Official Title: Atezolizumab in Combination With Bevacizumab in Patients With Unresectable Locally Advanced or Metastatic Mucosal Melanoma

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STATISTICAL ANALYSIS PLAN

TITLE:	**ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB IN PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC MUCOSAL MELANOMA**
PROTOCOL NUMBER:	ML41186
STUDY DRUG:	Atezolizumab, Bevacizumab
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EUDRACT NUMBER:	NA
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted]
DATE FINAL:	12Oct2020

STATISTICAL ANALYSIS PLAN APPROVAL

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Not applicable, because this is the first version of the Statistical Analysis Plan.

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1. BACKGROUND

This Statistical Analysis Plan (SAP) describes all planned methods of summarizing and analyzing data to be collected in Study ML41186.

The analysis plan was following protocol version 3.0. This analysis plan is meant to supplement the study protocol. Any deviations from this analysis plan will be described in the clinical study report.

2. STUDY DESIGN

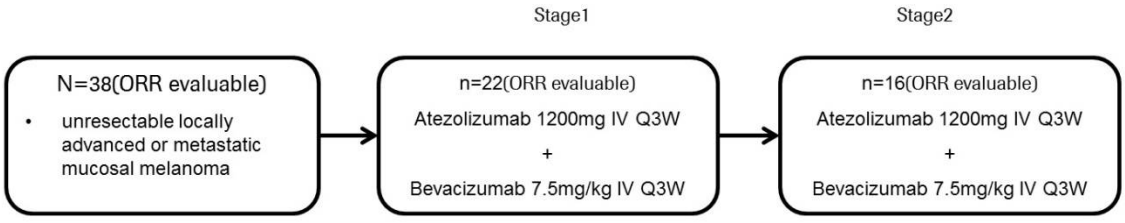
ML41186 is an open-label, multicenter, single arm, phase II study exploring the efficacy and safety of atezo + bev in patients with unresectable locally advanced or metastatic mucosal melanoma. The study will enroll approximately 43 patients (38 patients fully evaluable for ORR) at approximately 3 centers., including study Stages I and II.

The trial will consist of a Screening Period (Day –28 to −1), a Treatment Period, an Treatment Discontinuation Visit occurring when atezolizumab and bevacizumab are both discontinued for any reason and a Survival Follow-Up Period until death, loss to follow-up, or study termination. One cycle of therapy will be defined as 21 days of treatment. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

The study is divided into 2 stages. Stage I of the study is completed when 22 patients with measurable disease have been enrolled and completed ORR evaluation. If the number of responders in Stage I is more than 3, another 16 fully evaluable patients may be enrolled to Stage II.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



IV＝intravenous; Q3W= every 3 weeks

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. The end of the study is expected to occur 20 months after the last patient is enrolled. In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 2 years and 9 months.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Objectives and Endpoints

This study will evaluate the efficacy and safety of atezolizumab in combination with bevacizumab (atezo + bev) in patients with unresectable locally advanced or metastatic mucosal melanoma. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objective

- Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Secondary Efficacy Objective

- Progression-free survival (PFS), defined as the time from the date of first treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- Overall survival (OS), defined as the time from the date of first treatment to death from any cause
- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- Disease control rate (DCR) (defined as the sum of a complete or partial response or stable disease rates) as determined by the investigator according to RECIST v1.1.

Safety Objective

The primary safety objective for this study is to evaluate the safety of atezolizumab + bevacizumab on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0)
- Changes in vital signs, physical examination findings, and clinical laboratory results during and following study treatment

Study Design

Description of Study

This is an open-label, multicenter, single arm, phase II study exploring the efficacy and safety of atezo + bev in patients with unresectable locally advanced or metastatic mucosal melanoma.

The trial will consist of a Screening Period (Day –28 to −1), a Treatment Period, a Treatment Discontinuation Visit occurring when atezolizumab and bevacizumab are both discontinued for any reason and a Survival Follow-Up Period until death, loss to follow-up, or study termination. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

The study is divided into 2 stages. Stage I of the study is completed when 22 patients with measurable disease have been enrolled and completed ORR evaluation. If the number of responders in Stage I is more than 3, another 16 patients may be enrolled to Stage II.

Considering a drop-out rate of 10%, a total number of 25 subjects (if stops at the first stage) or 43 subjects (if runs into the second stage) will need to be enrolled in this study.

Atezolizumab and/or bevacizumab will be administered until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data (e.g., LDH level), local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Patients who transiently withhold or permanently discontinue either atezolizumab or bevacizumab may continue on single-agent therapy as long as the patients are experiencing clinical benefit in the opinion of the investigator.

Number of Patients

The study will enroll 38 subjects that fully evaluable for ORR (approximately 43 patients in total considering 10% dropout rate), including study Stages I and II.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Age ≥ 18 and ≤75 years at time of signing Informed Consent Form
3. Ability to comply with the study protocol, in the investigator's judgment
4. Histologically confirmed unresectable locally advanced(stage III) or metastatic(Stage IV) mucosal melanoma
5. May have received prior systemic treatment or treatment naive at enrollment
6. Measurable disease per RECIST v1.1
7. ECOG Performance Status of 0-1
8. Life expectancy ≥ 12 weeks
9. Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
    1) ANC ≥ 1.5 × 109/L (1500/μL) without granulocyte colony-stimulating factor support, G-CSF may be administered until 2 weeks prior to Cycle 1, Day 1
    2) Lymphocyte count ≥ 0.5 × 109/L (500/μL)
    3) Platelet count ≥ 100 × 109/L (100,000/μL) without transfusion, transfusion may be administered until 2 weeks prior to Cycle 1, Day 1
    4) Hemoglobin ≥ 90 g/L (9 g/dL)
        i. Patients may be transfused to meet this criterion.
    5) AST, ALT, and alkaline phosphatase (ALP) ≤ 2.5 × upper limit of normal (ULN), with the following exceptions:
        i. Patients with documented liver metastases: AST and ALT ≤ 5 × ULN
        ii. Patients with documented liver or bone metastases: ALP ≤ 5 × ULN
    6) Serum bilirubin ≤ 1.5 × ULN with the following exception:
        i. Patients with known Gilbert disease: serum bilirubin level ≤ 3 × ULN

