09 November 2023
EMA/537504/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tecentriq

International non-proprietary name: Atezolizumab

Procedure No. EMEA/H/C/004143/X/0076

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AE	Adverse event
Atezolizumab-IV	Atezolizumab for intravenous administration
Atezolizumab-SC	Atezolizumab for subcutaneous administration
ADR	Adverse drug reaction
AUC	Area under the concentration-time curve
CCOD	Clinical cutoff date
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CPP	Critical process parameter
CQA	Critical quality attributes
C_{trough}	Concentration at the end of a dosing interval
DOR	Duration of response
DP	Drug product
DS	Drug substance
EMA	European Medicines Agency
E-R	Exposure-response
freeze/thaw	F/T
HCCF	Harvested cell culture fluid
HMW	High molecular weight
IE-HPLC	Ion exchange high-performance liquid chromatography
IPC	In-process control
IRR	Infusion related reactions
ISR	Injection site reactions
ITT	Intent-to-treat
IV	Intravenous
LMW	low molecular weight
MAH	Marketing authorisation holder
MCB	Master cell bank
MHM	Roche Diagnostics GmbH, Mannheim, Germany
MAA	Marketing authorisation application
NR-CE-SDS	Non-reduced capillary electrophoresis sodium dodecyl sulfate
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PFS	Progression free survival
PDCO	The Paediatric Committee
PD-L1	IgG1 anti-programmed death-ligand 1
PK	Pharmacokinetic
PLCM	Product Lifecycle management
PS	Performance status
PTMs	Post-translational modifications

PT	Preferred term
PTMs	Post-translational modifications
PZ	Roche Diagnostics GmbH, Penzberg, Germany
QW2	Every 2 weeks
QW3	Every 3 weeks
QW4	Every 4 weeks
RMP	Risk Management Plan
rHuPH20	Recombinant human hyaluronidase
SAE	Serious adverse event
SAWP	Scientific advice working party
SC	Subcutaneous
SCS	Summary of Clinical Safety
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SE-HPLC	Size exclusion-high-performance liquid chromatography
SSF	Genentech South San Francisco, California, USA
SOC	System organ class
TTE	Time-to-event
UFDF	Ultrafiltration/Diafiltration
VF	Virus filtration
WCB	Working cell banks

1. Background information on the procedure

1.1. Submission of the dossier

Roche Registration GmbH submitted on 14 November 2022 extensions of the marketing authorisation.

Extension application to introduce a new pharmaceutical form (solution for injection) associated with a new strength (1875 mg) and new route of administration (subcutaneous use).
The RMP (version 24.0) is updated in accordance.

The MAH applied for the changes to Tecentriq 1875mg solution for injection (subcutaneous use) in all approved indications:

Urothelial carcinoma (UC)

[Tradename] as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic UC:

• *after prior platinum-containing chemotherapy, or*

• *who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥5% (see section 5.1).*

Early-stage non-small cell lung cancer (NSCLC)

[Tradename] as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1 for selection criteria).

Metastatic NSCLC

[Tradename] in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, [Tradename] in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies (see section 5.1).

[Tradename] in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1).

[Tradename] as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1).

[Tradename] as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving Tecentriq (see section 5.1).

Small cell lung cancer (SCLC)

[Tradename] in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) (see section 5.1).

Triple-negative breast cancer (TNBC)

[Tradename] in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥1% and who have not received prior chemotherapy for metastatic disease.

Hepatocellular carcinoma (HCC)

[Tradename] in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy (see section 5.1).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (c) (d) (e) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0384/2021 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH received Scientific advice from the CHMP on the development for the SC formulation from the CHMP on 15 November 2018 (EMEA/H/SA/2522/18/2018/III) and 27 February 2020 (EMEA/H/SA/2522/21/2019/II). The Scientific advice pertained to quality, non-clinical, and clinical aspects.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Aaron Sosa Mejia

The application was received by the EMA on	14 November 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 February 2023

The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	06 March 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 February 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	30 March 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	22 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	25 June 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 February 2023
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the MAH on	20 July 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	11 October 2023
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	25 October 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tecentriq on	9 November 2023

2. Scientific discussion

2.1. Problem statement

Tecentriq (atezolizumab), available as a concentrate for solution (60 mg/mL) for intravenous (IV) infusion, is approved in EU at dosing regimens of 840 mg every 2 weeks (Q2W), 1200 mg every 3 weeks (Q3W), 1680 mg every 4 weeks (Q4W) as single agent and/or in combination for the treatment of urothelial carcinoma (UC), non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), triple-negative breast cancer (TNBC) and hepatocellular carcinoma (HCC). Atezolizumab is infused over a period of 60 minutes for the initial infusion. Subsequent infusions may be delivered in 30 minutes if the previous infusion was tolerated. The usage of IV monoclonal antibodies (MAbs) with the observation time required after infusion has placed a strain on medical centres with respect to chair time and time and resources required to prepare and administer the infusion (De Cock et al, PLOS ONE 2016).

Additionally, the required procedure to establish IV access in a patient is considered invasive. PD-L1 inhibitors are usually given for long periods of time at least in the adjuvant settings.

2.1.1. Disease or condition

The proposed indications for atezolizumab fixed dose for subcutaneous use are the same as those approved for atezolizumab IV in the EU, as monotherapy or in combination with chemotherapy (ies) as follows:

Urothelial carcinoma (UC)

[Tradename] as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic UC:

• after prior platinum-containing chemotherapy, or

• who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥5% (see section 5.1).

Early-stage non-small cell lung cancer (NSCLC)

[Tradename] as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1 for selection criteria).

Metastatic NSCLC

[Tradename] in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, [Tradename] in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies (see section 5.1).

[Tradename] in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1).

[Tradename] as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1).

[Tradename] as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving Tecentriq (see section 5.1).

Small cell lung cancer (SCLC)

[Tradename] in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) (see section 5.1).

Triple-negative breast cancer (TNBC)

[Tradename] in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥1% and who have not received prior chemotherapy for metastatic disease.

Hepatocellular carcinoma (HCC)

[Tradename] in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy (see section 5.1).

2.2. About the product

Atezolizumab is a humanised immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells.

Atezolizumab SC formulation contains the recombinant human hyaluronidase (rHuPH20) at a concentration of 2,000 U/mL, an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously.

Mode of action: Atezolizumab targets human programmed death-ligand 1 (PD-L1) on tumour infiltrating immune cells (ICs) and tumour cells (TCs) and inhibits its interaction with its receptors programmed death1 (PD-1) and B7.1, both of which can provide inhibitory signals to T cells.

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies.

Claimed indications:

Atezolizumab SC at 1875 mg every 3 weeks (Q3W) will be indicated in all current dosing regimens of atezolizumab IV: 840 mg every 2 weeks (Q2W), 1200 mg every 3 weeks (Q3W), 1680 mg every 4 weeks (Q4W) as single agent and/or in combination with chemotherapy (ies) for the treatment of urothelial carcinoma (UC), non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), triple-negative breast cancer (TNBC) and hepatocellular carcinoma (HCC).

Atezolizumab SC formulation is administered subcutaneously, as a fixed non-weight-based dose, which is similar to the approved atezolizumab IV formulation. Atezolizumab SC was developed to offer patients a less invasive and faster administration of atezolizumab compared to atezolizumab IV infusion

2.3. Type of Application and aspects on development

The development programme/compliance with guidance/scientific advice

The underlying principle of the clinical development program (CDP) of the atezolizumab SC is that the atezolizumab active ingredient in the SC administration is identical to the active ingredient in the IV formulation. The CDP is based on the scientific consideration that atezolizumab serum trough concentrations (C_{trough}) after SC administration are at least as high as those C_{trough} after IV infusion in conjunction with a model-predicted area under the concentration-time curve (AUC), resulting in a comparable degree of target-site saturation and thus comparable degree of efficacy, regardless of the route of administration.

Prior to start of the randomised study IMscin001, the MAH sought scientific advice from the CHMP in two occasions, with two follow-up scientific advices in 2018 and 2020, to support the registration of atezolizumab SC formulation.

Overall, it is considered that the MAH has followed relevant CHMP guidance. Minor deviations found in the assessment of study data will be addressed in specific sections.

The Paediatric Committee (PDCO) recommended granting a product specific waiver for all subsets of the paediatric population for the treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, hematopoietic and lymphoid tissue neoplasms and melanoma).

General comments on compliance with GMP, GLP, GCP

The references nonclinical repeat dose study was performed in 2009, and was deemed to be compliant with GLP during the initial MAA. No new NC studies were performed in support of the of the current line extension to include an SC formulation of atezolizumab, including rHuPh20. The pivotal safety and toxicity studies were all submitted in support of the MAA for IV administration.

No GMP issues have been identified during assessment of the atezolizumab dossier, which call for a pre-approval inspection.

The MAH claims that the clinical studies in the application were conducted per Good Clinical Practices (GCP). No further request for GCP inspection is considered necessary at the moment.

2.4. Quality aspects

2.4.1. Introduction

This line extension application includes the registration of a new strength (1875 mg), new pharmaceutical form (solution for injection) and new route of administration (subcutaneous (SC) use).

Atezolizumab finished product (also referred to as FP) for subcutaneous administration (atezolizumab-SC) is a sterile, colourless-to-slightly yellow solution without preservatives. It is supplied in a 20 mL single-dose vials which contains 1875 mg/15 mL atezolizumab. Atezolizumab is formulated with recombinant hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-formulated substances when administered subcutaneously. rHuPH20 is not a novel excipient. The other excipients include L-histidine, acetic acid, sucrose, polysorbate 20, L-methionine and water for injections.

2.4.2. Active Substance

2.4.2.1. General information

Atezolizumab is a humanised monoclonal antibody based on a human IgG1 framework expressed in Chinese Hamster Ovary (CHO) cells and consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each). The structure of atezolizumab-SC active substance (also referred to as AS) is the same as that for the approved commercial atezolizumab for intravenous administration (atezolizumab-IV) AS.

2.4.2.2. Manufacture, characterisation and process controls

Description of the Manufacturing process and process controls

The atezolizumab-SC AS is manufactured at Roche Diagnostics GmbH, Penzberg, Germany (PZ).

Cell culture and harvest

Atezolizumab is produced in a fed batch process. The source of cells is the Working Cell Bank (WCB), which is derived from the Master Cell Bank (MCB). The cell culture process involves three stages: WCB thaw and seed train, inoculum train, and production culture. Upon completion of the production culture, atezolizumab in the cell culture fluid is physically separated from the cells by harvesting via centrifugation and filtration.

Purification

Atezolizumab in the harvested cell culture fluid is initially purified by affinity chromatography, the recovered low pH pool is held to ensure potential viruses are inactivated, the pH adjusted affinity pool is further purified over a cation and anion chromatography step, and the pH adjusted anion exchange pool is filtered over a virus removal filter. The final steps in the AS purification process (concentration of the product, conditioning and buffer exchange) ensures a AS concentration of 125 mg/mL atezolizumab in L-histidine acetate, sucrose, L-methionine, polysorbate 20, pH 5.8. The conditioned UF/DF pool is filtered into a 300 L freeze/thaw (F/T) vessel to produce the atezolizumab-SC AS, frozen, and stored at ≤ −20 °C.

Control of critical steps

To ensure the quality of the active substance, in-process controls (IPCs) have been established. IPC tests and limits apply to the cell culture and harvest process steps and the purification process step.

Control of materials

Atezolizumab is produced using a stably transfected CHO cell line. One of the clones resulting from this transfection was selected as the host cell for production cell-line construction. A two-tier cell banking system of master cell bank and working cell bank was developed and characterised in accordance with ICH guidelines.

Process validation

The atezolizumab-IV process has been previously validated and used for commercial supply since 2017. Thus, many of the validation studies performed for the atezolizumab-IV process are considered applicable to atezolizumab-SC.

Process characterisation and validation (PC/PV) studies were designed to demonstrate manufacturing process consistency for relevant product quality attributes for process parameters. These studies include a combination of qualified scale-down models and equipment and site-specific validation studies conducted at manufacturing scales.

The results from characterisation studies are used to identify critical process parameters (CPPs) and support acceptable parameter ranges for commercial production. These studies were designed based on process understanding developed during process development, platform knowledge, and scientific and engineering principles.

Manufacturing process development

Different versions of active substance manufacturing processes were used during development of atezolizumab-SC. The manufacturing process is based on the Applicant’s CHO antibody manufacturing platform.

The process changes occurring during development have been assessed for impact to product quality, and the atezolizumab manufactured at the commercial manufacturing site has been demonstrated to be comparable to the material used for clinical trials.

Characterisation

The extended characterisation data generated for atezolizumab-IV (including the reference standard) were leveraged for atezolizumab-SC product characterisation.

2.4.2.3. Specification

Specification

The release specifications for atezolizumab-SC AS have been suitably justified and are supported by consistent data from multiple batches. The specifications contain tests for pharmacopoeial methods as well as specific methods to ensure sufficient safety and quality with respect to identity, purity, potency and other general tests.

Analytical procedures

A description of the analytical procedures used for the testing of AS have been provided and summarised. **Reference material**

Atezolizumab-SC AS utilises the same reference standard as atezolizumab-IV AS

A two-tiered approach was established for the commercial Reference Standard whereby the primary Reference Standard will be used to qualify future Reference Standards. The secondary Reference Standard is used as the working Reference Standard for testing of the active substance and finished product in all assays requiring a Reference Standard. Qualification of the commercial Reference Standards was conducted by release testing and extensive characterisation.

Batch analysis

Batch analysis data were provided.**Container closure system**

2.4.2.4. The container closure system is already used for other approved biologics.Stability

The shelf life claimed for the active substance is 36 months at storage condition ≤ -20°C based on stability data obtained from batches manufactured with clinical and commercial manufacturing processes.

Batches obtained with the clinical manufacturing process are comparable and considered representative of the commercial process.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Atezolizumab-SC finished product is provided as a sterile, colourless-to-slightly yellow solution for subcutaneous injection, with no preservatives. Each 20 mL single-dose vial contains 1875 mg/15 mL of atezolizumab at target pH 5.8. The finished product is consists of 125 mg/mL atezolizumab formulated with recombinant hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-formulated substances when administered subcutaneously. The other excipients include L-histidine, acetic acid, sucrose, polysorbate 20, L-methionine and water for injections. . There are no novel excipients. The formulation does not contain any antimicrobial-preservative or bacteriostatic agents.

The container closure system consists of a Type I glass vial with a rubber stopper and crimped with an aluminium seal fitted with a plastic flip-off cap.

Pharmaceutical Development

Overall, the pharmaceutical development of Tecentriq SC finished product is described in sufficient details and found comprehensive.

In the atezolizumab-SC finished product, the atezolizumab active substance is formulated at a concentration of 125 mg/mL and is co-formulated with rHuPH20 as an aqueous solution. rHuPH20 facilitates the subcutaneous injection of larger volumes by acting as a permeation enhancer. A comparison of the commercial atezolizumab for intravenous administration (atezolizumab IV) and atezolizumab SC formulations was performed. The administration time for atezolizumab-SC finished product solution has been reduced to less than 10 minutes compared with the administration time of 30-60 minutes for the atezolizumab IV finished product solution.

A comparability exercise was performed and showed that atezolizumab SC batches manufactured with the clinical manufacturing process and the commercial manufacturing process are comparable.

Manufacturing process development

During development the finished product manufacturing was transferred to a different site. The finished product manufacturing process at both sites remained the same with some facility fit adaptations.

2.4.3.2. Manufacture of the product and process controls

Description of the process

Manufacture of atezolizumab-SC finished product is conducted at Roche Diagnostics GmbH, Sandhofer Strasse 116, 68305 Mannheim, Germany.

Atezolizumab-SC finished product is manufactured as a liquid dosage form in vials at the dose strength of 1875 mg/vial with nominal fill volume of 15 mL.

The commercial manufacturing process consists of thawing active substance, addition of rHuPH20 enzyme, bioburden reduction and sterile filtrations, aseptic filling into glass vials, stoppering, capping and crimping, and visual inspection, including vial integrity testing.

In-process controls composed of action limits and acceptance criteria for manufacture of the finished product are in place.

Process validation

The finished product process validation was performed on batches manufactured with the commercial process at the commercial site.

2.4.3.3. Product specification

Specifications

The specifications for the atezolizumab-SC FP include control of identity, purity and purities, potency, activity of rHuPH20 and other general tests.

Reference material

The Reference Standard used for finished product release and stability testing is the same as that used for the active substance.

Batch analysis

All atezolizumab-SC FP batches complied with all release specification that were in place at time of testing and also comply with the current proposed commercial specifications.

Container closure system

The container closure system for FP is adequately described. All product-contacting materials comply with relevant pharmacopoeial requirements. The container closure integrity studies demonstrate the compatibility of the FP solution with the primary container closure system and the ability of the container closure system to protect FP solution from microbial contamination.

2.4.3.4. Stability of the product

A shelf-life of 24 months is claimed for atezolizumab-SC FP at the recommended storage condition of 2°C - 8°C when stored in the commercial container closure system, which is stored in the marketing pack to protected it from light. The shelf-life is based on stability data from batches considered representative of the finished product.

The proposed shelf life of 24 months for the FP when stored at 2°C - 8°C protected from light is accepted.

Once transferred from the vial into the syringe (provided separately), Tecentriq SC formulation is physically and chemically stable for up to 30 days at 2°C to 8°C and for up to 8 hours at ≤ 30°C in diffuse daylight and from the time of preparation.

From a microbiological point of view, the solution should be used immediately once transferred from the vial to the syringe since the medicine does not contain any antimicrobial-preservative or bacteriostatic agents. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 °C to 8 °C, unless preparation has taken place under controlled and validated aseptic conditions.

2.4.3.5. Adventitious agents

There are no changes to the adventitious agent safety evaluation. This section remains as approved in the MAA for atezolizumab-IV commercial product.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of the dossier presented in support of the line extension application for atezolizumab-SC, is considered adequate. From a quality point of view, the benefit/risk ratio is not affected.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Tecentriq SC is considered acceptable when used in accordance with the conditions as defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, this line extension application for Tecentriq to add a new strength (1875 mg), new pharmaceutical form (solution for injection) and new route of administration (subcutaneous (SC) use) is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

The in vitro and in vivo pharmacology, pharmacokinetics, and toxicology of TECENTRIQ (atezolizumab) have been thoroughly investigated in nonclinical studies following intravenous (IV) administration (refer to European Medicines Agency Marketing Authorization Application Procedure No. EMEA/H/C/004143/0000); study reports cited and results discussed in this section were submitted in Module 4 of that application.

The nonclinical safety of subcutaneous (SC) and IV administration of recombinant human hyaluronidase enzyme (rHuPH20) has been extensively characterized in mice and cynomolgus monkeys with no relevant toxicological findings in the general toxicity studies.

The toxicology program was designed to support IV or SC administration of atezolizumab to patients. The toxicity and toxicokinetics of atezolizumab following SC administration were well characterized in a Good Laboratory Practice (GLP) repeat-dose study in cynomolgus monkey (Study 08-1148). Atezolizumab was given via either IV (5 mg/kg, 15 mg/kg, or 50 mg/kg) or SC administration (15 mg/kg or 50 mg/kg) weekly for 8 weeks (9 total doses). The toxicity was assessed for the reversibility or persistence of any effects after a 12-week treatment-free recovery period.

Scientific advice regarding the adequacy of the nonclinical studies performed to support SC formulation was given in November 2018, regarding the adequacy of the nonclinical studies performed to support the extension. It was concluded at that point in time, that no further animal studies were required.

Any increased exposure of atezolizumab due to hyaluronidase is covered by repeat-dose toxicity studies using the intravenous route of administration.

The differences in formulations between the non-clinical SC study and the Phase 1 and III clinical studies are not considered detrimental for the validity of the SC study in monkeys performed without hyaluronidase.

The non-clinical and clinical safety of hyaluronidase in subcutaneous formulations of monoclonal antibodies (e.g. Herceptin) is demonstrated in other products. Hence, it is accepted that the safety of the co-administration of atezolizumab and hyaluronidase was confirmed in the clinical setting.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Expression of programmed death-ligand 1 (PD-L1) is prevalent in many human tumours (Dong et al. 2002), and its overexpression is associated with poor prognosis for patients with any of several epithelial cancers (Thompson et al. 2006; Hamanishi et al. 2007; Okazaki and Honjo 2007; Hino et al. 2010). Elevated expression of PD-L1 on tumour cells has been reported to impede anti-tumour immunity, resulting in immune evasion by tumour cells. PD-L1 is one of two ligands that regulate the activity of programmed cell death1 (PD-1), an inhibitory receptor that modulates T-cell signalling and whose expression is induced on T cells following activation and sustained in sites of chronic stimulation such as the tumour microenvironment (Blank and Mackensen 2007). Ligation of PD-1 impairs the capacity of chronically activated T cells to proliferate, produce cytokines, or effectively kill target cells in response to their cognate antigen. Atezolizumab (MPDL3280A) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that targets PD-L1 and inhibits its interaction with PD-1.

Atezolizumab was engineered with an amino acid substitution at position 298, resulting in a nonglycosylated antibody, to impair Fcγ receptor binding and to prevent Fc-mediated depletion of cells expressing PD-L1.

In support of the MAA for IV administration, non-clinical in vitro data were submitted to describe the pharmacological mode of action of atezolizumab. The studies provide information on binding affinity of atezolizumab to its target PD-L1 and on the inhibition of the PD-L1/PD-1 interaction. Atezolizumab did not bind to recombinant PD-L2- Fc, while clear binding was detected with recombinant PD-L1-Fc. The lack of Fc functionality due to removal of the N-glycosylation site was demonstrated, except for the effect on CDC. The in vivo effect of blocking PD-L1 was adequately evaluated in murine syngeneic tumour models using chimeric anti-PD-L1 mAbs. These studies demonstrate that treatment with anti-PD-L1 mediates an effective anti-tumour response and provide sufficient proof-of-concept.

2.5.2.2. Secondary pharmacodynamic studies

No specific secondary pharmacodynamics studies have been conducted. In vitro tissue cross-reactivity studies were conducted with atezolizumab using a full panel of human and cynomolgus monkey tissues (Study 08-1174). In human tissues, biotin-atezolizumab-specific staining was detected in the placenta, lymph node, tonsil, and thymus. Frequent, moderate, apical cytoplasmic and membranous staining was observed in syncytiotrophoblasts of the placenta. Very rare, minimal to mild, cytoplasmic staining was observed in sinusoidal cells of lymph nodes and tonsil. Rare to frequent, mild to moderate, cytoplasmic staining was observed in thymic cortical and medullary cells. In cynomolgus monkey tissues, biotin-atezolizumab-specific staining was detected only in the lymph node. Rare to frequent, minimal to moderate, cytoplasmic staining was observed in sinusoidal cells of lymph nodes.

2.5.2.3. Safety pharmacology programme

As stated in the ICH S6(R1) guideline, dedicated safety pharmacology studies are not required for biotechnology-derived products (ICH 2011). Accordingly, no dedicated safety pharmacology studies evaluating cardiovascular, respiratory, neurologic, or ophthalmic toxicity were conducted. Although a dedicated safety pharmacology study of atezolizumab was not performed, central nervous system, cardiovascular (telemetry and/or surface leads), and respiratory safety pharmacology parameters were evaluated as part of the 8-week Good Laboratory Practice (GLP) cynomolgus monkey toxicology study (08-1148), which included subcutaneous (SC) dosing. No atezolizumab-related changes in central nervous system, cardiovascular, or respiratory safety pharmacology parameters were observed.

2.5.2.4. Pharmacodynamic drug interactions

No stand-alone pharmacodynamic drug interactions studies have been performed. Pharmacodynamic drug-drug interactions (PD DDIs) between a therapeutic monoclonal antibody (mAb) and conventional small-molecule drugs or other protein therapeutics may happen through two possible mechanisms. First, co-administrated immunosuppressive therapeutics may lead to lower incidence of immunogenicity and restore the exposure of atezolizumab at low concentration range. Preclinical assessment is not relevant since immunogenicity cannot be adequately predicted across species. Potential exposure modifications have been closely monitored in clinical setting. The second mechanism of PD DDI is the possible target modulation by other therapeutics. The clinically therapeutic dose of atezolizumab is within the linear range where the target-mediated disposition is negligible, and the impact of target modulation is minimal. Therefore, no pharmacodynamic drug interactions studies have been performed.

2.5.3. Pharmacokinetics

The nonclinical characterization of the pharmacokinetics of atezolizumab is described in previously approved dossiers (refer to Procedure No. EMEA/H/C/004143).

No dedicated pharmacokinetic studies with atezolizumab SC have been conducted, however, Toxicokinetic evaluation was included in one study (08-1148) submitted in the original MAA for IV atezolizumab, also had two dose groups receiving atezolizumab subcutaneously. See repeat dose toxicity section (2.5.4.2 below).

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No standalone single dose toxicity studies were performed with the SC formulation of atezolizumab.

As recommended in ICH guidance M3, no dedicated, single-dose toxicity studies were performed [ICH M3(R2) 2013]. However, a high dose was investigated with weekly IV and SC dose administration in the 8-week GLP repeat-dose toxicity study (08-1148), and without morbidity or mortality after the first dose administration.

2.5.4.2. Repeat dose toxicity

No new studies were performed. In support of the initial MAA for the IV route of administration, one study also included two dose groups administered atezolizumab (15 or 50 mg/kg) subcutaneously. No absorption enhancing excipient was included in this study.

In support of the initial MAA, a GLP repeat-dose study (08-1148) was conducted to evaluate the toxicity and toxicokinetics of atezolizumab when administered by IV or SC injection to cynomolgus monkeys weekly for 8 weeks (9 total doses), and to assess the reversibility, persistence, or delayed occurrence of any effects after a 12-week, treatment-free recovery period.

Seventy-two experimentally naïve cynomolgus monkeys (36 males and 36 females) were divided into 8 dose groups (n = 3-5/sex/group) and given either atezolizumab Vehicle or atezolizumab once weekly for 8 weeks (9 total doses). Animals in Group 1 received an IV and SC bolus dose of atezolizumab Vehicle; animals in Groups 2, 3, and 4 received an IV dose of atezolizumab (5, 15, or 50 mg/kg, respectively); Groups 5 and 6 received an SC dose of atezolizumab (15 or 50 mg/kg, respectively); and Groups 7 and 8 had telemetry units implanted before Day 1 and received IV doses of atezolizumab at 0 and 50 mg/kg, respectively. Animals (2 or 3/sex) were necropsied on Day 60 (terminal necropsy) or on Day 141 (recovery necropsy), with the exception of animals in the 2 telemetry groups that were released to the Testing Facility telemetry colony after Day 141.

Overall, the serum concentration-time profiles of all dose groups exhibited apparent biphasic disposition in which a rapid initial distribution phase was followed by a slower elimination phase. Average area under the serum concentration-time curve from Time 0 to Study Day 8 (Toxicokinetic [TK] Day 7) (AUC_{0-7}), AUC_{0-56}, and AUC_{0-140} values for all dose groups are summarized in Table 1. Mean AUC_{0-7} values appeared dose proportional in all dose groups. No differences by sex in the TK parameters were observed. Bioavailability of atezolizumab following SC administration of 15 or 50 mg/kg was estimated to be 54.3% and 51.8%, respectively (see Table 1, under toxicokinetics).

Weekly IV and SC administration of atezolizumab was well tolerated at dose levels up to 50 mg/kg for 8 weeks. All animals survived to scheduled necropsy or disposition. Atezolizumab administration had

no effects on clinical observations, body weight, food consumption, respiratory rate, heart rate, body temperature, blood pressure, electrocardiograms, pulse oximetry, physical, neurological, ophthalmologic, or cardiovascular examinations, clinical pathology (haematology, serum chemistry, coagulation, or urinalysis), immunologic endpoints (immunophenotyping via flow cytometry, serum cytokines, anti-nuclear antibodies, or anti-double-stranded [ds] DNA antibodies), organ weights, or macroscopic pathology.

At terminal necropsy, microscopic lesions that were considered related to atezolizumab administration included minimal to mild arteritis/periarteritis in various tissues in 1 of 6 animals in the 50 mg/kg IV and 15 mg/kg SC dose groups, and in 2 of 6 animals in the 50 mg/kg SC dose group. Atezolizumab-related arteritis/periarteritis were noted within the interstitium of parenchymal organs (heart, kidney, liver, pancreas, and epididymis), or within the submucosa or muscularis of tubular organs such as the gastrointestinal (GI) and female reproductive tracts at the terminal necropsy. These findings were not present at the recovery necropsy (Day 141), indicating either resolution during the recovery period or lack of occurrence in the recovery cohorts.

Although arteritis/periarteritis has been reported to occur spontaneously in cynomolgus monkeys to the same extent as in the present study (generally subclinical in severity, similar in tissue distribution) (Beach et al. 1974; Chamanza et al. 2006), this finding was considered atezolizumab related as it occurred only in test article-treated groups; the incidence appeared to be dose related and exceeded the test facility's historical control incidence, and is consistent with the primary pharmacology of programmed death-ligand 1 (PD-L1) inhibition and the deregulation of peripheral tolerance.

Local tolerance was assessed by macroscopic and microscopic examination of the injection sites as part of the 8-week repeat-dose cynomolgus monkey toxicology study. At terminal necropsy, minimal, focal to multifocal, and often perivascular mononuclear cell infiltrates were noted in the SC tissue at the injection sites for 3 of 6 and 6 of 6 animals in the 15 and 50 mg/kg atezolizumab SC dose groups, respectively; these findings were also considered related to atezolizumab administration. This injection-site change was not present at recovery necropsy, suggesting reversibility. The minimal injection-site findings are consistent with SC administration of heterologous protein and resolved during the recovery period; therefore, they were not considered adverse.

Taken together, these data demonstrate that the nonclinical safety profile of atezolizumab is similar between IV and SC administration.

2.5.4.3. Genotoxicity and Carcinogenicity

No dedicated genotoxicity nor carcinogenicity studies has been performed with atezolizumab. This is acceptable based on the nature of the pharmaceutical being a monoclonal antibody.

2.5.4.4. Reproductive and developmental toxicity

Reproductive toxicity studies (developmental or fertility) have not been conducted and are not planned, as atezolizumab is expected to have an adverse effect on pregnancy. Current literature suggests a risk to the human fetus, including embryo lethality, and a warning of this risk would be warranted on the atezolizumab label upon registration regardless of the outcome of any additional nonclinical studies.

The PD-L1/PD-1 signaling pathway is well established as essential in maternal/fetal tolerance and embryo-fetal survival during gestation. Inhibition of the PD-L1/PD-1 pathway by administration of an anti-PD-L1 mAb increased fetal rejection rates in an allogeneic pregnancy model, and PD-L1 deficient females exhibited a decrease in allogeneic fetal survival when compared with heterozygotes and wild-

type littermate controls (Guleria et al. 2005; Habicht et al. 2007; D'Addio et al. 2011). Fetal rejection was determined to be T-cell- but not B-cell-dependent. An increased expansion/frequency of IFN-λ producing lymphocytes responding to paternal alloantigens was detected in peripheral lymphocytes, as well as the fetomaternal interface in pregnant PD-L1-deficient females and in pregnant wild-type mice following anti-PD-L1 administration. Fetal rejection did not occur in syngeneic pregnancy models, consistent with the critical role of the PD-L1/PD-1 pathway in maintaining maternal tolerance to paternally derived allogeneic antigens.

In the human placenta, PD-L1 is expressed by villous syncytiotrophoblasts and cytotrophoblasts, the fetal cells that are in close contact with the maternal blood and tissue (Petroff et al. 2003; Petroff et al. 2005; Holets et al. 2006). PD-L1 expression is low in the first trimester but rises around the onset of the second trimester, coinciding with an increase in maternal blood flow to the placenta. Since the human fetus expresses several paternally derived alloantigens and is in close proximity to maternal leukocytes, atezolizumab administration is expected to inhibit maternal/fetal tolerance and negatively impact embryo-fetal survival. The weight of evidence suggests there is a risk to the human fetus, including embryo lethality. Based on the evidence provided above, Committee for Medicinal Products for Human Use (CHMP) agreed that additional embryofetal development studies are unlikely to provide additional safety insights and are not warranted (CHMP Scientific Advice EMA/CHMP/SAWP/214558/ 2013).

In the SmPC section 5.3. a paragraph on reproductive toxicity regarding rHuPh20 has been included. The paragraph is in line with the SmPC for Herceptin SC, which is co-administered with hyaluronidase (rHuPh20) and is acceptable.

2.5.4.5. Toxicokinetic data

Table 1: Non-compartmental PK parameter Estimates (Mean +_ SD) following 9 weekly doses of Atezolizumab to Cynomolgus Monkeys (Study 08-1148)

	Dose (mg/kg)				
	Intravenous Route			Subcutaneous Route	
Parameter	Group 2 (5 mg/kg)	Group 3 (15 mg/kg)	Group 4 (50 mg/kg)	Group 5 (15 mg/kg)	Group 6 (50 mg/kg)
AUC_{0-7} [a] (day • µg/mL)	486 ± 68.9	1860 ± 296	6990 ± 904	1010 ± 275	3620 ± 517
AUC_{0-56} [a] (day • µg/mL)	4870 ± 1630	28700 ± 8890	104000 ± 22200	11700 ± 10100	61400 ± 21700
AUC_{0-140} [b] (day • µg/mL)	5630 ± 3590	43800 ± 10300	170000 ± 37800	13400 ± 22900	115000 ± 21200
AUC_{last} [b] (day • µg/mL)	5220 ± 2360	35100 ± 13400	133000 ± 44300	14400 ± 15000	82100 ± 37300
AUC_{0-7}/Dose (day • µg/mL/mg/kg)	97.1	124	140	67.4	72.4
AUC_{0-56}/Dose (day • µg/mL/mg/kg)	957	1910	2080	781	1230
AUC_{0-140}/Dose (day • µg/mL/mg/kg)	1130	2920	3400	893	2300
AUC_{last}/Dose (day • µg/mL/mg/kg)	1040	2340	2660	958	1640
C_{max} [a] (µg/mL)	187 ± 44.0	959 ± 158	3310 ± 686	363 ± 230	1640 ± 486
t_{max} [a] (day)	NA	NA	NA	23.4 ± 20.8	47.6 ± 17.7
F (%)	NA	NA	NA	54.3	51.8

AUC_{0-7} = area under the serum concentration–time curve from Time 0 to Study Day 8 (TK Day 7); AUC_{0-56} = area under the serum concentration–time curve from Time 0 to time of the last measurable concentration just before terminal necropsy on Study Day 57 (TK Day 56); AUC_{0-140} = area under the serum concentration–time curve from Time 0 to time of the last measurable concentration just before terminal necropsy on Study Day 141 (TK Day 140); AUC/Dose = area under the serum concentration–time curve divided by the respective dose level; AUC_{last} = area under the serum concentration–time curve from Time 0 to the last measurable concentration; C_{max} = maximum observed concentration; F = bioavailability (calculated based on rounded table values); NA = not applicable; PK = pharmacokinetic; TK = toxicokinetic; t_{max} = time (days) to maximum observed concentration.

[a] n = 10.

[b] n = 4.

The repeat dose study had two SC administration dose groups, in which the dose level administered was comparable to the mid and high dose iv groups. The bioavailability following SC administration of atezolizumab at a dose of 15 or 50 mg/kg was 54.3 and 51.8 respectively. No nonclinical studies have been performed with atezolizumab and the absorption enhancer rHuPh20 – hence no nonclinical

knowledge is available regarding the effect and how much the bioavailability of atezolizumab is increased in this particular combination. However, this is shown in clinical studies to be to approximately 70%, although variable.

2.5.4.6. Local tolerance

In general, it is accepted that no additional studies are performed in support of atezolizumab SC formulation. Local tolerance endpoints were included in the study where atezolizumab was administered SC repeatedly for 8 weeks duration. Minimal, focal to multifocal, and often perivascular mononuclear cell infiltrates were noted in the SC tissue at the injection sites for 3 of 6 and 6 of 6 animals in the 15 and 50 mg/kg atezolizumab SC dose groups – but reversibility was observed in the recovery period.

