# A Single-Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) After Failure of Autologous Stem Cell Transplant (ASCT) or After Failure of At Least Two Prior Multi-Agent Chemotherapy Regimens in Subjects Who Are Not Candidates for ASCT

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Research Hypothesis: Treatment with nivolumab (BMS-936558) will lead to clinical benefit, as demonstrated by a clinically meaningful objective response rate, including durable responses with substantial magnitude of tumor burden reduction.Primary...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Lymphomas non-Hodgkin's B-cell |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON40237

**Source**
ToetsingOnline

**Brief title**
CA209-139

## Condition

- Lymphomas non-Hodgkin's B-cell

**Synonym**
Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** Autologous, BMS-936558, Nivolumab, Relapsed or Refractory DLBCL, Stem Cell Transplant (ASCT)

## Outcome measures

**Primary outcome**

The primary objective will be measured by the primary endpoint of independent radiological review committee (IRRC)-assessed objective response rate (ORR). It is defined as the number of subjects with a best overall response (BOR) of complete remission (CR) or partial remission (PR), according to the revised International Working Group Criteria for non-Hodgkin Lymphoma, divided by the number of treated subjects. The final analysis of the primary endpoint will occur at least 6 months after the last enrolled subject*s first dose of study therapy. 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 revised International Working group Criteria for non-Hodgkin Lymphoma or the date of subsequent therapy, whichever occurs first.

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-respondent).

**Secondary outcome**

The first secondary objective will be measured by the duration of ORR (DOR) 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 revised International Working Group Criteria for non-Hodgkin Lymphoma 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 evaluable tumor assessment. This endpoint will only be evaluated in subjects with objective response of CR or PR.

The second secondary objective will be measured by the complete remission rate (CRR) based on IRRC assessment. The CRR is defined as the number of subjects with a BOR of CR according to the revised International Working Group Criteria for non-Hodgkin Lymphoma, divided by the number of treated subjects. The BOR is defined similarly as above.

The third secondary objective will be measured by IRRC-assessed progression free survival (PFS). It is defined as the time from first dosing date to the date of the first documented progression, as determined by an IRRC, or death due to any cause, whichever occurs first.

Subjects who die without a reported progression will be considered to have

progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable assessment. Subjects who did not have any on study assessments and did not die will be censored on the first dosing date. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable assessment prior to initiation of the subsequent anti-cancer therapy.

The fourth secondary objective will be measured by investigator-assessed ORR. Investigator-assessed ORR is defined similarly as described for the primary endpoint above.

# Study description

**Background summary**

Nivolumab (BMS-936558) is in clinical development for the treatment of subjects with solid tumors and hematological malignancies as both monotherapy and in combination with ipilimumab. The purpose of this study (CA209-139) is to determine if nivolumab treatment of patients with diffuse large B-Cell lymphoma (DLBCL) will lead to clinical benefit. The patients* targeted have previously relapsed or were non-responsive to an autologous stem cell transplant (ASCT), or have failed at least two prior multi-agent chemotherapies and are not candidates for ASCT. In addition to study CA209139, studies to be conducted in the hematologic malignancies program will assess the efficacy of nivolumab in subjects with refractory follicular lymphoma. Nivolumab has shown preliminary activity in subjects with DLBCL and FL.

DLBCL is the most common lymphoid malignancy in adults and while many respond to initial chemotherapy, 30-40% fail first line therapy and have reduced success to further regimens or ASCT, leaving 10-15% with a poor prognosis. The initial approach to relapsed or refractory DLBCL management is to determine whether the patient is a candidate for ASCT. In general, patients achieving a complete response (CR) or partial response (PR) to 2nd line therapy, can be considered for ASCT. Commonly used exclusion criteria include advanced age (above 70 to 75 years), co-morbidities, and inadequate social support to assist in post-transplantation care. Using these criteria, approximately 60% of relapsed/refractory patients will be eligible for HD ASCT but only 20 to 25% of

these patients will be cured by high dose chemotherapy and ASCT. Although chemosensitivity is clearly the most important determinant of outcome for ASCT for relapsed or refractory DLBCL, a significant proportion of patients with chemosensitive disease have progressive disease after ASCT. Treatment options following ASCT failure are limited for patients with DLBCL; expectedly disease recurrence remains the predominant cause of treatment failure. Optimal management strategies for these patients have yet to be established and outcomes for patients requiring subsequent lines of therapy remain particularly poor. The median overall survival of non-responding patients after ASCT or salvage therapy in transplant ineligible patients is approximately 4.3 months.

