Product Name	Opdivo
Active substance	Nivolumab (BMS-936558)
Indication and conditions of use	Provide an option for patients suffering from locally advanced and metastatic Non-Small-Cell Lung Cancer (NSCLC) who have documented progression on or after prior chemotherapy. The dose and schedule of nivolumab in this compassionate use will be 3mg/kg in IV every 2 weeks

Conditions, delays and further rules for participation of patients	***Inclusion Criteria*** **1) Eligibility for clinical trials** The patient is not eligible for a clinical trial running with Nivolumab and/or a clinical trial running in the envisaged indication of this program. **2) Signed Written Informed Consent** Before any program procedures are performed, the details of the program will be described to the patient, and the patient will be given a written informed consent document to read. If the patient agrees to participate in the program, consent will be indicated by signing and dating of the informed consent document in the presence of program personnel. **3) Target Population** • Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of ≤ 2 • Patients with histologically- or cytologically-documented NSCLC who presented with Stage IIIB/Stage IV disease (according to Version 7 of the *International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology*) or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemo-radiation therapy for locally advanced disease). Note: Enrollees must not be eligible for another clinical study with nivolumab. A fresh biopsy is not required to take part in this program. • Subjects must have experienced disease progression or recurrence during or after at least one systemic therapy for advanced or metastatic disease ; all the following criteria should be met: i) Each subsequent line of therapy must be preceded by disease progression. A switch of an agent within a regimen in order to manage toxicity does not define the start of a new line of therapy. ii) Patients cannot be satisfactorily treated with the approved and commercially available alternative treatments, in accordance with clinical guidelines, because of efficacy and/or safety issues. Patients should have documented progression on, or after, at least one line of chemotherapy; prior treatment with platinum-doublet chemotherapy is mandatory. (1) Subjects who received platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible.

(2) Subjects with recurrent disease > 6 months after completing a platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a systemic regimen given to treat the recurrence, are eligible.

iii) Patients with driver mutations (such as EGFR mutation or ALK translocation) should also have documented progression on, or after, an approved and commercially available EGFR- or ALK-targeted agent in monotherapy.

- Prior chemotherapy, TKI, or immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer) must have been completed at least 2 weeks before program drug administration, and all AEs have either returned to baseline or stabilized.
- Prior palliative radiotherapy must have been completed at least 14 days prior to program drug administration
- Patients are eligible if CNS metastases are treated and patients have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 14 days prior to enrollment. In addition, patients must either be off corticosteroids or on a stable dose or decreasing dose of ≤ 10 mg daily prednisone (or equivalent)
- Patients with Type I diabetes mellitus, residual hypothyroidism due to an autoimmune condition 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
- Screening laboratory values must meet the following criteria prior to commencement of treatment:
  i) WBCs ≥ 2000/µL
  ii) Neutrophils ≥1500/µL
  iii) Platelets ≥ 100 X10^3/µL
  iv) Hemoglobin ≥ 9.0 g/dL
  v) Serum creatinine of ≤ 1.5 X ULN or creatinine clearance (CrCl) > 40 mL/minute (using Cockcroft/Gault formula)
  (1). Female CrCl= [(140- age in years) X weight in kg X 0.85) ÷ (72 X serum creatinine in mg/ dL)]
  (2). Male CrCl= [(140- age in years) X weight in kg X 1.00) ÷ (72 X serum creatinine in mg/ dL)]
  vi) AST ≤ 3 X ULN
  vii) ALT ≤ 3 X ULN
  viii) Total bilirubin ≤ 1.5 X ULN (except patients with Gilbert Syndrome, who must have total bilirubin < 3.0 mg/dL)

4) Age and Reproductive Status

a) Men and women aged ≥ 18 years old

	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 program drug c) Women must not be breastfeeding d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 halflives of nivolumab (5 x half-life = 125 days) plus 30 days (duration of ovulatory cycle) for a total of 155 days or 23 weeks post-treatment completion e) Males 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 the program drug (125 days) 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 this section. Investigators shall counsel WOCBP and male patients who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male patients who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. At a minimum, patients must agree to the use of 2 methods of contraception, with 1 method being highly effective and the other method being either highly effective or less effective as listed below: **HIGHLY EFFECTIVE METHODS OF CONTRACEPTION** Male condoms with spermicide ○ Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by WOCBP patient or male patient's WOCBP partner. Female partners of male patients participating in the program may use hormone-basedcontraceptives as one of the acceptable methods of contraception since they will not be receiving program drug. o Nonhormonal IUDs, such as ParaGard® o Tubal ligation o Vasectomy o Complete abstinence

NOTE: Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all program drugs. Patients who choose complete abstinence are not required to use a second method of contraception, but female patients must continue to have pregnancy tests. Acceptable alternative methods of highly effective contraception must be discussed in the event that the patients chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