The non-clinical and clinical safety of hyaluronidase in subcutaneous formulations of monoclonal antibodies (e.g. Herceptin) including Local Tolerance is demonstrated in other products. Hence, it is accepted that the safety of the co-administration of atezolizumab and hyaluronidase was confirmed in the clinical setting.

2.5.4.7. Other toxicity studies

No additional toxicity studies were performed.

2.5.5. Ecotoxicity/environmental risk assessment

Atezolizumab, the antineoplastic pharmaceutical active ingredient in Tecentriq, is an IgG1 monoclonal antibody. As an unaltered protein, being extensively degraded in the patient's body by regular proteolytic mechanisms before excretion, Atezolizumab is unlikely to result in a significant environmental exposure.

No specific ERA studies are required, in line with the current guideline.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, atezolizumab is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

The nonclinical safety of subcutaneous (SC) and IV administration of recombinant human hyaluronidase enzyme (rHuPH20) has been extensively characterized in mice and cynomolgus monkeys with no relevant toxicological findings in the general toxicity studies.

The toxicology program was designed to support IV or SC administration of atezolizumab to patients. The toxicity and toxicokinetics of atezolizumab following SC administration were well characterized in a Good Laboratory Practice (GLP) repeat-dose study in cynomolgus monkey (Study 08-1148). Atezolizumab was given via either IV (5 mg/kg, 15 mg/kg, or 50 mg/kg) or SC administration (15 mg/kg or 50 mg/kg) weekly for 8 weeks (9 total doses). The toxicity was assessed for the reversibility or persistence of any effects after a 12-week treatment-free recovery period.

Scientific advice regarding the adequacy of the nonclinical studies performed to support SC formulation was given in November 2018, regarding the adequacy of the nonclinical studies performed to support the extension. It was concluded at that point in time, that no further animal studies were required.

Any increased exposure of atezolizumab due to hyaluronidase is covered by repeat-dose toxicity studies using the intravenous route of administration.

The differences in formulations between the non-clinical SC study and the Phase 1 and III clinical studies are not considered detrimental for the validity of the SC study in monkeys.

The non-clinical and clinical safety of hyaluronidase in subcutaneous formulations of monoclonal antibodies (e.g. Herceptin) is demonstrated in other products. Hence, it is accepted that the safety of the co-administration of atezolizumab and hyaluronidase was confirmed in the clinical setting.

2.5.7. Conclusion on the non-clinical aspects

No new non-clinical studies were performed in support of this line extension to include SC administration of atezolizumab. The in vitro and in vivo pharmacology, pharmacokinetics, and toxicology of TECENTRIQ (atezolizumab) have been thoroughly investigated in nonclinical studies following intravenous (IV) administration

The toxicity and toxicokinetics of atezolizumab following SC administration were well characterized in a Good Laboratory Practice (GLP) repeat-dose study in cynomolgus monkey (Study 08-1148). These data demonstrate that the nonclinical safety profile of atezolizumab is similar between IV and SC administration. It is acceptable, that the safety of hyaluronidase, which is a consolidated excipient in SC formulations of other approved monoclonal antibodies, is confirmed in the clinical studies in combination with atezolizumab.

The application is approvable, from a nonclinical perspective.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

2.6.2. Clinical pharmacology

The pharmacokinetic (PK) and anti-drug antibodies (ADA) data to support atezolizumab pharmacokinetics and immunogenicity for the atezolizumab program across the clinical trials using the intravenous (IV) formulation has been described and assessed previously (EMEA/H/C/004143). This overview will thus focus on the differences and/or new information regarding the subcutaneous formulation. The intended treatment is 1875 mg Q3W SC in the thigh.

A 2-part PK bridging study (Study BP40657, hereinafter IMscin001) was conducted to support the approval of atezolizumab subcutaneous (SC) as shown in **Table 2**.

Table 2: Overview of clinical studies providing PK data for atezolizumab SC

Study Protocol No.	Study Title	PK-Evaluable population(s)	Key Objectives
Part 1 BP40657 (IMscin001)	A two-part, open-label, multicenter Phase Ib/III randomized study to investigate the pharmacokinetics, efficacy, safety and immunogenicity of atezolizumab SC compared with atezolizumab IV in patients with previously treated locally advanced or metastatic NSCLC who are CIT-naive and for whom prior platinum therapy has failed.	• PK-evaluable: All patients who had at least one post-baseline PK sample.	**Dose-finding:** • Identify the dose of atezolizumab SC that yields drug exposure that is comparable to that of atezolizumab IV
Part 2 BP40657 (IMscin001)		• Per protocol PK evaluable: All patients randomized to the atezolizumab SC and atezolizumab IV treatment arms who did not have protocol deviations[a] that could affect Cycle 1 observed C_{trough} results • PK-evaluable	**PK non-inferiority assessment:** • Demonstrate the non-inferiority of observed drug exposure following treatment with atezolizumab SC 1875 mg Q3W compared with drug exposure[b] following treatment with atezolizumab IV 1200 mg Q3W

CIT= cancer immunotherapy; C_{trough} = trough concentration; IV=intravenous; NSCLC= non-small cell lung cancer; PK=pharmacokinetics; SC=subcutaneous; Q3W =every 3 weeks.

[a] Reasons for exclusion from the Per Protocol PK-evaluable may include, but may not be limited to:
- Lack of the Cycle 1 C_{trough} (predose Cycle 2) PK sample
- A C_{trough} sample collected outside the pre-specified window (Day 21 ± 2 days)
- Administration of a dose amount that deviates from the planned dose by >20% at Cycle 1
- Use of an injection site other than the thigh at Cycle 1
- Duplicate times of collection for the Cycle 1 C_{trough} sample

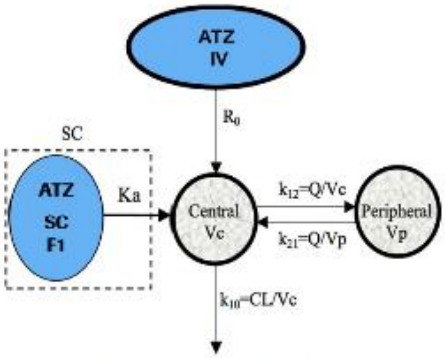
[b] Primary endpoints tested for non-inferiority are observed serum C_{trough} at Cycle 1 (predose Cycle 2) and model-predicted area under the concentration–time curve (AUC) from 0 to 21 days ($AUC_{0-21\,d}$) at Cycle 1

2.6.2.1. Pharmacokinetics

The atezolizumab assays used for quantification and for ADA testing were the same as used in previous procedures. A bridging immunoassay with electrochemiluminescence detection using the Meso Scale Discovery platform was developed and validated to quantify rHuPH20 concentrations in human plasma. Validated bioanalytical methods for detection, confirmation, and titration of anti-rHuPH20 antibodies in plasma were used to assess immunogenicity of rHuPH20.

A population PK model was previously developed for atezolizumab using Phase I PK data (subsequently called the "IV popPK model") from two clinical studies: Study PCD4989g and Study JO28944. The atezolizumab IV popPK model was a two-compartment disposition model with first-order elimination and have previously been applied for description of atezolizumab PK across different cancer types.

Figure 1: Schematic Representation of the population pharmacokinetic model of atezolizumab after intravenous and Subcutaneous administration



ATZ=atezolizumab; CL=clearance; F1=bioavailability; IV=intravenous; KA=first-order absorption rate constant; SC subcutaneous; Q inter-compartmental clearance; Vc volume of distribution of central compartment; Vp=volume of distribution of peripheral compartment.

An initial atezolizumab SC popPK model from the Phase Ib (Part 1) portion of Study IMscin001 was used as a starting point for IMscin001 Phase III (Part 2) model development. The absorption model structure and population parameters for absorption were estimated based on Part 1 and Part 2 data while CL, Q, Vc, and Vp were fixed to the values of the IV popPK model. The final IV/SC model included effects of albumin on Ka and haemoglobin on F1.

Table 3 shows final parameter estimates.

Table 3: Parameter Estimates of the final popPK model with atezolizumab SC and IV Administration for IMscin001

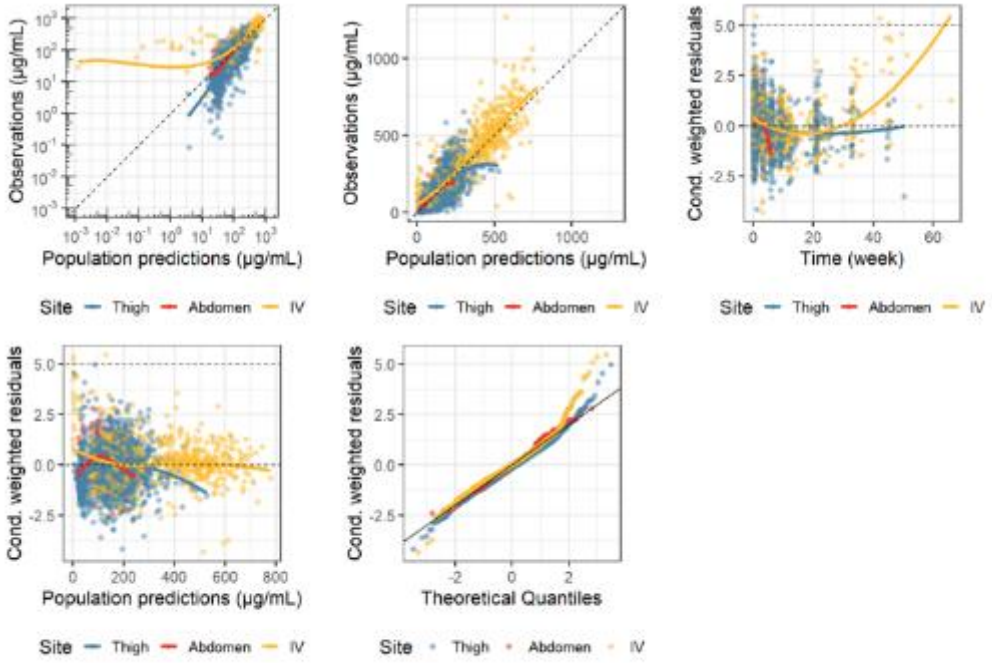
	Parameter (unit)	Estimate	RSE (%)	Shrinkage
1	CL (L/d)	0.200	FIX	
2	Vc (L)	3.28	FIX	
3	Vp (L)	3.63	FIX	
4	Q (L/d)	0.546	FIX	
5	Albumin on CL (ALB/40 in g/L)	-1.12	FIX	
6	ADA status on CL (additive effect for positive ADA)	0.159	FIX	
7	Tumor burden on CL (Tumor burden/63 mm)	0.125	FIX	
8	Bodyweight on CL (BWT/77 in kg)	0.808	FIX	
9	Albumin on Vc (ALB/40 in g/L)	-0.350	FIX	
10	Bodyweight on Vc (BWT/77 in kg)	0.559	FIX	
11	Sex on Vc (additive effect for female)	-0.129	FIX	
12	Sex on Vp (additive effect for female)	-0.272	FIX	
13	**KA (1/d)**	**0.304**	**3.0**	
14	**F1**	**0.718**	**1.8**	
15	**Albumin on KA** (ALB/40 in g/L)	**0.795**	**33.1**	
16	**Hemoglobin on F1** On logit scale (HGB/123 in g/L)	**1.76**	**37.8**	

	Parameter (unit)	Estimate	RSE (%)	Shrinkage
Omega (standard deviation scale) – Between subject variability				
1	POPIIV CL	29.4%	FIX	8.23
2	POPIIV Vc	18.1%	FIX	39.0
3	POPIIV Vp	33.8%	FIX	15.6
5	POPIIV KA	34.6%	23.7	38.1
6	POPIIV F1	83.0%	18.7	37.4
Sigma (residual error)				
1	Proportional error (%)	19.0	9.6	13.2
2	Additive error (µg/mL)	15.4	15.1	

ADA=anti-drug antibodies, CL=clearance from the central compartment, F1=bioavailability, KA–absorption rate constant, POPIIV–population inter-individual variability, Q–distributional clearance, RSE–relative standard error, SC–subcutaneous; Vc–volume of distribution of the central compartment, Vp–volume of distribution of the peripheral compartment.

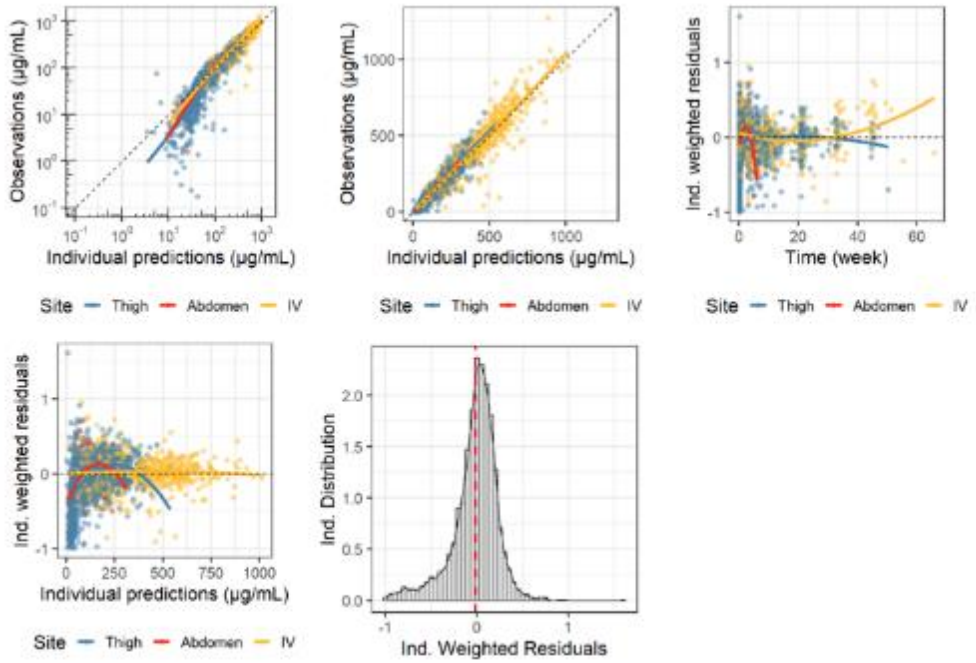
Figure 2 and **Figure 3** shows GoF plots stratified for site of administration, abdomen and thigh. Thigh is the recommended site of SC administration.

Figure 2: Goodness-of-fit for the Final popPK model and stratified by site of administration - Population Level



Cond.=conditional; LOESS=locally weighted scatterplot smoothing.
Grey lines are LOESS, dashed lines represent the identity lines or zero value.

Figure 3: Goodness-of-fit for the Final popPK model and stratified by site of administration - individual Level



Ind.=individual; LOESS=locally weighted scatterplot smoothing.
Grey lines are LOESS, dashed lines represent the identity lines or zero value.

Visual predictive check (VPC) plots s are shown for Cycle 1 in **Figure 4** and **Figure 5** and for Cycles 2-12 in **Figure 6**.

Figure 4: Prediction-Corrected VPC of Atezolizumab from cohort 4 and cohort 5 in linear scale (cohort 4=1200mg Q3W IV part 2 ; cohort 5 =1875 mg Q3W SC ,part 2)

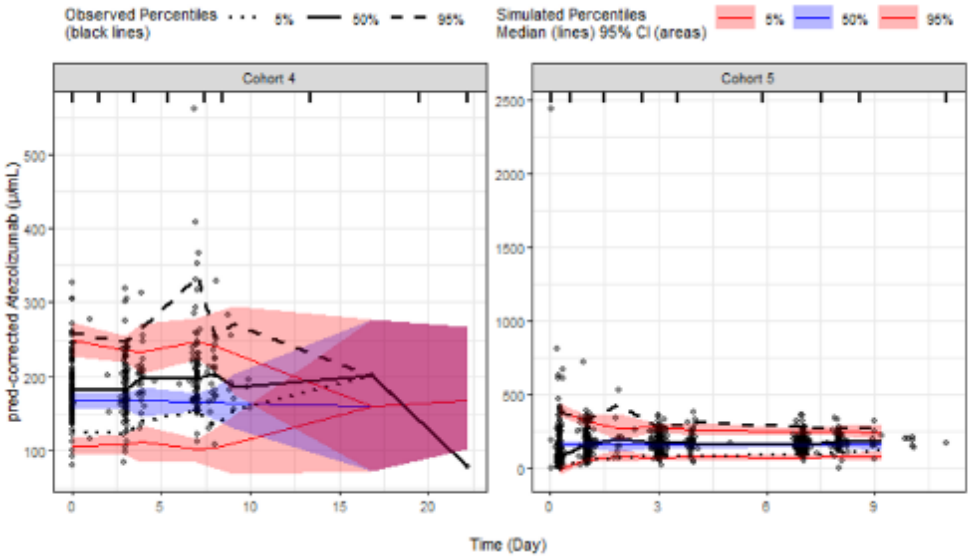


Figure 5: Prediction-Corrected VPC of Atezolizumab from cohort 4 and cohort 5 in semi-log scale

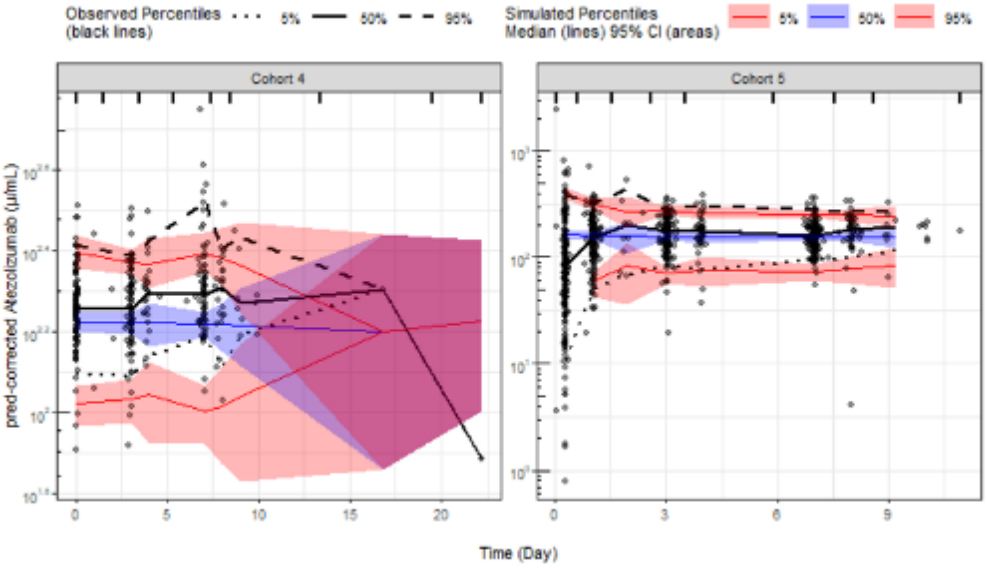
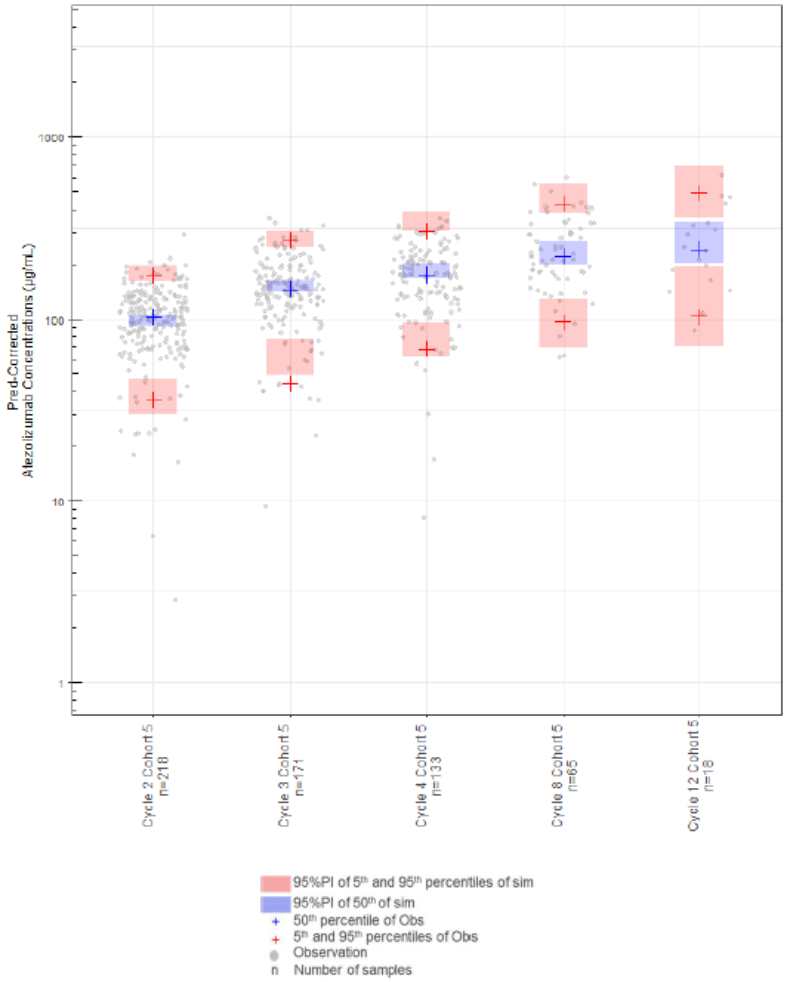


Figure 6: Prediction-Corrected VPC of Atezolizumab (cohort 5, semi-log scale)



n=number of observations; PI=prediction interval; Q3W=every 3 weeks; SC=subcutaneous; VPC=visual predictive check; Cohort 5=atezolizumab SC 1875 mg Q3W.

The model was updated to improve the fit of Cycle 1 using only data from Cohort 4 and 5 of IMscin001. Parameter estimates of the updated model are shown in the below table.

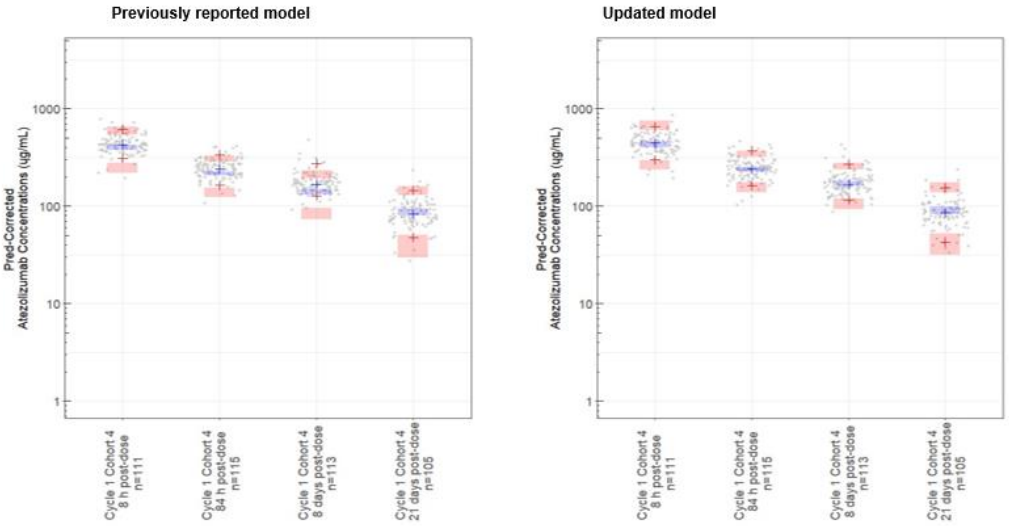
Table 4: Parameter Estimates of the Updated Model

Typical Values	Estimate	RSE (%)	95% CI
CL (L/d)	0.217	3	0.204 to 0.230
Vc (L)	2.74	2.6	2.60 to 2.88
Vp (L)	1.80	8	1.52 to 2.08
Q (L/d)	0.547	11.5	0.424 to 0.670
KA (1/d)	0.373	5.1	0.335 to 0.411
F1	0.609	2.1	0.584 to 0.634
LAG (d)	0.109	11.4	0.0847 to 0.133
Covariate Effect	**Estimate**	**RSE (%)**	**95% CI**
ALB on CL	--	--	--
ADA on CL	--	--	--
BSLD on CL	--	--	--
BWT on CL	0.065	146.5	-0.122 to 0.252
ALB on Vc	--	--	--
BWT on Vc	--	--	--
Sex on Vc	--	--	--
Sex on Vp	-0.328	22.1	-0.470 to -0.186
ALB on KA	--	--	--
HGB on F1	--	--	--
Inter-Individual variability	**SD**	**RSE (%)**	**Shrinkage (%)**
Cl	29.5%	18.6	30.5
Vc	23.2%	21.6	34.5
Vp	--	--	--
Q	--	--	--
KA	45.4%	22.9	35.2
F1	68.3%	22.7	40.2
LAG	-	--	--
Residual variability	**SD**	**RSE (%)**	**Shrinkage (%)**
PROP	0.0269	19.5	20.0
ADD	199	34.3	18.9

Note: ADA = treatment-emergent anti-drug antibody, ADD = additive error, ALB = baseline albumin, BSLD = baseline tumor burden, BWT = baseline body weight, CI = confidence interval, CL = clearance, F1 = bioavailability, HGB = baseline hemoglobin, IIV = inter-individual variability, KA = absorption rate constant, LAG = lag time, PROP = proportional error, Q = inter-compartmental clearance, RSE = relative standard error, Vc = volume of the central compartment, Vp = volume of the peripheral compartment. IIV and residual are in standard deviation scale.

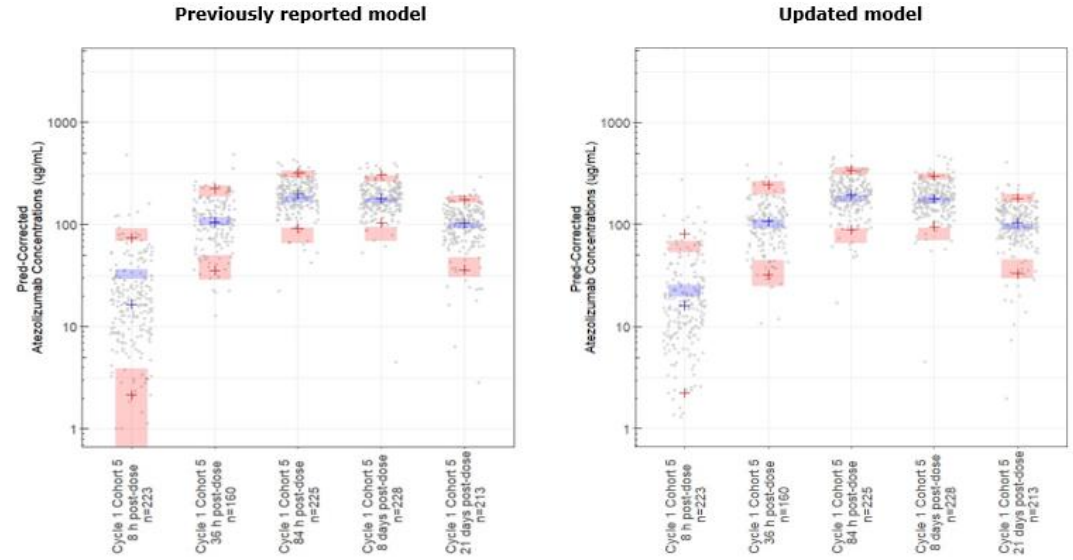
The fit of cycle 1 data using the updated model was compared to the previous model in pcVPCs. The fit of IV data is shown in **Figure 7** and the fit of SC data in **Figure 8**.

Figure 7: pcVPC plot of IMscin001 Part 2 cycle 1 Data from intravenous arm (cohort 4) using the previously reported model (left) and the updated Model (right) in Semi-log scale



Note: PK timepoints with fewer than 40 observed data were excluded from the plots.
Circle = observation; blue cross = 50th percentile of observation; red cross = 5th or 95th percentile of observation; blue shaded area = 95% prediction interval of 50th percentile of simulation; red shaded area = 95% prediction interval of 5th or 95th percentile of simulation.
Cohort 4 = atezolizumab IV 1200 mg Q3W; IV = intravenous; n = number of observations; PI = prediction interval; Q3W = every 3 weeks; pcVPC = prediction-corrected visual predictive check.

Figure 8: pcVPC Plot of IMscin001 part 2 cycle 1 data from SC arm (cohort 5) using the previously report model (left) and the updated Model (right) in semi-log scale



Note: 5th percentile (lower pink box) for the first time point (8 h post-dose) is below 1 µg/mL. 6 observations below 1 not displayed. PK timepoints with fewer than 40 observed data were excluded from the plots.
Circle = observation; blue cross = 50th percentile of observation; red cross = 5th or 95th percentile of observation; blue shaded area = 95% prediction interval of 50th percentile of simulation; red shaded area = 95% prediction interval of 5th or 95th percentile of simulation.
Cohort 5 = atezolizumab SC 1875 mg Q3W; n = number of observations; pcVPC = prediction-corrected visual predictive check; PI = prediction interval; Q3W = every 3 weeks; SC = subcutaneous.

Predicted exposure expressed as Cycle 1 AUC0-21d was compared using the previous model and the updated model and gave comparable results (**Table 5**).

Table 5: Comparison of geometric mean (Geometric mean CV%) of Cycle 1 AUC0-21d from IMscin001 part 2 predicted using previously model and the updated model vs updated model

Treatment arm	Model	Geo Mean (µg*day/mL)	Geo Mean CV%
IV (Cohort 4)	Previous	3328	19.4
	Updated	3564	19.1
SC (Cohort 5)	Previous	2907	35.9
	Updated	3042	35.4

Note: $AUC_{0\text{-}21d}$ = area under the concentration-time curve during dosing interval at Cycle 1; CV% = coefficient of variation; Geo Mean = geometric mean; IV = intravenous; SC = subcutaneous.

Non-inferiority testing

Non-inferiority testing between IV and SC treatments in Cohort 4 and 5 of Study IMscin001 was planned according to **Table 6**.

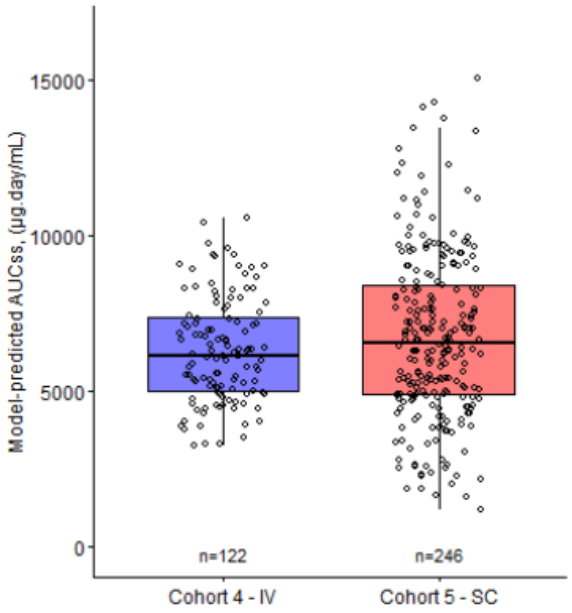
Table 6: Overview of Pharmacokinetic Analyses in Part 2

Variable	Statistical methods	General Description
Observed serum C_{trough} at Cycle 1 Model-predicted $AUC_{0-21\,d}$ at Cycle 1	Analysis of covariance	C_{trough} SC/C_{trough} IV geometric least-squares mean ratio (GMR) and $AUC_{0-21\,d}$ SC/$AUC_{0-21\,d}$ IV GMR of the SC dose of atezolizumab relative to the IV dose will be estimated together with the two-sided 90% CI based on the log- transformed concentration values. The null hypotheses of inferiority of the SC dose of atezolizumab to IV dose will be rejected and non–inferiority will be concluded if the lower bound of the 90% CI of C_{trough} SC/C_{trough} IV GMR and $AUC_{0-21\,d}$ SC/$AUC_{0-21\,d}$ IV GMR are ≥0.8

$AUC_{0-21\,d}$ = area under the time–concentration curve from 0 to 21 days; C_{trough} = trough plasma concentration; CI = confidence interval; GMR = geometric mean ratio; IV = intravenous; SC = subcutaneous.

Figure 9 shows the distribution of model derived AUCss in Cohort 4 and 5.

Figure 9: Distribution of model-predicted AUCss in Cohort 4 (atezolizumab IV 1200mg Q3W) compared with cohort 5 (atezolizumab SC 1875mg Q3W).



AUC_{ss}=$AUC_{0\text{-}21d}$ at steady state; IV = intravenous; n=number of patients; Q3W=every 3 weeks; SC = subcutaneous.

Model predicted AUCinf at Cycle 1 and AUCss,tau for Cohort 4 and 5 data indicated non-inferiority between the projected SC treatment 1875 mg Q3W and the approved IV treatment 1200 mg Q3W. Non-inferiority was also achieved based on the observed Ctrough at Cycle 1.

Exposure-response models

Exposure-response analyses were conducted based on data collected in Part 2 of IMscin001 and logistic regression models (for ORR and safety endpoints) or Kaplan Meier plots and Cox proportional hazard models (for PFS and OS). The patient characteristics of continuous and categorical variables in Cohort 5 in which all subjects received 1875 mg SC in the thigh were used to generate exposure metrics by the final IV/SC popPK model.

ADME characteristics

For comparison the ADME characteristics following atezolizumab IV are shown here:

Absorption	Atezolizumab is approved as an IV infusion. For the subcutaneous formulation of atezolizumab,
Distribution	V_1 is 3.28 L[a]; V_{ss} is 6.91 L[a]
Metabolism	Antibodies are cleared principally by catabolism (Deng et al. 2012).
Elimination	CL is 0.200 L/day[a]; terminal elimination $t_{1/2}$ is 27 days[a]; Maximum decrease of CL during treatment (from baseline CL) ranged from 17% (range -6 to -22%)[b].

CL = total clearance of drug; IV = intravenous; popPK= population pharmacokinetic; V_1 = volume of distribution for the central compartment; V_{ss} = volume of distribution under steady-state conditions.
[a] Derived from Phase I popPK analysis for the typical patient is a male with anti-drug antibodies (ADA) negative status, weighing 77 kg, with an albumin level of 40 g/L and a tumor burden of 63 mm (popPK report 1066935).
[b] Derived from time-varying popPK analysis (Combination Studies [IMpower150, Impower130, Impower133, IMpassion130, IMbrave150] popPK report 1104148; Monotherapy Studies [OAK, IMvigor211, and PCD4989g], popPK report 1093863)

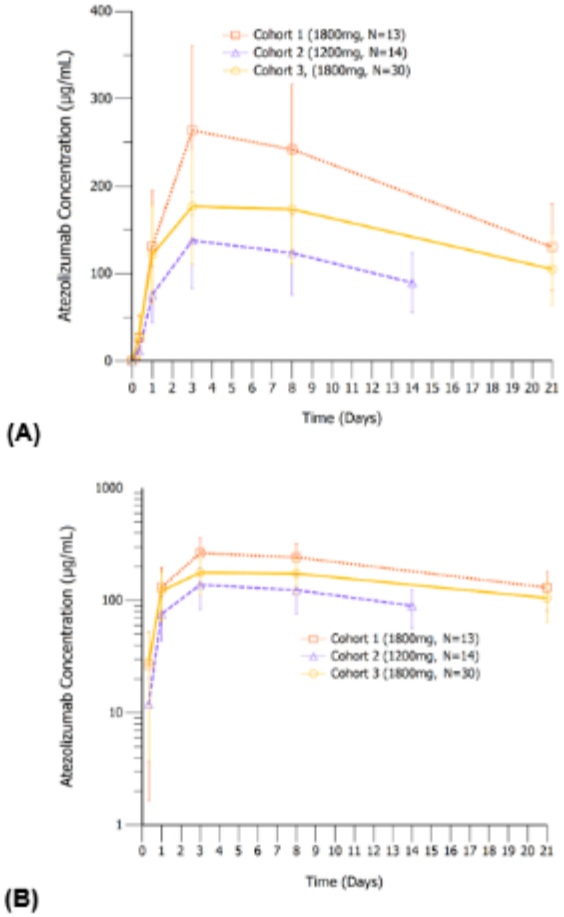
Part 1 of the study consisted of three single-arm SC dosing cohorts. The PK parameters of atezolizumab SC from part 1 of IMscin001 are shown in **Table 7**, concentration-time profiles in **Figure 10**.

