CLINICAL STUDY PROTOCOL
MYL-1402O-3001

Multicenter, Double-Blind, Randomized, Parallel-Group Study to Assess the Efficacy and Safety of MYL-1402O Compared with Avastin®, in the First-line Treatment of Patients with Stage IV Non-Squamous Non-Small Cell Lung Cancer

Sponsor: Mylan GmbH
Thurgauerstrasse, 40
CH-8050 Zürich, Switzerland

Sponsor Contacts:

Catherine E Micales, MT
Global Clinical Operations
Mylan
1000 Mylan Boulevard
Canonsburg, PA 15317 USA
Tel: +1 (724) 485 6596
catherine.micales@mylan.com

Dr. Eduardo Pennella, MD
Global Clinical Development
Mylan
1000 Mylan Boulevard
Canonsburg, PA 15317 USA
Tel: +1 (724) 514 2369
eduardo.pennella@mylan.com

CONFIDENTIAL

Protocol Approval – Sponsor Signatory

Study Title	Multicenter, Double-Blind, Randomized, Parallel-Group Study to Assess the Efficacy and Safety of MYL-1402O Compared with Avastin®, in the First-line Treatment of Patients with Stage IV Non-Squamous Non-Small Cell Lung Cancer
Protocol Number	MYL-1402O-3001
Version No.	3.0
Protocol Date	19 February, 2019

Protocol accepted and approved by:

Head of Global Clinical Research

Dr. Abhijit Barve, MD, PhD
Mylan
1000 Mylan Boulevard
Canonsburg, PA 15317 USA
abhijit.barve@mylan.com

Signature 3/19/2019 **Date**

Senior Director, Clinical Project Leader, Oncology/Hematology

Dr. Eduardo Pennella, MD
Mylan
1000 Mylan Boulevard
Canonsburg, PA 15317 USA
eduardo.pennella@mylan.com

Signature 25-FEB-2019 **Date**

Director, Global Clinical Operations - Oncology/Hematology

Catherine E Micales, MT (ASCP)
Mylan
1000 Mylan Boulevard
Canonsburg, PA 15317 USA
catherine.micales@mylan.com

19 March, 2019

Signature **Date**

Senior Director, Global Head of Clinical Safety

Dr. Dhaval Panchal, MD
Head of Global Safety Surveillance, Risk Management and Clinical Safety
Global Product Safety & Risk Management
Mylan Laboratories Ltd.
Hyderabad – 500032. India.
dhaval.panchal@mylan.com

Digitally signed by Dhaval Panchal-m290530
Date: 2019.03.20 18:05:38 +05'30'

Signature **Date**

Head of Biometrics and Biostatistics

Hans-Friedrich Koch, PhD
Mylan Healthcare GmbH
Freundallee 9A
30173 Hannover, Germany
hans-friedrich.koch@mylan.com

20 March, 2019

Signature **Date**

Declaration of Principal Investigator

I have read and understood all sections of the protocol (MYL-1402O-3001) entitled "Multicenter, Double-Blind, Randomized, Parallel-Group Study to Assess the Efficacy and Safety of MYL-1402O Compared With Avastin®, in the First-line Treatment of Patients with Stage IV Non-Squamous Non-Small Cell Lung Cancer".

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 3.0, dated 19 February 2019, the International Conference on Harmonisation, harmonised tripartite guideline E6 (R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Mylan GmbH or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer interventional treatment only to patients under my personal supervision or the supervision of a sub investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Mylan GmbH.

Signature of Principal Investigator	**Date**
Printed Name of Principal Investigator	**Date**

Document History

Version, Date	Summary of Changes
Version 3.0, February 19, 2019	• Update the definition of primary endpoint "The primary efficacy endpoint Overall Response Rate (ORR) will be based on best tumor responses as assessed by an independent review at any time point during the first 18 weeks, and assessed according to RECIST 1.1 • ORR based on confirmed tumor responses will be evaluated as sensitivity analysis
Version 2.0, April 04, 2018	• Change in Study Design including Removal of the Survival Period from the study; every subject will be part of the study till 42 weeks (Period 2), beyond which they can receive treatment under the extended period. During the Extended Period AEs related only to treatment (as described in the protocol, will be collected. AEs related to disease progression, will not be collected. • Change in sample Size; verbatim "It is estimated that approximately 864 screened patients will yield approximately 640 patients for 1:1 randomization for having at least 628 evaluable patients, taking into account the attrition rate of 2%." • Change in the Statistical consideration in the primary endpoint as per the FDA and EMA feedback. Details of Meta-analysis included. • End of Study modified to study Closure; "Study closure will occur when either all patients have discontinued the study, or 42 weeks from the date the last patient was randomized to treatment OR at the administrative closure of the study. Patients on treatment at study closure will be advised by the PI and/or their associated primary health care provider on alternate therapies as per standard for the country. All treatment provided under the auspices of this protocol will cease at study closure." • Preferred method for Urine Protein evaluation changed from UPCR to Urine dipstick; "Inclusion Criteria: Urine protein (via dipstick): 0 or 1+. Patients with ≥ 2+ can be included only if a 24-hour urine specimen yields <2g of protein." • Dose Modification Table, as recommended in the Avastin PI 2017 is included. • Editorial changes throughout the document for harmonization of the text. • Administrative changes for study conduct

Version 1.0, March 09, 2016	Not Applicable- First Version

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Title	Multicenter, Double-Blind, Randomized, Parallel-Group Study to Assess the Efficacy and Safety of MYL-1402O Compared with Avastin®, in the First-line Treatment of Patients with Stage IV Non-Squamous Non-Small Cell Lung Cancer		
Protocol Number	MYL-1402O-3001		
Version	3.0		
Protocol Date	19 February 2019	**Revision Date**	19 February 2019
EudraCT no.	2015-005141-32		
Product	Bevacizumab (MYL 1402O [test product] or Avastin [reference product])		
Study Type	Confirmatory Safety and Efficacy Study		
Study Sites:	This study will be conducted at approximately 190 study centers across the globe.		
Study Population:	Patients with stage IV unresectable, recurrent or metastatic non-squamous non-small cell lung cancer (nsNSCLC) eligible to receive first-line treatment with bevacizumab in combination with carboplatin and paclitaxel		
Rationale:	MYL-1402O is a monoclonal antibody currently being developed by Mylan GmbH, as a proposed biosimilar to European Union- and US-licensed Avastin (hereafter referred to as Avastin), which is approved as first-line treatment in combination with carboplatin and paclitaxel (CP) for patients with Stage IV unresectable, recurrent or metastatic nsNSCLC. This randomized equivalence study is designed to meet the global regulatory requirement for approval of a biosimilar product. For this study, both MYL-1402O and Avastin are considered investigational medicinal products (IMP).		
Objectives:	**Primary Objective:** Compare the overall response rate (ORR) of MYL-1402O with that of Avastin, in combination with CP chemotherapy during the first 18 weeks of first-line treatment in patients with Stage IV nsNSCLC		

	Secondary Objectives: • Assess the safety profile of MYL-1402O as compared with that of Avastin when administered in combination with CP as first-line treatment for Stage IV nsNSCLC and when administered alone in the maintenance setting • Assess other efficacy parameters at 18 weeks and 42 weeks: Disease Control Rate (DCR), Duration of Response (DOR), Progression-Free survival (PFS), and Overall Survival (OS) rate of MYL-1402O as compared to Avastin when administered in combination with CP as first-line treatment for Stage IV nsNSCLC • Assess the potential immunogenicity at Week 18 and 42 of treatment of MYL-1402O as compared with that of Avastin • Compare the pharmacokinetic (PK) profile of MYL-1402O and Avastin using a population PK (Pop PK) approach
Study Design:	This is a multicenter, randomized, double-blind, 2-arm, parallel group, equivalence study that consists of the following periods: **Screening/Baseline Period**: In this period, which has a duration of up to 4 weeks (or ≤28 days prior to first dose [Day 0 of Cycle 1]), tumor imaging assessments must be performed no more than 28 days prior to first dose (Day 0 of Cycle 1). The time between randomization (≤3 days prior to Day 0 of Cycle 1) and the first dose (Day 0 of Cycle 1) must be included in the 28-day window for tumor imaging assessment. Patients will be randomly assigned in a 1:1 ratio to one of the two treatment groups (MYL-1402O or Avastin) within 3 days before the start of Period 1 (first dose of bevacizumab plus CP on Day 0 of Cycle 1). Baseline assessments must be performed within 24 hours of Day 0 of Cycle 1 to confirm that the patient has remained eligible for treatment, except for baseline labs which could be drawn before randomization and up to 7 days prior to Day 0 of Cycle 1. **Period 1:** Patients will begin Period 1 receiving bevacizumab combination therapy (MYL1402O or Avastin, plus CP) on Day 0 of Cycle 1 for up to 6 cycles of therapy. Each cycle will consist of 3 weeks (21 days ± 3 days) and a cycle will start with the administration of bevacizumab (as either MYL-1402O or Avastin). In this period, tumor assessments should be performed every 6 weeks after Day 0 of Cycle 1 (the first dose of bevacizumab,

	either MYL-1402O or Avastin) and continuing every 6 weeks (window of ±3 days) through Week 18. Tumor assessments must be done consistently throughout the study as follows: employing a CT scan of thorax and abdomen and using the same technique - CT or MRI, slice interval, contrast agent. Period 1 will include 3 assessments at the pre-specified time points regardless of delays in treatment cycles. A blinded interim analysis with aim of a sample size re-estimation will be performed after at least 30% of the patients have completed week 18. The blinded interim analysis will be used to estimate the ORR at Week 18 and determine if any adjustments are required to the sample size. **Period 2:** A patient is eligible to continue into Period 2 if he/she has a response of stable disease or better (i.e., complete response [CR] or partial response [PR]) by RECIST 1.1 criteria at the Period 1 Week 18 tumor assessment. Eligible patients will continue to receive bevacizumab (either MYL-1402O or Avastin) every 3 weeks as monotherapy. In this period, tumor assessments will occur every 12 weeks (+/- 3 days) after the end of Period 1 (Week 18), at pre-specified time points (i.e., Week 30 and Week 42), regardless of delays of the cycles of treatment, until PD or discontinuation of interventional therapy (for any reason), or withdrawal of consent. The Week 42 efficacy assessments will be used to evaluate the secondary endpoints. Patients will be assessed for tumor response using the same type of radiographic examinations used in Period 1 (e.g., CT or MRI of the thorax and abdomen, contrast agent, slice intervals) for ongoing evaluation of tumors. If a patient is discontinued from treatment prior to completion of Period 2 due to an Adverse Event, tumor assessment will be performed as per schedule until week 42. Patients started on a new anticancer treatment (surgery, radiotherapy or systemic treatment) or disease progression (PD), will be followed for OS till week 42. **Extended Treatment Period:** During the Extended Treatment Period, bevacizumab monotherapy given every 3 weeks will be provided to patients who at Week 42 have maintained stable disease or better response (CR or PR) by RECIST 1.1 criteria. During the Extended Treatment Period a patient will receive bevacizumab monotherapy (either MYL-1402O or Avastin) until PD or discontinuation of treatment or termination of study. Safety

	assessments will be made after each cycle of therapy and will be , focused only on treatment related AEs. This extended treatment period is aimed to keep providing treatment if patients are having benefit. **Safety Follow-Up Visit:** The Safety Follow-Up Visit is designed to capture safety assessments for any patient(s) that completed Period 2 or discontinued the IMP at any time during the study for any reason (e.g., PD, treatment intolerance to bevacizumab). Safety follow-up visit will occur at 28 days (± 7 days) after the last dose of bevacizumab during an office visit. The End of Treatment Visit should occur after the last dose of any interventional therapy, mainly to capture the reason for discontinuation of the first-line treatment. The End of Treatment (EOT) Visit may occur at the same time as the safety follow-up visit. Patients who discontinue treatment prior to completion of Period 2, must have a Safety Follow Up Visit and End of Treatment Visit and will be followed up for survival status until Week 42. **Study Closure:** Study closure will occur when either all patients have discontinued the study, or 42 weeks from the date the last patient was randomized to treatment OR at administrative closure of study. Patients on study treatment at study closure will be advised by the PI and/or their associated primary health care provider on alternate therapies as per standard for the country. All treatment provided under the auspices of this protocol will cease at study closure.
Estimated Study Duration:	The estimated maximum planned study participation per patient is approximately 47 weeks.

Sample Size:	It is estimated that 864 screened patients will yield approximately 640 patients for 1:1 randomization;. resulting in 628 evaluable patients (taking into account an attrition rate of 2%). Patients will be stratified by gender (male or female), smoking status (smoker or <100 cigarettes in entire lifetime), and number of metastasis sites (one or multiple sites). To meet the different regulatory requirements, the primary endpoint of ORR will be analyzed using the risk ratio and risk difference. As the EMA-based approach using the risk difference requires a slightly larger sample size; the planned sample size for this study will be based on the EMA requirement: a sample size of 628 patients (314 per treatment group) provides at least 80% power for testing equivalence of MYL-1402O and Avastin at 1-sided 2.5% level of significance, for the primary endpoint ORR at Week 18 (from the independent review). This sample size will assume that the ORR at Week 18 will be 38% for both MYL-1402O and Avastin. A blinded interim analysis for primary endpoint will be done after at least 30% of the population have either discontinued or completed 18 weeks on the study to assess the estimated overall ORR. The sample size will be increased up to a sample size of 670 in case the estimated overall ORR is ≤ 36% or ≥40%. This blinded sample size re-estimation (BSSR) may have an effect on the actual type I error. When the magnitude of the Type I error increase was investigated by performing simulations for the situation with and without BSSR; results from the simulations suggest that the impact of a BSSR on the actual type I error is small.

Inclusion Criteria:	A patient is eligible for inclusion in the study if he or she meets all of the following criteria: 1. Has demonstrated the ability to understand verbal and/or written instructions, to provide written informed consent, and is capable and agreeable to comply with protocol requirements. 2. Male or female at least 18 years of age at the time of signing an informed consent form (ICF). 3. Has a documented imaging diagnosis of Stage IV unresectable, recurrent or metastatic nsNSCLC. 4. Has documented histologic or cytologic diagnosis of advanced nsNSCLC with negative or unknown sensitizing epidermal growth factor receptor (EGFR) mutation, and negative or unknown echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) rearrangement. 5. Has measurable disease with at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1; Section 12.1 [Appendix A]). All target (up to 5 lesions) and nontarget lesions (other measurable not included in target, nonmeasurable, nonevaluable, or evaluable lesions) should be included in the assessment or evaluation of disease response as defined by RECIST 1.1 (Eisenhauer et al 2009). NOTE: If in the staging assessment, bone metastases are discovered and are localized outside of the thorax and abdominal region, each non target metastasis or as multiple non target bone metastases should be included in the tumor response assessments and followed by X-ray, CT scan, or MRI as appropriate. 6. Has a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale. 7. Has at least 6 months of expected survival. 8. Has not received any prior systemic therapy for first-line treatment of advanced lung cancer, except adjuvant chemotherapy, and remained disease-free for at least 12 months

	from time of surgery, and at least 6 months from last dose of chemotherapy. 9. May have had prior radiation therapy provided <25% of bone marrow is involved (Section 12.3 [Appendix C]), except for previous mediastinal irradiation that is not allowed. a. Prior radiation therapy must have been completed at least 2 weeks prior to Day 0 of Cycle 1 b. Patient must have recovered from acute toxicities associated with radiation therapy. Radiation-related toxicities must have resolved to Grade 1 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 4.03) grade prior to Day 0 of Cycle 1. 10. May have brain metastasis provided the metastasis has been treated and is considered stable. Treated, stable brain metastasis is defined as: a. Metastasis having no evidence of progressive disease (PD) or hemorrhage after treatment. b. No ongoing requirement for dexamethasone, as ascertained by clinical examination and post-treatment brain imaging (computed tomography [CT] scan or magnetic resonance imaging [MRI]) at baseline. c. Anticonvulsants are allowed, provided the dose regimen has been unchanged (stable) for at least 2 weeks prior to patient signing informed consent. d. Treatment for brain metastasis may include whole brain radiotherapy, radiosurgery (Gamma Knife®, linear particle accelerator, or equivalent), or a combination thereof, as deemed appropriate by the treating physician. All brain metastasis treatments must be completed at least 14 days prior to Day 0 of Cycle 1. 11. Has adequate organ functions based on the following: a. Bone marrow reserve: i. White blood cell count $\geq 3 \times 10^3/\mu L$;

	ii. Absolute neutrophil count (segmented and bands) $\geq 1.5 \times 10^3/\mu L$; iii. Platelet count $\geq 100 \times 10^3/\mu L$; iv. Hemoglobin ≥9.0 g/dL with at least 2 weeks without transfusions before Day 0 of Cycle 1. b. Hepatic: i. Total bilirubin ≤1.5 × upper limit of normal (ULN); except if elevation is due to Gilbert's Syndrome with transitory elevations of indirect bilirubin. *ii.* Alkaline phosphatase, alanine transaminase, and/or aspartate transaminase ≤3 × ULN. Significant levels of alanine transaminase or aspartate transaminase should be further assessed for viral hepatitis, if not related with liver metastases. *(Note: Isolated alkaline phosphatase elevation beyond 3 × ULN due to bone metastasis is allowed).* c. Renal: i. Calculated creatinine clearance ≥45 mL/min based on the original, weight-based Cockcroft and Gault formula (Cockcroft and Gault 1976; Section 12.4 [Appendix D]) ii. Urine protein (via dipstick): 0 or 1+. Patients with ≥ 2+ can be included only if a 24-hour urine specimen yields <2g of protein 12. If capable of reproduction, patients and their partners must use contraceptive methods during the full duration of the study and for 6 months after discontinuation of study. a. A patient who is capable of reproduction must be willing to practice birth control by using 2 different highly effective double barrier methods of contraception, or abstinence from sexual intercourse for the duration of the study. i. In particular a female patient of childbearing potential must use a method that results in less than 1% failure rate per year when used consistently and correctly such as implants, injectables, combined oral contraceptives,

	intrauterine devices, sexual abstinence, or vasectomized partner. ii. A male patient of reproductive potential (defined as a male that has not had a vasectomy) must use a condom with spermicide and their female partner to use another highly effective form of contraception.

Exclusion Criteria:	A patient who meets any of the following criteria will be excluded from the study: 1. Is pregnant or breast-feeding. 2. Has documented histology/cytology confirming any of the following: a. Squamous non-small cell lung cancer. *(Note: In the event of mixed tumor histology/cytology or predominant cell type other than non-squamous, eligibility will be determined based on the predominant cell type, which must be non-squamous.)* b. A patient with any small cell type or large cell neuroendocrine histology. 3. Has a recent (within 6 months prior to Day 0 of Cycle 1) cardiac condition as defined by the New York Heart Association Class II, III, or IV (AHA 1994). 4. Has a recent (within 6 months prior to Day 0 of Cycle 1) history of a significant vascular event (such as aortic aneurysm requiring surgical repair or a recent peripheral arterial thrombosis) and/or history of significant and unstable vascular disease. 5. Has a history of stroke or transient ischemic attack within 6 months prior to Day 0 of Cycle 1, or has a long-term history of more than one of the following vascular thromboembolic events: a. Cerebrovascular accidents b. Transient ischemic attacks c. Myocardial infarctions d. Venous thromboembolic reactions, including pulmonary embolism 6. Is receiving anticoagulant therapy that: a. Is not considered ‘stable’, defined as dosage not maintained for at least 3 months prior to Day 0 of Cycle 1.

	b. Is not within the targeted international normalized ratio at the time of consent signing. 7. Has a current diagnosis, history, or risk of hemorrhage in the central nervous system (CNS), including the following: a. Patient with CNS metastasis treated by neurosurgical resection or brain biopsy performed within 8 weeks prior to Day 0 of Cycle 1. b. Patient should be off corticosteroids for at least 1 week (7 days) at the time of the post-treatment (for CNS metastasis) brain CT/MRI. 8. Has any prior history of hypertensive crisis and/or hypertensive encephalopathy, or has a current diagnosis or recent history of inadequately controlled hypertension (defined as systolic blood pressure >150 mm Hg and/or diastolic >100 mm Hg, while on antihypertensive medications). 9. Has a recent history of any of the following: a. A major surgical procedure, open biopsy, open pleurodesis, or significant traumatic injury within 28 days prior to Day 0 of Cycle 1. b. Documented history of conditions that may need surgery during the study or within 6 months of signing informed consent. *c.* Has had either a core biopsy or other minor surgical procedure within 7 days prior to Day 0 of Cycle 1. (*Note: Placement of a vascular access device, or a closed pleurodesis, thoracentesis, or mediastinoscopy are allowed).* 10. Has a history of any of the following: a. Hemoptysis (approximately >2.5 mL or a half teaspoon) within 3 months prior to Day 0 of Cycle 1. b. A thoracic, central, mediastinal tumor located within 2cm of carina <u>invading or abutting major blood vessels (based on radiologist assessment) and associated bleeding risk as per PI judgement.</u>

	c. A lung tumor with cavitation, <u>if more than 50% of the diameter of the lesion is cavitated, and/or involving the central bronchus or vessel.</u> - Major blood vessels are defined as: • Aorta • Superior and inferior vena cava • Main pulmonary artery • Intrapericardial portions of the right and left pulmonary arteries and pulmonary veins - Central location is defined as: • Distance of less than or equal to 2 cm from carina *EC 10 will be evaluated on a case by case basis taking into consideration the above criteria in discussion with the site radiologist, PI and the medical monitor.* 11. Has a history of gastrointestinal fistula, perforation, or abscess. 12. Has a current diagnosis or history of a nonhealing wound, active ulcer, or untreated bone fracture. 13. Has prior history of another active malignancy within the last 5 years, other than adequately treated superficial basal cell, superficial/skin squamous cell carcinoma, or carcinomas in situ. 14. Has a known hypersensitivity to any component of carboplatin, paclitaxel, bevacizumab, Chinese hamster ovary cell products, or other recombinant human or humanized antibodies. 15. Has received treatment with any other investigational drug prior to day 0 of cycle 1, within the last 30 days or 5 half-lives (if available); whichever is longer. 16. Has previously received treatment with the following: a. Paclitaxel.

	b. Bevacizumab *(Note: Prior intravitreal administration of bevacizumab does not preclude study participation)*. c. Anthracycline. *(Note: May be allowed on a case by case basis after consulting with the medical monitor to rule out an increased risk of cardiac failure).* 17. Has documented or known current alcohol/drug abuse that precludes his/her ability to adhere to the protocol. 18. Has any of the following concomitant treatments or conditions: a. Concomitant vaccination that contains an attenuated virus, for instance Yellow Fever vaccine. b. Has a known history of active or latent tuberculosis. c. Has a concomitant systemic disorder (e.g., active infection including known human immunodeficiency virus, viral hepatitis B or C) that, in the opinion of the principal investigator (PI; or designee), would compromise the patient's safety (for instance potential drug interactions, or ability to adhere to the protocol). d. Has any other concomitant condition that precludes the participation in the study through increased risk to the patient and/or potential to impact the PI's (or designee's) ability to administer this protocol.

Efficacy Assessments:	Efficacy assessments will consist of independently reviewed tumor assessments (at least a CT scan or MRI of the thorax and abdomen) using RECIST 1.1 criteria, but treatment decisions will be based on the Investigator's assessment. Tumor response (CR, PR, stable disease, or PD) will be evaluated using the international criteria proposed by the RECIST 1.1 committee. In Period 1, tumor assessments will occur every 6 weeks following first dose of bevacizumab (Week 6, Week 12, and Week 18). Tumor assessments will occur every 12 weeks in Period 2 (Week 30 and Week 42). Progression-free survival and OS will also be assessed at 18 weeks and at 42 weeks.
Pharmacokinetic Assessments:	For PK analysis, scheduled samples will be collected from each randomized patient at the following time points: baseline (if possible, within 1 hour prior to first dose of bevacizumab), pre dose (if possible within 1 hour prior infusion) at Cycles 2 through 6; post dose (immediately after infusion, < 15 minutes) at Cycles 1, 2, 4, and 6. Additional samples from all patients in any cycle (Cycles 1 to 6): 1 sample between Days 3 and 8 (inclusive) in any cycle, and 1 sample between Days 10 and 18 (inclusive) in any cycle; pre dose at Cycles 704 and 708 (Period 2); and an additional sample collected at Safety Follow-Up Visit/EOT visit. In case of a hypersensitivity reaction, an unscheduled blood sample will be collected for drug concentration along with one immunogenicity sample as quickly/soon as possible after the event occurs. *(Note: Post dose samples need to be taken from a different venipuncture location or catheter than the infusion one or should be taken after flushing the line).*
Immunogenicity Assessments:	For immunogenicity analysis, scheduled samples will be obtained on all patients at the following time points: baseline (6 × 5 mL) prior to Cycle 1 for analytical method optimization and validation; prior to administration of bevacizumab (4 × 5 mL) during Period 1 at Cycles 2, 4, 6, during Period 2 at Cycles 704 and 708, for antidrug (bevacizumab) antibody, and supplemental immunogenicity testing; and at Safety follow-up visit (4 × 5 mL). An unscheduled blood sample will be collected with a drug concentration sample if a hypersensitivity reaction occurs, as quickly/soon as possible after the event occurs. ***(Note: Immunogenicity samples are expected to be taken at the same time as the PK samples).***

Safety Assessments:	Safety assessments will include the following: causality, incidence, nature, and severity of AEs (CTCAE [version 4.03] severity grading to be used) including adverse drug reactions, the ECOG performance status, clinical laboratory evaluations, detection of antibodies to bevacizumab, vital signs, and physical examinations. Treatment-emergent AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Safety laboratory blood samples will be collected at Screening and prior to each administration of bevacizumab at each cycle of interventional therapy (Period 1: Cycle 1 through Cycle 6, Period 2: Cycles 704 and 708); and at Safety follow-up visit. In addition, women with childbearing potential must have a negative serum pregnancy test within 7 days prior to Day 0 of Cycle 1.

Study Drug, Dosage and Route of Administration:	Interventional therapy (bevacizumab and/or CP) is given on the first day of a cycle (21 days [± 3 days]). **IMP Name:** Bevacizumab (MYL-1402O [test product] or Avastin [reference product]) **Dose, route, and frequency:** The dose of bevacizumab is 15 mg/kg administered every 21 days (± 3 days). The first dose is to be administered by continuous intravenous (i.v.) infusion over 90 minutes (± 15 minutes). If the first infusion is tolerated without infusion-associated AEs (fever and/or chills), the second infusion may be delivered over 60 minutes (± 10 minutes). If the 60-minute infusion is well tolerated, subsequent infusions may be delivered over 30 minutes (± 10 minutes) every 21 days (± 3 days). During Period 1, bevacizumab combination therapy will be given with bevacizumab infusions sequentially followed by carboplatin infusions, paclitaxel pre-medications, and then paclitaxel on the first day of each cycle for up to 6 cycles and then in subsequent cycles, bevacizumab monotherapy may be used. **Chemotherapy Name:** Carboplatin **Dose, route, and frequency:** An area under the curve (AUC) dose of AUC 6 by continuous i.v. infusion over 30 minutes (+/- 15 minutes) (after the administration of bevacizumab) every 21 days up to 6 cycles. **NOTE:** Carboplatin must be administered at AUC 6 at Cycle 1. Thereafter (subsequent cycles); the minimal dose level of carboplatin allowed by this protocol is AUC 5. **Chemotherapy Name:** Paclitaxel **Dose, route, and frequency:** 200 mg/m^2 dose by continuous i.v. infusion over 3 hours (± 30 minutes) (after the administration of carboplatin and paclitaxel pre-medication) every 21 days up to 6 cycles. In countries where the initial dose is 175 mg/m^2, PIs are allowed to initiate dosing at 175 mg/m^2. For a patient that demonstrates tolerance of the 175 mg/m^2 dose in Cycle 1, the PI may increase the dose to 200 mg/m^2 in Cycle 2. The dose at subsequent cycles will be determined by the PI and tolerance of the individual patient. Dosing will be documented by the PI. If dose adjustment is needed, the minimum dose level of paclitaxel allowed by this protocol is 160 mg/m^2. If a lower dose of paclitaxel or carboplatin is required, then the PI must discuss dosing with the medical monitor and receive approval from the sponsor.