7) Serum creatinine ≤ 1.5 × ULN

8) Serum albumin ≥ 25 g/L (2.5 g/dL)

9) For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 × ULN

10. Negative HIV test at screening

11. Negative hepatitis B surface antigen (HBsAg) test at screening

12. Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by quantitative hepatitis B virus (HBV) DNA<500 IU/mL at screening

13. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

    1) The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

14. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:

    1) Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the final dose of atezolizumab, or 6 months after the final dose of bevacizumab, whichever is longer. Women must refrain from donating eggs during this same period.

    2) A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

    3) Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

    4) The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

15. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

    1) With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per

year during the treatment period and for 6 months after the final dose of bevacizumab. Men must refrain from donating sperm during this same period.

2) With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of bevacizumab to avoid exposing the embryo.

3) The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Symptomatic or actively progressing central nervous system (CNS) metastases

   1) Asymptomatic patients with treated or untreated CNS lesions are eligible, provided that all of the following criteria are met:

      i. Measurable disease, per RECIST v1.1, must be present outside the CNS.

      ii. The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.

      iii. The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment.

      iv. The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.

      v. Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).

      vi. There is no evidence of interim progression between completion of CNS-directed therapy (if administered) and initiation of study treatment.

   2) Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.

2. History of leptomeningeal disease

3. Uncontrolled tumor-related pain

   1) Patients requiring pain medication must be on a stable regimen at study entry.

   2) Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

   3) Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not

currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.

4. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
    1) Patients with indwelling catheters are allowed.
5. Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN)
6. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
    1) Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
    2) Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    3) Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
        i. Rash must cover < 10% of body surface area
        ii. Disease is well controlled at baseline and requires only low-potency topical corticosteroids
        iii. No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
7. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
    1) History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
8. Active tuberculosis
9. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
    1) Patients with known coronary artery disease, arrhythmias, congestive heart failure not meeting the above criteria must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac

risk factors and/or history of coronary artery disease or where low LVEF is suspected

2) Patients with known LVEF < 40%

10. Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
11. History of malignancy other than melanoma within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
12. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
13. Prior allogeneic stem cell or solid organ transplantation
14. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
15. Current treatment with anti-viral therapy for HBV
16. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
17. Current, recent (within 28 days prior to initiation of study treatment) or planned treatment with any other investigational agent or participation in another clinical study with anti-cancer therapeutic intent
18. Prior treatment with immune checkpoint agonists, including CD137 agonists and TLR9 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
19. Prior treatment with anti-angiogenic therapies
20. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment as well as prior cancer vaccines and cellular immunotherapy
21. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents, as well as T and B cell targeting biologic agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

1) Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained.

2) Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

22. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
23. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
24. Known allergy or hypersensitivity to any component of the bevacizumab formulation
25. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of atezolizumab, 6 months after the final dose of bevacizumab

    1) Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

26. Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)

    1) Anti-hypertensive therapy to achieve these parameters is allowable.

27. Prior history of hypertensive crisis or hypertensive encephalopathy
28. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Cycle 1, Day 1
29. Patients with a baseline ECG demonstrating a QTc > 460 msec (calculated with use of the Fridericia method)
30. History of Grade ≥ 2 hemoptysis (defined as ≥ 2.5 mL of bright red blood per episode) within 1 month prior to screening
31. History of stroke or transient ischemic attack within 6 months prior to Cycle 1, Day 1
32. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
33. Prophylactic or therapeutic use of low molecular weight heparin (e.g., enoxaparin), direct thrombin inhibitors, or warfarin are permitted, provided, where appropriate anticoagulation indices are stable. Patients should have been on a stable dose (for therapeutic use) for at least 2 weeks (or until reaching steady state level of the drug) prior to the first study treatment
34. Current or recent (< 10 days prior to initiation of study treatment) use of aspirin (> 325 mg/day), clopidogrel (> 75 mg/day) or treatment with dipyramidole, ticlopidine, or cilostazol

1) Note: The use of full-dose oral or parenteral anticoagulants for therapeutic purpose is permitted as long as the INR and/or aPTT is within therapeutic limits (according to institution standards) within 7 days prior to initiation of study treatment and the patient has been on a stable dose of anticoagulants for $\geqslant$ 2 weeks prior to initiation of study treatment. Prophylactic use of anticoagulants is allowed.

35. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 calendar days prior to the first dose of bevacizumab
36. History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to Cycle 1, Day 1
37. Clinical signs or symptoms of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
38. Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
39. Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
40. Proteinuria, as demonstrated by urinalysis or $>$ 1.0 g of protein in a 24-hour urine collection
    1) All patients with $\geq$ 2+ protein on urinalysis at baseline must undergo a 24-hour urine collection for protein.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. The end of the study is expected to occur 20 months after the last patient is enrolled. In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 2 years and 9 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

The dose of atezolizumab in this study will be 1200 mg administered by intravenous infusion every 3 weeks.

The dose of bevacizumab in this study will be 7.5 mg/kg administered by intravenous infusion every 3 weeks.

Statistical Methods

The efficacy analyses will be performed on the Full Analysis Set (FAS) population, defined as all enrolled patients who receive any amount of study treatment and evaluable for efficacy endpoints.

The safety analysis will be performed on the safety-evaluable population, defined as all enrolled patients who receive at least one dose of any study treatment.

