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FINAL STATISTICAL ANALYSIS PLAN

TITLE:	**A PHASE IIIB, SINGLE ARM, MULTICENTER STUDY OF ATEZOLIZUMAB (TECENTRIQ) IN COMBINATION WITH BEVACIZUMAB TO INVESTIGATE SAFETY AND EFFICACY IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA NOT PREVIOUSLY TREATED WITH SYSTEMIC THERAPY - AMETHISTA**
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FINAL STATISTICAL ANALYSIS PLAN.

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1. INTRODUCTION

Study ML42243 is a Phase IIIb, one arm, multicenter, open-label study designed to evaluate the safety and efficacy of atezolizumab + bevacizumab in patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic treatment. A sample of convenience (Lohr 2010) of approximately 150 patients in one arm of treatment will be enrolled. All patients receive Atezolizumab 1200 mg IV infusions Q3W (dosed in 3-week cycles) + bevacizumab 15 mg/kg Q3W (dosed in 3-week cycles). Patients treated with atezolizumab + bevacizumab arm who transiently discontinue or withdraw from 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 and after discussion with the Medical Monitor (i.e., patients transiently discontinue or withdraw from bevacizumab for adverse effects may continue atezolizumab monotherapy and vice versa). Treatment will be given until unacceptable toxicity or loss of clinical benefit occurs. No dose modification for atezolizumab or bevacizumab is allowed.

The primary endpoint of the study is to evaluate the safety of atezolizumab + bevacizumab in terms of incidence of Grade 3-5 NCI CTCAE v.5 bleeding/haemorrhage. Overall survival (OS) is the main secondary endpoint aimed to assess study treatment efficacy.

Detailed descriptions of the study design, study objectives, study population together with inclusion and exclusion criteria, and study conduct can be found in the protocol.

The present document details the statistical analysis foreseen for the final analysis, which ends when all enrolled patients have either died, withdrawn consent, are to follow-up, or have been followed for 36 months since the last patient is enrolled. The final analysis will take into account all the safety and efficacy endpoints with descriptive purposes.

The primary objective of the final analysis remains the incidence of Grade 3-5 NCI CTCAE v.5 bleeding/haemorrhage. The main secondary objective is to evaluate the efficacy of atezolizumab + bevacizumab. Other safety variables (Incidence and severity of adverse events (AEs) with severity determined according to NCI CTCAE v5.0, deaths, changes in vital signs and ECGs, changes in clinical laboratory test results) will also be considered. Other efficacy variables of atezolizumab + bevacizumab (Progression-free survival (PFS), Objective response rate (ORR), Time to progression (TTP), Duration of response (DOR), Post-progression survival (PPS), Number/Rate of patients starting second or further lines of treatment) will be considered. Evaluation of Patient Reported Outcomes (PROs) and description of patient's experience while receiving atezolizumab + bevacizumab (Patient self-reported symptomatic Adverse Events (AEs)) will be considered.

The final analysis will be performed considering the analysis sets defined in the study protocol, i.e.:

- **Intent-To-Treat Population (ITT):** consists of all recruited patients, i.e. all patients who signed the informed consent form and were enrolled in the study.

- **Safety Analysis Population:** consists of all enrolled patients who had at least one full or partial administration of atezolizumab + bevacizumab.

2. SAFETY

The final analysis will be focused on safety endpoints. The Safety Analysis Population will be considered.

The primary safety analysis is the Incidence of Grade 3-5 NCI CTCAE v.5 bleeding/haemorrhage. Standardized MedDRA Query (SMQ) for haemorrhages, according on MedDRA dictionary current version, will be applied to identify the bleeding events.

Others secondary safety endpoints include incidence and severity of adverse events (AEs), deaths, atezolizumab/bevacizumab exposure, changes in vital signs and ECGs and changes in clinical laboratory test results. Moreover, a Patient Reported Outcomes (PROs) will be evaluated together with a patient's experience while receiving atezolizumab + bevacizumab.

Detailed safety contents for the final analysis report are described in Appendix 1, section 14.3 Safety data.

2.1 QUARTERLY SEVERE ADVERSE EVENT REVIEWS

An independent Data Monitoring Committee (iDMC) has been considered as not necessary for this study.

To provide quality data for medical interpretation of safety and efficacy and for identification of safety observations of interest for further investigation, Medical Monitoring Report have been prepared every two months and then, starting from March 2023, every three months . Safety information including serious adverse events (SAEs), adverse events of special interest (AESIs) and other non-serious adverse events (AEs) have been reviewed in a complete and timely manner to recognize trends that may be indicative of hazards associated with study treatments or study conduct. Further details concerning the output are included in the Medical Monitoring Plan. The list of tables and listings to include in the Medical Monitoring Report are reported in Appendix 3.

2.2 INTERIM ANALYSES

A first interim analysis of safety was performed at the time of the first 50 recruited patients, occurred at approximately 6 months after first patient in (FPI). A second interim analysis was performed when patients completed a period of follow-up of approximately 10 months. The second interim analysis took into account all the primary safety and secondary efficacy endpoints with descriptive purposes.

3. EFFICACY

The final analysis will be also focused on efficacy analysis. The Intention-to-treat (ITT) Population will be considered.

The main secondary efficacy endpoint is the Overall survival (OS).

Others secondary efficacy endpoints include Progression-free survival (PFS), Objective response rate (ORR), Time to progression (TTP), Duration of response (DOR), Post-progression survival (PPS), Number/Rate of patients starting second or further lines of treatment.

4. STUDY CONDUCT

A detailed overview of the study design is provided in section 3.1 of the study protocol. The schedule of time and events is available in Appendix 1 of the study protocol.

Protocol deviations (PDs) definition, classification and handling strategies are detailed in the Protocol Deviation Plan document.

5. VARIABLE DEFINITIONS AND DATA HANDLING PLAN

5.1 DEFINITIONS OF KEY ENDPOINTS

Safety endpoints

Overall incidence of Grade 3-5 NCI CTCAE *v5.0* bleeding/haemorrhage events (Primary Endopoint)

The primary safety analysis is focused on the incidence of grade 3-5 NCI CTCAE bleeding/haemorrhage events. Bleeding/haemorrhage events will be detected applying the Standardized MedDRA Query (SMQ) for haemorrhages, according to MedDRA dictionary current version.

The Incidence of treatment emergent bleeding/haemorrhage events, regardless their CTCAE grade, will be described by System Organ Class and Preferred Term, by System Organ Class, Preferred Term and maximum toxicity and by System Organ Class, Preferred Term and toxicity considering only CTCAE grade ≥3 events separately .

The Incidence of treatment emergent bleeding/haemorrhage events related to any treatment, regardless their CTCAE grade, will be described by System Organ Class and Preferred Term, by System Organ Class, Preferred Term and maximum toxicity. The Incidence of treatment emergent bleeding/haemorrhage events related to any treatment CTCAE grade ≥3 events will be described by System Organ Class and Preferred Term .

The incidence will be reported for treatment emergent bleeding/haemorrhage events related to Atezolizumab only, treatment emergent bleeding/haemorrhage events related to Bevacizumab only and to treatment emergent bleeding/haemorrhage events related to both Atezolizumab and Bevacizumab.

The overall incidence of Grade 3-5 NCI CTCAE bleeding events, i.e. the proportion of patients experiencing grade 3-5 NCI CTCAE bleedings/haemorrhages out of the considered safety analysis population sample, will be calculated along with exact binomial (Clopper-Pearson method) 95% Confidence Interval (CI). No hypothesis testing is intended, as the focus of the statistical analyses is on the precision of the obtained estimate of the incidence of this key safety parameter.

Moreover, the annual bleeding rate (BR) will be calculated as follows:

$$BR = \frac{\#\ events}{PY}$$

Where:

- # *events* is the total number of Grade 3-5 bleeding events (including multiple occurrences per patient, if any);
- *PY* is the total number of patient-years “at risk of event” under observation.

The BR point estimate will be provided along with 95% CI, assuming a Poisson distribution (Poisson 1837; Agresti 2001; Hilbe 2014) for the underlying number of related events occurring in a fixed interval of time.

The following exact formula will be applied to compute lower and upper confidence limits:

$$CL_{Lower} = \frac{\chi^2_{(2\ \#events),\frac{\alpha}{2}}}{2}$$

$$CL_{Upper} = \frac{\chi^2_{2(\#events+1),1-\frac{\alpha}{2}}}{2}$$

where:

- # events is the total number of bleeding events (including multiple occurrences per patient, if any);
- $\chi^2_{a,b}$ is the chi-square quantile for upper tail probability on a degrees of freedom.

Adverse events

After initiation of study treatment, all adverse events are reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest are reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Adverse events occurring in patients during the study will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, current version and adverse event severity will be graded according to NCI CTCAE v5.0.

All tables summarizing adverse events will include both number of patients reporting each considered event (in absolute and relative terms) and the number of occurred events.

Treatment-Emergent Adverse Events (TEAEs) are defined as adverse events with onset date on or after the start of the first study treatment component (i.e. atezolizumab or bevacizumab).

