26 March 2026
EMADOC-1700519818-2975985
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hetronifly

International non-proprietary name: Serplulimab

Procedure No. EMA/VR/0000282407

Note

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

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List of abbreviations

ADA	Antidrug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time 0 to infinity
$AUC_{0\text{-}tau}$	Area under the concentration-time curve from time 0 to the end of dosing interval
AUC_{ss}	Area under the concentration-time curve at steady state
BIL	Bilirubin
BMI	Body mass index
BNP	Brain natriuretic peptide
BOIN	Bayesian Optimal Interval
BOR	Best overall response
BSA	Body surface area
C_{avg1}	Average concentration after the first cycle of treatment
$C_{avg,ss}$	Average concentration at steady state
CI	Confidence interval
CL	Clearance
CL_0	Clearance at baseline
CL_{ss}	Clearance at steady state
C_{max}	Maximum concentration
C_{max1}	Model-predicted maximum concentration after the first cycle of treatment
$C_{max,ss}$	Maximum concentration at steady state
CMC	Chemistry, Manufacturing and Controls
C_{min}	Minimum concentration

C_{min1}	Model-predicted minimum concentration after the first cycle of treatment
$C_{min,ss}$	Minimum concentration at steady state
COVID-19	Coronavirus disease 2019
CR	Complete response
CRCL	Creatinine or creatinine clearance
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
dMMR	Mismatch repair deficient
DLT	Dose-limiting toxicity
DOR	Duration of response
E-R	Exposure-Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module
EOT	End-of-treatment
ESCC	Esophageal Squamous Cell Carcinoma
ESMO	European Society for Medical Oncology
ES-SCLC	Extensive-stage small cell lung cancer
EU	European Union
exp(T_{max})	Ratio of clearance at the maximum change to clearance at baseline
FIH	First-in-human
HCC	Hepatocellular carcinoma
HXL10	Serplulimab
HLX04	a biosimilar to bevacizumab
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

iCPD	immune confirmed progressive disease
IgG	Immunoglobulin G
IL-2	Interleukin-2
irAE	Immune-related adverse event
iUPD	immune unconfirmed progressive disease
IRR	Infusion-related reaction
iRECIST	immune Response Evaluation Criteria in Solid Tumors / Modified RECIST 1.1 for immune-based therapeutics
IRR	Infusion-related reaction
IRRC	Independent Radiology Review Committee
ITSM	Immunoreceptor tyrosine-based switch motif
ITT	Intent-to-treat
ITT	Intention-to-treat
IV	Intravenous
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MTD	Maximum tolerated dose
NAb	Neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMPA	National Medical Products Administration
NSCLC	Non-small cell lung cancer
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PPS	Per protocol set

PR	Partial response
PS	Performance status
PT	Preferred term
Q	Quartile
Q2W	Once every 2 weeks
Q3W	Once every 3 weeks
Q4W	Once every 4 weeks
Q6W	Once every 6 weeks
Rac(AUC_{ss})	Accumulation ratio of steady state area under the concentration-time curve
Rac(C_{max})	Accumulation ratio of maximum concentration
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D/3D	Recommended phase II/III dose
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Standard deviation
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SS	Safety set
TBIL	Total bilirubin
TC_{50}	Time when half-maximum change in clearance is achieved
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TPS	Tumour proportion score
ULN	Upper limit of normal
V_c	Volume of distribution in central compartment
V_p	Volume of distribution in peripheral compartment
λ	Sigmoid factor of time-varying clearance

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Accord Healthcare S.L.U. submitted to the European Medicines Agency on 01 July 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include HETRONIFLY in combination with carboplatin and pemetrexed is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung carcinoma who do not have EGFR or ALK positive mutations based on interim results from study HLX10-002-NSCLC301; this is a pivotal Phase III clinical study. As a consequence, sections 4.1, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Hetronifly, was designated as an orphan medicinal product (EU/3/22/2731) on 9 December 2022 in the following indication: treatment of small cell lung cancer.

The new indication, which is the subject of this application, does not fall within any orphan designation. According to Article 7 of Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products, it is not possible to combine an orphan indication and a non-orphan indication in the same marketing authorisation. Consequently, the MAH has committed to request the withdrawal of the orphan designation from the Community Register of Orphan Medicinal Products within 2 days after the receipt of the CHMP opinion. Should the MAH not request the withdrawal of the orphan designation within the said deadline, nor request re-examination in accordance with Article 16(4) of Commission Regulation (EC) No. 1234/2008, the validation of this variation application becomes automatically null and void with retroactive effect.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0471/2020 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

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.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Eva Skovlund

Timetable	Actual dates
Submission date	1 Jul 2025
Start of procedure:	19 Jul 2025
CHMP Rapporteur's preliminary assessment report circulated on:	12 Sept 2025
PRAC Rapporteur AR	16 Sept 2025
PRAC RMP advice and assessment overview adopted by PRAC	2 Oct 2025
Joint Rapporteur's updated assessment report circulated on:	9 Oct 2025
Request for supplementary information adopted by the CHMP on:	16 Oct 2025
MAH's responses submitted to the CHMP on:	28 Nov 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 Dec 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	22 Jan 2026
Request for supplementary information adopted by the CHMP on:	29 Jan 2026
MAH's responses submitted to the CHMP on:	21 February 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 Mar 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	19 Mar 2026
CHMP opinion:	26 Mar 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Lung cancer has two primary histological subtypes, small-cell lung cancer and non-small-cell lung cancer (NSCLC). Of these, non-small cell lung cancer (NSCLC) is the most common, accounting for about 85% of all lung cancers. NSCLC, in turn, has three main histological subtypes, namely

adenocarcinoma (originating from the mucus gland cells), squamous cell carcinoma (originating from the airway squamous epithelium) and large cell carcinoma (a heterogeneous group of undifferentiated epithelium-derived tumours). In addition, there are rare cases of adenosquamous and sarcomatoid tumours (Hendriks, L.E.L. et al., 2024).

State the claimed therapeutic indication

The originally proposed therapeutic indication was as follows: "Hetronifly in combination with carboplatin and pemetrexed is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung carcinoma who do not have EGFR or ALK positive mutations."

Epidemiology and risk factors

Lung cancer is one of the malignant tumours with the highest incidence rate and mortality worldwide. According to GLOBOCAN, in 2022 there were about 2.5 million new cases of lung cancer worldwide, accounting for 12.4% of all cancers globally, and was the leading cause of cancer-related death (18.7%) worldwide (Bray, F. et al., 2024). The International Agency for Research on Cancer (IARC) reported in 2022 that the crude and age-standardized incidence of lung cancer per 100,000 inhabitants was 64.8 in Europe.

There is a higher prevalence of male patients with lung cancer. Epidemiological data suggest sex-based disparities, with women with lung cancer being younger, having fewer comorbidities, and being more likely to be never-smokers than men (MacRosty, C.R. and Rivera, M.P., 2020).

The median age of patients with lung cancer is 71 years, with fewer than 10% of cases diagnosed in individuals younger than 55 years.

Tobacco smoking remains the main cause of lung cancer, with a relative risk of lung cancer of 10-30 times higher compared with never-smokers. Up to 25% of all NSCLC cases occur in never-smokers and the incidence in non-smokers is increasing globally, especially among women and younger age groups. Besides smoking, several other risk factors have been described, including exposure to outdoor air pollution, asbestos, arsenic, radon, non-tobacco-related polycyclic aromatic hydrocarbons, indoor air pollution, obstructive lung diseases, pulmonary fibrosis or pulmonary infection, pathogenic germline variants (in TP53, ATM, CHEK2, EGFRT790M) and genetic ancestry (Hendriks, L.E.L. et al., 2024). A familial risk of lung cancer has been reported in several registry-based studies.

Biologic features, aetiology and pathogenesis

Adenocarcinoma accounts for approximately 50% of all NSCLC cases and squamous cell carcinoma for 20-30% of cases. The histological subtype of lung cancer correlates with the patient's smoking history and both factors (histology and smoking pattern) are associated with the incidence of druggable genomic alterations that are usually more common in adenocarcinoma and in patients with a never or light smoking history (Hendriks, L.E.L. et al., 2024).

Most adenocarcinomas arise in the terminal respiratory unit, where foci of atypical adenomatous hyperplasia may transform into adenocarcinoma in situ before invasion occurs, defining invasive adenocarcinoma. Several carcinogens may induce these processes. Once invasive, malignant tumours continue to evolve through further genomic alterations, driving subclonal development and, usually, more aggressive disease. Clinically apparent invasive lung cancers vary greatly in the tumour mutational burden (TMB), which can range from fewer than 10 to almost 1000 broadly

defined mutations per megabase of exonic DNA. In most lung cancers, especially those related to tobacco use, genomic complexity is high, with several genomic alterations contributing to tumour growth and a high degree of spatial heterogeneity. In others, genomic diversity is low and a single activating genomic alteration – the driver oncogene – is present in all tumour cells and is essential for tumour cell survival. This is referred to as oncogene addiction (Hendriks, L.E.L. et al., 2024). Most therapeutically relevant oncogenic drivers in lung cancer are kinases (e.g. EGFR, ALK, ROS1), and targeted therapies, primarily tyrosine kinase inhibitors (TKIs), against these drivers have been developed. Most tumours eventually become resistant to TKIs (Hendriks, L.E.L. et al., 2024).

One mechanism for tumour immune evasion, despite harbouring potential neo-antigens, is tumour cell expression of inhibitory immune checkpoints, which effectively switch off the antitumour immune response. In particular, the most frequently used immunotherapies in NSCLC target programmed cell death 1 (PD1) or its ligand PD-L1, which is an important immune checkpoint. In general, the expression of PD-L1 on tumour cell membranes is positively correlated with the probability of drug response and PD-L1 is used as a selective biomarker for many indications. High TMB may predict greater (neo)antigenicity and seems to predict therapy response but not patient survival benefit from immune checkpoint inhibitors (ICIs) (Hendriks, L.E.L. et al., 2024).

Clinical presentation, diagnosis and stage/prognosis

Lung cancer symptoms occur late in the disease, with non-specific early symptoms. Thus, the majority of patients with lung cancer present with advanced disease. The implementation of low-dose CT (LD-CT) screening programs worldwide is currently low.

Pathological diagnosis begins with the identification and classification of tumour type, according to criteria laid out in the WHO classification. Tumour tissue should be obtained for pathological confirmation of the diagnosis, histological subtyping of the lung cancer and tests to evaluate potential predictive biomarkers, for instance PD-L1 expression and genomic analysis (Hendriks, L.E.L. et al., 2024). Staging is according to the TNM system (8th edition). Response evaluation is recommended after two to three cycles of systemic therapy, using the same initial radiographic investigation that demonstrated tumour lesions. Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity. Measurement of lesions should follow Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. For patients treated with immune checkpoint inhibition (ICI), immune RECIST (iRECIST) immune-modified RECIST (imRECIST) and immune-related RECIST (irRECIST) measurements should be validated before implementation in clinical practice. Nonconventional responses and pseudoprogression are not often observed in NSCLC (Hendriks, L.E., 2023).

Despite improvements in the diagnosis, imaging, staging, and treatment of NSCLC, the 5-year overall survival rate of NSCLC patients remains low worldwide. In 2020, a cross-sectional epidemiological analysis in the US showed that the 5-year overall survival (OS) rate of NSCLC patients was about 26.4%, while the 5-year OS rate of patients with stage IV NSCLC was 5.8% (Ganti AK, 2021).

Management

Prior to the advent of immune checkpoint-inhibitor-based therapy, platinum-based doublet chemotherapy was the traditional first-line treatment regimen for patients with metastatic non-squamous NSCLC. With the rise and development of immunotherapy, anti-programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) inhibitors have become the standard first-line treatment regimen for stage IV non-squamous NSCLC without driver gene mutations.

According to the current ESMO guidelines, for patients with stage IV NSQ NSCLC, PS 0-1, regardless of tumour PD-L1 status and without contraindication for ICI, a combination of platinum-based chemotherapy (ChT) plus programmed cell death protein 1 (PD-1)/PDL1 blockade is the most common treatment approach. For the subset of patients with PD-L1 >50%, monotherapy with ICIs could also be relevant. Several combination regimens have successfully demonstrated improved overall survival (OS) compared with ChT alone and are recommended according to the ESMO guidelines for patients with stage IV NSQ NSCLC, PS 0-1, regardless of tumour PD-L1 status and without contraindication for ICI. These have included platinum-based ChT plus: pembrolizumab, atezolizumab with or without bevacizumab, nivolumab and ipilimumab, cemiplimab, sugemalimab, and durvalumab-tremelimumab.

Concerning patients with locally advanced (stage IIIB or IIIC) disease that are not candidates for platinum-based chemoradiation or surgery, the usual approach is the same as for patients with metastatic disease.

