Constipation
• Cough
• Creatinine increased: lab test result associated with decreased kidney function
• Decreased appetite
• Diarrhea
• Dry mouth
• Dry skin
• Fever
• Headache
• Lipase increased: lab test result associated with pancreas inflammation
• Inflammation of the colon
• Inflammation of the mouth
• Infusion related reaction
• Itching

• Joint pain or stiffness
• Loss of color (pigment) from areas of skin
• Lung inflammation (pneumonitis - see details below)
• Musculoskeletal pain
• Nausea
• Shortness of breath
• Swelling, including face, arms, and legs
• Thyroid gland function decreased
• Thyroid gland function increased
• Thyroid stimulating hormone increased: lab test result associated with abnormal thyroid function
• Tingling, burning, numbness or weakness, possibly in arms, legs, hands and feet
• Vomiting

Rare serious side effects of nivolumab include:
• Adrenal gland function decreased
• Allergic reaction
• Bilirubin (liver function blood test) increased
• Bronchitis
• Cranial nerve disorder
• Diabetes
• Dizziness
• Dry eye
• Hair loss
• Heart rate increased
• Heart rhythm abnormal
• High blood pressure
• Hives
• Increased blood sugar
• Inflammation of the eye
• Inflammation of the heart
• Inflammation of the kidney
• Inflammation of the pancreas
• Inflammation of the pituitary gland
• Inflammation of the stomach
• Inflammation of the thyroid gland
• Liver inflammation
• Low blood pressure
• Pituitary gland function decreased
• Psoriasis: characterized by patches of abnormal, scaly skin
• Redness
• Renal failure
• Respiratory failure
• Sodium levels in blood low
• Upper respiratory tract infection
• Vertigo

• Vision blurred

Very Rare side effects of nivolumab include:
• Anaphylactic reaction (severe allergic reaction)
• Damage to the protective covering of the nerves in the brain and spinal cord
• Diabetes complications resulting in excess blood acids and diabetic coma
• Erythema multiforme: skin inflammatory reaction
• Guillain-Barre syndrome, an autoimmune disorder associated with progressive muscle weakness or paralysis
• Inflammation of blood vessels
• Inflammation of the brain, potentially life-threatening or fatal
• Lung infiltrates, associated with infection or inflammation
• Muscle inflammation
• Myasthenic syndrome (neurologic syndrome characterized by muscle weakness) including myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles.
• Polymyalgia rheumatica, an inflammatory disorder causing muscle pain and stiffness
• Rhabdomyolysis: muscle fiber released into the blood stream which could damage your kidneys
• Rosacea: acne-like skin condition resulting in redness of face
• Sarcoidosis, a disease involving abnormal collections of inflammatory cells (granulomas) in organs such as lungs, skin, and lymph nodes
• Stevens Johnson syndrome: inflammatory disorder of skin and mucous membranes, resulting in blistering and shedding of skin
• Toxic epidermal necrolysis: a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn
• Histiocytic necrotizing lymphadenitis or Kikuchi lymphadenitis: disorder of the lymph nodes which causes the lymph nodes to become enlarged, inflamed and painful, commonly affecting lymph nodes of the neck and possibly associated with fever or muscle and joint pains

It is possible that nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported infrequently in patients treated with nivolumab. While many patients with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels, or fatigue.
Also, Complications, including fatal events, have occurred in patients who received allogeneic hematopoietic stem cell transplantation (HSCT) after nivolumab.
Because of the potential for the development of nivolumab related AEs including Adverse Events of Special Interest (AEOSI). management algorithms have been developed by BMS for suspected pulmonary toxicity, diarrhoea or suspected colitis, hepatotoxicity, endocrinopathy and renal toxicity and are contained