An overview of TEAEs occurring during the study will be provided for the number of subjects with any TEAEs, numbers of observed TEAEs, any serious TEAE, any serious TEAE related to any component of the study treatment, any TEAE related to any study treatment and related to each component separately, any TEAEs of CTCAE grade ≥3, any TEAEs with CTCAE grade ≥3 related to any component of the study treatment, any TEAE leading to discontinuation of study treatment (any component, atezolizumab only, bevacizumab only/both components), any TEAE leading to temporary interruptions (any component, atezolizumab only, bevacizumab only), fatal TEAEs, any fatal treatment-related TEAEs (any component, atezolizumab only, bevacizumab only, and both components), TEAEs of special interest (overall and separately for atezolizumab and bevacizumab).

The incidence of TEAEs will be tabulated:

- by System Organ Class (SOC) and Preferred Term (PT).

  Each subject could have more than one event, and multiple occurrences of each event, but it is only counted once for each PT category.

- by System Organ Class (SOC), Preferred Term (PT) and maximum toxicity grade.

  Each subject could have more than one event, and multiple occurrences of each event, but for each subject and each adverse event, the maximum toxicity grade will be selected.

- Focusing on events of CTCAE grade≥3 , by System Organ Class (SOC),Preferred Term (PT) and Toxicity.

Each subject could have more than one event, and multiple occurrences of each event, but it is only counted once for each PT category.

Moreover, a graphical representation of TEAEs with incidence of ⩾10% will be reported for any grade and for grades ≥3 separately.

The incidence of treatment emergent immuno-mediated AEs, im-TEAEs related to the study treatment (any treatment, atezolizumab only, bevacizumab only, both treatment components), im-TEAEs leading to permanent discontinuation of any treatment component/atezolizumab only/ bevacizumab only/both treatment components and im-TEAEs leading to temporary interruptions of any treatment component/atezolizumab only/ bevacizumab only/both treatment components will be similarly summarized.

Immuno-mediated AEs are defined as events treated with corticosteroids (preferred term: *Corticosteroids for Systemic Use*) or immunosuppressant drug (preferred term: *Other Immunosuppressant*).

Summary of TEAEs observed in at least 10% of patients or TEAEs of CTCAE grade ≥3 reported by at least 2% of patients will also be provided. The selected events will be presented according to their incidence, from the most frequently observed to the least frequently observed considering the preferred term.

An analogous summary of TEAEs related to any study treatment with incidence ⩾10% or of grade 3/4 with incidence ⩾2% will also be provided sorting the events by their incidence.

A summary of TEAEs leading to permanent discontinuation of any study treatment component with incidence ⩾2% in either treatment group will be performed sorting the events by their incidence.

A summary of Time-to-onset TEAEs will be provided. Time to resolution of TEAE will also be reported. They will be calculated as follows:

- Time-to-onset: Start of the first onset of TEAE - Date of first administration of treatment + 1.

- Time to resolution: Time it takes for first TEAE to achieve a complete resolution (for solved events only).

Time-to-onset and Time to resolution will be reported for each of the following TEAE:

- Bleeding/hemorrhage events any grade
- Bleeding/hemorrhage events CTCAE grade ⩾ 3
- Transaminases increased (includind PTs: Alanine aminotransferase increased; aspartate aminotransferase increased; hypertransaminasemia)
- Hypothyroidism

- Proteinuria
- Infusion related reaction
- Immune mediated events
- Hypertension
- Pulmonary embolism

Treatment-Emergent Serious Adverse Events (TESAEs) will also be described.

An overview of serious TEAEs will be provided, as well as summaries of the incidence of serious TEAEs, TESAEs related to any treatment component/atezolizumab only/bevacizumab only/both treatment components, TESAEs leading to permanent discontinuation of any treatment component/atezolizumab only/bevacizumab only/both treatment components, TESAEs leading to temporary interruption of any treatment component/atezolizumab only/bevacizumab only/both treatment components. Summary by SOC and PT, by SOC, PT and maximum toxicity grade, by SOC, PT and toxicity considering the events of CTCAE grade ≥3 will be provided.

A summary of TESAEs with incidence ⩾2% and their relationship to the study drugs will be performed sorting the events by their incidence.

Treatment-Emergent Adverse Events of Special Interest (TEAESIs)

Treatment emergent adverse events of special interest (TEAESIs) will be summarized separately “overall” and for atezolizumab and bevacizumab.

An overview of TEAESIs will be provided, as well as summaries of the incidence of TEAESIs, TEAESIs related to any treatment component/atezolizumab/bevacizumab/both treatment components, TEAESIs leading to permanent discontinuation of any treatment component/atezolizumab only/bevacizumab only/both treatment components, TEAESIs leading to temporary interruption of any treatment component/atezolizumab only/bevacizumab only/both treatment components. Summary by SOC and PT, by SOC, PT and maximum toxicity grade, by SOC, PT and toxicity considering the events of CTCAE grade ≥3 will be performed.

A summary of TEAESIs related to their respective study treatment component of any CTCAE grade and grade 3/4/5 will be performed sorting the events by their incidence.

Overviews will also be provided for atezolizumab and bevacizumab TEAESIs separately. The incidence of atezolizumab/bevacizumab TEAESIs will be summarized focusing on atezolizumab/bevacizumab TEAESI and atezolizumab/bevacizumab TEAESIs related to the respective treatment component. Summary by SOC and PT, by SOC, PT and maximum toxicity grade, by SOC, PT and toxicity considering the events of CTCAE grade ≥3 will be provided.

Atezolizumab adverse events of special interest are defined as:

- Systemic lupus erythematosus
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, Hemophagocytic Lymphohistiocytosis (HLH) and Macrophage Activation Syndrome (MAS);
- Nephritis;
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis);
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis);
- Vasculitis
- Autoimmune haemolytic anaemia
- Myelitis
- Facial paresis.

Bevacizumab adverse events of special interest included:

- Grade ≥3 hypertension;
- Grade ≥3 proteinuria;
- Any grade GI perforation, abscess, or fistula;
- Grade ⩾2 non-GI fistula or abscess;
- Grade ≥3 wound-healing complication;
- Hemorrhage;
    - Any grade CNS bleeding;
    - Grade ≥2 hemoptysis;
    - Other Grade ≥3 hemorrhagic event;
- Any arterial thromboembolic event;
- Grade ≥3 venous thromboembolic event;
- Any grade posterior reversible encephalopathy syndrome;
- Grade ≥3 congestive heart failure.

Adverse event of special interest in common for Atezolizumab and Bevacizumab included:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law;

- Suspected transmission of an infectious agent by the study treatment, as defined below:

    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent

may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

Listings of adverse events

Listings of all deaths, TEAEs with a fatal outcome, bleeding/haemorrhage events, non-fatal serious TEAEs, TEAEs related to any treatment component/atezolizumab only/bevacizumab only/Both treatment components, TEAEs with CTCAE grade ≥3, TEAEs leading to permanent discontinuation (of any treatment component/atezolizumab only/bevacizumab only/both treatment components), TEAEs leading to temporary interruption (of any treatment component/atezolizumab only/bevacizumab only/both drugs) will be provided.

Non-treatment-emergent adverse events will be listed as well.

Deaths

Deaths occurring during the study will be listed.

Drug exposure

The exposure to the study treatment will be defined separately for atezolizumab and bevacizumab and will be evaluated by means of the variables defined below.

The following definitions will be applied in the variable calculation:

- First administration: considering the study treatment, it is the earliest date when a non-zero dose of any component of study treatment (i.e. atezolizumab or bevacizumab) was administered and recorded on the eCRF. The time values are the times associated with the earliest date, if available.

  Focusing on each treatment component, the first administration is the earliest start date (with time, if any) when a non-zero dose of the considered treatment component was administered and recorded on the eCRF.

- Last administration: considering the study treatment, is the latest date when a non-zero dose of any component of study treatment (i.e., atezolizumab or bevacizumab) was administered and recorded on the eCRF. The time values are the times associated with the latest date, if available.

  Focusing on each treatment component, the last administration is the latest date (with time, if any) when a non-zero dose of the considered treatment component was administered and recorded on the eCRF.

Summary of duration of exposure will be reported overall and by presence of varices before starting study treatment, number of platelets at baseline (< 100 $10^{\wedge 9}$/L vs ≥ 100 $10^{\wedge 9}$/L and < 150 $10^{\wedge 9}$/L vs ≥ 150 $10^{\wedge 9}$/L).

- Cycle start date is defined, for each considered treatment component (i.e. atezolizumab or bevacizumab), as the date of administration in a given cycle. Therefore, for each subsequent cycle (i.e. CXD1), start date = date of administration within the considered cycle.

- Cycle end date is defined, for each considered treatment component (i.e. atezolizumab or bevacizumab), as:

  - the next cycle start date minus 1 day for cycles other than the last one. For example, Cycle 2 end date = Cycle 3 start date – 1 day.

  - min(last study treatment component administration date + 20 days, subsequent therapy start date - 1) for the last cycle. The last study treatment component administration date is the date of last infusion administered to patient for each considered treatment component.

The *number of cycles* is defined as the maximum number of cycles referred by patients for each treatment component. Treatment cycles for atezolizumab and bevacizumab will be derived from the exposure eCRF pages, including also temporary interruptions, if any. In case of last cycle with administered dose=0, it will not be considered for the number of cycles calculation.