2.1.2. About the product

Serplulimab is a recombinant humanised IgG4- monoclonal antibody targeting the anti-programmed targeting the anti-programmed cell death 1 (PD-1). and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Serplulimab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Serplulimab was granted a marketing authorisation on 03-Feb-25 (EMEA/H/C/006170) in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).”

Posology:

The recommended dose in both the induction and maintenance phases is 4.5 mg/kg bodyweight serplulimab every 3 weeks until disease progression or unacceptable toxicity. During the induction phase (4 cycles), carboplatin and pemetrexed are administered on day 1 of each 3-week cycle. During the maintenance phase, the administration of pemetrexed is continued at the discretion of the physician.

For use in combination, see the Summary of Product Characteristics (SmPC) for the concomitant therapies.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH has not sought scientific advice from the EMA regarding the currently sought indication in non-squamous NSCLC.

2.1.4. General comments on compliance with GCP

The application for extension of the indication to nonsquamous NSCLC is supported by the pivotal phase 3 efficacy and safety clinical study ASTRUM-002 (HLX10-002-NSCLC301), which was carried

out exclusively in China. There were 92 study sites opened in China, 75 of which enrolled participants.

The MAH included a statement that this trial, as well as dose-finding trial HLX10-001, which were both carried out outside the European Union, met the ethical requirements of Directive 2001/20/EC.

The CSR for study HLX10-002-NSCLC301 states that the study was conducted according to the protocol and in compliance with International Council for Harmonisation (ICH) guideline on Good Clinical Practice (GCP), the Declaration of Helsinki and relevant local laws and regulations of the study sites.

In addition, GCP inspections were carried out by the NMPA at 2 sites in relation to the study, both concluding: "On-site inspections of the clinical trial were carried out during the review of this product, and the issues identified in the inspections had no significant impact on the benefit-risk evaluation of this product". Audits of four sites were also carried out by the sponsor in relation to the study, without any critical findings.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The applicant has provided a justification for not submitting the environmental risk assessment (ERA), in accordance with current guidance (Guideline on the environmental risk assessment of medicinal products for human use, EMEA/CHMP/SWP/4447/ 00 Rev. 1- Corr.*). Serplulimab is a recombinant humanized monoclonal antibody expected to be degraded to small peptides and individual amino acids. Therefore, the lack of dedicated ERA studies is acceptable, as the product is not expected to pose a risk to the environment due to its nature.

2.2.2. Conclusion on the non-clinical aspects

Considering the above data, serplulimab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

Please refer also to Section 2.1.4. above.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1 Tabular overview of clinical studies

Type of Study	Study protocol	Study title	Countries where the studies were conducted
Phase 1 dose-finding and dose-expansion	HLX10-001	A phase 1 study of HLX10, a humanised monoclonal antibody targeting programmed cell death-1 (PD-1) protein in patients with advanced solid tumours	Taiwan
Phase III (pivotal) Efficacy and safety	HLX10-002-NSCLC301	A Phase III, three arm, randomized, double-blind, multicenter clinical study to evaluate serplulimab in combination with chemotherapy versus serplulimab +HLX04 in combination with chemotherapy versus chemotherapy as first-line therapy for advanced non-squamous non-small cell lung cancer	China

2.3.2. Pharmacokinetics

Serplulimab (HLX10) is a novel recombinant humanised anti-programmed cell death 1 (PD-1) monoclonal antibody (mAb) of IgG4 type developed by Shanghai Henlius Biotech, Inc. and belongs to the pharmacological class of anti-PD-1 inhibitors. The molecular weight (MW) is approximately 144-146 kDa.

Serplulimab is supplied as a sterile solution for injection and should be administered via intravenous (IV) infusion within 30-90 minutes on Day 1 of each cycle. The proposed dosage of serplulimab for the intended indication is 4.5 mg/kg administered once every 3 weeks.

Table 2. Overview of pharmacokinetic properties

Drug product	Serplulimab 10 mg/mL concentrate for infusion
Absorption	• Absolute bioavailability: not relevant
Distribution	• Tissue distribution: The mean Vd is in the range from 4.397 L to 7.882 L
Elimination	• The baseline clearance is in the range from 0.171 to 0.211 L/day • The mean half-life T1/2 at steady state is in the range of 25.0-31.2 days.
Metabolism	• Not characterised, expected to be catabolised into small peptides and amino acids by general protein degradation processes
Dose proportionality	• Linear PK established at 0.3 to 10 mg/kg Q2W (including flat doses of 200 mg Q2W, 300 mg Q3W and 400 mg Q4W), both after single and multiple doses • Mean accumulation ratios: 1.2 to 1.5 for C_{max}, 1.2 to 1.8 for AUC_{ss}.
Time dependency	• CL decreases over time with 221 days to reach half of the maximum effect.
Pharmacokinetic variability	• Between subjects: Moderate, CV 24.0% in base CL; high in Q: 54.3%. • Within subjects: Not studied

Sources of variability	• The predicted impact of albumin, alkaline phosphatase, tumour burden, tumour type and sex on exposure is limited.

All clinical studies on serplulimab PD and PK were conducted in patients with various tumour types.

A PopPK analysis was conducted using available PK data from a total of 11 clinical trials in patients with a variety of cancers , a summary of the type of cancer in the studies is in Table 3.

Table 3. Overview of types of cancer in the studies.

Variables	HLX10-001 (n=57)	HLX10-002-NSCLC301 (n=491)	HLX10-004-NSCLC303 (n=439)	HLX10-005-SCLC301 (n=389)	HLX10-007-EC301 (n=379)	HLX10-008-HCC201 (n=123)	HLX10-010-MSI201 (n=108)	HLX10-011-CC201 (n=21)	HLX10-015-mCRC301 (n=64)	HLX10-HLX04-001 (n=26)	HLX10-HLX07-001 (n=13)	Total (n=2110)
Colorectal cancer	6 (10.53%)	—	—	—	—	—	74 (68.52%)	—	64 (100.00%)	7 (26.92%)	—	151 (7.16%)
Squamous non-small cell lung cancer	2 (3.51%)	—	439 (100.00%)	—	—	—	—	—	—	—	—	441 (20.90%)
Non-squamous non-small cell lung cancer	7 (12.28%)	491 (100.00%)	—	—	—	—	—	—	—	—	—	498 (23.60%)
Small cell lung cancer	1 (1.75%)	—	—	389 (100.00%)	—	—	—	—	—	—	—	390 (18.48%)
Esophageal squamous cell carcinoma	8 (14.04%)	—	—	—	379 (100.00%)	—	2 (1.85%)	—	—	—	—	389 (18.44%)
Other tumor types	32 (56.14%)	—	—	—	—	—	32 (29.63%)	21 (100.00%)	—	18 (69.23%)	13 (100.00%)	116 (5.50%)

The clinical pharmacology of serplulimab in adult patients with non-squamous NSCLC is based primarily on the results from two clinical trials:

1. **HLX10-001**: A phase I, open-label, dose-escalation study of serplulimab monotherapy in patients with metastatic or recurrent solid tumours who failed standard treatment. ***PK sampling***: Before the first infusion in Cycle 1 and Cycle 3, at the end of infusion (within 30 minutes post-infusion), and at 2, 6, 24, 48, 96, and 168 hr post-infusion. Additionally, before the second infusion in Cycle 1, before the first infusion in Cycles 2-6, and during the 28-day follow-up.
2. **HLX10-002-NSCLC301**: Phase III pivotal study conducted in the targeted population (advanced non-squamous NSCLC patients), serplulimab was administered IV at a dose of 4.5 mg/kg once every 3 weeks, in combination with chemotherapy (carboplatin-pemetrexed) with or without HLX04 (recombinant humanized anti-VEGF monoclonal antibody injection). ***PK sampling***: Within 7 days before dosing in Cycle 1, within 3 days before dosing in Cycles 2, 4, 6, 8, and every 4 cycles thereafter, within 2 hr post-dose in Cycles 1 and 8 for serplulimab or placebo and HLX04 or placebo, and at the termination visit and/or during the safety follow-up.

Methods

Pharmacokinetic data analysis

A nonlinear mixed-effects modelling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM, version 7.5 (ICON, Maryland) was used for the PopPK analysis.

Evaluation and Qualification of Models

Objectives

The objectives of the main popPK model were to characterise population pharmacokinetics of serplulimab by developing a popPK model based on patient data and to estimate typical values and inter-individual variability of PK parameters.

A PopPK model was also used to evaluate the effects of demographics, renal and hepatic function, anti-drug antibodies, tumour types, tumour burden, ECOG (Eastern Cooperative Oncology Group), and combination treatment on PK parameters of serplulimab, as well as to generate exposures for E-R analysis. Furthermore, the popPK model was employed to simulate and compare the exposures with dosing regimens of 3 mg/kg Q2W, 4.5 mg/kg Q3W, 200 mg Q2W, 300 mg Q3W, and 10 mg/kg Q2W by using individual PK parameters estimated from the final model.

Database

Table 4. Summary of Clinical Studies Included in the serplulimab PopPK Analysis.

Clinical Study	Design	Serplulimab Regimen	Subject Number	Cut-off Date for Included Analysis Data	
				PK, ADA and Dosing	Safety and Efficacy
HLX10-001	Multiple dose, phase Ⅰ	0.3, 1, 3, 10 mg/kg Q2W, 200 mg Q2W, 300 mg Q3W, 400 mg Q4W	57	2022-08-01	2022-08-01
HLX10-004-NSCLC303	Multicenter, double-blind, phase Ⅲ	4.5 mg/kg, Q3W	439	2023-01-31	2023-01-31
HLX10-008-HCC201	Multicenter, open, single arm, phase Ⅱ	3 mg/kg, Q2W	123	2023-04-26	2023-04-26
HLX10-010-MSI201	Multicenter, single arm, phase Ⅱ	3 mg/kg, Q2W	108	2021-07-10	2021-07-10
HLX10-011-CC201	Multicenter, open, single arm, phase Ⅱ	4.5 mg/kg, Q3W	21	2022-10-24	2022-10-24
HLX10-HLX04-001	Multiple dose, phase Ⅰ	1, 3, 10 mg/kg Q2W	26	2022-10-11	2022-10-11
HLX10-HLX07-001	Multicenter, phase Ⅱ	3 mg/kg, Q2W	13	2022-09-16	2022-09-16
HLX10-005-SCLC301	Multicenter, double-blind, phase Ⅲ	4.5 mg/kg, Q3W	389	2022-06-13	2022-06-13
HLX10-002-NSCLC301	Multicenter, double-blind, phase Ⅲ	4.5 mg/kg, Q3W	491	2023-06-15	2023-06-15
HLX10-007-EC301	Multicenter, double-blind, phase Ⅲ	3 mg/kg, Q2W	389	2022-04-15	2022-04-15
HLX10-015-mCRC301	Multicenter, double-blind, phase Ⅱ/Ⅲ	300 mg, Q3W	64	2022-10-20	2022-10-20

Covariates

The effects of body weight, BSA (Body surface area), BMI (Body mass index), age, sex, ALB (Albumin), ALT (Alanine transaminase), AST (Aspartate aminotransferase), ALP (Alkaline phosphatase), serum creatinine, total bilirubin, creatinine clearance, lactate dehydrogenase, tumour burden, anti-drug antibodies, tumour type, ECOG, concomitant chemotherapy, concomitant antibody-based anti-tumour therapy and race on the PK parameters were investigated during PopPK model development. Covariates were selected using a stepwise forward addition and backward-elimination method (based on a significance level of $p < 0.01$ for the forward steps and $p < 0.001$ for the backward steps).

Data handling

Observations below the LLOQ were omitted (set MDV=1). Only the 3.24% (510/15742) of data points were below the LLOQ for serplulimab considering all the 11 studies.

Suspected data errors or inconsistencies were handled on an individual basis. Suspected data error and outliers were excluded from the analysis, as appropriate.

The PopPK analysis was performed with outliers omitted. Individual data points were considered outliers and were excluded from the covariate screening and parameter estimation of the final model if the absolute value of conditional weighted residuals (CWRES) exceeded 5.

The frequency of missing covariates in the database was determined, and missing covariates were handled as follows:

Covariates missing for ≤ 15% of the subjects: continuous covariates were imputed as the population median and categorical covariates were imputed as the most frequent category. Covariates missing for > 15% of the subjects were excluded from the analysis.

In total, 3.58% (545/15232) were excluded from the PopPK analysis. As a result, the final PopPK analysis dataset included 14,687 serplulimab serum concentration measurements from 2,110 subjects.

Model building

Serplulimab serum concentrations versus time profiles were initially explored graphically. This graphical analysis together with serplulimab PK characteristics provided initial directions to the structural model and the residual error model.

Random effects model

Inter-individual variability (IIV) and Residual variability (RV) were modelled Logarithmic transformations were applied to the observations during the analysis.

Covariate model

The covariates were selected based on physiologic plausibility, clinical relevance, prior knowledge of existing analogues and the feasibility of data included in the analysis.