Diaphragm with spermicide
Cervical cap with spermicide
Vaginal sponge
Male condom without spermicide
Progestin only pills by WOCBP patients or male patient's WOCBP partner
Female condom
NOTE: A male and female condom must not be used together

Exclusion Criteria

1. Target Disease Exceptions

a) Patients with ECOG PS ≥ 3
b) Patient with untreated CNS metastases are excluded. Patients are eligible if CNS metastases are treated and patients have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, patients must either be off corticosteroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).
c) Patients with carcinomatous meningitis are excluded
d) Patients with < 6 weeks life expectancy

2. Medical History and Concurrent Diseases

a) Patients with known active, known, or suspected autoimmune disease
b) Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose of program drug administration. Inhaled or topical steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.

c) Patients who received prior therapy with anti-PD-1, anti-PD-L1, anti-PDL2, anti-CT137 or anti-CTLA-4 antibody including ipilimumab or any other antibody or drug specifically targeting T cell costimulation or checkpoint pathways
d) Prior treatment in any nivolumab trial including prior treatment on either arms of nivolumab study CA209017, CA209026, or ipilimuamb study CA184104
e) Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
f) Other active malignancy requiring concurrent intervention
g) Patients with previous malignancies (except non-melanoma skin cancers and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 1 year prior to program entry AND no additional therapy is required during the program period
h) Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with program participation, program drug administration, or would impair the ability of the patient to receive program therapy
i) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of program drug
j) Patients must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of program treatment
k) Known alcohol or drug abuse

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 severe hypersensitivity reactions to other monoclonal antibodies
b) History of allergy or intolerance (unacceptable adverse event) to program drug components or Polysorbate-80-containing infusions

5. Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding

	b) Women with a positive pregnancy test at enrollment or prior to administration of program medication **6. Other Exclusion Criteria** a) Prisoners or patients who are involuntarily incarcerated b) Patients who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness Eligibility criteria for this patient have been carefully considered to ensure the safety of the program patients. It is imperative that patients fully meet all eligibility criteria. ***Women of Childbearing Potential*** Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In additional, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause. Women treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout periods below are suggested guidelines, and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal: • 1 week minimum for vaginal hormonal products, (rings, creams, gels) • 4 week minimum for transdermal products • 8 week minimum for oral products Other parenteral products may require washout periods as long as 6 months. The responsible physician will evaluate the eligibility of the patient and inform the requestor. Rejection or approval will be sent to the requesting physician within the 10 working days. If the request has been approved, the physician will receive the Compassionate use program protocol and all the procedural documents.

Duration of the program	This program will start as soon as accepted by health authorities. For patients starting nivolumab in this program, nivolumab will be provided free of charge by Bristol-Myers Squibb on an individual patient basis following the criteria stated in this protocol until the product will be commercially available (and reimbursed) in Belgium or until, in the clinical judgement of the treating physician, the patient is not longer benefiting from continuation of the treatment, whichever is sooner. As of marketing authorisation, Bristol-Myers Squibb can decide at any moment to terminate enrolment of new patients in the program.
Conditions of distribution	The drug will be provided to the pharmacy of the hospital of the treating physician.
Responsible of the program	Bristol-Myers Squibb Belgium NV Parc de l'Alliance, Avenue de Finlande ,4 1420 Braine l'Alleud – Belgium <u>Contact person:</u> Mr. Tom Van Lee Scientific Advisor Immuno-Oncology, Disease Area Lead 0493/51.11.29 Tom.VanLee@bms.com
Modalities for the disposal	Any unused medication needs to be returned to Bristol-Myers Squibb or destroyed in an appropriate facility as soon as possible after the patient's discontinuation from the Compassionate use program. For this program, program drugs (those supplied by BMS or sourced by the investigator) such as partially used program drug containers, vials, and syringes may be destroyed on site. Any unused program drugs can only be destroyed after being inspected and reconciled by the responsible program physician unless program drug containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxics or biologics). On-site destruction is allowed provided minimal standards are met (see protocol) If conditions for destruction cannot be met, the responsible Bristol-Myers Squibb will make arrangements for return of program drug.

The information for registration of suspected unexpected serious adverse reactions	The most common side effects of nivolumab are: • Fatigue • Skin reactions: including rash, itching, hives, redness, and dry skin • Diarrhea • Nausea • Abdominal pain • Decreased appetite • Low red blood cells • Fever • Joint pain of stiffness The treating physician should report any adverse event to the below contact person. <u>Adverse Events Reporting Contact:</u> Mrs. Patricia VANDAMME, Head of Country Pharmacovigilance Belgium Avenue de Finlande, 4 1420 Braine-l'Alleud Fax number: 02 352 75 66 Email: safety_belgium@bms.com