The *duration of exposure to study treatment*, for subjects who took at least one dose of any of the components of the study treatment, is calculated as:

Duration of exposure (days) = Last administration date of any treatment component - Date of first administration of any treatment component + 1.

The duration of exposure to study treatment includes the periods of temporary interruption of the study treatment for any reason.

The duration of exposure to study treatment will be summarized by means of the usual descriptive statistics.

The *duration of exposure to each treatment component* will be calculated as:

Duration of exposure (days) = Last administration date of study treatment component - Date of first administration of study treatment component + 1.
Duration of exposure (cycles) = Number of treatment cycles on study treatment component (i.e. dose administered >0).

The number of patients with at least one temporary interruption for each study treatment will be reported together with the number of temporary interruptions per patient and the corresponding reasons.

Monotherapy will be summarized as follows:

The number of patients who definitely discontinue one of the two treatments (Atezolizumab or Bevacizumab) and who continue with a single treatment will be reported in terms of absolute and relative frequencies together with the number of cycles in which the patient is treated with monotherapy in continuous terms by means of usual descriptive statistics. Additionally, the reasons for permanent discontinuation of the other treatment will be documented and reported.

The *cumulative dose* for each study treatment component, is defined as the total dose (unit) of atezolizumab/bevacizumab calculated as the sum of all non-missing/non-zero dose values of that study treatment component, regardless of visit. The dose units of the study treatment components are mg and mg/kg for atezolizumab and bevacizumab respectively.

The *Dose intensity (DI)* of each study treatment component for subjects with non-zero duration of exposure to the study treatment component is defined as the amount of drug delivered to a patient per considered unit of time.

DI (dose unit/unit of time) = Cumulative dose (dose unit) / Duration of exposure to study treatment component (unit of time)

Dose intensity (mg/cycle and mg/kg/cycle) for atezolizumab and bevacizumab is calculated as the total atezolizumab/bevacizumab doses (mg and mg/kg) received in all cycles divided by the number of cycles during which atezolizumab/bevacizumab was administered (dose >0).

The *planned dose intensity (PDI)* is the assigned dose by unit of time planned to be given to the patients as per protocol, in the same dose unit and unit of time as that of the DI. Therefore, the PDI for each treatment component is:

atezolizumab: 1200 mg/cycle
bevacizumab 15 mg/kg/cycle

the *relative dose intensity (RDI),* expressed as a percentage for each study treatment component, is defined as:

RDI = 100 * DI (dose unit/unit of time) / PDI (dose unit/unit of time)

The relative dose intensity (%) is the ratio of total actually received dose and total planned dose.

DI and RDI will be summarized by means of the usual descriptive statistics.

The number of patients with cycle delays and with cycle skipped will be presented, along with the relative reasons. Any atezolizumab/bevacizumab interruption will be listed.

Overdoses for atezolizumab and bevacizumab will be summarized.

The number of patients for each cycle will be summarized.

The cycles beyond progression are defined as cycles of atezolizumab and/or bevacizumab treatment after a disease progression. The number of patients with cycles beyond progression and the number of cycles will be summarized. Duration of treatment beyond progression will be summarized by means descriptive statistics.

Time between EGDS and atezolizumab/bevacizumab treatment start and together with type of drugs taken for the resolution of varices will be reported.

Patient Reported Outcomes (PROs)

Patient self-reported symptomatic Adverse Events (AEs) using National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) will be reported.

For each item (i.e., Patient self-reported symptomatic Adverse Event), the distribution of categorical responses will be analyzed, showing the proportion of patients in each response category at each visit. Moreover, the distribution of responses to categorical questions will be presented using histograms with percentages, illustrating the proportion of patients within each response category at each visit.

For each item, the categorical responses will also be converted into Likert scale scores (0 to 4):

- Severity: "None" = 0, "Mild" = 1, "Moderate" = 2, "Severe" = 3, "Very Severe" = 4.
- Frequency: "Never" = 0, "Rarely" = 1, "Occasionally" = 2, "Frequently" = 3, "Almost Constantly" = 4.
- Interference: "Not At All" = 0, "A Little Bit" = 1, "Somewhat" = 2, "Quite A Bit" = 3, "Very Much" = 4.

These calculated scores will be summarized by means of descriptive statistics at each visit.

Subgroups analysis

The following safety endpoints will be summarized within the subgroups detailed below.

The incidence of treatment emergent bleeding/haemorrhage events by System Organ Class and Preferred Term and also by maximum toxicity grade will be also reported by the following subgroups:

- Presence of varices before starting study treatment (Yes, No)
- Presence/absence of cirrhosis before starting study treatment (Yes, No)
- Presence/absence of macrovascular invasion and/or extrahepatic spread (Yes, No)
- Barcelona Clinic Liver Cancer (BCLC) stage B according to Prior loco-regional therapy (Yes, No)

The incidence of treatment emergent bleeding/haemorrhage events by System Organ Class and Preferred Term and maximum toxicity grade will be reported also only for patients receiving:

- prophylactic dose of low-molecular-weight heparin (LMWH) and/or Salicylic acid.

Laboratory test results

Laboratory data will be summarized by parameter at each considered visit together with their relative change vs. baseline. The usual descriptive statistics will be applied.

Values out of the normal ranges will be listed.

The ALBI score will be computed as:

$$\text{ALBI score} = (\log_{10} \text{vital umol/L} * 0.66) + (\text{albumin g/L} * -0.0852).$$

In the Final Analysis, the ALBI (ALBI) grade will be used. The categorization of the ALBI is reported below:

- Grade 1 (≤-2.60),
- Grade 2 (>-2.60 to ≤-1.39),
- Grade 3 (>-1.39).

Vital signs

Vital signs (systolic/diastolic blood pressure, pulse rate, temperature, respiratory rate) will be summarized by visit and timepoint (i.e. during each study treatment component administration according to what stated in study protocol), together with their changes vs. baseline, by means of the usual descriptive statistics.

Body Mass Index (BMI) will be computed dividing weight in kilograms by the square of height in meters. Body Mass Index [Kg/m2] will be also classified in the subsequent classes:

- “Underweight” if BMI < 18.5,
- “Normal” if BMI between 18.5 - 24.9 Kg/m2,
- “Overweight” if BMI between 25 - 29.9 Kg/m2
- “Obesity” if BMI ≥ 30 Kg/m2.

ECGs

ECGs results will be summarized by visit and timepoint (i.e. during each study treatment component administration according to what stated in study protocol), together with their changes vs. baseline, by means of the usual descriptive statistics.

Results of ECGs performed at screening will be listed.

Concomitant medications

Concomitant medications or significant non-drug therapy are medications or therapy starting from 7 days prior to initiation of study drug to the treatment discontinuation visit or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Concomitant medications assumed up to the end of study will be summarized by the WHO ATC class (2nd level) and Preferred Term.

Efficacy endpoints

Overall survival (OS)

The main secondary efficacy endpoint is the Overall survival (OS) defined as the time from initiation of study treatment to death from any cause or to the last collection date.

If a patient dies the time will be calculated in months as:

(Death date – start of study treatment date + 1)/30.4375

and the status will be “event”.

If a patient does not die the time will be calculated in months as:

(Last collection date – start of study treatment date + 1)/30.4375

and the status will be “censored”.

Last collection date in which the patient is known to be alive will be determined by the maximum collection/assessment date.

The OS will be analyzed by means of Kaplan-Meier Product-Limit method with Greenwood's formula and using descriptive statistics. The estimated median and the quartiles will be provided together with corresponding two-sided 95% confidence intervals. Moreover, the Kaplan-Meier curve with a 95% CI will be presented.

Progression-free survival (PFS)

The secondary efficacy endpoint is the Progression-free survival (PFS) defined as the time from initiation of study treatment to the first occurrence of disease progression (as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1]) or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1, or to the last assessment.

If a patient dies or has a PD the time will be calculated in months as:

(Death date / PD date – start of study treatment date + 1)/30.4375

and the status will be "event".

If a patient does not die and has not a PD the time will be calculated in months as:

(Last assessment date – start of study treatment date + 1)/30.4375

and the status will be "censored".

Last assessment date will be determined by the last tumor evaluation performed by patients.

For a patient who does not have any post-baseline disease assessments and who has not died, PFS time will be censored at start of study treatment date.

The PFS will be analyzed by means of Kaplan-Meier Product-Limit method with Greenwood's formula and using descriptive statistics. The estimated median and the quartiles will be provided together with corresponding two-sided 95% confidence intervals. Moreover, the Kaplan-Meier curve with a 95% CI will be presented.

Time to progression (TTP)

The secondary efficacy endpoint is the Time to progression (TTP) defined as the time from initiation of study treatment to the first occurrence of disease progression, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), or to the last assessment.

If a patient has a disease progression the time will be calculated in months as:

(PD date – start of study treatment date + 1)/30.4375

and the status will be “event”.

If a patient does not have a disease progression the time will be calculated in months as:

(Last assessment date / death date – start of study treatment date + 1)/30.4375

and the status will be “censored”.

Last assessment date will be determined by the last tumor evaluation performed by patients.

The TTP will be analyzed by means of Kaplan-Meier Product-Limit method with Greenwood’s formula and using descriptive statistics. The estimated median and the quartiles will be provided together with corresponding two-sided 95% confidence intervals. Moreover, the Kaplan-Meier curve with a 95% CI will be presented.