Statistical Methods:	The primary efficacy endpoint will be ORR, based on best tumor responses as assessed by an independent review at any time point during the first 18 Weeks. Since FDA and EMA use different approaches to determine equivalence based on the ORR, two primary analysis for the ORR will be done: Per FDA requirement, the ORRs for both MYL-1402O and Avastin will be calculated and the ratio of the ORRs will be used to determine if MYL-1402O is equivalent to Avastin. A 2-sided 90% CI for the ratio of the ORRs during the first Week 18 will be calculated with no adjustment for covariates. This analysis will be conducted in the intent-to-treat population. Per EMA requirement, the difference in the ORRs during the first 18 Weeks will be evaluated using an unstratified Cochran-Mantel-Haenszel (CMH) test. A 2-sided 95% CI for the difference in ORRs at Week 18 will be calculated. This analysis will be conducted in the intent-to-treat population As sensitivity analysis, ORR based on best tumor response confirmed at a second time point by an independent review and ORRs as assessed by investigators will also be presented and analyzed using the same methods as the primary efficacy endpoint. The secondary efficacy endpoints are DCR, PFS, OS, and DOR. DCR (Rate of CR + PR + SD) will be evaluated as a ratio and the 90% CI will be estimated using logarithmic transformation with no adjustment for covariates. The difference in the disease control rates between treatment groups will be estimated using an unstratified CMH test and an asymptotic 2-sided 95% CI. Efficacy data at Week 18 for the entire ITT population will be submitted during initial submission. PFS and OS for the secondary efficacy endpoints will be evaluated using Kaplan-Meier plots. Survival rates at Weeks18, 30, and 42 will be presented along with estimates of the relative risk and associated 95% CI at each time point. In addition, a Cox regression model will be used to estimate the hazard ratio of PFS and OS and the corresponding 95% CI for the treatment effect. DOR for the secondary efficacy endpoints will be evaluated using the same statistical analysis methods for the secondary efficacy endpoints of PFS and OS.

	Summary statistics of observed PK concentrations will be presented for all patients by treatment group. It is not intended that the study is powered for this secondary endpoint to demonstrate bioequivalence, but comparability of the results will be evaluated. Pharmacokinetic concentrations and covariate data will be analyzed by PopPK methods for all patients with evaluable PK data. Empiric Bayesian estimates of PK model parameters will be obtained for all patients. Pharmacokinetic parameters and exposure estimates (AUC, maximum concentration, minimum concentration, clearance, volume, and terminal elimination half-life) will be compared between treatment arms. Also, statistics of observed immunogenicity will be presented and analyzed. Treatment-emergent AEs and serious AEs will be descriptively summarized by system organ class, preferred term, and treatment group, as well as by severity and relationship to the IMP. Treatment-emergent AEs will be coded using the latest version of MedDRA. Descriptive summaries of observed values and change from baseline will be presented for clinical laboratory evaluations (hematology and biochemistry) by treatment group. The ECOG status and vital signs will be summarized for each visit. The number and percent of patients whose test results are positive for anti-bevacizumab antibodies will be provided for each treatment group. The descriptive statistics will include frequency and percentage of patients in each category for categorical variable, and the number of patients, arithmetic mean, standard deviation or standard error, median, first quartile, third quartile, minimum, and maximum for continuous variables.
Date of Protocol:	19 February 2019

List of Abbreviations

Abbreviation	Definition
AC	alternative contact
ADA	anti-drug antibody
AE	adverse event
AUC	area under the curve
BP	blood pressure
BSA	body surface area
CFR	Code of Federal Regulations
CI	confidence interval
CL	parameters of clearance
C_{min}	minimum concentration
C_{max}	maximum concentration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CP	carboplatin and paclitaxel
CR	complete response
CRF	case report form
CrCl	creatine clearance
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EML4-ALK	echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase
EOS	end of study
EOT	end of treatment
FDA	United States Food and Drug Administration

GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	Gastrointestinal
HR	hazard ratio
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
Ig	Immunoglobulin
IgG	immunoglobulin G class
INR	international normalized ratio
IMP	investigational medicinal product
IRB	institutional review board
ITT	intent to treat
i.v.	Intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
nsNSCLC	non-squamous non-small cell lung cancer
ORR	overall response rate
OS	overall survival
p	p-value
PD	progressive disease
PFS	progression-free survival
PI	principal investigator
PK	Pharmacokinetic
PopPK	population pharmacokinetic(s)
PP	per protocol
PPD	Pharmaceutical Product Development
PR	partial response

PRES	posterior reversible encephalopathy syndrome
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SmPC	summary of product characteristics
SS	safety set
SST	serum separator tube
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
V_c	volume of the central compartment
VEGFR	vascular endothelial growth factor receptor
V_p	volume of the peripheral compartment
VEGF	vascular endothelial growth factor

Definition of Terms

Protocol Term	Definition
Baseline	Study related assessments conducted within 24 hours prior to first dose of bevacizumab (either MYL-1402O or Avastin) combination therapy (plus carboplatin and paclitaxel) to confirm that the patient has remained eligible for treatment during the Screening Period.
Baseline Failure	Any patient that meets initial eligibility requirements, is randomized to treatment, however does not receive first dose of bevacizumab and is deemed ineligible for continuation in the MYL-1402O-3001 study.
Bevacizumab Combination Therapy	Treatment administration of MYL-1402O or Avastin 15 mg/kg intravenous (i.v.) infusion plus carboplatin and paclitaxel every 21 days.
Bevacizumab Monotherapy	Treatment with bevacizumab 15 mg/kg i.v. infusion (either MYL-1402O or Avastin) every 21 days until disease progression or treatment discontinuation.
Chemotherapy	Treatment with carboplatin and paclitaxel. Both are considered non-investigational medicinal products for this study.
Early Terminator	A patient that enters Period 1 and is terminated from the study prior to completing Week 18 assessments in Period 1 due to adverse event, progressive disease, withdrawal of consent, or discontinuation from interventional therapy.
End of Treatment Visit	A visit that occurs after last dose of all interventional therapy. Mainly to capture reason for ending first line therapy. The safety follow-up visit and the end of treatment visit may or may not occur on the same day.
Interventional therapy	Treatment with bevacizumab (investigational medicinal products: MYL-1402O [test product] or Avastin [reference product]) and chemotherapy (carboplatin, paclitaxel).
Investigational Medicinal Product	Blinded Bevacizumab (MYL-1402O [test product] or Avastin [reference product])
Period 1	Period of study from Day 0 of Cycle 1 through Week 18. During this period, tumor assessments are done every 6 weeks (±3 days) following Day 0 of Cycle 1 through Week 18 (overall response rate is assessed at Week 18).
Period 1 Completer	A patient that completes Period 1 through Week 18 tumor assessment.

Protocol Term	Definition
Period 2	Period of study following Week 18 through Week 42. During this period tumor assessments are done every 12 weeks (±3 days) following Week 18 (end of Period 1) through Week 42.
Period 2 Completer	A patient that has remained on the study per protocol through Week 42 tumor assessment (Period 2).
Period 2 Terminator	A patient that starts Period 2 and is terminated from the study prior to completing Week 42 tumor assessment due to adverse event, progressive disease, withdrawal of consent, or discontinuation from interventional therapy.
Randomization	Random assignment of patient to treatment (either MYL-1402O or Avastin); this may be up to 3 days prior to Day 0 of Cycle 1.
Reference Product	Avastin is the reference product of bevacizumab
Safety Follow-up Visit	A visit that occurs at 28 days (±7 days) after last dose of bevacizumab. Safety follow-up and end of treatment visits may or may not occur on the same day.
Screen Failure	A patient that has provided signed informed consent (via informed consent form) and that either through screening or occurrence of any event prior to randomization, is deemed ineligible for study participation. Within the 28-day Screening Period window, a patient that fails to meet initial inclusion/exclusion criteria should be re-evaluated once before being classified as a screen failure.
Screening	Assessment of eligibility of a patient to participate in the study during the period from patient signing informed consent up to randomization.
Screening/Baseline Period	Period up to 4 weeks (≤28 days) prior to first dose of bevacizumab (Day 0 of Cycle 1); includes baseline and randomization.
Study Closure	Study closure will occur when either **all** patients have discontinued the study, **OR** 42 weeks from the date the last patient was randomized OR upon the administrative closure of study. All treatment provided under the auspices of this protocol will cease at study closure
Test Product	MYL-1402O is the test product, proposed biosimilar of bevacizumab

Figure 1 Definitions Aligned with Study Design

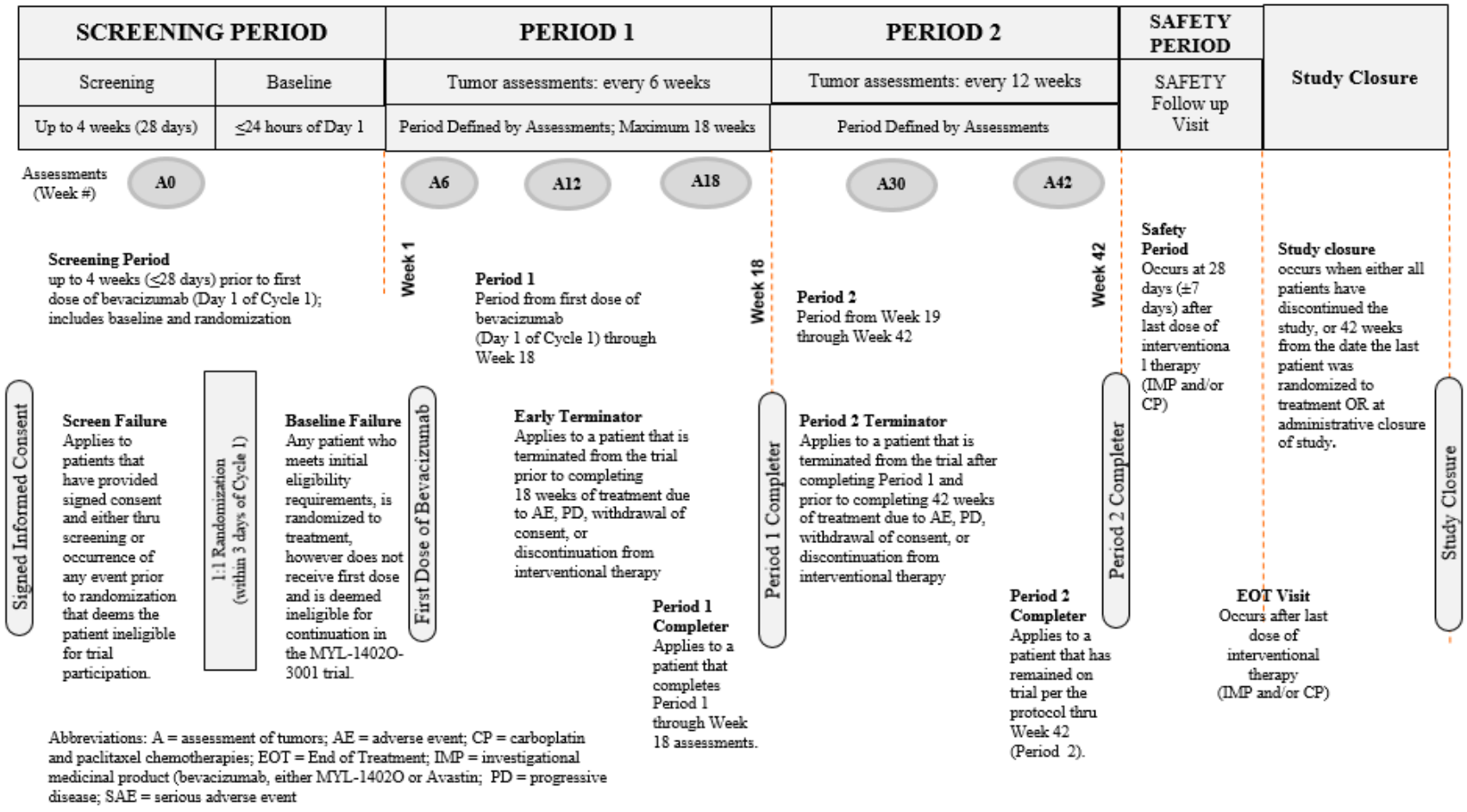


Table 1-1 Study Schedule of Events

	Screening	Random-ization	Baseline[a]	Period 1[b] 21 Day Cycles						Period 2[c] 21 Day Cycles				Safety Follow-Up Visit[d,e]
Cycle Number				1	2	3	4	5	6	701	702	703	70x	28 Day F/U / EOT[f, g]
Week Number				W1	W4	W7	W10	W13	W16	W19	W22	W25	Wx	
Day Number	≤28 Days of Day 0	≤3 Days of Day 0	≤24 Hrs of Day 0	Day 0	Day 21	Day 42	Day 63	Day 84	Day 105	Day 126	Day 147	Day 168	Day X	
Procedure														
Informed consent[h]	X													
Inclusion/exclusion criteria[i]	X	X	X											
Demographics	X													
Medical history	X													
Physical examination[j]	X		X	X	X	X	X	X	X	X	X	X	X	X
Randomization [k]		X												
Interval history[l]				X	X	X	X	X	X	X	X	X	X	X
BSA calculation[m]	X				X	X	X	X	X					
Prior and concomitant medications/treatments	X		X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X				X	X	X	X	X	X	X	X	X	X
AEs (with CTCAE grading)[n]	X			X	X	X	X	X	X	X	X	X	X	X
Tumor assessment, at least a CT Scan of thorax and abdomen (RECIST1.1)[o]	X[o]					X[o]		X[o]		X[o]			X[o]	X[o]

Brain image (MRI or CT scan) and bone X Rays (as required)[p]	X				X[p]		X[p]		X[p]			X[p]	X[p]
Survival information[r]												X	
IMP and/or Chemo Admin													
IMP/chemo or IMP alone [q]			X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	
Laboratory/diagnostic tests													
Hematology	X		X[a]	X	X	X	X	X	X	X	X	X	X
Chemistry	X		X[a]	X	X	X	X	X	X	X	X	X	X
Calculated CrCl	X		X[a]	X	X	X	X	X					
Immunogenicity[s]			X[s]	X[s]		X[s]		X[s]				X[s]	X[s]
PK[t]			X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]			X[t]	X[t]
Urine dipstick (and 24 hour urine protein, if indicated) [u]	X			X	X	X	X	X	X	X	X	X	X
Pregnancy test (if indicated)[v]	X[v]		X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]	X[v]
Prothrombin time or INR (if indicated)[w]	X		X[a]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]
Unscheduled visits[x]													

Abbreviations: AE=adverse events; BSA=body surface area; CT=computerized tomography; CrCl=creatinine clearance; CTCAE=Common Terminology Criteria for Adverse Events; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; F/U1=follow-up visit 1; F/U2=follow-up visit 2; hrs=hours; IMP=investigational medicinal product; INR=international normalized ratio; MRI=magnetic resonance imaging; PK=pharmacokinetics; RECIST=Response Evaluation Criteria in Solid Tumors; W=week.

a Baseline (≤24 hours prior to first dose of bevacizumab [Day 0 of Cycle 1] and Randomization (≤3 days prior to first dose of bevacizumab [Day 0 of Cycle 1] assessments are shown in same column. If safety blood lab assessments are more than 7 days prior to baseline, then a new set of safety blood samples will be collected for safety assessments.

b During Period 1, a treatment cycle is planned every 21 days until progressive disease, withdrawal of consent, or discontinuation from interventional therapy. Tumor assessments will still be conducted every 6 weeks (window of ±3 days). Week 18 efficacy assessments will be used to evaluate the primary and secondary endpoints, regardless of treatment at the time of Week 18 assessment.

c During Period 2, a treatment cycle is planned every 21 days until progressive disease, withdrawal of consent, or discontinuation from interventional therapy. Tumor assessments will still be conducted every 12 weeks (Period 2: Week 30 and Week 42;).

d For patients that will continue into the extended period (after confirmation via tumor assessment per RECIST 1.1 of SD or better post Wk 42) a visit should be conducted 28 days (± 7 days) post the last dose of IMP in Period 2. At this visit it will be important to collect the required labs inclusive of PK samples,

e For patients that are discontinued from bevacizumab (for any reason) a safety follow-up visit ,must be conducted 28 days (± 7 days) after discontinuation from bevacizumab Of note: Depending on a patients' circumstance - the safety follow-up visit and EOT may or may not occur at the same time point. If there is confusion about a combined visit, please contact your Mylan representative.

f End of treatment (EOT) will occur after discontinuation of interventional therapy. The end of treatment visit may occur at the safety follow-up visit (Safety Follow-Up visit) or as soon as possible after the decision was made to terminate interventional therapy

g If the patient continues to receive the study treatment in Extended Period, then only related AEs will be collected.

h Informed consent must be provided by the patient prior to any protocol related procedures or tests.

i The inclusion and exclusion criteria will be checked during the Screening Period and will be rechecked prior to randomization and prior to first dose of bevacizumab (Day 0 of Cycle 1) to confirm eligibility. During the Screening Period, an additional check of each patient's eligibility for the study will be conducted by the Independent image vendor. This check will confirm: measurability of the lesions (per RECIST definition) and followed by the Medical Monitor confirmation of patient eligibility per the protocol inclusion/exclusion criteria.

Serologic testing for hepatitis (Hepatitis A, Hepatitis B, or Hepatitis C virus) is required ONLY if alanine transaminase or aspartate transaminase values are elevated ≥ ULN (in the absence of liver metastasis) at screening. In case screening visit lab values are within ULN and baseline visit lab values are ≥ ULN, only clinically significant values (in the absence of liver metastasis) will need to be investigated further prior to dosing, but a sporadic rise of either of these do not need serology testing for viral hepatitis at baseline.

j Physical examination is to be conducted on the first day of each cycle.

k Randomization may occur up to 3 days prior to Day 0 of Cycle 1.

l Evaluation of any change (new, increase, or decrease) in signs/symptoms and/or medical conditions since the previous visit

m BSA will include assessing patient height and weight. (The dose does not need to be modified, if the change in weight is <10% from the prior calculation)

n All AEs will be collected from signing of the informed consent through the Safety Follow-Up visit..

o Tumor assessment per RECIST 1.1 will be conducted on CT scans or MRIs every 6 weeks during Period 1 (first 18 weeks of treatment) at Weeks 6, 12, and 18. During Period 1, the timing is critically important and is independent of the treatment cycles, every effort should be done to accomplish this timing without affecting patient safety. During Period 2 (Cycle 704 and Cycle 708), tumor assessments are to occur every 12 weeks thereafter until progression. A window of ±3 days is permitted for all tumor assessments.

No centralized tumor assessment will be conducted during the extended treatment period. Sites however will be expected to conduct regular tumor assessments to assure treatment efficacy on patients in the extended treatment period. PIs will assume the responsibility to continue to treat patients under the auspices of treatment benefit and safety management as per standard of care. Sites must record Progressive Disease tumor measurements as per RECIST 1.1 for patients in the extended treatment period.

p Brain image (MRI or CT scan) and/or bone scan (e.g., X-ray) if indicated should occur with tumor assessments. **NOTE: If in the screening / staging assessment, should bone metastasis be discovered and are localized outside of the thorax and abdominal region, each non target bone metastasis (or as multiple nontarget) should be included in the tumor response assessments. These lesions should be followed by X-ray, CT scan, or MRI as appropriate. During the study, bone scans may be used to confirm complete response or progression of disease.**

q On Day 0 of Cycle 1 (Period 1), patients will receive bevacizumab combination therapy: bevacizumab (either MYL-1402O [test product] or Avastin [reference product]) infusion followed by sequential infusions of carboplatin and paclitaxel (requires premedication). A cycle will last 21 days, including the first day of infusions. Patients may switch to bevacizumab monotherapy (either MYL-1402O or Avastin), provided the patient has stable disease or better (complete response or partial response) and either did not tolerate chemotherapy after Cycle 1 or has completed Week 18 assessments and is starting Period 2. Bevacizumab monotherapy may continue into the Extended Treatment period provided the patient's disease is deemed, at minimum - stable at week 42.

r Survival information will not be collected past week 42 unless there is a specific country level requirement.

s For immunogenicity evaluation, an unscheduled blood sample will be collected with a drug concentration sample if a hypersensitivity reaction occurs, as quickly/soon as possible after the event occurs. Scheduled samples will be obtained on all patients at the following time points: baseline (6 × 5 mL) that is prior to Cycle 1 for analytical method optimization and validation; prior to administration of bevacizumab (4 × 5 mL) during Period 1 at Cycles 2, 4, 6, during Period 2 at Cycles 704 and 708), for antidrug (bevacizumab) antibody, and supplemental immunogenicity testing; and at safety follow-up visit (4 × 5 mL).

t For PK, an unscheduled drug concentration blood sample will be collected with one immunogenicity sample if a hypersensitivity reaction occurs, as quickly/soon as possible after the event occurs. Scheduled samples will be collected from each randomized patient at the following time points: baseline (if possible within 1 hour prior to first dose of bevacizumab), predose (if possible within 1 hour prior infusion) at Cycles 2 through 6; postdose (immediately after infusion, < 15 minutes) at Cycles 1, 2, 4, and 6 , additional samples from all patients in any cycle (Cycles 1 to 6): 1 sample between Days 3 and 8 (inclusive) in any cycle, and 1 sample between Days 10 and 18 (inclusive) in any cycle; predose at Cycles 704 and 708 (Period 2); and an additional sample collected at safety follow-up visit. When PK sample is concomitant with immunogenicity samples it should be taken at the same time, after dose using a different site or after flushing the line.

u Urine protein will be done via a dipstick. However; should urine protein via dipstick be quantified at ≥ 2+ a 24 hour urine protein must be done. Patients will be considered eligible provided the 24 hour protein specimen yields <2g of protein.

v Pregnancy test will be conducted, if indicated. Women with childbearing potential must have a negative serum pregnancy test during screening and one urine test within 7 days prior to Day 0 of Cycle 1. Prior to each cycle of therapy, the women with childbearing potential must have a negative urine test.

w For all patients at screening and subsequent cycles, the patient who is receiving an anticoagulant therapy (i.e.,warfarin), prothrombin time and/or international normalized ratio should be determined, if indicated .

x Assessments performed during unscheduled visits should be guided by the reason for the visit and per the principal investigator's discretion. For example, when there is suspicion of progressive disease, assessments should include an unscheduled computerize d tomography (CT) or magnetic resonance imaging (MRI).

1 Introduction

Lung cancer is the most prevalent cancer worldwide and the leading cause of cancer-related mortality (DHHS, 1999). In 2012, lung cancer caused an estimated 1.6 million deaths and was the most common cause of cancer deaths in men and the second most common cause of cancer deaths in women (Globocan 2012). Most cases of lung cancer are of the non-small cell lung cancer (NSCLC) type, which has a poor prognosis especially when it is locally-advanced or metastatic (Soria et al. 2013). Despite the latest improvements in the treatment of lung cancer, 5-year survival still remains low, ranging from 10% to 20% worldwide (DHHS, 1999).

Vascular endothelial growth factor (VEGF) is a glycosylated angiogenic cytokine that is the key driver of vasculogenesis and angiogenesis in a variety of settings, especially in diseases such as cancer. Vascular endothelial growth factor is a mitogen, and specifically acts on endothelial cells to increase vascular permeability, induce angiogenesis, vasculogenesis, endothelial cell growth and cell migration, and inhibit apoptosis.

Bevacizumab (Avastin®, Genentech/Roche) is a recombinant humanized monoclonal antibody of the immunoglobulin (Ig) G1 class that selectively binds to VEGF. The binding of bevacizumab to VEGF inhibits the binding of VEGF to its receptors on the surface of endothelial cells, Flt-1 (also known as VEGF receptor-1 [VEGFR-1]) and kinase insert domain receptor (also known as VEGF receptor-2 [VEGFR-2]). Neutralizing the biological activity of VEGF inhibits the formation of new tumor vasculature, causes regression in newly-formed tumor vasculature, and normalizes the remaining tumor vasculature, thereby inhibiting tumor growth.

The pharmacokinetic (PK) parameters of bevacizumab are similar to those of other IgG antibodies and can be predicted by 2-compartment linear pharmacokinetics with a distribution half-life of 1.44 days and terminal elimination half-life of 19.9 days (Lu et al. 2008). Accumulation to steady-state would therefore be expected to occur during Cycle 5 (100 days) of a regimen with dosing every 21 days. The effect of other chemotherapy agents on bevacizumab PK parameters has been minimal. Body weight and gender are the most significant covariates of bevacizumab clearance (CL) with males having 26% faster CL than females (Lu et al. 2008).

In the Phase 3 study Eastern Cooperative Oncology Group (ECOG) 4599, patients were randomly assigned to either bevacizumab plus carboplatin and paclitaxel (CP) or CP alone (Sandler et al. 2006). Patients who received 6 cycles of bevacizumab plus CP and were

without disease progression (PD) continued on single-agent bevacizumab until PD. The median progression-free survival (PFS) time was significantly improved in the bevacizumab plus CP group (6.2 months versus 4.5 months in the CP group) with a hazard ratio (HR) for PD of 0.66 (95% confidence interval [CI], 0.57 to 0.77; p-value [p] <0.001). The overall response rate (ORR) was 35% (133/381) for patients on bevacizumab plus CP and 15% (59/392) for patients on CP (p<0.001). Median overall survival (OS) was also significantly improved for patients on the bevacizumab plus CP group (12.3 months versus 10.3 months for patients receiving CP) with HR of 0.79 (95% CI: 0.67 to 0.92; p = 0.003). One- and 2-year survival rates were 51% and 23%, respectively, for the bevacizumab plus CP regimen, compared with 44% and 15%, respectively, for the CP regimen. In Study ECOG 4599, the addition of bevacizumab resulted in modest changes to the expected toxicity profiles of chemotherapy alone (Genentech 2009). Similar to other bevacizumab studies, a number of safety signals (e.g., epistaxis, hypertension, proteinuria) were identified; the majority of these events were of low grade and did not require discontinuation of bevacizumab. The results of Study ECOG 4599 suggested that the addition of a third non-cytotoxic agent and/or maintenance therapy with an agent of low toxicity could result in improved outcomes in patients with advanced NSCLC. Study ECOG 4599 also demonstrated that the treatment paradigm for patients with non-squamous NSCLC (nsNSCLC), that are eligible for treatment with bevacizumab, is different than the treatment paradigm for patients with squamous histology NSCLC based on a safety differences (NCCN 2015).