within the IB. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the Investigator Brochure. Procedures and assessments are in place to help detect and monitor these potential adverse events (e.g. measurement of oxygen levels by pulse oximetry, frequent safety blood testing, CT scans etc.) Risks for men/women of childbearing potential (known and unknown). This risk will be minimised by regularly performing pregnancy testing, informing the participants and their partners that they must use contraception during study and for a specified time following end of treatment. Mild discomfort and pain may be experienced from taking vital signs and blood sampling (bruising, bleeding, and infection at the site of the needle stick). These tests and procedures will be conducted by trained medical professionals. Risks from exposure to radiation from CT/PET/MRI scans - The risk of these has been reviewed by an Independent Clinical Radiation Expert and they have concluded that the risk of a radiation induced cancer in this study population is low. Sometimes patients have allergic reactions to the dyes used in CT scans. This is rare. It can involve itching or rash and in severe cases, breathing difficulties and low blood pressure levels. Patients will be instructed to let the study doctor and radiologist know of any known allergies. Risks of biopsy: This procedure can be painful and depending on the location of the tumour may pose a substantial risk to the patient. This procedure will be carried out by qualified medical professionals in the hospital setting. Risks from taking prohibited medications. This risk will be minimised as the study team will frequently review all concomitant medication being taken by the subject* if applicable, cards listing all prohibited medications will be given to site staff/ participants and the participant*s GP will be informed of these prohibited medications. Participants will be required to attend the research unit on a regular basis whilst they are on the trial thus involving an increase in travel. Participants may have to alter any pre*existing plans/appointments to fit in with the required visits as laid out in the protocol. These visits are necessary to monitor the subject*s safety and wellbeing. Reasonable travel expenses will be reimbursed. Risks associated with a loss of privacy or confidentiality if a patient's identity as a participant in this study or their identifiable genetic or health information were disclosed to unauthorised persons. There is a possible risk of sponsor organising the research) believes that the risks of such improper disclosure are very small because they have adopted strict privacy and confidentiality procedures for this research. Occasionally during the course of a study, participants may be found to have a previously undiagnosed medical condition. In this situation their study doctor will take the necessary steps to ensure they receive appropriate treatment. If during the course of this study, new information becomes available about the treatment/drug that is being studied, it will be discussed with the participant and they will be asked if they would like to continue in the study. As a consequence of this new information and to ensure participant safety, it may be necessary to make modifications to the study design which would include changing the timing of dosing, changing the number of tests being performed or perhaps even stopping the study. In any event, the participant and investigator will be fully informed and the patient

will be given every opportunity to consider their continued participation in the trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Signed Written Informed Consent
a) Subjects must have signed and dated an IRB/IEC approved written informed consent
form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.
b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.

Target Population:
a) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1,
b) Must have received prior highdose conditioning chemotherapy followed by ASCT as a part of salvage therapy for cHL:
i) Cohort A: Subjects who are naïve to brentuximab vedotin treatment and who meet one of the following criteria according to the 2007 IWG criteria:
(1) Documented absence of CR after 90 days from stem cell infusion for the most recent ASCT* or,
(2) Documented relapsed disease (after CR) or disease progression (after PR or SD)
ii) Cohort B: Subjects who failed treatment with brentuximab vedotin which was administered following failure of ASCT, and who meet one of the following criteria
according to the 2007 IWG criteria:
(1) Documented failure to achieve at least PR after the most recent treatment* or,
(2) Documented relapse disease (after CR) or disease progression (after PR or SD)
C) Must have at least one lesion that is > 15mm (1.5cm) in the longest diameter on
crosssectional imaging and measureable in two perpendicular dimensions on CT (or MRI) and FDG avid by PET.
iii) Cohort C: Subjects who failed ASCT and who have received prior treatment* with brentuximab vedotin at any timepoint, and who meet one of the following criteria according to the 2007 IWG criteria:
(1) Documented absence of CR after 90 days from stem cell infusion for the most recent ASCT; or,
(2) Documented failure to achieve at least PR after the most recent chemotherapy or radiation therapy; or,
(3) Documented relapse disease (after CR) or disease progression (after PR or SD)
*This includes brentuximab vedotin treatment as an initial therapy or salvage therapy before ASCT, and/or brentuximab vedotin treatment after ASCT (eg salvage and maintenance therapy after ASCT)
d) Biopsy confirmation of cHL prior to the initiation of study drug. cHL should be pathologically confirmed by standard immunohistochemical or flow cytometric techniques.
e) Subject re-enrolment:
This study permits the re-enrolment of a subject who has discontinued the study as a pretreatment failure (ie, subject has not been randomised/has not been treated). If re-enrolled, the subject must be reconsented.
Age and Reproductive Status:
a) Males and Females, >= 18 years of age.
b) Women of childbearing potential (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.
c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug plus 5 half lives of study drug plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post treatment completion.
e) 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 halflives of study drug plus 90 days (duration of sperm turnover) for a total of 31 weeks posttreatment completion
f) Azospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy
testing as described in this section.
Physical and Laboratory Test Finding
a) Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to first dose:
i) Absolute neutrophil Count >= 750/µl (no WBC growth factors for prior 14 days).
ii) Platelets >= 50 x10*3/µl (no platelet transfusions for prior 14 days).
iii) Haemoglobin >= 8.5 g/dL (no RBC transfusions for prior 7 days).
iv) Serum creatinine <= 1.5 x Upper Limit of Normal (ULN) or creatinine clearance (CrCl) >= 40 ml/min (measured
using the CockcroftGault formula below):
Female CrCl = (140 age in years) x weight in kg x 0.85 /
(72 x serum creatinine in mg/dl)
Male CrCl = (140 age in years) x weight in kg x 1.00 /
(72 x serum creatinine in mg/dL)
v) AST/ALT <= 3 x ULN.
vi) Total bilirubin <= 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL).
b) Subjects with a prior history of chemotherapyinduced or radiation induced pulmonary toxicity require confirmation of diffusing capacity of the lung for carbon monoxide (DLCO) over 60%
(adjusted for hemoglobin) by a pulmonary function
test prior to study enrolment.