Body weight is considered a common covariate that influences the clearance and volumes of distribution, the covariate effects of body weight on PK parameters were investigated firstly.

A stepwise forward-addition and backward-elimination strategy was used to determine the final PopPK model. The model obtained at the end of the backward elimination process was to be considered the final PopPK model.

Results

The PopPK structural model for serplulimab started with a one-compartment model. The two-compartment model significantly improved the goodness-of-fit plots, with a notable decrease in OFV. Compared to the two-compartment model, the three-compartment model did not show a significant decrease in OFV ($p > 0.05$). Given the previous application and other PD-1 monoclonal antibodies, the OFV showed a significant decrease using a time-varying clearance, thus the two-compartment model with time-varying clearance was chosen as the structural model.

The effects of all the potential covariates on the PK parameters were investigated graphically. The inter-individual random effects of individual Bayesian post-hoc PK parameter generated from the final base PopPK model were plotted versus the covariates to identify potential relationships.

Final PopPK model

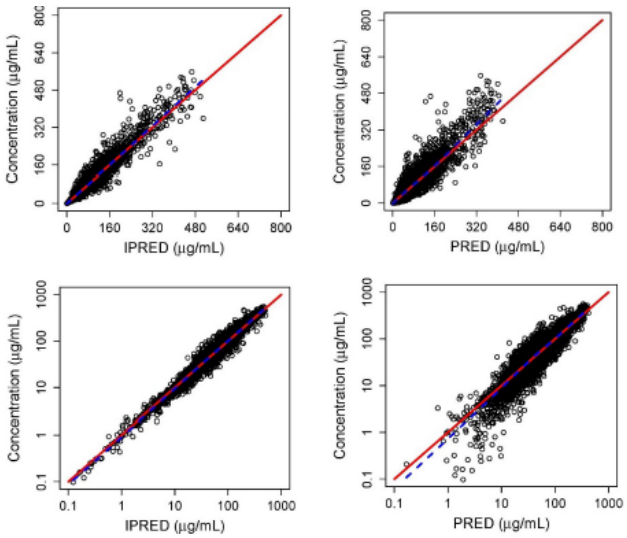
A summary if the final population parameters is in Table 5.

Table 5. Summary of serplulimab final population PK parameters

Parameter		Parameter Estimate (RSE%)	Inter-Individual Variability (RSE%)
Baseline clearance, CL_0 (L/day)	Squamous non-small cell lung cancer	0.204 (2.04%)	24.0 (2.9%)
	Hepatocellular carcinoma	0.204 (2.37%)	
	Colorectal cancer	0.182 (2.84%)	
	Non-squamous non-small cell lung cancer	0.184 (1.54%)	
	Small cell lung cancer	0.171 (1.8%)	
	Oesophageal squamous cell carcinoma	0.178 (1.98%)	
	Other tumour types	0.211 (3.18%)	
Volume of central compartment, V_c (L)	Squamous non-small cell lung cancer	3.38 (1.1%)	16.3 (3.98%)
	Hepatocellular carcinoma	3.20 (2.02%)	
	Colorectal cancer	3.19 (1.6%)	
	Non-squamous non-small cell lung cancer	3.25 (0.961%)	
	Small cell lung cancer	3.45 (1.22%)	
	Oesophageal squamous cell carcinoma	3.48 (1.51%)	
	Other tumour types	3.19 (1.68%)	
Inter-compartment clearance, Q (L/day)		0.405 (6.1%)	54.3 (8.98%)
Volume of peripheral compartment, V_p (L)		2.98 (2.77%)	45.9 (4.6%)
Maximum proportional change in clearance from baseline, exp(T_{max})		0.912 (2.11%)	34.1 (9.11%)
Time to half of the maximum change in clearance, TC_{50} (day)		221 (12.0%)	—
Impact factor of time-dependent clearance, λ		2.43 (6.21%)	—
Influence of body weight on CL		0.514 (6.46%)	—
Influence of body weight on V_c		0.47 (5.81%)	—
Influence of sex on CL		-0.145 (10.8%)	
Influence of sex on V_c		-0.14 (8.6%)	—
Influence of ALB on CL		-0.714 (9.39%)	—
Influence of ALB on V_c		-0.32 (14.2%)	—
Influence of ALB on V_p		-1.05 (15.5%)	—
Influence of ALP on CL		0.0553 (29.9%)	—
Influence of tumour burden on CL		0.0548 (20.8%)	—
Influence of tumour burden on V_p		0.107 (24.6%)	—
Covariance (CL, V_c)		0.0140 (11%)	—
Residual errors (%)		17.6 (1.75%)	—

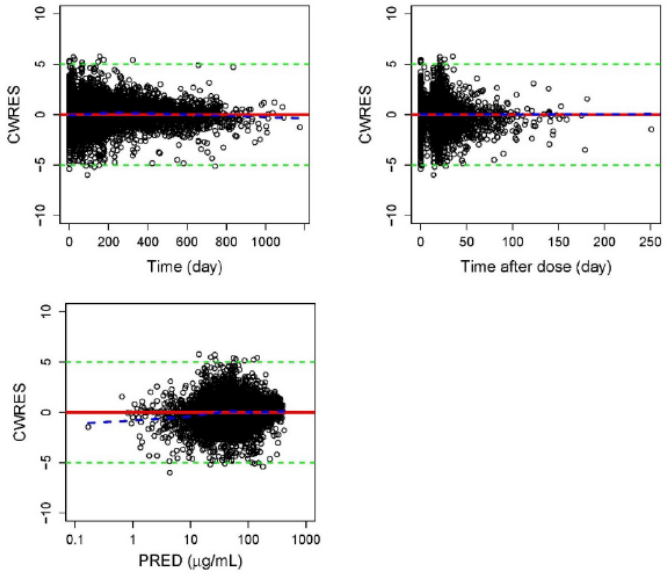
Model evaluation

Figure 1. Goodness-of-fit diagnostic plots for the final model of serplulimab



Observed versus individual predicted concentrations (upper left: constant coordinates; lower left: logarithmic coordinates) and observed versus population predicted concentrations (upper right: constant coordinates; lower right: logarithmic coordinates) for the final PopPK model. Red solid lines represent the unit diagonal and blue dashed lines represent the lowess smooth curves.

Figure 2. Diagnostic plots of conditional weighted residuals for the final model of serplulimab



Conditional weighted residuals (CWRES) vs time (upper left) and time after the dose (upper right), as well as CWRES vs population predicted concentrations (lower left). Red solid lines represent the unit line at zero. Green dotted lines represent |CWRES| of 5. The blue dashed lines are smooth curves (lowess) showing the relationship between 2 variables.

Bootstrap

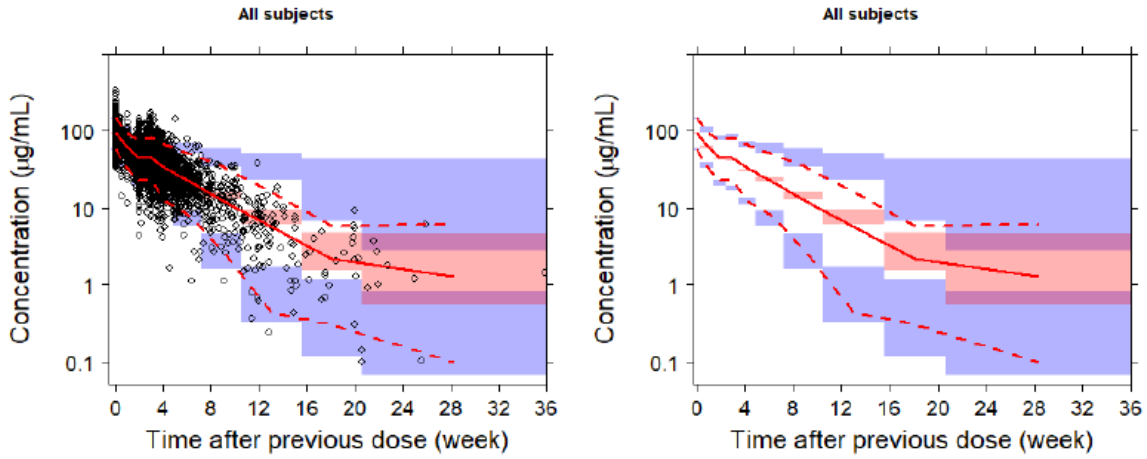
Table 6. Comparison of final model of serplulimab estimates and bootstrap results

Parameter Description		Final Model estimate (95% CI)	Bootstrap estimate Median (2.5-97.5%tiles)
Baseline clearance, CL_0 (L/day)	Squamous non-small cell lung cancer	0.204 (0.196 ~ 0.212)	0.204 (0.195 ~ 0.215)
	Hepatocellular carcinoma	0.204 (0.195 ~ 0.214)	0.205 (0.196 ~ 0.216)
	Colorectal cancer	0.182 (0.172 ~ 0.192)	0.182 (0.172 ~ 0.195)
	Non-squamous non-small cell lung cancer	0.184 (0.179 ~ 0.19)	0.185 (0.178 ~ 0.192)
	Small cell lung cancer	0.171 (0.165 ~ 0.177)	0.171 (0.165 ~ 0.179)
	Esophageal squamous cell carcinoma	0.178 (0.171 ~ 0.185)	0.179 (0.172 ~ 0.187)
	Other tumor types	0.211 (0.198 ~ 0.224)	0.211 (0.197 ~ 0.226)
Volume of central compartment, V_c (L)	Squamous non-small cell lung cancer	3.38 (3.31 ~ 3.45)	3.38 (3.31 ~ 3.46)
	Hepatocellular carcinoma	3.2 (3.08 ~ 3.33)	3.21 (3.08 ~ 3.33)
	Colorectal cancer	3.19 (3.09 ~ 3.29)	3.18 (3.08 ~ 3.28)
	Non-squamous non-small cell lung cancer	3.25 (3.18 ~ 3.31)	3.24 (3.18 ~ 3.31)
	Small cell lung cancer	3.45 (3.37 ~ 3.54)	3.45 (3.37 ~ 3.54)
	Esophageal squamous cell carcinoma	3.48 (3.38 ~ 3.59)	3.48 (3.37 ~ 3.59)
	Other tumor types	3.19 (3.09 ~ 3.3)	3.19 (3.08 ~ 3.31)
Inter-compartment clearance, Q (L/day)		0.405 (0.359 ~ 0.456)	0.408 (0.358 ~ 0.474)
Volume of peripheral compartment, V_p (L)		2.98 (2.82 ~ 3.14)	2.96 (2.77 ~ 3.14)
Maximum proportional change in clearance from baseline, T_{max}		0.912 (0.875 ~ 0.95)	0.909 (0.866 ~ 0.952)
Time to half of the maximum change in clearance, TC_{50} (day)		221 (169 ~ 273)	209 (147 ~ 319)
\Impact factor of time-dependent clearance, λ		2.43 (2.13 ~ 2.73)	2.52 (1.92 ~ 3.58)
Influence of body weight on CL		0.514 (0.449 ~ 0.579)	0.514 (0.448 ~ 0.583)
Influence of body weight on V_c		0.47 (0.416 ~ 0.523)	0.468 (0.421 ~ 0.529)
Influence of sex on CL		-0.145 (-0.175 ~ -0.114)	-0.145 (-0.177 ~ -0.112)
Influence of sex on V_c		-0.14 (-0.163 ~ -0.116)	-0.14 (-0.163 ~ -0.114)
Influence of ALB on CL		-0.714 (-0.845 ~ -0.582)	-0.72 (-0.873 ~ -0.579)
Influence of ALB on V_c		-0.32 (-0.409 ~ -0.231)	-0.319 (-0.411 ~ -0.232)
Influence of ALB on V_p		-1.05 (-1.37 ~ -0.732)	-1.03 (-1.42 ~ -0.664)
Influence of ALP on CL		0.0553 (0.0229 ~ 0.0877)	0.0565 (0.0236 ~ 0.0896)
Influence of tumor burden on CL		0.0548 (0.0325 ~ 0.0771)	0.056 (0.0339 ~ 0.0766)
Influence of tumor burden on V_c		0.107 (0.0554 ~ 0.158)	0.106 (0.0492 ~ 0.159)
Covariance (CL, V_c)		0.014 (0.011 ~ 0.017)	0.0141 (0.0111 ~ 0.0171)
Inter-individual variability in CL		24 (22.6 ~ 25.3)	23.9 (22.4 ~ 25.3)
Inter-individual variability in V_c		16.3 (15 ~ 17.5)	16.3 (14.9 ~ 17.5)
Inter-individual variability in Q		54.3 (43.7 ~ 63.1)	53.8 (33.2 ~ 63.1)
Inter-individual variability in V_p		45.9 (41.5 ~ 49.8)	45.6 (40.8 ~ 50)
Inter-individual variability in T_{max}		34.1 (27.3 ~ 39.7)	33 (25.7 ~ 45.2)
Residual errors (%)		17.6 (17 ~ 18.2)	17.6 (17 ~ 18.2)

Prediction-corrected visual predictive check (pcVPC)

The pcVPC evaluated the ability of the model to reproduce the distribution of the data. A total of 1000 replicates of the trials were simulated using the observed covariates for each subject, the final PopPK model parameter estimates, the estimated subject specific random effects, and the residual error. The pcVPC of the serplulimab final model are shown in Figure 3.