The overall safety profile of Avastin is based on data from over 5700 patients with various malignancies, predominantly treated with Avastin in combination with chemotherapy in clinical trials (Roche 2017). The most frequently observed adverse reactions across clinical studies in patients receiving Avastin were hypertension, fatigue or asthenia, diarrhea, and abdominal pain. The most serious adverse reactions were gastrointestinal (GI) perforations, hemorrhage (including pulmonary hemorrhage/hemoptysis) which is more common in patients with NSCLC, and arterial thromboembolism. Major or massive pulmonary hemorrhage/hemoptysis, can occur suddenly and up to two-thirds of the serious pulmonary hemorrhages resulted in a fatal outcome (Roche 2017). Patients with predominantly squamous cell carcinoma, hemoptysis, or both have been excluded from more recent clinical studies due to a relationship between fatal hemoptysis and central lesions with squamous histology in lung cancer patients treated with bevacizumab (Johnson et al. 2004).

Mylan GmbH is developing MYL-1402O as a proposed biosimilar product to Avastin. MYL-1402O has been extensively characterized using state-of-the-art physicochemical and

functional tests. Critical quality attributes including peptide sequence, secondary and tertiary structure, and potency have been compared in side-by-side analyses with multiple batches of Avastin. These in vitro assays demonstrate that MYL-1402O is similar to Avastin in all critical quality attributes that might potentially affect the structure, safety, and efficacy.

A biosimilar approach has been employed throughout the MYL-1402O development program, which depends on the demonstration of comparability to Avastin from the perspective of chemical, pharmaceutical, and biological attributes. Avastin, used throughout the comparability program, has been granted a marketing authorization in all major markets based on a complete quality, safety, and efficacy data set.

MYL-1402O was well tolerated in single-dose and repeat-dose toxicity studies; and had a similar toxicological profile as Avastin in a repeat-dose toxicity study in Swiss albino mice. In repeat-dose studies, the no observed adverse effect level of MYL-1402O was found to be 445 mg/kg body weight in Swiss albino mice (Study 9335) and 133.5 mg/kg body weight in New Zealand white rabbits (Study 9340). Similarly, results from 28-day repeat-dose toxicokinetic study (Study TOX 070-002) in cynomolgus monkeys showed that there were no notable differences in pathological toxic effects jn terms of serum concentrations or toxicokinetic parameters following treatments with MYL-1402O or Avastin (Investigator's Brochure, V2.0, Mylan, Jan 2016).

The PK and safety profile of MYL-1402O was further evaluated in the randomized, single-blind MYL-1402O-1002 study, where 111 healthy male volunteers were randomly assigned to receive a single dose administration (1 mg/kg during a 90 minute intravenous [i.v.] infusion) of MYL-1402O, European Union-marketed Avastin or US-marketed Avastin. The 90% CIs for the primary PK parameter, $AUC_{0\text{-inf}}$, fell within the bioequivalence limits of 0.80 to 1.25 for all 3 pairwise comparisons, MYL-1402O/US-Avastin®, MYL-1402O/EU-Avastin®, and EU-Avastin/US-Avastin, following a single, 1 mg/kg iv dose in healthy adult male volunteers.

This study demonstrates that MYL-1402O is bioequivalent to US-Avastin® and EU-Avastin®, and that EU-Avastin® is bioequivalent to US-Avastin®. Safety and tolerability of MYL-1402O, US-Avastin® and EU-Avastin® were similar. There were no SAEs or discontinuations due to TEAEs. Generally, most TEAEs reported during the study were consistent with the clinical data of bevacizumab (Avastin®). The large majority of the reported TEAEs were of Grade 1 (mild) severity and none was higher than Grade 2 (moderate). There were no clinically relevant findings with respect to clinical laboratory, vital signs, or physical examination. Overall, the local tolerability of MYL-1402O was good

and was similar to that of US-Avastin® and EU-Avastin®. The immune response was comparable across the 3 treatments, transient in nature and with no correlation with any infusion-related adverse event or with the PK parameters. (Investigator's Brochure, V3.0, Mylan, May 2017).

Biocon Limited, development partner of Mylan GmbH, has completed a randomized double-blind active-controlled, parallel-design, comparative PK, efficacy, safety and immunogenicity study of MYL-1402O compared with Avastin both in combination with XELOX chemotherapy in metastatic colorectal cancer patients in India (BM100-CC-03-I-01). A total of 136 patients were randomized in Part 2. (MYL-1402O: 68; Avastin: 68). The primary end point of the study was to evaluate the single dose pharmacokinetic parameters. The 90% CIs were within the predefined bioequivalence range of 80.00%–125.00% (C_{max}: 85.86% to 100.54%; and AUC_{0-t} 87.56% to 104.79%), confirming bioequivalence of the two bevacizumab formulations. All primary and secondary single-dose PK parameters were comparable between MYL-1402O and Avastin. The PFS rate at 18 weeks was 61.76% in the MYL-1402O arm and 60.29% in the Avastin arm, indicating a high degree of comparability in the response to treatment. There was no statistically significant difference between the two arms (p =0.8604). The ORR and disease control rate (DCR) were also comparable between the two arms and did not have any statistically significant difference (p >0.05). The treatment with MYL-1402O was well-tolerated in combination with XELOX chemotherapy and no new or unexpected safety signals were observed. The overall safety profile of Bmab-100 was comparable to that of Avastin. The study concluded that MYL-1402O is similar to Avastin with respect to pharmacokinetics, efficacy, safety, and immunogenicity. (Investigator's Brochure, V3.0, Mylan, May 2017).

In the clinical development program, MYL-1402O is being investigated in comparison with the EU-reference product Avastin and both treatments (MYL-1402O and Avastin) are being administered at a dose of 15 mg/kg bevacizumab by i.v. infusion once every 21 days until PD or treatment discontinuation according to the Avastin Summary of Product Characteristics (SmPC; Roche 2017). The current study is being conducted to compare the efficacy, safety, and immunogenicity between MYL-1402O and Avastin, when used as a first-line treatment of Stage IV nsNSCLC. For the purpose of this protocol (MYL-1402O-3001), EU-sourced Avastin (Roche 2017) will be referred to as Avastin. The first part of the study will evaluate both treatments in combination with CP, and the second part of the study will evaluate

continued treatment with MYL-1402O or Avastin in those patients who have at least stable disease to first-line therapy, including continued safety and immunogenicity.

Rationale of Study Design

Some study design considerations were based on a Genentech-sponsored, randomized, Phase 2 study AVF0757g, where bevacizumab was added to the ECOG reference regimen established in Study ECOG 1594 with CP. This Phase 2 study identified a relationship between fatal hemoptysis and central lesions with squamous histology in lung cancer patients treated with bevacizumab (Johnson et al. 2004). Based on this safety data, the subsequent Phase 3 study excluded patients with predominantly squamous cell carcinoma, hemoptysis, or both.

Interactions with the FDA and European Medicinal Agency indicated that the confirmatory efficacy and safety study should be conducted in a cancer indication with an ORR primary endpoint with a long term follow up to compare the safety profile and the immunogenicity. The demonstration of therapeutic equivalence in the nsNSCLC was expected to be applicable to other approved indications for Avastin, based on the fact that Avastin has the same mechanism of action in all indications and the dose used for NSCLC was highest amongst all indications.

Thus, this confirmatory safety and efficacy study is a multicenter, double-blind, randomized, parallel-group study and is designed to develop MYL-1402O as a proposed biosimilar to the reference product, Avastin.

As discussed in the introduction (Section 1), the dose of 15 mg/kg bevacizumab delivered by i.v. infusion once every 21 days until PD or treatment discontinuation has been chosen according to the EU-approved Avastin SmPC (Roche 2017).

2 Study Objectives

2.1 Primary Objective(s)

The primary objective of this study is to compare the ORR of MYL-1402O with that of Avastin, in combination with CP chemotherapy during the first 18 weeks of first-line treatment in patients diagnosed with Stage IV nsNSCLC.

2.2 Secondary Objective(s)

The secondary objectives of this study are as follows:

- Assess the safety profile of MYL-1402O as compared with that of Avastin when administered in combination with CP as first-line treatment for Stage IV nsNSCLC and when administered alone in the maintenance setting.
- Assess other efficacy parameters at 18 weeks and 42 weeks: Disease Control Rate (DCR), Duration of Response (DR), Progression-Free survival (PFS), and Overall Survival (OS) rate of MYL-1402O as compared to Avastin when administered in combination with CP as first-line treatment for Stage IV nsNSCLC.
- Assess the potential immunogenicity during 42 weeks of treatment of MYL-1402O as compared with that of Avastin.
- Compare the PK profile of MYL-1402O and Avastin using a population PK (PopPK) approach.
-

3 Study Design

3.1 Endpoints

3.1.1 Primary Endpoints

The primary efficacy endpoint is the ORR as assessed by an independent review during the first 18 Weeks, assessed according to RECIST 1.1.

3.1.2 Secondary Endpoints

The secondary efficacy endpoints will consist of the following.

- DCR (CR, PR, or stable disease) during the first 18 weeks
- PFS, defined as the time from randomization to the first documentation of PD or to death due to any cause, whichever comes first; PFS rate will be calculated at 18 weeks and 42 weeks, median PFS will be determined at 42 weeks.
- OS, defined as the time from randomization to date of death due to any cause, OS rates will be calculated at 18 weeks and 42 weeks.
- DOR, is defined as the time from start of the first documentation of objective tumor response (CR or PR) to the first documentation of tumor progression (i.e., PD) or to death due to any cause, whichever comes first.

3.1.3 Pharmacokinetic Endpoints

The pharmacokinetics endpoints will be as follows:

- PopPK measures of exposure of MYL-1402O and the reference product Avastin (e.g., AUC, C_{max}, C_{min}, CL, V_c, and the terminal elimination half-life).

3.1.4 Safety Endpoints

The safety endpoints will be as follows:

- Incidence, nature, and severity of AEs including adverse drug reactions graded according to CTCAE.
- Detection of antibodies to bevacizumab.

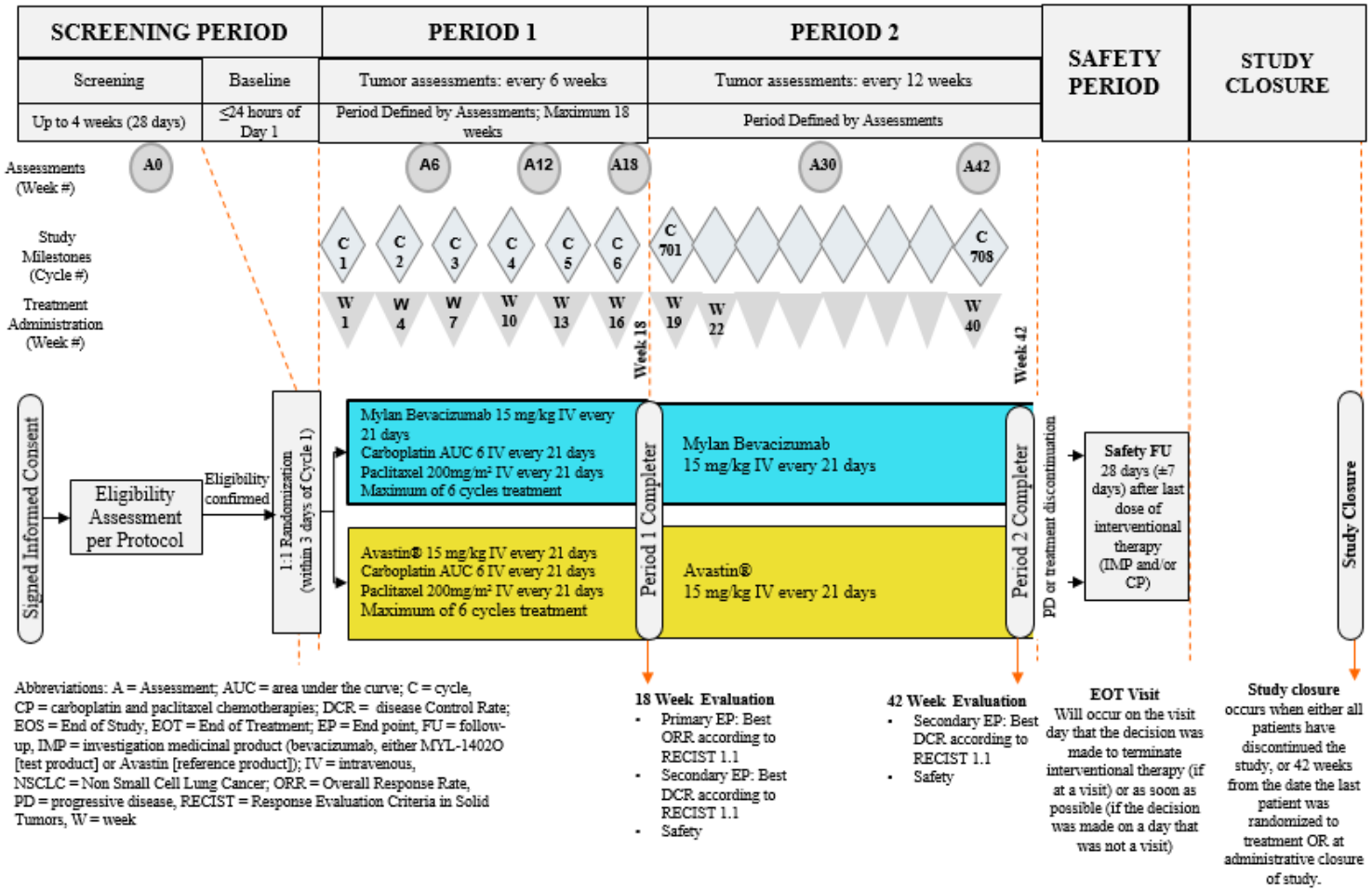
3.2 Description of the Type/ Design of Study

The study is a multicenter, randomized, double-blind, 2-arm, parallel-group, equivalence study to evaluate patients with Stage IV nsNSCLC when treated in first-line with bevacizumab (either MYL-1402O [test product] or Avastin [reference product]) in combination with CP and subsequently, with monotherapy of bevacizumab (either MYL-1402O or Avastin).

The study is comprised of 4 periods: Screening/Baseline Period, Period 1, Period 2 and Extended Treatment Period. For Period 1 and Period 2, the length of the period is defined by the tumor assessments interval (every 6 weeks or every 12 weeks, respectively).

The periods are shown in Figure 3-1 and are described in detail in Section 3.4. Assessments will be conducted per the Schedule of Events (Table 1-1).

Figure 3-1 Study Design



3.3 Randomization and Blinding

3.3.1 Randomization

Patients who meet all of the inclusion and none of exclusion criteria and who are approved by the medical monitor will be considered eligible for entry into the study and will be randomly assigned to treatment in the study within 3 days prior to Day 0 of Cycle 1.

Approximately 640 eligible patients (320 patients per group; Section 7.4) from approximately 120 sites worldwide will be randomly assigned to one of 2 treatment arms (MYL-1402O or Avastin). An interactive voice or web response system (IVRS/IWRS) will be used to administer the randomization schedule. Biostatistics will generate the randomization schedule using SAS software Version 9.3 or later (SAS Institute Inc, Cary, North Carolina) for IVRS/IWRS, which will link sequential patient randomization numbers to treatment kit numbers. The randomization schedule will be stratified by gender (male or female), smoking status (smoker or <100 cigarettes in entire lifetime), and number of metastasis sites (one site or multiple sites). It will also use an appropriate block size, which will not be revealed.

3.3.2 Blinding

An unblinded pharmacist will be identified at each center; whose role will be limited to handling the blinded study treatment. Treatment allocation via the IVRS/IWRS will be provided only to the unblinded pharmacist (or authorized designee); and will be sent to the pre-specified fax/email accessible only to unblinded team members.

The unblinded pharmacist will prepare infusion bags of MYL-1402O and Avastin and provide the infusion bags to the PI (or designee) in a blinded manner. Treatment assignment must **NOT** be disclosed to the PI (or designee), site or study personnel, or any sponsor representative except for the designated site monitor responsible for unblinded monitoring.

The assessors (i.e., the PI and site personnel assessing safety and efficacy), the study patients as well as both the local and central radiologists must remain blinded throughout the study (Period 1 and Period 2).

The sponsor plans to report results after all patients have completed Week 18 or discontinued the study. After Week 18, the study will continue as a blinded study for patients, PIs (or

designees), vendors, blinded clinical research organization personnel, and blinded clinical team until completion.

After all patients have completed Week 18 or discontinued the study, part of the sponsor clinical team will be unblinded to the randomization list, and the primary efficacy analysis will be performed. A clinical study report will be written to report the results of the primary efficacy analysis and all other efficacy and safety results up to that point in time, a second report will be written after all patients reach 42 weeks.

3.4 Expected Duration of Subject Participation and Study Periods

The maximum planned study participation from Screening/Baseline Period through Safety Follow up Visit is approximately 47 weeks.

Screening/Baseline Period: In this period, which has a duration of up to 4 weeks (or ≤28 days prior to first dose [Day 0 of Cycle 1]), tumor imaging assessments must be performed no more than 28 days prior to first dose (Day 0 of Cycle 1). The time between randomization (≤3 days prior to Day 0 of Cycle 1) and the first dose (Day 0 of Cycle 1) must be included in the 28-day window for tumor imaging assessment. Patients will be randomly assigned in a 1:1 ratio to one of the two treatment groups (MYL-1402O or Avastin) within 3 days before the start of Period 1 (first dose of bevacizumab plus CP on Day 0 of Cycle 1). Baseline assessments must be performed within 24 hours of Day 0 of Cycle 1 to confirm that the patient has remained eligible for treatment.

Period 1: Patients will start Period 1 receiving bevacizumab combination therapy (MYL1402O or Avastin, plus CP) on Day 0 of Cycle 1 for up to 6 cycles of therapy. Each cycle will consist of 3 weeks (21 days ± 3 days) and a cycle will start with the administration of bevacizumab (as either MYL-1402O or Avastin).

In this period, tumor assessments should be performed every 6 weeks after Day 0 of Cycle 1 (the first dose of bevacizumab, either MYL-1402O or Avastin) and continuing every 6 weeks (window of ±3 days) through Week 18.

Tumor assessments must be done consistently throughout the study, using at least a CT scan of thorax and abdomen and using the same technique - CT or MRI, slice interval, contrast agent. Period 1 will include 3 assessments at the pre-specified time points regardless of delays in treatment cycles.

Period 2: A patient is eligible to continue into Period 2 if he/she has a stable disease or better response (i.e., complete response [CR] or partial response [PR]) by RECIST 1.1 criteria at

the Period 1 Week 18 tumor assessment. The eligible patient will continue to receive bevacizumab (either MYL-1402O or Avastin) every 3 weeks as a monotherapy.

In this period, tumor assessments should occur every 12 weeks after the end of Period 1 (Week 18), at pre-specified time points (i.e., Week 30 and Week 42), regardless of delays of the cycles of treatment, until PD or discontinuation of interventional therapy (for any reason), or withdrawal of consent. The Week 42 efficacy assessments will be used to evaluate the secondary endpoints. Patients will be assessed for tumor response using the same type of radiographic examinations used in Period 1 (e.g., CT or MRI of the thorax and abdomen, contrast agent, slice intervals) for ongoing evaluation of tumors.

If a patient is discontinued from treatment prior to completion of Period 2 due to an Adverse Event, tumor assessment will be performed as per schedule until week 42, patient is started on a new anticancer treatment (surgery, radiotherapy or systemic treatment) or disease progression (PD), and will be followed for OS till week 42.

Extended Treatment Period: During the Extended Treatment Period, continued bevacizumab monotherapy may be provided to any patient that has maintained stable disease or better response (CR or PR) by RECIST 1.1 criteria at Week 42.

During the Extended Treatment Period, a patient will receive bevacizumab monotherapy (either MYL-1402O or Avastin) until PD or discontinuation of treatment or termination of study. Safety assessments will be made for each cycle of therapy.

Safety Follow-Up Visit: The Safety Follow-Up Visit is designed to capture safety assessments for any patient(s) that discontinue the IMP at any time during the study, for any reason (e.g., PD, treatment intolerance to bevacizumab). Safety follow-up visit will occur at 28 days (± 7 days) after the last dose of bevacizumab during an office visit. The End of Treatment Visit should occur after the last dose of any interventional therapy, mainly to capture the reason for discontinuation of the first-line treatment. The End of Treatment (EOT) Visit may occur at the same time as the safety follow-up visit.

Study Closure:

Study closure will occur when ***one*** of the following is reached:

1. All patients have discontinued from the study
2. 42 weeks from the date the last patient was randomized to treatment.
3. Administrative closure of study.

NOTE: Patients on study treatment at time of study closure will be advised by the PI and/or their associated primary health care provider on alternate therapies as per standard for the country. All treatment provided under the auspices of this protocol will cease at study closure.

3.5 Stopping Rules or Discontinuation Criteria

Discontinuation from interventional therapy is terminology specific to patients who stop receiving interventional therapy under the auspices of the protocol. Patients can continue to participate in study evaluations and provide data (e.g., second line therapies, OS data collection points).

It will be vitally important to capture in both the source document and the electronic case report form (eCRF) the reason a patient has decided or the PI decided to discontinue from interventional therapy.

It is the patients' right to consider whether they wish to continue to participate in study-related procedures and to have their data collected under the protocol (for instance, assessments related to the key primary endpoints) or other key assessments (such as safety, survival, disease response).

Should a patient not wish to be followed (i.e., contacted by the investigative site, and/or participate in further assessments and/or have additional data collected), the patient must specifically sign a withdrawal of consent form.

Treatment should be discontinued if any of the following reasons apply (but not limited to):

- Progression of Disease
- Severe infusion reactions to MYL-1402O or Avastin or carboplatin or paclitaxel
- Pregnancy: If pregnancy occurs in a female patient, the patient will be discontinued from study and followed until the outcome of the pregnancy is known
- Any other physical examination finding, change in vital signs, AE* or laboratory abnormality that in the opinion of the PI (or designee), would cause an excessive risk if the patient continues the study treatment
- Unacceptable toxicity

- In the PI's (or designee's) opinion it is in the patient's best interest to discontinue treatment, e.g., due to changes in medical or social condition.
- Patient withdrawal of consent
- Patient indicates unwillingness to comply with study treatment or protocol requirements
- Patient is lost to follow-up
- Patient enters the study in violation of the protocol
- Use of prohibited therapy (as defined in Section 5.4.2)
- Non-compliance that in the opinion of the PI will compromise possible response to therapy
- Administrative reasons, such as inability of the patient, the PI or the sponsor to continue the study.

* Upon occurrence of a serious or intolerable AE, the PI (or designee) will confer with the sponsor. If a patient is discontinued because of an AE, the event will be followed until it is resolved.

3.6 Accountability procedures for the investigational product(s)

Mylan GmbH will provide adequate supplies of interventional therapies (MYL-1402O, Avastin, carboplatin, and paclitaxel). Chemotherapy pre-medications and any other medications will be procured locally by the site. Sites will also provide the infusion supplies from their stock. For this protocol, carboplatin and paclitaxel are considered non-investigational.

MYL-1402O (test product) and Avastin (reference product) will be packaged, labelled and supplied centrally to all sites from the Mylan-approved packaging vendor.

The CP chemotherapy will be administered sequentially after IP. This will also be packaged, labelled, and supplied centrally to all sites from the Mylan approved packaging vendor.

MYL-1402O and Avastin vials are not blinded. Each vial will be labelled with a blinded label as per local language and regulatory requirement. Each individual vial will then be placed into a labelled carton. The carton will have a blinded label applied to it. Once the vial is

placed into the carton and tamper sealed, it is then blinded. The dosage amount to be given to a patient will be determined based on a patient weight calculation and will be prepared for administration by the unblinded pharmacist as described in Section 3.3.2.

The premedication and saline will be procured locally by the sites.

All IMP must be protected from moisture, and kept in a refrigerator at 2°C to 8°C. Temperature monitoring in the form of an in-house management system is required that is, for example, alarmed if the refrigerator stops working. Regular refrigerator maintenance checks will be conducted. Quarantine management of supplies will be available on site if required within a refrigerator at 2°C to 8°C, for example, temperature variations at site or during distribution to site. Chemotherapy (i.e., carboplatin and paclitaxel) does not need to be refrigerated (see the package insert for each product for handling full details; Paraplatin 2010, Taxol 2011).

Each shipment will come with a calibrated temperature monitor, which will require stopping upon receipt at site and the data will require to be downloaded and sent to the packaging vendor. Instruction on how to perform this activity will be provided in writing to each site as well as instruction on actions to be performed in IWRS and physically at site.

An IWRS will be used for drug inventory and distribution management. There will be instructions provided to the site on what to do in the event of a temperature deviation, and how to manage the product in IWRS, and physically at the site. There will be return instructions put into place on how the IMP/chemotherapy needs to be returned back to the shipping depot if the site is not able to reconcile. Destruction of the IMP/chemotherapy must be pre-approved by the sponsor, if locally destroyed. If the site does destroy locally, a certificate of destruction will be required clearly linking which drug has been destroyed, using what method and when.

The randomization list will be prepared by PPD and supplied to the packaging vendor who will use the randomization list to label supplies, and upload into IWRS. An approved third party courier will make the shipments and temperature monitor the shipments to the site. All updates will be made in the IWRS.

Labelling text will be compliant with local regulatory requirements. Dispensation will be conducted via the IWRS and preparation by the unblinded pharmacist on site as described in Section 3.3.2.

The label should include but not be limited to: Sponsor name/address, Dosage, Route of administration, Quantity, Name/strength, Packaging batch number/code, Trial reference or protocol number, Kit's number, Directions for use, Statement 'For Clinical Trial Use Only', Storage conditions, Expiry/use by date

The PI (or designee) will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

3.7 Maintenance and Breaking of Randomization Codes

A patient's treatment assignment will not be broken until the end of the study unless medical treatment of the patient depends on knowing the study treatment the patient received. In the extraordinary event that the blind needs to be broken because of a medical emergency, the PI may unblind an individual patient's treatment allocation. As soon as possible, the PI should first contact the medical monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that patient. The treatment assignment will be unblinded through IVRS/IWRS. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible (i.e., medical monitor from the sponsor or PPD) must also be documented.

4 Selection and Withdrawal of Subjects

4.1 Subject Inclusion Criteria

A patient is eligible for inclusion in the study if he or she meets all of the following criteria:

1. Has demonstrated the ability to understand verbal and/or written instructions, to provide written informed consent, and is capable and agreeable to comply with protocol requirements.
2. Male or female at least 18 years of age at the time of signing an informed consent form (ICF).
3. Has a documented imaging diagnosis of Stage IV unresectable, recurrent or metastatic nsNSCLC.
4. Has documented histologic or cytologic diagnosis of advanced nsNSCLC with negative or unknown sensitizing epidermal growth factor receptor (EGFR) mutation, and negative or unknown echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) rearrangement.
5. Has measurable disease with at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1; Section 12.1 [Appendix A]). All target (up to 5 lesions) and nontarget lesions (other measurable not included in target, nonmeasurable, nonevaluable, or evaluable lesions) should be included in the assessment or evaluation of disease response as defined by RECIST 1.1 (Eisenhauer et al 2009).