Exclusion criteria

1. Target Disease Exceptions
a) Known central nervous system lymphoma.
b) Subjects with nodular lymphocytepredominant HL., 2. Medical History and Concurrent Diseases, a) Subjects with active interstitial pneumonitis.
b) 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 subject to receive protocol therapy, or interfere with the interpretation of study results.
c) 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.
d) Subjects with active, known or suspected autoimmune disease. Subjects with 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 are permitted to enroll.
e) Subjects with a condition requiring systemic treatment with either corticosteroids(> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease., 3. Physical and Laboratory Test Findings
a) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.
b) Known history of testing positive for human immunodeficiency virus (HIV) or known
acquired immunodeficiency syndrome (AIDS)., 4. Allergies and Adverse Drug Reaction
a) History of allergy to study drug components.
b) History of severe hypersensitivity reaction to any monoclonal antibody., 5. Prohibited Treatments and/or Therapies
a) Prior treatment history with brentuximab vedotin administered before first ASCT (for cohorts A and B).
b) ASCT <= 90 days prior to first dose of study drug.
c) Prior chemotherapy within 4 weeks, nitrosureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio or toxin immunoconjugates (excluding brentuximab vedotin) within 10 weeks and brentuximab vedotin within 4 weeks or major surgery within 2 weeks prior to first dose of study drug.
d) Carmustine BCNU) >= 600 mg/m² received as part of the pretransplant conditioning regimen.
e) Prior radiation therapy within 3 weeks, or chest radiation <= 24 weeks prior to first dose of the study drug.
f) Prior treatment with an antiPD1, antiPDL1, antiPDL2, antiCD137, or antiCTLA4 antibody (including ipilimumab or any other antibody or drug specifically targeting Tcell costimulation or checkpoint pathways).
g) Prior allogeneic SCT.
6. Other Exclusion Criteria
a) Prisoners or subjects who are involuntarily incarcerated
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical(eg, infectious disease) illness
Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-09-2014
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BMS-936558
Generic name:	nivolumab

Ethics review

Approved WMO Date:	08-07-2014
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-09-2014
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	05-12-2014
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	10-12-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-02-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-08-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-11-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-12-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-08-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-08-2016
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	23-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-11-2020
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-10-2022
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-001509-42-NL
CCMO	NL49314.031.14

Study results

Results posted: 08-11-2023

First publication
01-01-1900