Figure 3. pcVPC of serplulimab concentration-time profiles



Points are prediction-corrected concentrations, solid red line represents the median observed value, and dashed red lines represent the 2.5th and 97.5th percentiles of the observed values. Pink shaded area represents the spread of the median predicted values (2.5th and 97.5th percentiles), and purple shaded areas represent the spread (2.5th and 97.5th percentiles) of the 2.5th and 97.5th predicted percentile concentrations. The left figure includes observed data points, while the right figure excludes observed data points.

Numerical predictive check (NPC)

A total of 1000 replicates of the trials were simulated using the observed covariates for each subject, the final PopPK model parameter estimates, the estimated subject specific random effects, and the residual error. NPC simulations of serplulimab were performed independently to evaluate the final PopPK model, as shown in Table 7.

Table 7. Summary of numerical predictive check

Range	Expected (%)	Observation (%)
Above 95th percentile	5.00	2.08
Above 75th percentile	25.00	24.3
Above 50th percentile	50.00	55.6
Below 50th percentile	50.00	44.4
Below 25th percentile	25.00	18.2
Below 5th percentile	5.00	2.14

Shrinkage

Shrinkage of the final serplulimab model parameters is presented in Table 8. The greater η-shrinkage (>30%) of Q, Vp, and Tmax may be related to the sparse sampling in the dataset and the shorter dosing duration in some subjects.

Table 8. Shrinkage of the final serplulimab model parameters

Parameters	Description	Shrinkage (%)
ETA1	Inter-individual variability in CL	14.9
ETA2	Inter-individual variability in V_c	27.0
ETA3	Inter-individual variability in Q	67.3
ETA4	Inter-individual variability in V_p	35.8
ETA5	Inter-individual variability in T_{max}	46.7
EPS1	Residual errors	15.7

Absorption

Serplulimab is administered via IV infusion. Absorption is not applicable.

Distribution

In HLX10-001 study, the mean volume of distribution at steady state of serplulimab is in the range from 4.397 L to 7.882 L. In the PopPK analysis, the central volume ranges from 3.19 to 3.48 L, while the peripheral volume is 2.98 L and the volume of distribution of serplulimab in popPK analysis for the typical subject is approximately in the range from 6.17 L to 6.46 L.

Elimination

degradation process and is not expected to be eliminated by renal or biliary excretion. Metabolism does not contribute to its clearance.

In HLX10-001 study, the mean clearance at steady state of serplulimab is in the range from 0.007 L/h to 0.022 L/h. The mean half-life is in the range of 7.7-20.0 days after the first administration and in the range of 7.5 - 27.5 days at steady state.

In popPK analysis, the baseline clearance (CL_0) of serplulimab for the typical subject is in the range from 0.171 L/day to 0.211 L/day. Clearance decreased with the duration of administration, with the lowest value estimated as 0.912 times (8.8%, CV 34.1%) the baseline clearance which is in the range of 0.156-0.192 L/day (approximately 0.006-0.008 L/h), . The time to half-maximum change in CL is 221 days. Model-predicted half-life values of serplulimab at the first dose and steady state for a typical male patient (with body weight of 62 kg, albumin of 41.4 g/L, tumour burden of 73.0 mm and ALP of 94 U/L) were in the range of 23.1- 28.7 days and 25.0-31.2 days, respectively.

Dose proportionality and time dependencies

The analysis of dose proportionality was based on rich pharmacokinetic data collected at C1D1 and C3D1 in the ongoing phase 1, first-in-human, dose escalation and dose expansion study HLX10-001.

Table 9. Statistical assessment of dose proportionality for serplulimab (power model - PK data set)

Period	Dose Range	Parameter (Unit)	N/Nx*	Slope Estimate (SE)	90% CI of Slope	P-value
Single dose (Cycle 1 first infusion)	13.26 mg - 1146 mg	C_{max} (μg/mL)	57/58	1.03 (0.05)	(0.94, 1.11)	<0.0001
		$AUC_{0-\infty}$ (h*μg/mL)	57/56	1.13 (0.05)	(1.04, 1.22)	<0.0001
Steady state (Cycle 3 first infusion)	13.26 mg - 1146 mg	$C_{max,ss}$ (μg/mL)	57/35	1.04 (0.05)	(0.95, 1.12)	<0.0001
		$AUC_{0-\infty,ss}$ (h*μg/mL)	57/35	1.18 (0.15)	(0.92, 1.43)	<0.0001

Figure 4. Statistical assessment of dose proportionality for serplulimab after single-dose (power model) (pharmacokinetic data set)

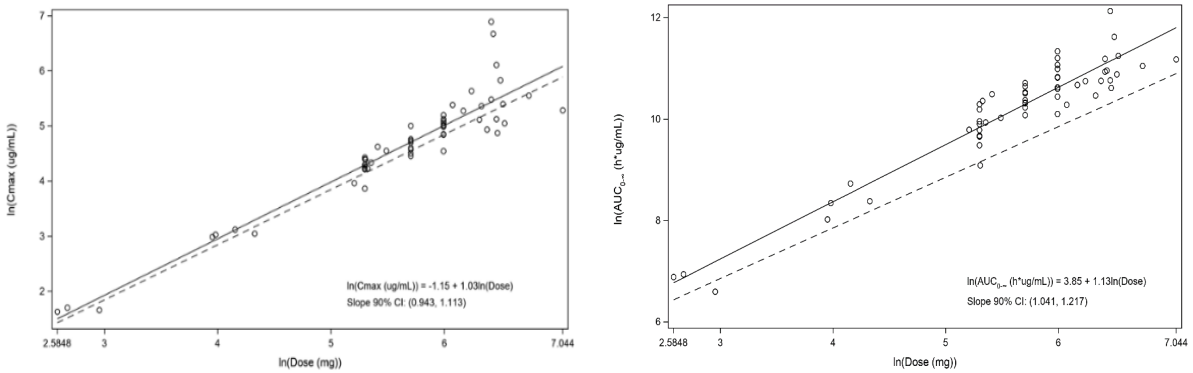
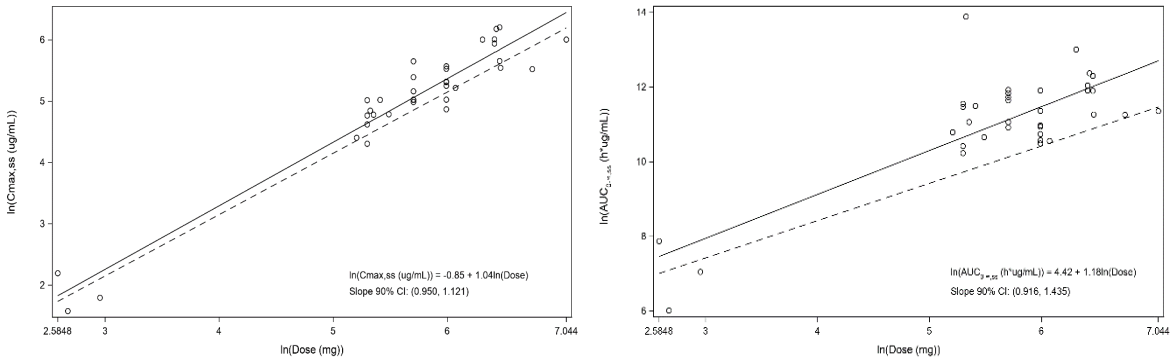


Figure 5. Statistical assessment of dose proportionality for serplulimab after multiple doses (power model) (PK data set)



Target populations

The PK results of serplulimab in subjects with advanced non-squamous NSCLC showed that the mean pre-dose serum serplulimab concentrations in each cycle gradually increased with the dosing cycles and tended to be stable in Cycle 8. The PK exposures of serplulimab are summarized in Table 10.

Table 10. Summary of Serplulimab PK Parameters (pivotal study HLX10-002-NSCLC301)

Group	Statistics	Cycle 1		Cycle 8			
		C_{max} (ng/mL)	C_{trough} (ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)	R_{ac_Cmax}	$R_{ac\_Ctrough}$
serplulimab + HLX04 + chemotherapy	n	209	199	134	142	131	141
	mean	89604.8622	20233.7317	136700.6578	51967.5853	1.5964	2.7461
	SD	25039.0050	6386.6175	31496.2060	22216.6377	0.4931	1.5588
	CV%	27.9	31.6	23.0	42.8	30.9	56.8
serplulimab + chemotherapy	n	213	200	133	140	133	138
	mean	93380.6134	19422.8566	133986.4910	52072.0252	1.5636	3.0493
	SD	48816.0314	7262.7916	28836.0970	18502.9228	0.4817	3.4848
	CV%	52.3	37.4	21.5	35.5	30.8	114.3
Placebo +	n	4	27	0	8	0	2

Group	Statistics	Cycle 1		Cycle 8			
		C_{max} (ng/mL)	C_{trough} (ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)	R_{ac_Cmax}	$R_{ac\_Ctrough}$
chemotherapy switching to serplulimab + HLX04	mean	88034.8283	18907.5183	NC	31166.2200	NC	NC
	SD	25020.5288	7718.6488	NC	10400.6322	NC	NC
	CV%	28.4	40.8	NC	33.4	NC	NC
Total	n	426	426	267	290	264	281
	mean	91477.9957	19768.9834	135348.6571	51444.1738	1.5799	2.8833
	SD	38776.3684	6895.7063	30174.2986	20489.1132	0.4868	2.6840
	CV%	42.4	34.9	22.3	39.8	30.8	93.1

Notes: Cycle 1 C_{max} was obtained from the Cycle 1 post-dose sample. Cycle 1 C_{trough} was obtained from the Cycle 2 pre-dose sample. Cycle 8 C_{max} was obtained from the Cycle 8 post-dose sample. Cycle 8 C_{trough} was obtained from the Cycle 8 pre-dose sample.

Abbreviations: C_{max}=maximum concentration, C_{trough}=trough concentration, CV=coefficient of variation, PK=pharmacokinetic, PKS=pharmacokinetic set, R=accumulation ratio, SD=standard deviation, NC=not calculated.

PopPK in the target population

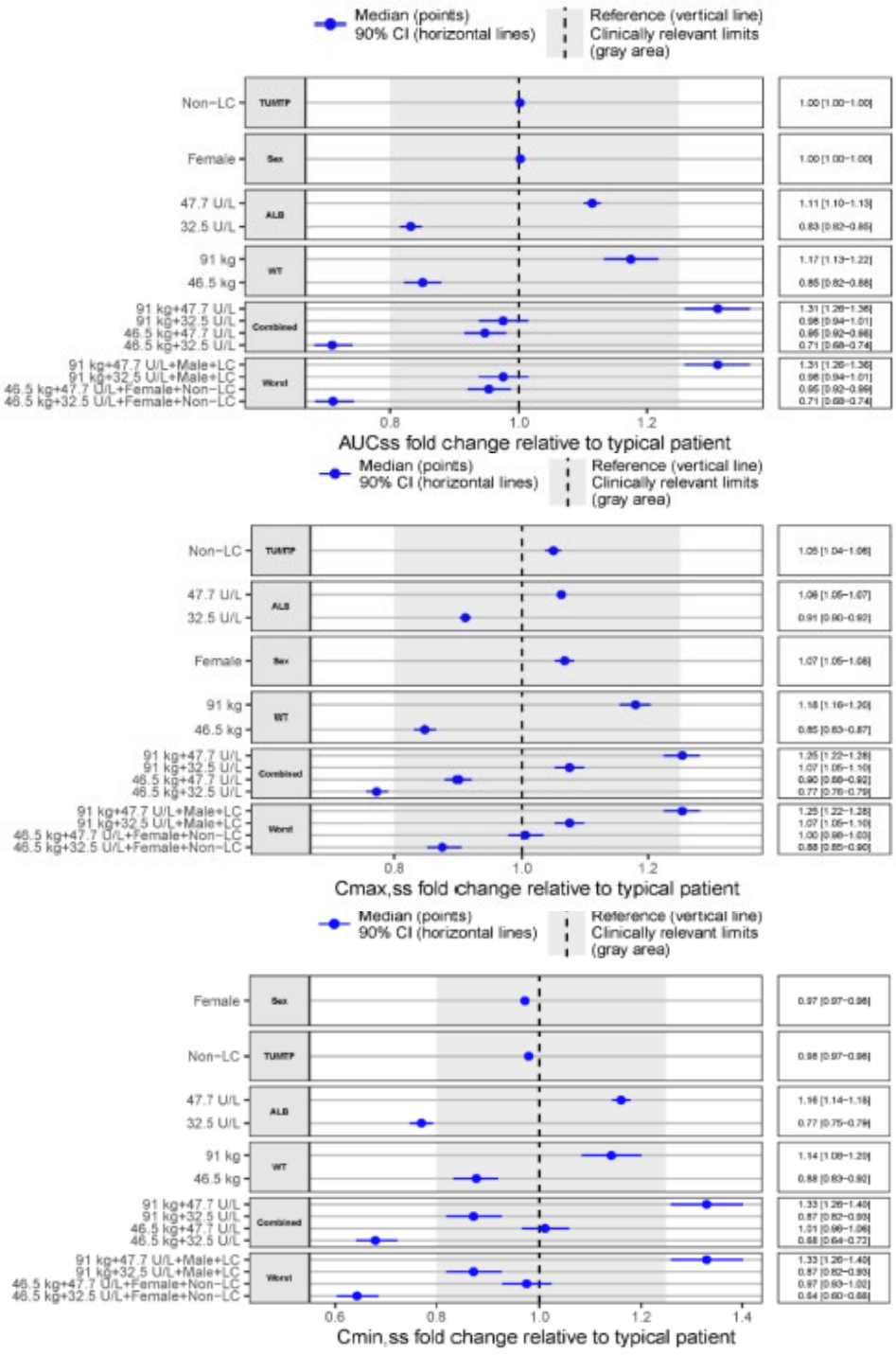
All studied subjects were cancer patients. The pivotal trial, HLX10-002-NSCLC301, was conducted to evaluate the efficacy and safety of serplulimab in the target population. In the population PK analysis, tumour type was tested as covariate, but it was considered clinically not relevant.