Other analyses (Demography, Baseline Characteristics, .etc.) will be performed on the basis of all enrolled patients (the ITT population), regardless of whether they receive any assigned study drug.

Primary Analysis

The primary efficacy endpoint is ORR, as assessed by the Investigator using RECIST, v1.1.

Number and percentage of responders with corresponding Clopper-Pearson 95% confidence intervals will be provided.

Estimates for the time-to-event variables, such as PFS, OS, DOR, will be obtained by using the Kaplan-Meier (KM) approach together with associated 90% and 95% CI.

Determination of Sample Size

The sample size calculation was based on a Simon two-stage design, and the primary end point was ORR (H0 = 20%, H1 = 40%). Alpha is set to be 0.05 and statistical power is set to be 80%.

22 fully evaluable subjects will be included at the first stage, and if the study continues another 16 fully evaluable subjects will be included in the second stage. Thus, considering a drop-out rate of 10%, a total number of 25 subjects (if stops at the first stage) or 43 subjects (if runs into the second stage) will need to be finally enrolled in this study.

Interim Analyses

One interim analysis is planned. The interim analysis will be performed for futility at the time of 22 subjects completes ORR evaluation. According to preplanned stopping rules of Simon 2-stage design, further testing of Atezolizumab and Bevacizumab would be halted if the number of subjects that respond in the first evaluable 22 patients (stage 1) is less or equal than 3. This study has a probability of 33.2% to terminate at the first stage. The optimal or minimax are not used because of their high probability of termination at the first stage.

At the end of the study, if more than 12 patients out of 38 patients have responses, we can conclude that the therapy is statistically significant in improving the ORR in curing mucosal melanoma.

The sample size and stopping rule are calculated with SAS 9.4

Appendix 2.

2.2 STUDY ENDPOINTS

Primary and secondary endpoints are provided.

2.2.1 Primary Efficacy Endpoint

The primary efficacy outcome measure for this study is Objective Response Rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions $\geqslant$ 4 weeks apart, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1).

2.2.2 Secondary Efficacy Endpoints

- Progression-free survival (PFS), defined as the time from the date of first treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1. A patient without a PFS event will be censored at the time of the last evaluable tumor assessment. Patients with no tumor assessment after the baseline visit will be censored at the time of the first day of study treatment plus 1 day.
- Overall survival (OS), defined as the time from the date of first treatment to death from any cause. Patients for whom no death is captured on the clinical database will be censored at the most recent date they were known to be alive.
- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1. For patients who do not die or experience disease progression before the end of the study or who are lost to follow-up, duration of objective response will be censored at the day of the last tumor assessment.
- Disease control rate (DCR), defined as the sum of a complete or partial response or stable disease (SD) rates, as determined by the investigator according to RECIST v1.1.

2.2.3 Safety Outcome Measures

The primary safety objective for this study is to evaluate the safety of atezo+bev on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0)
- Changes in vital signs, physical examination findings, and clinical laboratory results during and following study treatment

2.3 DETERMINATION OF SAMPLE SIZE

The sample size calculation was based on a Simon two-stage design (Simon 1989).

In this Phase II study, an ORR of 20% is a level of activity that is not of interest for further clinical development, whereas an ORR of 40% is of clinical interest.

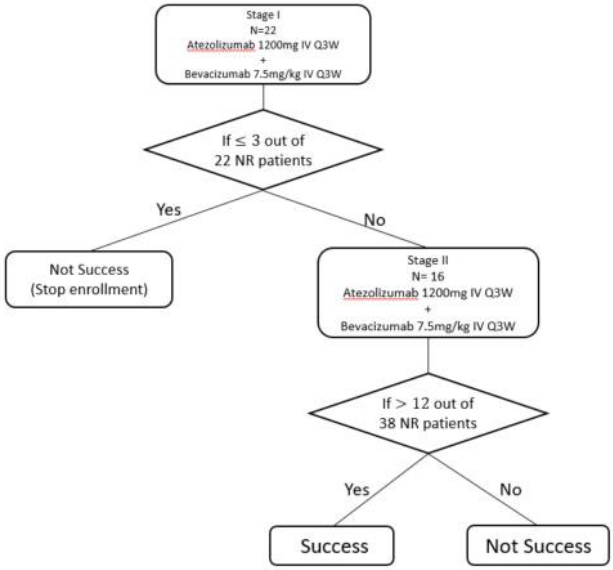
The study hypotheses are:

H_0: $\pi \leq \pi_0$
H_1: $\pi > \pi_1$

Where π_0= 20% and the assumed ORR under the alternative π_1= 40%.

The type I error will be 5% and the study will have 80% power to reject the null hypothesis when the true ORR is 40%.

Figure 2 Sample Size Allocation



NR: Non-Response; ORR: Overall Response Rate

The Simon design in this study requires 22 fully evaluable patients for the first stage. If at the end of first stage there are less than or equal to 3 patients with ORR, the enrollment in to the study will be terminated. Otherwise, if more than 3 patients with ORR are observed at the end of the stage I, an additional 16 fully-evaluable patients may be enrolled into stage II.

2.4 ANALYSIS TIMING

The analysis for the primary endpoints are planned

- At stage I, i.e. when 22 fully evaluable patients have passed the tumor assessment.

- At stage II, i.e. when 38 fully evaluable patients have passed the tumor assessment. (Second part of the primary analysis, provided stage I concluded in a decision to continue enrollment into stage II. For primary analysis and related parts, covered by this SAP, too.)

Stage II analysis and sample size of subsequent analyses are conditional on stage I conclusion to continue enrollment into the study.

The final analysis will occur after all patients have completed the end-of-study assessment. The final analysis will take place when all patients satisfy at least one of the following conditions:

- Died
- Withdrawn consent
- Lost to follow-up
- Has been followed for survival for a minimum of 20 months after the last patient has been enrolled
- The study is stopped due to safety or efficacy reasons, whichever occurs first.