Duration of response (DOR)

The secondary efficacy endpoint is the Duration of response (DOR), defined as the time from the first occurrence of a documented objective response (see below) to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1, or to the last assessment.

If a patient dies or has a PD the time will be calculated in months as:

(Death date / PD date – response date + 1)/30.4375

and the status will be “event”.

If a patient does not die nor has a PD the time will be calculated in months as:

(Last assessment date – response date + 1)/30.4375

and the status will be “censored”.

Thus, a subject with response who does not have a progression disease nor dies will be censored at the same time they were censored under the definition of PFS.

Patients who don’t achieve objective response will not be considered for the DOR calculation.

The DOR will be analyzed by means of Kaplan-Meier Product-Limit method with Greenwood’s formula and using descriptive statistics. The estimated median and the quartiles will be provided together with corresponding two-sided 95% confidence intervals. Moreover, the Kaplan-Meier curve with a 95% CI will be presented.

Post-progression survival (PPS)

The secondary efficacy endpoint is the Post-progression survival (PPS), defined as the time from the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 to death from any cause or to the last assessment.

If a patient has a PD and dies the time will be calculated in months as:

(Death date – PD date + 1)/30.4375

and the status will be "event".

If a patient does not die the time will be calculated in months as:

(Last collection date – PD date + 1)/30.4375

and the status will be "censored".

Patients who don't report a progression disease will not be considered for the PPS calculation.

Last collection date in which the patient is known to be alive will be determined by the maximum collection/assessment date available.

The PPS will be analyzed by means of Kaplan-Meier Product-Limit method with Greenwood's formula and using descriptive statistics. The estimated median and the quartiles will be provided together with corresponding two-sided 95% confidence intervals. Moreover, the Kaplan-Meier curve with a 95% CI will be presented.

Objective response rate (ORR)

Another efficacy endpoint is the Objective response rate (ORR), defined as the achieving of the objective response i.e., complete or partial response, as determined by the investigator according to RECIST v1.1.

ORR will simply be summarized as the percentage of patients who have a CR or PR before any evidence of progression. A 95% CI will be derived for the ORR using Wilson score intervals (CIs for a single proportion).

Best Response

The Best Response is the best response recorded for each patient from the start of the treatment until confirmed disease progression or study discontinuation, whichever occurs first. A frequency summary of the best overall response will be provided. The number and percentage of patients achieving each of the following best responses will be reported:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD).

Patterns of tumor progression

The patterns of tumor progression (determined according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), as assessed by the investigator) will be evaluated on the basis of the following characteristics:

- >20% increase in tumor size against a known baseline lesion (intrahepatic growth [IHG] or extrahepatic growth [EHG])
- new intrahepatic lesion (NIH)
- new extrahepatic lesion (NEH) and/or vascular invasion
- non-target lesions indicative of progressive disease

In cases where multiple patterns of progression are observed for the same patient on the same progression date, a hierarchy will be applied to classify the worst pattern of progression. The hierarchy will be as follows:

1. New Extrahepatic Lesion (NEH) and/or Vascular Invasion.
2. Extrahepatic Growth (EHG) or Intrahepatic Growth (IHG).
3. New Intrahepatic Lesion (NIH).
4. Non-target lesions indicative of progressive disease

This hierarchy ensures that when multiple progression patterns are detected on the same date, the worst pattern according to this hierarchy is used for the final classification of disease progression.

Note that tumor growth is assessed based on the changes in the total tumor size relative to the reference (refer to Study Protocol – Appendix 2, section “CRITERIA FOR TARGET LESIONS” for details) while non-target lesion progression was assessed based on investigator-reported qualitative evaluations (refer to Study Protocol – Appendix 2, section “CRITERIA FOR NON-TARGET LESIONS” for details).

The Overall Survival (OS) will be analyzed using the Kaplan-Meier Product-Limit method with Greenwood’s formula and descriptive statistics. The estimated median and quartiles will be provided together with the corresponding two-sided 95% confidence intervals. Kaplan-Meier curves will be compared using the Log-Rank Test. Moreover, hazard ratios will be estimated using the Cox proportional hazards model and presented together with 95% two-sided confidence intervals (CIs).

The Post-Progression Survival (PPS) will also be analyzed using the Kaplan-Meier Product-Limit method with Greenwood's formula and descriptive statistics. The estimated median and quartiles will be provided along with two-sided 95% confidence intervals. Kaplan-Meier curves will be presented together with 95% confidence intervals. In addition, hazard ratios will be estimated for PPS using the Cox proportional hazards model and presented together with 95% two-sided confidence intervals (CIs).

Landmark Analysis

A landmark analysis will be conducted for Overall Survival (OS) and Progression-Free Survival (PFS) at 12, 24, and 36 months to assess survival probabilities at these specified time points.

Overall Survival (OS)

The landmark OS analysis will be conducted at 12, 24, and 36 months, where only patients still at risk at each respective time point will be included in the analysis.

For the 12-month landmark, only patients who have survived up to 12 months without an event will be included. Similarly, for the 24-month and 36-month landmarks, only patients without an event by those times will be considered in each respective analysis.

The Kaplan-Meier Product-Limit method will be applied at each landmark to estimate survival curves up to and beyond each specified time point. Kaplan-Meier survival curves with 95% confidence intervals will be presented for OS at each landmark time.

Patients who are lost to follow-up or alive at the cutoff date for each landmark time point will be censored in the calculation of OS at that landmark.

Progression-Free Survival (PFS)

Similarly, landmark analysis for PFS will be conducted at the same predefined intervals: 12, 24, and 36 months.

At each landmark time (12, 24, and 36 months), the analysis will include only those patients who have not experienced progression or death by the landmark date.

Kaplan-Meier survival curves with 95% confidence intervals will be presented for PFS at each landmark time.

For patients who remain alive without progression at the time of the respective landmark cutoff, PFS will be censored at the latest assessment date prior to the landmark.

Monotherapy

The efficacy of monotherapy will be analyzed concerning Overall Survival (OS), Progression-Free Survival (PFS), Time to Progression (TTP), and Duration of Response (DoR). These analyses will focus specifically on patients who have permanently discontinued one of the treatments (Atezolizumab or Bevacizumab) and continued with monotherapy.

Kaplan-Meier survival curves will be generated for each endpoint, providing a visual representation of survival trends in patients receiving monotherapy.

Subgroup analysis

Overall survival will be summarized stratifying by the following characteristics:

- Barcelona Clinic Liver Cancer (BCLC) stage B according to Prior loco-regional therapy (Yes vs No)
- Second line treatment (Yes vs No)
- ALBI grade at baseline (Grade 1 vs Grade 2 vs Grade 3)
- Alpha-Fetoprotein at screening (<400 ul/L or $\geqslant$400 ul/L)
- Aetiology at baseline (Viral vs Non-viral)
- Presence/absence of varices before starting study treatment (Yes vs No)
- Presence/absence of macrovascular invasion and/or extrahepatic spread (Yes vs No)
- Presence/absence of cirrhosis before starting study treatment (Yes vs No)
- Prior loco-regional therapy at screening (0, 1-2 vs >2)
- Reason of treatment withdrawal

The OS will be analyzed by means of Kaplan-Meier Product-Limit method with Greenwood's formula and using descriptive statistics. The estimated median and the quartiles will be provided together with corresponding two-sided 95% confidence intervals. Kaplan-Meier curves will be compared using the Log-Rank Test.

Moreover, hazard ratios will be estimated using the Cox proportional hazards model and presented together with 95% two-sided Cls.

Progression-free survival (PFS) will be summarized by the following characteristics:

- Barcelona Clinic Liver Cancer (BCLC) stage B according to Prior loco-regional therapy (Yes vs No)
- Prior loco-regional therapy at screening (0 vs 1-2 vs >2)
- Second line treatment (Yes vs No)
- ALBI grade at baseline (Grade 1 vs Grade 2 vs Grade 3)
- Aetiology at baseline (Viral vs Non-viral)
- Presence/absence of varices before starting study treatment (Yes vs No)
- Presence/absence of macrovascular and/or extrahepatic spread (Yes vs No)
- Presence/absence of cirrhosis before starting study treatment (Yes vs No)

- Alpha-Fetoprotein at screening (<400 ul/L or ⩾400 ul/L)

The PFS will be analyzed by means of Kaplan-Meier Product-Limit method with Greenwood's formula and using descriptive statistics. The estimated median and the quartiles will be provided together with corresponding two-sided 95% confidence intervals. Kaplan-Meier curves will be compared using the Log-Rank Test.

Moreover, hazard ratios will be estimated using the Cox proportional hazards model and presented together with 95% two-sided Cls.

Time to Progression will be summarized by the following characteristics:

- Barcelona Clinic Liver Cancer (BCLC) stage B according to Prior loco-regional therapy (Yes vs No)
- ALBI grade at baseline (Grade 1 vs Grade 2 vs Grade 3)
- Presence/absence of macrovascular and/or extrahepatic spread (Yes vs No)
- Alpha-Fetoprotein at screening (<400 ul/L or ⩾400 ul/L)

The Time to Progression will be analyzed by means of Kaplan-Meier Product-Limit method with Greenwood's formula and using descriptive statistics. The estimated median and the quartiles will be provided together with corresponding two-sided 95% confidence intervals. Kaplan-Meier curves will be compared using the Log-Rank Test.