   NOTE: If in the staging assessment, bone metastases are discovered and are localized outside of the thorax and abdominal region, each non target metastasis or as multiple non target bone metastases should be included in the tumor response assessments and followed by X-ray, CT scan, or MRI as appropriate.
6. Has a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale.
7. Has at least 6 months of expected survival.
8. Has not received any prior systemic therapy for first-line treatment of advanced lung cancer, except adjuvant chemotherapy, and remained disease-free for at least 12 months from time of surgery, and at least 6 months from last dose of chemotherapy.
9. May have had prior radiation therapy provided <25% of bone marrow is involved (Section 12.3 [Appendix C]), except for previous mediastinal irradiation that is not allowed.

a. Prior radiation therapy must have been completed at least 2 weeks prior to Day 0 of Cycle 1

b. Patient must have recovered from acute toxicities associated with radiation therapy. Radiation-related toxicities must have resolved to Grade 1 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 4.03) grade prior to Day 0 of Cycle 1.

10. May have brain metastasis provided the metastasis has been treated and is considered stable.

    Treated, stable brain metastasis is defined as:

    a. Metastasis having no evidence of progressive disease (PD) or hemorrhage after treatment.

    b. No ongoing requirement for dexamethasone, as ascertained by clinical examination and post-treatment brain imaging (computed tomography [CT] scan or magnetic resonance imaging [MRI]) at baseline.

    c. Anticonvulsants are allowed, provided the dose regimen has been unchanged (stable) for at least 2 weeks prior to patient signing informed consent.

    d. Treatment for brain metastasis may include whole brain radiotherapy, radiosurgery (Gamma Knife®, linear particle accelerator, or equivalent), or a combination thereof, as deemed appropriate by the treating physician. All brain metastasis treatments must be completed at least 14 days prior to Day 0 of Cycle 1.

11. Has adequate organ functions based on the following:

    a. Bone marrow reserve:

        i. White blood cell count ≥3 × 103/μL;

        ii. Absolute neutrophil count (segmented and bands) ≥1.5 × 10^3/μL;

        iii. Platelet count ≥100 × 10^3/μL;

        iv. Hemoglobin ≥9.0 g/dL with at least 2 weeks without transfusions before Day 0 of Cycle 1.

    b. Hepatic:

        i. Total bilirubin ≤1.5 × upper limit of normal (ULN); except if elevation is due to Gilbert's Syndrome with transitory elevations of indirect bilirubin.

        ii. Alkaline phosphatase, alanine transaminase, and/or aspartate transaminase ≤3 × ULN. Significant levels of alanine transaminase or aspartate transaminase

should be further assessed for viral hepatitis, if not related with liver metastases. *(Note: Isolated alkaline phosphatase elevation beyond 3 × ULN due to bone metastasis is allowed).*

c. Renal:

i. Calculated creatinine clearance ≥45 mL/min based on the original, weight-based Cockcroft and Gault formula (Cockcroft and Gault 1976; Section 12.4 [Appendix D])

ii. Urine protein (via dipstick): 0 or 1+. Patients with ≥ 2+ can be included only if a 24-hour urine specimen yields <2g of protein

12. If capable of reproduction, patients and their partners must use contraceptive methods during the full duration of the study and for 6 months after discontinuation of study.

a. A patient who is capable of reproduction must be willing to practice birth control by using 2 different highly effective double barrier methods of contraception, or abstinence from sexual intercourse for the duration of the study.

i. In particular a female patient of childbearing potential must use a method that results in less than 1% failure rate per year when used consistently and correctly such as implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence, or vasectomized partner.

ii. A male patient of reproductive potential (defined as a male that has not had a vasectomy) must use a condom with spermicide and their female partner to use another highly effective form of contraception.

4.2 Subject Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Is pregnant or breast-feeding.
2. Has documented histology/cytology confirming any of the following:

a. Squamous non-small cell lung cancer. *(Note: In the event of mixed tumor histology/cytology or predominant cell type other than non-squamous, eligibility will be determined based on the predominant cell type, which must be non-squamous.)*

b. A patient with any small cell type or large cell neuroendocrine histology.

3. Has a recent (within 6 months prior to Day 0 of Cycle 1) cardiac condition as defined by the New York Heart Association Class II, III, or IV (AHA 1994).

4. Has a recent (within 6 months prior to Day 0 of Cycle 1) history of a significant vascular event (such as aortic aneurysm requiring surgical repair or a recent peripheral arterial thrombosis) and/or history of significant and unstable vascular disease.

5. Has a history of stroke or transient ischemic attack within 6 months prior to Day 0 of Cycle 1, or has a long-term history of more than one of the following vascular thromboembolic events:

    a. Cerebrovascular accidents

    b. Transient ischemic attacks

    c. Myocardial infarctions

    d. Venous thromboembolic reactions, including pulmonary embolism

6. Is receiving anticoagulant therapy that:

    a. Is not considered ‘stable’, defined as dosage not maintained for at least 3 months prior to Day 0 of Cycle 1.

    b. Is not within the targeted international normalized ratio at the time of consent signing.

7. Has a current diagnosis, history, or risk of hemorrhage in the central nervous system (CNS), including the following:

    a. Patient with CNS metastasis treated by neurosurgical resection or brain biopsy performed within 8 weeks prior to Day 0 of Cycle 1.

    b. Patient should be off corticosteroids for at least 1 week (7 days) at the time of the post-treatment (for CNS metastasis) brain CT/MRI.

8. Has any prior history of hypertensive crisis and/or hypertensive encephalopathy, or has a current diagnosis or recent history of inadequately controlled hypertension (defined as systolic blood pressure >150 mm Hg and/or diastolic >100 mm Hg, while on antihypertensive medications).

9. Has a recent history of any of the following:

    a. A major surgical procedure, open biopsy, open pleurodesis, or significant traumatic injury within 28 days prior to Day 0 of Cycle 1.

    b. Documented history of conditions that may need surgery during the study or within 6 months of signing informed consent.

c. Has had either a core biopsy or other minor surgical procedure within 7 days prior to Day 0 of Cycle 1. (*Note: Placement of a vascular access device, or a closed pleurodesis, thoracentesis, or mediastinoscopy are allowed).*

10. Has a history of any of the following:

a. Hemoptysis (approximately >2.5 mL or a half teaspoon) within 3 months prior to Day 0 of Cycle 1.

b. A thoracic, central, mediastinal tumor located within 2cm of carina invading or abutting major blood vessels (based on radiologist assessment) and associated bleeding risk as per PI judgement.

c. A lung tumor with cavitation, if more than 50% of the diameter of the lesion is cavitated, and/or involving the central bronchus or vessel.

- Major blood vessels are defined as:

  • Aorta

  • Superior and inferior vena cava

  • Main pulmonary artery

  • Intrapericardial portions of the right and left pulmonary arteries and pulmonary veins

- Central location is defined as:

  • Distance of less than or equal to 2 cm from carina

  EC 10 will be evaluated on a case by case basis taking into consideration the above criteria in discussion with the site radiologist, PI and the medical monitor.

11. Has a history of gastrointestinal fistula, perforation, or abscess.

12. Has a current diagnosis or history of a nonhealing wound, active ulcer, or untreated bone fracture.

13. Has prior history of another active malignancy within the last 5 years, other than adequately treated superficial basal cell, superficial/skin squamous cell carcinoma, or carcinomas in situ.

14. Has a known hypersensitivity to any component of carboplatin, paclitaxel, bevacizumab, Chinese hamster ovary cell products, or other recombinant human or humanized antibodies.

15. Has received treatment with any other investigational drug prior to day 0 of cycle 1, within the last 30 days or 5 half-lives (if available); whichever is longer.

16. Has previously received treatment with the following:

    a. Paclitaxel.

    b. Bevacizumab *(Note: Prior intravitreal administration of bevacizumab does not preclude study participation)*.

    c. Anthracycline. *(Note: May be allowed on a case by case basis after consulting with the medical monitor to rule out an increased risk of cardiac failure).*

17. Has documented or known current alcohol/drug abuse that precludes his/her ability to adhere to the protocol.

18. Has any of the following concomitant treatments or conditions:

    a. Concomitant vaccination that contains an attenuated virus, for instance Yellow Fever vaccine.

    b. Has a known history of active or latent tuberculosis.

    c. Has a concomitant systemic disorder (e.g., active infection including known human immunodeficiency virus, viral hepatitis B or C) that, in the opinion of the principal investigator (PI; or designee), would compromise the patient's safety (for instance potential drug interactions, or ability to adhere to the protocol).

    d. Has any other concomitant condition that precludes the participation in the study through increased risk to the patient and/or potential to impact the PI's (or designee's) ability to administer this protocol.

4.3 Withdrawal of Consent

Withdrawal of consent is a specific action whereby the patient verbally and/or in writing declares to the PI that they no longer wish to participate in the study and likewise no longer consents to collection of data associated with the study. In this regard, the patient is effectively withdrawing his/her consent from study participation. In the occurrence and specific instance of withdrawal of consent, there are a series of steps that the investigational site staff must engage with the patient. The purpose of these steps is to demonstrate prudence/due diligence in both acknowledging the patient's request as well as appropriate management of the request. The reason a patient decides to withdraw consent or discontinue from interventional therapy should be captured both in the source documentation as well as the eCRF.

All data generated up to the date whereby the patient makes this declaration is to be collected and monitored. This applies to medical/clinic-generated data, as well as any laboratory/blood/tissue analysis data. All patients who discontinue from interventional therapy or withdraw their consent from the study will undergo all safety and EOT assessments (Safety Follow-Up Visit, Section 6.8).

Patients who withdraw early from the study prior to first dose of study drug (i.e., Baseline Failure) will not be replaced.

4.3.1 Efforts to Mitigate Missing Data

Missing data and the impact on a clinical study can be extreme and serious. In the most extreme of cases, missing data could lead to a study having to be repeated due to loss of statistical power and/or significant bias impacting primary endpoints and overall protocol objectives.

In order to better address missing data as a whole within the pharmaceutical industry, the US FDA convened a panel titled "Panel on Handling Missing Data in Clinical Trials – Committee of National Statistics – Division of Behavioral and Social Sciences and Education" in 2009 (FDA 2009).

Based on discussions within the panel, a report titled "The Prevention and Treatment of Missing Data in Clinical Trials" – was generated which focuses on a number of approaches sponsor companies and PIs can utilize to mitigate missing data.

Within this protocol, language that is specific to withdrawal of consent versus discontinuation from interventional therapy – is one approach to mitigate missing data.

Additionally, patient education will be an important element to assure patients clearly understand the following:

- Visit schedule associated with the study.
- Amount of patient personal time/commitment to participate in the study.
- The need to be communicative with the investigative site staff in the event a scheduled visit cannot be met.
- Difference between withdrawal of consent versus discontinuation from interventional therapy.

A variety of patient directed materials will be produced to assist patients in understanding the importance of their commitment to a clinical study as well as begin to explain the differences between withdrawal of consent versus discontinuation of interventional therapy. This basic reference will be available in the informed consent template. In addition, the use of patient directed materials (aside from the ICF) will be at the discretion of the site specific Institutional Review Board (IRB)/Ethics Committee.

In the event a patient fails to return for final assessments, it will be important that the investigative site be prudent in attempts to contact the patient. If the patient cannot be contacted, the site will make attempts to contact the patient's Alternate Contact (AC). Contacting the patient or patient's AC can be done in a variety of methods via telephone, email, postal mail, and/or certified letter/messenger service. Attempts to contact the patient will be documented in the source document and only, after all attempts are exhausted, will the patient be deemed as “Lost to Follow Up”.

It is vital to obtain follow-up data on any patient withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

5 Study Treatments

This protocol refers to bevacizumab as the IP, either as MYL-1402O (test product) and/or Avastin (reference product). In addition to IP, carboplatin (Section 5.2.2) and paclitaxel (Section 5.2.4) chemotherapy will be given to patients. All patients will receive standard premedication per the paclitaxel label (Taxol 2011) or local institutional protocols.

For safety information Refer to IB, and Avastin SmPC (Investigator's Brochure V3.0, Mylan, May 2017; Roche 2017).

5.1 Investigational Medicinal Product (Test and Reference)

Both, MYL-1402O and Avastin are supplied at a concentration of 25 mg/mL as a sterile, concentrated solution for i.v. infusion, in preservative-free, single-use 100 mg/4 mL and 400 mg/16 mL vials.

The formulation and excipients used for MYL-1402O are identical to that of Avastin. These include trehalose dihydrate, sodium phosphate, polysorbate 20 and water for injections, per the Avastin EU-SmPC (Roche 2017).

5.2 Treatment Administration

Patients will receive bevacizumab (as either MYL-1402O or Avastin) administered as an i.v. infusion, at a dose of 15 mg/kg of body weight given once every 21 days in combination with CP (bevacizumab combination therapy) and subsequently without CP (bevacizumab monotherapy). A cycle will start with administration of bevacizumab (MYL-1402O or Avastin; Section 5.2.1). In Period 1, bevacizumab will be followed by carboplatin (Section 5.2.2) and then paclitaxel (Section 5.2.4; and include pre-medications [Section 5.2.3]).

Bevacizumab monotherapy will only include treatment with bevacizumab (MYL-1402O or Avastin; Section 5.2.1) and will not include any chemotherapy.

Preparation for administration requires the use of appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Reconstitution of MYL-1402O or Avastin is described in the study Procedure Manual. Any unused portion left in a vial is to be discarded, as the product contains no preservatives; additional information on the destruction of the interventional therapies is provided in the study Procedure Manual. **Do not administer or mix with dextrose solution.**

The study treatment may only be administered by experienced and trained study team personnel. The body weight of the patient and the dose calculated by the trained study team member(s) must be documented in the source document (e.g., medical record) before the administration of treatment. Facilities and equipment for resuscitation must be immediately available: medications such as antihistamines, corticosteroids, and epinephrine and equipment such as electrocardiogram (ECG) monitors, and defibrillators. Hospitalization facilities should be accessible and within a short distance from the chemotherapy facility.

5.2.1 Bevacizumab (MYL-1402O or Avastin)

Bevacizumab (MYL-1402O or Avastin) will be administered by i.v. infusion at a dose of 15 mg/kg i.v. infusion every 21 days (± 3 days) for up to 6 treatment cycles (1 treatment cycle = 21 days based on bevacizumab administration) in combination with CP and then alone as a maintenance.

Adjustments for bevacizumab (MYL-1402O or Avastin) are located in Section 5.2.5.1.

In Period 1, the first dose of bevacizumab (either MYL-1402O or Avastin) will be administered over 90 minutes (±15 minutes). If the first infusion is tolerated without infusion-associated AEs (i.e., infusion reactions), then the second infusion (Cycle 2) may be delivered over 60 minutes (±10 minutes). If the 60-minute infusion (Cycle 3) is well tolerated, subsequent infusions (i.e., other cycles in Period 1) may be delivered over 30 minutes (± 10 minutes).

Patients will receive blinded bevacizumab (either MYL-1402O or Avastin) monotherapy, based on the randomization/blinded schema that was applied to Period 1. The length of bevacizumab infusion will be the same tolerated infusion length used in Period 1.

Bevacizumab monotherapy will consist of bevacizumab (MYL-1402O or Avastin) administered alone by i.v. infusion at a dose of 15 mg/kg i.v. infusion every 21 days until PD or treatment discontinuation. Infusion may be delivered over 30 minutes (±10 minutes) if well tolerated during Period 1.

The bevacizumab monotherapy may start if the patient has stable disease or better response (CR or PR), the PI or designee considers continued treatment with bevacizumab to be of benefit, and the following occurred:

- The patient received at least one cycle of bevacizumab combination therapy (either MYL-1402O or Avastin, in combination with CP) and treatment with CP is

terminated prior to receiving a total of 6 cycles of combination therapy due to intolerance of the CP therapy.

- The patient received 6 cycles of bevacizumab combination therapy (either MYL-1402O or Avastin, in combination with CP) and continued treatment with bevacizumab monotherapy as planned.

5.2.2 Carboplatin

Carboplatin will be prepared and administered in accordance with the package insert for the relevant registered product (Paraplatin 2010).

Calculation of the carboplatin dose will be based on the creatinine clearance calculations using Cockcroft and Gault Formula (Section 12.4, Appendix D). For AUC 6, the **maximum dose is 900 mg.**

Patients will receive carboplatin dose of AUC 6 by continuous i.v. infusion over 30 minutes every 21 days up to 6 cycles. If the infusion of bevacizumab (MYL-1402O or Avastin) is tolerated without infusion-associated AEs, then the infusion of carboplatin may be delivered over 30 minutes (±15 minutes) for the first infusion (Cycle 1). For subsequent infusion cycles, carboplatin may be delivered at 15 to 30 minutes.

Adjustments for dosing are located in Section 5.2.5.2. **NOTE: Carboplatin at AUC 6 is the required dose at cycle 1. For Subsequent cycles, Carboplatin dose may be lowered to AUC 5 ONLY after discussion with the medical monitor.**

5.2.3 Paclitaxel Premedications

All patients will receive standard premedication per the paclitaxel package insert (Taxol 2011) or local institutional protocols.

5.2.4 Paclitaxel

Paclitaxel will be prepared and administered in accordance with the package insert for the relevant registered product (Taxol 2011).

The calculation of the paclitaxel dose will use the Mosteller formula (Mostellar 1987) equation (Section 12.5, Appendix E), which is calculated based on the patient's body surface area (BSA).

After each administration of carboplatin, patients will receive a paclitaxel dose of 200 mg/m^2 by continuous i.v. infusion over 3 hours (± 30 minutes) every 21 days up to 6 cycles. If the

infusion of paclitaxel is well tolerated in Cycle 1, then subsequent infusions of paclitaxel may be delivered over 60 to 120 minutes.

In countries where the initial dose is 175 mg/m^2 based on institutional protocol, PIs are allowed to initiate dosing at 175 mg/m^2. For a patient that demonstrates tolerance of the 175 mg/m^2 dosing in Cycle 1, the PI may increase the dose to 200 mg/m^2 in Cycle 2. The dose at subsequent cycles will be determined by the PI and tolerance of the individual patient. Dosing will be documented by the PI. If in the best interest of the patient, the PI does not increase the dose to 200 mg/m^2, then the patient may remain at 175 mg/m^2 for the remaining cycles of therapy. The minimum dose of paclitaxel allowed on this protocol is 160 mg/m^2. Any patient unable to tolerate the minimal dose level of paclitaxel will be discontinued from chemotherapy or the case will be discussed with the Medical Monitor if a lower dose is required by the Investigator and then needs approval by the sponsor. Dosing will be documented by the PI.

For details on dosing adjustments, refer to Section 5.2.5.3.

5.2.5 Treatment Adjustments

Treatment adjustments are recommendations per the product label. In the event the Investigator does not feel the recommendations are appropriate for a patient; then the Investigator MUST contact the Medical Monitor prior to dosing. It is critical to document any dose adjustments done which are not as per the recommendations of the product label, in the patient's medical records.

5.2.5.1 Adjustments for Bevacizumab (MYL-1402O or Avastin)

Initial dose level of bevacizumab is 15 mg/kg (Roche 2017).

There will be no modification of bevacizumab dose during this study; however, if the patient's weight changes by ≥10% during the study, the dose of bevacizumab will be recalculated.

If chemotherapy is held for a low ANC or thrombocytopenia, bevacizumab will also be held. During bevacizumab combination therapy, bevacizumab may be held for 1 cycle and the patient may only receive CP for that given cycle; the following cycle, patient should return to bevacizumab combination therapy or be switched to CP alone for the remaining cycles.

Any patient who is delayed must be evaluated on a weekly basis until adequate non-hematologic parameters have been met, as described below. Treatment delays are to be

kept to a minimum and every effort should be made to maintain the intended schedule. No treatment delays are permitted for other than documented toxicity, however a window of ± 3 days is permissible without incurring a protocol violation for the next cycle to allow for holidays.

Reasons for the withdrawal or discontinuation of patients from treatment or from the study are provided in Section 4.3. Clinical safety data indicate that the safety issues can be dose dependent (Roche 2017).

Table 5-1 Dose Modifications for Adverse Reactions

Adverse Reaction	Severity	Dose Modification
Gastrointestinal Perforation and fistulae	Gastrointestinal perforation, any grade Tracheoesophageal fistula, any grade Fistula, Grade 4 Fistula formation involving any internal organ	Discontinue Avastin
Wound Healing Complications	Wound healing complications requiring medical intervention Necrotizing fasciitis	Discontinue Avastin
Hemorrhage	Grade 3 or 4	Discontinue Avastin
	Recent history of hemoptysis of 1/2 teaspoon (2.5 mL) or more	Withhold Avastin
Thromboembolic Events	Arterial thromboembolism, severe	Discontinue Avastin
	Venous thromboembolism, Grade 4	Discontinue Avastin
Hypertension	Hypertensive crisis Hypertensive encephalopathy	Discontinue Avastin
	Hypertension, severe	Withhold Avastin if not controlled with medical management; resume once controlled
Posterior Reversible Encephalopathy Syndrome (PRES)	Any	Discontinue Avastin
Renal Toxicity and Proteinuria	Nephrotic syndrome	Discontinue Avastin

Adverse Reaction	Severity	Dose Modification
	Proteinuria greater than or equal to 2 grams per 24 hours in absence of nephrotic syndrome	Withhold Avastin until proteinuria less than 2 grams per 24 hours
Infusion Reaction	Severe infusion reaction	Discontinue Avastin
	Clinically significant	Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve
	Mild, clinically insignificant	Decrease infusion rate
Congestive Heart Failure	Any	Discontinue Avastin

5.2.5.1.1 Infusion-Related Reactions

In clinical studies, infusion reactions with the first dose occurred in < 3% of patients and severe reactions occurred in 0.2% of patients. Infusion reactions reported across clinical studies and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis.

In case of infusion reaction, decrease the rate of infusion for mild, clinically insignificant infusion reactions. Interrupt the infusion in patients with clinically significant infusion reactions and consider resuming at a slower rate following resolution. Discontinue in patients who develop a severe infusion reaction and administer appropriate medical therapy (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators and/or oxygen). (Roche 2017)

5.2.5.1.2 Hypertension

Hypertension is common in patients treated with bevacizumab, with an incidence of 20% to 30% across studies. Initiation or increase of antihypertensive medications may be required, but in most cases, BP can be controlled with routine oral drugs. However, incidents of hypertensive crisis with encephalopathy or cardiovascular sequelae have been rarely reported. BP should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with general medical practice.

Patients should have BP measured prior to each dose of bevacizumab; dosing rules based on degree of hypertension are as follows:

- For controlled hypertension, defined as systolic <150 mm Hg and diastolic <90 mm Hg, continue bevacizumab therapy.
- For uncontrolled hypertension (systolic >150 mm Hg or diastolic >100 mm Hg) or symptomatic hypertension less than CTCAE Grade 4, hold bevacizumab treatment (and cytotoxic chemotherapy for up to 1 week if indicated), with antihypertensive therapy initiated, increased, or continued. During the period of combination chemotherapy with bevacizumab, if hypertension is controlled and symptomatic hypertension has resolved by 1 week after holding treatment, continue all therapy.
- For patients with continued uncontrolled hypertension despite medication after a one week delay, treatment of bevacizumab will be withheld and patients will be treated with chemotherapy alone.
- Bevacizumab will be permanently discontinued for patients with uncontrolled hypertension that has not resolved after three weeks of holding bevacizumab (i.e., the patient is discontinued from treatment if there is a maximum of 42 days from last infusion).
- Finally, for any patient developing CTCAE grade 4 hypertension, bevacizumab will be discontinued and the patient will not be re-started on bevacizumab therapy.

5.2.5.1.3 Proteinuria

Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from an asymptomatic increase in urine protein (incidence of about 20%) to rare instances of nephrotic syndrome (0.5% incidence). Pathologic findings on renal biopsies in 2 patients showed proliferative glomerulonephritis. National Cancer Institute (NCI) CTCAE grade 3 proteinuria (> 3.5 g/24-hour urine) is uncommon. The safety of continuing bevacizumab in patients with moderate or severe proteinuria has not been adequately tested.

If proteinuria is monitored by urine dipstick, patients with a 2+or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. If therapy is held for > 6 weeks from the last dose due to proteinuria, then bevacizumab will be discontinued and the patient will not be re-started on bevacizumab therapy.

Data from a postmarketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24-hour urine protein [Pearson Correlation 0.39 (95% CI: 0.17, 0.57)]. (Roche 2017)

5.2.5.1.4 Nephrotic syndrome

Bevacizumab will be discontinued and the patient will not be re-started on bevacizumab therapy.

5.2.5.1.5 Hemorrhage

Serious or fatal pulmonary hemorrhage occurred in 31% of patients with squamous NSCLC and 4% of patients with non-squamous NSCLC receiving Avastin with chemotherapy compared to none of the patients receiving chemotherapy alone.

Do not administer Avastin to patients with recent history of hemoptysis of 1/2 teaspoon or more of red blood. Discontinue in patients who develop a Grade 3-4 hemorrhage. (Roche 2017)

5.2.5.1.6 Thromboembolic Events

The risk of arterial thromboembolic events is increased with bevacizumab therapy, and such events included cerebral infarction, transient ischemic attack, myocardial infarction and other peripheral or visceral arterial thrombosis. Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk. Venous thromboembolic events reported in bevacizumab studies included lower extremity deep vein thrombosis, pulmonary embolism and rarely, mesenteric or portal vein thrombosis.

Arterial Thrombosis: Patients with any grade arterial thromboembolic events (including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia) will discontinue bevacizumab but may continue on chemotherapy.

Venous Thrombosis: Bevacizumab treatment will be discontinued for symptomatic grade 4 venous thrombosis.

Bevacizumab treatment will be held for asymptomatic CTCAE grade 3 venous thrombosis. If the planned duration of full-dose anticoagulation is ≤2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if ALL of the following criteria are met:

- The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin (or other anticoagulant) or on stable dose of heparin prior to restarting bevacizumab treatment.

- The patient must not have pathological conditions that carry high risk of bleeding (e.g., tumor involving major vessels).
- The patient must not have had hemorrhagic events while on study treatment.
- The patient is benefiting from the bevacizumab therapy (no evidence of disease progression).

5.2.5.1.7 Coagulopathy

For CTCAE grade 3 or 4 coagulopathy, bevacizumab will be held until prothrombin time or partial thromboplastin time resolves to grade 1. If therapy is held for >6 weeks from the last dose, then bevacizumab will be discontinued and the patient will not be re-started on bevacizumab therapy.

For patients with prothrombin time or partial thromboplastin time greater than therapeutic range while on therapeutic warfarin, bevacizumab will be held until prothrombin time or partial thromboplastin time is within the therapeutic range.

5.2.5.1.8 Hematological Toxicities

5.2.5.1.8.1 Thrombocytopenia

For platelet count $<50 \times 10^3$ /μL, at the day of the administration, bevacizumab will be held. If platelet count of $<50 \times 10^3$ /μL persists for 3 weeks, the patient will discontinue bevacizumab.

5.2.5.1.8.2 Neutropenia

When combined with chemotherapy, bevacizumab increased the risk of neutropenia compared with chemotherapy alone. Additional information is provided in Section 5.2.5.2 and Section 5.2.5.3.

5.2.5.1.9 Gastrointestinal Perforation/Fistula

Gastrointestinal perforations/fistulas were rare but occurred at an increased rate in bevacizumab-containing therapies. **Gastrointestinal perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain, fever of unclear source, or rectal/abdominal abscess.**

Bowel perforation: For new development of bowel perforation, fistula, or GI leak (any grade), the patient will discontinue bevacizumab but may continue on chemotherapy.

5.2.5.1.10 Wound Healing Complications

The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in patients receiving Avastin (bevacizumab). Avastin (bevacizumab) has to be discontinued in patients who develop wound healing complications that require medical intervention. Avastin (bevacizumab) has to be witheld at least 28 days prior to elective surgery. Avastin (bevacizumab) should not be administered for at least 28 days after surgery, and until the wound is fully healed. (Roche 2017)

Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined.