Special populations

No study has been performed in special populations. PK parameters of serplulimab in special populations were evaluated in the popPK analysis.

Body weight, albumin, sex, and tumour type were significant covariates of PK parameters.

Figure 6. Model-predicted impact of covariates on exposures



(a) impact on steady state AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$

Body weight

Body weight was identified as a statistically significant covariate influencing the PK parameters CL and Vc in the population PK analysis. To assess the impact of body weight on PK exposure, the final population PK model predicted steady state exposures were compared in body weight stratified by 10 kg weight bands .

Table 11 Summary of model-derived observed and simulated exposures of serplulimab stratified by body weight following 4.5 mg/kg Q3W

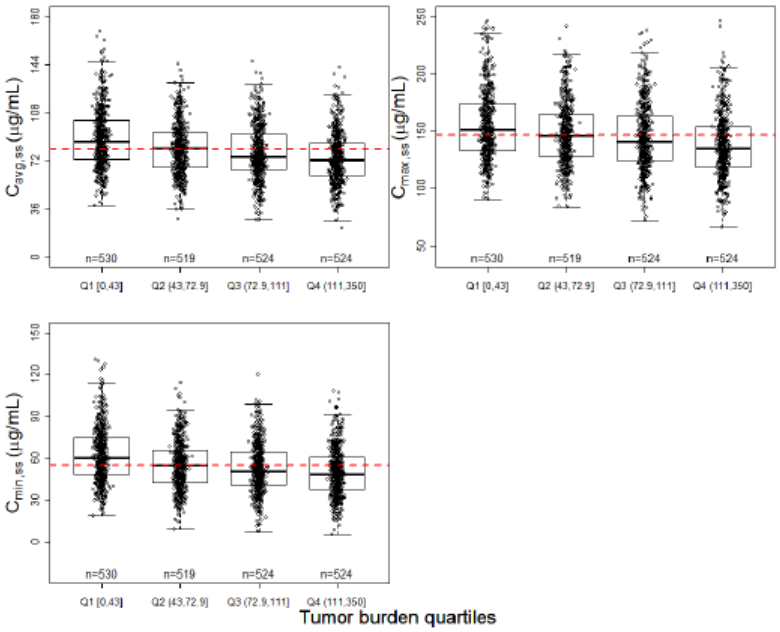
Metrics	Data source	Statistics	Weight group										Corresponding timepoints for model-derived observed data
			[32.9, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	[100, 110)	[110, 120)	[120, 131]	
AUC_1 (μg*day/mL)	Model-derived Observed	n	8	108	356	401	274	124	33	24	8	3	Cycle 1, Day 0-21 (AUC over the first dose interval)
		geometric mean (%CV)	521.58 (12.2)	597.88 (16.1)	678.51 (16.3)	739.22 (15.4)	809.87 (14.7)	865.04 (12.1)	988.32 (13.8)	972.09 (15.3)	1012.61 (17.4)	1075.09 (9.42)	
		median (min- max)	530.78 (428.25-636.78)	596.96 (322.09-981.7)	684.11 (386.52-1436.16)	747.21 (461.55-1234.25)	807.7 (524.62-1330.21)	871.93 (621.37-1190.46)	1035.14 (721.49-1287.82)	1003.01 (705.57-1220.53)	1013.3 (734.05-1315.84)	1102.71 (966.77-1165.6)	
	Simulated	n	24	260	794	868	632	268	79	55	16	4	NA
		geometric mean (%CV)	513 (14.1)	593.7 (21.6)	676 (19.6)	760.09 (19.4)	826.01 (18.8)	882.38 (18.7)	974.8 (20.4)	997.25 (20.3)	1114.8 (17.6)	1108.05 (21.9)	
		median (min- max)	517.56 (380.24-670.5)	596.72 (333.28-1080.27)	682.2 (350.92-1246.3)	759.06 (379.32-1386.36)	825 (467.85-1403.74)	882.48 (512.66-1425.8)	947.63 (645.69-1599.5)	971.06 (693.67-1807.54)	1113.14 (803.41-1554.79)	1134.42 (821.61-1426.2)	
	*Relative Difference %		-1.65	-0.699	-0.37	2.82	1.99	2	-1.37	2.59	10.1	3.07	
C_{avg1} (μg/mL)	Model-derived Observed	n	8	108	356	401	274	124	33	24	8	3	Cycle 1, Day 0-21 (average concentration at the first dose interval)
		geometric mean (%CV)	25.18 (13.9)	28.63 (16.2)	32.48 (16.4)	35.46 (15.4)	38.81 (14.7)	41.38 (12.2)	47.44 (14.5)	46.98 (14.4)	48.54 (17)	51.25 (9.52)	
		median (min- max)	25.28 (20.41-31.92)	28.51 (16.08-46.75)	32.64 (18.41-68.39)	35.67 (22.03-58.77)	38.52 (24.98-63.34)	41.52 (29.59-56.69)	49.29 (34.36-64.53)	48.01 (33.6-58.12)	48.25 (34.95-62.66)	52.56 (46.04-55.62)	
	Simulated	n	24	260	794	868	632	268	79	55	16	4	NA
		geometric mean (%CV)	24.43 (14.1)	28.27 (21.6)	32.19 (19.6)	36.19 (19.4)	39.33 (18.8)	42.02 (18.7)	46.42 (20.4)	47.49 (20.3)	53.09 (17.6)	52.76 (21.9)	
		median (min- max)	24.65 (18.11-31.93)	28.42 (15.87-51.44)	32.49 (16.71-59.35)	36.15 (18.06-66.02)	39.29 (22.28-66.84)	42.02 (24.41-67.9)	45.13 (30.75-76.17)	46.24 (33.03-86.07)	53.01 (38.26-74.04)	54.02 (39.12-67.91)	
	*Relative Difference %		-2.98	-1.25	-0.878	2.06	1.35	1.53	-2.16	1.08	9.36	2.96	
C_{max1} (μg/mL)	Model-derived Observed	n	8	108	356	401	274	124	33	24	8	3	Cycle 1, Day 0-21 (maxima at the first dose interval)
		geometric mean (%CV)	69.34 (7.81)	74.19 (15.4)	80.4 (14.5)	86.44 (13.9)	92.01 (13.4)	96.12 (10.5)	106.04 (14.2)	109.09 (12.2)	107.98 (20.5)	113.75 (12.4)	
		median (min- max)	69.94 (61.64-77.22)	73.84 (47.71-110.9)	79.77 (51.48-135.63)	85.74 (56.2-128.29)	92.21 (63.55-140.38)	97.43 (72.23-125.97)	105.52 (66.1-151.5)	111.63 (85.11-146.8)	108.28 (71.78-152.33)	115.84 (99.49-127.7)	
	Simulated	n	24	260	794	868	632	268	79	55	16	4	NA
		geometric mean (%CV)	64.42 (13.6)	73.78 (19.5)	80.3 (19.1)	86.74 (18)	93.59 (17.4)	96.41 (17.9)	105.85 (21.5)	110.33 (19)	120.4 (17.4)	140.39 (10.2)	

Metrics	Data source	Statistics	Weight group										Corresponding timepoints for model-derived observed data
			[32.9, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	[100, 110)	[110, 120)	[120, 131]	
		median (min- max)	63.03 (51.96-86.47)	73.2 (46.13-127.56)	79.96 (44.91-159.23)	86.99 (49.98-154.57)	93.87 (55.39-177.76)	96.38 (49.71-146.04)	104.72 (72.93-189.92)	112.62 (72.78-163.6)	121.25 (93.8-161.68)	140.93 (126.3-155.57)	
	*Relative Difference %		-7.1	-0.552	-0.121	0.345	1.72	0.299	-0.186	1.14	11.5	23.4	
C_{min1} (µg/mL)	Model-derived Observed	n	8	108	356	401	274	124	33	24	8	3	Cycle 1, Day 0-21 (minima at the first dose interval)
		geometric mean (%CV)	13.92 (25.2)	15.72 (27.6)	18.14 (27.4)	19.37 (26.6)	21.35 (25.6)	22.77 (21.8)	27.44 (22.5)	24.97 (24.3)	26.75 (21.4)	26.54 (31.5)	
		median (min- max)	15.04 (9.53-20.65)	16.25 (4.23-30.53)	18.89 (5.25-46.9)	20.1 (6.43-41.5)	21.67 (7.47-50.33)	23.04 (12.25-37.59)	29.49 (16.24-42.47)	26.92 (12.63-36.52)	26.73 (18.51-35)	31.13 (17.7-33.95)	
	Simulated	n	24	260	794	868	632	268	79	55	16	4	NA
		geometric mean (%CV)	13 (22.3)	15.25 (32.9)	17.42 (29.3)	19.99 (29.1)	21.52 (28.6)	22.78 (27.8)	24.73 (29.7)	26.54 (29.2)	27.36 (27.6)	27.53 (21.5)	
		median (min- max)	12.91 (8-20.93)	15.66 (5.57-33.08)	18.06 (5.96-40.06)	20.42 (6.4-43.89)	21.74 (8.4-44.17)	23.3 (9.67-47.56)	25.65 (9.12-53.2)	26.81 (15.03-54.4)	27.85 (15.48-40.84)	26.86 (22.62-35.67)	
	*Relative Difference %		-6.63	-3.03	-3.94	3.2	0.777	0.0461	-9.87	6.27	2.27	3.72	
AUC_{ss} (µg*day/mL)	Model-derived Observed	n	4	59	195	205	169	59	14	9	3	2	Cycle 8, Day 0-21 (AUC over steady state interval)
		geometric mean (%CV)	1131.97 (9.99)	1308.67 (21.9)	1450.46 (23.5)	1553.23 (21.9)	1628.86 (23.7)	1624.32 (23.8)	1980.55 (21.5)	1760.62 (20.5)	2191.77 (10.7)	1881.91 (28.8)	
		median (min- max)	1121.64 (1020.06-1281.24)	1372.8 (473.72-2063.31)	1503.73 (658.56-3180.96)	1589.51 (763.5-2509.68)	1635.21 (669.22-3833.81)	1687.48 (855.7-2520.92)	2051.18 (1290.74-2827.62)	1858.26 (1193.49-2335.21)	2211.22 (1958.68-2431.02)	1922.12 (1531.01-2313.23)	
	Simulated	n	24	260	794	868	632	268	79	55	16	4	NA
		geometric mean (%CV)	1120.71 (22.7)	1274.2 (29.6)	1396.3 (28.7)	1552.47 (28.8)	1663.2 (28.8)	1726.09 (28.2)	1873.29 (29.7)	2087.6 (33.5)	2112.44 (22)	2330.51 (6.62)	
		Median (min- max)	1129.71 (712.07-1819.55)	1291.1 (477.58-2928.92)	1413.41 (633.29-3480.08)	1562.6 (643.41-3808.15)	1681.42 (722.72-3672.56)	1703.19 (912.13-3580.52)	1812.33 (936.35-3392.32)	2046.29 (1054.36-5119.13)	2220.78 (1227.15-2940.32)	2331.82 (2175.24-2498.53)	
	*Relative Difference %		-0.994	-2.63	-3.73	-0.0486	2.11	6.27	-5.42	18.6	-3.62	23.8	
$C_{avg,ss}$ (µg/mL)	Model-derived Observed	n	4	59	195	205	169	59	14	9	3	2	Cycle 8, Day 0-21 (average concentration at steady state interval)
		geometric mean (%CV)	54.76 (12.3)	62.83 (22)	69.69 (23.4)	74.67 (21.9)	78.16 (23.5)	78.19 (23.8)	95.31 (21.4)	83.92 (20.4)	113.5 (15.2)	89.61 (28.8)	
		median (min- max)	53.8 (48.57-64.06)	65.73 (22.56-98.25)	72.21 (31.36-151.99)	75.76 (36.36-119.82)	78.53 (31.87-182.56)	80.68 (40.75-120.4)	103.59 (61.46-134.65)	88.49 (57.23-111.2)	105.4 (103.25-134.37)	91.53 (72.91-110.15)	
	Simulated	n	24	260	794	868	632	268	79	55	16	4	NA
		geometric mean (%CV)	53.37 (22.7)	60.68 (29.6)	66.49 (28.7)	73.93 (28.8)	79.2 (28.8)	82.19 (28.2)	89.2 (29.7)	99.41 (33.5)	100.59 (22)	110.98 (6.62)	