Table 7: Summary statistics of Atezolizumab observed PK parameters at Cycle 1 following a single dose of 1800mg Q3W SC thigh, 1200mg Q2W SC thigh and 1800mg Q2W abdomen Atezolizumab Part 1

Treatment	PK Parameter	n	Mean	SD	Mean CV%	GM	GM CV%	Median	Min	Max
PART1-COHORT1 (N=13)	AUC_{last} (day*µg/mL)	13	4100	1340	32.7	3870	38.6	4310	1990	5730
	AUC_{all} (day*µg/mL)	13	4100	1340	32.7	3870	38.6	4310	1990	5730
	C_{max} (µg/mL)	13	268	97.4	36.3	251	40.9	285	128	428
	T_{max} (day)	13	4.61	2.12	46	4.2	46.3	3.02	2.93	7.8
	T_{last} (day)	13	21.01	0.07	0.3	21.01	0.3	21	20.96	21.24
	C_{trough} (µg/mL)	13	130	49.4	38.3	121	42.8	131	61.9	236
PART1-COHORT2 (N=15)	AUC_{last} (day*µg/mL)	14	1520	584	37.2	1410	41.8	1480	661	2460
	AUC_{all} (day*µg /mL)	14	1520	584	37.2	1410	41.8	1480	661	2460
	C_{max} (µg /mL)	14	139	54.4	39.1	129	42.5	128	63	246
	T_{max} (day)	14	4.36	2.09	47.8	4.02	41.2	3.45	3	8.95
	T_{last} (day)	14	14.04	0.12	0.9	14.04	0.9	14.03	13.83	14.33
	C_{trough} (µg/mL)	15	85.5	36.2	42.3	77.5	51.4	85.2	28.5	136
PART1-COHORT3 (N=39)	AUC_{last} (day*µg /mL)	30	2990	974	32.6	2820	38.6	2750	924	5030
	AUC_{all} (day*µg /mL)	30	2990	974	32.6	2820	38.6	2750	924	5030
	C_{max} (µg /mL)	30	192	63.3	33	181	38.3	179	52.6	344
	T_{max} (day)	30	4.74	1.8	38.1	4.43	38.4	3.92	2.99	7.11
	T_{last} (day)	30	20.95	0.09	0.4	20.95	0.4	20.98	20.67	21.08
	C_{trough} (µg/mL)	35	94.7	46.8	49.4	78.3	88.6	93.6	5.15	191

PART1-COHORT1: 1800 mg atezo SC thigh for Cycle 1 (21 days), followed by 1200 mg atezo IV Q3W. PART1-COHORT2: 1200 mg atezo SC thigh Q2W for 3 cycles (Cycles 1-3), followed by 1200 mg atezo IV Q3W. PART1-COHORT3: 1800mg atezo SC Q3W for 3 cycles (abdomen for Cycle 1, then thigh for Cycles 2 & 3), followed by 1200mg atezo IVQ3W.
*Patient has at least one post-baseline PK sample. Table excludes the following samples: a) Measurable PK concentration before the first dose; b) Incomplete or missing PK sample date/time [PC.PCDTC]; c) Duplicate observations by either VISIT/TIMEPOINT or DATETIME.
Note: the list of patients excluded from the NCA analysis are provided in Appendix 1.
AUC=area under the concentration-time curve for one dosing interval; AUC_{last} or AUC_{all} represents AUC 0-21 days for Cohorts 1 and 3 or AUC 0- 14 days for Cohort 2; C_{max}=maximum serum concentration; C_{trough}= minimum serum trough concentration; CV=coefficient of variation; SD=standard deviation; GM= geometric mean; T_{max}=time from dosing to maximum concentration; T_{last} = time of last measurable concentration.
Table truncated by PDRD.
Source: IMscin001 CSR Report 1116043, Section 5.1.4, Table 36; t_pkct01_trt_AT2_pke_10MAR2020_40657.

Figure 10: Mean (+/- SD) concentration time profiles of Atezolizumab following a single dose SC administration of 1800mg in the thigh, 1200mg in the thigh and 1800mg in the abdomen : Linear scale (A) and semi-log scale (B)



Cohort 1: 1800 mg atezo SC thigh for Cycle 1 (21 days); Cohort 2: 1200 mg atezo SC thigh for Cycle 1 (14 days); Cohort 3: 1800mg atezo SC abdomen for Cycle 1 (21 days).

The primary objective of Part 1 was to determine the dose of atezolizumab SC that yields comparable exposure to atezolizumab IV on the basis of Ctrough at Cycle 1 (predose Cycle 2). PopPK modeling was used to select the atezolizumab SC dose to achieve comparable exposure to atezolizumab IV. **Table 8**shows two of the cohorts compared to historical IV data.

Table 8: Summary Statistics of Atezolizumab Observed C_{trough} (µg/mL) at Cycle 1 Following a Single Dose of 1800 mg Q3W Thigh, 1800 mg Q3W SC Abdomen, and 1200 mg Q3W IV (Historical OAK data)

	1800 mg SC Thigh (BP40657-Cohort 1)	**1800 mg SC Abdomen (BP40657-Cohort 3)**	**1200 mg Q3W IV (OAK)**
Cycle 1 observed C_{trough} (µg/mL)			
N	13	35	534
Mean	130	94.7	83.2
SD	49.9	46.8	31.0
CV%	38.3	49.4	37.3
Geo Mean	121	78.3	74.9
Geo Mean CV%	42.8	88.6	66.9
Median	131	93.6	81.8
Min	61.9	5.15	0.03
Max	236	191	184

	1800 mg SC Thigh (BP40657-Cohort 1)	1800 mg SC Abdomen (BP40657-Cohort 3)	1200 mg Q3W IV (OAK)

C_{trough} = minimum atezolizumab serum concentration in a dosing interval; CV = coefficient of variation; Geo mean = geometric mean; IV = intravenous; SC = subcutaneous; SD = standard deviation.
Note: BP40657 popPK model was used to derive Cycle 1 model-predicted $AUC_{0-21\ d}$ (µg•day/mL)
Sources: IMscin001 CSR Report 1116043, Section 5.1.2, Table 33.

The selected dosage of 1875 mg was determined based on the results of Part 1 of IMscin001. This study and its model-based evaluation determined 1875 mg Q3W SC would demonstrate exposure non-inferior to 1200 mg Q3W IV.

Model-based simulations using the Part 2 study design (i.e., 2:1 randomization, OAK demographics) demonstrated a high probability (>0.99) that atezolizumab SC 1800 mg Q3W in the thigh would result in non-inferior exposures of model-predicted Ctrough and AUC0-21 d at Cycle 1 compared to atezolizumab 1200 mg Q3W IV. A lower dose of 1600 mg SC in the thigh may have provided insufficient AUC coverage to the 1200 mg Q3W IV dosing regimen (GM 2625 µg•day/mL vs 2990 µg•day/mL for Cycle 1 AUC0-21 d). In addition, the results suggested 1875 mg SC dose in the abdomen provided insufficient AUC exposure to the 1200 mg Q3W IV dosing regimen (GM 2322 µg•day/mL vs 2990 µg•day/mL for Cycle 1 AUC0-21 d) (**Table 9**).

Summary statistics of Atezolizumab observed PK parameters at Cycle 1 following a single dose of 1800mg Q3W SC thigh, 1200mg Q2W SC thigh and 1800mg Q2W abdomen Atezolizumab Part 1

Table 9: Summary of Geomean (%CV), [90% CI] exposure metrics from clinical trial simulation in abdomen

Parameter/ Dose/ Formulation	1600 mg SC	1800 mg SC	1875 mg SC	2000 mg SC	1200 mg IV
Cycle 1 C_{trough} (µg/mL)	71.6 (65.6%) [24.6, 160]	80.7 (65.1%) [27.7, 180]	84.1 (64.8%) [28.9, 187]	89.8 (64.6%) [30.9, 199]	76.2 (42.7%) [38.6, 141]
Cycle 1 AUC_{0-21d} (µg•day/mL)	1981 (54.1%) [732, 3811]	2229 (54.1%) [823, 4288]	2322 (54.1%) [857,4467]	2476 (54.1%) [914, 4764]	2990 (23.5%) [2096, 4403]
SS C_{trough} (µg/mL)	166 (75.8%) [50.6, 439]	186 (75.6%) [57.0, 494]	194 (75.6%) [59.4, 514]	207 (75.5%) [63.4, 549]	169 (61.3%) [65.9, 399]
SS AUC_{0-21d} (µg•day/mL)	4724 (62.8%) [1676, 10484]	5315 (62.8%) [1885, 11797]	5537 (62.8%) [1963, 12289]	5906 (62.8%) [2093, 13108]	5823 (38%) [3237, 10523]
Cycle 1 C_{trough} <6 µg/mL[a]	0.0823%	0.0692%	0.0643%	0.0599%	0.0134%

CI = confidence interval; CV = coefficient of variation; IV = intravenous; SC = subcutaneous; SS = steady state.
[a] Percent of Cycle 1 C_{trough} below 6 µg/mL.
Source: BP40657 Part 1 Population PK Analysis Methods and Results.

Based on Part 1 results and to allow more precise dosing, the 1875 mg (15 mL) Q3W SC in the thigh dosing regimen of atezolizumab was selected for Part 2 to achieve atezolizumab drug exposure (observed serum Ctrough and model-predicted AUC at Cycle 1 [AUC0-21 d]) non-inferior to the approved 1200 mg Q3W IV atezolizumab dosing regimen.

The typical patient's bioavailability was estimated as 61% with an inter-individual variability of 68.3% using the updated PopPK model.

Non-inferiority testing of atezolizumab PK following administration of single agent atezolizumab SC versus atezolizumab IV in second line (2L) CIT-naïve NSCLC patients in **Part 2 of IMscin001**

Table 10: Observed serum Ctrough (μg/mL) at Cycle 1 (pre-dose cycle 2) (90% CI) (Part 2, per protocol PK-Evaluable population)

	Atezo IV N=97	Atezo SC N=205
n	97	205
Mean	90.1	107.9
Geometric mean	85.4	89.4
Geometric %CV	34.1	127.1
Median	87.7	104.0
Range	37.2 - 189.0	0.0 - 256.0
SD	29.7	46.6
%CV	33.0	43.2
GMR [1]	1.05	
90% CI of the GMR	0.88 - 1.24	

Atezo IV=Atezolizumab intravenous 1200mg Q3W; Atezo SC=Atezolizumab subcutaneous 1875mg Q3W; CI=confidence interval; CV=coefficient of variation; GMR=geometric mean ratio; PK=pharmacokinetic; Q3W=once every three weeks; SD=standard deviation.
[1]ratio of test treatment group (SC arm) to reference treatment group (IV arm). RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022
Trucated by PDRD.
Source: IMscin001 CSR Report 1116043, Section 5.4.2.1, Table 48.

Table 11: Model-predicted AUC0-21 d (μg.day/mL) at Cycle 1 (90% CI) (Part 2, PK-Evaluable population)

	Atezo IV N=122	Atezo SC N=247
n	122	246
Mean	3391.1	3073.9
Geometric mean	3327.9	2907.1
Geometric %CV	19.4	35.9
Median	3232.3	2974.1
Range	1995.2 - 6490.3	665.7 - 6572.1
SD	684.8	990.6
%CV	20.2	32.2
GMR [1]	0.87	
90% CI of the GMR	0.83 - 0.92	

AUC=area under curve; Atezo IV=Atezolizumab intravenous 1200mg Q3W; Atezo SC=Atezolizumab subcutaneous 1875mg Q3W; CI=confidence interval; CV=coefficient of variation; GMR=geometric mean ratio; PK=pharmacokinetic; Q3W= every three weeks; SD=standard deviation.
[1]ratio of test treatment group (SC arm) to reference treatment group (IV arm). Patient 339925 - 20168 model-predicted AUC was not generated because of wrong injection site.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.
Trucated by PDRD.
Source: IMscin001 CSR Report 1116043, Section 5.4.2.2, Table 49.

The secondary endpoints of model-predicted exposure metrics at steady state (Ctrough,SS and AUCSS) and Ctrough, Cycle 1 were shown to be similar between the SC and IV arms (**Table 12**). A sensitivity analysis on model-predicted AUCSS demonstrated the geometric mean ratio (GMR) of SC/ IV values was 1.01 (90% CI: 0.94, 1.08).

Table 12: Summary Statistics geometric Mean (Geometric Mean CV%) of Atezolizumab Model predicted Exposure Metrics at Cyle 1 and steady state following SC (1875 mg Q3W) and IV (1200mg Q3W) Administration using PopPK model.

Arm	PK Parameters	Mean	SD	Geo Mean	Geo Mean %CV	90% CI	Median	Min	Max
IV (N=122)	$C_{trough\ Cycle\ 1}$ (µg/mL)	91.6	23.6	88.7	26.2	57.2–133	89.7	47.4	174
	$C_{trough,ss}$ (µg/mL)	191	68.0	179	38.8	98.4–313	182	63.1	375
	AUC_{ss} (µg•day/mL)	6326	1671	6107	27.3	3890–9334	6166	3260	10568
SC (N=246)	$C_{trough\ Cycle\ 1}$ (µg/mL)	104.6	37.8	97.2	42.3	43.4–169	99.2	20.0	218
	$C_{trough,ss}$ (µg/mL)	233	107	205	58.1	70.3–427	220	35.7	576
	AUCss (µg•day/mL)	6730	2664	6163	46.7	2561-11340	6558	1174	15062

AUC_{ss} = AUC at steady state; $C_{trough\ Cycle\ 1}$ = C_{trough} at Cycle 1; $C_{trough,ss}$ = C_{trough} at steady state; CV% = coefficient of variation; IV = intravenous; N = number of patients; SC = subcutaneous.
The Mean CV% values were obtained with the following formula: Mean CV% = SD/Mean*100.
Source: Roche Report 1116043, Section 5.4.3.1, Table 50

The observed serum atezolizumab PK parameters at Cycle 1 performed via NCA for the atezolizumab SC and IV arms are shown in **Table 13**.

Table 13: Summary statistics of Atezolizumab PK parameters at cycle 1 following a single dose of Atezolizumab 1200mg Q3W IV and 1875mg Q3W SC (per protocol PK-Evaluable population)

Treatment	PK Parameter	n	Mean	SD	Mean CV%	GM	GM CV%	Median	Min	Max
Atezolizumab 1200 mg Q3W IV (N=97)	AUC_{INF} (day*µg/mL)	81	5530	1950	35.2	5270	31.3	5100	2670	15700
	AUC_{last} (day*µg/mL)	82	3700	933	25.2	3600	23.4	3540	2050	8170
	AUC_%Extrap_obs(%)	81	30.6	10.8	35.2	28.8	36.5	28.8	9.5	75.9
	C_{max} (µg/mL)	82	461	125	27.2	445	26.2	444	207	981
	T_{max} (day)	82	0.06	0	6.5	0.06	7	0.06	0.04	0.08
	T_{last} (day)	82	20.94	0.23	1.1	20.93	1.1	20.97	19.81	21.87
Atezolizumab 1875 mg Q3W SC (N=205)	$AUC_{INF\ obs}$ (day*µg/mL)	123	6580	3960	60.2	5610	67.1	5860	208	24700
	AUC_{last} (day*µg/mL)	197	3110	1140	36.7	2880	45	2990	194	7060
	AUC_%Extrap_obs(%)	123	46	15.6	33.9	40	116.5	46.4	0	88.7
	C_{max} (µg/mL)	197	214	82.8	38.7	198	42.6	203	30.4	584
	T_{max} (day)	197	4.83	2.7	55.9	4.25	54.6	3.22	0.35	21.1
	T_{last} (day)	197	20.98	0.27	1.3	20.98	1.3	20.97	19.92	22.92

*Patient did not meet any of the following exclusion criteria for RO5541267 treated patients
1)If Patients are missing the Ctrough pre-dose Cycle 2 Day 1 PK sample
2)If Patients had a Ctrough sample collected with at least 2 days deviation from the planned on Day 21
3)If Patients were given a Cycle 1 dose amount that deviates from the planned dose by >20%
4)If Patients with a subcutaneous injection site other than thigh is used on Cycle 1
5)If Patients had a Duplicate Ctrough sample collected

Note: the list of patients excluded from the NCA analysis is provided in Appendix 1.

Analysis.
AUC=area under the concentration time curve for one dosing interval; AUClast represents AUC 0 to last measurable serum concentration (21 days); AUCINF_obs represents AUC 0 to infinity; AUC_%Extrap_obs is the percentage of AUC extrapolated from last measurable serum concentration out to infinity; Cmax=maximum serum concentration; CV=coefficient of variation; SD=standard deviation; GM=geometric mean; Tmax=time from dosing to maximum serum concentration; Tlast = time of last measurable concentration.

Table truncated by PDRD

Source: IMscin001 CSR Report 1116043, Section 5.4.4, Table 5.1; 1.pkc A17 18MAR2020 40857

There was high inter-individual variability for SC bioavailability (124%) according to the PopPK analysis, based on a small sample size for the SC cohorts in Part 1 of IMscin001. Higher variability was observed following SC administration compared to historical IV.

2.6.2.2. Pharmacodynamics

Exposure-response

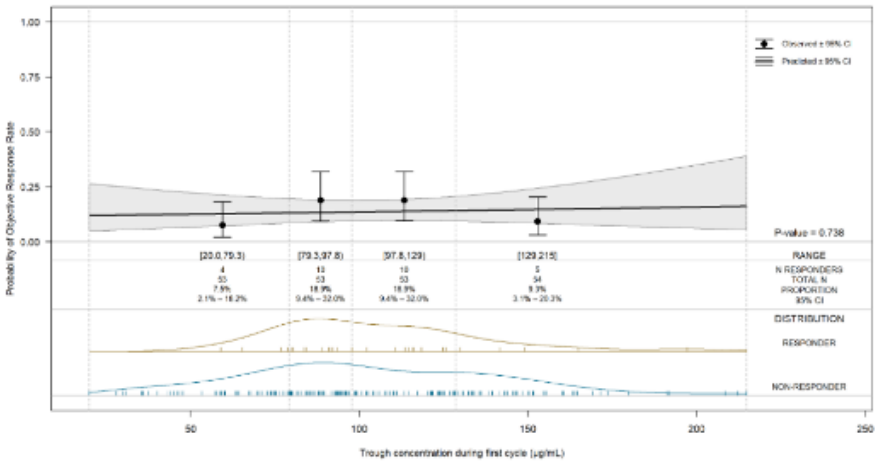
The exploratory PK objective for **Part 2 of IMscin001** was to evaluate potential relationships between atezolizumab exposure and efficacy and safety.

Individual exposure metrics, Cycle 1 model-predicted Ctrough, Cmax, and AUC0-21d, were derived based on the individual EBE from the atezolizumab IV/SC popPK model for patients receiving atezolizumab SC and IV in Part 2 of IMscin001.

Exposure-Efficacy Relationship

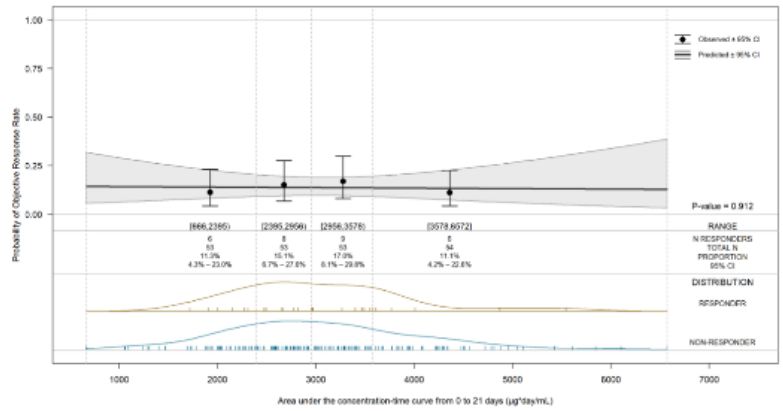
The ORR proportion in this population was 11.8% (29 responders out of 246 patients). Neither of the atezolizumab exposure metrics (Ctrough [**Figure 11**] and AUC0-21d [**Figure 12**] at Cycle 1) were significantly related to the probability of ORR.

Figure 11: Objective response rate vs Atezolizumab Cthrough (Atezolizumab SC 1875mg Q3W)



CI = confidence interval; C_{trough} = minimum serum concentration at Cycle 1; N = number of patients; Q3W = every three weeks; SC = subcutaneous.
Yellow line: Density of responder across range of trough concentration
Blue line: Density of non-responder across range of trough concentration
Note: Density of responder and non-responder do not share the same scale on the y-axis

Figure 12: Objective response rate vs Atezolizumab AUC0-21d (Atezolizumab SC 1875mg Q3W)



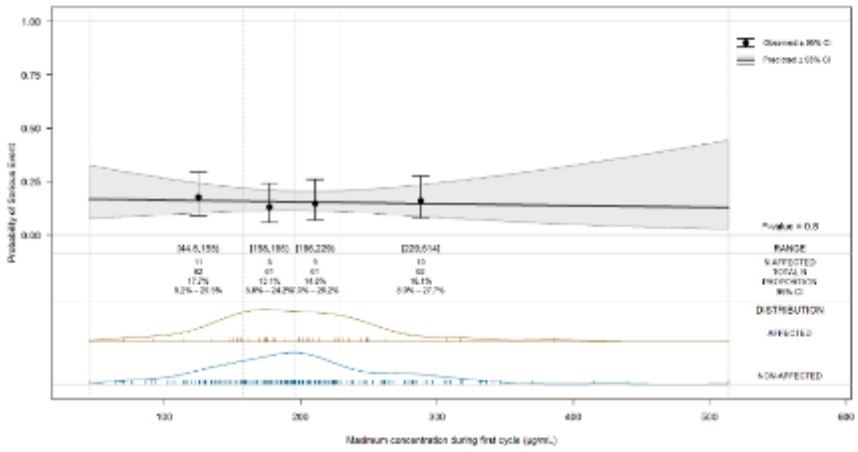
$AUC_{0\text{-}21d}$ – area under the serum concentration-time curve at Cycle 1; CI – confidence interval; N – number of patients; Q3W – every three weeks; SC – subcutaneous.
Yellow line: Density of responder across range of $AUC_{0\text{-}21d}$
Blue line: Density of non-responder across range of $AUC_{0\text{-}21d}$
Note: Density of responder and non-responder do not share the same scale on the y-axis

Cox proportional hazard models of PFS did not show any statistically significant relationship with exposure. The same goes for OS.

Exposure-Safety Relationship

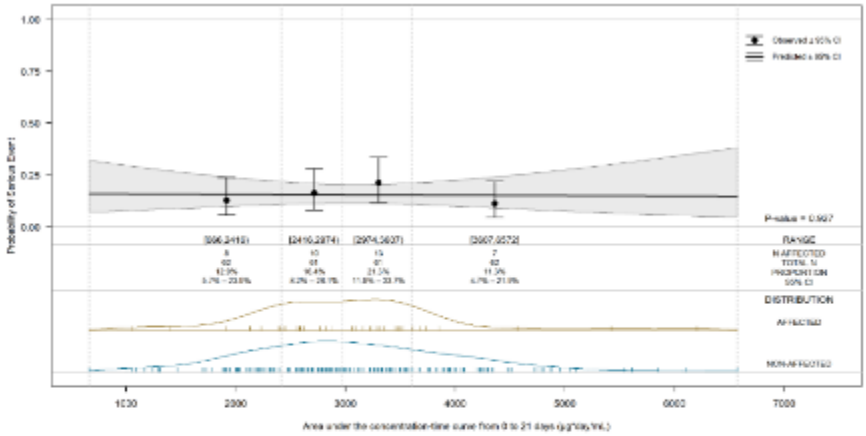
The analysis of the incidence of SAE showed no statistically significant relationship with atezolizumab Cycle 1 Cmax or AUC0-21d (**Figure 13**).

Figure 13: Incidence of SAE vs. Atezolizumab Cmax (Atezolizumab SC 1875mg Q3W)



CI – confidence interval; C_{max} – maximum concentration during cycle 1; N – number of patients; Q3W – every three weeks; SAE – serious adverse event; SC – subcutaneous.
Yellow line: Density of responder across range of atezolizumab exposure
Blue line: Density of non-responder across range of atezolizumab exposure
Note: Density of responder and non-responder do not share the same scale on the y-axis.

Figure 14: Incidence of SAE vs. Atezolizumab AUC0-21d (Atezolizumab SC 1875mg Q3W)



AUC_{0-21d} = area under the serum concentration-time curve at Cycle 1; CI = confidence interval; N = number of patients; SAE = serious adverse event; Q3W = every three weeks; SC = subcutaneous.
Yellow line: Density of responder across range of atezolizumab exposure
Blue line: Density of non-responder across range of atezolizumab exposure
Note: Density of responder and non-responder do not share the same scale on the y-axis

The analysis of the incidence of AESI, AEG35 and ISR showed no statistically significant relationship with atezolizumab Cycle 1 AUC0-21d.

2.6.3. Discussion on clinical pharmacology

The atezolizumab assays used for quantification and for ADA testing were the same as used in previous procedures. Validated bioanalytical methods for detection, confirmation, and titration of anti-rHuPH20 antibodies in plasma were used to assess immunogenicity of rHuPH20.

The data to support the application is based on the clinical data from IMscin001, a two-part, open-label, multicentre Phase Ib/III randomized study to investigate the pharmacokinetics (PK), safety and efficacy of atezolizumab SC compared with atezolizumab IV in patients with previously treated locally advanced or metastatic NSCLC who are cancer immunotherapy (CIT)-naive and for whom prior platinum therapy has failed.

A previous IV model based on Phase 1 data were used as the base to fit the initial SC data. All disposition parameters were fixed and only absorption parameters were estimated. An initial SC model based on data from Part 1 of Study IMscin001 was used as a starting point for IMscin001 Part 2 model development. The SC model did not account for the exposure difference observed between sites of injection, abdomen or thigh. Different SC formulations were used between Part 1 and Part 2. VPCs of Study IMscin001 Part 2 Ctrough Cycle 1, Cohort 4 (IV) and Cohort 5 (SC) revealed bias in the model fit with the absorption phase following SC dosing not being captured and the IV data of Cycle 1 being underpredicted. A model update based solely on Cohort 4 and 5 Cycle 1 data improved the fit and resulted in comparable geometric mean ratios of model-predicted Cycle 1 AUC0-21d to the previous reported model. The non-inferiority testing of Tecentriq IV and SC for the model predicted end-point Cycle 1 AUC0-21d is therefore considered acceptable.

The results from Part 1 based on observed PK data as well as popPK modelling and simulation (dose-finding) provided the rationale for the dosing regimen selected for atezolizumab SC in Part 2.

Regarding the different absorption process after SC administration, thigh as administration site resulted in on average ~30% higher exposures as did abdomen. SC administration produced dose-dependent exposure increases over a dose range of 1200 mg to 1800 mg Q3W in the thigh. Following

a single dose of 1800 mg SC administered in the thigh (Cohort 1), the geometric mean of observed Ctrough at Cycle 1 (121 µg/mL) was 1.6-fold higher compared to that of the historical OAK IV PK data (74.9 µg/mL). Tmax was 4.5 days, with a range of 2.2-9 days after SC administration. A similar terminal elimination half-life (t1/2) and accumulation ratio were demonstrated in both treatment arms (SC or IV) with medians varying from 20.0 to 22.3 days for t1/2 and 1.2 to 4.1 for accumulation ratio. Inter-individual variability was high and higher in SC than IV.

In the two-compartmental disposition popPK model with first-order absorption (SC only) and elimination describing atezolizumab PK following SC or IV administration six significant covariates were found to influence atezolizumab PK parameters: albumin on apparent first-order absorption rate constant (KA) and clearance (CL), haemoglobin on F, body weight on CL, Vc and Vp, tumor burden on CL, ADA status on CL, and sex on Vc and Vp accounting for <30% change from typical value. The existing wording in section 5.2 of the SmPC regarding special populations does not need to be updated. The model-predicted exposure metrics were in general consistent with observed PK findings.

When covariate effects based on body weight, sex, age, race, ethnicity, renal impairment, and hepatic impairment on atezolizumab exposure were numerically compared, exposure metrics were lower in patients with higher body weight or in female patients compared to male which is consistent with the known atezolizumab PK. A minor trend was observed with ethnicity, Hispanics having marginally higher exposure metrics (22% higher GM model-predicted AUC0-21d) than non-Hispanics, their 90% confidence intervals still largely overlapping.

In light of the high variability it is overall acceptable that these changes do not translate into dose modifications. As the study is conducted in patients with previously treated locally advanced or metastatic NSCLC, which could count as a part of the target population, but do not represent it (the target population) as a whole and these are a subset of often very severely ill patients in a bad (nutritional) condition, the MAH has justified the representativeness to other populations with e.g. a higher albumin status.

The main objective of Part 2 (Phase III, randomized, dose confirmation) was to demonstrate the non-inferiority of Cycle 1 drug exposure (with respect to atezolizumab trough concentration [Ctrough] and model-predicted area under the concentration-time curve from 0 to 21 days [AUC0–21 d]) following treatment with Atezo SC at the 1875 mg Q3W dosing regimen compared with drug exposure following treatment with Atezo IV at the approved 1200 mg Q3W dosing regimen.

The non-inferiority testing of co-primary endpoints (observed Ctrough and model-predicted AUC0-21 d at Cycle 1) was met. The GMR of serum atezolizumab Ctrough, SC/Ctrough,IV values at Cycle 1 was 1.05 (90% CI: 0.88, 1.24). The GMR of model predicted serum atezolizumab AUC0-21 d,SC/AUC0-21 d,IV values at Cycle 1 was 0.87 (90% CI: 0.83, 0.92). The corresponding lower limit of the two-sided 90% CI for both co-primary endpoints were above the prespecified non-inferiority margin of 0.8.

Nevertheless, even if the prespecified non-inferiority margin of 0.8 for the PK endpoints is met, the model-predicted exposure in the SC arm was 13% lower than for the IV arm and the CI limits were narrow around the point estimate and did not include 1.0, i.e. the difference was statistically significant. The secondary endpoints of model-predicted exposure metrics at steady state (Ctrough,SS and AUCSS) and Ctrough, Cycle 1 were shown to be similar between the SC and IV arms. It is not required that unity should be included. When the new model was used to predict Cycle 1 AUC0-21d for non-inferiority testing of the SC versus IV doses in IMScin001, it resulted in a GMR of 0.86 and a 90% CI of 0.81 to 0.91. This result is comparable to the initial result obtained with the previous model, however, the updated Pop PK model shows that a better description of e.g. the absorption phase does not influence the non-inferiority test outcome. Therefore, the conclusion that the test of non-inferiority is also met for the model predicted serum atezolizumab AUC0-21d co primary endpoint. This was confirmed after updating the Pop PK model to be considered appropriate for the description of subjects

receiving SC doses and repeat non-inferiority tests using model exposures also including observed Ctrough (cycle 1).

No statistically significant exposure-efficacy relationships were identified with ORR, PFS, or OS in patients treated with SC atezolizumab 1875 mg Q3W. However, noting that the claim is to extrapolate all the indications of the IV formulation to its subcutaneous counterparts, a thorough discussion on exposure-response (E-R) for each of the approved indications was provided, justifying that the differences seen in exposure, including the variability in Ctrough, are compatible with retained efficacy for each indication. This was done as the results from the dose-ranging IV clinical study showed that no statistically significant relationship was associated with efficacy and atezolizumab exposures ranging from 0.597 µg/mL to 242.6 µg/mL for MP Ctrough at Cycle 1 and all patients in the SC arm of IMscin001 Part 2 had drug exposures within this range. Additionally, all patients in the SC arm of IMscin001 Part 2 at the lowest end of exposure had MP Ctrough at Cycle 1 (20 µg/mL minimum) as high as that in each of the combination IV studies at the lowest end (5.88 to 34.9 µg/mL minimum). All SC patients had drug exposure within the full E-R range for atezolizumab IV and > 99% of SC patients had drug concentrations above the receptor saturation threshold of 6 µg/mL. Further similar dose exposure response relationship was observed in all of the IV indications. It is thus accepted that patients treated with SC, including patients with drug exposure at the extreme lower end, achieve adequate drug exposures despite the higher variability.

No statistically significant exposure-safety relationships were identified with serious adverse events (SAE), adverse events of special interest (AESI), adverse events (AE) of Grade 3-5, or injection site reactions (ISR) in patients treated with SC atezolizumab 1875 mg Q3W.

In Part 2 of IMscin001, the treatment-emergent atezolizumab ADA incidence was comparable between arms (19.5% in the Atezo SC arm and 13.9% in the Atezo IV arm). The atezolizumab ADA incidence for both arms were within the range of ADA incidence observed across multiple Phase II and III studies with atezolizumab administered by IV (13.1% to 54.1%). There did not appear to be a clinically relevant impact of ADAs on PK, efficacy, or safety in both treatment arms. However, development of ADAs appears to be more frequent in the SC than the IV arm. This could be a concern, since presence of ADAs may decrease atezolizumab PK exposure which could, in turn, result in sub-optimal efficacy. As ADAs were more frequent in the SC arm, this could affect the benefit-risk in patients treated with SC atezolizumab. The limited number of ADA + patients in the IV arm (n = 15) however restrain the interpretability of the findings. Since there was an overlapping distribution in exposure between ADA subgroups in the SC study, 99% of both ADA positive and negative had Cmin concentrations above the target serum concentration of 6 µg/mL and the exposure-response relationship is flat, is seems acceptable to conclude that the benefit-risk is not impacted negatively.

2.6.4. Conclusions on clinical pharmacology

The non-inferiority testing of Tecentriq 1200 mg IV Q3W and 1875 mg SC Q3W was met for both co-primary endpoints: observed Ctrough at Cycle 1, and model-predicted AUC0-21d at Cycle 1.

Moreover, it was sufficiently justified that all patients in the SC arm had drug exposure within the full E-R range for atezolizumab IV and >99% of SC patients had drug concentrations above the receptor saturation threshold of 6 µg/mL. Further similar dose exposure response relationship was observed in all of the IV indications. It is thus considered that patients treated with atezolizumab SC, including patients with drug exposure at the extreme lower end, achieve adequate drug exposures despite the higher variability.