5.2.5.1.11 Fertility and Pregnancy

Pregnant women have to be advised of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with and for 6 months after the last dose of Avastin.

Because of the potential for serious adverse reactions in breastfed infants from bevacizumab, advise women not to breastfeed during treatment with Avastin and for 6 months following the final dose. (Roche 2017)

5.2.5.1.12 Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES; also known as reversible posterior leukoencepalopathy syndrome) is a clinical syndrome related to vasogenic edema of the white matter and has rarely been reported in association with bevacizumab therapy (<1%). Clinical presentations may include altered mental status, seizure, and cortical blindness. MRI scans are required for diagnosis: typical finding are vasogenic edema in the white matter of the posterior parietal and occipital lobes, and less frequently in the anterior distributions and the gray matter. In PRES associated with bevacizumab mild or significant BP elevations were seen in some but not all cases. PRES should be in the differential diagnosis in patients presented with unexplained mental status change, visual disturbance, seizure or other CNS finding. MRI is the key to diagnosis. This syndrome is potentially reversible, but timely

correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent irreversible tissue damage.

Treatment Guidelines for Posterior Reversible Encephalopathy Syndrome (PRES):

If a patient experiences PRES, bevacizumab should be permanently discontinued. Resuming bevacizumab should not be considered even if there is evidence that PRES is completely resolved.

5.2.5.1.13 Congestive Heart Failure

In previously untreated patients with a hematological malignancy, the incidence of CHF and decline in left ventricular ejection fraction (LVEF) were increased in patients receiving Avastin with anthracycline-based chemotherapy compared to patients receiving placebo with the same chemotherapy regimen. The proportion of patients with a decline in LVEF from baseline of ≥ 20% or a decline from baseline of 10% to < 50%, was 10% in patients receiving Avastin with chemotherapy compared to 5% in patients receiving chemotherapy alone. Time to onset of left ventricular dysfunction or CHF was 1 to 6 months after the first dose in at least 85% of the patients and was resolved in 62% of the patients who developed CHF in the Avastin arm compared to 82% in the placebo arm. Discontinue Avastin in patients who develop CHF. (Roche 2017)

5.2.5.2 Adjustments for Carboplatin

Carboplatin dose adjustments should be in accordance with its package insert (Paraplatin 2010).

NOTE: Adjustments to Carboplatin AUC 6 at baseline is not an option. All patients MUST be able to tolerate Carboplatin AUC 6 as their baseline dose. If there are concerns regarding tolerability at baseline then, this MUST be discussed with the Medical Monitor to confirm appropriate patient selection.

In subsequent cycles, Carboplatin may be adjusted from AUC 6 to AUC 5 (a one level reduction) based on toxicities shown in Table 5-2. If the dose would need to be adjusted to AUC 4, then the patient must be discontinued. Dose adjustments outside of toxicities is not permissible.

Table 5-2 Carboplatin Dose Adjustments

Toxicity Grade	Peripheral Neuropathy	Gastrointestinal	Other
0	None	None	None
1	None	None	None
2	Decrease 1 level	None	None
3	Hold	None	Decrease 1 level
4	Hold	Decrease 1 level	Hold

If Carboplatin is held for an AE, Carboplatin is not to be restarted. Likewise, if Carboplatin is dose reduced to an AE, Carboplatin should not be re-escalated. Multiple AEs occurring across multiple organ / body systems must be resolved or returned to a grade 1 prior to reintroduction (re treatment).

The Calvert formula incorporates glomerular filtration rate (GFR) to calculate the patient's carboplatin dose. Although the CrCl is always slightly higher than the GFR, the 2 estimates of renal function are used interchangeably in the Calvert formula. The GFR used in the Calvert formula for carboplatin dosing should not exceed 125 mL/min. Maximum carboplatin dose is based on target AUC.

Calvert Formula

Total Carboplatin Dose (mg) = (target AUC) x (GFR + 25)

Table 5-3 Maximum AUC-based Carboplatin Dose

AUC	Maximum Carboplatin Dose
6	900 mg
5	750 mg
4	600 mg

Reference: http://ctep.cancer.gov/content/docs/Carboplatin_Information_Letter.pdf

Patients who experience CTCAE ≥ grade 2 renal toxicity (serum creatinine >1.5 ULN) require recalculation of the carboplatin dose for subsequent cycles.

The dose of Carboplatin is recalculated by IXRS at each cycle based on the patient's actual /current weight and serum creatinine value to ensure all parameters are considered and the appropriate dose is calculated/administered.

For patients who require carboplatin dose modification, if the creatinine at the time of dose modification is lower than the baseline creatinine that was used, the prior (higher) creatinine value should be used for the dose calculation. If the creatinine at the time of dose modification is higher than the baseline creatinine value, the current (higher) value should be used for the dose calculation. This is to ensure that patients receive the intended dose. Dose adjustment in case of renal toxicity should be as per protocol and managed by the site in consultation with the medical monitor, if there is any doubt.

5.2.5.3 Adjustments for Paclitaxel

For further details, not specified in the following sections of the protocol, referring to the use of paclitaxel, please refer to its package label (Taxol 2011).

5.2.5.3.1 Dose Modifications for Hematologic Toxicity

No cycle of treatment is to begin until ANC $\geq 1.5 \times 10^3/\mu L$ and platelets $\geq 100 \times 10^3/\mu L$. Initiation of a new cycle will be delayed for a maximum of 3 weeks until these values are achieved. Patients who fail to recover adequate counts within a 3 week delay will be removed from chemotherapy treatment (both carboplatin and paclitaxel).

Dose modifications for hematologic toxicity are based on nadir counts.

5.2.5.3.1.1 Neutropenia

Uncomplicated (absence of sepsis or fever) neutropenia of any grade does not require dose modification unless the neutropenia occurs with an ANC $<0.5 \times 10^3/\mu L$ lasting more than 7 days. A 1-dose level reduction in the paclitaxel dose (reduction to175 mg/m^2 or 160 mg/m^2 in countries where is 175 mg/m^2 the starting dose recommended in the label) is required for neutropenic fever (defined as grade 3 or 4 nadir neutropenic toxicity with temperature of 38.0°C twice within 2 hours, or single temperature of 38.5°C). Patients who are hospitalized for fever with either grade 3 or 4 neutropenia may be treated with growth factors during the episode at the discretion of the treating physician. At least 2 days should elapse between the discontinuation of growth factors and the initiation of another cycle of chemotherapy in order to allow bone marrow progenitors to cease cell cycling. If febrile neutropenia occurs despite a 1 dose level reduction, then with subsequent cycles the patient will receive growth factors

starting 24 hours to 48 hours after the completion of the subsequent cycle of chemotherapy and continuing until the ANC is ≥1.5 × 10^3/μL. At least 2 days should elapse between the last dose of growth factors and the initiation of another treatment cycle. If febrile neutropenia occurs despite the use of growth factors then with subsequent cycles the patient will receive a second dose reduction of paclitaxel (160 mg/m^2).

The dose of 160 mg/m^2 is the lowest allowable dose for the protocol. Should a lower dose be required; the case MUST be discussed with the medical monitor and approved by the sponsor followed by appropriate documentation of the discussion by the PI.

Note: Patients who receive growth factors for febrile neutropenia but who do not undergo a 1-dose level reduction, are supposed to have a dose reduction and be evaluated if growth factors are required with the next cycle.

5.2.5.3.1.2 Anemia

Anemia is not an indication for dose reduction in any patient; however, a record of transfusions required should be detailed. Erythropoietin may be utilized, following international guidelines, and at the discretion of the treating physician in the event that patient's hemoglobin drops below 9 g/dL while on therapy, and should be documented.

5.2.5.3.2 Adjustment of Paclitaxel for Other Non-Hematological Toxicities

Paclitaxel may be adjusted for other toxicities and all dose reductions are based on one-level reduction from a starting dose of 200 mg/m^2 with a one dose level reduction to 175 mg/m^2 (Table 5-3). For countries where the recommended start level is 175 mg/m^2, a one dose level reduction would be 160 mg/m^2.

If Paclitaxel is held for an AE, Paclitaxel is not to be restarted. Likewise, if Paclitaxel is dose reduced due to an AE, Paclitaxel should not be re-escalated. Multiple AEs occurring across multiple organ/body systems must be resolved or returned to a grade 1 prior to re-introduction (re treatment).

Please see additional guidance within this section for dosing adjustments for specific toxicities.

Table 5-3 Paclitaxel Dose Adjustments for Other Non-Hematological Toxicities

Toxicity Grade	Peripheral Neuropathy	Gastrointestinal	Hepatic	Other[a]
0	None	None	None	None
1	None	None	None	None
2	Decrease 1 level	None	Decrease 1 level	Decrease 1 level
3	Hold	Decrease 1 level	Hold	Decrease 1 level
4	Hold	Hold	Hold	Hold

[a]All Other Adverse Events MUST be resolved or returned to grade 1 prior to re treatment.

5.2.5.3.2.1 Management of Hypersensitivity Reactions

Hypersensitivity reactions to paclitaxel or its vehicle (Cremophor) occur almost universally during the first few minutes of infusion. Continued treatment may be considered if the reaction was not life-threatening; however, patients must be cautioned of potential recurrences of the reaction. If the PI decides in the patients' best interest continuation with treatment is recommended and the patient agrees; then treatment should continue on the same day of the occurrence. A suggested procedure would be to repeat the patient's premedication with dexamethasone 20 mg i.v., cimetidine 300 mg (or ranitidine 50 mg) i.v., and diphenhydramine 50 mg i.v. 30 minutes before the paclitaxel reinfusion is to begin. Slowly infuse the paclitaxel by administering the drug first with 1 mL of the original i.v. solution diluted in 100 ml over 1 hour, then 5 mL in 100 mL over 1 hour, then 10 mL in 100 mL over 1 hour, and finally the original solution at the original infusion rate. No additional dose adjustments should be made for other hypersensitivity reactions.

Discontinuation of therapy due to hypersensitivity reaction requires notification of the medical monitor within 48 hrs.

5.2.5.3.2.2 Adjustments to Paclitaxel for Peripheral Neuropathy

Grade 3 or 4 peripheral neuropathy requires interruption of paclitaxel therapy until adverse effects resolve to grade 1 or less (Table 5-3). Grade 2 peripheral neuropathy will require a one-dose level reduction in paclitaxel. **The medical monitor should be notified if grade 3 or 4 neuropathy does not resolve to a grade 1 neuropathy or less 2 weeks after a cycle is due to be given (5 weeks after a previous dose). At this time consideration will be given with the medical monitor to removing the patient from chemotherapy**.

5.2.5.3.2.3 Adjustments to Paclitaxel for Hepatic Toxicity

Paclitaxel has significant hepatic metabolism. No dose modification is necessary for grade 1 toxicity but a grade 2 toxicity requires a dose reduction of one level after resolution of the toxicity to grade 1 or less (Table 5-3). **If resolution from grade 2 to grade 1 or lower does not occur within 2 weeks after a dose of paclitaxel is due (5 weeks after the last dose), the medical monitor should be notified.**

Grade 3 and 4 hepatic toxicity requires notification of the medical monitor.

5.3 Management of Overdose and Medication Errors

An overdose is any dose of study treatment given to a patient or taken by a patient that exceeds the dose described in the protocol. A rounding of 5% or a deviation in between 5% to 10% without associated AEs should not be reported, in between 5% to 10% with associated AEs or any beyond 10% must be promptly reported to the medical monitor (see study contact list for medical monitor telephone and fax details). Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF. Any overdose above 10% should be reported as a deviation whether or not an AE occurs. Treatment of overdose should consist of general supportive measures.

Signs or symptoms associated with medication errors must be recorded as AEs and should be reported on the relevant AE/SAE sections in the eCRF.

5.4 Prior and Concomitant Therapy

Concomitant medications will be any drug taken at any time from Day 0 of Cycle 1, through the end of the treatment periods (i.e., Period 1, Period 2, and Extended Treatment Period), other than the interventional therapy (including bevacizumab, carboplatin, paclitaxel) and premedication (as described in Section 5.2).

Prior medications will be any drug taken up to 6 months prior to Day 0 of Cycle 1.

Use of all concomitant medications and prior medications will be recorded in the patient's eCRF, along with the respective indication. The minimum requirement is that drug name and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in the patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the PI (or designee). However, it is the responsibility of the PI to ensure that details regarding the medication are recorded in full in the eCRF.

5.4.1 Permitted Medications and Procedures

The following prior and concomitant medications and procedures are permitted:

- Prior treatment for brain metastases including whole brain radiotherapy, radiosurgery (Gamma Knife®, linear particle accelerator, or equivalent), or a combination, as deemed appropriate by the treating physician. However, it must be completed >14 days prior to Day 0 of Cycle 1.
- Prior radiation therapy, completed >14 days prior to Day 0 of Cycle 1, is permitted provided <25% of bone marrow is involved, no mediastinal irradiation is involved and patient must have recovered from acute toxicities associated with radiation therapy.
- Premedication according to the local standard of care prior to the administration of paclitaxel.
- Placement of a vascular access device, or a closed pleurodesis, thoracentesis, or mediastinoscopy.

5.4.2 Prohibited Medications and Procedures

The following prior and concomitant medications and procedures are prohibited:

- A major surgical procedure, open biopsy, open pleurodesis, or significant traumatic injury within 28 days prior to Day 0 of Cycle 1
- A core biopsy or other minor surgical procedure within 7 days prior to Day 0 of Cycle 1
- Treatment with any other investigational drug, within the last 30 days or at least 5 half lives (if available), whichever is longer prior to Day 0 of Cycle 1.
- Concomitant vaccination that contains an attenuated virus
- Any drug that has not received regulatory approval for any indication at the time of study entry, from 30 days prior to Day 0 of Cycle 1 (Exclusion Criterion 15).

- The use of any other systemic treatment for lung cancer. The use of treatments for bone metastases should be avoided related to the risk of jaw osteonecrosis, also if started during the study the patient will be considered to have progression of the disease, as in the event of any manipulation of target or non-target lesions with surgery or radiotherapy.

In addition, caution should be exercised during concurrent administration of paclitaxel and active substances which are metabolized in the liver as such active substances may inhibit the metabolism of paclitaxel. The metabolism of paclitaxel is catalyzed, in part, by CYP450 isoenzymes, CYP2C8, and 3A4. Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel (to 6α-hydroxypaclitaxel) is the major metabolic pathway in humans.

- Based on current knowledge, clinically relevant interactions between paclitaxel and other CYP2C8 substrates are not anticipated.
- Concurrent administration of ketoconazole (a known potent inhibitor of CYP3A4) does not inhibit the elimination of paclitaxel in patients; thus, both medicinal products may be administered together without dosage adjustment.
- Further data on the potential of interactions between paclitaxel and other CYP3A4 substrates/inhibitors are limited. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g., erythromycin, fluoxetine, gemfibrozil) or induce (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or 3A4.

5.5 Treatment Compliance

The unblinded pharmacist (or authorized designee) is responsible for maintaining accurate records of the receipt and administration of all study treatment supplies during the course of the study and recorded in both the eCRF and the appropriate study drug accountability log by the patient. The unblinded study monitor will periodically monitor compliance by inspecting the source documents, study treatment accountability, inventory, and storage.

Handling and accountability of MYL-1402O and Avastin will be performed only by the unblinded pharmacist, or designee, and the authorized unblinded study monitor.

Chain of custody of the study drug will be followed in accordance with the individual site's standard procedures, which will be documented by the site.

Patients who miss 2 consecutive treatment cycle visits will be considered noncompliant and will be withdrawn from the study.

For patients that withdraw from treatment or withdraw from the study please refer to Section 4.3. For patients who do not respond to treatment, please refer to Section 6.5 (Period 1) or Section 6.6 (Period 2).

6 Study Procedures and Assessments

For the timing of assessments and procedures throughout the study, refer to the Schedule of Events (Table 1-1). Throughout the study, every reasonable effort should be made to follow the timing of assessments and procedures in the Schedule of Events for each patient. Deviations from the schedule should be avoided; however, a ± 3-day visit window for cycle visits is allowed. Study treatment cycles should be scheduled with respect to the previous cycle.

6.1 Informed Consent

Before performing any study procedures, all potential patients will sign an ICF. All potential patients will be informed of the full nature and purpose of the study, including possible risks and side effects, and given ample time and opportunity to read and understand this information. Patients will have the opportunity to have any questions answered before signing the ICF. The PI must address all questions raised by the patient. The PI or delegated designee will also sign the ICF.

6.2 Screening

Screening will start from the time of signing the ICF and will last no more than 4 weeks (≤28 days) prior to the first dose of bevacizumab (Day 0 of Cycle 1 [Period 1]). Screening procedures also include baseline (Section 6.4) and randomization (Section 6.3) procedures.

The following procedures will occur:

- Signing of ICF
- Evaluation for inclusion (Section 4.1) and exclusion (Section 4.2) criteria
- Demographics
- Collection of medical history
- Physical examination
- BSA calculation
- Prior and concomitant medications
- ECOG performance status
- AEs with CTCAE (version 4.03) grading

- Tumor assessment (RECIST 1.1; Section 12.1 [Appendix A]) (CT scan of thorax and abdomen). The CT scan will be transferred to the central imaging vendor for review and confirmation of readability and measurability of lesions
- Brain imaging and/or bone scan (confirmatory X-rays/CT if Bone scan is positive), if required
- Safety blood collection for laboratory assessments (Section 12.6 [Appendix F], Table 12-4)
    - Hematology (approximately 5 mL of blood)
    - Chemistry (approximately 5 mL of blood)
- Calculated CrCL
- Urine dipstick
- Prothrombin time or INR, if indicated (approximately 5 mL of blood)
- Pregnancy serum test, if indicated

The site will collect all the laboratory tests (including normal ranges) and complete all the screening pages of the CRF before consulting the medical monitor. The medical monitor will review all the inclusion and exclusion criteria, and then notify the site and any other parties, if the patient can be randomized.

The RECIST tumor assessment should be within 28 days before the first dose. The sites need to consider that the time in between the randomization until the first dose be included in that 28 days period. A patient will have tumor(s) assessed using radiographic exams (at least computed tomography [CT] or magnetic resonance imaging [MRI] of the thorax and abdomen). If any image study was done as the standard of care and accomplishes the specifications of the study and in the time frame that is allowed in the protocol, then it could be used for the study.

During Screening, an additional check of each patient's eligibility for the study will be conducted by the Independent image Vendor, to check measurability of the lesions and then by Medical Monitor to ensure that the patient is not failing any inclusion/exclusion criteria (example: patient having a Stage IV lung cancer with histologic or cytologic diagnosis of advanced non-squamous non-small cell lung carcinoma with unknown or negative sensitizing EGFR mutation, and negative or unknown EML4-ALK rearrangement, and all the safety conditions).

Serologic testing for hepatitis (Hepatitis A, Hepatitis B, or Hepatitis C virus) is only required before confirming eligibility if alanine transaminase or aspartate transaminase ≥ ULN (in the absence of liver metastases) at screening. In case screening visit lab values are within ULN and baseline visit lab values are ≥ ULN, only clinically significant values (in the absence of liver metastases) will need to be investigated further prior to dosing, but a sporadic rise of either of these do not need serology testing for viral hepatitis at baseline.

Screen Failure: Applies to patients that have provided signed informed consent (via ICF) and either through screening or occurrence of any event prior to randomization the patient is deemed ineligible for study participation.

6.3 Randomization

Patients who meet all of the inclusion and none of exclusion criteria and who are approved by the medical monitor will be considered eligible for entry into the study and will be randomly assigned in a 1:1 ratio to one of the two treatment groups (MYL-1402O or Avastin) within 3 days prior to Day 0 of Cycle 1. The randomization procedures are described in Section 3.3.1. Patients will be stratified by the following criteria: gender (male or female), smoking status (smoker or <100 cigarettes in entire lifetime), and number of metastasis sites (one site or multiple sites).

The following procedures will occur:

- Re-evaluation for inclusion (Section 4.1) and exclusion (Section 4.2) criteria.
- Randomization

A patient who failed the screening process, could be re-consented with a new number assigned and complete a re-screening process within 56 days of the date of the first signed consent form; all the assessment should be performed in the appropriate time in accordance with protocol specifications.

6.4 Baseline

Baseline assessments must be performed within 24 hours of Day 0 of Cycle 1 to confirm that the patient has remained eligible for treatment. The following procedures will occur:

- Physical examination
- Concomitant medications
- Bioanalytical blood collection (Section 12.6 [Appendix F], Table 12-4)

- Hematology and Chemistry: If safety blood lab assessments are more than 7 days prior to baseline, then a new set of safety blood samples will be collected for safety assessments (Table 6-5).
- Immunogenicity (6 samples of approximately 5 mL of blood immediately prior to the first dose of bevacizumab. If possible, within 1 hour before the first dose.
- PK (approximately 5mL of blood) prior to the first dose of bevacizumab. PK samples when concomitant with Immunogenicity should be taken at the same time.

- A pregnancy urine test will be done in female patients with childbearing potential.

Baseline Failure: Any patient that meets initial eligibility requirements, is randomized to treatment, however does not receive first dose of bevacizumab and is deemed ineligible for continuation in Study MYL-1402O-3001.

6.5 Treatment Period 1

Period 1 is defined as the period of study whereby tumor assessments are performed every 6 weeks following Day 0 of Cycle 1 (the first dose of bevacizumab, either MYL-1402O or Avastin, in combination with CP) and continue every 6 weeks (window of ±3 days) through Week 18), regardless of delays of the cycles of treatment. Total duration of Period 1 will be 18 weeks. Period 1 will include 3 assessments at the pre-specified time points (Week 6, Week 12, and Week 18) regardless of delays in treatment cycles. Tumor assessments must be done consistently throughout the study, using at least a CT scan of thorax and abdomen and using the same technique - CT or MRI, slice interval, contrast agent.

If in the staging assessment, bone metastasis are discovered and are localized outside of the thorax and abdominal region, each metastasis should be included in the tumor response assessments and followed by X-ray, CT scan, or MRI as appropriate. In the event of central nervous system (CNS) involvement at baseline, imaging (CT/MRI) should include the CNS localization at each disease assessment time point. Should a patient demonstrate signs and/or symptoms of metastasis at any time and in the opinion of the PI imaging is warranted, such imaging may be performed (even if outside the imaging schedule per this study).

Patients will start Period 1 receiving bevacizumab (MYL-1402O or Avastin) combination therapy (plus CP) on Day 0 of Cycle 1. Each cycle will start with the administration of bevacizumab (as either MYL-1402O or Avastin) followed by carboplatin and then paclitaxel.

Each cycle will consist of 3 weeks (21 days ± 3 days) and patients may receive up to 6 cycles of bevacizumab combination therapy. Additional dosing information for bevacizumab (either MYL-1402O or Avastin) and CP is provided in Section 5.2. In addition, all patients will receive standard premedication per the paclitaxel label (Taxol 2011) or local institutional protocols.

For each cycle of interventional therapy, safety and tolerability will be assessed from the start of bevacizumab infusion until prior to the next treatment cycle.

In cases where treatment is delayed, discontinued, switched to bevacizumab monotherapy (due to intolerance of CP), or switched to CP (due to intolerance of bevacizumab), tumor assessments will still be performed at the selected time points (every 6 weeks after first dose of bevacizumab; Week 6, Week 12, and Week 18). At Week 18 assessments, the following may occur:

If treatment is delayed during Period 1 and the principal investigator (PI) (or designee) considers continuing treatment with bevacizumab combination therapy (MYL-1402O plus CP or Avastin plus CP), then the assessment of tumor response will still occur at Week 18 and the patient may continue to receive combination therapy for up to 6 cycles, even if treatment continues after Week 18 tumor assessment (i.e., into Period 2).

- If bevacizumab treatment is discontinued during Period 1 (i.e., intolerance to bevacizumab) the assessment of tumor response will still occur at Week 18. When the patient discontinues bevacizumab, then the patient will undergo the safety follow-up visit at 28 days (±7 days) after the last dose of bevacizumab. If the patient continues to receive treatment with CP, then treatment may continue for up to 6 cycles. Even if treatment continues after Week 18 tumor assessment, the patient will not enter Period 2. Once the 6 cycles are complete, the patient will not receive any additional interventional therapy per protocol. The EOT visit will occur after the last dose of interventional therapy (in this situation, CP).
- If CP treatment is discontinued during Period 1 (i.e., intolerance to CP), then the assessment of tumor response will still occur at Week 18. At the time of CP discontinuation, if the patient has stable disease or better response (i.e., partial response [PR] or complete response [CR]), then the patient may receive bevacizumab monotherapy until PD or treatment discontinuation and even if treatment continues after Week 18 tumor assessment (i.e., into Period 2). If the patient discontinues bevacizumab at any time, then a safety follow-up visit (Section 6.8) will occur at

28 days (±7 days) of last dose of bevacizumab. The EOT visit should also occur at the safety follow-up visit.

Dose adjustment details are provided in Section 5.2.5.

In cases where there is suspected PD, an additional scan may be conducted to confirm progression. If PD is confirmed prior to Week 18, no additional tumor assessments are required at Week 18. If a patient discontinues study therapy due to PD, then the PI (or designee) will update the patient's contact information and will discuss with the patient the importance of continuing study participation for collecting safety and survival data (Table 12-4). A safety follow-up visit (Section 6.8) will occur at 28 days (± 7 days) of last dose of bevacizumab and the EOT visit should also occur at the safety follow-up visit.

In cases where there is withdrawal of consent, no further data collection will occur (Table 12-4), effective on the date of patient providing signed withdrawal of consent (Section 4.3).

The following procedures will occur:

- Physical examination (Cycle 1 through Cycle 6)
- Interval history (Cycle 1 through Cycle 6)
- BSA calculation (Cycles 2 through Cycle 6, only if a change in the weight is more than 10%)
- Concomitant medications (Cycle 1 through Cycle 6)
- ECOG performance status (Cycles 2 through 6)
- Adverse events with CTCAE grading (Cycle 1 through Cycle 6)
- Tumor assessments are to be conducted every 6 weeks (± 3 days) during the first 18 weeks. (Week 6 [Cycle 2], Week 12 [Cycle 4], and Week 18 [Cycle 6]). Although the tumor assessments are independent of the cycles, if there is a delay in the administration of the cycles due to toxicity, then the tumor assessment should keep the same schedule of every 6 weeks ± 3 days (Week 6, Week 12, and Week 18).
- Brain imaging and/or bone X Rays, if required (Cycle 2, Cycle 4, and Cycle 6) with the tumor assessments
- Bioanalytical blood collections for laboratory assessments (Section 12.6 [Appendix F], Table 12-4).

- Hematology (Cycles 2 through 6) (approximately 5mL of blood at each Cycle): At each cycle, collect blood samples prior bevacizumab administration.
- Chemistry (Cycles 2 through 6) (At each cycle, approximately 5mL of blood): At each cycle, collect blood samples prior bevacizumab administration.
- Immunogenicity (Cycles 2, 4, and 6) (At each cycle, 4 samples of approximately 5 mL of blood): At each cycle, collect blood samples prior bevacizumab administration.
- PK (predose [if possible within 1 hour prior to bevacizumab dosing] and postdose [within 15 minutes after infusion]) to be collected at the following time points: (approximately 5mL of blood at each time point)
  - In Cycle 1: postdose
  - In Cycle 2: predose and postdose
  - In Cycle 3: predose
  - In Cycle 4: predose and postdose
  - In Cycle 5: predose
  - In Cycle 6: predose and postdose
  - All patients will have 2 additional PK samples collected in any cycle (1 to 6): 1 sample will be collected between Days 3 and 8 (inclusive) in any cycle, and 1 sample should be collected between Days 10 and 18 (inclusive) in any cycle.
  - When a PK sample is concomitant with an immunogenicity sample it should be taken at the same time

- Urine dipstick (Cycle 2 through Cycle 6)
- Pregnancy urine test: A pregnancy urine test will be performed for female patients with childbearing ability prior to any interventional treatment (Cycle 2 through Cycle 6).