Moreover, hazard ratios will be estimated using the Cox proportional hazards model and presented together with 95% two-sided Cls.

Objective response rate (ORR) will be summarized by following characteristics:

- Barcelona Clinic Liver Cancer (BCLC) stage B according to Prior loco-regional therapy (Yes vs No)
- Aetiology at baseline (Viral vs Non-viral)

The ORR will be analyzed by means of Kaplan-Meier Product-Limit method with Greenwood's formula and using descriptive statistics. The estimated median and the quartiles will be provided together with corresponding two-sided 95% confidence intervals. Kaplan-Meier curves will be compared using the Log-Rank Test.

Moreover, hazard ratios will be estimated using the Cox proportional hazards model and presented together with 95% two-sided Cls.

Second line of treatment

Number and rate of patients starting second or further lines of treatment will be summarized.

Second line of treatment refers to medication collected on the 'Follow-up Cancer Therapy' eCRF started after a permanent discontinuation of atezolizumab and bevacizumab.

5.2 DATA HANDLING FOR THE FIRST INTERIM ANALYSIS

NA

5.3 DATA HANDLING FOR THE SECOND INTERIM ANALYSIS

General Methodology

Statistical tables, listings and analyses will be produced using SAS® release 9.4 (64 bit) or later (SAS Institute, Inc., Cary, NC, USA).

The data from all sites will be pooled and summarized.

Continuous data will be summarized with mean, standard deviation (SD), median, q1, q3, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %) or contingency tables. The percentage calculation will be based on total values (i.e. count will be shown also in the missing category, unless otherwise specified).

Study Phases

The following phases are identifiable within the study:

- Screening phase (day -28 – day -1)

  The period started after the Informed Consent signature, during which screening assessments are done within 1 to 28 days prior to start of study treatment.

- Treatment phase (Day 1 of each cycle)

  The period during which the study treatment is administered. It starts with the first assumption of atezolizumab/bevacizumab and ends with the last drug (atezolizumab/bevacizumab) intake.

- End of Treatment

  End of study treatment (EOT) visit should be done within 30 days from the last dose of study treatment and prior to initiating any subsequent therapy.

- Follow-up phase

The period after the treatment discontinuation during which information on survival follow-up and new anti-cancer therapy will be collected approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by Sponsor, whichever occurs first.

Definition of Baseline

The last available assessment on or before the start date of treatment is defined as the baseline value.

Study day

The study day describes the day of the event or assessment date, relative to the reference start date (i.e. the treatment start date for the present interim analysis).

The study day will be calculated as the difference between the date of each considered efficacy/safety assessment and the start of study treatment plus 1 day.

If the considered event starts before the start of study treatment, the study day will be calculated as the difference between the date of the assessment and the start of study treatment. Therefore, the study day will be negative.

The study day will be displayed in patient data listings. It is not to be used in numerical computations.

Last contact date

The last contact date will be derived for patients not known to be dead using the last complete date among the following:

- All assessment dates (e.g. vital signs assessment, performance status, etc.)

  Note, only a true on study assessment date or patient contact date will be used. If there is a visit date without evidence of any actual assessment performed, that date will not be used.
- Medication dates including study medications, concomitant medications, and antineoplastic therapies administered after study treatment discontinuation (with non-missing medication/procedure term).
- Adverse event dates (with non-missing verbatim AE term present).
- Last known date patient alive collected on the 'Survival information' eCRF.
- Date of discontinuation from end of treatment page and 'End of post-treatment follow-up' eCRF.

The last contact date is defined as the latest complete date from the above list, whichever comes first.

The last contact date will be used for censoring of patients in the analysis of overall survival (refers to section 5.1 of the present document).

Missing or Partial Dates

In the present interim analysis, the imputation of partial dates will be performed only if the date involved in the computation of variables needed for the study analysis and if at least the year is present (i.e. no imputation will be performed if the date is completely missing).

If not otherwise specified, the following general assumptions will be made in case of partially missing information:

- In case of day missing, the day will be replaced with 15;
- In case of day and month missing, the day will be replaced with 1, the month with July.

Handling of Missing Data/Imputation/Censoring Rules

For the present final analysis, patients will be included in each analysis based on available assessments. No methodology for missing data handling will be applied, unless otherwise specified.

Censoring rules will be applied to time-to-event endpoints (see section 5.1 of the present document for further details).

Study Patients

Patients' screening disposition will be summarized with the number of patients screened (i.e., patients who signed a valid Informed Consent Form collected in IXRS), screening failures, enrolled patients entered the study with data inserted in eCRF and patients treated with any study treatment component. The number of patients who permanently discontinued the study treatment will also be summarized, as well as the number of patients in follow-up, the number of patients who discontinued the follow-up and the number of patients who discontinued the study.

Reasons for screening failure, reasons for discontinuation from the study treatment and reasons for discontinuation from the study will be described.

The number of patients reporting any major protocol deviation will be described, and the number of patients reporting each considered PD will be summarized.

The number of subjects in each of the analysis populations will be summarized, as well as proportion of subjects excluded from any analysis set.

For the present final analysis, the observation time on study will be defined as time (in months) elapsed from the patients' enrollment to their last contact date, plus one day. It will be described by means of the usual descriptive statistics for all the enrolled patients. For the bimestrial/quarterly MM report, the observation time on study is defined as time (in months) elapsed from the patients' enrollment to their last contact date entered in eCRF at the date of each report plus one day. It is described on ITT population.

Background and Demographic Characteristics

Background and demographic characteristics will be summarized descriptively for patients valid for safety population.

Age, gender and race and presence of cirrhosis will be summarized by means of the usual descriptive statistics.

History of alcohol use will also be summarized.

Patients' hepatocellular carcinoma history will be described considering the following variables:

- Cause of disease (hepatitis B, hepatitis C, alcohol, Non-Alcoholic Related Liver Damage -with relative causes-, unknown);
- Aetiology at baseline;
- Histological Grade of cancer at initial diagnosis;
- Barcelona Clinic Liver Cancer (BCLC) staging classification at diagnosis;
- Barcelona Clinic Liver Cancer (BCLC) staging classification at study entry;
- Extrahepatic spread at study entry;
- Macro-Vascular Invasion at study entry;
- Presence of extrahepatic spread and macro-vascular Invasion at study entry;
- Presence of extrahepatic spread or macro-vascular Invasion at study entry;
- Performance of esophagogastroduodenoscopy within 6 months prior to study entry;
- Presence of varices at the time of enrollment; if present, patients with treated varices and treatments administered;
- Presence of prior bleeding event due to esophageal and/or gastric varices within 6 months prior to initiation of study treatment.

Patients' hepatocellular carcinoma history will be described considering the variables reported above by Aetiology. Aetiology will be classified in Viral (HBsAg +, HCVab +) and Non-Viral (Alcohol, Non Alcohol liver damaged, Healthy liver) where Viral refers to all patients with Hepatitis B or Hepatitis C and Non-Viral refers to all patients without Hepatitis B (HBsAg-) and Hepatitis C (HCVab-). If a patient has double aetiology, viral and non-viral, he will be counted in the viral group. In case of negative serology, the aetiology will be missing.

ECOG performance status and Child-Pugh score (class and point) will be summarized.

Prior HCC surgery will be described by means of number of patients who performed liver resection, transplant or other, and of summary of intents of therapy. The proportion of patients reporting a prior transplant will also be provided.

Similarly, prior loco-regional therapy will be described by means of subjects who performed each type of therapy and of summary of intents of therapy. The prior loco-regional therapy categories are "0", "1-2" and ">2".

Medical history (excluding prior transplant) will be coded with MedDRA dictionary, current version, and summarized by system organ class and preferred term.

Prior medications will be summarized by ATC code (2^{nd} level) and preferred term.

Patients' serology at screening will be described, and the level of alpha-fetoprotein at screening will be summarized both by means of usual descriptive statistics and in terms of number of patients reporting values <400 ul/L or ≥400 ul/L.

6. REFERENCES

Not applicable.

Appendix 1 Analyses for Open Report

Lists of Tables, Figures and Listings (TFL) foreseen for the present final analysis are reported below.