3. STUDY CONDUCT

The study conduct is described in Section 2 (Study Design). Only the following rules need to be considered additionally:

Stopping rules for each stage:

Rules for Stage I:

- Enrollment into the study will stop at the end of Stage I if the number of patients that respond (CR or PR) is 0, 1, 2, or 3 in the first evaluable 22 patients.

All decisions above will be made by the SMT in discussion with the study Steering committee members.

Rules for Stage II and for conclusions at it ends:

The study treatment will be considered promising if:

- There is no unacceptable toxicity (Clinical Assessment, no pre-set criteria), and

- There are more than 12 patients with response (CR or PR) out of 38 fully-evaluable patients (quantitative Stage II criterion).

Other efficacy endpoints and safety may also be evaluated for a final decision at the end of Stage II.

3.1 RANDOMIZATION

This will be an open-label, unblinded trial involving only one treatment arm.

3.2 DATA MONITORING

The study team or advisory committee will be discussing the study status on an ongoing basis.

4. STATISTICAL METHODS

The primary analysis will be based on two consecutive ORR using a Simon's two-stage design for a single proportion.

4.1 STATISTICAL CONSIDERATIONS

4.1.1 General Rules

Continuous data will be summarized using n, mean, standard deviation, median, minimum and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the CRF, mean and median will be presented to one more decimal place than the raw data, standard deviation will be presented to two more decimal places than the raw data.

Categorical variables will be expressed as absolute and relative number. Percentages will be rounded to one decimal place, with the denominator being the number of patients in the relevant population with non-missing data, unless otherwise stated.

Time to event variables will be assessed with median survival time, lower quartile, upper quartile and its corresponding 95% CI using Kaplan-Meier method, these statistical will be presented to one more decimal place than the raw data. Besides, Kaplan-Meier product-limit plot will be produced.

Statistical programming and analyses will be performed using SAS® Software (SAS Institute Inc., Cary, NC) Version 9.4 or higher.

4.1.2 Baseline Definitions

The baseline value is defined as the last non-missing value prior to start of Atezolizumab or Bevacizumab treatment whichever comes first.

4.1.3 Study Day

The first dose date is considered as Day 1, patients' time on study will be determined in study days. Study day is defined as follows:

Study Day = the current date – Day 1 + 1, if the current date ≥ date of Day 1;

Study Day = the current date – Day 1, if current date < date of Day 1.

4.2 ANALYSIS POPULATIONS

Patients that included in the analysis populations will be listed.

4.2.1 Full Analysis Set

Full Analysis Set (FAS) is defined as all enrolled patients who receive any amount of study treatment and evaluable for efficacy endpoints. The primary efficacy analysis and other efficacy analyses will be performed on the FAS population.

Stage I Analysis Population

The Stage I analysis population will be the first 22 ORR evaluable patients in corresponding FAS population. The Stage I analysis population will be the main population for the primary efficacy endpoint evaluations at the end of Stage I.

Stage II Analysis Population

Stage II analysis population will be the first 38 (22 patients in Stage I are included) patients with ORR fully evaluable selected from the corresponding FAS population. Selection must augment the Stage I analysis population by all applicable patients subsequently enrolled after the Stage I analysis has been conducted and after decision to continue enrollment is made.

The Stage II analysis population will be the main population for primary efficacy endpoint evaluations at the end of Stage II.

4.2.2 Intention-to-treat Population

Intention-to-treat (ITT) population is defined as all enrolled patients regardless of whether they receive any assigned study drug. The ITT population will be used for the analyses such as Demography, Subject Disposition, and .etc.

4.2.3 Safety Population

Safety population is defined as all enrolled patients who receive any amount at least one dose of any study treatment. The safety analysis will be performed on the safety population.

4.3 ANALYSIS OF STUDY CONDUCT

Enrollment, fulfillment of eligibility criteria, reasons for treatment discontinuation, reasons for study discontinuation and duration of follow-up will be summarized. Major protocol deviations, as identified in the project deviation management plan, will be listed.

4.4 ANALYSIS OF TREATMENT GROUP COMPARABILITY

This is a single arm study and, consequently, no formal treatment group comparisons will be conducted. Demographics (age, sex, and ethnicity/race), disease history, medical history, prior therapies, concomitant medications, on study cancer surgery and procedure, and ECOG performance status will be summarized. Concomitant medications includes the medications used at any time from first dose of study drug through 7 days after last dose of study drug.

4.5 EFFICACY ANALYSIS

4.5.1 Primary Efficacy Endpoint

The primary analysis will be based on Objective Response Rate (ORR), defined as the proportion of patients with a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1. The confirmation rules are displayed in Table 4. This endpoint will be assessed at the end of Stage I and Stage II on the basis of the corresponding analysis population (cf. Sections 4.1.4 and 4.1.5), presenting the number and percentage of the patients with CR or PR along with the corresponding Clopper-Pearson 90% confidence interval. 95% confidence interval for confirmed ORR will also be provided. Patients treated with study drug who have no post-baseline tumor assessment (per protocol mandated timelines), and enrolled patients who do not receive any dose of study drug will be replaced.

Enrollment into the cohort may continue into Stage II if more than 3 patients (out of 22) with ORR are observed at the end of Stage I. In the Stage II, if more than 12 patients out of 38 patients have responses and there is no unacceptable toxicity, we can conclude that the therapy is statistically significant in improving the ORR in curing mucosal melanoma. The primary analysis will be based on the Stage I analysis population for the stage I, and stage II analysis population for the stage II (cf. Section 4.1.3).

4.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints (PFS, OS, DOR, BOR and DCR) are defined in section 2.2 above. In general, secondary efficacy endpoint analyses will be based on the FAS (cf. Section 4.1.1).