Metrics	Data source	Statistics	Weight group										Corresponding timepoints for model-derived observed data
			[32.9, 40)	[40, 50)	[50, 60)	[60, 70)	[70, 80)	[80, 90)	[90, 100)	[100, 110)	[110, 120)	[120, 131]	
		median (min- max)	53.8 (33.91-86.65)	61.48 (22.74-139.47)	67.31 (30.16-165.72)	74.41 (30.64-181.34)	80.07 (34.42-174.88)	81.1 (43.43-170.5)	86.3 (44.59-161.54)	97.44 (50.21-243.77)	105.75 (58.44-140.02)	111.04 (103.58-118.98)	
	*Relative Difference %		-2.54	-3.42	-4.59	-0.998	1.33	5.12	-6.41	18.5	-11.4	23.8	
$C_{max,ss}$ (µg/mL)	Model-derived Observed	n	4	59	195	205	169	59	14	9	3	2	Cycle 8, Day 0-21 (maxima at steady state interval)
		geometric mean (%CV)	112.88 (7.84)	119.14 (16.4)	127.47 (17.7)	136.77 (17)	142.9 (17.4)	145.84 (17.5)	171.45 (16.3)	159.13 (16.1)	193.11 (17.3)	159.03 (14.2)	
		median (min- max)	112.82 (102.67-124.24)	120.21 (63.74-162.36)	128.35 (75.98-223.16)	138.48 (87.55-203.99)	143.32 (81.1-236.89)	148.14 (92.79-209.97)	176.33 (122.25-217.96)	162.53 (125.4-206.42)	184.49 (167.74-232.69)	159.84 (143.81-175.86)	
	Simulated	n	24	260	794	868	632	268	79	55	16	4	NA
		geometric mean (%CV)	100.3 (16.2)	114.7 (21.8)	124.63 (21)	136.04 (20.7)	146.06 (19.8)	150.01 (19.7)	163.36 (23.1)	177.37 (23)	184.68 (14.7)	209.75 (5.61)	
		Median (min- max)	99.04 (72.19-138.2)	114.46 (63.36-196.87)	123.79 (66.49-233.18)	136.75 (71.02-269.84)	146.26 (74.26-265.29)	151.44 (86.23-229.17)	156.88 (102.27-287.17)	177.07 (99.39-340.95)	185.47 (128.21-235.06)	207.27 (199.01-226.43)	
	*Relative Difference %		-11.1	-3.73	-2.23	-0.534	2.22	2.86	-4.72	11.5	-4.36	31.9	
$C_{min,ss}$ (µg/mL)	Model-derived Observed	n	4	59	195	205	169	59	14	9	3	2	Cycle 8, Day 0-21 (minima at steady state interval)
		geometric mean (%CV)	33.61 (17.8)	38.23 (31.7)	43.47 (33)	46.63 (30.4)	46.68 (34.8)	46.27 (34.3)	59.13 (29.4)	49.4 (29.1)	69.87 (11.8)	47 (63.7)	
		median (min- max)	33.39 (27.98-41.29)	43.74 (2.46-73.73)	46.88 (0.54-120.27)	48.33 (9.23-92.3)	49.7 (1.34-139.74)	49.94 (17.36-85.53)	65.05 (30.18-92.61)	56.31 (25.78-75.13)	65.67 (65.16-79.71)	52.63 (28.94-76.33)	
	Simulated	n	24	260	794	868	632	268	79	55	16	4	NA
		geometric mean (%CV)	35.85 (33.3)	40.67 (38.7)	43.61 (38.7)	48.39 (39.1)	51.25 (39.8)	52.39 (39.1)	55.9 (39.8)	66.18 (45.3)	61.56 (32.6)	73.47 (13.5)	
		median (min- max)	36.9 (18.73-67.56)	42.14 (10.85-117.65)	43.84 (10.31-132.91)	49.66 (11.28-151.24)	52.81 (11.96-148.6)	53.47 (19.4-137.04)	56.89 (17.38-120.63)	64.65 (26.97-193.31)	67.43 (26.4-95.8)	78.7 (59.04-79.68)	
	*Relative Difference %		6.64	6.38	0.332	3.79	9.8	13.2	-5.46	34	-11.9	56.3	
* Relative Difference%= (Simulated geometric mean - Observed geometric mean) / Observed geometric mean*100%													

Impact of tumour burden on exposure

Figure 7. Impact of tumour burden on steady state exposure of serplulimab



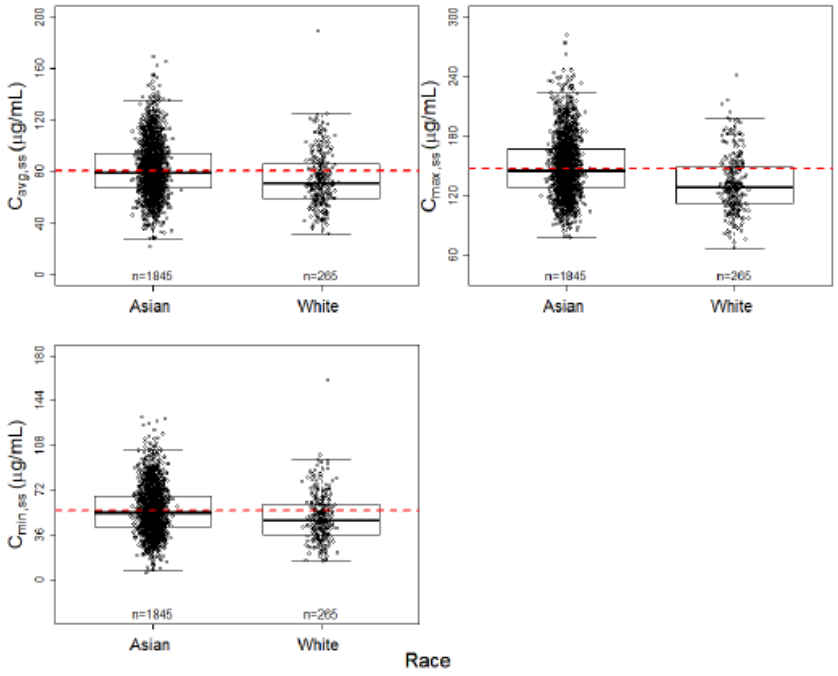
Open points are the model-predicted PK exposures. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents overall geometric mean of post hoc estimates in all subjects.

Impact of ethnicity on exposure

Table 12. Impact of ethnicity on geometric mean (%CV) steady state exposure of serplulimab

Group		Race	
		Asian	White
No. of subjects (%)		1845 (87.4)	265 (12.6)
$C_{avg,ss}$ (μg/mL)	Geometric mean (%CV)	79.3 (25.3)	71.2 (28.4)
	% Change [a]	—	-10.1
$C_{max,ss}$ (μg/mL)	Geometric mean (%CV)	146 (19.8)	129 (21.9)
	% Change [a]	—	-11.8
$C_{min,ss}$ (μg/mL)	Geometric mean (%CV)	52.5 (33.1)	47.1 (37.5)
	% Change [a]	—	-10.3
Baseline body weight (kg) [min, median, max]		[32.9; 60.6; 115]	[40.1; 76; 131]
ALB (g/L) [min, median, max]		[23.8; 41.7; 67.9]	[25; 40; 50.5]
Baseline tumor burden (mm) [min, median, max]		[0; 68.8; 350]	[5; 99; 324]
ALP (U/L) [min, median, max]		[30; 93; 910]	[10.7; 96; 512]
Sex	Male (%)	1440(78)	235(88.7)
	Female (%)	405(22)	30(11.3)
Tumor type	Hepatocellular carcinoma (%)	125(6.78)	—
	Colorectal cancer (%)	151(8.18)	—
	Squamous non-small cell lung cancer (%)	303(16.4)	138(52.1)
	Non-squamous non-small cell lung cancer (%)	498(27)	—
	Small cell lung cancer (%)	263(14.3)	127(47.9)
	Esophageal squamous cell carcinoma (%)	389(21.1)	—
	Other tumor types (%)	116(6.29)	—
[a] :%change from the geometric mean of Asian subjects.			

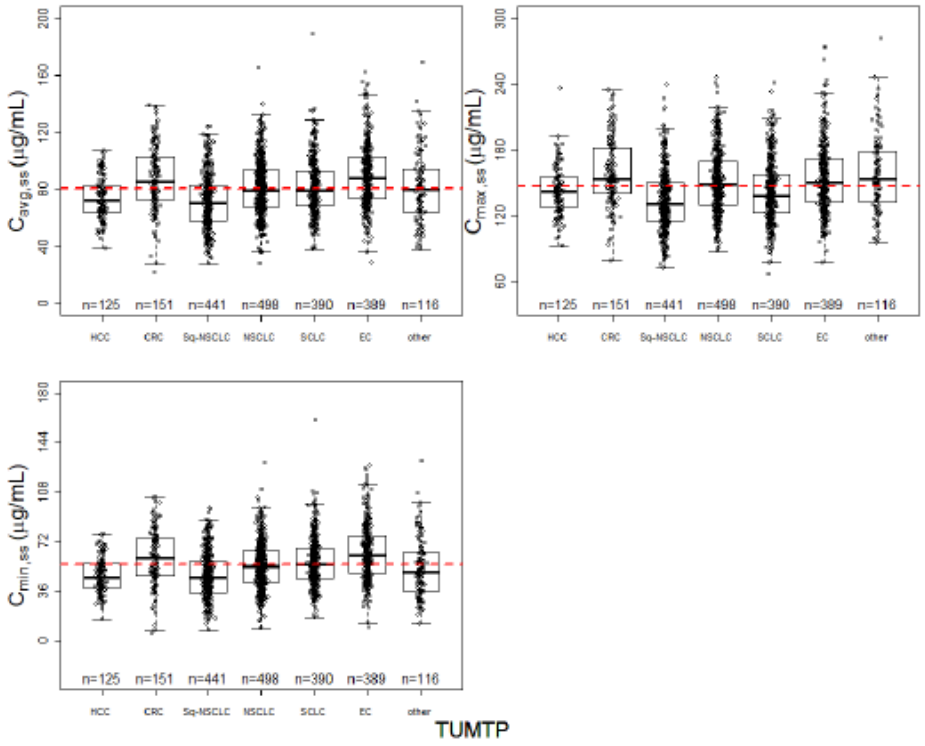
Figure 8. Impact of ethnicity on steady state exposure of serplulimab



Open points are the model-predicted PK exposures. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents overall geometric mean of post hoc estimates in all subjects.

Impact of tumour type on exposure

Figure 9. Impact of tumour type on steady state exposure of serplulimab



Open points are the model-predicted PK exposures. The median is represented by the horizontal black line in the middle of each box. The lower and upper ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extend to the most extreme data point which is no more than 1.5×IQR from the box. The dashed red horizontal line represents overall geometric mean of post hoc estimates in all subjects.