List of TFLs:

14.1 DEMOGRAPHIC DATA

- Table 14.1-1.1 Screened disposition (Screened patients)
- Table 14.1-1.2 Patients' disposition (Enrolled patients)
- Table 14.1-2 Summary of protocol deviations (Enrolled patients)
- Table 14.1-3.1 Analysis population (Enrolled patients)
- Table 14.1-3.2 Summary of patients excluded from any analysis (Enrolled patients)
- Table 14.1-4 Summary of patients' observation time (Enrolled patients)

Background and Demographic Characteristics

- Table 14.1-5.1 Demographic characteristics (Safety Analysis population)
- Table 14.1-5.2 History of alcohol use (Safety Analysis population)
- Table 14.1-5.3.1 HCC Diagnosis (Safety Analysis population)
- Table 14.1-5.3.2 HCC Diagnosis by Aetiology (Safety Analysis population)
- Table 14.1-5.4 ECOG performance status (Safety Analysis population)
- Table 14.1-5.5 Child-Pugh Score (Safety Analysis population)
- Table 14.1-5.6 Prior transplant (Safety Analysis population)
- Table 14.1-5.7 Prior HCC surgery (Safety Analysis population)
- Table 14.1-5.8 Prior loco-regional therapy (Safety Analysis population)
- Table 14.1-5.9 Medical history (excluding transplant) (Safety Analysis population)
- Table 14.1-5.10.a Prior medications (Safety Analysis population)
- Table 14.1-5.10.b Prior medications by Preferred Term (Safety Analysis population)
- Table 14.1-5.11 Serology (Safety Analysis population)

- Table 14.1-5.12 Alpha-Fetoprotein at screening (Safety Analysis population)

14.2 EFFICACY AND OTHER NON-SAFETY DATA

Efficacy endpoints

- Table 14.2-1.1 Overall survival (ITT Population)
- Figure 14.2-1.1 Kaplan-Meier of Overall survival (ITT Population)
- Table 14.2-1.2 Progression-free survival (ITT Population)
- Figure 14.2-1.2 Kaplan-Meier of Progression-free survival (ITT Population)
- Table 14.2-1.3 Time to progression (ITT Population)
- Figure 14.2-1.3 Kaplan-Meier of Time to progression (ITT Population)
- Table 14.2-1.4 Duration of response (ITT Population)
- Figure 14.2-1.4 Kaplan-Meier of Duration of response (ITT Population)
- Table 14.2-1.5 Post-progression survival (ITT Population)
- Figure 14.2-1.5 Kaplan-Meier of Post-progression survival (ITT Population)
- Table 14.2-1.6 Best Response (ITT Population)
- Table 14.2-1.7 Objective response rate (ITT Population)
- Table 14.2-1.8 Summary of second lines of treatment (ITT Population)

14.3 SAFETY DATA

14.3.1 Display of adverse events

Bleeding/haemorrhage events

- Table 14.3.1-1.1.1 Incidence of treatment emergent bleeding/haemorrhage events by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-1.1.2 Incidence of treatment emergent bleeding/haemorrhage events by System Organ Class, Preferred Term and maximum toxicity (Safety Analysis Population)
- Table 14.3.1-1.1.3 Incidence of treatment emergent bleeding/haemorrhage events of CTCAE grade ≥3 by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-1.1.4a Incidence of treatment emergent bleeding/haemorrhage events related to any treatment component by System Organ Class and Preferred Term (Safety Analysis Population)

- Table 14.3.1-1.1.4b Incidence of treatment emergent bleeding/haemorrhage events of CTCAE grade ≥3 related to any treatment component by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-1.1.5a Incidence of treatment emergent bleeding/haemorrhage events related to atezolizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-1.1.5b Incidence of treatment emergent bleeding/haemorrhage events of CTCAE grade ≥3 related to atezolizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-1.1.6a Incidence of treatment emergent bleeding/haemorrhage events related to bevacizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-1.1.6b Incidence of treatment emergent bleeding/haemorrhage events of CTCAE grade ≥3 related to bevacizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-1.1.7a Incidence of treatment emergent bleeding/haemorrhage events related to both atezolizumab and bevacizumab by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-1.1.7b Incidence of treatment emergent bleeding/haemorrhage events of CTCAE grade ≥3 related to both atezolizumab and bevacizumab by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-1.2.1 Summary of patients with bleeding/haemorrage events (Safety Analysis Population)
- Table 14.3.1-1.2.2 Annual incidence rate of bleeding/haemorrhage events CTCAE grade ≥3 (Safety Analysis Population)

Treatment emergent adverse events

- Table 14.3.1-2.1 Summary of patients with treatment-emergent Adverse Events (Safety Analysis Population)

Treatment Emergent Adverse Events

- Table 14.3.1-2.2.1 Incidence of treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.2.2 Incidence of treatment-emergent Adverse Events by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)

- Table 14.3.1-2.2.3 Incidence of treatment-emergent Adverse Events of CTCAE grade ≥3 by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.2.4 Summary of treatment-emergent Adverse Events with incidence of ≥10% or CTCAE grade ≥ 3 treatment-emergent Adverse Events with incidence ≥2% (Safety Analysis Population)
- Figure 14.3.1-2.2.4 Summary of treatment-emergent Adverse Events with incidence of ≥10% (Safety Analysis Population)

Treatment Emergent Immune-mediated Adverse Events

- Table 14.3.1-2.3.1 Incidence of treatment-emergent immune-mediated Adverse Events by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.3.2 Incidence of treatment-emergent immune-mediated Adverse Events by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-2.3.3 Incidence of treatment-emergent immune-mediated Adverse Events of CTCAE grade ≥3 by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.3.4a Incidence of treatment-emergent immune-mediated Adverse Events related to any treatment component by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.3.4b Incidence of treatment-emergent immune-mediated Adverse Events of CTCAE grade ≥3 related to any treatment component by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.3.5a Incidence of treatment-emergent immune-mediated Adverse Events related to atezolizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.3.5b Incidence of treatment-emergent immune-mediated Adverse Events of CTCAE grade ≥ 3 related to atezolizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.3.6a Incidence of treatment-emergent immune-mediated Adverse Events related to bevacizumab component only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.3.6b Incidence of treatment-emergent immune-mediated Adverse Events of CTCAE grade ≥3 related to bevacizumab component

only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)

- Table 14.3.1-2.3.7a Incidence of treatment-emergent immune-mediated Adverse Events related to both atezolizumab and bevacizumab by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.3.7b Incidence of treatment-emergent immune-mediated Adverse Events of CTCAE grade ≥3 related to both atezolizumab and bevacizumab by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.3.8 Incidence of treatment-emergent immune-mediated Adverse Events leading to permanent discontinuation of any treatment component by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.3.9 Incidence of treatment-emergent immune-mediated Adverse Events leading to permanent discontinuation of atezolizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.3.10 Incidence of treatment-emergent immune-mediated Adverse Events leading to permanent discontinuation of bevacizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.3.11 Incidence of treatment-emergent immune-mediated Adverse Events leading to permanent discontinuation of both atezolizumab and bevacizumab by System Organ Class and Preferred Term (Safety Analysis Population)
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Treatment Emergent Related Adverse Events

- Table 14.3.1-2.4.1.1 Incidence of treatment-emergent Adverse Events related to any treatment component by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.4.1.2 Incidence of treatment-emergent Adverse Events related to any treatment component by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-2.4.1.3 Incidence of treatment-emergent Adverse Events of CTCAE grade ≥3 related to any treatment component by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)

- Table 14.3.1-2.4.2.1 Incidence of treatment-emergent Adverse Events related to atezolizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.4.2.2 Incidence of treatment-emergent Adverse Events related to atezolizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-2.4.2.3 Incidence of treatment-emergent Adverse Events of CTCAE grade ≥3 related to atezolizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.4.3.1 Incidence of treatment-emergent Adverse Events related to bevacizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.4.3.2 Incidence of treatment-emergent Adverse Events related to bevacizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-2.4.3.3 Incidence of treatment-emergent Adverse Events of CTCAE grade ≥3 related to bevacizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.4.4.1 Incidence of treatment-emergent Adverse Events related to both atezolizumab and bevacizumab by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.4.4.2 Incidence of treatment-emergent Adverse Events related to both atezolizumab and bevacizumab by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-2.4.4.3 Incidence of treatment-emergent Adverse Events of CTCAE grade ≥3 related to both atezolizumab and bevacizumab by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.4.5 Summary of treatment-emergent Adverse Events related to any study treatment with incidence ≥10% or CTCAE grade ≥3 treatment-emergent Adverse Events related to any study treatment with incidence ≥2% (Safety Analysis Population)

Treatment Emergent Adverse Events leading to permanent discontinuation

- Table 14.3.1-2.5.1.1 Incidence of treatment-emergent Adverse Events leading to permanent discontinuation of any treatment component by System Organ Class and Preferred Term (Safety Analysis Population)

- Table 14.3.1-2.5.1.2 Incidence of treatment-emergent Adverse Events leading to permanent discontinuation of any treatment component by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-2.5.1.3 Incidence of treatment-emergent Adverse Events of CTCAE grade ≥3 leading to permanent discontinuation of any treatment component by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.5.2.1 Incidence of treatment-emergent Adverse Events leading to permanent discontinuation of atezolizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.5.2.2 Incidence of treatment-emergent Adverse Events leading to permanent discontinuation of atezolizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-2.5.2.3 Incidence of treatment-emergent Adverse Events of CTCAE grade ≥3 leading to permanent discontinuation of atezolizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.5.3.1 Incidence of treatment-emergent Adverse Events leading to permanent discontinuation of bevacizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.5.3.2 Incidence of treatment-emergent Adverse Events leading to permanent discontinuation of bevacizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-2.5.3.3 Incidence of treatment-emergent Adverse Events of CTCAE grade ≥3 leading to permanent discontinuation of bevacizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.5.4.1 Incidence of treatment-emergent Adverse Events leading to permanent discontinuation of both atezolizumab and bevacizumab by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.5.4.2a Incidence of treatment-emergent Adverse Events leading to permanent discontinuation of both atezolizumab and bevacizumab by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)