4.5.2.1 Progression Free Survival (PFS)

PFS is defined as the interval between the start date of treatment and the date of progression or death for any cause, whichever comes first.

6 months and 1 year PFS is defined as the percentage of people in this study who are not experience the disease progression and still alive for 6 months and 1 year after they started atezolizumab treatment for mucosal melanoma.

Because progression data can be collected from multiple sources (including physical exams at unscheduled visits and radiological scans of various types) and at different times, data collection for each assessment visit should be limited to a specified short time interval around the scheduled visit. The study assigns the progression date to the earliest time when any progression is observed and censoring at the date when the last radiological assessment determined a lack of progression.

Disease progression will be determined based on investigator's assessment with use of RECIST v1.1 or based on investigator's claim of clinical progression.

The PFS censoring rules in this SAP and definition of progression date follow the Food and Drug Administration (FDA) “Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)”, as displayed in Table 3.

The median and quartiles for PFS, and the PFS rates will be calculated using the Kaplan-Meier product-limit method, and presented with two-sided 95% CI, and the Kaplan-Meier estimate of PFS will be plotted over time.

Table 3 Censoring Rules for Primary PFS Analysis

Sequence	Situation	End date	Outcome
1	No baseline tumor assessments	Date of first dose date of study drug	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression	Date of last adequate radiologic assessment	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment visits	Date of death	Progressed
7	Death or progression after more than two missed visit/tumor assessment	Date of last adequate radiologic assessment before missed tumor assessments	Censored
8	No tumor progression (per RECIST 1.0) and Treatment discontinuation for reasons other than PD	Date of last adequate radiological assessment	Censored

4.5.2.2 Overall Survival (OS)

Overall survival is defined as the interval between the date of study drug and the date of death for any cause.

6 months and 1 year overall survival rate is defined as the percentage of people in this study who are still alive for 6 months and 1 year after they started atezolizumab treatment for mucosal melanoma.

The median and quartiles for overall survival will be provided using the Kaplan- Meier product-limit method, and presented with two-sided 95% CI, and the Kaplan-Meier plot will be produced by time. And censoring rules will be in accordance with Table 3.

4.5.2.3 Duration of Response (DOR)

DOR is defined as the interval between the date of the earliest qualifying response and the date of PD or death for any cause, whichever comes first. This will be calculated only for patients who had a best overall response of CR or PR. And censoring rules will keep consistent with Table 3.

The median and quartiles for DOR, and the DOR will be calculated using the Kaplan-Meier product-limit method, and presented with two-sided 95% CI, and the Kaplan-Meier plot will be produced by time.

4.5.2.4 Rates Analysis

Number and percentage of disease control patients (DCR) with corresponding Clopper-Pearson 95% confidence intervals will be provided. Both Confirmed and unconfirmed DCR will be analyzed.

The confirmation rules follow the New Response Evaluation Criteria in Solid Tumours: Revised RECIST guideline (version 1.1). The confirmation rules are displayed in table 4.

Table 4 Confirmation Rules of Best Overall Response

First Overall Response	Subsequent Overall Response	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR*
CR	SD	SD if >= 6 weeks for SD, otherwise PD
CR	PD	SD if >= 6 weeks for SD, otherwise PD
CR	NE	SD if >= 6 weeks for SD, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD if >= 6 weeks for SD, otherwise PD?
PR	NE	SD if >= 6 weeks for SD, otherwise NE?
NE	NE	NE

* 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 >=6 weeks for SD was met. 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.

The confirmed and unconfirmed ORR and BOR will be analyzed in the FAS population using the same statistical method.

4.5.3 Subgroup Analysis

To assess the consistency of the study ORR and PFS results, results in subgroups will be examined. The following subgroups will be considered:

Lactate Dehydrogenase

- Lactate Dehydrogenase (LDH) Level (≤ ULN and > ULN)
- ECOG (0 and 1)
- Line of Therapy (1 and ≥ 2)
- Number of Metastasis Sites (<3 and ≥3)
- Clinical Stage (III and IV)

Results of ORR and PFS will be descriptively summarized with corresponding 95% CI. No comparisons between subgroups will be performed.

4.6 SAFETY ANALYSES

Safety will be assessed through summaries of AEs, changes in laboratory test results, changes in vital signs and ECGs, and exposure to Atezolizumab. The safety variables will be summarized for the safety population.

No key (confirmatory) safety analyses are defined and no comparative statistics will be generated. The main and final time point for safety assessments is at the final analysis. However, decisions at the different stages of this study (such as stage I) may require insight into safety as well. Therefore, a selection or all of the specified safety evaluations of this section will be conducted at each analysis time point.

4.6.1 Exposure of Study Medication

Number of cycles and duration on study medication will be summarized by means of frequency tables and descriptive statistics for continuous variable (N, median, inter-quartile range, mean, SD, minimum, maximum). Exposure information (such as planned dose and actual dose, infusion delay, etc.) will be similarly summarized by cycle. A listing of exposure data will include the dates of progression (by RECIST 1.1) as well as related data on treatment discontinuation/continuation.

4.6.2 Adverse Events

Verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. Classifications of seriousness, severity and causality are described in the protocol sections 5.2 and 5.3. While listings will show all events. Overviews and summaries will only include events occurring on or after treatment on Day 1.

One overview table of Adverse events will present the number and proportion of patients experiencing any AE, related AE, any SAE, related SAEs, AEs by (maximum) grade, AESI, AEs leading to treatment discontinuation/interruption, AEs leading to death, additionally showing the number of events in each of these event categories.

Besides, events (as specified above) will be summarized by SOC and PT showing frequencies and percentages of patients experiencing (at least) one event in that category. A similar summary will be produced for non-serious AEs, which occur in at least 5% of patients.