2.6.5. Clinical efficacy

Table 14: Tabular overview of IMscin001 and IMscin002

Study Number (Phase)	Patient Population	Number of Patients	Key Objectives	Status
BP40657 (IMscin001) (Phase Ib/III)-	Patients with NSCLC who are CIT-naïve and for whom prior platinum therapy has failed	371 patients	**Part 1** **Primary Endpoint** • Determine the dose of Atezo SC predicted to yield drug exposure comparable to Atezo IV based on the endpoint of serum atezolizumab trough concentration (C_{trough}) at Cycle 1 (i.e., predose Cycle 2). **Part 2:** **Primary Endpoints** • Non-inferiority of exposure to Atezo SC compared with Atezo IV on the basis of: i) serum atezolizumab C_{trough} at Cycle 1 (predose Cycle 2); ii) Model-predicted area under the concentration-time curve (AUC) from 0 to 21 days (AUC_{0-21d}) at Cycle 1. **Secondary Endpoints** • Safety and efficacy (ORR, DOR, PFS and OS) of atezolizumab SC compared with Atezo IV. • Incidence of ADAs to atezolizumab and rHuPH20. • Patient and HCP-reported experience with Atezo SC administration compare with Atezo IV.	Patients in Follow-up Ongoing[a]

Study Number (Phase)	Patient Population	Number of Patients	Key Objectives	Status
MO43576 (IMscin002) (Phase II)	PD-L1 positive patients with resected Stage IIB-IIIB (early stage) NSCLC who have completed adjuvant platinum-based chemotherapy without evidence of disease relapse/recurrence and CIT-naïve Stage IV NSCLC	140 patients (planned)	**Primary Endpoints** Evaluate the proportion of participants who preferred Atezo SC to Atezo IV, with treatment preference assessed using Question 1 of the Patient Preference Questionnaire. **Secondary Endpoints** To evaluate: • Participant-reported satisfaction with Atezo SC and Atezo IV. • Choice of Atezo SC for the treatment continuation period. • HCP perception of time/resource use and convenience of administration of Atezo SC and IV. • HROoL. • Safety of each study administration modality alone, and after transition from one modality to the other.	Recruiting[b]

[a]Primary analysis results available [b]Primary analysis results not available
ADA = anti-drug antibodies; AUC_{ss} = area under the curve at steady state; AUC_{0-21d} = area under the time–concentration curve from 0 to 21 days; C_{trough} = trough plasma concentration; CIT = cancer immunotherapy; HCP = health care professional; HROoL = health-related quality of life; IV = intravenous; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; SC = subcutaneous.

2.6.5.1. Main study(ies)

BP40657 (IMscin001-part 2)

Figure 15: Part 2: Dose confirmation study design of IMscin001

CIT = cancer immunotherapy; LOCB = loss of clinical benefit; N = planned number of patients; NSCLC = non–small cell lung cancer; Q3W = every three weeks; R = randomization.

Methods

Study Participants

The study population consisted of immunotherapy-naïve patients with advanced/metastatic NSCLC for whom prior platinum-based therapy had failed.

Key inclusion criteria

- Measurable disease as defined by RECIST v1.1. Previously irradiated lesions were only considered as measurable disease if disease progression had been unequivocally documented at that site since radiation, and the previously irradiated lesion was not the only site of disease.
- Histologically or cytologically documented NSCLC that is currently locally advanced or metastatic (i.e., Stage IIIB not eligible for definitive chemoradiotherapy, Stage IV, or recurrent) NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 8th edition).
- Disease progression during or following treatment with a platinum-containing regimen for locally advanced, unresectable/inoperable or metastatic NSCLC or disease recurrence within 6 months of treatment with a platinum-based adjuvant/neoadjuvant regimen or combined modality (e.g., chemoradiation) regimen with curative intent.

  Patients may have received one additional cytotoxic chemotherapy regimen provided no interval disease progression has occurred. Chemotherapy regimens will be counted based on interval disease progression and not the number of agents or switches in agents (e.g., a first-line therapy that consists of several cycles of a platinum doublet and subsequent maintenance therapy that introduces or switches to a new chemotherapy agent without interval disease progression will all be considered one chemotherapy regimen).

  Adjuvant/neoadjuvant chemotherapy or chemoradiation was considered a prior chemotherapy regimen if <6 months had elapsed between the last dose and the date of recurrence.

  Patients with advanced lung cancer and a sensitizing EGFR mutation were additionally required to have experienced disease progression (during or after treatment) or intolerance with one or more EGFR tyrosine kinase inhibitors appropriate for the treatment of EGFR-mutant NSCLC.
- Patients were required to have recovered (i.e., improvement to Grade 1 or better) from all acute toxicities from previous therapy, excluding alopecia. For peripheral neuropathy, improvement to Grade ≤2 was considered acceptable.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
- Life expectancy ≥12 weeks.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:

  - Absolute neutrophil count (ANC) ≥1.5 x $\mu 10^9$/L (1500/µL) without granulocyte colony-stimulating factor support.

  - Lymphocyte count ≥0.5 x 10^9/L (500/µL).

- Platelet count ≥100 x 109/L (100,000/µL) (without transfusion).
- Haemoglobin ≥90 g/L (9 g/dL); patients could be transfused to meet this criterion.
- AST, ALT, and ALP ≤2.5 x upper limit of normal (ULN), with the following exceptions:
    - o Patients with documented liver metastases: AST and ALT ≤5 x ULN.
    - o Patients with documented liver or bone metastases: ALP ≤5 x ULN.
- Total bilirubin ≤1.5 x ULN with the following exception:
    - o Patients with known Gilbert disease: total bilirubin level ≤3 x ULN.
- Serum creatinine ≤1.5 x ULN.
- Serum albumin ≥25 g/L (2.5 g/dL).
- For patients not receiving therapeutic anticoagulation: INR or a PTT ≤1.5 x ULN.

Inclusion Criteria specific to Part 1 patients

- Body mass index (BMI) between 18 and 32 kg/m2 (inclusive).

Inclusion Criteria specific to Part 2 patients

- Patients whose tumour may harbour a sensitizing EGFR mutation must have known EGFR test results at the time of randomisation. However, patients with sensitizing EGFR mutations were to be excluded once 10% of the total sample size was reached. Of note, the 10% limit was not reached so no such patients were excluded.
- Availability of a pre-study treatment representative formalin-fixed paraffin embedded (FFPE) tumour specimen in paraffin block (preferred) or at least six slides containing unstained, freshly cut, serial sections from an FFPE tumour specimen for exploratory biomarker analysis.

Key Exclusion Criteria

- Symptomatic, untreated, or actively progressing CNS metastases; asymptomatic CNS lesions were permitted provided the following criteria were met:

  – Measurable disease, per RECIST v1.1, should have been present outside the CNS.

  – No history of intracranial haemorrhage or spinal cord haemorrhage.

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

  – The patient had no ongoing requirement for corticosteroids as therapy for CNS disease. Anti-convulsant therapy at a stable dose was permitted.

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

  – No evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment.

  Patients with new asymptomatic CNS metastases detected at the screening scan were required to receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients could then be eligible without the need for an additional brain scan prior to enrolment, if all other criteria were met.

- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥2 weeks prior to enrolment.
- History of leptomeningeal disease.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). Patients with indwelling catheters were allowed.
- Uncontrolled tumour-related pain.

  – Patients requiring pain medication should have been on a stable regimen at study entry.

  – Symptomatic lesions amenable to palliative radiotherapy should have been treated prior to enrolment.

  – Asymptomatic metastatic lesions that could cause functional deficits or intractable pain with further growth should have been considered for locoregional therapy if appropriate prior to enrolment.

- Uncontrolled or symptomatic hypercalcemia (ionized calcium >1.5 mmol/L, calcium >12 mg/dL, or corrected serum calcium >ULN).
- History of malignancy other than NSCLC within 5 years prior to screening, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to initiation of study treatment, unstable arrhythmias, or unstable angina.

  – Patients with a known left ventricular ejection fraction (LVEF) <40% were excluded.

  – Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF <50% were required to be on a stable medical regimen that was optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

- General medical criteria or medications that would preclude the patient's safe participation in and completion of the study.

<u>Exclusion Criteria specific to Part 1 patients</u>

- Any pathology that could interfere with any protocol-specified outcome assessment (e.g., pharmacokinetics).

<u>Exclusion Criteria specific to Part 2 patients</u>

- Tested tumour PD-L1 expression status with an intention to treat the patient if positive.

<u>General Medical Exclusions</u>

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

- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of atezolizumab

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

- History of severe anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or any component of the atezolizumab formulation
- Active or history of autoimmune disease or immune deficiency, including, but not limited to (for a comprehensive list, see Appendix 8), myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

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

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

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

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

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

  – There is no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Active tuberculosis
- Current treatment with anti-viral therapy for HBV
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to initiation of study treatment, unstable arrhythmias, or unstable angina

  Patients with a known left ventricular ejection fraction (LVEF) <40% will be excluded.

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF <50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, or that may affect the interpretation of the results, or may render the patient at high risk from treatment complications

Exclusion Criteria related to medications

- Prior treatment with CD137 agonists or immune checkpoint blockade therapies including anti-TIGIT, anti−PD-1, and anti−PD-L1 therapeutic antibodies

Patients who have had prior anti−CTLA-4 treatment may be enrolled, provided the following requirements are met:

– Last dose of anti−CTLA-4 at least 6 weeks prior to enrollment

– No history of severe immune-mediated adverse effects from anti-CTLA-4 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 3 or 4)

- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment

Prior treatment with cancer vaccines is allowed.

- Treatment with systemic immunosuppressive medication (including but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-α agents) within 2 weeks prior to enrollment

Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study.

The use of corticosteroids (≤ 10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency is allowed.

- Known allergy or hypersensitivity to hyaluronidase, bee or vespid venom, or any other ingredient in the formulation of rHuPH20

Treatments

In Part 2, patients were randomized in a 2:1 ratio to receive monotherapy with either 1875 mg of atezolizumab SC Q3W or 1200 mg of atezolizumab IV Q3W, respectively, starting on Day 1 of each 21-day cycle. No dose reduction was allowed.

Objectives

Primary objective

To demonstrate non-inferiority of exposure to atezolizumab SC compared with atezolizumab IV based on the corresponding co-primary endpoints.

Secondary objectives

- To evaluate exposure following administration of atezolizumab SC compared with atezolizumab IV
- To evaluate the safety of atezolizumab SC compared with atezolizumab IV
- To evaluate the efficacy of atezolizumab SC compared with atezolizumab IV
- To evaluate patient experience with atezolizumab SC compared with atezolizumab IV
- To evaluate the incidence of ADAs to atezolizumab and rHuPH20

Secondary utility objective

- To evaluate health care professional (HCP)-reported experience with administration of atezolizumab SC and atezolizumab IV

Exploratory objectives

- To characterize the PK profile of rHuPH20
- To evaluate the immune response to atezolizumab SC and rHuPH20
- To evaluate potential relationships between atezolizumab exposure and efficacy and safety
- To evaluate potential effects of ADAs to atezolizumab
- To evaluate biomarkers that may be:
  - Predictive of response to atezolizumab (predictive biomarkers)
  - Early surrogates of efficacy
  - Associated with progression to a more severe disease state (prognostic biomarkers)
  - Associated with acquired resistance to atezolizumab
  - Able to provide evidence of atezolizumab activity (pharmacodynamic biomarkers)

Outcomes/endpoints

Primary endpoints

- Observed serum Ctrough at Cycle 1 (predose Cycle 2)
- Model-predicted area under the concentration-time curve (AUC) from 0 to 21 days (AUC0–21 d) at Cycle 1

Secondary pharmacokinetic endpoints

- Model-predicted Ctrough at Cycle 1 (Ctrough Cycle 1)
- Model-predicted Ctrough at steady state (Ctrough, ss)
- Model-predicted AUC at steady state (AUCss)

Secondary safety endpoints

- Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0
- Overall patient-reported adverse event burden over time, as assessed by the treatment-related symptom burden item from the European Organization for Research and Treatment of Cancer (EORTC) IL57

Secondary efficacy endpoints

- ORR, defined as the proportion of patients with a complete response (CR) or partial response (PR), as determined by the investigator according to Response Evaluation Criteria in Solid Tumours, Version 1.1 (RECIST v1.1)
- PFS, defined as the time from study entry to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- OS, defined as the time from study entry to death from any cause
- Duration of response (DOR), defined as the time from first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- Functioning and global health status over time, as assessed by the physical functioning, role functioning, and global health status/quality of life scales of the EORTC IL57
- Overall satisfaction with treatment over time, as assessed by the modified satisfaction with therapy (SWT) scale of the Cancer Therapy Satisfaction Questionnaire (CTSQ)

Secondary immunogenicity endpoints

- Incidence of ADAs to atezolizumab after SC administration or IV administration relative to the prevalence of ADAs at baseline
- Incidence of ADAs to rHuPH20 after SC administration relative to the prevalence of ADAs at baseline

Secondary utility endpoints

- Convenience, potential time savings, and overall satisfaction with atezolizumab SC compared with atezolizumab IV, as assessed by the HCP SC versus IV Perspective Questionnaire
- Convenience, ease of administration, and overall satisfaction with atezolizumab SC as assessed by the HCP Subcutaneous Perspective Questionnaire

Exploratory pharmacokinetic endpoint

- Relationship between atezolizumab exposure (e.g., Ctrough, Cmax, and AUC at Cycle 1) and safety (Grade 3-5 adverse events, adverse events of special interest) and efficacy (ORR, PFS and/or OS) endpoints

Exploratory immunogenicity endpoint

- Relationship between post-baseline ADA status and PK, safety, or efficacy endpoints

Exploratory biomarker endpoint

- Relationship between biomarkers in tumour tissue and efficacy, or other biomarker endpoints

Sample size

Initially, it is expected that up to 20% of randomized patients will need to be excluded from the Per Protocol PK population. a total of approximately 327 patients were planned to be randomized. Later on as per protocol, to account for the increase in PK-unevaluable dropout rate (20% initially assumed vs. 23.9% observed (including missing samples)) in the blinded review of the JMC meeting, the minimum sample size needed for this study was increased to 355 patients. This was discussed in the JMC meeting on 09 February 2022 and the JMC approved to increase the sample size. The re-estimated sample size provides sufficient power for the statistical hypothesis testing for the co-primary endpoints (observed Ctrough and model-predicted AUC0-21 d at Cycle 1) based on the assumptions of the BP40657 SAP (v3). Under these assumptions, a sample size of ≥261 pharmacokinetic (PK)-evaluable patients in the atezolizumab SC and atezolizumab IV arms would provide at least 80% power to conclude non-inferiority of atezolizumab SC compared to atezolizumab IV based on Cycle 1 Ctrough,and AUC0–21 d with a non-inferiority margin of 0.8 for the GMR, or more concisely: Ctrough, SC >0.8 Ctrough, IV and AUC0–21 d, SC >0.8 AUC0-21 d, IV. .

Randomisation and blinding (masking)

Patients in Part 2 were randomly assigned to one of two treatment arms: atezolizumab 1875 mg SC Q3W (21 days) or atezolizumab 1200 mg IV Q3W. Randomisation occurred in a 2:1 ratio using a permuted-block randomisation method to ensure a balanced assignment to each treatment arm.

Given the open-label nature of this study, the study management team (SMT) was unblinded to study treatments. However, to further protect the integrity of the study, any treatment assignment information, such as randomisation files from the interactive voice/web response system (IxRS) and PK data, was withheld from the Sponsor until the primary analysis. Data for safety purposes were not reviewed at an aggregate level prior to the primary analysis by the SMT.

Statistical methods

Analysis sets Part 1

PK analyses was performed on data from PK evaluable patients, i.e. at least one dose and at least one post-dose PK sample, enrolled in part 1. Safety analysis was performed on all subjects with at least one dose.

Analysis sets Part 2

The primary analysis was conducted on the PK analysis population, including all patients without protocol deviations that could affect PK. Efficacy analyses on OS and PFS were done for the full analysis set, FAS, consisting of all patients randomised and by assigned treatment. Analyses on OR and DoR were done on the subpopulation of FAS with measurable disease at baseline. Safety analysis was done on the full analysis set by actual treatment.

CO-PRIMARY ENDPOINTS ANALYSIS

The primary comparisons of interest are the geometric mean ratios (GMR) and confidence intervals of PK parameters for atezolizumab SC versus atezolizumab IV. The PK objective for Part 2 is to demonstrate non-inferiority of exposure to atezolizumab SC compared with atezolizumab IV based on the following co-primary endpoints:

- Observed serum C_{trough} at Cycle 1 (predose Cycle 2)

- Model-predicted area under the concentration-time curve (AUC) from 0 to 21 days ($AUC_{0-21\ d}$) at Cycle 1

MULTIPLICITY ADJUSTMENT

Cycle 1 observed serum Ctrough (predose Cycle 2) and model-predicted AUC0–21 d were tested using the Hochberg procedure (Hochberg and Tamhane 1987; FDA 2017). In step 1 of this procedure, if the lower bounds of the 90% CI for both the GMR Ctrough,SC/Ctrough,IV and the GMR AUC0–21 d, SC/AUC0–21 d, IV are ≥ 0.8, both null hypotheses is rejected. In this case, it is concluded that SC administration is non-inferior to IV administration in terms of Ctrough and AUC in Cycle 1.

If in Step 1 the null hypotheses are not rejected, the procedure continues to Step 2. In Step 2, if the 95% CI for one GMR (i.e., either Ctrough,SC/Ctrough,IV or AUC0– 21 d, SC/AUC0−21 d, IV) is ≥ 0.8, the corresponding null hypothesis is rejected. In this case, it is concluded that SC administration is non-inferior to IV administration in terms of Ctrough or AUC in Cycle 1.

Definition of Co-Primary Endpoints

Following the estimand framework introduced in the ICH-E9 addendum (ICH 2020), the estimand for the primary analysis follows a principal stratum strategy based on the following attributes:

Co-Primary Estimand 1:

- **Population:** Patients with locally advanced or metastatic NSCLC who are CITnaive and for whom prior platinum therapy has failed. The analysis population will consist of the Per Protocol PK population, with patients grouped according to their received treatment.
- **Variable:** The Cycle 1 observed serum C_{trough} (predose Cycle 2), using the measured concentration from the PK sample.
- **Treatment:** Atezolizumab IV versus atezolizumab SC, at the determined dose at baseline. All randomized patients are expected to receive the baseline infusion or injection.
- **Intercurrent Events and Handling Strategy:**
  - **Premature discontinuation from treatment:** Every effort will be made to ensure all randomized patients will receive the treatment at baseline and will have the PK sample collected appropriately. Treatment will start within 5 days of randomization. Withdrawal after randomization, prior to baseline treatment is not expected. In case of such an event, those patients are excluded from the analysis population and those patients will not be replaced.
  - **Premature discontinuation from study:** Some patients could discontinue the study prior to the time point of predose Cycle 2 due to death or other reasons. Considering the short interval between randomization and Cycle 2, this situation is expected to be exceptional. Those patients are excluded from the population.
  - **Missing or outside of window PK samples:** Some patients could have a Cycle 1 C_{trough} PK sample missing or outside of the accepted window, due to early withdrawal or other reasons. Every effort will be made to collect PK samples on schedule. Those patients are excluded from the analysis population.
- **Summary measure:** Geometric mean ratio (GMR) and 90% CI of atezolizumab SC versus atezolizumab IV of Cycle 1 C_{trough}. The non-inferiority would be established if the lower bound of the 90% CI is ≥ 0.8.

Co-Primary Estimand 2:

- **Population:** Patients with locally advanced or metastatic NSCLC who are CITnaive and for whom prior platinum therapy has failed. The analysis population will consist of the PK Evaluable population, with patients grouped according to their received treatments.
- **Variable:** Model-predicted Cycle 1 $AUC_{0-21\ d}$ derived from the popPK model.
- **Treatment:** same as for co-primary endpoint Cycle 1 observed serum C_{trough}
- **Intercurrent Events and Handling Strategy:**
  - **Absence of post-treatment PK blood sample:** Some patients could discontinue the study following their Cycle 1 dose prior to providing a post- baseline PK blood sample or PK blood samples could not be collected. Considering the short interval between the first study drug treatment (Cycle 1) and the first PK blood sample (8+/- 2 hours) as well as the numerous PK blood samples collected on study, these situations are expected to be exceptional. Those patients are excluded from the analysis population.
  - **Premature discontinuation from treatment:** Every effort will be made to ensure all randomized patients will receive the study drug treatment and corresponding PK sample collected. Treatment will start within 5 days of randomization. Withdrawal after randomization, prior to baseline treatment is not expected. In case of such an event, those patients are excluded from the analysis population and those patients will not be replaced
  - **Missing or inaccurate time and date reported for treatment administration or PK blood samples:** Every effort will be made to ensure all randomized patients will receive the treatment and will have the time and date of dosing and PK blood samples reported accurately. Missing or inaccurate dosing time and date can occur during any cycle however, it is very rare. In case of such an event, only such affected samples are excluded, and patients are retained as long as they have a single reportable dose and corresponding PK sample, regardless of the cycle.
- **Summary measure:** GMR and 90% CI of atezolizumab SC versus atezolizumab IV of Cycle 1 model predicted $AUC_{0\text{-}21d}$. The non-inferiority would be established if the lower bound of the 90% CI is ≥ 0.8.

Main Analytical Approach for Co-Primary Endpoints

The primary analysis of C_{trough} is based on logarithmic values of observed C_{trough} in Cycle 1 to compensate the known skewness of its distribution. For natural logarithm (Ln) trough plasma concentration (C_{trough}), the statistical hypothesis will be tested using an analysis of covariance model:

$$Ln(C_{trough})_{ij} = \mu + \tau_i + \varepsilon_{ij} \quad (i=SC, IV; j=1, 2, \ldots, n_i)$$

where μ denotes the overall mean, τ_i the effect of atezolizumab route of administration i (SC or IV), n_i the number of patients in arm i (SC or IV), and ε_{ij} a random error variable assumed to be independently and identically normally distributed with mean zero and variance σ_ε^2.

The contrast $\tau_{SC} - \tau_{IV}$, its 90% confidence limits, and the variance σ^2 will be estimated from the model. An estimate of the treatment effects ratio and the corresponding 90% confidence limits for the untransformed variables will be calculated by exponentiation of the estimate of contrast $\tau_{SC} - \tau_{IV}$ and the 90% confidence limits. The CV for the untransformed primary variable will be estimated using the relationship $CV_\varepsilon = sqrt(exp(\sigma_\varepsilon^2)-1)$.

If the lower confidence interval bound of $exp(Ln[C_{trough,SC}]-Ln[C_{trough,IV}])=C_{trough,SC}/C_{trough,IV}$ is equal or greater than 0.8, then the null hypothesis can be rejected.

The model-predicted Cycle 1 $AUC_{0-21\ d}$ is a co-primary endpoint and will be analyzed using the same method as for the other co-primary endpoint, Cycle 1 observed serum C_{trough}.

The co-primary endpoints will be statistically tested at the same α-level (one-sided significance level of 0.05) using the Hochberg procedure.

Supplementary Analysis for Co-Primary Endpoints

A supplementary sensitivity analysis may be conducted on Cycle 1 C_{trough} values derived from the popPK model. The aim of using predicted C_{trough} is to take into account possible deviations from the protocol (i.e., sampling schedule or dosing interval) and to reduce noise (i.e., precision of analytical measurement).

The Cycle 1 C_{trough} values derived from the popPK model is a different estimand with respect to the observed serum $C_{trough.}$ The attributes such as treatment and summary measure have the same definition as the primary endpoint (C_{trough}), while the population and intercurrent events will be defined and handled using the same approach and strategies specified for the model-predicted Cycle 1 AUC.

PK Analyses

For secondary PK and popPK analyses, the PK evaluable population will be used.

Model- predicted C_{trough} at Cycle 1 (C_{trough} Cycle 1), model-predicted C_{trough} at steady state ($C_{trough,ss}$), and model-predicted AUC at steady state (AUC_{ss}) will be descriptively compared between atezolizumab SC and IV.

The PK data will be analyzed using statistical summary measures, listings, and graphs as appropriate, documented in more detail in a Clinical Pharmacology Analysis Plan (2022), and also reported in a standalone PK report.

Efficacy Analyses

The Response-evaluable population will be used for key secondary endpoint analysis of objective response rate (ORR) whilst a subset who achieved objective response, will be used for duration of response (DOR). The Full Analysis Set will be used for key secondary endpoint analyses such as progression-free survival (PFS) and overall survival (OS). The analysis mentioned below will be performed at the time of primary analysis and at the end of the study. However, efficacy endpoints at the time of primary analysis given the nature of the trial and extremely small follow-up time will be immature. Therefore, for the primary analysis, secondary endpoints will be descriptively compared between atezolizumab SC and IV, followed by more formal analysis in the final report, which will include more follow-up time.

Objective Response Rate

The analysis population for ORR will be the Response-evaluable population. Patients not meeting the criteria for ORR, including patients without any post baseline tumor assessment, will be considered non-responders.

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population**: All randomized patients with measurable disease at baseline included in the Response-evaluable population.
- **Variable**: ORR, defined as the proportion of patients with a CR or PR, as determined by the investigator according to RECIST v1.1.

- **Treatment**: As defined for the primary estimand
- **Intercurrent events and Handling Strategy**:
  - Use of any non-protocol anti-cancer treatment (NPT) prior to disease progression as detailed in Protocol Section 4.4.3.
  - Discontinuation of study treatment prior to disease progression
  - **ICE Handling Strategy:** Following treatment policy, all the ICE's will be ignored, and tumor assessment data collected after the ICE will be included in the ORR analysis.
- **Population-level summary:** Difference in proportion.

The ORR and 95% confidence intervals according to Clopper-Pearson will be calculated and presented by treatment arm. For the difference in response rates, 95% two-sided confidence intervals (Hauck-Anderson) will be calculated. The above analysis will be repeated as apart of sensitivity analysis for confirmed ORR (CR or PR on two consecutive occasions ≥ 28 days apart, as determined by the investigator according to RECIST v1.1.)

Progression-Free Survival

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population**: All randomized patients with locally advanced or metastatic NSCLC who are CIT-naive and for whom prior platinum therapy has failed.
- **Variable**: PFS, defined as the time from the date of study entry to the date of documented disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever is earlier.
- **Treatment**: As defined for the primary estimand.
- **Intercurrent events and Handling Strategy**:
  - Use of any non-protocol anti-cancer treatment (NPT) prior to disease progression as detailed in Protocol Section 4.4.3.
  - Discontinuation of study treatment prior to disease progression
  - **ICE Handling Strategy:** Following treatment policy, all the ICE's will be ignored, and observations collected after the ICE will be included in the PFS analysis.
- **Population-level summary:** Median duration and corresponding 95% CI.

If participants have any intercurrent event(s), then the strategies defined above to handle the intercurrent events will be implemented. Otherwise, data for participants without the occurrence of disease progression or death as of the clinical cutoff date (CCOD) will be censored at the time of the last tumor assessment prior to the CCOD (or at the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit). PFS will be analyzed using Kaplan-Meier methodology, including survival plots, median duration and corresponding 95% confidence intervals according to the

Brookmeyer- Crowley method (Brookmeyer and Crowley, Biometrics 1982). The proportion of patients who are PFS event-free at 6 and 12 months after study entry will be estimated at the final analysis of the study when sufficient follow-up data are available. The corresponding 95% CI will be calculated using the standard error derived from Greenwood's formula. The hazard ratio (HR), and 95% CI for descriptive comparison will be estimated using a Cox regression model.

At the time of final analysis, additional sensitivity analyses of PFS may be conducted as appropriate in order to investigate the effect of baseline characteristics imbalances (if any) on the result.

Overall Survival

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population**: All randomized patients with locally advanced or metastatic NSCLC who are CIT-naive and for whom prior platinum therapy has failed.
- **Variable**: OS, defined as the time from randomization to death from any cause
- **Treatment**: As defined for the primary estimand
- **Intercurrent events and Handling Strategy**:
  - Use of any non-protocol anti-cancer treatment (NPT) prior to disease progression as detailed in Protocol Section 4.4.3.
  - Discontinuation of study treatment prior to disease progression
  - **ICE Handling Strategy**: Following treatment policy, all the ICE's will be ignored, and observations collected after the ICE will be included in the OS analysis.
- **Population-level summary:** Median duration and corresponding 95% CI.

If participants have any intercurrent events, then the strategies defined above to handle the intercurrent events will be implemented. Otherwise, data for patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Data from patients without postbaseline information will be censored at the date of randomization plus 1 day. OS will be analyzed using Kaplan-Meier methodology, including survival plots, median duration and corresponding 95% confidence intervals according to the Brookmeyer- Crowley method

(Brookmeyer and Crowley, Biometrics 1982). The proportion of patients alive at one and two years after study entry will be estimated at the final analysis of the study when sufficient follow-up data are available. The corresponding 95% CI will be calculated using the standard error derived from Greenwood's formula. The hazard ratio (HR), and 95% CI for descriptive comparison will be estimated using a Cox regression model.

At the time of final analysis, additional sensitivity analyses of OS may be conducted as appropriate in order to investigate the effect of baseline characteristics imbalances (if any) on the result.

Duration of Response

Analysis of DOR will include only patients who had an objective response. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a complete or partial response, DOR will be censored at the date of the first occurrence of a complete or partial response plus 1 day.

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population**: All patients with a measurable disease at baseline and a post-baseline objective response.
- **Variable**: DOR, defined as the time interval from the date of the first occurrence of a complete or partial response (whichever status is recorded first) until the first date that progressive disease or death is documented, whichever occurs first.

- **Treatment**: As defined for the primary estimand
- **Intercurrent events and Handling Strategy**:
  - Use of any non-protocol anti-cancer treatment (NPT) prior to disease progression as detailed in Protocol Section 4.4.3.
  - Discontinuation of study treatment prior to disease progression
  - **ICE Handling Strategy:** Following treatment policy, all the ICE's will be ignored and observations collected after the ICE will be included in the DOR analysis.
- **Population-level summary:** Median duration and corresponding 95% CI.

DOR is based on a non-randomized subset of patients (specifically, patients who achieved an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the PFS analysis will be used for the DOR analysis. The HR and 95% CI for descriptive comparison will be estimated using a Cox regression model.

The above analysis will be repeated for confirmed objective response as defined above.

Patient Reported Outcomes

An additional secondary objective for Part 2 is to evaluate patient experience with atezolizumab SC compared with atezolizumab IV, based on the following endpoints:

- Functioning and global health status over time, as assessed by the physical functioning, role functioning, and global health status/quality of life scales of the EORTC interleukin 57 (IL57)
- Overall satisfaction with treatment, as assessed by the modified satisfaction with therapy (SWT) scale of the Cancer Therapy Satisfaction Questionnaire (CTSQ)

Descriptive analyses, including summary statistics, will be performed, and presented by treatment arm for each patient-reported experience measure (item- and scale-level, as appropriate). Item-level analyses will include frequencies and proportions and change from baseline at each visit by treatment arm. Summary statistics (e.g., mean, median, minimum, maximum, interquartile range) of scale scores and score changes from baseline at each visit will be evaluated by treatment arm.

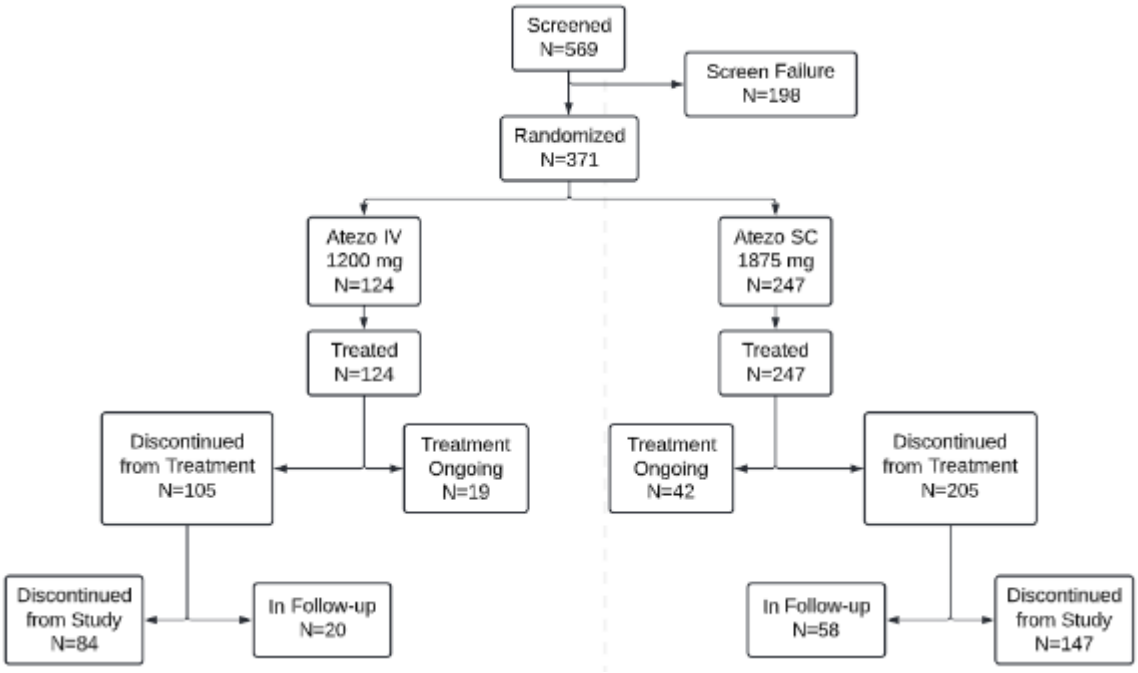
For each of the EORTC scales, a prorated scale score will be calculated if 50% or more of the constituent items in the scale are completed. The scale score will be considered missing if ☐ 50% of the constituent items were not completed. A SWT scale score will be calculated if five or more items have been completed (out of seven). The scale score will be considered missing if fewer than five items have been completed.

PRO completion, compliance rates, and reasons for missing data will be summarized at each time point by treatment arm for each measure in full analysis set. The compliance rate will be based on the total number of patients expected to complete the questionnaire at a particular time point.

Results

- **Participant flow**

Figure 16 : Patient Disposition-Part 2 (All Patients)



- **Recruitment**

First patient randomized and enrolled in part 2 took place on 2-DEC-2020. Last patient was enrolled on 30-MARCH-2022. The initial CCOD was 26-APR-2022 and updated data with an additional 9 months of follow up has been provided with the DCO of 16 January 2023

Part 2 of this study was conducted at 68 centres in 19 countries (number of centres, number of patients at time of CCOD):

Thailand (8; 69), Russian Federation (8; 44), Turkey (5; 54), Brazil (5; 22), China (5; 10), Ukraine (4; 28), Peru (4; 18), Guatemala (4; 7), Chile (3; 32), New Zealand (3; 13), Argentina (3; 7), South Africa (3; 3), Spain (2; 20), Greece (2; 9), Costa Rica (2; 8), Mexico (2; 8), Hungary (2; 7), Poland (2; 6), and Latvia (1; 6). Of note, 3 of the 6 patients from Poland were initially enrolled in Ukraine but were moved to Poland at the time of the clinical data cut-off.

- **Conduct of the study**

Key protocol amendments

The first version of the protocol is dated 5-AUG-2018. There were 5 amendments and version 6 is dated 25-FEB-2022. Version 2 affects only part 1 of the protocol. The main changes to the protocol and their rationale are summarised below:

- The term "immune-related" has been changed to "immune-mediated" when describing events associated with atezolizumab (Section 5.1.1).

- The procedures for reporting infusion-related reactions and injection-related reactions (IRRs) have been modified to include reporting of cytokine-release syndrome (CRS), as there may be significant overlap in signs and symptoms of IRRs and CRS (Sections 5.1.1).

- For patients who do not initially meet all eligibility criteria for participation in this study, an additional re-screening opportunity has been added (for a total of three screenings per patient) at the investigator's discretion, provided all initial and subsequent screening assessments are performed within 56 days prior to Day 1 (Section 3.1.1).

- Immunosuppressive medications have been removed from the prohibited therapy section and added to the cautionary therapy section to align with management guidelines that permit use of immunosuppressive medications for the treatment of corticosteroid-refractory immune-mediated adverse events (Sections 4.4.2.1 and 4.4.3).

- Lists of identified risks for atezolizumab have been revised to include severe cutaneous adverse reactions (Section 5.1.1).

- Appendix 8 has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent.

- Guidelines for management of atezolizumab-associated dermatologic adverse events have been revised to provide guidance on severe cutaneous adverse reactions of Stevens-Johnson syndrome and toxic epidermal necrolysis (Appendix 10).

- Benefit-risk assessment and guidance on concomitant administration of severe acute respiratory syndrome coronavirus 2 vaccines with atezolizumab has been added (Sections 1.5, 4.4.1, 5.1, and Appendix 10).