For the complete list of assessments to be performed on Day 0 of each cycle, refer to the Schedule of Events. (Table 1-1)

Period 1 Completer: Applies to a patient that completes Period 1 through Week 18 assessments.

Early Terminator: Applies to a patient that enters Period 1 and is terminated from the study prior to completing Week 18 assessments due to an adverse event (AE), death, PD, withdrawal of consent, or discontinuation from interventional therapy (bevacizumab [MYL-1402O or Avastin] and/or chemotherapy [carboplatin and paclitaxel]).

6.6 Treatment Period 2

Period 2 is defined by the tumor assessments starting after the end of Period 1 (Week 18 tumor assessments) and occurring every 12 weeks, regardless of delays of the cycles of treatment, at pre-specified time points (i.e., Week 30 and Week 42) until PD, discontinuation. Total duration of Period 2 will be 24 weeks.

A patient is eligible to enter Period 2, provided the patient is a Period 1 Completer, has a demonstrated disease response of stable disease or better response (i.e., CR or PR), and had been receiving during Period 1 either bevacizumab combination therapy or bevacizumab monotherapy.

A patient will be assessed for tumor response using the same type of radiographic exam(s) used in Screening Period and Period 1 (e.g., CT or MRI, contrast agent, slice intervals) for ongoing evaluation of tumors (e.g., target, non-target).

- If the patient has not completed 6 cycles of bevacizumab combination therapy (bevacizumab plus CP) at Week 18 because of delays, then the patient may continue to receive combination therapy for up to 6 cycles. If the patient continues to have stable disease or better response (PR or CR), then the patient may subsequently receive bevacizumab monotherapy every 21 days until PD, death, withdrawal of consent, or discontinuation from interventional therapy.
- If the patient has completed 6 cycles of bevacizumab combination therapy, then at the end of Cycle 6, the patient should be evaluated for tolerability to receive bevacizumab monotherapy in Period 2.
    - If it is determined after discussion with the medical monitor that the patient would be able to tolerate bevacizumab monotherapy then, after 6 cycles of bevacizumab combination therapy the patient will be considered a Period 1 Completer, provided the patient completes Week 18 tumor assessments. If the patient continues to have stable disease or better response (PR or CR), then

the patient may subsequently receive bevacizumab monotherapy (as per same randomization as Period 1) every 21 days until PD, death, withdrawal of consent, or discontinuation from interventional therapy.

- If it is determined after discussion with the medical monitor that the patient would not be able to tolerate bevacizumab monotherapy then, after 6 cycles of bevacizumab combination therapy the patient will be considered a Period 1 Completer, provided the patient completes Week 18 tumor assessments. The patient will not receive any additional interventional therapy. The patient will participate in a safety follow-up visit (Section 6.8) at 28 days (±7 days) of last dose of bevacizumab; the EOT visit should also occur at the safety follow-up visit.

The first cycle of Period 2 will be designated as Cycle 701. If bevacizumab monotherapy is started earlier because of earlier discontinuation of chemotherapy, the tumor assessment will be continued as scheduled. The first assessments for Period 2 will be 12 weeks (± 3 days) after the assessment at Week 18.

Patients experiencing PD will be discontinued from interventional therapy. A safety follow-up visit (Section 6.8) will occur at 28 days (± 7 days) of last dose of bevacizumab; the EOT visit should also occur at the safety follow-up visit.

Week 42 efficacy assessments will be used to evaluate secondary endpoints. During Period 2, safety assessments will be collected for each cycle of therapy.

The following procedures will occur:

- Physical examination
- Interval history
- BSA calculation (only if a change in the weight is more than 10%)
- Concomitant medications
- ECOG performance status
- AEs with CTCAE grading
- Tumor assessments are to be conducted every 12 weeks (± 3 days; Week 30 [Cycle 704] and Week 42 [Cycle 708]).
- Brain imaging and/or bone scan, if required with tumor assessments

- Bioanalytical blood collections for laboratory assessments (Section 12.6 [Appendix F], Table 12-4).
    - Hematology (approximately 5mL of blood): At each time cycle, collect blood samples prior bevacizumab administration.
    - Chemistry (approximately 5mL of blood): At each cycle, collect blood samples prior bevacizumab administration.
    - Immunogenicity (4 samples of approximately 5 mL of blood at each time point)
        - Cycle 704: predose
        - Cycle 708: predose.
    - PK (approximately 5mL of blood)
        - Cycle 704: predose.
        - Cycle 708: predose.
- Urine dipstick
- Pregnancy urine test: A pregnancy urine test will be performed for female patients with childbearing ability prior to any interventional treatment.

For the complete list of assessments to be performed on Day 0 of each cycle for Period 2, refer to the Schedule of Events (Table 1-1).

6.7 Extended Treatment Period

The Extended Treatment Period provides continued bevacizumab monotherapy to any patient that at Week 42 has maintained stable disease or better response (CR or PR) and is receiving benefit to continue treatment. During the Extended Treatment Period, a patient will receive bevacizumab monotherapy (either MYL-1402O or Avastin) until PD, death, unacceptable AE, withdrawal of consent, discontinuation from IMP for any reason, or 42 weeks post last patient randomized (trial closure). Centralized tumor assessment will not be performed during the extended treatment period. All dosing of IP should continue to follow the guidelines put forth in the protocol. Assessment of disease status should occur per the institutions standards. Safety evaluations should occur per the label recommendations for Avastin at minimum and per the institutions standards. Only AE/SAEs deemed by the investigator to be related to IP are to be reported during the Extended Treatment Period.

6.8 Safety Follow-Up Visit/End of Treatment Visit

Patients withdrawing or terminating from the study or discontinuing bevacizumab treatment or after the dosing at week 42 are to complete a safety follow-up visit at 28 days (± 7 days) following last dose on bevacizumab therapy. Patients that have discontinued all interventional therapy will have an EOT visit as well, which may or may not occur with the safety follow-up visit.

Potential reasons for termination from interventional therapy include: PD, withdrawal of consent, discontinuation from interventional therapy, or discontinuation due to SAE or AE.

The following procedures will occur:

- Physical examination
- Interval history
- Concomitant medications
- ECOG performance status
- AEs with CTCAE grading
- Tumor assessments are at safety follow-up visit (F/U visit) if needed.

  Tumor assessments are performed only if needed to confirm a response for instance if a patient has discontinued after a first partial or complete response because toxicity or withdrawal of consent to treatment but not to tumor assessments and follow-up
- Brain imaging and/ bone scan/or bone X-rays, if required (F/U visit)
- Blood collections for laboratory assessments (Section 12.6 [Appendix F], Table 12-4).
  - Hematology (F/U visit) (approximately 5mL of blood)
  - Chemistry (F/U visit) (approximately 5mL of blood)
  - Immunogenicity (F/U visit) (4 samples of approximately 5 mL of blood)
  - PK (F/U visit) (approximately 5mL of blood)
- Urine dipstick (F/U visit)
- Pregnancy urine test (F/U visit): A pregnancy urine test will be performed for female patients with childbearing potential).

For the complete list of assessments to be performed at the Safety Follow-Up visit, refer to the Schedule of Events (Table 1-1).

6.9 Study Closure

Study closure will occur when one of the following is reached:

1. All patients have discontinued from the study
2. 42 weeks from the date the last patient was randomized to treatment.
3. Administrative closure of study

NOTE: Patients on study treatment at time of study closure will be advised by the PI and/or their associated primary health care provider on alternate therapies as per standard for the country.

All treatment provided under the auspices of this protocol will cease at study closure.

6.10 Unscheduled Visits

Assessment during unscheduled visits should be guided by the reason for the visit. Unscheduled visits with all needed assessments are to be performed when there is suspicion of PD. An unscheduled MRI/CT can be performed at any scheduled/unscheduled visit when PD is suspected. If an event of death due to PD, a narrative description should be provided in the eCRF that includes clinical course and PD complications leading to death.

6.11 Assessment of Efficacy

6.11.1 Tumor Response (RECIST)

Tumor response will be assessed using RECIST 1.1 criteria (Section 12.1, Appendix A). Response (CR, PR, stable, and PD) will be evaluated using the international criteria proposed by the RECIST version 1.1 committee. (Eisenhauer et al 2009).

Tumor assessments are to be conducted every 6 weeks (± 3 days) up to 18 weeks, independent of delays in treatment administration (Period 1 [Section 6.5]) and every 12 weeks (± 3 days) independent of delays in treatment administration after 18 weeks.

Imaging procedures are to be performed locally throughout the study. Please note, imaging is sent for central review through week 42. Confirmation of measurable disease is required prior to randomization. Although scans will be submitted for central review, local assessments will be used to determine disease response while on treatment

One to 5 target lesions (with a maximum of 2 lesions per organ) should be identified at baseline and recorded in the eCRF. For the purpose of this protocol, measurable lesions such as bone (except bone lesion with measurable soft tissue), CNS, and skin lesions (except skin lesion with measurable tumoral lesion by CT scan), as well as irradiated, biopsied, or surgically-manipulated lesions are excluded. These measurable lesions are considered as non-target lesions. If radiation or manipulation is performed throughout the study, a target lesion is categorized as non-measurable.

After radiation or manipulation of a target lesion, the assessment of the patient will be considered a PD, unless the extraordinary case that reasonable comments justify why such lesion shall still be considered measurable. The patient or the lesion may be censored, depending on the intervention performed. Any such on-study interventions shall be discussed beforehand with the medical monitor.

At least a CT scan or MRI of thorax and abdomen will be performed in every assessment. The imaging method and settings used at baseline to document and assess a specific lesion shall be used throughout the study to consistently follow lesions according to RECIST 1.1. Details of imaging studies are provided in the Radiology Manual.

Tumor assessments and eligibility of patients at screening will be determined by central medical imaging. To assess tumor response, a central radiology review of all images will be performed for data analysis. All routine protocol-planned imaging and any additional imaging performed due to clinical suspicion of PD (such as positron emission tomography, bone scan, correlative imaging of hot-spots) should also be provided to the central review.

After each assessment PIs (or designees) will enter their evaluations in the eCRFs and will submit the images to the central image vendor no later than 5 days after the assessment. The PIs will make clinical decisions based in their evaluations. The central image vendor will not interact with the sites for treatment decisions. If PD is detected during the any period, the PI should inform the medical monitor.

In the case of bone metastases evaluated by a bone scan during the staging and confirmed with either X-Ray or CT/MRI, images of these lesions are needed at every tumor assessment timepoint. The bone lesions that are not captured by the CT scan or MRI of the thorax and abdomen must be followed by X-rays or scans.

6.11.1.1 Progressive Disease

Progressive disease is defined according to RECIST as a >20% increase in the sum of diameters of target lesions; taking as reference the smallest sum on study (this includes the baseline sum, if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered PD. A substantial worsening of non-target lesions can be a trigger for PD.

In accordance with the Council for International Organizations of Medical Sciences VI recommendations, progression of the underlying disease and its consequences will not be collected as an AE even if they lead to hospitalization or meet any other seriousness criteria including death. Rather, progression of the underlying disease and its consequences should be reported in the eCRF within no more than 48 hours. The report will include:

- Description of PD (e.g., increase in the sum of diameters of target lesions, appearance of new lesions, substantial worsening of non-target lesions, or clinically determined PD).
- Date on which PD was declared in accordance with FDA Guidance for Industry - Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.
- For PD based on a new lesion, the date of the first observation that the new lesion was detected.
- If multiple assessments based on the sum of target lesion measurements are done at different times, the date of the last observation or radiological assessment of target lesions that shows a predefined increase in the sum of the target lesion measurements according to RECIST.
- For PD based on substantial worsening of non-target lesions, the date of the first observation of substantial worsening.
- For clinically-determined PD, the date of objectively assessed worsening.

6.11.2 Survival

Progression-Free Survival (PFS): Progression-free survival is defined as the time from randomization to the first documentation of PD or to death due to any cause, whichever comes first. Analysis of PFS is described in Section 7.7.2.

Overall Survival: Overall survival is defined as the time from randomization to date of death due to any cause. Analysis of OS is described in Section 7.7.2. If a patient dies because of disease progression during treatment, then a verbatim explanation of the circumstances of the death is expected, including evaluating the cause and if a treatment toxicity may be involved.

6.12 Safety and Tolerability Assessments

Safety and tolerability will be assessed based on the nature, frequency and severity of the reported AEs, the results of laboratory assessments, the immunogenicity results, and physical examination. Details of AEs and concomitant medications and procedures will be recorded on a continuous basis throughout the study.

6.12.1 Definitions of Adverse Events

Adverse Event

As per International Conference on Harmonisation (ICH) E2A, an AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding or physical finding, symptom, or disease), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

Treatment-Emergent Adverse Event

A treatment-emergent AE is an AE that started or deteriorated after the first administration of blinded MYL-1402O or Avastin through 100 days following the last dose of blinded MYL-1402O or Avastin.

Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

All AEs judged by either the reporting PI (or designee) or the sponsor as having a reasonable causal relationship (i.e., “possible”, “probable”, or “definite”) to a study drug will be designated as adverse drug reactions.

If the relationship to MYL-1402O or Avastin is not given by the PI (or designee), then the AE must be treated as if the relationship were "possible."

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  - NOTE: The term **"life-threatening"** in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly
  - NOTE: **A congenital anomaly** in an infant born to a mother who was exposed to the study drug during pregnancy is considered an SAE. However, a newly diagnosed pregnancy in a patient that has received the study drug is not considered an AE unless it is suspected that the study drug interacted with a contraceptive method and led to the pregnancy. The patient with newly diagnosed pregnancy will discontinue receiving study drug and will be followed-up every 3 months until delivery or termination to gather information about the outcome of the pregnancy.
- Is an important medical event
  - NOTE: **Important Medical Event**: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Requires inpatient hospitalization or prolongation of existing hospitalization
    - NOTE: **Inpatient hospitalization** is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the study drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.

Events **NOT** to be reported as SAEs are hospitalizations for the following:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
- Admission to a hospital or other institution for general care due to social or economic reasons (e.g., no access to local ambulatory medical care)
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

Hospitalization also does not include the following:

- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes

6.12.2 Collection, Evaluation and Documentation of Adverse Events

As referenced in Section 5 of the protocol, MYL-14O20 (test product) and Avastin (reference product) will be considered as the IMP. As such, and in relation to causality assessments, PIs should consider causality as it relates specifically to bevacizumab (either MYL-1402O or Avastin). The active collection period for AEs will be from the time the patient signs the ICF

through the Safety Follow up Visit. SAEs only need to be reported after the Safety Follow up Visit if considered reasonably related to the IMP. Pre-existing diseases or conditions (reported at time of screening in medical history) will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition. All SAEs should be immediately reported (within 24 hours) as per the study protocol contact list.

Progression of NSCLC and its consequences will not be collected as an AE even if they lead to hospitalization or meet any other seriousness criteria including death. Rather, progression of NSCLC and its consequences should be entered in the relevant eCRF page within 48 hours. A narrative description should be provided in the eCRF that includes clinical course and PD complications leading to death.

6.12.2.1 Collection

The PI (or designee) is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as described previously. At each visit, the patient will be allowed time to spontaneously report any issues since the last visit or evaluation. The PI (or designee) will then monitor and/or ask about or evaluate AEs using non-leading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

Any AE recorded in the proper section of the study diary (paper or electronic) will also be transferred onto the eCRF.

6.12.2.2 Evaluation

6.12.2.2.1 Severity Assessment of Adverse Events

The clinical severity of an AE will be graded whenever possible using the NCI-CTCAE criteria Version 4.03. A copy of these criteria will be provided to each study site. If an AE is not listed in the NCI-CTCAE, its clinical severity will be classified as follows (Table 6-1):

Table 6-1 Clinical Severity of Events

The PI (or designee) will assess each AE as MILD, MODERATE, SEVERE, LIFE-THREATENING, or FATAL to describe the maximum intensity of the AE.	
Grade 1: MILD	Does not interfere with patient's usual function
Grade 2: MODERATE	Interferes to some extent with patient's usual function
Grade 3: SEVERE	Interferes significantly with patient's usual function
Grade 4: LIFE-THREATENING	Risk of death at time of event
Grade 5: DEATH	Death related to AE

Abbreviations: AE = adverse event; PI = principal investigator

It is important to distinguish between severe AEs and serious AEs. Severity is a classification of intensity based on the NCI-CTC AE grading or on the above Table 6-1, whereas an SAE is an AE that meets any of the regulatory specified criteria required for designation as seriousness is described in Section 6.12.1.

6.12.2.2.2 Action Taken with Investigational Medicinal Product and Chemotherapy

The undertaken actions for an AE following treatment with IP (MYL-1402O or Avastin) are described in Table 6-2 for IP. The undertaken actions for an AE following chemotherapy are described in Table 6-3 for CP. Dose modification is also described in Section 5.2.5.

Table 6-2 Action Taken for an Adverse Event Associated with Investigational Medicinal Product (MYL-1402O or Avastin)

Treatment interrupted	The treatment was temporarily interrupted, with intent to restart.
Treatment withdrawn	The treatment was permanently discontinued
Unknown	Not known, not observed, not recorded, or refused
No action taken	The AE did not result in any modification of dose or frequency of dosing
Not applicable	The AE occurred prior to first dose or following last study dose

Abbreviation: AE = adverse event;

Table 6-3 Action Taken for an Adverse Event Associated with Chemotherapy

Dose reduced	The dose regimen was reduced by changing its frequency, strength, or amount
Treatment interrupted	The treatment was temporarily interrupted, with intent to restart.
Treatment withdrawn	The treatment was permanently discontinued
Unknown	Not known, not observed, not recorded, or refused
No action taken	The AE did not result in any modification of dose or frequency of dosing
Not applicable	The AE occurred prior to first dose or following last dose

Abbreviation: AE = adverse event;

6.12.2.2.3 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than one AE is possibly related to the patient's death, the outcome of death should be indicated for the AE

which is the most plausible cause of death in the opinion of the PI (or designee). All other ongoing AE/SAEs will be recorded as not recovered/not resolved at the time of death.

Note: Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

6.12.2.2.4 Causality Assessment – Relationship to Study Medication

A causality assessment is the determination of whether there exists a reasonable possibility that the study product caused or contributed to an AE. The PI (or designee) must make an assessment of the relationship of each AE (serious and non-serious) to the study drug(s) and record this relationship in the eCRF.

In addition, if the PI (or designee) determines an AE or SAE is associated with study procedures, the PI (or designee) must record this causal relationship in the source documents and eCRF as unrelated to study medication, while noting study related procedures as an alternative etiology, as appropriate. Adverse events related to study procedures must still be recorded in the eCRF in accordance with the reporting requirements, and as applicable, reported as an SAE in expedited manner.

Factors that need to be considered when making a causality assessment include:

- Temporal relationship with drug administration (e.g., time of onset)
- Clinical and pathological characteristics of the event(s)
- Pharmacological plausibility
- Exclusion of confounding factors (medical and medication history)
- Drug Interactions
- De-challenge/re-challenge
- Dose relationship

A suspected relationship (definite, probable, possible) between the events and the study drug(s) means, in general, that there are facts (evidence) or arguments to suggest a causal relationship. Receipt of additional or clarifying information may warrant reassessment of causality.

The PI (or designee) is responsible for assessing relationship of AEs to study drug in accordance with the following definitions (Table 6-4):

Table 6-4 Causality Assessment Categories

DEFINITELY	Causal relationship is certain	For example: The temporal relationship between drug exposure and the AE onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated; the event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
PROBABLY	High degree of certainty for causal relationship	For example: The temporal relationship between drug exposure and AE onset/course is reasonable, there is a clinically compatible response to de-challenge (re-challenge is not required), unlikely to be attributed to disease or other drugs.
POSSIBLY	Causal relationship is uncertain	For example: The temporal relationship between drug exposure and the AE onset/course is reasonable or unknown, de-challenge information is either unknown or equivocal, could also be explained by disease or other drugs.
UNLIKELY	Causal relationship is improbable	Another explanation is more likely such as disease, environment, or other medication. Does not represent a known reaction to study drug.
UNRELATED/NOT RELATED	No possible relationship	The temporal relationship between drug exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to study drug is impossible.

If the relationship to the study drug(s) is considered to be unlikely or not related, an alternative suspected etiology should be provided if available (e.g., CP, other concomitant medications, intercurrent illness/events).

6.12.2.2.5 Documentation

All AEs occurring within the study period must be documented in the eCRF with the following information; where appropriate:

- AE name or term in standard medical terminology
- Start date and time – for SAEs, start date is defined as the date the AE became serious

- When the AE stopped (stop date and time, or date and time of last observation if ongoing, recovering or not recovered)
- Severity of the AE
- Serious criteria (hospitalization, death)
- Actions taken with study drug
- Treatment (pharmacologic and non-pharmacologic) for the event
- Outcome
- The PI's opinion regarding the AE relationship to blinded MYL-1402O or Avastin
- Alternative etiology for the SAE if not considered related to blinded MYL-1402O or Avastin

6.12.2.3 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care and per the PI's (or designee's) medical judgment.

6.12.2.4 Emergency Unblinding

Treatment assignment for an individual patient should be unblinded only in case of a medical/surgical emergency by the PI (or designee), when knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the patient.

If an SAE occurred, an SAE Report Form must be completed and forwarded to the Mylan PSRM. The PI must document the breaking of the code, and the reasons for doing so on the eCRF, in the site file, and in the medical notes.

See Section 3.7 for unblinding procedures.

6.12.2.5 Adverse Events of Special Interest

Any non-serious AE that is not related to disease progression and results in permanent discontinuation of bevacizumab (MYL-1402O or Avastin) is considered an AE of special interest. These are to be reported on the SAE Reporting Form by checking the AE of Special Interest box within 24 hours of decision to terminate the patient's participation in the study.

Special attention will be paid to hypertension, proteinuria, bleeding, fistulas, GI perforations, wound healings, jaw osteonecrosis, leukoencephalopathies, venous and arterial

thromboembolic events, and cardiac failure to fully characterize and compare the safety profile of the proposed biosimilar (MYL-1402O) and Avastin.

6.12.2.6 Notification to Sponsor or Designee

The SAE Reporting Form is to be completed, signed by the PI, and emailed (preferred) or faxed with supporting documentation (e.g., eCRFs, hospital records, laboratory reports) to Mylan PSRM for all SAEs and AEs that lead to discontinuation of blinded MYL-1402O/Avastin. Patient identity details (such as but not limited to name or clinic/hospital number) must not be visible on SAE forms or any supporting documentation provided by the PI. These should be "blacked out", signed and dated before submission to Mylan or its designee. **The patient identification number must be provided on every document.**

Note that Email is the preferred method of submission of Immediate Safety Reports including SAEs, AEs Leading to Discontinuation, and Pregnancy Exposures

All Immediate Safety Reports must be notified within 24 hours to Mylan Product Safety & Risk Management:

PV MAIL HUB FOR IMMEDIATE SAFETY REPORTS pvclinical@mylan.com If an acknowledgement is not received within 24 hours, forward via Fax: +1 304 285 6409

At that time of first notification, the investigator/designee should at least provide the following information:

- Protocol number
- Reporter (study site and PI (or designee) full name)
- Study drug
- Patient's study number/identifier
- SAE term
- The seriousness criteria that were met
- PI's (or designee's) opinion of the relationship to blinded MYL-1402O/Avastin and chemotherapy

And if available:

- Severity
- Patient's age
- Date of first dose of interventional therapy
- Date of last dose of interventional therapy, if applicable
- Start and stop of the event (date and time)
- A brief description of the event, outcome to date, and any actions taken
- Concomitant medication at onset of the event
- Relevant past medical history
- Relevant laboratory test findings
- Whether and when the PI (or designee) was unblinded to the patient's treatment assignment

If the initial notification of an SAE is by telephone, within 24 hours of the initial telephone notification the investigator must email the written SAE Report Form that describes the SAE to the Mylan PSRM email listed above.

6.12.2.7 Follow-Up of Adverse Events

Any AE will be followed-up to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the patient's medical record and recorded on the appropriate eCRF page.

The investigator may be requested by Mylan GmbH/designee to obtain specific additional follow up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE eCRF. In general, this will include a description of the SAE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a fatal SAE, autopsy findings/death certificate (if available) may be requested by Mylan GmbH or its designated representative.

Any missing or additional relevant information concerning the SAE should be provided on a follow-up SAE Report Form. Ensure that any additional information requested by sponsor or designee about the event, as outlined above (e.g., hospital reports, autopsy report) is provided to sponsor/designee as soon as it is available.

6.12.2.8 Notification and Submission to Regulatory Authorities and Ethics Committees

The PI (and any designee) is required to comply with applicable regulations (including local law and guidance) regarding notification to his/her regulatory authority, IRB, independent ethics committees (IECs), institutional ethics committees, and institutions.

Suspected unexpected serious adverse reactions, SAEs or other cases as required by the concerned competent authorities and IECs will be reported by the sponsor/representative to all concerned parties within applicable timelines. The sponsor/representative will also submit periodic safety reports (e.g., Development Safety Update Reports) as required by local and international regulations.

6.12.3 Pregnancy

All patients of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation and during the 6 months following last study drug. Patient should be instructed to contact the PI (or designee) or other study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted as detailed in the Schedule of Events (Table). A woman who is found to be pregnant at the screening visit will be excluded from the study and will be considered to be a screening failure.

A woman who becomes pregnant following administration of any study drug will be immediately discontinued from further study drug. The Pregnancy Report Form must be completed and reported to Mylan PSRM (pvclinical@mylan.com or fax: +1 304 285 6409) within 24 hours from the time of initial awareness.

A male patient that has a partner that becomes pregnant during the study l will not be discontinued from study drug. Exposed partner pregnancies (conception during study or within 6 months of last dose) are also reportable to Mylan provided that consent and any required releases are obtained from the patient's partner. Study personnel should contact their clinical research associate to obtain a partner pregnancy informed consent form upon

learning of a partner pregnancy. Consent of the pregnant partner must be obtained before any details of the pregnancy can be shared with the sponsor. If the pregnant partner provides consent to have the pregnancy followed, the site should collect the information specified on the Pregnancy Report Form and forward the completed form to Mylan PSRM.

Non-exposed pregnancies (before randomization and >6 months following last study drug administration) are not reportable.

The PI (or designee) is responsible for following up the pregnancy at 3 monthly intervals until delivery or termination. While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE. Any SAE in the mother, fetus, or newborn is to be reported on the SAE. A spontaneous abortion or congenital anomaly is always considered to be an SAE.

Elective termination (i.e., without medical reasons) of an uncomplicated pregnancy is considered to be an elective procedure and not an AE; nevertheless, Mylan requests that the outcome (e.g., elective termination) be reported within 24 hours and sent as a follow up on the Delivery and Infant Follow-up Form.