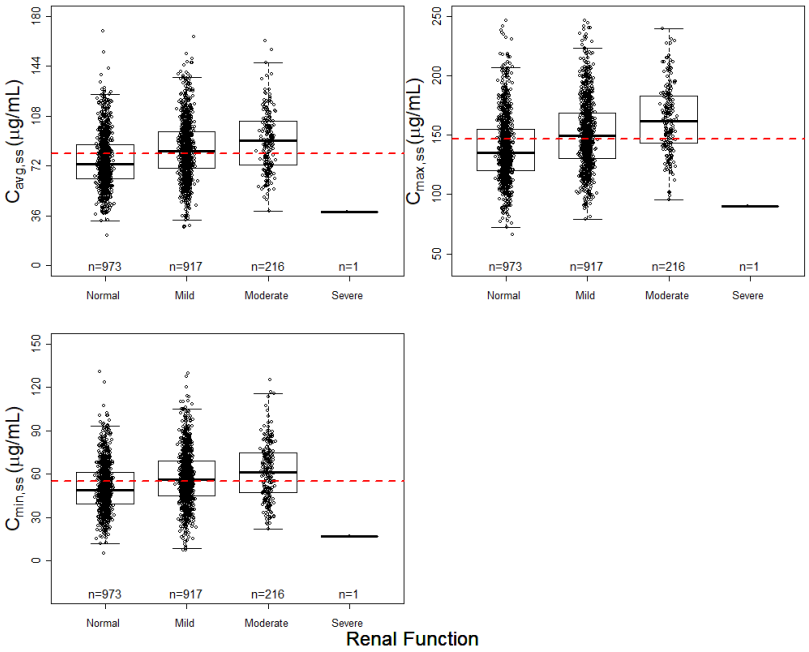
Table 13 - Impact of tumour type on geometric mean (%CV) steady state exposure of HLX10

Group		Tumor Type						
		Hepatocellular carcinoma	Colorectal cancer	Squamous non-small cell lung cancer	Non-squamous non-small cell lung cancer	Small cell lung cancer	Esophageal squamous cell carcinoma	Other tumor types
No. of subjects (%)		125 (5.92)	151 (7.16)	441 (20.9)	498 (23.6)	390 (18.5)	389 (18.4)	116 (5.5)
$C_{avg,ss}$ (μg/mL)	Geometric mean (%CV)	72.3 (20.1)	84.3 (25.6)	69.2 (25.8)	78.8 (23.5)	79.7 (24)	87.2 (24.4)	77.7 (30.2)
	% Change [a]	-7.54	7.77	-11.5	0.793	1.83	11.5	-0.634
$C_{max,ss}$ (μg/mL)	Geometric mean (%CV)	142 (15.6)	157 (19.3)	131 (20)	148 (18.8)	140 (19.5)	151 (20.3)	154 (22)
	% Change [a]	-1.66	8.86	-8.75	3.06	-2.95	4.89	6.90
$C_{min,ss}$ (μg/mL)	Geometric mean (%CV)	45.3 (27.5)	56 (32.7)	44.2 (34.7)	51.6 (30.9)	54.6 (31)	60.7 (30.3)	48.9 (40.1)
	% Change [a]	-12.4	8.10	-14.6	-0.309	5.39	17.3	-5.48
Baseline body weight (kg) [min, median, max]		[45; 63; 86]	[41; 61.5; 93]	[38.2; 65; 131]	[35; 61; 94.2]	[33; 67; 120]	[37; 58; 92]	[32.9; 60.6; 115]
ALB (g/L) [min, median, max]		[30.6; 43.2; 49.2]	[30.9; 42.4; 52.1]	[25; 40.2; 53.8]	[23.8; 41.7; 51]	[23.9; 41; 67.9]	[27.4; 41.3; 53.2]	[26; 42.5; 53]
ALP (U/L) [min, median, max]		[37; 104; 579]	[40.6; 99; 863]	[35; 96; 823]	[30; 97; 910]	[10.7; 95; 607]	[30; 84.9; 831]	[30; 85; 774]
Baseline tumor burden (mm) [min, median, max]		[10.4; 60.8; 166]	[10; 65; 241]	[0; 80; 298]	[0; 76.1; 288]	[13.8; 117; 324]	[11; 39; 250]	[12.4; 58; 350]
Sex	Male (%)	111(88.8)	98(64.9)	401(90.9)	362(72.7)	317(81.3)	334(85.9)	52(44.8)
	Female (%)	14(11.2)	53(35.1)	40(9.07)	136(27.3)	73(18.7)	55(14.1)	64(55.2)

[a] :%change from the geometric mean of the all subjects.

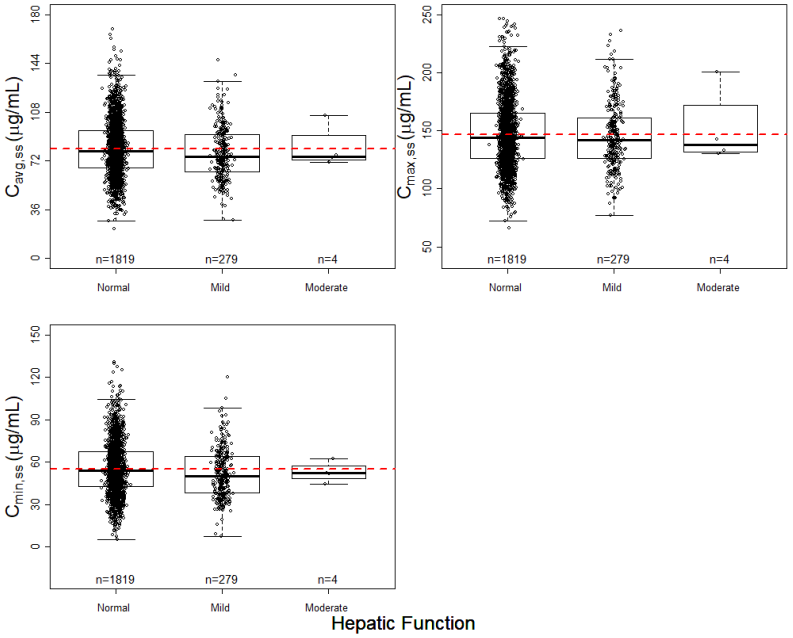
Impaired renal functions

Figure 10. Effect of renal function on steady-state exposure of serplulimab



Impaired hepatic function

Figure 11. Effect of hepatic function on steady-state exposure of serplulimab



Dose - Exposure

The individual PK parameters estimated from the final model were used to simulate the exposures in all subjects with body weight records (N = 2109) following multiple dosing regimens (3 mg/kg Q2W, 4.5 mg/kg Q3W, 200 mg Q2W, 300 mg Q3W and 10 mg/kg Q2W).

Figure 12. Concentration-time profiles of different dosing regimens

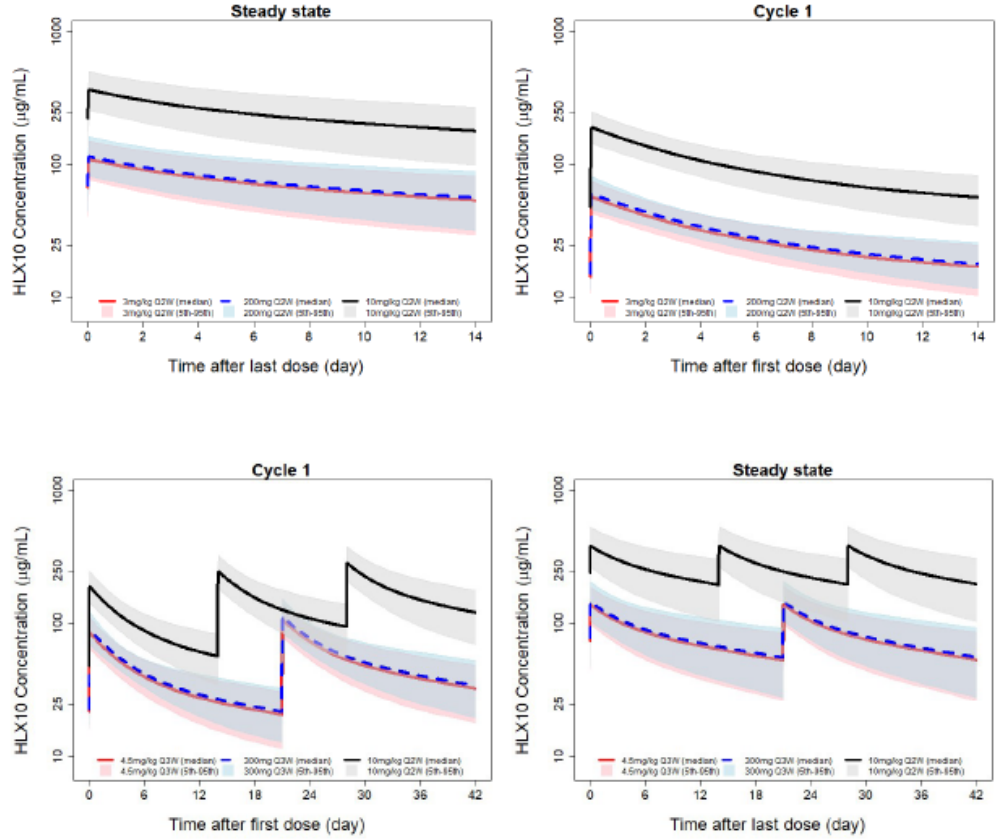


Table 14. Summary of serplulimab exposures following 3 mg/kg Q2W and 200 mg Q2W dosing - stratified by body weight quartiles (geometric mean [CV])

Exposures	Body Weight (kg)											
	Q1 [32.9,55]			Q2 (55,62]			Q3 (62,70.5]			Q4 (70.5,131]		
	3 mg/kg Q2W	200 mg Q2W	Change (%)#	3 mg/kg Q2W	200 mg Q2W	Change (%)#	3 mg/kg Q2W	200 mg Q2W	Change (%)#	3 mg/kg Q2W	200 mg Q2W	Change (%)#
AUC_{ss} (μg*day/mL)	952.71 (26.2)	1275.68 (25.6)	33.9	1051.43 (27.6)	1187.4 (27.5)	12.93	1089.45 (24.8)	1094.56 (24.7)	0.47	1200.08 (23.6)	996.69 (24.3)	-16.95
$C_{max,ss}$ (μg/mL)	103.4 (20.6)	138.45 (20.3)		112.75 (21.3)	127.33 (21.2)		118.36 (19)	118.91 (18.9)		128.51 (18.6)	106.73 (19.3)	
$C_{min,ss}$ (μg/mL)	51.04 (32.1)	68.34 (31.5)		56.29 (34.2)	63.57 (34.1)		57.36 (30.9)	57.63 (31)		63.25 (29.3)	52.53 (30.3)	
$C_{avg,ss}$* (μg/mL)	68.05 (26.2)	91.12 (25.6)		75.1 (27.6)	84.81 (27.5)		77.82 (24.8)	78.18 (24.7)		85.72 (23.6)	71.19 (24.3)	
AUC_1 (μg*day/mL)	339.87 (16.2)	455.08 (15.6)		377.75 (14.4)	426.6 (14.3)		409.87 (13.7)	411.79 (13.4)		456.84 (13.9)	379.42 (13.4)	
C_{max1} (μg/mL)	51.29 (16.2)	68.68 (16.8)		55.29 (15.1)	62.44 (15)		59.75 (14.3)	60.03 (14.1)		64.5 (14.1)	53.57 (14.4)	
C_{min1} (μg/mL)	14.41 (25.6)	19.3 (24.9)		16.17 (23.4)	18.26 (23.4)		17.4 (22.3)	17.48 (22.3)		19.53 (21)	16.22 (21.1)	
C_{avg1}* (μg/mL)	24.28 (16.2)	32.51 (15.6)		26.98 (14.4)	30.47 (14.3)		29.28 (13.7)	29.41 (13.4)		32.63 (13.9)	27.1 (13.4)	

*C_{avg1} and $C_{avg,ss}$ were calculated by dividing AUC_1 and AUC_{ss} by the dosing interval of the corresponding regimen, respectively.

#Change=(200 mg-3 mg/kg)/(3 mg/kg)*100.

Table 15. Summary of serplulimab exposures following 4.5 mg/kg Q3W and 300 mg Q3W dosing - stratified by body weight quartiles (geometric mean [CV])

Exposures	Body Weight (kg)											
	Q1 [32.9,55]			Q2 (55,62]			Q3 (62,70.5]			Q4 (70.5,131]		
	4.5 mg/kg Q3W	300 mg Q3W	Change (%)#	4.5 mg/kg Q3W	300 mg Q3W	Change (%)#	4.5 mg/kg Q3W	300 mg Q3W	Change (%)#	4.5 mg/kg Q3W	300 mg Q3W	Change (%)#
AUC_{ss} (μg*day/mL)	1428.07 (26.1)	1912.19 (25.5)	33.9	1575.92 (27.5)	1779.72 (27.4)	12.93	1633.01 (24.7)	1640.66 (24.7)	0.47	1798.71 (23.5)	1493.87 (24.3)	-16.95
$C_{max,ss}$ (μg/mL)	124.33 (18.9)	166.48 (18.8)		135.07 (19.4)	152.54 (19.3)		142.43 (17.3)	143.1 (17.2)		154.11 (17.1)	127.99 (17.8)	
$C_{min,ss}$ (μg/mL)	46.05 (34)	61.66 (33.4)		50.65 (36.5)	57.2 (36.4)		51.2 (33.1)	51.44 (33.2)		56.37 (31.5)	46.82 (32.6)	
$C_{avg,ss}$* (μg/mL)	68 (26.1)	91.06 (25.5)		75.04 (27.5)	84.75 (27.4)		77.76 (24.7)	78.13 (24.7)		85.65 (23.5)	71.14 (24.3)	
AUC_1 (μg*day/mL)	646.44 (18.2)	865.58 (17.5)		719.33 (16.4)	812.36 (16.3)		777.9 (15.5)	781.54 (15.3)		867.33 (15.4)	720.33 (15.1)	
C_{max1} (μg/mL)	76.93 (16.2)	103.01 (16.8)		82.94 (15.1)	93.66 (15)		89.62 (14.3)	90.04 (14.1)		96.76 (14.1)	80.36 (14.4)	
C_{min1} (μg/mL)	17.31 (28.5)	23.18 (27.9)		19.33 (27.1)	21.83 (27.1)		20.54 (25.7)	20.64 (25.7)		22.94 (24.2)	19.05 (24.7)	
C_{avg1}* (μg/mL)	30.78 (18.2)	41.22 (17.5)		34.25 (16.4)	38.68 (16.3)		37.04 (15.5)	37.22 (15.3)		41.3 (15.4)	34.3 (15.1)	

*C_{avg1} and $C_{avg,ss}$ were calculated by dividing AUC_1 and AUC_{ss} by the dosing interval of the corresponding regimen, respectively.