Key SAP amendments

The statistical analysis plan (SAP) was developed based on Roche model document Version 2, 20-OCT-2020 for Study BP40657 (IMscin001) and has been amended to incorporate the following changes:

- The name of Population PK analysis set has been changed to PK evaluable set.

- Minor updates have been made to the definition of Per Protocol PK population and PK evaluable population to improve clarity.

- Confirmed duration of response evaluable population has been added to the analysis set in Section 4.

VERSION 1, 10-NOV-2021:

- The approximate number of patients expected to be enrolled in Part 2 of the study has been increased to 327 to accommodate the new co-primary PK endpoint (Cycle 1 AUC 0–21 d). It has also been clarified that the total number of patients to be enrolled in Part 2 may be increased or decreased after taking into account the actually observed PK variability during the blinded sample-size re-estimation (Sections 3.1.1.2, 4.1, 6.3.2, 6.8.1, 6.14, and 9.5).

VERSION 2, 25-MARCH-2022:

· Estimand language in Section 6.6.2 has been corrected to match the definition of Per Protocol PK analysis population provided in Section 6.2.2. In the same section, the lower bound of the interval has been corrected to ≥0.8 instead of >0.8.

Protocol deviations

Table 15: Summary of major protocol deviations (Part 2 , FAS)

Summary of Major Protocol Deviations, Part 2, Full Analysis Set
Protocol: BP40657

Category Description	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Total number of patients with at least one major protocol deviation	64 (51.6%)	103 (41.7%)	167 (45.0%)
Total number of major protocol deviations	111	156	267
EXCLUSION CRITERIA			
Total	6 (4.8%)	10 (4.0%)	16 (4.3%)
Exclusion-related test not done	3 (2.4%)	3 (1.2%)	6 (1.6%)
Symptomatic, untreated or actively progression CNS metastases	1 (0.8%)	3 (1.2%)	4 (1.1%)
Clinically significant cardiovascular disease	0	2 (0.8%)	2 (0.5%)
Major surgical procedure within 4 weeks prior to study treatment or anticipation of need	0	1 (0.4%)	1 (0.3%)
Prior treatment with immunotherapy or immunostimulatory or immunosupressive agents	0	1 (0.4%)	1 (0.3%)
Tested PD-L1 expression status	1 (0.8%)	0	1 (0.3%)
Uncontrolled or symptomatic hypercalcemia	1 (0.8%)	0	1 (0.3%)
INCLUSION CRITERIA			
Total	12 (9.7%)	19 (7.7%)	31 (8.4%)
Inclusion-related test not done	9 (7.3%)	10 (4.0%)	19 (5.1%)
Lung cancer criteria not met	2 (1.6%)	5 (2.0%)	7 (1.9%)
Inadequate hematologic & organ function at baseline	0	2 (0.8%)	2 (0.5%)
No signed informed consent	1 (0.8%)	1 (0.4%)	2 (0.5%)
Non-measurable disease only	0	2 (0.8%)	2 (0.5%)
Unknown EGFR status at the time of randomization	1 (0.8%)	0	1 (0.3%)
MEDICATION			
Total	8 (6.5%)	8 (3.2%)	16 (4.3%)
Dose (atezo SC co-mix/atezo SC/atezo IV) missed or significantly out of window	8 (6.5%)	7 (2.8%)	15 (4.0%)
Other significant medication deviation affecting patient's safety, PK or immunogenicity	0	1 (0.4%)	1 (0.3%)
PROCEDURAL			
Total	56 (45.2%)	87 (35.2%)	143 (38.5%)
Key PK or ADA sample not done or outside of window	37 (29.8%)	55 (22.3%)	92 (24.8%)
Key assessment not done or done outside of window	17 (13.7%)	24 (9.7%)	41 (11.1%)
Tumor assessment not done or repetitively done out of window	7 (5.6%)	5 (2.0%)	12 (3.2%)
Other significant procedural deviation affecting safety/PK/immunogenicity	3 (2.4%)	8 (3.2%)	11 (3.0%)
Failure to report SAE/AESIs per protocol	3 (2.4%)	7 (2.8%)	10 (2.7%)
New ICF version not signed at next patient's visit	3 (2.4%)	4 (1.6%)	7 (1.9%)
Patient Questionnaires not completed at BL	2 (1.6%)	1 (0.4%)	3 (0.8%)
Complete blood panel (haem/biochem/coagulation) not done or done out of window	1 (0.8%)	1 (0.4%)	2 (0.5%)
Incorrect place of SC administration	0	1 (0.4%)	1 (0.3%)

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once.
For the total number of deviations, multiple occurrences of the same deviation in an individual are counted separately.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/t_dv.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/CSRPrimary_20220426/prod/output/t_dv_P2_FAS_26APR2022_40657.out
25JUL2022 15:23 Page 1 of 1

Baseline data

- **Table 16: Summary of baseline demographic characteristics (Part 2 , FAS)**

Patient Demographics, Part 2, Full Analysis Set
Protocol: BP40657

	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Age (years)			
n	124	247	371
Mean (SD)	64.4 (9.5)	62.2 (9.5)	63.0 (9.9)
Median	66.0	63.0	64.0
Min - Max	42 - 85	27 - 85	27 - 85
Age Group (years)			
n	124	247	371
< 65	58 (46.8%)	137 (55.5%)	195 (52.6%)
>= 65	66 (53.2%)	110 (44.5%)	176 (47.4%)
Age Group (years)			
n	124	247	371
< 65	58 (46.8%)	137 (55.5%)	195 (52.6%)
65 to 74	50 (40.3%)	86 (34.8%)	136 (36.7%)
75 to 84	15 (12.1%)	23 (9.3%)	38 (10.2%)
>= 85	1 (0.8%)	1 (0.4%)	2 (0.5%)
Sex			
n	124	247	371
Male	82 (66.1%)	175 (70.9%)	257 (69.3%)
Female	42 (33.9%)	72 (29.1%)	114 (30.7%)
Race			
n	124	247	371
American Indian or Alaska Native	9 (7.3%)	15 (6.1%)	24 (6.5%)
Asian	33 (26.6%)	47 (19.0%)	80 (21.6%)
Black or African American	1 (0.8%)	2 (0.8%)	3 (0.8%)
Native Hawaiian or other Pacific Islander	2 (1.6%)	1 (0.4%)	3 (0.8%)
White	74 (59.7%)	174 (70.4%)	248 (66.8%)
Multiple	5 (4.0%)	6 (2.4%)	11 (3.0%)
Unknown	0	2 (0.8%)	2 (0.5%)
Ethnicity			
n	124	247	371
Hispanic or Latino	36 (29.0%)	61 (24.7%)	97 (26.1%)
Not Hispanic or Latino	88 (71.0%)	185 (74.9%)	273 (73.6%)
Unknown	0	1 (0.4%)	1 (0.3%)
Region			
n	124	247	371
Asia-Pacific	32 (25.8%)	47 (19.0%)	79 (21.3%)
Australia	5 (4.0%)	8 (3.2%)	13 (3.5%)
Central or South America	37 (29.8%)	65 (26.3%)	102 (27.5%)
Europe and Middle East	50 (40.3%)	127 (51.4%)	177 (47.7%)
Weight (kg) at baseline			
n	124	244	368
Mean (SD)	69.27 (15.12)	69.85 (16.06)	69.69 (15.74)
Median	69.10	67.80	68.00
Min - Max	34.6 - 114.0	30.0 - 117.0	30.0 - 117.0
Body Mass Index (kg/m2) at baseline			
n	123	243	366
Mean (SD)	25.29 (4.42)	24.96 (4.81)	25.07 (4.68)
Median	24.81	24.60	24.67
Min - Max	15.3 - 35.7	12.9 - 41.4	12.9 - 41.4
ECOG Score			
n	124	247	371
0	28 (22.6%)	67 (27.1%)	95 (25.6%)
1	96 (77.4%)	180 (72.9%)	276 (74.4%)
Tobacco Use History			
n	124	247	371
Never	40 (32.3%)	71 (28.7%)	111 (29.9%)
Current	20 (16.1%)	40 (16.2%)	60 (16.2%)
Previous	64 (51.6%)	136 (55.1%)	200 (53.9%)

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SAS/prod/program/t_dm.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/CSRPrimary_20220426/prod/output/t_dm_P2_FAS_26APR2022_40657.out

Table 17: Baseline disease characteristics and NSCLC history (Part 2 FAS)

Baseline Disease Characteristics and NSCLC History, Part 2, Full Analysis Set
Protocol: BP40657

	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Staging at Initial Diagnosis			
n	124	247	371
STAGE IA	2 (1.6%)	4 (1.6%)	6 (1.6%)
STAGE IB	3 (2.4%)	3 (1.2%)	6 (1.6%)
STAGE ILA	2 (1.6%)	3 (1.2%)	5 (1.3%)
STAGE IIB	6 (4.8%)	9 (3.6%)	15 (4.0%)
STAGE IIIA	10 (8.1%)	32 (13.0%)	42 (11.3%)
STAGE IIIB	14 (11.3%)	25 (10.1%)	39 (10.5%)
STAGE IIIC	5 (4.0%)	9 (3.6%)	14 (3.8%)
STAGE IVA	52 (41.9%)	92 (37.2%)	144 (38.8%)
STAGE IVB	30 (24.2%)	70 (28.3%)	100 (27.0%)
Current Disease Status			
n	124	247	371
Locally Recurrent Disease	0	4 (1.6%)	4 (1.1%)
Locally Advanced Unresectable Disease	10 (8.1%)	8 (3.2%)	18 (4.9%)
Metastatic Disease	114 (91.9%)	235 (95.1%)	349 (94.1%)
Histology at Initial Diagnosis			
n	124	247	371
Squamous	48 (38.7%)	82 (33.2%)	130 (35.0%)
Non-Squamous	76 (61.3%)	165 (66.8%)	241 (65.0%)
Histology if Non-Squamous			
n	76	165	241
Adenocarcinoma	72 (94.7%)	153 (92.7%)	225 (93.4%)
Large Cell	0	2 (1.2%)	2 (0.8%)
Large Cell with Neuroendocrine Diff.	0	0	0
Poorly Differentiated	1 (1.3%)	5 (3.0%)	6 (2.5%)
Mixed (Not Including Small Cell)	0	0	0
NSCLC/NOS	1 (1.3%)	2 (1.2%)	3 (1.2%)
Other	2 (2.6%)	3 (1.8%)	5 (2.1%)
Number of Anatomical Locations of Metastatic Disease at Enrollment			
n	124	247	371
Mean (SD)	2.87 (1.36)	3.15 (1.44)	3.06 (1.42)
Median	3.00	3.00	3.00
Min - Max	1.0 - 7.0	1.0 - 8.0	1.0 - 8.0

Baseline Disease Characteristics and NSCLC History, Part 2, Full Analysis Set
Protocol: BP40657

	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Time from 1st Diagnosis of Locally Recurrent Disease to Initial Dose Admin. (Months)			
n	0	4	4
Mean (SD)	NE (NE)	8.54 (7.92)	8.54 (7.92)
Median	NE	6.95	6.95
Min - Max	NE - NE	0.8 - 19.5	0.8 - 19.5
Time from 1st Diagnosis of Locally Advanced Unresectable Disease to Initial Dose Admin. (Months)			
n	10	8	18
Mean (SD)	8.27 (6.53)	8.25 (7.32)	8.26 (6.68)
Median	7.67	7.43	7.43
Min - Max	1.4 - 18.8	1.1 - 24.6	1.1 - 24.6
Time from 1st Diagnosis of Metastatic Disease to Initial Dose Admin. (Months)			
n	114	234	348
Mean (SD)	13.51 (14.40)	12.67 (13.31)	12.95 (13.66)
Median	9.40	9.02	9.22
Min - Max	0.5 - 95.8	0.2 - 88.6	0.2 - 95.8
EGFR Mutation Status			
n	124	247	371
Positive	8 (6.5%)	11 (4.5%)	19 (5.1%)
Negative	95 (76.6%)	198 (80.2%)	293 (79.0%)
Not-Evaluable	2 (1.6%)	2 (0.8%)	4 (1.1%)
Not Done	16 (12.9%)	33 (13.4%)	49 (13.2%)
Unknown	3 (2.4%)	3 (1.2%)	6 (1.6%)
EML4-ALK Mutation Status			
n	124	247	371
Positive	2 (1.6%)	4 (1.6%)	6 (1.6%)
Negative	100 (80.6%)	196 (79.4%)	296 (79.8%)
Not-Evaluable	3 (2.4%)	3 (1.2%)	6 (1.6%)
Not Done	19 (15.3%)	44 (17.8%)	63 (17.0%)
Other Mutations (KRAS, RET, ROS1, MET, B-RAF)			
n	124	247	371
Positive	9 (7.3%)	14 (5.7%)	23 (6.2%)
Negative	20 (16.1%)	57 (23.1%)	77 (20.8%)
Not-Evaluable	7 (5.6%)	8 (3.2%)	15 (4.0%)
Not Done	74 (59.7%)	143 (57.9%)	217 (58.5%)
Unknown	14 (11.3%)	25 (10.1%)	39 (10.5%)

	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Baseline Target Tumor Sum Longest Diameter (mm)			
n	124	245	369
Mean (SD)	80.74 (49.63)	91.18 (58.36)	87.67 (55.73)
Median	68.45	79.00	74.00
Min - Max	14.0 - 245.0	10.0 - 319.0	10.0 - 319.0
Liver Metastases at Baseline			
n	124	247	371
Yes	26 (21.0%)	77 (31.2%)	103 (27.8%)
No	98 (79.0%)	170 (68.8%)	268 (72.2%)
Brain Metastases at Baseline			
n	124	247	371
Yes	19 (15.3%)	42 (17.0%)	61 (16.4%)
No	105 (84.7%)	205 (83.0%)	310 (83.6%)
Bone Metastases at Baseline			
n	124	247	371
Yes	35 (28.2%)	84 (34.0%)	119 (32.1%)
No	89 (71.8%)	163 (66.0%)	252 (67.9%)
Albumin at Baseline			
n	123	247	370
Mean (SD)	40.26 (5.73)	39.38 (7.03)	39.67 (6.63)
Median	41.00	40.00	40.85
Min - Max	4.0 - 53.6	3.9 - 51.0	3.9 - 53.6
Prior (Neo) Adjuvant Treatment			
n	124	247	371
Yes	26 (21.0%)	42 (17.0%)	68 (18.3%)
No	98 (79.0%)	205 (83.0%)	303 (81.7%)
PD-L1 Status			
n	115	218	333
Positive	37 (32.2%)	97 (44.5%)	134 (40.2%)
Negative	78 (67.8%)	121 (55.5%)	199 (59.8%)
TC / IC categories			
TC0 and IC0	78 (62.9%)	121 (49.0%)	199 (53.6%)
TC1/2/3 or IC1/2/3	37 (29.8%)	97 (39.3%)	134 (36.1%)
TC2/3 or IC2/3	14 (11.3%)	38 (15.4%)	52 (14.0%)
TC3 or IC3	3 (2.4%)	13 (5.3%)	16 (4.3%)
Number of prior therapies			
n	124	247	371
1	97 (78.2%)	200 (81.0%)	297 (80.1%)
2	21 (16.9%)	41 (16.6%)	62 (16.7%)
3	5 (4.0%)	6 (2.4%)	11 (3.0%)
4	1 (0.8%)	0	1 (0.3%)

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
For EGFR, EML4-ALK central values are used, if central value is not available for a patient, local value is used instead. For Other Mutations (KRAS, RET, ROS1, MET, B-RAF) local values are used. For PDL1 and TC/IC scores central values are used.
EGFR mutation = Sensitizing EGFR mutations include all EGFR activating mutations in exons 18-21.
EML4-ALK positive = ALK translocation.
NOS: Not Otherwise Specified.
Number of prior therapies is calculated as the number of unique start dates of agents administered entered in the Prior Cancer Therapy eCRF page, with a start date available, and placebo is excluded.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Note: for PD-L1 status, the analysis were not done for 32 patients (n=22 had no samples available for testing, n=10 enrolled in China with no Human Genetics Resources Administration of China [HGRAC] approval of exploratory application). For 6 patients, the samples were tested but yielded "not evaluable" results. PD-L1 data were missing for n=9 and n=29 in the Atezo IV and Atezo SC arms, respectively.

- **Numbers analysed**

Table 18: Summary of Analysis populations (Part 2, All patients)

Analysis Populations, Part 2, All Patients
Protocol: BP40657

Analysis Populations	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Full Analysis Set (FAS)	124	247	371
Per Protocol PK-Evaluable Set	97	205	302
Total Exclusions	27	42	69
Patients are missing the Ctrough pre-dose Cycle 2 Day 1 PK sample	19	31	50
Patients had a Ctrough sample collected with at least 2 days deviation from the planned on Day 21	8	11	19
Patients had a Duplicate Ctrough sample collected	0	0	0
Patients were given a Cycle 1 dose amount that deviates from the planned dose by >20%	0	0	0
Patients with a subcutaneous injection site other than thigh is used on Cycle 1	0	1	1
PK-Evaluable Set	122	247	369
Total Exclusions	2	0	2
No post-baseline PK sample	2	0	2
Safety-Evaluable Set	124	247	371
Response-Evaluable Set	124	245	369
Total Exclusions	0	2	2
No measurable disease at baseline	0	2	2
DOR-Evaluable Set	12	29	41
Total Exclusions	112	218	330
No PR or CR response	112	216	328
No measurable disease at baseline	0	2	2
Confirmed DOR-Evaluable Set	10	21	31
Total Exclusions	114	226	340
No PR or CR response	112	216	328
No confirmed response	2	8	10
No measurable disease at baseline	0	2	2
Post-Treatment ADA-Evaluable Set	108	221	329
Total Exclusions	16	26	42
No post-baseline ADA result	16	26	42

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
ADA = anti-therapeutic antibodies; Per Protocol PK-Evaluable, PK-Evaluable, Safety-Evaluable and ADA-Evaluable sets are actual treatment received, other sets are randomized treatment.
For Per Protocol PK-Evaluable Set, a patient can have more than 1 exclusion reason.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/t_pop.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/CSRPrimary_20220426/prod/output/t_pop_P2_AP_26APR2022_40657.out

- **Outcomes and estimation**

The primary and main secondary endpoints of the study have been discussed in the PK section.

- **Main secondary efficacy endpoints:**

ORR (confirmed):

Table 19: Objective response rates (confirmed) (Part 2, Response Evaluable population) (CCOD 16 Jan 2023)

Overall Response Rates (Confirmed), Part 2, Response-Evaluable Population
Protocol: BP40657

	Atezo IV (N=124)		Atezo SC (N=245)
Responders	13 (10.5%)		27 (11.0%)
95% CI	(5.70, 17.26)		(7.39, 15.63)
Unstratified Analysis			
Difference in Overall Response Rates (95% CI)		0.54 (-6.56, 7.63)	
p-value (Cochran-Mantel-Haenszel)		0.8757	
Odds Ratio for Overall Response (95% CI)		1.06 (0.53, 2.13)	
Complete Response (CR)	0		0
95% CI	(0.00, 2.93)		(0.00, 1.49)
Partial Response (PR)	13 (10.5%)		27 (11.0%)
95% CI	(5.70, 17.26)		(7.39, 15.63)
Stable Disease (SD)	47 (37.9%)		97 (39.6%)
95% CI	(29.35, 47.05)		(33.42, 46.02)
Progressive Disease (PD)	45 (36.3%)		90 (36.7%)
95% CI	(27.85, 45.40)		(30.69, 43.11)
Not Evaluable (NE)	1 (0.8%)		2 (0.8%)
Missing	18 (14.5%)		29 (11.8%)

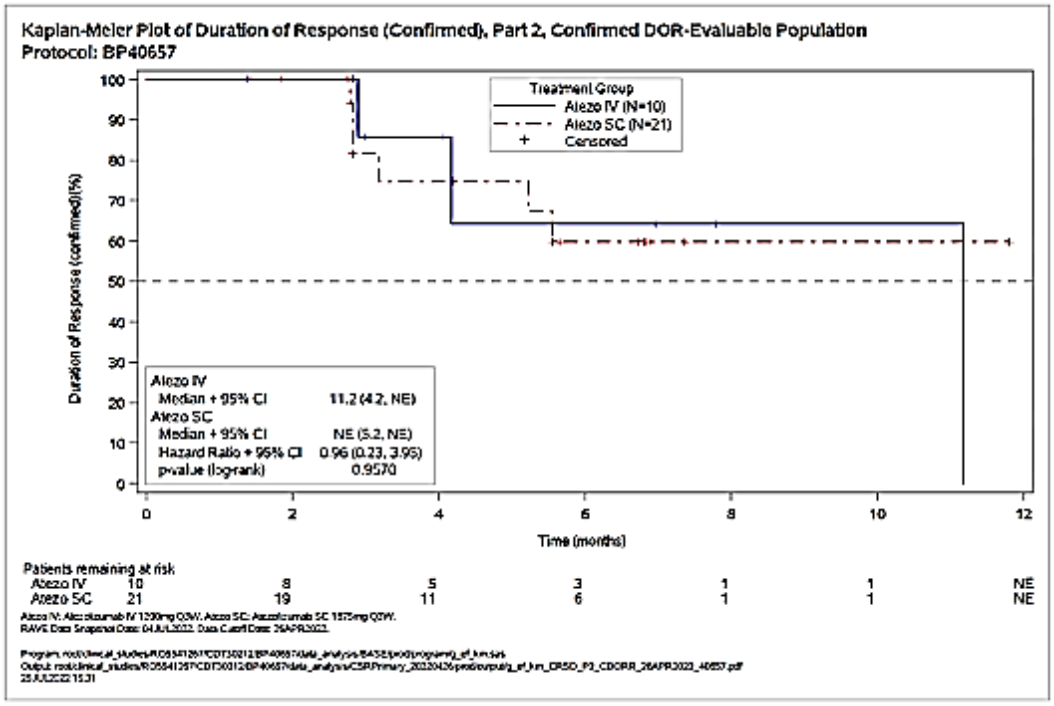
Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
95% CI for rates were constructed using Clopper-Pearson method. 95% CI for difference in rates were constructed using Continuity Correction of Anderson and Hauck. 95% CI for odds ratio was constructed using the Wald method. Responses were confirmed after 4 weeks. Patients were classified as "Stable Disease" if assessment was at least 6 weeks from baseline. Patients were classified as "Not Evaluable" if all post-baseline response assessments were reported as not evaluable, or SD assessment occurred within 6 weeks from baseline. Patients were classified as "Missing" if no post-baseline response assessments were available.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.

Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/t_ef_rsp.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/t_ef_rsp_CBOR_P2_ORR_16JAN2023_40657.out
28FEB2023 18:32 Page 1 of 1

DOR:

With regard to confirmed DOR, the proportion of patients with an event was 28.6% in the Atezo SC arm and 30.0% in the Atezo IV arm.

Figure 17: Kaplan-Meier Plot of duration of response (Part 2, DOR-Evaluable population)



PFS:

Table 20: Time to event summary for progression free survival (Part 2, FAS)

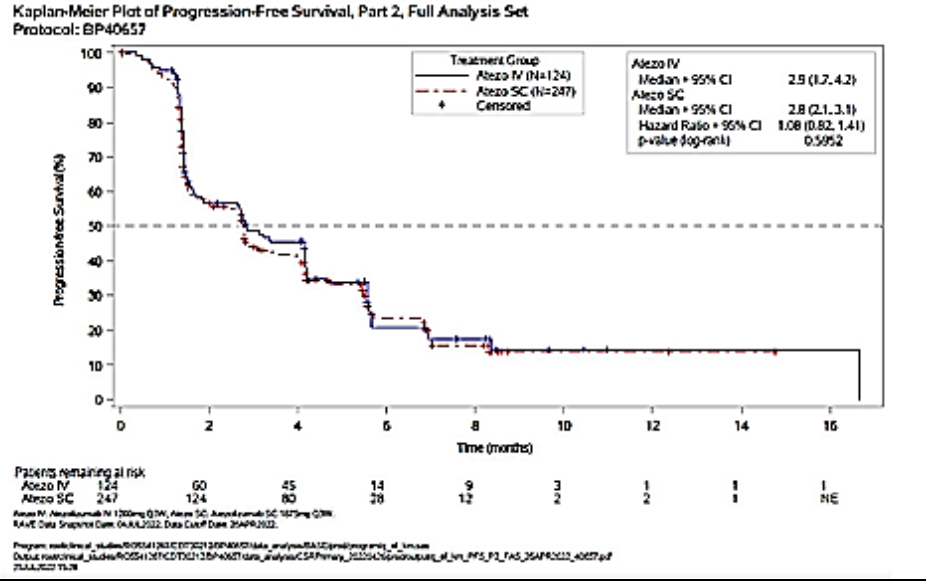
Time to Event Summary for Progression-Free Survival, Part 2, Full Analysis Set
Protocol: BP40657

	Atezo IV (N=124)		Atezo SC (N=247)
Patients with event (%)	84 (67.7%)		168 (68.0%)
Earliest contributing event			
Death	15		31
Disease Progression	69		137
Patients without event (%)	40 (32.3%)		79 (32.0%)
Time to Event (months)			
Median	2.9		2.8
95% CI	(1.7, 4.2)		(2.1, 3.1)
25% and 75%-ile	1.4 - 5.7		1.4 - 5.6
Range	0* - 17		0* - 15*
Unstratified Analysis			
p-value (log-rank)		0.5952	
Hazard Ratio		1.08	
95% CI		(0.82, 1.41)	
6 Month Survival			
Patients remaining at risk	14		28
Event Free Rate (%)	20.89		23.65
95% CI	(12.14, 29.64)		(17.27, 30.04)
Difference in Event Free Rate		2.77	
95% CI		(-5.07, 13.60)	
p-value (Z-test)		0.6167	
12 Month Survival			
Patients remaining at risk	1		2
Event Free Rate (%)	14.51		13.70
95% CI	(5.71, 23.30)		(7.17, 20.24)
Difference in Event Free Rate		-0.80	
95% CI		(-11.76, 10.16)	
p-value (Z-test)		0.8858	

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
* Censored value.
Summaries of Progression-Free Survival (median, percentiles) are Kaplan-Meier estimates.
95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/t_ef_tte.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/CSR2primary_20220426/prod/output/t_ef_tte_PFS_P2_FAS_26APR2022_40657.out

Figure 18: Kaplan-Meier Plot of progression free survival (Part 2, FAS)



OS:

Table 21: Time to event summary for Overall survival (Part 2, FAS)

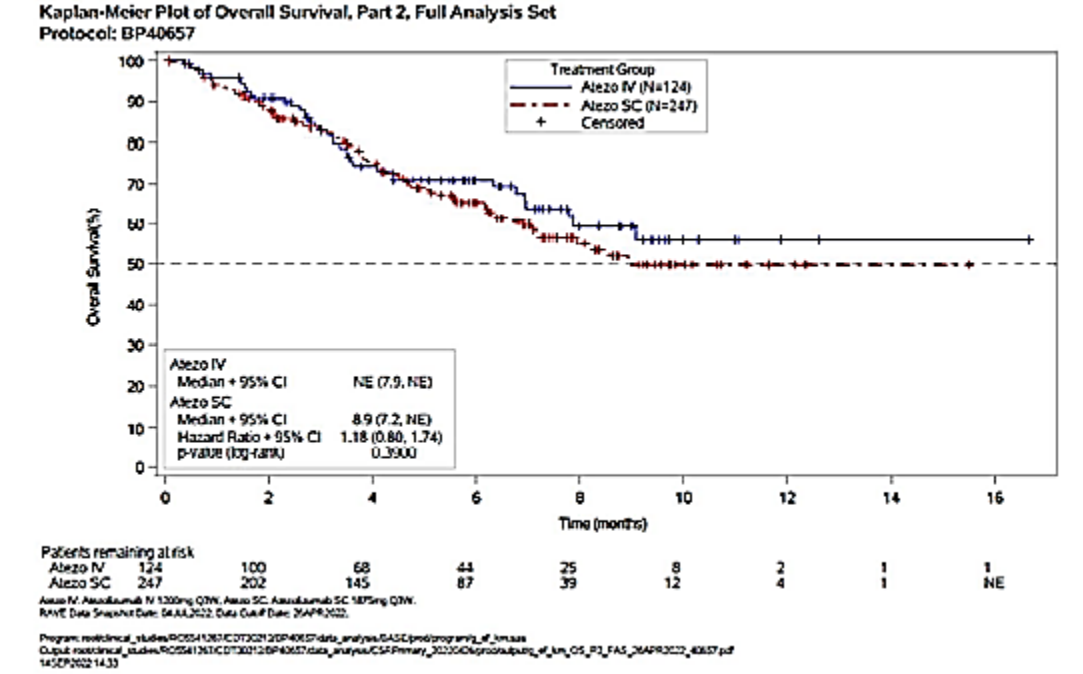
Time to Event Summary for Overall Survival, Part 2, Full Analysis Set
Protocol: BP40657

	Atezo IV (N=124)		Atezo SC (N=247)
Patients with event (%)	37 (29.8%)		86 (34.8%)
Earliest contributing event			
Death	37		86
Patients without event (%)	87 (70.2%)		161 (65.2%)
Time to Event (months)			
Median	NE		8.9
95% CI	(7.9, NE)		(7.2, NE)
25% and 75%-ile	3.6 - NE		4.1 - NE
Range	0 - 17*		0* - 16*
Unstratified Analysis			
p-value (log-rank)		0.3900	
Hazard Ratio		1.16	
95% CI		(0.80, 1.74)	
6 Month Survival			
Patients remaining at risk	44		87
Event Free Rate (%)	70.92		65.32
95% CI	(62.01, 79.82)		(58.68, 71.96)
Difference in Event Free Rate		-5.60	
95% CI		(-16.70, 5.51)	
p-value (Z-test)		0.3233	
12 Month Survival			
Patients remaining at risk	2		4
Event Free Rate (%)	55.86		49.78
95% CI	(43.27, 68.45)		(40.56, 59.01)
Difference in Event Free Rate		-6.08	
95% CI		(-21.68, 9.53)	
p-value (Z-test)		0.4454	

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
* Censored value.
Summaries of OS (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/t_ef_tte.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/CSRPrimary_20220426/prod/output/t_ef_tte_OS_P2_FAS_26APR2022_40657.out

Figure 19: Kaplan-Meier Plot of overall survival (Part 2, FAS)



Updated efficacy results from DCO 16 January 2023

Table 22: Overview of Efficacy

	Primary Analysis (CCOD 26 April 2022)		Updated Analysis (CCOD 16 January 2023)	
	Atezo IV 1200 mg (N = 124)	**Atezo SC 1875 mg (N = 247)**	**Atezo IV 1200 mg (N = 124)**	**Atezo SC 1875 mg (N = 247)**
Key Secondary Endpoints				
ORR (Unconfirmed)	N = 124	N = 245	N = 124	N = 245
Responders, N (%)	12 (9.7%)	29 (11.8%)	15 (12.1%)	34 (13.9%)
(95% CI)	(5.10, 16.29)	(8.07, 16.56)	(6.93, 19.17)	(9.81, 18.85)
ORR (Confirmed)	N = 124	N = 245	N = 124	N = 245
Responders, N (%)	10 (8.1%)	21 (8.6%)	13 (10.5%)	27 (11.0%)
(95% CI)	(3.94, 14.33)	(5.38, 12.80)	(5.70, 17.26)	(7.39, 15.63)
PFS	N = 124	N = 247	N = 124	N = 247
Patients with event (%)	84 (67.7%)	168 (68.0%)	107 (86.3%)	219 (88.7%)
Median time to event, months (95% CI)	2.9 (1.7, 4.2)	2.8 (2.1, 3.1)	2.9 (1.8, 4.2)	2.8 (2.7, 4.1)
OS	N = 124	N = 247	N = 124	N = 247
No. of deaths (%)	37 (29.8%)	86 (34.8%)	79 (63.7%)	144 (58.3%)
Median time to event, months (95% CI)	NE (7.9, NE)	8.9 (7.2, NE)	10.1 (7.5, 12.1)	10.7 (8.5, 13.8)
DOR (Unconfirmed)	N = 12	N = 29	N = 15	N = 34
Patients with event (%)	5 (41.7%)	10 (34.5%)	8 (53.3%)	19 (55.9%)
Median time to event, months (95% CI)	11.2 (2.9, NE)	5.6 (3.2, NE)	9.5 (4.2 NE)	7.5 (4.2 NE)
DOR (Confirmed)	N = 10	N = 21	N = 13	N = 27
Patients with event (%)	3 (30.0%)	6 (28.6%)	6 (46.2%)	12 (44.4%)
Median time to event, months (95% CI)	11.2 (4.2, NE)	NE (5.2, NE)	11.2 (4.2, NE)	15.1 (5.6, NE)

	Primary Analysis (CCOD 26 April 2022)		Updated Analysis (CCOD 16 January 2023)	
	Atezo IV 1200 mg (N = 124)	Atezo SC 1875 mg (N = 247)	Atezo IV 1200 mg (N = 124)	Atezo SC 1875 mg (N = 247)

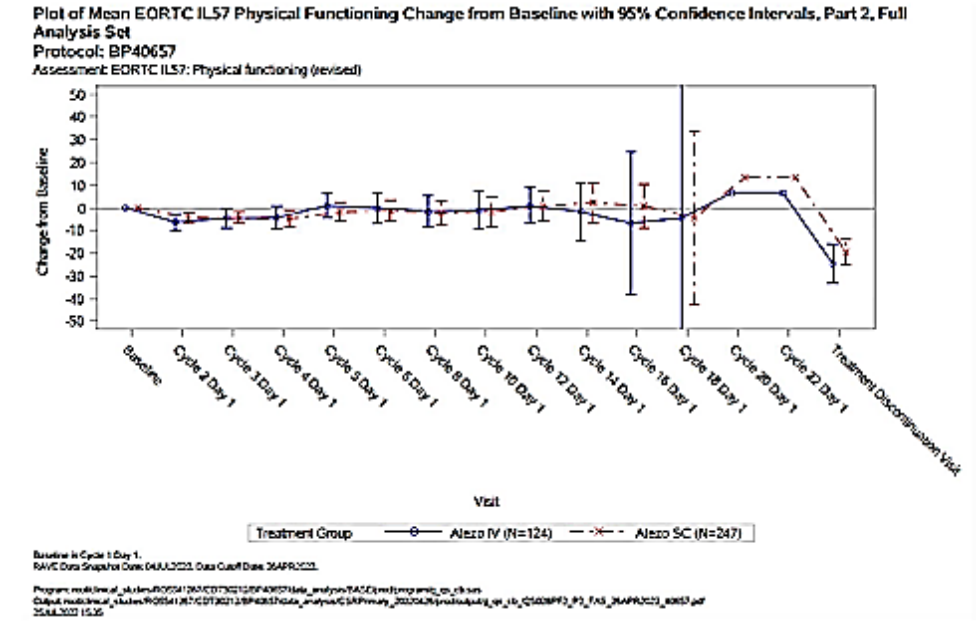
Atezo = atezolizumab; CCOD = clinical cutoff date; CI = confidence interval; DOR = duration of response; IV = intravenous; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SC = subcutaneous.
Source: Efficacy Update Report

Patient- and health care professional-reported experience assessments:

Patient reported-outcome (PRO) data were collected using the European Organization for Research and Treatment of Cancer (EORTC) Item Library (EORTC IL57) and the modified satisfaction with therapy (SWT) scale from the CTSQ. Health care providers (HCP) reported experience data were collected using the HCP SC versus IV Perspective Questionnaire and the HCP Subcutaneous Perspective Questionnaire.