6.12.4 Physical Examination

A complete physical examination will be performed at the screening visit before exposure to any study treatment, and then at selected time points during the study (Schedule of Events Table). Vital signs and patient weight will be routinely recorded as part of the physical examination, whereas patient height will be recorded only at baseline.

6.12.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance scale (Oken et al 1982) is a 6-point categorical scale, ranging from 0 (asymptomatic) to 5 (death). The ECOG performance scale is evaluated at selected visits during the study and a change from baseline calculated. The ECOG performance scale score changes from baseline can then be categorized on a 3-point categorical scale: deteriorated, unchanged, and improved. Improvement or deterioration of performance status requires a decrease or an increase from baseline, respectively, of at least 1 point on the ECOG performance scale.

6.13 Safety Monitoring

Safety will be evaluated periodically internally by Mylan and Medical Monitors and Mylan Safety personnel, and externally with the Steering Committee and in an ad hoc frequency with a designated data and safety monitoring board (DSMB)

Safety blinded evaluations will be done against historical data from 5 historical published randomized trials that evaluated this combination in lung cancer and safety information from regulatory documents of bevacizumab publicly available. The Sponsor or the Steering Committee will call an independent DSMB evaluation of unblinded data if there is any concern about the risk to the population of the study during the periodic safety evaluations, the decisions will be documented.

6.14 Laboratory Analyses

Samples for the laboratory tests listed in Table 6-5 will be collected and analyzed locally at the time points specified in the Schedule of Events (Table 1-1). It should be ensured that variability is minimized by using the same laboratory facility throughout the study. The required laboratory tests are to be analyzed and reviewed by the treating investigator before each new cycle of treatment. Additionally, the review will be documented in source by either signing and dating the laboratory report or noting the review in the patient's note.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the PI (or designee) are to be recorded as AEs or SAEs.

Table 6-5 Laboratory Tests

Chemistry Panel	Hematology Panel	Urinalysis Panel
BRt (Total Bilirubin) Alk Phos (Alkaline Phosphatase) ALT (Alanine Aminotransferase) AST (Aspartate Aminotransferase) CCr (Creatinine Clearance) Creatinine NA (Sodium) K (Potassium) Total Protein Albumin PT/INR (International Normalized Ratio), and aPTT (at screening, if on anticoagulants)	WBC (White Blood Cell count) ANC (Absolute Neutrophil Count) Hb (Hemoglobin) Platelet count	Urine dipstick (and 24-hour urine protein, if indicated) Pregnancy test (only if child bearing potential) [Serum hCG only at screening) Total protein (conditional, only if urine dipstick 2+ or more)

6.15 Sample Collections

The following procedures are performed centrally throughout the study: PK and immunogenicity blood sampling. Safety laboratory assessments will be performed locally. Details of blood sample collections are provided in the Schedule of Events and summary of total blood collected in Table 12-4. All blood samples for bioanalysis that are collected at each time point must be processed immediately according to the following general procedure:

1. Draw blood into a properly labeled 5 mL gold top serum separator tube (SST) and fill completely.

   NOTE: It is important to make every reasonable effort to collect a full 5 mL volume of blood at each sample draw. For the immediately post-dose samples use a different venipuncture location or catheter than the infusion or take it after flushing the line.

2. Thoroughly mix the blood with the clotting activation agent by inverting the tube 5 times.

3. Place tubes in an upright position and allow the blood to clot at room temperature at least 30 minutes.
4. Centrifuge SST tubes within 60 minutes of collection for 10 minutes at 1100 to 1300 × g.
5. After centrifugation, transfer the serum from the SST collection tube evenly into the 2 labeled cryo-vials (Primary and Back-up) and immediately cap the tubes tightly.

   NOTE: Ensure that the label information on the cryo-vials matches the label information on the blood collection tube. It is important to transfer as much serum as possible from the serum separator tube into the cryo-vials.
6. Place the serum storage tubes upright in a freezer at or below –20°C (–70°C preferred where available) within 90 minutes of collection. In the circumstance where the sample will be stored for more than 60 days prior to shipment, ensure immediate transfer to a –70°C freezer.

   NOTE: Ensure the samples have been frozen 24 hours prior to shipment.

   Primary and back up samples from the same subject visit must not be shipped together, ship the back-up aliquot once the central laboratory confirms receipt of the primary aliquot.

   Premium courier with temperature monitoring is required for the shipment of these samples, please refer to your courier information.

6.15.1 Immunogenicity Blood Sampling

Blood samples will be collected for immunogenicity analysis from all patients and will be analyzed at a central laboratory. Up to 4 blood samples will be collected at each time point, 1 sample will be used to determine the presence of antidrug (bevacizumab) antibody (ADA) and 1 sample will be used to determine the presence of neutralizing antibodies against bevacizumab, if applicable. The other 2 samples collected will be stored in reserve for potential supplemental immunogenicity testing and/or characterization.

For the assessment of immunogenicity, blood samples will be collected at the following time points as presented in Table (a summary total blood collected in Table 12-4 and will correspond to collection of PK samples Section 6.15.2), as follows:

- For immunogenicity analysis, an unscheduled blood sample will be collected with a drug concentration sample if a hypersensitivity reaction occurs, as quickly/soon as possible after the event occurs.
- Baseline (pre-dose): Six samples of 5 mL each will be collected if possible within 1 hour before administration of drug in Cycle 1 for use in analytical method optimization and validation.
- In Period 1 at Cycles 2, 4, and 6: Four blood samples of 5 mL each for immunogenicity testing will be collected before dosing.
- Period 2: At Cycle 704 and Cycle 708, four blood samples of 5 mL each for immunogenicity testing will be collected before dosing and at the same time when the corresponding PK samples are collected.
- Safety Follow-Up visit: Four blood samples of 5 mL each for immunogenicity testing will be collected at the safety follow-up visit (28 days [±7 days] after last dose of interventional therapy), which is the same time when the corresponding PK samples are collected.

The blood samples will be collected via an indwelling i.v. catheter or by direct venipuncture, and the exact times of blood sampling will be recorded in the appropriate eCRF and individual source documents. Sample handling instructions are specified in the laboratory manual.

Immunogenicity will be analyzed for ADA using fully validated analytical methods. Bioanalytical methodology and procedures will be documented in a sample analysis protocol.

Details of immunogenicity assessment methodology and procedures will be documented in a sample analysis protocol.

6.15.2 Pharmacokinetic Blood Sampling

Blood samples will be collected for PK analysis from all patients and will be analyzed at a central laboratory. To facilitate an accurate PopPK evaluation, it is imperative that the actual date/time of the start and end of dosing is accurately recorded for all patients, in addition to the actual date/time of all PK blood sample collections. Details of blood sample collections are provided in the Schedule of Events (Table 1-1) and summary of total blood collected in Table 12-4.

For the assessment of bevacizumab concentrations in serum, a blood sample (1 × 5 mL) will be collected at the following time points:

- For PK analysis, an unscheduled drug concentration blood sample will be collected with one immunogenicity sample if a hypersensitivity reaction occurs, as quickly/soon as possible after the event occurs.
- Baseline (pre-dose): If possible within 1 hour before administration of drug in Cycle 1, a PK sample will be collected from all patients in both treatment arms.
- PK (predose [if possible within 1 hour prior to bevacizumab dosing] and postdose [within 15 minutes after bevacizumab infusion, the postdose samples need to be taken from a different catheter or vein puncture location than the infusion catheter or after flushing the line]) to be collected at the following time points: (approximately 5mL of blood at each time point).
    - In Cycle 1: postdose
    - In Cycle 2: predose and postdose
    - In Cycle 3: predose
    - In Cycle 4: predose and postdose
    - In Cycle 5: predose
    - In Cycle 6: predose and postdose
    - All patients will have 2 additional PK samples collected in any cycle (1 to 6): 1 sample will be collected between Days 3 and 8 (inclusive) in any cycle, and 1 sample should be collected between Days 10 and 18 (inclusive) in any cycle.
- Period 2: A sample will be collected prior to dosing (approximately 5mL of blood at each time point) in Cycle 704 and 708, which is the same time that the corresponding immunogenicity samples are collected.
    - During Period 2, a PK sample will be collected at predose of Cycle 704 and Cycle 708.
- An unscheduled drug concentration blood sample (approximately 5mL of blood) will be collected with one immunogenicity sample if a hypersensitivity reaction occurs, as quickly/soon as possible after the event occurs.

- Safety Follow-Up Visit: Sample collected at the safety follow-up visit (28 days [±7 days] after last dose of interventional therapy) (approximately 5mL of blood), which is the same time that the corresponding immunogenicity samples are collected.

In total, up to 18 PK samples (18 samples × 5 mL each = 90 mL of blood) will be collected during the study.

The blood samples will be collected via an indwelling i.v. catheter or by direct venipuncture into serum separator tubes, and the exact times of blood sampling will be recorded in the eCRF and individual source documents. The PK dose samples need to be taken from a different catheter or vein puncture location than the infusion catheter or after flushing the line. Sample handling instructions can be found in the laboratory manual.

Pharmacokinetic samples will be analyzed for bevacizumab concentrations by using fully validated analytical methods. Bioanalytical methodology and procedures will be documented in a sample analysis protocol.

6.15.3 Safety Blood Sampling

The following procedures are performed locally throughout the study: hematology, chemistry, coagulation, urinalysis, and pregnancy testing. Details of blood sample collections are provided in the Schedule of Events (Table 1-1) and summary of total blood collected in Table 12-4.

The total amount of blood collected per patient is not expected to exceed 355 mL over the study (Table 12-4).

All samples for the scheduled safety laboratory tests must be taken before study treatment administration. Blood samples will be taken using standard venipuncture techniques.

All samples should be stored and shipped as described in the Laboratory Manual.

7 Statistical and Analytical Plan

7.1 Efficacy Endpoints

7.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the ORR based on best tumor responses as assessed by an independent review at any time point during the first 18 weeks, according to RECIST 1.1. The ORR is defined as the proportion of patients with CR or PR as the best overall timepoint response during the first 18 weeks.

An ORR based on the best tumor responses confirmed at a second time point will be evaluated as a sensitivity analysis. This ORR is defined as the proportion of patients with CR or PR as the best overall response during the first 18 weeks and whose tumor responses has been confirmed at least 4 weeks after the first assessment or 6 weeks at subsequent assessments.

Patients with response that cannot be evaluated per RECIST 1.1 will be scored as non-responders. In addition, ORRs as assessed by investigators will also be presented and analyzed using the same methods for the ORRs assessed by the independent review.

7.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will consist of the following.

- DCR (CR, PR, or stable disease) during the first 18 weeks
- PFS, defined as the time from randomization to the first documentation of PD or to death due to any cause, whichever comes first
- OS, defined as the time from randomization to date of death due to any cause
- DR, is defined as the time from start of the first documentation of objective tumor response (CR or PR) to the first documentation of tumor progression (i.e., PD) or to death due to any cause, whichever comes first.

7.2 Pharmacokinetic Endpoints

The pharmacokinetics endpoints will be as follows:

- PopPK measures of exposure of MYL-1402O and the reference product Avastin (e.g., AUC, C_{max}, C_{min}, CL, V_c, and the terminal elimination half-life).

7.3 Safety Endpoints

The safety endpoints will be as follows:

- Incidence, nature, and severity of AEs including adverse drug reactions graded according to CTCAE.
- Detection of antibodies to bevacizumab.

7.4 Sample Size Calculations

To meet the different regulatory requirements, the primary endpoint will be analyzed using two approaches (ratio of ORR and difference of ORR between treatments). These different approaches lead to different sample size requirements. The sample size calculations for this study are presented in Section 7.4.3

7.4.1 FDA Regulatory Requirements

The primary efficacy analysis is based on the ratio of the MYL-1402O ORR to the Avastin ORR at Week 18.

Following FDA's advice, four randomized clinical studies were included in a meta-analysis to estimate the treatment effect of bevacizumab in combination with chemotherapy inpatients with NSCLC and to derive a similarity margin for the ratio of the ORRs. These four studies were Johnson et al, 2004; Sandler et al, 2006; Reck et al, 2010; and Niho et al, 2012. The control arm in three studies used was paclitaxel plus carboplatin as background chemotherapy regimen while in the study by Reck et al, 2010 gemcitabine was used as chemotherapy.

Table 7-1 Meta-Analysis

	Control CT		Bevacizumab plus CT			
Study	(CR+PR)/ N	ORR %	(CR+PR)/ N	ORR %	Risk ratio	Weight (fixed)
Johnson et al	6/32	18.8	11/34	32.4	0.580	3.5%
Nishio et al	20/59	33.9	68/121	56.2	0.603	14.7%
Reck et al	71/327	21.7	114/329	34.7	0.627	37.4%

Sandler	59/392	15.1	133/381	34.9	0.431	44.4%
Meta-analysis	156/810	19.3	326/865	37.7	0.535	70% CI 0.49-0.58

The p-value for testing the heterogeneity among the four selected studies was 0.230, indicating that the heterogeneity among the four studies in the meta-analysis was not significant. Hence, a fixed effects approach was used for the meta-analysis. The meta-analysis yields a risk ratio of 0.53 and an ORR for Bevacizumab plus Chemotherapy of 38%. This selection of studies and meta-analysis has been also discussed by He K at al., 2016.

Based on the meta-analysis, a symmetric equivalence margin for the risk ratio of (0.73, 1.36) was derived by maintaining 50% of the treatment effect.

The limits for the equivalence margin have been derived using the following approach: The reverse of the upper bound of 70% CI, 1/0.58 = 1.72, indicates 72% more effect with bevacizumab. The biosimilar should retain a substantial portion of that benefit. The clinical margin representing the acceptable level of inferiority was therefore set at 50% of this 72% increase, i.e., 1.362 [= (1.72-1)/2+1]. The lower margin is the reciprocal of the upper margin, i.e., 1/1.362 =0.730

A sample size of 588 patients (294 per treatment group) will provide 80% power for testing equivalence of MYL-1402O and Avastin at 1-sided 5 % level of significance, for the primary endpoint ORR at Week 18. This sample size assumes that the ORR at Week 18 will be 38.0% for both MYL-1402O and Avastin. Statistical equivalence will be declared if the 2-sided 90% confidence interval (CI) of the ratio of the 2 treatment groups falls wholly within an asymmetrical equivalence region defined as (0.73, 1.36).

7.4.2 EU/EMA Regulatory Requirements

The efficacy analysis for EMA requirement is based on the difference of the MYL-1402O ORR and the Avastin ORR at Week 18.

The meta-analysis of the four studies results in a risk difference of -17.1% with a 70% a CI of (-19.3%, -14.3%). The proposed equivalence margin of (-12.5%, 12.5%) maintains 65% of lower limit of the CI for the risk difference.

A sample size of 628 patients (314 per treatment group) will provide 80% power for testing equivalence of MYL-1402O and Avastin at 1-sided 2.5 % level of significance, for the

primary endpoint ORR at Week 18. This sample size assumes that the ORR at Week 18 will be 38.0% for both MYL-1402O and Avastin. Statistical equivalence will be declared if the 2-sided 95% CI of the difference of the 2 treatment groups falls wholly within an equivalence.

7.4.3 Study Sample Size Determination

The EMA requirement needs a larger sample size, therefore the planned sample size for this study will be based on the size for the EMA requirement which is 628 patients (314 per treatment group). The proposed sample size is also in the same range (620-671 patients) of other studies (ClinTrials Identifiers: NCT02272413 and NCT02754882) conducted by other sponsors that have evaluated a biosimilar bevacizumab using NSCLC indication.

Given that a single post baseline assessment is needed for ITT, an attrition rate of 2% is assumed for the study, which leads to the number of 640 patients (320 per treatment group) to be randomized

As described in Section 7.7.7 a blinded interim analysis with aim of a sample size re-estimation will be performed after at least 30% of the patients have completed week 18. This blinded sample size re-estimation (BSSR) may have an effect on the actual type I error. (see Friede T, 2004; Kieser M, 2000). The magnitude of the Type I error increase was investigated by performing simulations for the situation with and without BSSR. Results from the simulations suggest that the impact of a BSSR on the actual type I error is small. Therefore, a Type I error adjustment has not been considered for the sample size estimation.

It is estimated that approximately 864 screened patients will yield approximately 640 patients for 1:1 randomization for having at least 628 evaluable patients, taking in to account the attrition rate of 2%.

7.5 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Intent-to-Treat (ITT) Set: The ITT set will consist of all randomized patients. All analyses using the ITT set will group patients according to randomized treatment. The ITT set will be used for the efficacy and other analyses.

Safety Set (SS): The SS will consist of all randomized patients who complete at least one dose or partial dose of MYL-1402O or Avastin. All analyses using the SS will group patients according to treatment actually received. The SS will be used for the safety analyses and the immunogenicity analyses.

Per Protocol (PP) set: The PP set will consist of all randomized patients who complete at least one dose of MYL-1402O or Avastin and do not have protocol deviations having significant impact on the (study) endpoints during the study. Major protocol deviations will be defined in the SAP. Further exclusions from the PP set due to major protocol deviations will be decided in a Blinded Data Review Meeting prior to study unblinding. All analyses using the PP set will group patients according to randomized treatment. The PP set will be used for the sensitivity analyses of the efficacy endpoints.

Population PK (PopPK) Set: The PopPK set will consist of all randomized patients who complete at least 1 dose of allocated study medication and who provide at least 1 evaluable post-dose drug concentration for PopPK analysis. All analyses using the PopPK set will group patients according to treatment actually received.

7.6 Description of Subgroups to be Analyzed

The analysis of primary and key secondary endpoints will be done for the following subgroups, if applicable:

- Age (<65 years of age median or ≥65 years of age median)
- Gender (Male or Female)
- Race (Caucasian or non-Caucasian; Asian or non-Asian)
- Smoking status (smoker or <100 cigarettes in entire lifetime)
- Number of metastasis sites (1 or multiple)
- Prior weight loss (≥5% from the historical weight during the last 3 months or <5%).
- Prior radiation therapy (0 or ≥1)
- Prior adjuvant chemotherapy (0 or 1)
- ECOG performance scale at screening (0 or 1)
- EGFR mutation status (unknown or negative)
- EML4-ALK alterations (unknown or negative)

Additional subgroups will be detailed in the SAP.

7.7 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.2 or later (SAS Institute, Inc., Cary, North Carolina). Continuous variables will be summarized using mean, standard

deviation, median, minimum and maximum values. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

Details of the statistical analyses, methods, and data conventions will be described in the SAP.

The statistical test for the primary efficacy endpoint will be performed using a 5% significance level (1-sided), leading to a 90% (2-sided) CI for FDA requirement, while using a 2.5% significance level (1-sided), leading to a 95% (2-sided) CI for EMA requirement.

For the secondary efficacy endpoints, no formal hypothesis testing will be performed. The time to event secondary endpoints will be analyzed using log-rank tests.

No adjustments for multiplicity will be made.

7.7.1 Analysis of Primary Efficacy Endpoint

The primary endpoint is analyzed differently to meet the requirements of the FDA (Section 7.7.1.1) and the EMA (Section 7.7.1.2). It is expected that both approaches, will lead to congruent conclusions, although the results will be discussed separately for the two requirements to a certain extent. Therefore, no adjustment of the type I error is done for the primary analysis.

7.7.1.1 Efficacy Endpoint Analysis to Meet the FDA Requirements

The overall response rates by independent review up to Week 18 for both MYL-1402O and Avastin will be calculated and the ratio of the ORRs will be used to determine if MYL-1402O is equivalent to Avastin. A 2-sided 90% CI for the ratio of the ORRs at Week 18 will be calculated based on the method of logarithmic transformation with no adjustment for covariates (Blackwelder 1993). This primary endpoint analysis will be conducted using in the ITT set.

The statistical hypotheses associated with the primary analysis of ORR at Week 18 are as follows:

- H_0: ($ORR_{MYL\text{-}1402O}$ / $ORR_{Avastin} \leq 0.73$) or ($ORR_{MYL\text{-}1402O}$ / $ORR_{Avastin} \geq 1.36$)
- H_1: $0.73 <$ ($ORR_{MYL\text{-}1402O}$ / $ORR_{Avastin} < 1.36$,

  where $ORR_{MYL\text{-}1402O}$ and $ORR_{Avastin}$ are the ORRs for MYL-1402O and Avastin, respectively.

The use of a 90% CI to evaluate equivalence is the same as performing two 1-sided tests at an alpha level of 0.05 for each test.

7.7.1.2 Efficacy Endpoint Analysis to Meet the EMA Requirements

The difference in the ORRs at Week 18 will be evaluated using an unstratified Cochran-Mantel-Haenszel (CMH) test. An asymptotic 2-sided 95% CI for the difference in ORRs at Week 18 will be calculated.

The statistical hypotheses associated with the primary analysis of ORR at Week 18 for EMA are as follows:

- H_0: ($ORR_{MYL\text{-}1402O}$ - $ORR_{Avastin} \leq -12.5\%$) or ($ORR_{MYL\text{-}1402O}$ - $ORR_{Avastin} \geq 12.5\%$)
- H_1: $-12.5\% < (ORR_{MYL\text{-}1402O} - ORR_{Avastin}) < 12.5\%$,

  Where $ORR_{MYL\text{-}1402O}$ and $ORR_{Avastin}$ are the ORR for MYL-1402O and Avastin, respectively.

In addition, ORRs by PI will also be presented and analyzed using the same methods for the ORRs by independent reviewer.

7.7.2 Analyses of Secondary Efficacy Endpoints

Disease control rate will be calculated for each treatment group. The ratio of the DCRs and its 90% CI will be estimated using the method of logarithmic transformation with no adjustment for covariates. The difference in the DCRs between treatment groups will be estimated using an unstratified CMH test and an asymptotic 2-sided 95% CI for the difference in DCRs will be also calculated.

Progression-free survival and OS will be evaluated. Kaplan-Meier plots by treatment will be presented. For descriptive purposes, the estimate of the median PFS and OS (in months) will be presented along with the p-value from the log-rank test. Survival rates at Weeks 18, 30 and 42, will be presented along with estimates of the relative risk and associated 95% CI at each time point (Brookmeyer 1982). In addition, a Cox regression model will be used to estimate the HR and the corresponding 95% CI for the treatment effect. The main Cox PH model will have treatment and no covariates. Sensitivity analyses may be performed if necessary with covariates added to the main model. In addition, results of analysis of DCR and PFS by PI (or designee) will also be presented

The secondary efficacy endpoints of duration of response and time to response will be evaluated using the same statistical analysis methods that were used for the secondary endpoints PFS and OS. It is not intended that the study is powered for this secondary endpoint to demonstrate bioequivalence, but comparability of the results will be evaluated.

To comply with differing expectations from FDA and EMA, for all secondary endpoints that evaluates ratio, a 90% CI will be used, while a 95% CI will be used when difference is evaluated.

7.7.3 Population Pharmacokinetic Analyses

Serum concentrations of bevacizumab will be listed and summarized.

Population PK methods will be used to compare exposure parameters between treatment arms. Population PK analysis will be conducted using NONMEM version 7 or later (ICON Solutions, Roche 2017; Beal 2009).

In accordance with the FDA Guidance for Industry, Population Pharmacokinetics, (FDA 1999), in order to enable a timely PopPK analysis, the PopPK analysis dataset will be constructed using a real-time data assembly approach. CRF data (e.g., patient demographics, lab values, dose administration times, and PK sample collection times) will be assembled in analysis dataset format and merged with reported concentration values as they become available prior to database lock, but without the treatment assignment.

Graphical exploration of the concentration compared with time data will be conducted to provide visual inspection of the PK profile of MYL-1402O compared with that of Avastin and to guide the modelling process.

Model building will start from published population analyses using a two-compartment model. Prior model structure, covariates, and model parameters will be used as Bayesian priors to support the analysis to the extent appropriate for the dataset and final model structure.

Consistent with the literature, a 2-compartment linear model will initially be described with CL, inter-compartmental clearance, V_c, and volume of the peripheral compartment (V_p). Other model adjustments (e.g., target-mediated disposition) may be made if required to provide appropriate description of the data.

Also consistent with the literature, inter-individual variability in CL and V_c will initially be assigned with log-normal distribution. Model appropriateness will be evaluated. An attempt

to add inter-individual variability to additional structural parameters will be explored, but may not be feasible based on the sparseness of the data. Residual variability will initially be modelled with a constant coefficient of variation model. The inclusion of an additional term for additive residual variability will be evaluated.

Potentially influential covariates will be evaluated using a forward selection followed by backward elimination process. The evaluated covariates will be limited to those reported as significant in the prior literature, or any other covariate (e.g., other demographic or laboratory values, ADA titer levels, or ADA status) for which there is graphical evidence for a potentially strong effect.

First-order conditional estimation method will be used initially for parameter estimation. Individual patient empirical Bayesian parameter estimates will be produced for each model parameter with inter-individual variability included in the model. Pharmacokinetic parameters reflecting exposure to drug (e.g. AUC, C_{max}, C_{min}, CL, V_c, and the terminal elimination half-life) will be reported for each patient. Only descriptive and exploratory statistics of each treatment arm will be provided.

Final population fixed- and random-effect parameter estimates will be presented in tabular form with estimates of uncertainty (i.e., standard errors of the estimates), according to the most appropriate assumptions retained during model building.

Full details of the PopPK analysis, including methods for handling data (missing values, outliers), will be documented in a PopPK analysis plan, in accordance with FDA guidance.

7.7.4 Safety Analyses

Treatment-emergent AEs and SAEs will be descriptively summarized by system organ class, preferred term, and treatment group. Overall, descriptive summaries will be produced along with severity and relationship to the IMP. TEAEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

The ECOG performance status will be summarized for each visit. Shifts from baseline to the best and worst post-baseline score may be tabulated.

Descriptive summaries of observed values and change from baseline will be presented for clinical laboratory evaluations (hematology and biochemistry) by treatment group. Assessments of laboratory variables according to clinical relevance will be summarized by visit and treatment group for each clinical laboratory parameter in frequency tables.

Additionally, for each laboratory parameter, shifts in value from baseline to all post-baseline visits will be presented by treatment arm in shift tables.

The assessment of categorical urinalysis variables will be summarized by visit for each urine parameter by treatment arm (frequency tables). Additionally, for each of the urine parameter, shifts in assessments from baseline to all post-baseline visits will be presented for each treatment arm (shift tables).

For vital signs and physical exam data, descriptive summaries of observed values and changes from baseline will be presented by visit and treatment group.

7.7.5 Immunogenicity Analysis

The number and percent of patients who are tested positive for ADA until week 42 will be provided for each treatment group. In addition, the number of samples that are positive for ADA until week 42 for each treatment group will also be provided.

7.7.6 Other Analyses

Summary statistical analyses will be provided for demographics and baseline characteristics, medical history, prior and concomitant medications, and risk factor variables at baseline.

7.7.7 Interim Analyses

A blinded sample size re-estimation (BSSR) interim analysis will be conducted when at least 30% of the required patients have either discontinued early or completed Week 18 on study. This interim analysis will be used to estimate the ORR at Week 18 for total sample in the ITT analysis. The estimated ORR will be used to perform a BSSR for the primary endpoints based on, the risk ratio and difference. Three outcomes for the estimated overall ORR are possible

(1) The ORR in the interim analysis ≤ 36 %

Then sample size will be re-estimated for the risk ratio and increased up to a maximum of 670 patient to maintain the power for testing for FDA requirement

(2) The ORR in the interim analysis is > 36 % and < 40 %

Then sample size will be unchanged

(3) The ORR in the interim analysis ≥ 40 %

Then sample size will be re-estimated for the risk difference and increased up to a maximum of 670 patient to maintain the power for testing for EMA requirement

Simulations for estimating the actual type I error rate have been performed for the primary endpoints of risk ratio and the risk difference for a study conduct with and without sample size increase. The impact on actual type I error is small also in the case of a BSSR compared to the conduct without a BSSR. The method to adjust the sample size will be detailed in the SAP together with results for the simulation of the actual type I error rate.