Adverse event data will be listed by study site, patient number and study day of onset. In addition, SAEs, deaths as recorded on the CRF and AESIs (cf. Protocol section 5.2.3) will be listed separately. AE leading to treatment discontinuation will also be listed.

Should further summaries or listings on selected types of adverse events (e.g. summary of AESIs or listing of immune related adverse events) be required, these will follow the same output specifications as described above with the selection principles clarified in the title or as footnote.

4.6.3 Laboratory Data

Laboratory data will be displayed (i.e. listed at the time of Stage I and II analyses and summarized descriptively and listed at the follow-up period and final analysis) by time of measurement, with NCI CTCAE Grade 3 and 4 values identified where appropriate. Additionally, selected laboratory (Hematology, Chemistry, Urinalysis, 24-Hour Urine Protein Collection and Thyroid Function Test) data will be summarized in incidence tables by grade with use of NCI CTCAE v5.0.

4.6.4 Vital Signs

Descriptive statistics for vital signs parameters (blood pressure, pulse, temperature, respiratory rate) and change from baseline will be present by visit. These vital signs will be listed for each subject by visit.

4.6.5 ECG results

At each visit, the ECG result is to be assessed as being normal, abnormal - not clinically significant, abnormal - clinically significant. Changes from baseline to post-baseline visit will be presented showing numbers and proportions of patients. A listing of ECG findings and parameter values will be provided by patients.

4.7 MISSING DATA

Missing data in the primary endpoint will be minimized by the rule for the replacement of patients treated with Atezolizumab with no post-baseline tumor assessment, and enrolled patients who do not receive any dose of Atezolizumab.

Handling of missing dates

In general, imputation of missing dates will be made for adverse event (AE) onset date, AE resolution date, date of death, start and end dates of prior and subsequent therapies, start and end date of concomitant therapy, date of initial diagnosis and date of birth.

If dates are completely missing, no imputation will be made. For any partial date with missing year, no imputation will be made.

If only day is missing, then the 15th of the month will be used.

If only year is present, then June 30th will be used.

If such imputed date for prior therapies or initial diagnosis is on or after date of first dose, then date of first dose - 1 will be used. If such imputed date for subsequent therapies is before date of last dose, then date of last dose +1 will be used.

If the imputed date is for a date of death and is before the last date that the subject is known to be alive, the latter date will be used.

The imputation rules for adverse event (AE) onset date, AE resolution date, start and end date of concomitant therapy will be specified as below.

Adverse events

A. Start Dates

1) If the year is unknown, then,

i) if the first dose date is not missing, set the date the same as the first dose date.

2) If both the month and day is unknown, then:

i) If the year matches the first dose date year, then set the month and day to the same as the first dose date.

ii) Otherwise, assign 1 January.

3) If only the day is unknown, then:

i) If the month and year match the first dose date month and year, set the day to that of the first dose date.

ii) Otherwise, assign the first day of the month.

B. Stop Dates

1) If the year is unknown, then the date will not be imputed and will remain a missing date.

2) If the month is unknown, then assign 31 December

3) If the day is unknown, then assign the last day of the month.

Prior/concomitant medications

Partial start dates of the prior and concomitant medications (including new anti-cancer therapy and cancer-related surgery and procedure) will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. In the case of the completely missing stop date, medication will be assumed to be ongoing.

4.8 INTERIM ANALYSES

The study will be analyzed for efficacy at Stage I and Stage II. This corresponds to the interim analysis and final analysis of the primary efficacy endpoint. (See section 4.4.1 for related statistical considerations).

The efficacy endpoints that included in the interim analysis are listed as follows:

Efficacy Endpoint	Statistical Analysis
• ORR • DCR	90% Confidence interval for confirmed ORR 95% Confidence Interval for ORR and DCR Chisq-square test/Fisher exact test[a]

	Waterfall plot for confirmed BOR
• PFS • OS • DOR[b]	Kaplan-Meier estimates and curves; Landmark analysis for 6-month PFS, and 6-month OS.

[a] if the sample size is too small, the fisher exact test will be applied as the sensitivity analysis.

[b] Analysis on DOR will only be performed when >=10 patients have response.

The safety endpoints that included in the interim analysis are listed as follows:

Safety Modules	Safety Endpoints
• Adverse Event	AE, related AE, SAE, related SAEs, G≥3 AEs , AESI, AEs leading to treatment discontinuation, AEs leading to death
• Laboratory	Safety laboratory parameters

No additional (interim) analysis for efficacy will be performed in this study. However, safety evaluations may be conducted along with the above planned interim analysis.

5. REFERENCES

1. ICH guidance for industry E9 Statistical Principles for Clinical Trials, 1998

2. ICH guidance for industry E3 Structure and Content of Clinical Study Reports, 1996

3. SAS Institute, Inc. SAS Product Documentation (http://support.sas.com/documentation/index.html).

4. Simon, R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989; 10:1-10.

5. Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., Rubinstein, L., Shankar, L., Dodd, L., Kaplan, R., Lacombe, D., & Verweij, J. (2009). New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *European Journal of Cancer*, *45*(2), 228-247.

Appendix 1
Protocol Synopsis

Objectives and Endpoints

This study will evaluate the efficacy and safety of atezolizumab in combination with bevacizumab (atezo + bev) in patients with unresectable locally advanced or metastatic mucosal melanoma. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objective

- Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Secondary Efficacy Objective

- Progression-free survival (PFS), defined as the time from the date of first treatment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- Overall survival (OS), defined as the time from the date of first treatment to death from any cause
- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- Disease control rate (DCR) (defined as the sum of a complete or partial response or stable disease rates) as determined by the investigator according to RECIST v1.1.

Safety Objective

The primary safety objective for this study is to evaluate the safety of atezolizumab + bevacizumab on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0)
- Changes in vital signs, physical examination findings, and clinical laboratory results during and following study treatment

Study Design

Description of Study

This is an open-label, multicenter, single arm, phase II study exploring the efficacy and safety of atezo + bev in patients with unresectable locally advanced or metastatic mucosal melanoma.