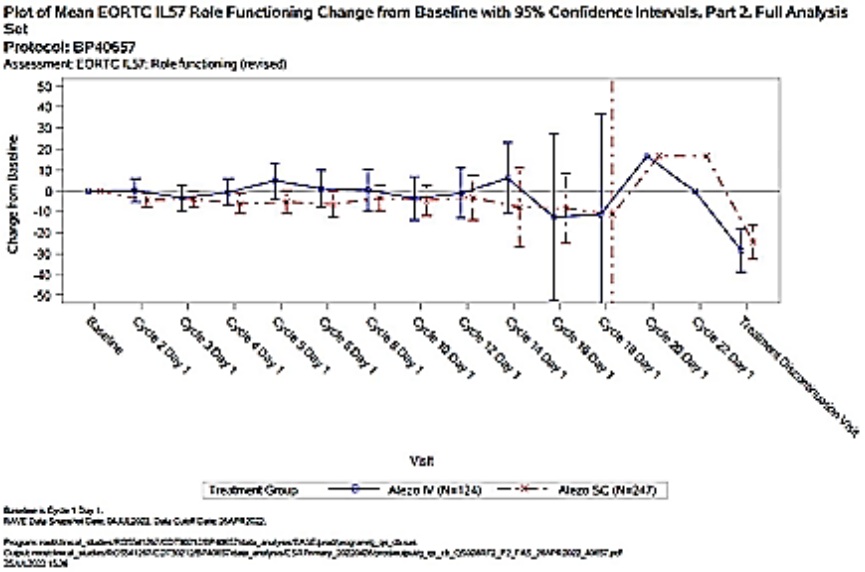
Physical functioning:

Figure 20: Plot of Mean EORTC IL57 Physical functioning change from baseline with 95% confidence intervals (Part 2, FAS)



Role functioning:

Figure 21: Plot of Mean EORTC IL57 Role functioning change from baseline with 95% confidence intervals (Part 2, FAS)



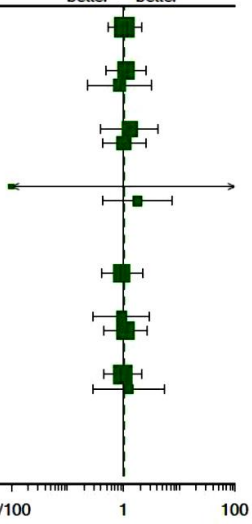
- **Ancillary analyses**

Subgroup analyses (CCOD 16 January 2023)

Table 23: Updated Forrest plot of HR for confirmed ORR by baseline characteristics subgroups:

Forest Plot of Odds Ratio for Overall Response Rates (Confirmed) by Baseline Characteristics Subgroups, Part 2, Response-Evaluable Population
Protocol: BP40657

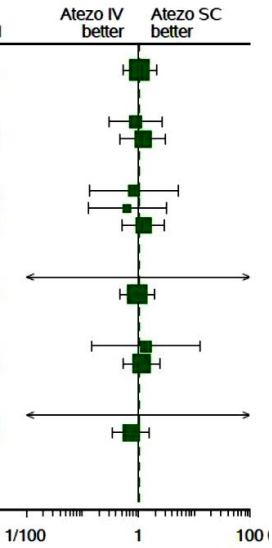
Baseline Risk Factors	Total n	Atezo IV (N=124) n	Atezo IV (N=124) Response (%)	Atezo SC (N=245) n	Atezo SC (N=245) Response (%)	Odds Ratio	95% CI
All Patients	369	124	10.5	245	11.0	1.06	(0.53, 2.13)
Sex							
Male	255	82	11.0	173	12.1	1.12	(0.49, 2.57)
Female	114	42	9.5	72	8.3	0.86	(0.23, 3.25)
Age Group (yr)							
< 65	195	58	6.9	137	8.8	1.30	(0.40, 4.20)
>= 65	174	66	13.6	108	13.9	1.02	(0.42, 2.49)
Race							
American Indian or Alaska Native	24	9	11.1	15	NE	<0.01	(0.00, NE)
Asian	79	33	9.1	46	15.2	1.79	(0.43, 7.53)
Black or African American	3	1	NE	2	NE	NE	NE
Multiple	11	5	NE	6	NE	NE	NE
Native Hawaiian or other Pacific Islander	3	2	NE	1	NE	NE	NE
Unknown	2			2	NE	NE	NE
White	247	74	12.2	173	11.6	0.94	(0.41, 2.18)
ECOG Performance Score							
0	94	28	17.9	66	16.7	0.92	(0.29, 2.95)
1	275	96	8.3	179	8.9	1.08	(0.44, 2.62)
Number of prior therapies							
1	295	97	10.3	198	10.1	0.98	(0.44, 2.18)
2	62	21	14.3	41	17.1	1.24	(0.28, 5.36)
3	11	5	NE	6	NE	NE	NE
4	1	1	NE			NE	NE



Odds ratios and the associated Wald confidence intervals were estimated using unstratified logistic regression.
The vertical dashed line indicates the hazard ratio for all patients (reference: Atezo IV).
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.
Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/g_ef_fp_rs.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/g_ef_fp_rs_CBOR_P2_ORR_16JAN2023_40657.pdf 24MAR2023 12:14

Forest Plot of Odds Ratio for Overall Response Rates (Confirmed) by Baseline Characteristics Subgroups, Part 2, Response-Evaluable Population
Protocol: BP40657

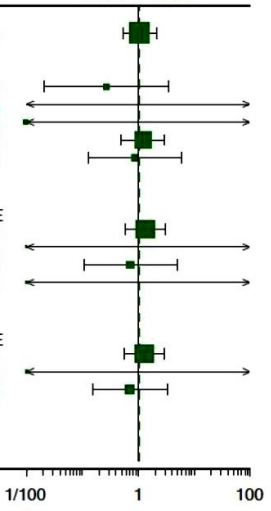
Baseline Risk Factors	Total n	Atezo IV (N=124) n	Response (%)	Atezo SC (N=245) n	Response (%)	Odds Ratio	95% CI
All Patients	369	124	10.5	245	11.0	1.06	(0.53, 2.13)
Histology at Initial Diagnosis							
Squamous	128	48	12.5	80	11.3	0.89	(0.30, 2.67)
Non-Squamous	241	76	9.2	165	10.9	1.21	(0.48, 3.02)
Tobacco Use History							
Never	111	40	5.0	71	4.2	0.84	(0.13, 5.24)
Current	60	20	15.0	40	10.0	0.63	(0.13, 3.13)
Previous	198	64	12.5	134	14.9	1.23	(0.51, 2.96)
Brain Metastases at Baseline							
Yes	61	19	NE	42	7.1	>999.99	(0.00, >999.99)
No	308	105	12.4	203	11.8	0.95	(0.46, 1.95)
Liver Metastases at Baseline							
Yes	103	26	3.8	77	5.2	1.37	(0.15, 12.83)
No	266	98	12.2	168	13.7	1.14	(0.54, 2.40)
Bone Metastases at Baseline							
Yes	119	35	NE	84	10.7	>999.99	(0.00, NE)
No	250	89	14.6	161	11.2	0.74	(0.34, 1.58)



Odds ratios and the associated Wald confidence intervals were estimated using unstratified logistic regression.
The vertical dashed line indicates the hazard ratio for all patients (reference: Atezo IV).
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.
Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/g_ef_fp_rs2.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/g_ef_fp_rs2_CBOR_P2_ORR_16JAN2023_40657.pdf 24MAR2023 12:15

Forest Plot of Odds Ratio for Overall Response Rates (Confirmed) by Baseline Characteristics Subgroups, Part 2, Response-Evaluable Population
Protocol: BP40657

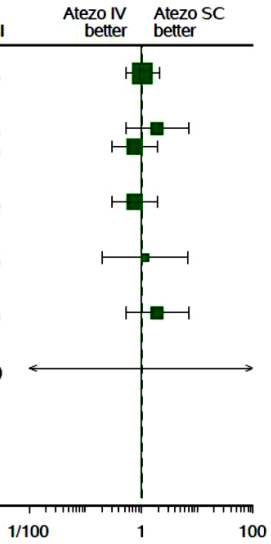
Baseline Risk Factors	Total n	Atezo IV (N=124) n	Response (%)	Atezo SC (N=245) n	Response (%)	Odds Ratio	95% CI
All Patients	369	124	10.5	245	11.0	1.06	(0.53, 2.13)
Other Mutations (KRAS, RET, ROS1, MET, B-RAF)							
Positive	23	9	22.2	14	7.1	0.27	(0.02, 3.52)
Negative	77	20	NE	57	8.8	>999.99	(0.00, NE)
Not-Evaluable	15	7	14.3	8	NE	<0.01	(0.00, NE)
Not Done	216	74	10.8	142	12.7	1.20	(0.49, 2.90)
Unknown	38	14	14.3	24	12.5	0.86	(0.13, 5.87)
EGFR Mutation Status							
Positive	19	8	NE	11	NE	NE	NE
Negative	292	95	9.5	197	12.2	1.33	(0.59, 2.98)
Not-Evaluable	4	2	50.0	2	NE	<0.01	(0.00, >999.99)
Not Done	48	16	12.5	32	9.4	0.72	(0.11, 4.84)
Unknown	6	3	33.3	3	NE	<0.01	(0.00, >999.99)
EML4-ALK Mutation Status							
Positive	6	2	NE	4	NE	NE	NE
Negative	295	100	9.0	195	11.3	1.29	(0.57, 2.91)
Not-Evaluable	6	3	33.3	3	NE	<0.01	(0.00, >999.99)
Not Done	62	19	15.8	43	11.6	0.70	(0.15, 3.29)



Odds ratios and the associated Wald confidence intervals were estimated using unstratified logistic regression.
The vertical dashed line indicates the hazard ratio for all patients (reference: Atezo IV).
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.
Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/g_ef_fp_rs3.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/g_ef_fp_rs3_CBOR_P2_ORR_16JAN2023_40657.pdf 24MAR2023 12:16

Forest Plot of Odds Ratio for Overall Response Rates (Confirmed) by Baseline Characteristics Subgroups, Part 2, Response-Evaluable Population
Protocol: BP40657

Baseline Risk Factors	Total n	Atezo IV (N=124) n	Atezo IV (N=124) Response (%)	Atezo SC (N=245) n	Atezo SC (N=245) Response (%)	Odds Ratio	95% CI
All Patients	369	124	10.5	245	11.0	1.06	(0.53, 2.13)
PD-L1 Status							
Positive	133	37	8.1	96	14.6	1.93	(0.52, 7.17)
Negative	199	78	11.5	121	9.1	0.77	(0.30, 1.94)
TC0 and IC0							
Yes	199	78	11.5	121	9.1	0.77	(0.30, 1.94)
TC2/3 or IC2/3							
Yes	51	14	14.3	37	16.2	1.16	(0.21, 6.57)
TC1/2/3 or IC1/2/3							
Yes	133	37	8.1	96	14.6	1.93	(0.52, 7.17)
TC3 or IC3							
Yes	16	3	NE	13	7.7	>999.99	(0.00, NE)

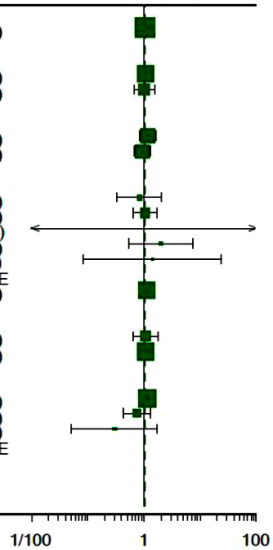


Odds ratios and the associated Wald confidence intervals were estimated using unstratified logistic regression.
The vertical dashed line indicates the hazard ratio for all patients (reference: Atezo IV).
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.
Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/g_ef_fp_rs4.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/g_ef_fp_rs4_CBOR_P2_ORR_16JAN2023_40657.pdf 24MAR2023 12:16

Table 24: Updated forest plot of HR for PFS by baseline characteristics subgroups:

Forest Plot of Hazard Ratio for Progression-Free Survival by Baseline Characteristics Subgroups, Part 2, Full Analysis Set
Protocol: BP40657

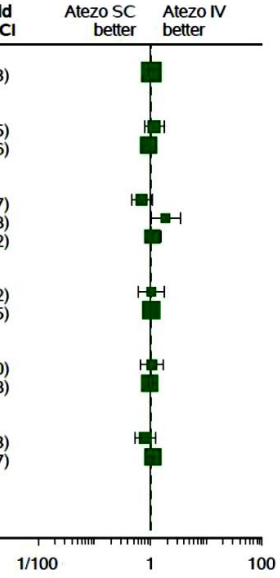
Baseline Risk Factors	Total n	Atezo IV (N=124) n	Atezo IV (N=124) Median Events(Months)	Atezo SC (N=247) n	Atezo SC (N=247) Median Events(Months)	Hazard Ratio	95% Wald CI
All Patients	371	124	107 2.9	247	219 2.8	1.05	(0.83, 1.33)
Sex							
Male	257	82	71 2.9	175	156 2.8	1.06	(0.80, 1.41)
Female	114	42	36 2.8	72	63 2.8	1.02	(0.67, 1.55)
Age Group (yr)							
< 65	195	58	48 2.9	137	125 2.5	1.17	(0.83, 1.64)
>= 65	176	66	59 3.2	110	94 4.2	0.93	(0.67, 1.29)
Race							
American Indian or Alaska Native	24	9	9 2.7	15	15 1.4	0.83	(0.34, 2.07)
Asian	80	33	27 2.7	47	40 2.7	1.04	(0.63, 1.71)
Black or African American	3	1	1 0.5	2	2 4.8	<0.01	(0.00, NE)
Multiple	11	5	5 1.4	6	6 1.3	1.99	(0.54, 7.35)
Native Hawaiian or other Pacific Islander	3	2	2 3.5	1	1 4.1	1.41	(0.08, 23.57)
Unknown	2			2	2 5.4	NE	NE
White	248	74	63 4.2	174	153 2.9	1.12	(0.83, 1.50)
ECOG Performance Score							
0	95	28	20 3.1	67	56 4.2	1.07	(0.64, 1.81)
1	276	96	87 2.8	180	163 2.7	1.06	(0.81, 1.38)
Number of prior therapies							
1	297	97	83 3.8	200	178 2.8	1.15	(0.88, 1.50)
2	62	21	19 1.8	41	35 3.4	0.75	(0.42, 1.32)
3	11	5	4 1.6	6	6 4.2	0.30	(0.05, 1.68)
4	1	1	1 4.2			NE	NE



Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients (reference: Atezo IV).
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.
Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/g_ef_fp.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/g_ef_fp_PFS_P2_FAS_16JAN2023_40657.pdf 28FEB2023 18:19

Forest Plot of Hazard Ratio for Progression-Free Survival by Baseline Characteristics Subgroups, Part 2, Full Analysis Set
Protocol: BP40657

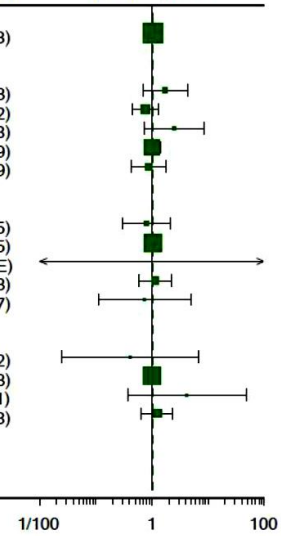
Baseline Risk Factors	Total n	Atezo IV (N=124) n	Atezo IV (N=124) Median Events(Months)		Atezo SC (N=247) n	Atezo SC (N=247) Median Events(Months)		Hazard Ratio	95% Wald CI
All Patients	371	124	107	2.9	247	219	2.8	1.05	(0.83, 1.33)
Histology at Initial Diagnosis									
Squamous	130	48	40	4.4	82	69	4.2	1.18	(0.79, 1.75)
Non-Squamous	241	76	67	1.8	165	150	2.7	0.94	(0.70, 1.26)
Tobacco Use History									
Never	111	40	37	1.5	71	63	2.7	0.70	(0.46, 1.07)
Current	60	20	16	6.3	40	37	2.8	1.86	(1.02, 3.38)
Previous	200	64	54	3.1	136	119	3.3	1.10	(0.79, 1.52)
Brain Metastases at Baseline									
Yes	61	19	19	1.5	42	41	1.4	1.04	(0.60, 1.82)
No	310	105	88	3.4	205	178	3.6	1.04	(0.81, 1.35)
Liver Metastases at Baseline									
Yes	103	26	25	1.5	77	73	1.5	1.07	(0.67, 1.70)
No	268	98	82	3.5	170	146	4.1	0.97	(0.74, 1.28)
Bone Metastases at Baseline									
Yes	119	35	33	1.5	84	79	1.5	0.81	(0.53, 1.23)
No	252	89	74	4.2	163	140	4.1	1.10	(0.83, 1.47)



Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients (reference: Atezo IV).
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.
Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/g_ef_fp2.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/g_ef_fp2_PFS_P2_FAS_16JAN2023_40657.pdf 28FEB2023 18:20

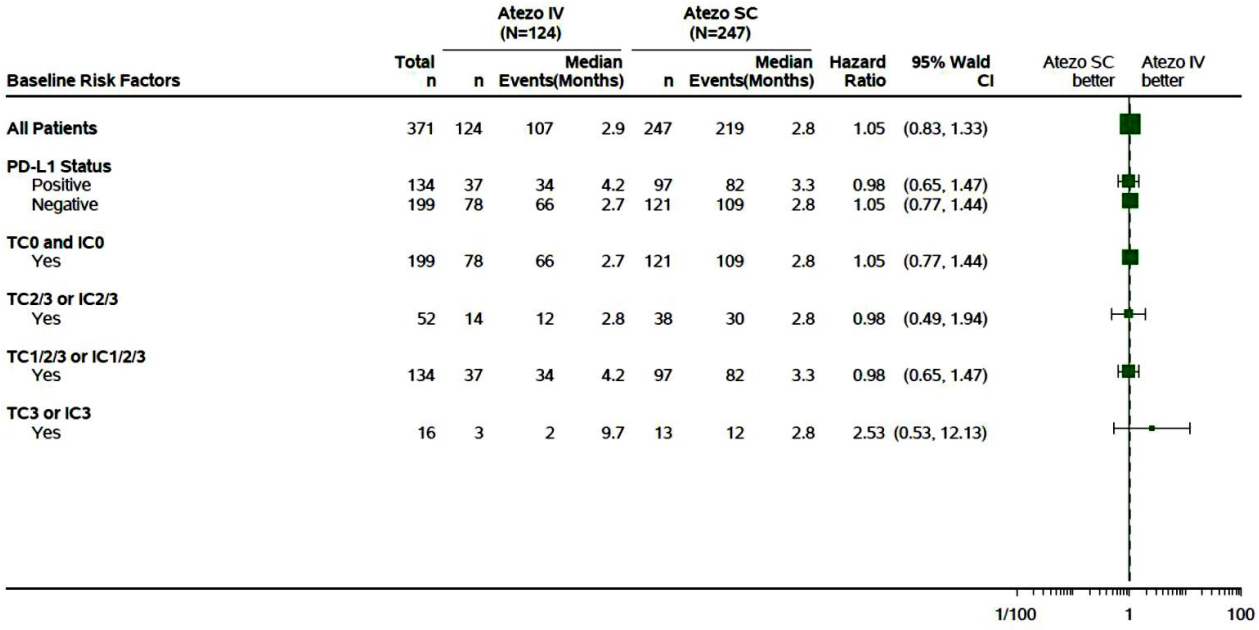
Forest Plot of Hazard Ratio for Progression-Free Survival by Baseline Characteristics Subgroups, Part 2, Full Analysis Set
Protocol: BP40657

Baseline Risk Factors	Total n	Atezo IV (N=124) n	Atezo IV (N=124) Median Events(Months)		Atezo SC (N=247) n	Atezo SC (N=247) Median Events(Months)		Hazard Ratio	95% Wald CI
All Patients	371	124	107	2.9	247	219	2.8	1.05	(0.83, 1.33)
Other Mutations (KRAS, RET, ROS1, MET, B-RAF)									
Positive	23	9	9	1.8	14	14	1.4	1.72	(0.69, 4.28)
Negative	77	20	20	1.4	57	54	2.0	0.77	(0.45, 1.32)
Not-Evaluable	15	7	5	2.7	8	8	1.5	2.49	(0.73, 8.53)
Not Done	217	74	61	4.0	143	121	3.0	1.01	(0.74, 1.39)
Unknown	39	14	12	2.4	25	22	4.1	0.87	(0.42, 1.79)
EGFR Mutation Status									
Positive	19	8	8	1.5	11	11	1.6	0.80	(0.30, 2.15)
Negative	293	95	83	2.9	198	175	2.8	1.03	(0.79, 1.35)
Not-Evaluable	4	2	1	NE	2	1	1.0	>999.99	(0.00, NE)
Not Done	49	16	12	6.2	33	29	4.9	1.15	(0.58, 2.28)
Unknown	6	3	3	1.6	3	3	1.5	0.74	(0.11, 4.87)
EML4-ALK Mutation Status									
Positive	6	2	1	2.7	4	4	3.1	0.41	(0.03, 6.62)
Negative	296	100	91	2.7	196	175	2.7	0.99	(0.76, 1.28)
Not-Evaluable	6	3	2	8.4	3	2	4.2	4.22	(0.37, 47.51)
Not Done	63	19	13	6.2	44	38	4.3	1.23	(0.65, 2.33)



Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression (reference: Atezo IV).
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.
Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/g_ef_fp3.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/g_ef_fp3_PFS_P2_FAS_16JAN2023_40657.pdf 28FEB2023 18:21

Forest Plot of Hazard Ratio for Progression-Free Survival by Baseline Characteristics Subgroups, Part 2, Full Analysis Set
Protocol: BP40657



Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression (reference: Atezo IV).
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.
Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/g_ef_fp4.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/g_ef_fp4_PFS_P2_FAS_16JAN2023_40657.pdf 28FEB2023 18:21

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25*:* Summary of efficacy for trial BP40657 (IMscin001)

Title: A randomized, multicenter, Phase Ib/III study to investigate the pharmacokinetics, efficacy, and safety of atezolizumab subcutaneous compared with atezolizumab intravenous in patients with previously treated locally advanced or metastatic non-small cell lung cancer.			
Study identifier	BP40657, Report Number 1116043, IMscin001		
Design	Part 1 of this study was dose finding, not randomised and comprised of three cohorts. Part 2 of this study (dose confirmation) was an open-label, randomised 2:1, multicentre study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		15 months (21- DEC-2018 to 10-MAR-2020) not applicable 17 months (2-DEC-2020 to 26-APR-2022)
Hypothesis	Non-inferiority		
Treatments groups	Atezolizumab IV		Atezolizumab IV 1200 mg Q3W. Treatment continued until disease progression, loss of clinical benefit or study withdrawal, n=124
	Atezolizumab SC		Atezolizumab SC 1875 mg Q3W. Treatment continued until disease progression, loss of clinical benefit or study withdrawal, n=247
Endpoints and definitions			
	Secondary efficacy endpoints [a, b]	ORR	Overall Response Rate

Title: A randomized, multicenter, Phase Ib/III study to investigate the pharmacokinetics, efficacy, and safety of atezolizumab subcutaneous compared with atezolizumab intravenous in patients with previously treated locally advanced or metastatic non-small cell lung cancer.			
Study identifier	BP40657, Report Number 1116043, IMscin001		
		DOR	Duration of Response
		PFS	Progression-Free Survival
		OS	Overall Survival
Clinical cut-off	26-APR-2022/15-AUG-2022		
Database lock	NA		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) was identical with the Full Analysis Set (FAS): All patients who were randomised, with patients grouped according to their assigned treatment.		
Descriptive statistics and estimate variability	Treatment group	Atezolizumab 1200 mg IV Q3W	Atezolizumab 1875 mg SC Q3W
	Number of subjects	124	247
	ORR, number of subjects (rate) 95% CI ORR rate	10 (8.1%) 3.94, 14.33	21 (8.6%) 5.38, 12.80
	DOR, median time to event, months 95% CI months	11.2 4.2, NE	NE 5.2, NE
	PFS, median time to event, months 95% CI months	2.9 1.7, 4.2	2.8 2.1, 3.1
	OS, median time to event, months 95% CI months	NE 7.9, NE	8.9 7.2, NE
Analysis description	**Updated Analysis**		
Analysis population and time point description	FAS at DCO January 2023 (post hoc analysis)		
Descriptive statistics and estimate variability	Treatment group	Atezolizumab 1200 mg IV Q3W	Atezolizumab 1875 mg SC Q3W
	Number of subjects	124	247
	Confirmed ORR, 95% CI	13 (10.5%) 5.70; 17.26	27 (11%) 7.39; 15.63
	Confirmed DOR, median time to event, months 95% CI months	11.2 4.2, NE	15.1 5.6, NE
	PFS, median time to event, months 95% CI months	2.9 1.8, 4.2	2.8 2.7, 4.1
	OS, median time to event, months 95% CI months	10.1 7.5, 12.1	10.7 8.5, 13.8
Notes	[a] PK was the primary endpoint of the study, so all efficacy analyses were considered secondary or exploratory		

2.6.5.2. Clinical studies in special populations

Table 26

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
BP40657 (IMscin001)	IV: 50/124 SC: 86/247	IV: 15/124 SC: 23/247	IV: 1/124 SC: 1/247
Non-Controlled trials	Not applicable	Not applicable	Not applicable

2.6.5.3. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.5. Supportive study(ies)

Not applicable.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The claim of non-inferior efficacy of SC atezolizumab vs IV atezolizumab for all approved indications of atezolizumab IV is solely based on the pivotal IMscin001 studyfc. This was a randomised, open-label, multicentre, Phase III study in immunotherapy-naïve patients with advanced NSCLC in the second-line or beyond (2L+) setting. The patients were enrolled in countries in Asia, Eastern Europe, Europe, Central- and South America, Oceania and Africa. A total of 371 patients were randomised 2:1 to either atezolizumab monotherapy SC (n=247) or atezolizumab monotherapy IV (N=124). The median survival follow-up was 4.7 months in the overall population at DCO.

The overall 2-part design of the single pivotal study, the IMscin001 trial –the targeted population, open-label design, 2:1 randomisation, definition of primary and secondary objectives/endpoints and choice of control arm– were extensively discussed in Scientific Advice meetings between 2018 and 2020. Originally, the MAH had considered evaluating patients in the first-line setting, but changed to the 2L+ setting in the subsequent advice, adducing that atezolizumab monotherapy (in the 2L+ setting) would spare the possible confounding effects from added chemotherapy in the 1L setting. Hence, the chosen study population mimics that from the randomised phase III OAK study (Study GO28915), which investigated atezolizumab versus docetaxel, and was the basis for the approval of atezolizumab in the 2L+ setting of advanced NSCLC.

Efficacy was not the primary endpoint of the single pivotal IMscin001 study, but it was evaluated as a secondary objective. The secondary endpoints were ORR, DoR, PFS, and OS, which are considered appropriate.

Since the chosen study population has a short life expectancy and an expected PFS of less than 3 months, the exposure of atezolizumab was also short.

The screening failure rate was (35%) in the pivotal study and the main reasons for this issue are considered acceptable. Overall, major protocol deviations occurred more often in the Atezo IV arm than in the Atezo SC arm in the pivotal IMscin001 study (51.6% vs 41.7%, respectively). Most of those deviations were procedural (Atezo IV 45.2% vs Atezo SC 35.2%) and related to adherence to the protocol-defined schedule of PK assessments, e.g. key PK or ADA samples were not done or done outside of window in 25% of the cases.

The distribution of baseline demographic characteristics is not completely balanced between both arms of the study, probably because there were no stratification factors used. Hence, the patients in the Atezo SC arm were slightly younger than those from the Atezo IV arm (63 vs 66 years), there were more white patients in the Atezo SC arm than in the Atezo IV arm (70.4% vs 59.7%), and there were more patients from Europe/Middle East in the Atezo SC arm than in the Atezo IV arm (51.4% vs 40.3%). Of note, there were also more patients with ECOG PS (Performance Status) 0 in the Atezo SC arm than in the Atezo IV arm (27.1% vs 22.6%), which could have affected the overall study results in favour of the SC arm, because ECOG PS is a well-known prognostic factor in the advanced cancer setting.

There was also a difference in the fraction of PD-L1 positive patients between the arms, because fewer patients in the IV arm had positive PD-L1 status than in the SC arm (32.2% vs 44.5%). However, this imbalance is not considered to have had a significant impact on the conclusion and interpretability of the efficacy and overall study results. Most patients were current or previous smokers (70%).

Efficacy data and additional analyses

The MAH had initially submitted data from the primary analysis of the pivotal study IMscin001 with a median follow-up time of 4.7 months (DCO 26 April 2022). A post hoc updated analysis was performed 9 months after the primary analysis with a median survival duration of follow-up of 9.5 months. The updated confirmed ORR in the Atezo IV arm compared to the Atezo SC arm was 10.5% (95%CI: 5.70; 17.26) vs. 11% (95%CI: 7.39; 15.63), respectively. All responders achieved PR and no CRs were observed in either arm. To contextualise, the observed ORR in a similar study population from the OAK study was 14%, so the currently observed ORR in the pivotal study is slightly lower than expected.

The updated confirmed median DoR was 15.1 months (95%CI: 5.6; NE) in the Atezo SC arm versus 11.2 months (95%CI: 4.2, NE) in the IV Atezo arm.

Approximately 88% of the patients had a PFS event at the updated DCO of 16 January 2023, which provided an additional 9 months of follow-up. The updated median PFS was 2.8 months (95%CI: 2.7;4.1) in the Atezo SC arm and 2.9 months (95%CI: 1.8;4.2) in the Atezo IV arm. The KM curves overlap and PFS is considered comparable between both arms. Of note, a similar median PFS was observed in the atezolizumab arm from the referenced OAK study (2.8 months).

At the time of the updated DCO, 58.3% of patients had died in the Atezo SC arm versus 63.7% in the Atezo IV arm; hence, the OS data is now quite mature. The updated median OS is 10.7 months and 10.1 months in the SC vs IV arm, respectively, which is considered similar. It is noted that the updated data now shows that there were slightly more deaths in the IV arm compared to the SC arm, so the initial signal of more deaths in the SC arm is no longer an issue. Moreover, it should be noted that the single pivotal study was not powered for OS although overall survival is considered an important

efficacy endpoint in this patient population, as the OAK study showed an OS benefit with Atezo compared to docetaxel in a similar study population.

Subgroup analyses of ORR and PFS were conducted initially and after updated subgroup analyses of PFS have been provided. These updated results minimise concerns regarding efficacy in the subgroups of the patients who had tumours with squamous histology and presence of liver metastases at baseline.

2.6.7. Conclusions on the clinical efficacy

Updated efficacy data from the single pivotal study support non-inferior efficacy of SC atezolizumab vs IV atezolizumab for all approved indications of atezolizumab IV.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Table 27: Updated exposure to Atezolizumab (Safety-Evaluable Population)

Atezolizumab Exposure, Part 2, Safety-Evaluable Population
Protocol: BP40657

	Atezo IV (N=124)	Atezo SC (N=247)
Treatment Duration (Months)		
n	124	247
Mean (SD)	5.6 (5.7)	5.5 (5.5)
Median	3.2	3.5
Min - Max	0 - 25	0 - 24
Treatment Duration		
0 to <= 3 months	62 (50.0%)	118 (47.8%)
>3 months to <= 6 months	17 (13.7%)	41 (16.6%)
>6 months to <= 12 months	27 (21.8%)	48 (19.4%)
>12 months	18 (14.5%)	40 (16.2%)
Number of Doses Received		
n	124	247
Mean (SD)	8.7 (7.9)	8.7 (7.9)
Median	5.0	6.0
Min - Max	1 - 37	1 - 36
Dose Intensity (%)		
n	124	247
Mean (SD)	99.8 (1.8)	100.0 (0.0)
Median	100.0	100.0
Min - Max	80 - 100	100 - 100

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
Treatment duration is the date of new treatment/end of treatment minus the date of the first dose of the study drug plus one day.
Dose Intensity is the number of doses actually received divided by the expected number of doses.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.

Program:
root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/program/t_ex.sas
Output:
root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/t_ex_P2_SE_16JAN2023_40657.out
28FEB2023 19:24

Source: t_ex_P2_SE_16JAN2023_40657

Table 28: Updated duration of safety follow-up

Duration of Safety Follow-Up, Part 2, Safety-Evaluable Population
Protocol: BP40657

	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Duration of Safety Follow-up (months)			
n	124	247	371
Mean (SD)	7.45 (5.36)	7.41 (5.24)	7.42 (5.27)
Median	5.14	5.59	5.52
Min - Max	0.4 - 25.5	0.1 - 24.3	0.1 - 25.5

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.

Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/t_saffup.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/t_saffup_P2_SE_16JAN2023_40657.out
28FEB2023 18:50 Page 1 of 1

2.6.8.2. Adverse events

Table 29: Overview of Adverse Events

	Primary Analysis (CCOD 26 April 2022)		**Updated Analysis (CCOD 16 January 2023)**	
	Atezo IV (N = 124)	**Atezo SC (N = 247)**	**Atezo IV (N = 124)**	**Atezo SC (N = 247)**
Total number of patients with at least one adverse event	104 (83.9%)	212 (85.8%)	104 (83.9%)	218 (88.3%)
Total number of events	451	874	619	1162
Total number of patients with at least one:				
Atezo-related AE	47 (37.9%)	93 (37.7%)	51 (41.1%)	104 (42.1%)
Grade 3-4 AE	32 (25.8%)	44 (17.8%)	39 (31.5%)	51 (20.6%)
Atezo-related Grade 3-4 AE	4 (3.2%)	9 (3.6%)	7 (5.6%)	11 (4.5%)
Grade 5 AE	4 (3.2%)	14 (5.7%)	8 (6.5%)	16 (6.5%)
Atezo-related Grade 5 AE	0	2 (0.8%)	0	2 (0.8%)
Serious AE	22 (17.7%)	38 (15.4%)	34 (27.4%)	48 (19.4%)
Atezo-related serious AE	3 (2.4%)	4 (1.6%)	4 (3.2%)	5 (2.0%)
AE leading to Atezo withdrawal	4* (3.2%)	4* (1.6%)	9 (7.3%)	9 (3.6%)
AE leading to Atezo interruption	33 (26.6%)	61 (24.7%)	39 (31.5%)	81 (32.8%)

AE = adverse event; Atezo = atezolizumab; CCOD = clinical cut-off date; intravenous = IV; subcutaneous = SC.
Atezo IV dose = 1200 milligram (mg); Atezo SC dose = 1875 mg
Only events reported in the adverse events form are included.