7.8 Data Quality Assurance

The progress of the study will be monitored by onsite, written, e-mail, and telephone communications between personnel at the study center and Mylan GmbH. The PI (or designee) will allow Mylan GmbH, monitors, or designee(s) to inspect all: eCRFs; patient records (source documents); signed ICF; records of study medication receipt, storage, and disposition, and regulatory files related to the study.

At the time of database lock, the clinical database will be audited in order to ensure accuracy of the key variables as well as to provide an estimated error rate for the final, locked database. The audit will involve a comparison of CRF values with values from data listings generated from the clinical database. Values identified as critical safety and efficacy variables will be confirmed for 100% of the patients. In addition, a random sample of patients will be selected for which all data values, excluding comment fields, will be checked. The number of patients to be randomly reviewed will be determined in order to provide sufficient accuracy for the estimated error rate of the clinical database.

This study will be subject to audit by the sponsor or designee at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the study protocol; ICH, Good Clinical Practice (GCP) E6 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity and enrolment rate. The sponsor or designee may conduct audits on any selected study sites, requiring access to patient notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for ethics committees or regulatory affairs according to GCP guidelines. The PI (or designee) agrees to cooperate with the auditor

during the visit and will be available to supply the auditor with eCRF print-outs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a Regulatory Authority informs the PI (or designee) that it intends to conduct an inspection, the PI (or designee) shall notify the sponsor immediately.

7.8.1 Data Management

As part of the responsibilities assumed by participating in the study, the PI (or designee) agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The PI (or designee) agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips.

PPD will supply the eCRFs. Study center personnel will enter patient data into an electronic system for capturing, managing and reporting clinical research data. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable Mylan GmbH standards and data cleaning procedures to ensure the integrity of the data, e.g, removing errors and inconsistencies in the data. Adverse events and concomitant medication terms will be coded using the MedDRA and WHO Drug Dictionary, respectively.

After the final database lock, each study site will receive a CD-ROM containing all of their center-specific eCRF data as entered into the electronic system for data capture for the study, including full discrepancy and audit history. Additionally, a CD-ROM copy of all of the study site’s data from the study will be created and sent to Mylan GmbH for storage. PPD will maintain a duplicate CD-ROM copy for their records. In all cases, patient initials will not be collected or transmitted to the Mylan GmbH.

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

Government regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study l patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6 (R2): GCP will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The PI (or designee) is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The PI (or designee) must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

8.3 Patient Information and Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50, ICH E6 (R2) guidelines, and local regulations as appropriate, shall be obtained from each patient before entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the PI to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the PI (or designee) is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The PI (or designee) shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

9 Principal Investigator's Obligations

The following administrative items are meant to guide the PI in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, regulatory authorities or the IRB/IEC.

The PI (or designee) and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure and Obligations

The PI (or designees) are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the PI (or designee) must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the patient's disease.

9.3 Investigator Documentation

Prior to beginning the study, the PI (or designee) will be asked to comply with ICH E6 (R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval

- Original PI-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the PI and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the PIs must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493

9.4 Study Conduct

The PI agrees that the study will be conducted according to the principles of ICH E6 (R1). The PI (or designee) will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins.

9.5 Adherence to Protocol

The PI agrees to conduct the study as outlined in this protocol in accordance with ICH E6 (R1) and all applicable guidelines and regulations.

9.6 Adverse Events and Study Report Requirements

By participating in this study the PI agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the PI agrees to submit annual reports to the study site IRB/IEC as appropriate.

9.7 Investigator's Final Report

Upon completion of the study, the PI, where applicable will provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

9.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the PI/institution as to when these documents no longer need to be retained.

9.8.1 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the PIs to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

10 Study Management

The administrative structure will include an external Steering Committee and a DSMB.

10.1 Monitoring

10.1.1 External Steering Committee

An External Steering Committee will be established to review safety and medical issues to collaborate on medical expert decisions. The details will be described in the charter and will include responsibilities, membership, and meeting frequency and structure.

10.1.2 Data and Safety Monitoring Board

The Data and Safety Monitoring Board details will be described in the charter and will include responsibilities, membership, and meeting frequency and structure.

10.1.3 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the PI and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the PI and personnel.

The eCRF will be compared with the source documents to ensure that there are no discrepancies between them for critical data. All entries, corrections, and alterations are to be made by the responsible PI or his or her designee. The monitor cannot enter data in the eCRF.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

10.1.4 Inspection of Records

The PIs and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the PI agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (e.g, FDA or other regulatory agency) access to all study records.

The PI should promptly notify the sponsor and PPD of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the PI's IRB/IEC for approval before patients can be enrolled into an amended protocol.

10.2.2 Protocol Deviations

The PI or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The PI may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the PI. A significant deviation occurs when there is nonadherence to the protocol by the patient or PI that results in a significant, additional risk to the patient. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the patient without prior sponsor approval, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 3.5, Section 4.3).

Protocol deviations will be observed throughout the course of monitoring visits. Principal investigators will be notified by the monitor of deviations and they need to be documented. The IRB/IEC should be notified by the site of all protocol deviations in a timely manner.

10.3 Study Termination

Although Mylan GmbH has every intention of completing the study, Mylan GmbH reserves the right to discontinue the trial at any time for clinical or administrative reasons.

The end of the study is defined as the time when all patients have completed at least 15 months after the randomization of the last patient, 250 death events are recorded, all patients have discontinued the study, or administrative end of the study, whichever occurs first.

10.4 Interim and Final Clinical Study Report

An interim clinical study report will be written at the time of the 18 week assessment and an addendum as the final clinical study report will be written at the EOS with all final data included.

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, a PI signatory will be identified for the approval of the clinical study report. The PI will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor will provide the PI with the full summary of the study results. The PI is encouraged to share the summary results with the study patients, as appropriate. The study results will be posted on publicly available clinical trial registers.

11 Reference List

AHA 1994: The Criteria Committee of the New York Heart Association. (1994). Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. (9th ed.). Boston: Little, Brown & Co. pp. 253–256.

Avastin (bevacizumab) [package insert]. Genentech, Inc. South San Francisco, CA; 2017.

Beal S, Sheiner LB, Boeckmann A, Bauer, RJ, NONMEM User's Guides. (1989-2009), Icon Development Solutions, Ellicott City, MD, USA, 2009.

Blackwelder W.C. (1993). "Sample size and Power for prospective analysis of relative risk", Statistics in Medicine, 12: 691-698.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38: 29-41.

ClinicalTrials.gov [Internet]. US National Library of Medicine. Identifier NCT02272413. Boehringer Ingelheim. Phase III Trial BI 695502 Plus Chemotherapy vs. Avastin® Plus Chemotherapy in Patients with Lung Cancer [cited April 04, 2018]; Available from: https://clinicaltrials.gov/ct2/show/NCT02272413

ClinicalTrials.gov [Internet]. US National Library of Medicine. Identifier NCT02754882. Samsung Bioepis Co., Ltd. A Study Comparing SB8 and Avastin® in Patients with Advanced Non-squamous Non-small Cell Lung Cancer [cited April 04, 2018]; Available from: https://clinicaltrials.gov/ct2/show/NCT02754882

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.*1976; 16(1):31-41. Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research (US). Guidance for Industry, Population Pharmacokinetics. February, 1999.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research (US). Guidance for industry: Population pharmacokinetics. February 1999. [35 screens]. Available from: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133184.pdf

Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The Eighth Edition Lung Cancer Stage Classification. Chest. 2017 Jan;151(1):193-203.

Eillis, RE. The distribution of active bone marrow in the adult. Phys Med Biol 1961; 5(3):255-8.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Euro J Cancer*. 2009;45(2):228-47.

Ellis LM, Bernstein DS, Voest EE, Berlin JD, Sargent D, Cortazar P, Garrett-Mayer E, Herbst RS, Lilenbaum RC, Sima C, Venook AP, Gonen M, Schilsky RL, Meropol NJ, Schnipper LE. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014 Apr 20;32(12):1277-80.

Friede T, Kieser M. Sample size recalculation for binary data in internal pilot study designs. *Pharmaceutical Statistics* 2004; 3:269-279.

Globocan 2012. Estimated cancer incidence, mortality, prevalence, and disability-adjusted life years (DALYs) worldwide in 2012. International Agency for Research on Cancer. WHO. Available from: http://globocan.iarc.fr/. American Cancer Society Inc. Cancer Facts & Figures 2012. Available from: http://www.cancer.org/acs/groups/content/@research/documents/document/acspc 044738.pdf

He K, Chen H, Gwise T. Statistical Considerations in Evaluating a Biosimilar Product in an Oncology Clinical Study. Clin Cancer Res. 2016; 22: 5167-5170

Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2004; 22(11):2184-91.

Kieser M, Friede T. Recalculating the sample size in internal pilot study designs with control of the type I error rate. *Statistics in Medicine* 2000; 19:901-911.

Lu JF, Bruno R, Eppler S, et al. Clinical pharmacokinetics of bevacizumab in patients with solid tumors. Cancer Chemother Pharmacol. 2008; 62:779–786.

Mosteller RD. Simplified calculation of body-surface area. N Engl J Med. 1987; 317(17):1098.

Mylan Biologics Switzerland. MYL 1402O. Investigator's brochure, Edition 3.0. Zurich; 2017.

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-small cell lung cancer. Version 2.2018

Niho S, Kunitoh H, Nokihara H, et al; JO19907 Study Group. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. Lung Cancer. 2012; 76(3):362-7.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655.

Paraplatin (carboplatin) [package insert], Bristol-Myers Squibb Company, Princeton, (NJ); 2010. 21 p.

Reck M, von Pawel J, Zatloukal P, et al; BO17704 Study Group. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol. 2010; 21(9):1804-9.

Roche 2017: Avastin (bevacizumab) [package insert]. Roche Registration Ltd. Welwyn Garden City, United Kingdom; 2017 [last updated 27 July 2017]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000582/human_med_000663.jsp&mid=WC0b01ac058001d124

Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006; 355(24):2542-50.

Soria JC, Mauguen A, Reck M, et al; meta-analysis of bevacizumab in advanced NSCLC collaborative group. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. Ann Oncol. 2013; 24(1):20-30.

Taxol (paclitaxel) [package insert] Bristol-Myers Squibb Company, Princeton, NJ; 2011, 53 p.

Zhou C, Wu YL, Chen G, et al. BEYOND: A randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non–small-cell lung cancer. J Clin Oncol. 2015; 33(19):2197-2204.

12 Appendices

12.1 Appendix A: Tumor Assessment According to RECIST Criteria Version 1.1 (Eisenhauer 2009)

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement to be recorded) as ≥10 mm with CT or MRI scan (using a slice thickness no greater than 5 mm), ≥10 mm caliper measurement by clinical examination, or ≥20 mm by chest x-ray. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT or MRI scan (scan slice thickness recommended to be no greater than 5 mm).

Ultrasound: Ultrasound should not be used to assess tumor lesions. The same holds true for endoscopy or laparoscopy.

Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm), are considered non-measurable disease. Bone lesions (without measurable soft tissue by CT scan or MRI), CNS and leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis pulmonis, abdominal masses, skin (without tumoral lesion measurable by CTscan) and cystic lesions are all non-measurable.

Clinical lesions: Clinical lesions will only be considered as lesions when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Skin and palpable lesions are to be assessed as non-measurable non-target disease (without tumoral lesion measurable by CT scan).

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ (bilateral organs are considered as one organ: left kidney + right kidney = kidney) and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by

imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as reference by which to characterize the objective tumor response.

Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as nonmeasurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up. Bone lesions need to be followed by CT scan or X-Rays

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph node must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study with at least a 5 mm absolute increase in the sum of all lesions. The appearance of one or more new lesions* denotes disease progression.

Stable Disease (SD): Neither sufficient nor shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-complete Response/Non-Progressive Disease: Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Substantial, unequivocal progression of existing non-target lesions.

Evaluation of Overall Response at week 18

In this study the overall response at week 18 is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's overall response at 18 weeks assignment will depend on the achievement of both measurement and confirmation criteria (for additional sensitivity analysis of ORR) based on assessment every 6 weeks (Table 12-2). The overall response for all combination of tumor responses (target and non-target lesions) with and without appearance of new lesion is given in Table 12-1.

Table 12-1 Overall Responses for Target and Non-Target Lesions With and Without the Appearance of New Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	non-CR/non-PD	No	PR
CR	NE	No	PR
PR	non-PD or not all evaluated	no	PR
SD	non-PD or not all evaluated	no	SD
Not all evaluated	Non-PD	no	NE
PD	Any	yes or no	PD
Any	PD	yes or no	PD
Any	Any	yes	PD

Abbreviations CR=complete response; PR=partial response; NE=nonevaluable; SD=stable disease; PD=progressive disease.

Table 12-2 Best Overall Response at 18 weeks with Confirmed Assessment at subsequent Time Point

Overall Response any Time Point during the first 18 weeks of treatment	Overall Response Subsequent Time Point	Overall Response at 18 weeks[b,c]
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met; otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met; otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met; otherwise, NE
PR	CR	PR or CR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met; otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met; otherwise, NE
NE	NE	NE

Abbreviations CR=complete response; PR=partial response; NE=nonevaluable; SD=stable disease; PD=progressive disease; BOR=best overall response.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met, ***i.e., 6 weeks***. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[b] Best Overall Response, with confirmed assessment, is done as part of the sensitivity analysis

[c] In cases, when a response is observed first time at week 18 a confirmation of imaging scan may be scheduled after week 18

12.2 1Appendix B Eastern Cooperative Oncology Group Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Oken et al 1982; available at http://ecog-acrin.org/resources/ecog-performance-status

12.3 Appendix C Bone Marrow

Table 12-3 Distribution of Bone Marrow (by Weighing Cadaveric Bones)

Site	% Total Red Marrow
Pelvis (made up of)	**40.0**
Pelvic bones	22.3
Sacrum	13.6
Femoral head/neck	3.8
Thoracic spine	**14.1**
Lumbar spine	**10.9**
Head	**13.1**
Upper limb girdle (made up of)	**8.3**
Scapulae	4.8
Humeri	1.9
Clavicles	1.5
Ribs	**7.9**
Cervical spine	**3.4**
Sternum	**2.3**

Source: Eillis, RE. The distribution of active bone marrow in the adult. *Phys Med Biol* 1961; 5(3):255-88.

12.4 Appendix D Creatinine Clearance Calculations using Cockcroft and Gault Formula

For the calculation of the carboplatin dose:

Calvert Formula

Total Carboplatin Dose (mg) = (target AUC) × (GFR + 25)

Calvert Formula Worksheet

You Need:

- Patient age: _____
- Patient weight in Kg: _____
- Male or Female: _____
- Serum Creatinine: _____
- AUC (6 or 5): _____

$$\frac{\{140 - (\text{patient age})\} \times (\text{patient weight in kg}) \textit{ (× 0.85 in women)}}{72 \times (\text{serum creatinine})} = \text{GFR}$$

Cockcroft & Gault Method

(Can use Creatinine Clearance for GFR)

(GFR + 25) × AUC = dose in mg

12.5 Appendix E Calculation of Paclitaxel Dose using Montseller Formula and based on Body Surface Area

For the calculation of the paclitaxel dose, the Mosteller formula (Mosteller 1987) equation is to be used to calculate the patient's body surface area (BSA) where *BSA* is in m^2, *W* is weight in kg, and *H* is height in cm (the dose does not need to be modified, if the change in weight is <10% from the prior calculation):

$$BSA = \sqrt{W \times H}/60$$

or if height is in m:

$$BSA = \sqrt{W \times Ht}/6$$

12.6 Appendix F: Bioanalytical Blood Sampling Collection Summary for Immunogenicity, Pharmacokinetics, and Safety Samples

Blood samples will be collected for analyses of immunogenicity, PK, and Safety and a summary of the total blood draw at each time point is summarized in Table 12-4.

Table 12-4 Summary of Blood Sampling by Time Point

Period	Time Point	Immunogenicity Samples[a]	Pharmacokinetics Samples[a]	Safety Samples	Total Amount	Number of Tubes
Screening	Screening[b]			2 × 5 mL[b]; 1 × 5 mL[c]	15 mL	3
	Baseline, if possible within 1 hour prior of Day 0 of Cycle 1 dose	6 × 5 mL predose[a]	1 × 5 mL predose[a],	2 × 5 mL within 24 hrs. predose[e]	45 mL	9
Period 1	Cycle 1		1 × 5 mL postdose[d]		5 mL	1
	Cycle 2	4 × 5 mL predose[a]	1 × 5 mL predose[a], 1 × 5 mL postdose[d]	2 × 5 mL within 72 hrs. predose[e]	40 mL	8
	Cycle 3		1 × 5 mL predose[d]	2 × 5 mL within 72 hrs. predose[e]	15 mL	3
	Cycle 4	4 × 5 mL predose[a]	1 × 5 mL predose[a], 1 × 5 mL postdose[d]	2 × 5 mL within 72 hrs predose[e]	40 mL	8
	Cycle 5		1 × 5 mL predose[d]	2 × 5 mL within 72 hrs predose[e]	15 mL	3
	Cycle 6	4 × 5 mL predose[a]	1 × 5 mL predose[a], 1 × 5 mL postdose[d]	2 × 5 mL within 72 hrs. predose[e]	40 mL	8
	Any cycle: Day 3 through Day 8		1 × 5 mL [f]		5 mL	1
	Any cycle: Day 10 and Day 18		1 × 5 mL [f]		5 mL	1
Period 2	Cycle 704	4 × 5 mL predose[a]	1 × 5 mL predose[a]	2 × 5 mL within 72 hrs. predose[e]	35 mL	7
	Cycle 708	4 × 5 mL predose[a]	1 × 5 mL predose[a]	2 × 5 mL within 72 hrs. predose[e]	35 mL	7
Unplanned	Hypersensitivity Reaction[g]	4 × 5 mL predose[a]	1 × 5 mL predose[a]		25 mL	5
Safety Follow-Up visit[h]	Safety Follow-Up visit/End of Treatment Visit	4 × 5 mL	1 × 5 mL	2 × 5 mL	35 mL	7

a Immunogenicity and pharmacokinetic predose samples should be collected at the same timepoint. If possible, predose samples should be collected within 1 hour prior to dosing.

b Two samples will be collected at Screening as part of evaluation of hematology and chemistry inclusion/exclusion criteria.

c Female patients that are of child bearing potential will have a serum pregnancy test conducted during screening.

d Postdose blood draws should occur < 15 minutes after dosing.

e Predose for safety samples for Cycle 1 should be within 24 hours prior to dosing. However, if the safety screening lab was done during the last 7 days prior the first dose it would not be necessary to repeat it. Predose for safety samples for Cycle 2 onwards should be within 72 hours prior to dosing.

f Two additional samples collected for pharmacokinetics: One sample will be collected between Day 3 and Day 8 (inclusive) in any cycle, and 1 sample should be collected between Day 10 and Day 18 (inclusive) in any cycle.

g In the event of a hypersensitivity reaction, immunogenicity sample and PK sample should be drawn as quickly as possible after the reaction occurs.

h Safety follow-up visit samples to be collected ≤28 days ±7 days after bevacizumab discontinuation.

12.7 Appendix G: Initial Disease Diagnosis

Disease Stage at Initial Disease Diagnosis

TNM staging as per AJCC 8th Edition Classification along with Diagrams (Detterbeck et al 2017).

Table 12-5 Definitions for T, N, and M Descriptors

T (Primary Tumor)		Label
T0	No Primary Tumor	
Tis	Carcinoma in situ (Squamous or Adenocarcinoma)	Tis
T1	Tumor≤3 cm,	
T1a (mi)	***Mi***nimally ***I***nvasive adenocarcinoma	T1a **(mi)**
T1**a**	***S***uperficial ***S***preading tumor in central ***A***irways[a]	T1***ass***
T1a	Tumor≤1 cm	T1a≤*1*
T1b	Tumor>1 but ≤2 cm	T1b>*1-2*
T1c	Tumor>2 but ≤3 cm	T1c>*2-3*
T2	Tumor >3 but ≤5 cm or tumor involving: **Visc**eral **Pl**eura[b] main bronchus (not carina), atelectasis to hilum[b]	 T2***Visc Pl*** *T2****Centr***
T2a	Tumor >3 but ≤4 cm	T2a>*3-4*
T2b	Tumor >4 but ≤5 cm	T2b>*4-5*
T3	Tumor >5 but ≤7 cm Or **Inv**ading chest wall, pericardium, phrenic nerve, Or separate tumor nodule(s) in the same lobe	T3 >*5-7* T3 ***Inv*** T3 ***Satell***
T4	Tumor >7 Or tumor ***Inv***ading; mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus spine; Or tumor ***Nod***ule(s) in the different ***Ipsi***lateral lobe	T4>7 T4 ***Inv*** T4 ***Nod Ipsi***
N (Regional Lymph Nodes)		
N0	No regional node metastasis	
N1	Metastasis in ipsilateral pulmonary or hilar nodes	
N2	Metastasis in ipsilateral mediastinal/subcarinal nodes	

N3	Metastasis in contralateral mediastinal/hilar, or supraclavicular nodes	
M (Distant Metastasis)		
M0	No distant Metastasis	
M1a	Malignant pleural/ pericardial effusion[c] or pleural/ pericardial nodules Or separate tumor ***Nod***ule(s) in a ***Contra***lateral lobe	M1a M1a ***Contra Nod***
M1b	**Single** extrathoracic metastasis	M1b***Single***
M1c	**Multi**ple extrathoracic metastasis (1 or >1organ)	M1c***Multi***
TX, NX, T or N status not able to be assessed		

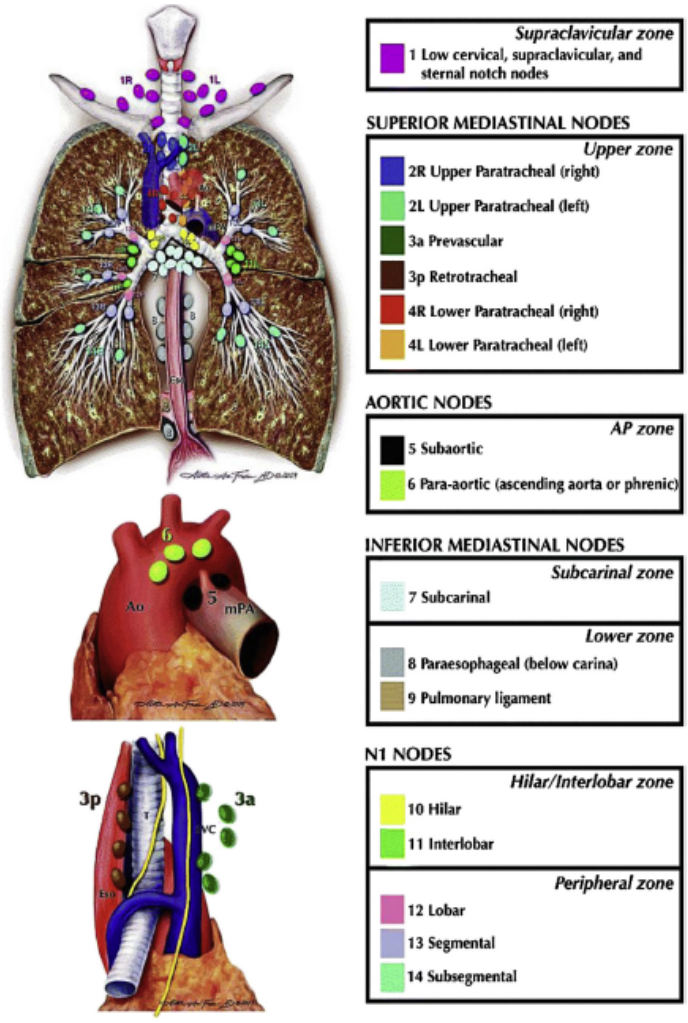
[a] Superficial spread of tumor(s), of any size AND confined to the tracheal and/or bronchial wall

[b] T2a classification if >3 ≤4cm, T2b classification if >4 ≤5cm.

[c] Pleural effusion(s) must have positive (malignant) cytology to be considered M1a.

Table 12-6 Lung Cancer Stage Grouping (Eighth Edition)

STAGE	T	N	M
Occult	TX	NO	MO
O	Tis	NO	MO
IA1	T1a (mi)/T1a	NO	MO
IA2	T1b	NO	MO
IA3	T1c	NO	MO
IB	T2a	NO	MO
IIA	T2b	NO	MO
IIB	T1a - T2b	N1	MO
	T3	NO	MO
IIIA	T1a - T2b	N2	MO
	T3	N1	MO
	T4	NO/ N1	MO
IIIB	T1a - T2b	N3	MO
	T3/ T4	N2	MO
IIIC	T3/ T4	N3	MO
IVA	Any T	Any N	M1a/M1b
IVB	Any T	Any N	M1c



ure 1 – *The International Association for the Study of Lung Cancer node map for lung cancer. With permission from Rusch et al.*[13]

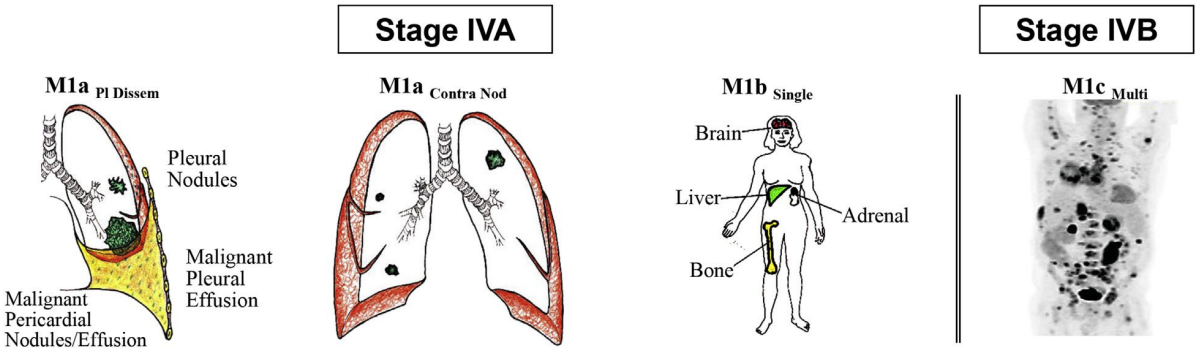
M1A - Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion

M1B - Single extra thoracic metastasis in a single organ

(M1A and M1B will be stratified as one metastatic site in IXRS)

M1C - Multiple extra thoracic metastases in one or several organs

(M1C will be stratified as multiple metastatic sites in IXRS)



Important Points:

- If multiple ribs are involved then staging will be considered as M1C. If ribs are part of an encroaching lesion, then staging will be considered M1B.
- Even if there are multiple lesions in the contralateral (opposite) lung, staging will be classified as M1A.
- For pleural and/or pericardial effusions without any other metastatic lesion(s): In order to be considered metastatic disease; effusions must have a confirmatory pathology report (cytology) confirming malignancy. Confirmed malignant effusions w/o any other metastatic lesion will be classified as M1A.