- Table 14.3.1-2.5.4.2b Incidence of treatment-emergent Adverse Events leading to permanent discontinuation of both atezolizumab and bevacizumab by System Organ Class, Preferred Term and site (Safety Analysis Population)
- Table 14.3.1-2.5.4.3 Incidence of treatment-emergent Adverse Events of CTCAE grade ≥3 leading to permanent discontinuation of both atezolizumab and bevacizumab by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.5.5 Summary of treatment-emergent Adverse Events leading to permanent discontinuation of any treatment component with incidence ≥2% in either treatment component groups (i.e atezolizumab only, bevacizumab only, both atezolizumab and bevacizumab, atezolizumab or bevacizumab) (Safety Analysis Population)

Treatment Emergent Adverse Events leading to temporary interruption

- Table 14.3.1-2.6.1.1 Incidence of treatment-emergent Adverse Events leading to temporary interruption of any treatment component by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.6.1.2 Incidence of treatment-emergent Adverse Events leading to temporary interruption of any treatment component by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-2.6.1.3 Incidence of treatment-emergent Adverse Events of CTCAE grade ≥3 leading to temporary interruption of any treatment component by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.6.2.1 Incidence of treatment-emergent Adverse Events leading to temporary interruption of atezolizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.6.2.2 Incidence of treatment-emergent Adverse Events leading to temporary interruption of atezolizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-2.6.2.3 Incidence of treatment-emergent Adverse Events of CTCAE grade ≥3 leading to temporary interruption of atezolizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)

- Table 14.3.1-2.6.3.1 Incidence of treatment-emergent Adverse Events leading to temporary interruption of bevacizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.6.3.2 Incidence of treatment-emergent Adverse Events leading to temporary interruption of bevacizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-2.6.3.3 Incidence of treatment-emergent Adverse Events of CTCAE grade ≥3 leading to temporary interruption of bevacizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-2.6.4.1 Incidence of treatment-emergent Adverse Events leading to temporary interruption of both atezolizumab and bevacizumab by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-2.6.4.2 Incidence of treatment-emergent Adverse Events leading to temporary interruption of both atezolizumab and bevacizumab by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-2.6.4.3 Incidence of treatment-emergent Adverse Events of CTCAE grade ≥3 leading to temporary interruption of both atezolizumab and bevacizumab by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)

Treatment-emergent serious adverse events

- Table 14.3.1-3.1 Summary of patients with treatment-emergent Serious Adverse Events (Safety Analysis Population)

Treatment Emergent Serious Adverse Events

- Table 14.3.1-3.2.1 Incidence of treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-3.2.2 Incidence of treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-3.2.3 Incidence of treatment-emergent Serious Adverse Events of CTCAE grade ≥3 by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-3.2.4 Summary of treatment-emergent Serious Adverse Events with incidence ≥2% (any CTCAE grade, CTCAE grade 3/4, CTCAE

grade 5, related to atezolizumab and related to bevacizumab) (Safety Analysis Population)

Treatment Emergent Related Serious Adverse Events

- Table 14.3.1-3.3.1.1 Incidence of treatment-emergent Serious Adverse Events related to any treatment component by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-3.3.1.2 Incidence of treatment-emergent Serious Adverse Events related to any treatment component by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-3.3.1.3 Incidence of treatment-emergent Serious Adverse Events of CTCAE grade ≥3 related to any treatment component by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-3.3.2.1 Incidence of treatment-emergent Serious Adverse Events related to atezolizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-3.3.2.2 Incidence of treatment-emergent Serious Adverse Events related to atezolizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-3.3.2.3 Incidence of treatment-emergent Serious Adverse Events of CTCAE grade ≥3 related to atezolizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-3.3.3.1 Incidence of treatment-emergent Serious Adverse Events related to bevacizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-3.3.3.2 Incidence of treatment-emergent Serious Adverse Events related to bevacizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-3.3.3.3 Incidence of treatment-emergent Serious Adverse Events of CTCAE grade ≥3 related to bevacizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-3.3.4.1 Incidence of treatment-emergent Serious Adverse Events related to both atezolizumab and bevacizumab by System Organ Class and Preferred Term (Safety Analysis Population)

- Table 14.3.1-3.3.4.2 Incidence of treatment-emergent Serious Adverse Events related to both atezolizumab and bevacizumab by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-3.3.4.3 Incidence of treatment-emergent Serious Adverse Events of CTCAE grade ≥3 related to both atezolizumab and bevacizumab by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)

Treatment Emergent Serious Adverse Events leading to permanent discontinuation

- Table 14.3.1-3.4.1.1 Incidence of treatment-emergent Serious Adverse Events leading to permanent discontinuation of any treatment component by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-3.4.1.2 Incidence of treatment-emergent Serious Adverse Events leading to permanent discontinuation of any treatment component by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-3.4.1.3 Incidence of treatment-emergent Serious Adverse Events of CTCAE grade ≥3 leading to permanent discontinuation of any treatment component by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-3.4.2.1 Incidence of treatment-emergent Serious Adverse Events leading to permanent discontinuation of atezolizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-3.4.2.2 Incidence of treatment-emergent Serious Adverse Events leading to permanent discontinuation of atezolizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-3.4.2.3 Incidence of treatment-emergent Serious Adverse Events of CTCAE grade ≥3 leading to permanent discontinuation of atezolizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-3.4.3.1 Incidence of treatment-emergent Serious Adverse Events leading to permanent discontinuation of bevacizumab only by System Organ Class and Preferred Term (Safety Analysis Population)

- Table 14.3.1-3.4.3.2 Incidence of treatment-emergent Serious Adverse Events leading to permanent discontinuation of bevacizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-3.4.3.3 Incidence of treatment-emergent Serious Adverse Events of CTCAE grade ≥3 leading to permanent discontinuation of bevacizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-3.4.4.1 Incidence of treatment-emergent Serious Adverse Events leading to permanent discontinuation of both atezolizumab and bevacizumab by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-3.4.4.2 Incidence of treatment-emergent Serious Adverse Events leading to permanent discontinuation of both atezolizumab and bevacizumab by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-3.4.4.3 Incidence of treatment-emergent Serious Adverse Events of CTCAE grade ≥3 leading to permanent discontinuation of both atezolizumab and bevacizumab by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)

Treatment Emergent Serious Adverse Events leading to temporary interruption

- Table 14.3.1-3.5.1.1 Incidence of treatment-emergent Serious Adverse Events leading to temporary interruption of any treatment component by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-3.5.1.2 Incidence of treatment-emergent Serious Adverse Events leading to temporary interruption of any treatment component by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-3.5.1.3 Incidence of treatment-emergent Serious Adverse Events of CTCAE grade ≥3 leading to temporary interruption of any treatment component by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-3.5.2.1 Incidence of treatment-emergent Serious Adverse Events leading to temporary interruption of atezolizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-3.5.2.2 Incidence of treatment-emergent Serious Adverse Events leading to temporary interruption of atezolizumab only by

System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)

- Table 14.3.1-3.5.2.3 Incidence of treatment-emergent Serious Adverse Events of CTCAE grade ≥3 leading to temporary interruption of atezolizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-3.5.3.1 Incidence of treatment-emergent Serious Adverse Events leading to temporary interruption of bevacizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-3.5.3.2 Incidence of treatment-emergent Serious Adverse Events leading to temporary interruption of bevacizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-3.5.3.3 Incidence of treatment-emergent Serious Adverse Events of CTCAE grade ≥3 leading to temporary interruption of bevacizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-3.5.4.1 Incidence of treatment-emergent Serious Adverse Events leading to temporary interruption of both atezolizumab and bevacizumab by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-3.5.4.2 Incidence of treatment-emergent Serious Adverse Events leading to temporary interruption of both atezolizumab and bevacizumab by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-3.5.4.3 Incidence of treatment-emergent Serious Adverse Events of CTCAE grade ≥3 leading to temporary interruption of both atezolizumab and bevacizumab by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)

Treatment-emergent adverse events of special interest

- Table 14.3.1-4.1.1 Summary of patients with treatment-emergent Adverse Events of Special Interest (Safety Analysis Population)

Treatment Emergent Adverse Events of Special Interest

- Table 14.3.1-4.1.2.1 Incidence of treatment-emergent Adverse Events of Special Interest by System Organ Class and Preferred Term (Safety Analysis Population)

- Table 14.3.1-4.1.2.2 Incidence of treatment-emergent Adverse Events of Special Interest by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.1.2.3 Incidence of treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-4.1.2.4 Incidence of Potential Drug Induced Liver Injury (DILI) by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.1.2.5 Incidence of suspected transmission of an infectious agent by the study treatment (STIAMP) by System Organ Class and Preferred Term (Safety Analysis Population)

Treatment Emergent Related Adverse Events of Special Interest

- Table 14.3.1-4.1.3.1.1 Incidence of treatment-emergent Adverse Events of Special Interest related to any treatment component by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.1.3.1.2 Incidence of treatment-emergent Adverse Events of Special Interest related to any treatment component by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.1.3.1.3 Incidence of treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 related to any treatment component by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-4.1.3.2.1 Incidence of treatment-emergent Adverse Events of Special Interest related to atezolizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.1.3.2.2 Incidence of treatment-emergent Adverse Events of Special Interest related to atezolizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.1.3.2.3 Incidence of treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 related to atezolizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-4.1.3.3.1 Incidence of treatment-emergent Adverse Events of Special Interest related to bevacizumab only by System Organ Class and Preferred Term (Safety Analysis Population)