Investigator text for AEs encoded using MedDRA v25.0 (primary analysis) and MedDRA v25.1 (safety update). Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade, the patients are counted once at the highest grade.
* The total number of patients who discontinued treatment due to AEs reported in the CSR/SCS (Primary Analysis) should be 13 patients and not 8. See note at Table 1 for explanation of this discrepancy.
Source: IMscin001 Primary CSR Table 57, t_saf_sum_P2_SE_16JAN2023_40657

Table 30: Adverse events with an incidence of at least 5% in any treatment arm by system organ class and preferred term (safety evaluable population)

Adverse Events with an Incidence Rate of at Least 5%, Part 2, Safety-Evaluable Population
Protocol: BP40657

MedDRA System Organ Class MedDRA Preferred Term	Atezo IV (N=124)	Atezo SC (N=247)
Metabolism and nutrition disorders		
Decreased appetite	15 (12.1%)	28 (11.3%)
Hyponatraemia	12 (9.7%)	15 (6.1%)
Hyperglycaemia	13 (10.5%)	9 (3.6%)
Hyperkalaemia	9 (7.3%)	9 (3.6%)
Hypomagnesaemia	7 (5.6%)	6 (2.4%)
Hypercalcaemia	8 (6.5%)	2 (0.8%)
Hypercreatininaemia	7 (5.6%)	2 (0.8%)
Infections and infestations		
COVID-19	14 (11.3%)	17 (6.9%)
Pneumonia	6 (4.8%)	17 (6.9%)
Urinary tract infection	10 (8.1%)	10 (4.0%)
General disorders and administration site conditions		
Fatigue	16 (12.9%)	30 (12.1%)
Asthenia	8 (6.5%)	18 (7.3%)
Chest pain	10 (8.1%)	11 (4.5%)
Pyrexia	7 (5.6%)	11 (4.5%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	19 (15.3%)	27 (10.9%)
Cough	9 (7.3%)	28 (11.3%)
Blood and lymphatic system disorders		
Anaemia	21 (16.9%)	46 (18.6%)
Thrombocytopenia	7 (5.6%)	7 (2.8%)
Gastrointestinal disorders		
Constipation	9 (7.3%)	18 (7.3%)
Diarrhoea	3 (2.4%)	20 (8.1%)
Nausea	2 (1.6%)	16 (6.5%)
Musculoskeletal and connective tissue disorders		
Back pain	9 (7.3%)	21 (8.5%)
Arthralgia	7 (5.6%)	16 (6.5%)
Pain in extremity	6 (4.8%)	13 (5.3%)
Investigations		
Aspartate aminotransferase increased	13 (10.5%)	21 (8.5%)
Alanine aminotransferase increased	9 (7.3%)	19 (7.7%)
Blood alkaline phosphatase increased	6 (4.8%)	18 (7.3%)
Weight decreased	6 (4.8%)	13 (5.3%)
Skin and subcutaneous tissue disorders		
Pruritus	11 (8.9%)	13 (5.3%)
Rash	10 (8.1%)	13 (5.3%)
Nervous system disorders		
Headache	7 (5.6%)	16 (6.5%)
Endocrine disorders		
Hypothyroidism	6 (4.8%)	18 (7.3%)
Psychiatric disorders		
Insomnia	8 (6.5%)	8 (3.2%)

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
Investigator text for AEs encoded using MedDRA version 25.1. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
Includes AEs with onset from first dose of study drug through the clinical cut-off.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.

Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/t_ae_inc_5per.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/t_ae_inc_5per_P2_SE_16JAN2023_40657.out
28FEB2023 19:06

Table 31: Adverse events with an a difference of at least 5% between treatment arms (safety evaluable population)

Adverse Events with a Difference of at Least 5% between Treatment Arms, Part 2, Safety-Evaluable Population
Protocol: BP40657

MedDRA System Organ Class MedDRA Preferred Term	Atezo IV (N=124)	Atezo SC (N=247)
Metabolism and nutrition disorders		
Hyperglycaemia	13 (10.5%)	9 (3.6%)
Hypercalcaemia	8 (6.5%)	2 (0.8%)
Gastrointestinal disorders		
Diarrhoea	3 (2.4%)	20 (8.1%)

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
Investigator text for AEs encoded using MedDRA version 25.1. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
Includes AEs with onset from first dose of study drug through the clinical cut-off.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.

Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/t_ae_diff_5per.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/t_ae_diff_5per_P2_SE_16JAN2023_40657.out
28FEB2023 19:05 Page 1 of 1

Table 32: Adverse Events with a Difference of at Least 5% Relative to IMscin001 Atezo SC Arm by Preferred Term (Safety-Evaluable Population)

	IMSCIN001		Pooled Population	
MedDRA Preferred Term	Atezo IV (N=124)	Atezo SC (N=247)	Atezo Mono[1] (N=3178)	Atezo Mono[2] (N=4349)
Fatigue	17 (13.7%)	25 (10.1%)	1142 (35.9%)	1308 (30.1%)
Decreased appetite	10 (8.1%)	24 (9.7%)	810 (25.5%)	926 (21.3%)
Nausea	2 (1.6%)	15 (6.1%)	747 (23.5%)	871 (20.0%)
Cough	7 (5.6%)	23 (9.3%)	650 (20.8%)	808 (18.6%)
Pyrexia	7 (5.6%)	11 (4.5%)	639 (20.1%)	826 (19.0%)
Dyspnoea	16 (12.9%)	23 (9.3%)	651 (20.5%)	750 (17.2%)
Constipation	5 (4.0%)	14 (5.7%)	652 (20.5%)	768 (17.7%)
Diarrhoea	3 (2.4%)	11 (4.5%)	624 (19.6%)	779 (17.9%)
Arthralgia	5 (4.0%)	15 (6.1%)	573 (18.0%)	709 (16.3%)
Asthenia	6 (4.8%)	16 (6.5%)	461 (14.5%)	574 (13.2%)
Back pain	7 (5.6%)	17 (6.9%)	480 (15.1%)	549 (12.6%)
Vomiting	4 (3.2%)	7 (2.8%)	477 (15.0%)	545 (12.5%)
Pruritus	10 (8.1%)	8 (3.2%)	406 (12.8%)	573 (13.2%)
Rash	8 (6.5%)	9 (3.6%)	358 (11.3%)	469 (10.8%)
Headache	5 (4.0%)	10 (4.0%)	352 (11.1%)	447 (10.3%)
Urinary tract infection	7 (5.6%)	8 (3.2%)	336 (10.6%)	445 (10.2%)
Oedema peripheral	1 (0.8%)	3 (1.2%)	332 (10.4%)	394 (9.1%)
Insomnia	8 (6.5%)	8 (3.2%)	281 (8.8%)	339 (7.8%)
Weight decreased	5 (4.0%)	8 (3.2%)	277 (8.7%)	319 (7.3%)
Dizziness	2 (1.6%)	3 (1.2%)	250 (7.9%)	297 (6.8%)
Upper respiratory tract infection	3 (2.4%)	4 (1.6%)	227 (7.1%)	290 (6.7%)
Chills	0	1 (0.4%)	210 (6.6%)	250 (5.7%)
Blood creatinine increased	4 (3.2%)	1 (0.4%)	171 (5.4%)	247 (5.7%)
Influenza like illness	1 (0.8%)	0	186 (5.9%)	219 (5.0%)
COVID-19	11 (8.9%)	13 (5.3%)	0	0

Atezo = Atezolizumab; Atezo IV is 1200mg; Atezo SC is 1875mg. Atezo Mono[1]: GO27831(PCD4989g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + WO29636(IMVIGOR010) + GO29431(IMPOWER110) + GO29527(IMPOWER130).
Investigator text for AEs encoded using MedDRA v25.0. All treatment emergent AEs are included. All counts represent patients.
Multiple occurrences of the same AE in one individual are counted once at the highest NCI CTCAE grade.
Clinical cut-off dates: BP40657:26APR2022, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04FEB2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019.

Grade 3-4 AEs

Table 33: Grade 3-4 Adverse events with a difference of at least 2% between treatment arms (Safety evaluable population)

Grade 3-4 Adverse Events with a Difference of at Least 2% between Treatment Arms, Part 2,
Safety-Evaluable Population
Protocol: BP40657

MedDRA System Organ Class MedDRA Preferred Term	Atezo IV (N=124)	Atezo SC (N=247)
Infections and infestations		
Pneumonia	5 (4.0%)	3 (1.2%)
Blood and lymphatic system disorders		
Anaemia	2 (1.6%)	11 (4.5%)
Musculoskeletal and connective tissue disorders		
Back pain	3 (2.4%)	1 (0.4%)

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
Investigator text for AEs encoded using MedDRA version 25.1. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Includes AEs with onset from first dose of study drug through the clinical cut-off. Include only patients with grade 3-4 AEs at the highest grade.
RAVE Data Snapshot Date: 27FEB2023. Data Cutoff Date: 16JAN2023.

Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/t_ae_diff_2per.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/SEUR_EMA_20230116/prod/output/t_ae_diff_2per_CTC34_P2_SE_16JAN2023_40657.out
28FEB2023 19:03 Page 1 of 1

2.6.8.3. Serious adverse event/deaths/other significant events

Updated SAEs

As of the Safety Update CCOD, the proportion of patients who experienced SAEs was lower in the Atezo SC arm compared to the Atezo IV arm (19.4% Atezo SC vs. 27.4% Atezo IV; Table 5). The most frequently reported (≥2%) SAEs by PT were pneumonia and COVID 19. There were no SAEs that were at least 2% higher in incidence in the Atezo SC arm compared to the Atezo IV arm. The proportions of patients with treatment-related SAEs were comparable between the two treatment arms (2.0% Atezo SC vs. 3.2% Atezo IV).

Deaths

Of the 14 Grade 5 AEs in the Atezo SC arm, 2 were considered by the investigator as treatment-related (pneumonia aspiration and toxic epidermal necrolysis) versus none in the IV arm. As of the Safety Update CCOD, Grade 5 AEs were reported in 6.5% in both the Atezo SC arm and Atezo IV arm. Since the primary CCOD, a total of six additional Grade 5 AEs were reported (2 in the Atezo SC arm and 4 in the Atezo IV arm), however, none of the Grade 5 AEs reported in either arms since the primary CCOD were considered related to atezolizumab by the investigator.

Table 34: Summary of Grade 5 Adverse events (safety evaluable population)

Adverse Events Resulting in Death, Part 2, Safety-Evaluable Population
Protocol: BP40657

MedDRA System Organ Class MedDRA Preferred Term	Atezo IV (N=124)	Atezo SC (N=247)
Total number of patients with at least one adverse event	8 (6.5%)	16 (6.5%)
Overall total number of events	8	16
Infections and infestations		
Total number of patients with at least one adverse event	2 (1.6%)	8 (3.2%)
Total number of events	2	8
COVID-19 pneumonia	0	2 (0.8%)
Pneumonia	0	2 (0.8%)
Pneumonia aspiration	0	2 (0.8%)
COVID-19	1 (0.8%)	0
Respiratory tract infection	0	1 (0.4%)
Sepsis	0	1 (0.4%)
Upper respiratory tract infection	1 (0.8%)	0
Cardiac disorders		
Total number of patients with at least one adverse event	1 (0.8%)	3 (1.2%)
Total number of events	1	3
Myocardial infarction	0	3 (1.2%)
Cardiac failure	1 (0.8%)	0
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	2 (1.6%)	1 (0.4%)
Total number of events	2	1
Pulmonary embolism	1 (0.8%)	1 (0.4%)
Pulmonary haemorrhage	1 (0.8%)	0
Gastrointestinal disorders		
Total number of patients with at least one adverse event	2 (1.6%)	0
Total number of events	2	0
Enterocolitis	1 (0.8%)	0
Intestinal perforation	1 (0.8%)	0
General disorders and administration site conditions		
Total number of patients with at least one adverse event	0	1 (0.4%)
Total number of events	0	1
Death	0	1 (0.4%)
Injury, poisoning and procedural complications		
Total number of patients with at least one adverse event	0	1 (0.4%)
Total number of events	0	1
Head injury	0	1 (0.4%)
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	1	0
Hypercalcaemia	1 (0.8%)	0
Nervous system disorders		
Total number of patients with at least one adverse event	0	1 (0.4%)
Total number of events	0	1
Ischaemic stroke	0	1 (0.4%)
Skin and subcutaneous tissue disorders		
Total number of patients with at least one adverse event	0	1 (0.4%)
Total number of events	0	1
Toxic epidermal necrolysis	0	1 (0.4%)

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.

Other significant events

AESIs for atezolizumab were selected based on its mechanism of action. These AESIs represent risks with an established or potential causal association of atezolizumab use and are grouped by medical concepts.

Table 35: Updated overview of Adverse Events of Special Interest for Atezolizumab

	Primary Analysis (CCOD 26 April 2022)		Safety Update (CCOD 16 January 2023)	
	Atezo IV (N = 124)	Atezo SC (N = 247)	Atezo IV (N = 124)	AtezoSC (N = 247)
Total number of patients with at least one AESI	27 (21.8%)	65 (26.3%)	35 (28.2%)	76 (30.8%)
Total number of events	48	112	75	158
Total number of patients with at least one				
Atezo-related AESI	19 (15.3%)	46 (18.6%)	27 (21.8%)	56 (22.7%)
Grade 3-4 AESI	3 (2.4%)	9 (3.6%)	5 (4.0%)	10 (4.0%)
Atezo-related Grade 3-4 AESI	2 (1.6%)	6 (2.4%)	4 (3.2%)	6 (2.4%)
Grade 5 AESI	0	1 (0.4%)	0	1 (0.4%)

Atezo-related Grade 5 AESI	0	1 (0.4%)	0	1 (0.4%)
Serious AESIs	2 (1.6%)	3 (1.2%)	3 (2.4%)	4 (1.6%)
Atezo-related serious AESI	2 (1.6%)	3 (1.2%)	3 (2.4%)	3 (1.2%)
AESIs leading to Atezo withdrawal	2 (1.6%)	1 (0.4%)	3 (2.4%)	1 (0.4%)
AESIs leading to Atezo interruption	2 (1.6%)	11 (4.5%)	5 (4.0%)	16 (6.5%)
AESIs requiring the use of systemic corticosteroids	3 (2.4%)	13 (5.3%)	6 (4.8%)	16 (6.5%)
Medical concepts: patients with at least one				
Immune-Mediated Rash	11 (8.9%)	15 (6.1%)	14 (11.3%)	21 (8.5%)
Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)	10 (8.1%)	25 (10.1%)	17 (13.7%)	29 (11.7%)
Immune-Mediated Hepatitis (Lab Abnormalities)	10 (8.1%)	23 (9.3%)	17 (13.7%)	27 (10.9%)
Immune-Mediated Hypothyroidism	5 (4.0%)	17 (6.9%)	9 (7.3%)	26 (10.5%)
Immune-Mediated Pneumonitis	1 (0.8%)	1 (0.4%)	1 (0.8%)	5 (2.0%)
Immune-Mediated Hepatitis (Diagnosis)	0	2 (0.8%)	0	3 (1.2%)
Immune-Mediated Hyperthyroidism	1 (0.8%)	6 (2.4%)	2 (1.6%)	5 (2.0%)
Infusion-Related Reactions	4 (3.2%)	0	4 (3.2%)	0
Immune-Mediated Colitis	0	0	1 (0.8%)	0
Immune-Mediated Severe Cutaneous Reactions	0	1 (0.4%)	0	2 (0.8%)
Immune-Mediated Pancreatitis	0	0	0	0
Immune-Mediated Ocular Inflammatory Toxicity	0	0	0	0
Immune-Mediated Adrenal Insufficiency	0	0	0	1 (0.4%)
Immune-Mediated Myositis (Myositis+Rhabdomyolysis)	0	0	0	0
Immune-Mediated Meningoencephalitis	0	0	0	0
Immune-Mediated Diabetes Mellitus	0	0	0	0
Injection site reactions	0	11 (4.5%)	0	11 (4.5%)
Immune-Mediated Meningitis	0	0	0	0
Immune-Mediated Myositis	0	0	0	0
Immune-Mediated Vasculitis	0	0	0	0
Immune-Mediated Nephritis	0	0	0	0
Rhabdomyolysis	0	0	0	0
Autoimmune Hemolytic Anaemia	0	0	0	0
Immune-Mediated Hypophysitis	0	0	0	0
Immune-Mediated Encephalitis	0	0	0	0
Immune-Mediated Myocarditis	0	0	0	0
Haemophagocytic Lymphohistiocytosis	0	0	0	0
Immune-Mediated Myasthenia Gravis	0	0	0	0

AESI = adverse event of special interest; Atezo = atezolizumab; CCOD = clinical cut-off date; IV = intravenous; SC = subcutaneous
Source: IMscin001 Primary CSR Table 66 and Table 67, t_saf_sum_aesi_P2_SE_16JAN2023_40657

Atezo = Atezolizumab; Atezo IV is 1200mg; Atezo SC is 1875mg. Atezo Mono[1]: GO27831(FCD4959g All Cohorts) + GO28625(FIR) + GO28753(POPLAR) + GO28754(BIRCH) + GO28915(OAK) + GO29293(IMVIGOR210) + GO29294(IMVIGOR211) + WO29074(IMMOTION150 Arm B prior to crossover); Atezo Mono [2]: Atezo Mono [1] + WO29636(IMVIGOR010) + GO29431(IMPOWER110) + GO29527(IMPOWER010).
Only events reported in the Adverse Events Form are included.
Investigator text for AEs encoded using MedDRA v25.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately. All treatment emergent AEs are included. For the counts in the rows by grade,the patients are counted once at the highest grade. The protocol defined selected adverse events (Injection site reactions) have been included in this output due to an upgrade to the AESI basket.
Clinical cut-off dates: BP40657:26APR2022, GO27831:31MAR2016, GO28625:07JAN2015, GO28753:01DEC2015, GO28754:01DEC2015, GO28915:07JUL2016, GO29293:04JUL2016, GO29294:13MAR2017, GO29431:04MAY2020, GO29527:21JAN2021, WO29074:17OCT2016, WO29636:30NOV2019.

Table 36: Injection site reactions

Adverse Events of Special Interest by Highest NCI CTCAE Grade and by Medical Concept and Preferred Term
Safety Evaluable Patients
Protocol: BP40657

Medical Concept MedDRA Preferred Term	Grade	IMSCIN001 Atezo IV (N=124)	IMSCIN001 Atezo SC (N=247)	Pooled Population Atezo Mono[1] (N=3178)	Pooled Population Atezo Mono[2] (N=4349)
Injection site reactions - Overall -	- Any Grade -	0	11 (4.5%)	8 (0.3%)	8 (0.2%)
	Grade 1-2	0	11 (4.5%)	8 (0.3%)	8 (0.2%)
	1	0	8 (3.2%)	5 (0.2%)	5 (0.1%)
	2	0	3 (1.2%)	3 (<0.1%)	3 (<0.1%)
Injection site reaction	- Any Grade -	0	4 (1.6%)	4 (0.1%)	4 (<0.1%)
	Grade 1-2	0	4 (1.6%)	4 (0.1%)	4 (<0.1%)
	1	0	3 (1.2%)	2 (<0.1%)	2 (<0.1%)
	2	0	1 (0.4%)	2 (<0.1%)	2 (<0.1%)
Injection site pain	- Any Grade -	0	6 (2.4%)	2 (<0.1%)	2 (<0.1%)
	Grade 1-2	0	6 (2.4%)	2 (<0.1%)	2 (<0.1%)
	1	0	5 (2.0%)	2 (<0.1%)	2 (<0.1%)
	2	0	1 (0.4%)	0	0
Injection site pruritus	- Any Grade -	0	0	1 (<0.1%)	1 (<0.1%)
	Grade 1-2	0	0	1 (<0.1%)	1 (<0.1%)
	1	0	0	1 (<0.1%)	1 (<0.1%)
Injection site vasculitis	- Any Grade -	0	0	1 (<0.1%)	1 (<0.1%)
	Grade 1-2	0	0	1 (<0.1%)	1 (<0.1%)
	2	0	0	1 (<0.1%)	1 (<0.1%)
Injection site erythema	- Any Grade -	0	1 (0.4%)	0	0
	Grade 1-2	0	1 (0.4%)	0	0
	1	0	1 (0.4%)	0	0
Injection site rash	- Any Grade -	0	1 (0.4%)	0	0
	Grade 1-2	0	1 (0.4%)	0	0
	2	0	1 (0.4%)	0	0

Table 37: AESI (Injection site reactions) by ADA Status

Adverse Events of Special Interest by Highest NCI CTCAE Grade by Anti-Drug Antibody (ADA) Status to Atezolizumab, Part 2, Post-Treatment ADA-Evaluable Population
Protocol: BP40657

Medical Concept Category MedDRA Preferred Term	Grade	Atezo IV (N=108) ADA- (N=93)	Atezo IV (N=108) ADA+ (N=15)	Atezo SC (N=221) ADA- (N=178)	Atezo SC (N=221) ADA+ (N=43)
Injection site reactions - Overall -	- Any Grade -	0	0	8 (4.5%)	3 (7.0%)
	Grade 1-2	0	0	8 (4.5%)	3 (7.0%)
	1	0	0	7 (3.9%)	1 (2.3%)
	2	0	0	1 (0.6%)	2 (4.7%)
Injection site pain	- Any Grade -	0	0	5 (2.8%)	1 (2.3%)
	Grade 1-2	0	0	5 (2.8%)	1 (2.3%)
	1	0	0	5 (2.8%)	0
	2	0	0	0	1 (2.3%)
Injection site reaction	- Any Grade -	0	0	3 (1.7%)	1 (2.3%)
	Grade 1-2	0	0	3 (1.7%)	1 (2.3%)
	1	0	0	2 (1.1%)	1 (2.3%)
	2	0	0	1 (0.6%)	0
Injection site erythema	- Any Grade -	0	0	1 (0.6%)	0
	Grade 1-2	0	0	1 (0.6%)	0
	1	0	0	1 (0.6%)	0
Injection site rash	- Any Grade -	0	0	0	1 (2.3%)
	Grade 1-2	0	0	0	1 (2.3%)
	2	0	0	0	1 (2.3%)

2.6.8.4. Laboratory findings

Table 38: Summary of Clinically Relevant Laboratory Shifts from Baseline in Laboratory Safety Parameters (Part 2, Safety-Evaluable Population)

Laboratory Test Shifts to NCI-CTCAE Grade 3-4 Post-Baseline, Part 2, Safety-Evaluable Population
Protocol: BP40657

Laboratory Test	Direction of Abnormality	Atezo IV (N=124)	Atezo SC (N=247)
Chemistry			
Albumin	Low	0/123	2/242 (0.8%)
Alkaline Phosphatase	High	0/124	3/247 (1.2%)
SGPT/ALT	High	1/124 (0.8%)	6/247 (2.4%)
SGOT/AST	High	2/124 (1.6%)	5/247 (2.0%)
Calcium	Low	0/123	4/247 (1.6%)
	High	2/124 (1.6%)	6/247 (2.4%)
Creatinine	High	3/124 (2.4%)	6/246 (2.4%)
Glucose	Low	0/124	0/247
Magnesium	Low	0/123	1/247 (0.4%)
	High	0/124	1/246 (0.4%)
Potassium	Low	5/124 (4.0%)	4/246 (1.6%)
	High	1/123 (0.8%)	3/244 (1.2%)
Sodium	Low	5/124 (4.0%)	8/247 (3.2%)
	High	0/124	0/247
Bilirubin	High	1/124 (0.8%)	4/247 (1.6%)
Coagulation			
International Normalized Ratio	High	0/122	1/246 (0.4%)
Activated Partial Thromboplastin Time	High	0/123	0/247
Hematology			
Hemoglobin	Low	5/124 (4.0%)	13/246 (5.3%)
	High	1/123 (0.8%)	6/247 (2.4%)
Lymphocytes Abs	Low	19/118 (16.1%)	28/238 (11.8%)
	High	0/124	0/247
Neutrophils, Total, Abs	Low	3/118 (2.5%)	5/227 (2.2%)
Platelet	Low	0/124	7/247 (2.8%)
Total Leukocyte Count	Low	2/124 (1.6%)	4/247 (1.6%)
	High	0/124	1/246 (0.4%)

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events. NCI CTCAE v5 was used.
For each laboratory test, patients with at least one post-baseline assessment were included in the analysis. For each cell, the denominator is the number of patients with baseline values of NCI CTCAE Grade 0-2 in the specified direction of abnormality or with missing baseline values.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Table 39: Summary of Shifts in TSH from Baseline to Worst Post-Baseline (Part 2, Safety-Evaluable Population)

Thyroid Stimulating Hormone, shift table of post-baseline changes, Part 2, Safety-Evaluable Population
Protocol: BP40657

Treatment	Post-Baseline Status	Status at Baseline: Normal	Status at Baseline: High	Status at Baseline: Low
Atezo IV (N=86)	Normal	56/67 (83.6%)	3/13 (23.1%)	3/6 (50.0%)
	High	6/67 (9.0%)	10/13 (76.9%)	1/6 (16.7%)
	Low	3/67 (4.5%)	0/13	2/6 (33.3%)
	Total	65/67 (97.0%)	13/13 (100.0%)	6/6 (100.0%)
Atezo SC (N=165)	Normal	101/144 (70.1%)	3/13 (23.1%)	2/8 (25.0%)
	High	23/144 (16.0%)	10/13 (76.9%)	0/8
	Low	26/144 (18.1%)	0/13	6/8 (75.0%)
	Total	144/144 (100.0%)	13/13 (100.0%)	8/8 (100.0%)

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
Denominators are based on patients who have valid baseline values. Only patients with both baseline and post-baseline TSH labs are displayed for the shifts.
Counts were based on worst post-baseline in value in one direction. If a patient has bi-directional shifts outside of reference range, the patient is counted once in each scenario.
Local lab reference ranges are used to assess the out of range values.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Table 40: Summary of Patients Meeting the Criteria for Hy's Law (Part 2, Safety-Evaluable Population)

Summary of Patients Meeting the Criteria for Hy's Law, Part 2, Safety-Evaluable Population
Protocol: BP40657

	Atezo IV (N=124)	Atezo SC (N=247)
Hy's Law Criteria Met	0	6 (2.4%)

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
Patients who met Hy`s Law Criteria reported at least one TBILI > 2 x ULN within 7 days after latest ALT or AST > 3 x ULN.
Reference Range of Local Labs are used.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

No additional patients met the Hy's law criteria since the primary CCOD.

Table 41: Summary of Vital Sign Abnormalities Among Subjects Without Abnormality at Baseline (Part 2, Safety-Evaluable Population)

Vital Signs Outside Normal Limits Among Subjects Without Abnormality at Baseline, Part 2, Safety-Evaluable Population
Protocol: BP40657

Assessment	Direction of Abnormality	Atezo IV (N=124)	Atezo SC (N=247)	All Patients (N=371)
Diastolic Blood Pressure	Low	20/117 (17.1%)	47/234 (20.1%)	67/351 (19.1%)
	High	42/ 80 (52.5%)	75/177 (42.4%)	117/257 (45.5%)
Systolic Blood Pressure	Low	3/123 (2.4%)	16/244 (6.6%)	19/367 (5.2%)
	High	43/ 61 (70.5%)	71/115 (61.7%)	114/176 (64.8%)
Pulse Rate	Low	10/121 (8.3%)	13/239 (5.4%)	23/360 (6.4%)
	High	32/115 (27.8%)	52/230 (22.6%)	84/345 (24.3%)
Respiratory Rate	Low	0/123	3/246 (1.2%)	3/369 (0.8%)
	High	27/ 60 (45.0%)	75/144 (52.1%)	102/204 (50.0%)
Temperature	Low	47/ 72 (65.3%)	84/132 (63.6%)	131/204 (64.2%)
	High	12/122 (9.8%)	16/245 (6.5%)	28/367 (7.6%)

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
Baseline is the patient's last observation prior to initiation of study drug.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

Safety in special populations

Age

Table 42: Overview of Safety by Age (Safety-Evaluable Population)

	Atezo IV (N=124)				Atezo SC (N=247)			
	< 65 (N=53)	65 to 74 (N=50)	75 to 84 (N=15)	>= 85 (N=1)	< 65 (N=137)	65 to 74 (N=86)	75 to 84 (N=23)	>= 85 (N=1)
Total number of patients with at least one AE	43 (82.8%)	44 (88.0%)	12 (80.0%)	0	124 (90.5%)	69 (79.1%)	19 (82.6%)	1 (100%)
Total number of AEs	175	221	55	0	477	311	76	3
Total number of patients with Confirmed/Suspected COVID-19 AE	2 (3.4%)	6 (12.0%)	4 (26.7%)	0	12 (8.8%)	4 (4.7%)	1 (4.3%)	0
Total number of patients with at least one								
AE with fatal outcome	2 (3.4%)	2 (4.0%)	0	0	7 (5.1%)	5 (5.8%)	2 (8.7%)	0
Related AE with fatal outcome	0	0	0	0	2 (1.5%)	0	0	0
Serious AE	12 (20.7%)	7 (14.0%)	3 (20.0%)	0	21 (15.3%)	12 (14.0%)	5 (21.7%)	0
Related Serious AE	2 (3.4%)	1 (2.0%)	0	0	4 (2.9%)	0	0	0
Grade 3-4 AE	13 (22.4%)	14 (28.0%)	5 (33.3%)	0	26 (19.0%)	11 (12.8%)	6 (26.1%)	1 (100%)
Related Grade 3-4 AE	2 (3.4%)	2 (4.0%)	0	0	3 (2.2%)	4 (4.7%)	1 (4.3%)	1 (100%)
Related AE	24 (41.4%)	16 (32.0%)	7 (46.7%)	0	49 (35.8%)	33 (38.4%)	10 (43.5%)	1 (100%)
AE leading to Atezolizumab discontinuation	2 (3.4%)	2 (4.0%)	0	0	2 (1.5%)	2 (2.3%)	0	0
AE leading to dose interruption of Atezolizumab	13 (22.4%)	11 (22.0%)	9 (60.0%)	0	38 (27.7%)	16 (18.6%)	7 (30.4%)	0

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
Actual treatment arms are presented.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug through the clinical cut-off. Grade 3-4 categories include only patients with grade 3-4 AEs at the highest grade.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/t_saf_sum.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/CSRPrimary_20220426/prod/output/t_saf_sum_BYACE_P2_SE_26APR2022_40657.out

Race

Table 43: Overview of Safety by Race (Safety-Evaluable Population)

	Atezo IV (N=124)						
	American Indian or Alaska Native (N=9)	Asian (N=33)	Black or African American (N=1)	Native Hawaiian or other Pacific Islander (N=2)	White (N=74)	Multiple (N=5)	Unknown (N=0)
Total number of patients with at least one AE	8 (88.9%)	28 (84.8%)	1 (100%)	2 (100%)	64 (86.5%)	1 (20.0%)	0
Total number of AEs	37	97	2	13	301	1	0
Total number of patients with Confirmed/Suspected COVID-19 AE	1 (11.1%)	4 (12.1%)	0	0	7 (9.5%)	0	0
Total number of patients with at least one							
AE with fatal outcome	1 (11.1%)	0	1 (100%)	0	2 (2.7%)	0	0
Related AE with fatal outcome	0	0	0	0	0	0	0
Serious AE	1 (11.1%)	6 (18.2%)	1 (100%)	1 (50.0%)	13 (17.6%)	0	0
Related Serious AE	0	1 (3.0%)	0	0	2 (2.7%)	0	0
Grade 3-4 AE	2 (22.2%)	9 (27.3%)	0	2 (100%)	19 (25.7%)	0	0
Related Grade 3-4 AE	0	1 (3.0%)	0	0	3 (4.1%)	0	0
Related AE	6 (66.7%)	11 (33.3%)	0	2 (100%)	27 (36.5%)	1 (20.0%)	0
AE leading to Atezolizumab discontinuation	0	0	0	0	4 (5.4%)	0	0
AE leading to dose interruption of Atezolizumab	2 (22.2%)	6 (18.2%)	0	1 (50.0%)	24 (32.4%)	0	0

	Atezo SC (N=247)						
	American Indian or Alaska Native (N=15)	Asian (N=47)	Black or African American (N=2)	Native Hawaiian or other Pacific Islander (N=1)	White (N=174)	Multiple (N=6)	Unknown (N=2)
Total number of patients with at least one AE	15 (100%)	38 (80.9%)	2 (100%)	1 (100%)	149 (85.6%)	5 (83.3%)	2 (100%)
Total number of AEs	70	113	10	9	645	15	12
Total number of patients with Confirmed/Suspected COVID-19 AE	1 (6.7%)	4 (8.5%)	0	0	12 (6.9%)	0	0
Total number of patients with at least one							
AE with fatal outcome	2 (13.3%)	0	0	0	12 (6.9%)	0	0
Related AE with fatal outcome	1 (6.7%)	0	0	0	1 (0.6%)	0	0
Serious AE	2 (13.3%)	7 (14.9%)	0	0	29 (16.7%)	0	0
Related Serious AE	1 (6.7%)	0	0	0	3 (1.7%)	0	0
Grade 3-4 AE	1 (6.7%)	12 (25.5%)	0	0	28 (16.1%)	2 (33.3%)	1 (50.0%)
Related Grade 3-4 AE	0	1 (2.1%)	0	0	7 (4.0%)	0	1 (50.0%)
Related AE	12 (80.0%)	11 (23.4%)	2 (100%)	1 (100%)	65 (37.4%)	1 (16.7%)	1 (50.0%)
AE leading to Atezolizumab discontinuation	0	1 (2.1%)	0	0	3 (1.7%)	0	0
AE leading to dose interruption of Atezolizumab	5 (33.3%)	6 (12.8%)	0	0	49 (28.2%)	0	1 (50.0%)

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
Actual treatment arms are presented.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug through the clinical cut-off. Grade 3-4 categories include only patients with grade 3-4 AEs at the highest grade.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/t_saf_sum.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/CSRPrimary_20220426/prod/output/t_saf_sum_BYRACE_P2_SE_26APR2022_40657.out

ECOG

Table 44: Overview of Safety by ECOG (Safety-Evaluable Population)

	Atezo IV (N=124)		Atezo SC (N=247)	
	0 (N=28)	1 (N=96)	0 (N=67)	1 (N=180)
Total number of patients with at least one AE	19 (67.9%)	85 (88.5%)	60 (89.6%)	152 (84.4%)
Total number of AEs	70	381	228	646
Total number of patients with Confirmed/Suspected COVID-19 AE	2 (7.1%)	10 (10.4%)	3 (4.5%)	14 (7.8%)
Total number of patients with at least one				
AE with fatal outcome	0	4 (4.2%)	6 (9.0%)	8 (4.4%)
Related AE with fatal outcome	0	0	1 (1.5%)	1 (0.6%)
Serious AE	4 (14.3%)	18 (18.8%)	15 (22.4%)	23 (12.8%)
Related Serious AE	0	3 (3.1%)	3 (4.5%)	1 (0.6%)
Grade 3-4 AE	5 (17.9%)	27 (28.1%)	14 (20.9%)	30 (16.7%)
Related Grade 3-4 AE	1 (3.6%)	3 (3.1%)	3 (4.5%)	6 (3.3%)
Related AE	11 (39.3%)	36 (37.5%)	28 (41.8%)	65 (36.1%)
AE leading to Atezolizumab discontinuation	0	4 (4.2%)	2 (3.0%)	2 (1.1%)
AE leading to dose interruption of Atezolizumab	6 (21.4%)	27 (28.1%)	19 (28.4%)	42 (23.3%)

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
Actual treatment arms are presented.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug through the clinical cut-off. Grade 3-4 categories include only patients with grade 3-4 AEs at the highest grade.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Program: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/BASE/prod/program/t_saf_sum.sas
Output: root/clinical_studies/RO5541267/CDT30212/BP40657/data_analysis/CSRPrimary_20220426/prod/output/t_saf_sum_BYECOG_P2_SE_26APR2022_40657.out

Immunological events

Table 45: Baseline Prevalence of ADAs and Post-Baseline Incidence of Treatment-Emergent ADAs to Atezolizumab (Part 2, Safety-Evaluable Population)

Baseline Prevalence and Incidence of Treatment Emergent Anti-Drug Antibodies (ADAs) to Atezolizumab (RO55
Protocol: BP40657, Part 2; Clinical Data Cutoff Date: 26April2022

Analyte: Anti-RO6541267 Antibody

	Atezolizumab IV (n=124)	Atezolizumab SC (n=247)
Baseline Prevalence of ADAs		
Baseline evaluable patients	115	241
Patients with a positive sample at baseline	3 (2.6%)	7 (2.9%)
Patients with no positive samples at baseline	112	234
Incidence of Treatment Emergent ADAs		
Post-baseline evaluable patients	108	221
Patients positive for Treatment Emergent ADA	15 (13.9%)	43 (19.5%)
Treatment-induced ADA	15	42
Treatment-enhanced ADA	0	1
Patients negative for Treatment Emergent ADA	93	178
Treatment unaffected	3	5

Table 46: Duration of Atezolizumab Treatment by Treatment-Emergent ADA Status (ADA-Evaluable Atezolizumab Patients in Safety-Evaluable Population)

Atezolizumab Exposure by Anti-Drug Antibody (ADA) Status to Atezolizumab, Part 2, Post-Treatment ADA-Evaluable Population
Protocol: BP40657

	Atezo IV (N=108)		Atezo SC (N=221)	
	ADA- (N=93)	ADA+ (N=15)	ADA- (N=178)	ADA+ (N=43)
Treatment Duration (Months)				
n	93	15	178	43
Mean (SD)	3.9 (3.3)	4.3 (3.2)	3.9 (3.1)	3.2 (2.4)
Median	2.8	2.8	2.8	2.3
Min - Max	0 - 16	1 - 9	0 - 15	1 - 11
Treatment Duration				
0 to <= 3 months	51 (54.8%)	8 (53.3%)	96 (53.9%)	24 (55.8%)
>3 months to <= 6 months	22 (23.7%)	1 (6.7%)	38 (21.3%)	14 (32.6%)
>6 months to <= 12 months	18 (19.4%)	6 (40.0%)	43 (24.2%)	5 (11.6%)
>12 months	2 (2.2%)	0	1 (0.6%)	0
Number of Doses Received				
n	93	15	178	43
Mean (SD)	6.4 (4.5)	7.1 (4.7)	6.3 (4.3)	5.5 (3.4)
Median	5.0	5.0	5.0	4.0
Min - Max	1 - 24	2 - 14	1 - 23	2 - 17
Dose Intensity (%)				
n	93	15	178	43
Mean (SD)	100.0 (0.0)	98.7 (5.0)	100.0 (0.0)	100.0 (0.0)
Median	100.0	100.0	100.0	100.0
Min - Max	100 - 100	80 - 100	100 - 100	100 - 100
Total Dose (mg)				
n	93	15	178	43
Mean (SD)	7677.4 (5445.1)	8448.7 (5633.0)	11871.5 (8127.2)	10247.1 (6395.8)
Median	6000.0	6000.0	9375.0	7500.0
Min - Max	1200 - 28800	1931 - 16800	1875 - 43125	3750 - 31875

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
ADA = Anti-Drug Antibodies (is also referred to as ADA, or Anti-Therapeutic Antibodies); ADA- = Without TX Enhanced/Induced; ADA+ = With TX Enhanced/Induced; TX = Treatment.
Treatment duration is the date of new treatment/end of treatment minus the date of the first dose of the study drug plus one day.
Dose Intensity is the number of doses actually received divided by the expected number of doses.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Table 47: Objective Response Rate and Progression-Free Survival by Treatment-Emergent ADA Status (ADA-Evaluable Atezolizumab Patients in Safety-Evaluable Population)

Parameter	Atezo IV		Atezo SC	
	ADA-Negative N=93	ADA-Positive N=15	ADA-Negative N=178	ADA-Positive N=43
Objective Response Rate (Unconfirmed)				
Evaluable[a]	N=93	N=15	N=176	N=43
Responders (%)	11 (11.8)	1 (6.7)	24 (13.6)	5 (11.6)
95% CI for response rates	6.05, 20.18	0.17, 31.95	8.94, 19.61	3.89, 25.08
Progression-Free Survival				
Evaluable[b]	N=93	N=15	N=178	N=43
Patients with event (%)	64 (68.8)	10 (66.7)	115 (64.6)	30 (69.8)
Median duration of PFS months (95% CI)	3.1 2.7, 4.2	4.2 1.4, NE	2.9 2.7, 4.2	2.8 1.4, 4.2

ADA = anti-drug antibody; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IV = intravenous; NE = not estimable; PFS = progression-free survival; SC = subcutaneous.