**Study objective**

Research Hypothesis: Treatment with nivolumab (BMS-936558) will lead to clinical benefit, as demonstrated by a clinically meaningful objective response rate, including durable responses with substantial magnitude of tumor burden reduction.

Primary Objective
To assess the clinical benefit of nivolumab, as measured by independent radiologic review committee (IRRC)
assessed objective response rate (ORR) in subjects with DLBCL who are refractory or have relapsed following
ASCT (Autologous Stem Cell Transplant) or after failure of at least two prior multi-agent chemotherapy regimens in ASCT ineligible patients.

Secondary Objectives(s)
- To assess the duration of response (DOR) based on IRRC assessments
- To assess the complete remission rate (CRR) based on IRRC assessment
- To assess the progression free survival (PFS) based on IRRC assessment
- To assess the ORR, based on investigator assessments

Exploratory Objective(s)
- To assess the overall safety and tolerability of nivolumab, as measured by incidence and severity of adverse events, serious adverse events, and specific laboratory abnormalities
-To assess the objective response rate and duration of objective response of nivolumab in PD-L1 positive and PD-L1 negative subgroups, using both investigator and IRRC assessments
- To assess progression-free survival in all treated subjects, as well as in PD-L1 positive and PD-L1 negative subgroups, using both investigator and IRRC assessments
-To assess overall survival in all treated subjects, as well as in PD-L1 positive and PD-L1 negative subgroups
- To characterize pharmacokinetics of nivolumab and explore exposure-response relationships with respect to selected safety and efficacy endpoints
- To characterize 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 EORTC QLQ-C30
- To evaluate the pharmacodynamic activity of nivolumab monotherapy in the peripheral blood and tumor tissue as measured by flow cytometry, immunohistochemistry, soluble factor analysis, and gene expression (microarray technology, quantitative RT-PCR)

**Study design**

This is a single-arm Phase 2 study in subjects * 18 years old with relapsed or refractory DLBCL or
transformed lymphoma (TL) after failure of ASCT or after failure of at least two prior multi-agent chemotherapy
regimens in subjects who are not ASCT candidates. Approximately 120 subjects will be treated with nivolumab 3 mg/kg IV every 2 weeks. Subjects will be placed into treatment groups based on prior ASCT failure [n=90] or ASCT ineligibility [n=30].
For the ASCT-failed cohort, a two-stage design will be used to test whether nivolumab yields a clinically compelling objective response rate. In the first stage, responses will be evaluated by the IRRC on the first 37 subjects treated. If there are 8 or fewer responses in these 37 subjects, the study will be stopped. In this case, the study will be terminated in both the ASCT-failed cohort as well as the ASCT ineligible cohort. Otherwise, approximately 53 additional subjects will be accrued into the ASCT-failed cohort to target a total of 90 treated subjects.
The tolerability of the regimen will continue to be evaluated by the sponsor with the investigators to
ensure that it is acceptable for continued enrollment. Recruitment and treatment of subjects in both groups (ASCT failure and ASCT ineligible) will continue as described during the evaluation of the first 37 ASCT failure subjects treated.
For the ASCT ineligible cohort a single stage design will be used to estimate the objective response rate using approximately 30 treated subjects.
This study will consist of three phases: screening, treatment, and follow-up. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Study drug is administered as an IV infusion on Treatment Day 1 of each Cycle. Each 14-day dosing period will constitute a cycle. Subjects will be evaluated for tumor response by spiral CT/MRI beginning at week 9 (Day 1 of Cycle 5) and continuing every 8 weeks (+/- 1 week) through the first 8 months, every 12 weeks (+/- 2 weeks) months 9-24, and then every 6 months (+/-3 weeks) thereafter until disease progression is documented.
Collection of fresh tumor tissue (FFPE tumor tissue block or 10 unstained slides from a biopsy
performed during the screening phase or collected as a standard of care procedure within 90 days prior to obtaining informed consent) for determination of PD-L1 expression status is mandatory. Archival tissue should be submitted

for all subjects if available. Treatment will continue until disease progression or discontinuation due to toxicity, withdrawal of study consent, or the study ends. Subjects will be followed every 3 months for survival after completion of the follow up visits.