The trial will consist of a Screening Period (Day –28 to −1), a Treatment Period, a Treatment Discontinuation Visit occurring when atezolizumab and bevacizumab are both discontinued for any reason and a Survival Follow-Up Period until death, loss to follow-up, or study termination. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

The study is divided into 2 stages. Stage I of the study is completed when 22 patients with measurable disease have been enrolled and completed ORR evaluation. If the number of responders in Stage I is more than 3, another 16 patients may be enrolled to Stage II.

Considering a drop-out rate of 10%, a total number of 25 subjects (if stops at the first stage) or 43 subjects (if runs into the second stage) will need to be enrolled in this study.

Atezolizumab and/or bevacizumab will be administered until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data (e.g., LDH level), local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Patients who transiently withhold or permanently discontinue either atezolizumab or bevacizumab may continue on single-agent therapy as long as the patients are experiencing clinical benefit in the opinion of the investigator.

Number of Patients

The study will enroll 38 subjects that fully evaluable for ORR (approximately 43 patients in total considering 10% dropout rate), including study Stages I and II.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

16. Signed Informed Consent Form
17. Age ≥ 18 and ≤75 years at time of signing Informed Consent Form
18. Ability to comply with the study protocol, in the investigator's judgment
19. Histologically confirmed unresectable locally advanced(stage III) or metastatic(Stage IV) mucosal melanoma
20. May have received prior systemic treatment or treatment naive at enrollment
21. Measurable disease per RECIST v1.1
22. ECOG Performance Status of 0-1
23. Life expectancy ≥ 12 weeks
24. Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
    10) ANC ≥ 1.5×10^9/L (1500/μL) without granulocyte colony-stimulating factor support, G-CSF may be administered until 2 weeks prior to Cycle 1, Day 1
    11) Lymphocyte count ≥ 0.5×10^9/L (500/μL)
    12) Platelet count ≥ 100×10^9/L (100,000/μL) without transfusion, transfusion may be administered until 2 weeks prior to Cycle 1, Day 1
    13) Hemoglobin ≥ 90 g/L (9 g/dL)
        ii. Patients may be transfused to meet this criterion.
    14) AST, ALT, and alkaline phosphatase (ALP) ≤ 2.5 × upper limit of normal (ULN), with the following exceptions:
        iii. Patients with documented liver metastases: AST and ALT ≤ 5 × ULN
        iv. Patients with documented liver or bone metastases: ALP ≤ 5 × ULN
    15) Serum bilirubin ≤ 1.5 × ULN with the following exception:
        ii. Patients with known Gilbert disease: serum bilirubin level ≤ 3 × ULN
    16) Serum creatinine ≤ 1.5 × ULN
    17) Serum albumin ≥ 25 g/L (2.5 g/dL)
    18) For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 × ULN

25. Negative HIV test at screening
26. Negative hepatitis B surface antigen (HBsAg) test at screening
27. Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by quantitative hepatitis B virus (HBV) DNA<500 IU/mL at screening
28. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening
    2) The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
29. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:
    5) Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 5 months after the final dose of atezolizumab, or 6 months after the final dose of bevacizumab, whichever is longer. Women must refrain from donating eggs during this same period.
    6) A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.
    7) Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    8) The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
30. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:
    4) With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for 6 months after the final dose of bevacizumab. Men must refrain from donating sperm during this same period.
    5) With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of bevacizumab to avoid exposing the embryo.
    6) The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

41. Symptomatic or actively progressing central nervous system (CNS) metastases

    3) Asymptomatic patients with treated or untreated CNS lesions are eligible, provided that all of the following criteria are met:

        i. Measurable disease, per RECIST v1.1, must be present outside the CNS.

        ii. The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.

        iii. The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment.

        iv. The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.

        v. Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).

        vi. There is no evidence of interim progression between completion of CNS-directed therapy (if administered) and initiation of study treatment.

    4) Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.

42. History of leptomeningeal disease

43. Uncontrolled tumor-related pain

    4) Patients requiring pain medication must be on a stable regimen at study entry.

    5) Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

    6) Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.

44. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

    2) Patients with indwelling catheters are allowed.

45. Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL or corrected serum calcium $>$ ULN)

46. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

4) Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

5) Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

6) Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

iv. Rash must cover < 10% of body surface area

v. Disease is well controlled at baseline and requires only low-potency topical corticosteroids

vi. No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

47. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

2) History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

48. Active tuberculosis

49. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina

3) Patients with known coronary artery disease, arrhythmias, congestive heart failure not meeting the above criteria must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease or where low LVEF is suspected

4) Patients with known LVEF < 40%

50. Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study

51. History of malignancy other than melanoma within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer

52. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
53. Prior allogeneic stem cell or solid organ transplantation
54. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
55. Current treatment with anti-viral therapy for HBV
56. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
57. Current, recent (within 28 days prior to initiation of study treatment) or planned treatment with any other investigational agent or participation in another clinical study with anti-cancer therapeutic intent
58. Prior treatment with immune checkpoint agonists, including CD137 agonists and TLR9 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
59. Prior treatment with anti-angiogenic therapies
60. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment as well as prior cancer vaccines and cellular immunotherapy
61. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents, as well as T and B cell targeting biologic agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
    3) Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained.
    4) Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
62. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
63. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
64. Known allergy or hypersensitivity to any component of the bevacizumab formulation

65. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of atezolizumab, 6 months after the final dose of bevacizumab

    2) Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

66. Inadequately controlled hypertension (defined as systolic blood pressure $>$ 150 mmHg and/or diastolic blood pressure $>$ 100 mmHg)

    2) Anti-hypertensive therapy to achieve these parameters is allowable.