[a] Response-evaluable and post-baseline ADA results available

[b] FAS and post-baseline ADA results available

Data cutoff: 26 Apr 2022.

Source: t_ef_all_P2_ADA_26APR2022_40657.

Table 48: Safety Summary Profile by Treatment-Emergent Atezolizumab ADA Status (ADA-Evaluable Atezolizumab Patients in Safety-Evaluable Population)

Safety Summary by Anti-Drug Antibody (ADA) Status to Atezolizumab, Part 2, Post-Treatment
ADA-Evaluable Population
Protocol: BP40657

	Atezo IV (N=108)		Atezo SC (N=221)	
	ADA- (N=93)	ADA+ (N=15)	ADA- (N=178)	ADA+ (N=43)
Total number of patients with at least one AE	82 (88.2%)	12 (80.0%)	154 (86.5%)	40 (93.0%)
Total number of AEs	383	52	640	179
Total number of patients with Confirmed/ Suspected COVID-19 AE	10 (10.8%)	1 (6.7%)	12 (6.7%)	4 (9.3%)
Total number of patients with at least one				
AE with fatal outcome	1 (1.1%)	1 (6.7%)	5 (2.8%)	2 (4.7%)
Related AE with fatal outcome	0	0	1 (0.6%)	0
Serious AE	15 (16.1%)	4 (26.7%)	25 (14.0%)	6 (14.0%)
Related Serious AE	2 (2.2%)	1 (6.7%)	3 (1.7%)	0
Grade 3-4 AE	27 (29.0%)	3 (20.0%)	31 (17.4%)	9 (20.9%)
Related Grade 3-4 AE	2 (2.2%)	2 (13.3%)	8 (4.5%)	1 (2.3%)
Related AE	35 (37.6%)	9 (60.0%)	73 (41.0%)	18 (41.9%)
AE leading to Atezolizumab discontinuation	3 (3.2%)	1 (6.7%)	2 (1.1%)	0
AE leading to dose interruption of Atezolizumab	27 (29.0%)	3 (20.0%)	45 (25.3%)	11 (25.6%)

ADA = Anti-Drug Antibodies (is also referred to as ATA, or Anti-Therapeutic Antibodies); ADA- = Without TX Enhanced/Induced; ADA+ = With TX Enhanced/Induced; TX = Treatment. Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of AEs' row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug through the clinical cut-off. Grade 3-4 categories include only patients with grade 3-4 AEs at the highest grade. RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Table 49: Baseline Prevalence of ADAs and Post-Baseline Incidence of Treatment-Emergent ADAs to rHuPH20 (Part 2, Safety-Evaluable Population)

Baseline Prevalence and Incidence of Treatment Emergent Anti-Drug Antibodies (ADAs) to RHUPH20 (rHuPH20), Safety Population
Protocol: BP40657, Part 2; Clinical Data Cutoff Date: 26April2022

Analyte: Anti-rHuPH20 Antibody

	Atezolizumab SC (n=247)
Baseline Prevalence of ADAs	
Baseline evaluable patients	237
Patients with a positive sample at baseline	27 (11.4%)
Patients with no positive samples at baseline	210
Incidence of Treatment Emergent ADAs	
Post-baseline evaluable patients	224
Patients positive for Treatment Emergent ADA	12 (5.4%)
Treatment-induced ADA	9
Treatment-enhanced ADA	3
Patients negative for Treatment Emergent ADA	212
Treatment unaffected	20

2.6.8.6. Safety related to drug-drug interactions and other interactions

No formal pharmacokinetic drug-drug interaction studies have been conducted with atezolizumab. Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

2.6.8.7. Discontinuation due to adverse events

Table 50: Adverse events leading to any study treatment discontinuation

Adverse Events Leading to Any Study Treatment Discontinuation, Part 2, Safety-Evaluable Population
Protocol: BP40657

MedDRA System Organ Class MedDRA Preferred Term	Atezo IV (N=124)	Atezo SC (N=247)
Total number of patients with at least one adverse event	4 (3.2%)	4 (1.6%)
Overall total number of events	4	6
Infections and infestations		
Total number of patients with at least one adverse event	1 (0.8%)	2 (0.8%)
Total number of events	1	2
COVID-19	1 (0.8%)	0
COVID-19 pneumonia	0	1 (0.4%)
Pneumonia aspiration	0	1 (0.4%)
General disorders and administration site conditions		
Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	1	0
Fatigue	1 (0.8%)	0
Injury, poisoning and procedural complications		
Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	1	0
Infusion related reaction	1 (0.8%)	0
Investigations		
Total number of patients with at least one adverse event	0	1 (0.4%)
Total number of events	0	3
Alanine aminotransferase increased	0	1 (0.4%)
Aspartate aminotransferase increased	0	1 (0.4%)
Gamma-glutamyltransferase increased	0	1 (0.4%)
Nervous system disorders		
Total number of patients with at least one adverse event	0	1 (0.4%)
Total number of events	0	1
Ischaemic stroke	0	1 (0.4%)
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	1	0
Pneumonitis	1 (0.8%)	0

Atezo IV: Atezolizumab IV 1200mg Q3W, Atezo SC: Atezolizumab SC 1875mg Q3W.
Investigator text for AEs encoded using MedDRA version 25.0. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset from first dose of study drug through the clinical cut-off.
RAVE Data Snapshot Date: 04JUL2022. Data Cutoff Date: 26APR2022.

Table 51: Adverse events leading to any dose interruption

Adverse Events Leading to Any Dose Interruption, Part 2, Safety-Evaluable Population
Protocol: BP40657

MedDRA System Organ Class MedDRA Preferred Term	Atezo IV (N=124)	Atezo SC (N=247)
Total number of patients with at least one adverse event	33 (26.6%)	61 (24.7%)
Overall total number of events	40	92
Infections and infestations		
Total number of patients with at least one adverse event	17 (13.7%)	24 (9.7%)
Total number of events	19	28
COVID-19	7 (5.6%)	10 (4.0%)
Pneumonia	3 (2.4%)	5 (2.0%)
Respiratory tract infection viral	1 (0.8%)	3 (1.2%)
Bronchitis	2 (1.6%)	0
COVID-19 pneumonia	0	2 (0.8%)
Conjunctivitis	0	1 (0.4%)
Coronavirus infection	1 (0.8%)	0
Enteritis infectious	0	1 (0.4%)
Gastroenteritis	0	1 (0.4%)
Herpes virus infection	0	1 (0.4%)
Influenza	0	1 (0.4%)
Oral candidiasis	1 (0.8%)	0
Pneumonia bacterial	1 (0.8%)	0
Post-acute COVID-19 syndrome	1 (0.8%)	0
Pyelonephritis	1 (0.8%)	0
Respiratory tract infection	0	1 (0.4%)
Subcutaneous abscess	0	1 (0.4%)
Tracheobronchitis	0	1 (0.4%)
Urinary tract infection	1 (0.8%)	0
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	3 (2.4%)	9 (3.6%)
Total number of events	3	10
Dyspnoea	0	2 (0.8%)
Pleural effusion	1 (0.8%)	1 (0.4%)
Pneumothorax	1 (0.8%)	1 (0.4%)
Asthma	1 (0.8%)	0
Bronchial obstruction	0	1 (0.4%)
Dyspnoea at rest	0	1 (0.4%)
Haemoptysis	0	1 (0.4%)
Hypoxia	0	1 (0.4%)
Pneumonitis	0	1 (0.4%)
Pulmonary oedema	0	1 (0.4%)
General disorders and administration site conditions		
Total number of patients with at least one adverse event	3 (2.4%)	6 (2.4%)
Total number of events	4	6
Pyrexia	2 (1.6%)	2 (0.8%)
Fatigue	0	2 (0.8%)
Gait disturbance	0	2 (0.8%)
Chest pain	1 (0.8%)	0
Malaise	1 (0.8%)	0

MedDRA System Organ Class MedDRA Preferred Term	Atezo IV (N=124)	Atezo SC (N=247)
Investigations		
Total number of patients with at least one adverse event	0	8 (3.2%)
Total number of events	0	14
Alanine aminotransferase increased	0	4 (1.6%)
Aspartate aminotransferase increased	0	4 (1.6%)
Blood lactate dehydrogenase increased	0	2 (0.8%)
Blood sodium decreased	0	1 (0.4%)
Fibrin D dimer increased	0	1 (0.4%)
Gamma-glutamyltransferase increased	0	1 (0.4%)
Weight decreased	0	1 (0.4%)
Nervous system disorders		
Total number of patients with at least one adverse event	3 (2.4%)	4 (1.6%)
Total number of events	3	5
Amnesia	0	1 (0.4%)
Balance disorder	1 (0.8%)	0
Brain oedema	0	1 (0.4%)
Headache	0	1 (0.4%)
Hemiparesis	0	1 (0.4%)
Neuropathy peripheral	1 (0.8%)	0
Transient ischaemic attack	1 (0.8%)	0
Tremor	0	1 (0.4%)
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	4 (3.2%)	2 (0.8%)
Total number of events	5	2
Hypercreatininaemia	2 (1.6%)	0
Decreased appetite	0	1 (0.4%)
Hyperkalaemia	1 (0.8%)	0
Hypochloraemia	1 (0.8%)	0
Hypokalaemia	0	1 (0.4%)
Hyponatraemia	1 (0.8%)	0
Gastrointestinal disorders		
Total number of patients with at least one adverse event	1 (0.8%)	4 (1.6%)
Total number of events	1	5
Nausea	0	2 (0.8%)
Diarrhoea	1 (0.8%)	0
Dysphagia	0	1 (0.4%)
Inguinal hernia	0	1 (0.4%)
Vomiting	0	1 (0.4%)

MedDRA System Organ Class MedDRA Preferred Term	Atezo IV (N=124)	Atezo SC (N=247)
Musculoskeletal and connective tissue disorders		
Total number of patients with at least one adverse event	0	5 (2.0%)
Total number of events	0	5
Arthralgia	0	2 (0.8%)
Back pain	0	1 (0.4%)
Bone pain	0	1 (0.4%)
Pain in extremity	0	1 (0.4%)
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	1 (0.8%)	3 (1.2%)
Total number of events	1	3
Anaemia	0	2 (0.8%)
Thrombocytopenia	1 (0.8%)	1 (0.4%)
Injury, poisoning and procedural complications		
Total number of patients with at least one adverse event	1 (0.8%)	3 (1.2%)
Total number of events	1	3
Exposure to SARS-CoV-2	0	1 (0.4%)
Fall	0	1 (0.4%)
Hip fracture	0	1 (0.4%)
Infusion related reaction	1 (0.8%)	0
Cardiac disorders		
Total number of patients with at least one adverse event	0	3 (1.2%)
Total number of events	0	3
Acute coronary syndrome	0	1 (0.4%)
Cardiac failure	0	1 (0.4%)
Myocardial infarction	0	1 (0.4%)
Renal and urinary disorders		
Total number of patients with at least one adverse event	1 (0.8%)	2 (0.8%)
Total number of events	1	2
Acute kidney injury	0	2 (0.8%)
Nephropathy toxic	1 (0.8%)	0
Skin and subcutaneous tissue disorders		
Total number of patients with at least one adverse event	1 (0.8%)	2 (0.8%)
Total number of events	1	2
Rash	1 (0.8%)	0
Rash maculo-papular	0	1 (0.4%)
Rash pruritic	0	1 (0.4%)
Endocrine disorders		
Total number of patients with at least one adverse event	0	2 (0.8%)
Total number of events	0	2
Hyperthyroidism	0	2 (0.8%)

MedDRA System Organ Class MedDRA Preferred Term	Atezo IV (N=124)	Atezo SC (N=247)
Eye disorders		
Total number of patients with at least one adverse event	0	1 (0.4%)
Total number of events	0	1
Dry eye	0	1 (0.4%)
Hepatobiliary disorders		
Total number of patients with at least one adverse event	0	1 (0.4%)
Total number of events	0	1
Immune-mediated hepatitis	0	1 (0.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	1	0
Tonsil cancer	1 (0.8%)	0

2.6.8.8. Post marketing experience

Since the International Birth Date (18 May 2016) through 17 May 2022, an estimated cumulative total of 310,426 patients have received atezolizumab from marketing experience (United States n=115,794; European Union n=91,547; Japan n=34,890; Rest of the World n=68,196). No new or unexpected safety findings were identified in the post-marketing setting for atezolizumab when used as a monotherapy in the most recent Periodic Benefit Risk Evaluation Report (PBRER 1114851).

2.6.9. Discussion on clinical safety

Intravenous formulations of atezolizumab has been approved in Europe since 2017, so the safety profile of atezolizumab has been well characterised.

The safety evaluation of Atezo SC to treat patients in all approved indications with Atezo IV is based on data of atezolizumab as monotherapy from part 2 of the IMscin001 study comparing the incidence and severity of AEs between its two treatment arms: Atezo IV and Atezo SC. The size of the safety pool of Atezo SC (n=247) is considered acceptable as similar safety pool sizes has been accepted in earlier conducted IV/SC trials. The safety profile of Atezo SC has been compared to the Atezo Mono pool 2 of the SmPC consisting of studies with atezolizumab as monotherapy (n=4349).

Updated exposure with a median exposure of 3.5 months and 3.2 months in the treatment arms, respectively, has been provided DCO (16 January 2023), respectively. The median number of doses administered increased from 4 to 6 for Atezo SC and 5 for Atezo IV. Longer exposure is not considered obtainable in the pivotal study setting of 2L NSCLC, which is supported by the information that only 16% of the patients are still on treatment at DCO.

Updated safety results from IMscin001 study showed that AEs any Grade observed in both arms across the study period were observed in slightly more patients in the Atezo SC arm (Atezo IV 83.9% vs Atezo SC 88.3%). The most common AEs observed were for both arms fatigue, dyspnoea, decreased appetite, cough, hyponatraemia and hyperglycaemia, which is comparable with the known safety profile of atezolizumab IV and is as expected in the studied patient population.

Grade 3/4 AEs were observed in 31.5% vs 20.6% in the Atezo IV and the Atezo SC treatment arms, respectively. The most frequent Grade 3/4 AEs in both arms were pneumonia, hyponatraemia, COVID-19, hypokalaemia, and anaemia. Grade 5 AEs were similar in both arms (6.5%) and although six additional Grade 5 AEs were reported with updated data (2 in the Atezo SC arm and 4 in the Atezo IV arm), none of the events were considered treatment-related.

Serious adverse events (SAEs) were observed in 27.4% in the Atezo IV and 19.4% in the Atezo SC arm of the trial. The most frequent observed SAE in both treatment arms was pneumonia and Covid-19. Updated data show that the frequency of deaths was similar in both arms, i.e. 58.3% in the Atezo SC arm and 63.7% in the Atezo IV arm, with the leading cause of death being progressive disease (86.8% vs. 87.3%, respectively).

There were a similar proportion of patients who experienced immune-mediated events in both treatment arms (30.8% Atezo SC vs. 28.2% Atezo IV), and the most frequently reported immune-mediated events were hepatitis (diagnosis and lab abnormalities), rash and hypothyroidism, mostly of grade 1-2.

Grade 3 adverse events of special interest (AESIs) were reported in a similar frequency in both arms (4.0%), with no Grade 4 AESIs reported. No new Grade 5 AESIs, infusion related reactions (IRR) or injection site reactions (ISR) were reported since the primary safety CCOD One Grade 5 event of toxic epidermal necrolysis (TEN) was reported in the Atezo SC arm, which was considered to be treatment-

related. TEN is already mentioned in section 4.4 and 4.8 of the existing SmPC for the IV presentations. More patients needed dose interruptions and systemic corticosteroids in the Atezo SC arm compared to the Atezo IV arm.

Reactions related to the administration route of atezolizumab treatment differed between arms: while systemic Grade 1-2 reactions was more common in the IV arm (3.2% vs. 0%), local injection site reactions (ISR) were more frequent in the SC arm (4.5% vs. 0%). This is reflected in section 4.8 of the SmPC. No serious events were reported or led to treatment interruptions, discontinuations or required the use of corticosteroids. The most frequent events were injection site pain (2.4%) and injection site reaction (1.6%).

The Applicant was asked to discuss the higher frequency of electrolyte disturbances (hyponatriaemia, hyperglycaemia, hyperkaliaemia, hypercalcaemia, hypomagnesiamia and hypercreatinaemia) in the IV atezo arm and it was clarified that although the updated safety results show a higher frequency of electrolyte disturbances in the atezo IV arm, most events were of grade 1-2 severity, so they were generally manageable. The difference may be due to a higher frequency of concomitant medications that could impact electrolyte balance in the Atezo IV arm compared to the Atezo SC arm, such as diuretics (15.3% vs. 9.3%), agents acting on the renin-angiotensin system (18.5% vs. 15.8%), drugs for constipation (16.1% vs. 13.0%), and analgesics (58.9% vs. 51.0%). Moreover, there were also a higher number of patients with concurrent medical conditions that could impact electrolyte balance in the IV arm compared to the SC arm such as hypertension (41.1% vs. 35.2%), dyslipidemia (15.3% vs. 7.3%), and diabetes mellitus (12.1% vs. 4.9%). This explanation is considered clinically plausible and acceptable.

In the pivotal IMscin001 study, the incidence of treatment-emergent anti-atezolizumab antibodies (ADA's) in patients treated with the subcutaneous versus the intravenous formulation of atezolizumab could be considered comparable (19.5% [43/221] and 13.9% [15/108], respectively), following a median of 2.8 months of treatment. The limited exposure and sample size preclude any firm conclusion regarding the development of ADA's with the SC formulation. The incidence of treatment-emergent anti-rHuPH20 antibodies in patients treated with the subcutaneous formulation of atezolizumab was 5.4% (12/224); however, the clinical relevance of the development of these are unknown.

Overall, a similar frequency of any Grade AEs, Grade 3-4 AEs and SAEs were observed in both treatment arms and no new safety signals were observed.

2.6.10. Conclusions on the clinical safety

In conclusion, updated safety data from the pivotal study IMscin001 study show a similar and acceptable safety profile in both treatment arms (atezolizumab IV and SC), except for numerically higher incidence of injection site reactions in the SC arm. This is reflected in the product information. No new safety signals have been observed.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 52: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Immune-mediated adverse reactions Infusion-related reactions
Important potential risks	Attenuated efficacy or reduced tolerability in patients with anti-drug antibodies Embryo-fetal toxicity
Missing information	Long term use

2.7.2. Pharmacovigilance plan

Table 53: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
There are no Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
There are no Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Category 3 – Required additional pharmacovigilance activities				
MO29983 (SAUL): An Open-Label, Single Arm, Multicenter, Safety Study of atezolizumab in Locally Advanced or Metastatic Urothelial or Non-Urothelial Carcinoma of the Urinary Tract Ongoing	To evaluate the safety of atezolizumab based on the following endpoints: Nature, severity, duration, frequency and timing of AEs and changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab administration.	Long-term use	Final CSR	31 December 2023

- AE = adverse event; CSR = Clinical Study Report; .

2.7.3. Risk minimisation measures

Table 54: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Immune-mediated adverse reactions	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimization measures:** • Patient Cards: all immune-mediated adverse reactions, excluding SCARs • SCARs: DHPC: To inform healthcare professionals that immune-mediated SCARs which were previously known to be potentially associated with use of Tecentriq (atezolizumab), are now considered to be an identified risk.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** SCARs: Metrics on the distribution and receipt of the DHPC will be taken to assess the effectiveness of this risk minimization activity.
Infusion-related reactions	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects Relevant information for patient in PIL **Additional risk minimization measures:** Patient Cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Attenuated efficacy or reduced tolerability in patients with anti-drug antibodies	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.8 Undesirable effects **No additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Embryo-fetal toxicity	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.6 Fertility, pregnancy and lactation Section 5.3 Preclinical safety data Relevant information for patient in PIL **No additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Long-term use	**Routine risk minimization measures:** Proposed text in E.U. SmPC: None **No additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study MO29983 and MO39171

DHPC = direct healthcare professional communication; E.U. = European Union; PIL = Patient Information Leaflet; SCAR = severe cutaneous adverse reaction; SmPC = Summary of Product Characteristics.

2.7.4. Conclusion

The list of safety concerns, pharmacovigilance plan and risk minimisations measures remain unchanged for the new SC formulation. The existing pharmacovigilance plan and risk minimisations measures are considered sufficient to mitigate the risks of Tecentriq for both the IV formulation and the SC formulation in all approved indications.

The CHMP considered that the risk management plan version 24.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- No significant changes impacting the readability of the package leaflet are made. In particular, key safety messages are not affected by this extension. The new additions follow the same structure and use similar descriptions and terminology as used in the approved package leaflet.
- The target group of users for the SC formulation will be the same group of users as for the IV formulation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The line extension for atezolizumab SC at 1875 mg (flat dose) solution for injection every 3 weeks includes all current and future approved indications for atezolizumab IV, i.e., as monotherapy and in combination with chemotherapy (ies) for the treatment of urothelial carcinoma (UC), non-small cell lung cancer (NSCLC), small-cell lung cancer (SCLC), triple-negative breast cancer (TNBC) and hepatocellular carcinoma (HCC) in various clinical settings.

3.1.2. Available therapies and unmet medical need

The pivotal study (IMscin001) that serves as basis for this application is conducted in a study population with advanced non-small-cell lung cancer (NSCLC) in the 2L+ setting.

The claimed added benefit that atezolizumab SC would address (in comparison to already available atezolizumab IV) is a less invasive and faster administration, which can reduce the strain on medical centres with respect to time and resources required to prepare and administer IV therapy.

3.1.3. Main clinical studies

The pivotal study for the claimed indications is the open-label, 2:1 randomized, multicentre Phase Ib/III Study BP40657 (IMscin001), in which 371 patients with previously treated locally advanced or metastatic NSCLC were randomised to either atezolizumab SC 1875 mg Q3W (n=247) or atezolizumab IV 1200 mg Q3W (n=124).

The study population was immunotherapy-naïve, with any PD-L1 status and for whom prior platinum-based therapy had failed.

The primary endpoint was to show non-inferiority of PK for the SC vs. the IV formulation of atezolizumab. Secondary endpoints were ORR, DOR, PFS and OS and safety. The MAH had initially submitted data from the primary analysis of the pivotal study IMscin001 with a median follow-up time of 4.7 months (DCO 26 April 2022). During the procedure, updated efficacy and safety data were also provided with an additional 9 months of follow-up (DCO 16 January 2023).

3.2. Favourable effects

- The PK co-primary endpoints (observed Ctrough and model-predicted AUC0-21 d at Cycle 1) were met: GMR of serum atezolizumab Ctrough,SC/Ctrough,IV values at Cycle 1 was 1.05 (90% CI: 0.88, 1.24), while GMR of model predicted serum atezolizumab AUC0-21 d,SC/AUC0-21 d,IV values at Cycle 1 was 0.87 (90% CI: 0.83, 0.92). The corresponding lower limit of the two-sided 90% CI for both co-primary endpoints were above the prespecified non-inferiority margin of 0.8, and thus PK non-inferiority of SC over IV is established.
- All patients in the SC arm had drug exposure within the full E-R range for atezolizumab IV and $>$99% of SC patients had drug concentrations above the receptor saturation threshold of 6 μg/mL. Further similar dose exposure response relationship was observed in all of the IV indications.
- The updated confirmed ORR was 10.5% (95%CI: 5.70, 17.26) for Atezo IV vs. 11.0% (95%CI: 7.39, 15.63) for Atezo SC, respectively. All responders achieved PR and no CRs were observed in both arms.
- The median DoR was 15.1(95%CI: 5.6, NE) in the SC arm vs 11.2 (95%CI: 4.2, NE) in the IV arm.
- The median PFS was 2.8 months (95% CI: 2.7;4.1) in the Atezo SC arm and 2.9 months (95% CI: 1.8;4.2) in the Atezo IV arm.
- The median OS was 10.7 months (95% CI: 8.5; 13.8) in the Atezo SC arm and 10.1 months (95% CI: 7.5; 12.1) in the Atezo IV arm.

3.3. Uncertainties and limitations about favourable effects

None.

3.4. Unfavourable effects

- Updated safety results from IMscin001 study showed that AEs any Grade observed in both arms across the study period were observed with slightly more patients in the Atezo SC arm (Atezo IV 83.9% vs Atezo SC 88.3%). The most common AEs observed in the study were for both arms fatigue, dyspnoea, decreased appetite, cough, hyponatraemia and hyperglycaemia.
- Grade 3/4 AEs were observed in 31.5% vs 20.6% in the Atezo IV and the Atezo SC treatment arms, respectively. The most frequent Grade 3/4 AEs in both arms were pneumonia, hyponatraemia, COVID-19, hypokalaemia, and anaemia.
- Grade 5 AEs were similar in both arms (6.5%) and although six additional Grade 5 AEs were reported with updated data, none of the events were considered treatment-related.
- SAEs were observed in 27.4% in the Atezo IV and 19.4% in the Atezo SC arm of the trial. The most frequent observed SAE in both treatment arms was pneumonia and Covid-19. Updated data show that the frequency of deaths was similar in both arms, i.e. 58.3% in the Atezo SC arm and 63.7% in the Atezo IV arm, with the leading cause of death being progressive disease (86.8% vs. 87.3%, respectively).
- Updated safety data show a similar proportion of patients who experienced immune-mediated events in both treatment arms (30.8% Atezo SC vs. 28.2% Atezo IV). Consistent with the primary DCO, the most frequently reported immune-mediated reactions were hepatitis (diagnosis and lab abnormalities), rash and hypothyroidism.
- Reactions related to the administration route of atezolizumab treatment differed between arms: while systemic Grade 1-2 reactions were more common in the IV arm (3.2% vs. 0%), local injection site reactions (ISR) were predominant in the SC arm (4.5% vs. 0%), most commonly injection site pain (2.4%) and injection site reaction (1.6%).

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 55: Effects Table for Atezolizumab SC for all the already approved indications for atezolizumab IV (data cut-off: 16 Jan 2023).

Effect	Short Description	Unit	Treatment Atezolizumab SC N=247	Control Atezolizumab IV N=124	Uncertainties/ Strength of evidence	References
Favourable Effects (updated)						
ORR (confirmed)	Number of subjects (rate) 95% CI	(n)%	27 (11.0) 7.39, 15.63	13 (10.5) 5.70, 17.26	Efficacy data with a median follow-up time of 13.7 months	
mDOR	Median duration of response 95% CI	months	15.1 5.6, NE	11.2 4.2, NE		
mPFS	Median progression free survival 95% CI	months	2.8 2.7, 4.1	2.9 1.8, 4.2		
mOS	Median overall survival 95% CI	months	10.7 8.5, 13.8	10.1 7.5, 12.1		
Unfavourable Effects						
AEs any grade		%	88.3	83.9	Updated safety data	
AEs grade 3/4		%	20.6	31.5		
AEs grade 5		%	6.5	6.5		
SAEs		%	19.4	27.4		
AESIs		%	30.8	28.2		
AEs leading to atezolizumab discontinuation		%	3.6	7.3		

Abbreviations: AEs=Adverse Events, SAEs=Serious Adverse Events, AESIs=Adverse Events of Special Interest.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The line extension for atezolizumab SC is based on a single pivotal trial (IMscin001). The primary objective was to show non-inferiority of atezolizumab SC over atezolizumab IV from a PK perspective, and secondary objectives included efficacy and safety endpoints.

Even if the non-inferiority testing of co-primary endpoints (observed Ctrough and model-predicted AUC0-21 d at Cycle 1) was met, the model-predicted exposure in the SC arm was 13% lower than for the IV arm and the CI limits were narrow around the point estimate and did not include 1.0, i.e. the difference seemed significant. Upon request, the Applicant developed a new Pop PK model based only on Cycle 1 PK data from IMScin001 Cohort 4 and Cohort 5. The new model had a similar structure to the previous model but included a lag time for absorption. The bioavailability was estimated to 0.609. Only two covariates were retained in the model, namely body weight effect on CL and sex on Vp. The effect of body weight on CL was low with a high RSE and the 95% CI containing the null. The IIV shrinkage was moderate to high. However, from the provided diagnostic plots, the new Cycle 1 based model provided a better fit of the Cycle 1 data (IV and SC) compared to the previous model even the absorption was still slightly overpredicted.

When the new model was used to predict Cycle 1 AUC0-21d for non-inferiority testing of the SC versus IV doses in IMScin001, it resulted in a GMR of 0.86 and a 90% CI of 0.81 to 0.91. This result is comparable to the initial result obtained with the previous model, however, the updated Pop PK model shows that a better description of e.g. the absorption phase does not influence the non-inferiority test outcome. It is therefore agreed that non-inferiority of atezolizumab SC versus IV have been established, based on both the observed (Cycle 1 Ctrough) and the model-predicted (Cycle 1 AUC0-21d) end-points.

Moreover, the results from the dose-ranging IV clinical study showed that no statistically significant relationship was associated with efficacy and atezolizumab exposures and all SC patients had drug exposure within the full E-R range for atezolizumab IV and $>$99% of SC patients had drug concentrations above the receptor saturation threshold of 6 μg/mL. Further, a similar dose-exposure-response relationship was observed in all of the IV indications. It is thus accepted that patients treated with SC atezolizumab, including patients with drug exposure at the extreme lower end, achieve adequate drug exposures despite the higher variability.

Updated efficacy data show a similar ORR, DoR, PFS and median OS in both arms. The short median PFS of ~2.8 months in both treatment arms does not allow for a long exposure; which is to be expected in the chosen 2L+ setting of advanced NSCLC.

3.7.2. Balance of benefits and risks

PK non-inferiority of SC vs IV atezolizumab, the primary objective of pivotal study IMscin001, has been established. Moreover, the efficacy of SC and IV atezolizumab is considered comparable regarding ORR, DoR, PFS and OS. Since the safety profiles of both administrations were similar except for more injection site reactions in the SC arm, and no new safety signals were observed, the benefit-risk balance for the subcutaneous formulation is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Tecentriq is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Tecentriq new strength (1875mg), new pharmaceutical form (solution for injection) and new route of administration (subcutaneous use) is favourable in the following indication(s):

Urothelial carcinoma (UC)
Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic UC:

- after prior platinum-containing chemotherapy, or
- who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5% (see section 5.1).

Early-stage non-small cell lung cancer (NSCLC)
Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1 for selection criteria).

Metastatic NSCLC
Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies (see section 5.1).

Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1).

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1).

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving Tecentriq (see section 5.1).

Small cell lung cancer (SCLC)
Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) (see section 5.1).

Triple-negative breast cancer (TNBC)
Tecentriq in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

Hepatocellular carcinoma (HCC)
Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy (see section 5.1).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Tecentriq subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**
- Prior to launch of Tecentriq in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.
- The educational programme is aimed at increasing awareness and providing information concerning the signs and symptoms of important identified risks of atezolizumab, including certain immune-mediated adverse reactions, and infusion-related reactions, and how to manage them.
- The MAH shall ensure that in each Member State where Tecentriq is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Tecentriq have access to/are provided with the following educational package:
- Patient Card
- **The patient card** shall contain the following key messages:
  - Brief introduction to atezolizumab (indication and purpose of this tool)
  - Information that atezolizumab can cause serious side effects during or after treatment, that need to be treated right away

- Description of the main signs and symptoms of the following safety concerns and reminder of the importance of notifying their treating physician immediately if symptoms occur, persist or worsen:
  - Immune-Mediated Hepatitis
  - Immune-Mediated Pneumonitis
  - Immune-Mediated Colitis
  - Immune-Mediated Pancreatitis
  - Immune-Mediated Endocrinopathies (Type 1 Diabetes Mellitus, Hypothyroidism, Hyperthyroidism, Adrenal Insufficiency and Hypophysitis)
  - Immune-Mediated Neuropathies (Guillain-Barre Syndrome, Myasthenic Syndrome / Myasthenia Gravis, Facial Paresis)
  - Immune-Mediated Myelitis
  - Immune-Mediated Meningoencephalitis
  - Immune-Mediated Myocarditis
  - Immune-Mediated Nephritis
  - Immune-Mediated Myositis
  - Immune-Mediated Pericardial Disorders
  - Haemophagocytic lymphohistiocytosis
  - Infusion-Related Reactions

- Warning message for patients on the importance of consulting their doctor immediately in case they develop any of the listed signs and symptoms and on the important not attempting to treat themselves.
- Reminder to carry the Patient Card at all times and to show it to all healthcare professionals that may treat them.
- The card should also prompt to enter contact details of the physician and include a warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Tecentriq.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post-authorisation efficacy study (PAES): In order to further evaluate the efficacy of atezolizumab for the treatment of patients with locally advanced or metastatic urothelial cancer, the MAH should submit the final OS results of study IMvigor210.	Submission of study results: 31 December 2023