- Table 14.3.1-4.1.3.3.2 Incidence of treatment-emergent Adverse Events of Special Interest related to bevacizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.1.3.3.3 Incidence of treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 related to bevacizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-4.1.3.4.1 Incidence of treatment-emergent Adverse Events of Special Interest related to both atezolizumab and bevacizumab by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.1.3.4.2 Incidence of treatment-emergent Adverse Events of Special Interest related to both atezolizumab and bevacizumab by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.1.3.4.3 Incidence of treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 related to both atezolizumab and bevacizumab by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-4.1.3.5 Summary of Atezolizumab/Bevacizumab-related treatment-emergent Adverse Events of Special Interest of any CTCAE grade and CTCAE grade 3/4/5 (Safety Analysis Population)

Treatment Emergent Adverse Events of Special Interest leading to permanent discontinuation

- Table 14.3.1-4.1.4.1.1 Incidence of treatment-emergent Adverse Events of Special Interest leading to permanent discontinuation of any treatment component by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.1.4.1.2 Incidence of treatment-emergent Adverse Events of Special Interest leading to permanent discontinuation of any treatment component by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.1.4.1.3 Incidence of treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 leading to permanent discontinuation of any treatment component by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-4.1.4.2.1 Incidence of treatment-emergent Adverse Events of Special Interest leading to permanent discontinuation of

atezolizumab only by System Organ Class and Preferred Term (Safety Analysis Population)

- Table 14.3.1-4.1.4.2.2 Incidence of treatment-emergent Adverse Events of Special Interest leading to permanent discontinuation of atezolizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.1.4.2.3 Incidence of treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 leading to permanent discontinuation of atezolizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-4.1.4.3.1 Incidence of treatment-emergent Adverse Events of Special Interest leading to permanent discontinuation of bevacizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.1.4.3.2 Incidence of treatment-emergent Adverse Events of Special Interest leading to permanent discontinuation of bevacizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.1.4.3.3 Incidence of treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 leading to permanent discontinuation of bevacizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-4.1.4.4.1 Incidence of treatment-emergent Adverse Events of Special Interest leading to permanent discontinuation of both atezolizumab and bevacizumab by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.1.4.4.2 Incidence of treatment-emergent Adverse Events of Special Interest leading to permanent discontinuation of both atezolizumab and bevacizumab by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.1.4.4.3 Incidence of treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 leading to permanent discontinuation of both atezolizumab and bevacizumab by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)

Treatment Emergent Adverse Events of Special Interest leading to temporary interruption

- Table 14.3.1-4.1.5.1.1 Incidence of treatment-emergent Adverse Events of Special Interest leading to temporary interruption of any treatment component by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.1.5.1.2 Incidence of treatment-emergent Adverse Events of Special Interest leading to temporary interruption of any treatment component by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.1.5.1.3 Incidence of treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 leading to temporary interruption of any treatment component by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-4.1.5.2.1 Incidence of treatment-emergent Adverse Events of Special Interest leading to temporary interruption of atezolizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.1.5.2.2 Incidence of treatment-emergent Adverse Events of Special Interest leading to temporary interruption of atezolizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.1.5.2.3 Incidence of treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 leading to temporary interruption of atezolizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-4.1.5.3.1 Incidence of treatment-emergent Adverse Events of Special Interest leading to temporary interruption of bevacizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.1.5.3.2 Incidence of treatment-emergent Adverse Events of Special Interest leading to temporary interruption of bevacizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.1.5.3.3 Incidence of treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 leading to temporary interruption of bevacizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)
- Table 14.3.1-4.1.5.4.1 Incidence of treatment-emergent Adverse Events of Special Interest leading to temporary interruption of both atezolizumab

and bevacizumab by System Organ Class and Preferred Term (Safety Analysis Population)

- Table 14.3.1-4.1.5.4.2 Incidence of treatment-emergent Adverse Events of Special Interest leading to temporary interruption of both atezolizumab and bevacizumab by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.1.5.4.3 Incidence of treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 leading to temporary interruption of both atezolizumab and bevacizumab by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)

Atezolizumab Treatment-emergent adverse events of special interest

- Table 14.3.1-4.2.1 Summary of patients with Atezolizumab treatment-emergent Adverse Events of Special Interest (Safety Analysis Population)

Atezolizumab Treatment Emergent Adverse Events of Special Interest

- Table 14.3.1-4.2.2.1 Incidence of Atezolizumab treatment-emergent Adverse Events of Special Interest by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.2.2.2 Incidence of Atezolizumab treatment-emergent Adverse Events of Special Interest by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.2.2.3 Incidence of Atezolizumab treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)

Atezolizumab Treatment Emergent Related Adverse Events of Special Interest

- Table 14.3.1-4.2.3.1.1 Incidence of Atezolizumab treatment-emergent Adverse Events of Special Interest related to atezolizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.2.3.1.2 Incidence of Atezolizumab treatment-emergent Adverse Events of Special Interest related to atezolizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.2.3.1.3 Incidence of Atezolizumab treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 related to atezolizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)

Bevacizumab Treatment-emergent adverse events of special interest

- Table 14.3.1-4.3.1 Summary of patients with Bevacizumab treatment-emergent Adverse Events of Special Interest (Safety Analysis Population)

Bevacizumab Treatment Emergent Adverse Events of Special Interest

- Table 14.3.1-4.3.2.1 Incidence of Bevacizumab treatment-emergent Adverse Events of Special Interest by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.3.2.2 Incidence of Bevacizumab treatment-emergent Adverse Events of Special Interest by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.3.2.3 Incidence of Bevacizumab treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)

Bevacizumab Treatment Emergent Related Adverse Events of Special Interest

- Table 14.3.1-4.3.3.3.1 Incidence of Bevacizumab treatment-emergent Adverse Events of Special Interest related to bevacizumab only by System Organ Class and Preferred Term (Safety Analysis Population)
- Table 14.3.1-4.3.3.3.2 Incidence of Bevacizumab treatment-emergent Adverse Events of Special Interest related to bevacizumab only by System Organ Class, Preferred Term and maximum toxicity grade (Safety Analysis Population)
- Table 14.3.1-4.3.3.3.3 Incidence of Bevacizumab treatment-emergent Adverse Events of Special Interest of CTCAE grade ≥3 related to bevacizumab only by System Organ Class, Preferred Term and Toxicity (Safety Analysis Population)

14.3.2 Listings of deaths, other serious and significant adverse events

- Listing 14.3.2-1 Listing of deaths (Safety Analysis Population)
- Listing 14.3.2-2 Listing of treatment-emergent Adverse Events with fatal outcome (Safety Analysis Population)
- Listing 14.3.2-3 Listing of bleeding/haemorrhage events (Safety Analysis Population)
- Listing 14.3.2-4 Listing of non-fatal treatment-emergent Serious Adverse Events (Safety Analysis Population)
- Listing 14.3.2-5.1 Listing of treatment-emergent Adverse Events related to any treatment component (Safety Analysis Population)
- Listing 14.3.2-5.2 Listing of treatment-emergent Adverse Events related to atezolizumab only (Safety Analysis Population)

- Listing 14.3.2-5.3 Listing of treatment-emergent Adverse Events related to bevacizumab only (Safety Analysis Population)
- Listing 14.3.2-5.4 Listing of treatment-emergent Adverse Events related to both atezolizumab and bevacizumab (Safety Analysis Population)
- Listing 14.3.2-6 Listing of treatment-emergent Adverse Events of CTCAE grade ≥3 (Safety Analysis Population)
- Listing 14.3.2-7.1 Listing of treatment-emergent Adverse Events leading to permanent discontinuation of any treatment component (Safety Analysis Population)
- Listing 14.3.2-7.2 Listing of treatment-emergent Adverse Events leading to permanent discontinuation of atezolizumab only (Safety Analysis Population)
- Listing 14.3.2-7.3 Listing of treatment-emergent Adverse Events leading to permanent discontinuation of bevacizumab only (Safety Analysis Population)
- Listing 14.3.2-7.4 Listing of treatment-emergent Adverse Events leading to permanent discontinuation of both atezolizumab and bevacizumab (Safety Analysis Population)
- Listing 14.3.2-8.1 Listing of treatment-emergent Adverse Events leading to temporary interruption of any treatment component (Safety Analysis Population)
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Appendix 2 Analyses for Closed Report

Not applicable.

The primary objective of this study is to assess the safety profile of atezolizumab + bevacizumab in a non-comparative fashion. Thus, as all patients are pre-specified to receive active treatment, the study will have an open-label and non-randomized design.

FINAL STATISTICAL ANALYSIS PLAN APPROVAL

CONFIDENTIAL

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Envelope Summary Events	Status	Timestamps
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Certified Delivered	Security Checked	02-Dec-2024 | 18:49
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Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

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