### 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

As part of the trial, patients will be expected to attend multiple clinic visits where they will undergo physical examinations, vital sign measurements including oxygen saturation levels, blood tests for safety assessment, pregnancy testing (for females of child bearing potential) and monitoring for adverse events. In addition, every 8 weeks (from week 9 onwards) patients will undergo radiographic assessment of their tumour(s) (by Spiral CT or MRI) through the first 8 months, every 12 weeks through months 9-24, and then every 6 months thereafter until disease progression or treatment discontinuation whichever occurs later. An additional PET scan would be required to confirm CR. Blood samples will be collected at certain visits for research purposes (PK and immunogenicity) including Biomarker samples. The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard over care. These procedures are carried out by trained medical professionals and every effort will be made to minimize any risks or discomfort to the patient. Treatment for cancer often have side effects, including some that are life-threatening. Because of the potential for clinically meaningful nivolumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and nephrotoxicity.
The clinical benefit of nivolumab, as measured by independent radiologic review committee (IRRC)
assessed objective response rate (ORR) will be utilized.

## Contacts

**Public**
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**Scientific**
Bristol-Myers Squibb

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

1. a) Signed written Informed consent
b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.
2. a) Tumor Biopsy confirmation of relapsed or refractory DLBCL, or transformed lymphoma (TL), prior to the initiation of study drug.
i) TL is limited to DLBCL. Subjects with Grade 3b follicular lymphoma are excluded.
ii) DLBCL or TL should be pathologically confirmed by standard immunohistochemical or flow cytometric techniques.
iii) Documentation of the above should be present in the subject*s medical record.
b) Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
c) Measurable disease: Subjects must have at least one lesion that is > 1.5 cm in the longest diameter on cross-sectional imaging and measureable in two perpendicular dimensions per computed tomography (spiral CT).
d) Prior treatment as defined below;
i) Subjects with relapsed DLBCL or TL after high-dose conditioning chemotherapy and ASCT, OR
ii) Subjects with relapsed or refractory DLBCL or TL after at least 2 prior multi-agent chemotherapy regimens if ASCT ineligible. Ineligibility for ASCT will be determined using local institutional criteria.
Definition of Relapsed DLBCL

- the appearance of new lesions > 6 months after obtaining a CR
-an increase <50% in the size of previously involved sites > 6 months after completing planned therapy.
Definition of Refractory DLBCL:
- < 50% decrease in lesion size after planned therapy,
- the appearance of new lesions < 6 months after completion of planned therapy
- an increase of >50% in the size of previously involved sites < 6 months after completion of planned therapy.
e) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized /has not been treated). If re-enrolled, the subject must be re-consented.
3. 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 x103/µL (no platelet transfusions for prior 14 days)
iii) Hemoglobin > 8.5 g/dL (no RBC transfusions for prior 7 days)
iv) Serum creatinine * 1.5 x ULN or creatinine clearance (CrCl)*40 ml/min (measured using the Cockcroft-Gault 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*s Syndrome, who can have total bilirubin < 3.0 mg/dL).
4. a) Men and women *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 nivolumab plus 5 half-lives of nivolumab 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 nivolumab plus 5 half-lives of nivolumab plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion.
f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in these sections

## Exclusion criteria

1. a) Known central nervous system lymphoma.
2. a) History of interstitial lung disease.
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. 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. a) History of allergy to study drug components.
b) History of severe hypersensitivity reaction to any monoclonal antibody.
5. a) Autologous Stem Cell Transplant (ASCT) * 12 weeks prior to first dose of the study drug.
b) Prior chemotherapy within 2 weeks, nitrosureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin immunoconjugates within 10 weeks, radiation therapy within 3 weeks, or major surgery within 2 weeks of first dose of the study drug.
c) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways
d) Prior allogeneic SCT.
e) Chest radiation * 24 weeks prior to the first dose of study drug
f) Carmustine (BCNU) * 1000 mg received as part of pre-transplant conditioning regimen
6. 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

# Study design

## Design

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| Study phase: | 2 |
| Study type: | Interventional |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |

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| Primary purpose: | Treatment |

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 14-08-2014 |
| Enrollment: | 11 |
| Type: | Actual |

### Medical products/devices used

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

## Ethics review

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|---|---|
| Approved WMO Date: | 20-02-2014 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 31-07-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 05-08-2014 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 26-09-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 28-10-2014 |
| Application type: | Amendment |

| | |
|---|---|
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 25-11-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 07-01-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 22-01-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 26-05-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 22-06-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 16-10-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 08-12-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 18-11-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 02-03-2017 |
| Application type: | Amendment |

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|---|---|
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 09-03-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 29-03-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 25-09-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 27-09-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

# 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 | EUCTR2013-003621-28-NL |
| CCMO | NL47125.041.14 |

# Study results

Results posted: 16-09-2021

**First publication**
15-09-2021