67. Prior history of hypertensive crisis or hypertensive encephalopathy

68. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Cycle 1, Day 1

69. Patients with a baseline ECG demonstrating a QTc > 460 msec (calculated with use of the Fridericia method)

70. History of Grade ≥ 2 hemoptysis (defined as ≥ 2.5 mL of bright red blood per episode) within 1 month prior to screening

71. History of stroke or transient ischemic attack within 6 months prior to Cycle 1, Day 1

72. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)

73. Prophylactic or therapeutic use of low molecular weight heparin (e.g., enoxaparin), direct thrombin inhibitors, or warfarin are permitted, provided, where appropriate anticoagulation indices are stable. Patients should have been on a stable dose (for therapeutic use) for at least 2 weeks (or until reaching steady state level of the drug) prior to the first study treatment

74. Current or recent (< 10 days prior to initiation of study treatment) use of aspirin (> 325 mg/day), clopidogrel (> 75 mg/day) or treatment with dipyramidole, ticlopidine, or cilostazol

    2) Note: The use of full-dose oral or parenteral anticoagulants for therapeutic purpose is permitted as long as the INR and/or aPTT is within therapeutic limits (according to institution standards) within 7 days prior to initiation of study treatment and the patient has been on a stable dose of anticoagulants for $\geqslant$ 2 weeks prior to initiation of study treatment. Prophylactic use of anticoagulants is allowed.

75. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 calendar days prior to the first dose of bevacizumab

76. History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to Cycle 1, Day 1

77. Clinical signs or symptoms of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding

78. Evidence of abdominal free air not explained by paracentesis or recent surgical procedure

79. Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture

80. Proteinuria, as demonstrated by urinalysis or $>$ 1.0 g of protein in a 24-hour urine collection

2) All patients with ≥ 2+ protein on urinalysis at baseline must undergo a 24-hour urine collection for protein.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. The end of the study is expected to occur 20 months after the last patient is enrolled. In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 2 years and 9 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

The dose of atezolizumab in this study will be 1200 mg administered by intravenous infusion every 3 weeks.

The dose of bevacizumab in this study will be 7.5 mg/kg administered by intravenous infusion every 3 weeks.

Statistical Methods

The efficacy analyses will be performed on the Full Analysis Set (FAS) population, defined as all enrolled patients who receive any amount of study treatment and evaluable for efficacy endpoints.

The safety analysis will be performed on the safety-evaluable population, defined as all enrolled patients who receive at least one dose of any study treatment.

Other analyses (Demography, Baseline Characteristics, .etc.) will be performed on the basis of all enrolled patients (the ITT population), regardless of whether they receive any assigned study drug.

Primary Analysis

The primary efficacy endpoint is ORR, as assessed by the Investigator using RECIST, v1.1.

Number and percentage of responders with corresponding Clopper-Pearson 95% confidence intervals will be provided.

Estimates for the time-to-event variables, such as PFS, OS, DOR, will be obtained by using the Kaplan-Meier (KM) approach together with associated 90% and 95% CI.

Determination of Sample Size

The sample size calculation was based on a Simon two-stage design, and the primary end point was ORR (H_0 = 20%, H_1 = 40%). Alpha is set to be 0.05 and statistical power is set to be 80%.

22 fully evaluable subjects will be included at the first stage, and if the study continues another 16 fully evaluable subjects will be included in the second stage. Thus, considering a drop-out rate of 10%, a total number of 25 subjects (if stops at the first stage) or 43 subjects (if runs into the second stage) will need to be finally enrolled in this study.

Interim Analyses

One interim analysis is planned. The interim analysis will be performed for futility at the time of 22 subjects completes ORR evaluation. According to preplanned stopping rules of Simon 2-stage design, further testing of Atezolizumab and Bevacizumab would be halted if the number of subjects that respond in the first evaluable 22 patients (stage 1) is less or equal than 3. This study has a probability of 33.2% to terminate at the first stage. The optimal or minimax are not used because of their high probability of termination at the first stage.

At the end of the study, if more than 12 patients out of 38 patients have responses, we can conclude that the therapy is statistically significant in improving the ORR in curing mucosal melanoma.

The sample size and stopping rule are calculated with SAS 9.4

Appendix 2
Schedule of Assessments

	Screening Period [a]	Treatment Period	Treatment Discontinuation [b]	Follow-Up
	Days –28 to –1	Day 1 (±3 days) of each 3-week treatment cycle	≤ 30 Days after Final Dose	(every 3 months)
Informed consent [c]	x [c]			
Demographic data	x			
Medical history and baseline conditions	x			
Vital signs [d]	x	x	x	
Weight	x	x	x	
Height	x			
Complete physical examination [e]	x		x	
Limited physical examination [f]		x		
ECOG Performance Status	x	x	x	
ECG [g]	x	x [k]		
LVEF [h]	x			
Hematology [i]	x [j]	x [k]	x	
Chemistry [l]	x [j]	x [k]	x	
Pregnancy test [m]	x [j]	x [k]		
Coagulation (INR, aPTT)	x [j]		x	
TSH, free T3 (or total T3), free T4 [n]	x	x [k, n]	x	
Viral serology [o]	x			
Urinalysis [p]	x [j]	x [q]		
Tumor response assessments	x [r]	x [s, t]	x [s, t]	x [s, t]
Concomitant medications [u]	x [u]	x	x	
Adverse events [v]	x [v]	x [v]	x	x [v]
Study treatment administration [w]		x		
Survival follow-up and anti-cancer treatment				x [x]

eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; NA = not applicable; RECIST = Response Evaluation Criteria in Solid Tumors; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone;

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

a Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

b Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after their final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

c Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

d Includes respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

e Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

f Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

g ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Clinically indicated situation include when investigators consider it necessary to monitor ECG. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease or where low LVEF is suspected