#Change= (300 mg-4.5 mg/kg)/(4.5 mg/kg)*100.

2.3.3. Pharmacodynamics

The pharmacodynamics was evaluated in the phase I HLX10-001 study. Pharmacodynamic analyses included PD-1 receptor occupancy on peripheral CD3+ T cells and interleukin-2 (IL-2) stimulation ratio, which were used to evaluate the functional regulation of serplulimab on target activity on peripheral T cells.

Across all dose groups from 0.3 to 10 mg/kg, the PD-1 receptor on the peripheral circulating T cells was almost completely occupied at 24 hours after serplulimab administration on Cycle 1 Day 1, and the mean range was 98.13% to 102.4%. The mean PD-1 receptor occupancy remained high through the end of the study. In all dose groups, the changes in the PD-1 receptor occupancy of individual subjects were similar to the trend of change in the mean values.

Despite fluctuations in mean serum serplulimab concentrations across dose groups and cycles, the PD-1 receptor occupancy remained high, indicating that the PD-1 receptor occupancy was unrelated to dose levels. Serplulimab reached saturation within the dose range of 0.3 mg/kg to 10 mg/kg and remained stable over the 28-day treatment cycle of serplulimab administered once every 2 weeks (Q2W). The median PD-1 receptor occupancy of subjects receiving 0.3 mg/kg of serplulimab treatment remained above 88% throughout the study, indicating that the 0.3 mg/kg dose was sufficient to induce target binding. It was concluded that serplulimab had a high affinity to the PD-1 receptor.

Before the first drug administration on Cycle 1 Day 1, the mean IL-2 stimulation ratio was approximately 2 in the 0.3 mg/kg and 3 mg/kg dose groups and 1.5 in the 1 mg/kg and 10 mg/kg dose groups. At 24 hours after the initial dose of serplulimab on Cycle 1 Day 1, the mean IL-2 stimulation ratio decreased to approximately 1 in all dose groups (range: 0.9400–1.167), indicating that serplulimab reached maximum functional blockade of peripheral circulation. IL-2 stimulation ratios remained generally stable at approximately 1 through the end of the study, indicating the maintenance of functional blockade.

2.3.4. Discussion on clinical pharmacology

No dedicated PK studies have been submitted, which is acceptable given that serplulimab is a monoclonal antibody (mAb).

Pharmacokinetic data supporting the current application are based on eleven clinical studies in cancer patients with serplulimab administered over the dose range of 0.3-10 mg/kg. These clinical

studies were conducted exclusively in adult populations, which is considered appropriate based on the safety and pharmacodynamic profile of the product.

The eleven clinical studies are primarily conducted outside the EU, with 87.44% of the patients being of Asian ethnicity. Additionally, studies on patients with non-squamous NSCLC are limited to Asian populations.

The extension of indication to patients with non-squamous non-small cell lung cancer is mainly based on two studies: The phase I study HLX10-001 provided PK data from a broader range of weight-based and flat doses administered to patients with various cancers, and the phase III pivotal study HLX10-002-NSCLC301 for the extension of indication to NSCLC patients.

No dedicated PK studies (e.g., bioavailability, renal or hepatic impairment, DDI) have been performed, which is acceptable for monoclonal antibodies. No dose adjustments for special populations have been proposed.

PopPK analysis

Population PK modelling was performed using non-linear mixed effect models.

An overview of the baseline demographic characteristics shows that 79.38% of subjects are male, 87.44% are Asian, while 12.56% are Caucasians (Caucasian patients are only in the studies HLX10-004-NSCLC303 and HLX10-005-SCLC301, both studies with lung cancer patients). Sparse PK sampling was performed in pivotal study HLX10-002-NSCLC301, while rich sampling was performed for the FIH dose escalation and expansion study HLX10-001. The database appears overall appropriate for the intended use of the model. In total, 545 out of 15,232 (3.58 %) data were excluded from the PopPK analysis. Overall, the approach used for data cleaning is appropriate.

In general, the popPK model building follows the same approach used in the serplulimab MA with indication for adult patients with extensive-stage small cell lung cancer (ES-SCLC). The model building methodology, rationale for model selection and evaluation are in general considered appropriate for the intended use of the model.

The new PopPK model developed is similar to the previous one (ES-SCLC), and it is based on 14687 serum concentration measurements from 2110 subjects in 11 studies, while the previous model was based on 6677 concentration samples from 1144 subjects in 8 studies.

The Population PK model is based on a structural two compartment model with time-varying CL from the central compartment, similarly to the previous model.

The covariates tested appear appropriate, even if more significant covariates are present in the new PopPK model. Body weight, tumour burden, and race are covariates of specific interest in the current application. In the pivotal study, and in the dose escalation study, all the patients with nsq-NSCLC are Asians (see discussion in the Clinical efficacy section).

The typical subject is a male with a body weight of 62 kg, albumin of 41.4 g/L, tumour burden of 73.0 mm and ALP of 94 U/L, the estimated serplulimab CL0 and Vc for subjects with non-squamous non-small cell lung cancer was 0.184 L/day and 3.25 L. For a typical subject with any tumour type, the estimated Q, Vp, exp(Tmax), TC50 and λ were 0.405 L/day, 2.98 L, 0.912, 221 days and 2.43. Interindividual variability of CL, Vc, Q, Vp , and Tmax were 24.0%, 16.3%, 54.3%, 45.9%, and 34.1%.

The RSEs for the final model estimates of the PK parameters CL0, Vc, Q, Vp, Tmax, TC50, and λ were no more than 12%, indicating that these parameters were estimated accurately.

Inter-individual variability (coefficient of variation, CV) ranges from 16.3% to 54.3%. The mean (CV) observed trough concentration at steady state ranges from 44.2 (34.7) to 60.7 (30.3) across all tumour types.

The robustness of the model is further supported by prediction-corrected visual predictive check (pcVPC) plots, which demonstrate adequate alignment with observed data.

The regulatory impact of the model is low as it is mainly used to describe serplulimab PK in cancer patients, to evaluate the impact of covariates and to inform the SmPC.

ADME

The absorption, distribution, and elimination of Serplulimab are similar to the characteristics observed in other monoclonal antibodies.

Special populations

Instead of dedicated clinical studies, PK in special populations have been investigated with covariates in the popPK modelling, which is supported. Body weight, race, and tumour burden are covariates of specific interest in the current application.

The initial assessment of body weight based on quartiles was considered unreliable. The MAH provided exposure data (AUC, Cavg, Cmax, and Cmin) presented in boxplots stratified by 10 kg weight bands, spanning from 30 kg to 140 kg (data not shown) and a comprehensive table summarizing all exposure data, including minimum and maximum values for each parameter using the appropriate dosing regimen (Table 11).

The analysis of the impact of tumour burden on drug exposures indicates only minimal variations in exposure levels.

In the PopPK dataset, 87.44% of patients are Asians, while 12.56% of patients are Caucasians. However, the difference in exposures observed between Caucasian and Asian patients ranges between 10% and 11.8%. For this reason, it can be considered not of importance.

The available data are insufficient to support dosing recommendations for patients with severe renal impairment or moderate and severe hepatic impairment; therefore, the use of serplulimab is not recommended in these populations. No dose adjustment is required in patients with mild hepatic impairment and mild and moderate renal impairment.

ADA

No evidence of ADA impact on pharmacokinetics was observed.

Pharmacodynamics

The PD data were previously assessed in the approved serplulimab application for first-line treatment of adult patients with extensive stage-small cell lung cancer (ES-SCLC). No new PD data have been submitted in support of this extension of indication, which is agreed.

2.3.5. Conclusions on clinical pharmacology

The development of the PopPK model is considered appropriate for the intended objectives.

The clinical pharmacology is adequately described in the context of this extension of indication.

2.4. Clinical efficacy

The current application is based on pivotal trial HLX10-002-NSCLC301.

The originally proposed indication for serplulimab in combination with chemotherapy (carboplatin-pemetrexed) was the first-line treatment of adult patients with locally advanced or metastatic non-squamous NSCLC without EGFR or ALK positive mutations. In the course of the procedure, the sought indication was modified to: "HETRONIFLY in combination with carboplatin and pemetrexed is indicated for the first-line treatment of adult non-squamous NSCLC patients with no EGFR, ALK or ROS1 positive mutations and who have: locally advanced NSCLC who are not candidates for surgery or radiotherapy, or metastatic NSCLC.

2.4.1. Dose response study HLX10-001

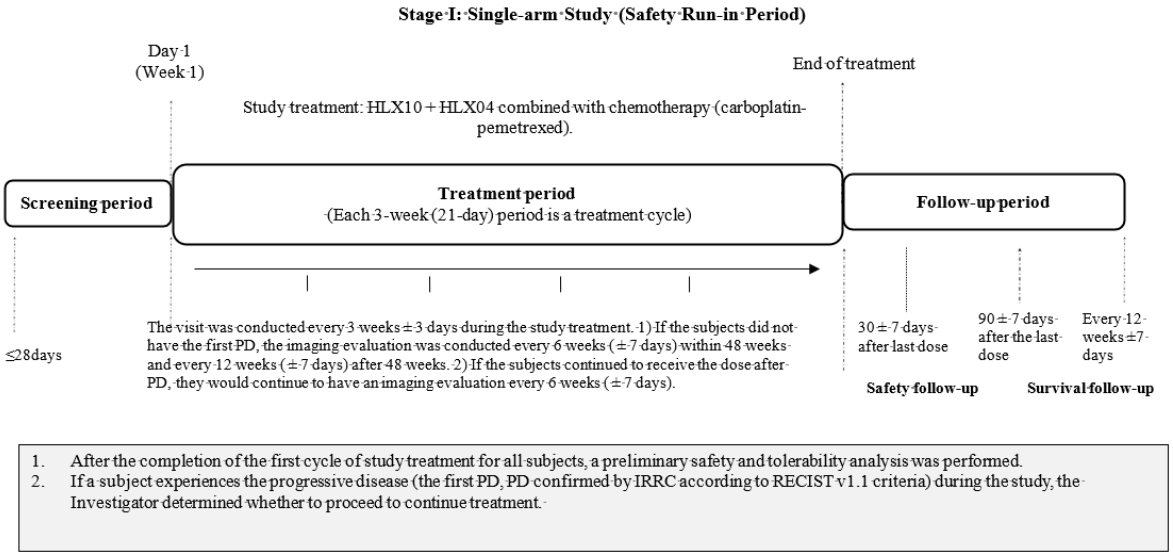
The HLX10-001 was a prospective, open-label FIH study of serplulimab in patients with advanced or metastatic tumours refractory to standard therapy, with different histological types and anatomical locations. Briefly, the study included a dose-finding cohort and a dose expansion cohort. Serplulimab was administered IV at doses from 0.3 to 10 mg/kg once every 2 weeks in dose escalation cohorts and 200 mg Q2W, 300 mg Q3W, 400 mg Q4W and 600 mg Q6W in the dose expansion cohorts.

The dose regimens of 3 mg/kg Q2W and 4.5 mg/kg Q3W were both oversaturated doses and expected to have similar safety and efficacy base on above analysis and experience of the flat E-R (safety and efficacy) of serplulimab in the previous analysis and similar anti-PD-1 antibodies. In addition, the frequency of administration of platinum-based chemotherapy is usually every 3 weeks. Therefore, 4.5 mg/kg Q3W of serplulimab was selected as the dose regimen for pivotal study HLX10-002-NSCLC301 in Non-Squamous Non-Small Cell Lung Cancer (NSCLC) patients in order to ensure uniform administration frequency and increase compliance.

2.4.2. Main study HLX10-002-NSCLC301

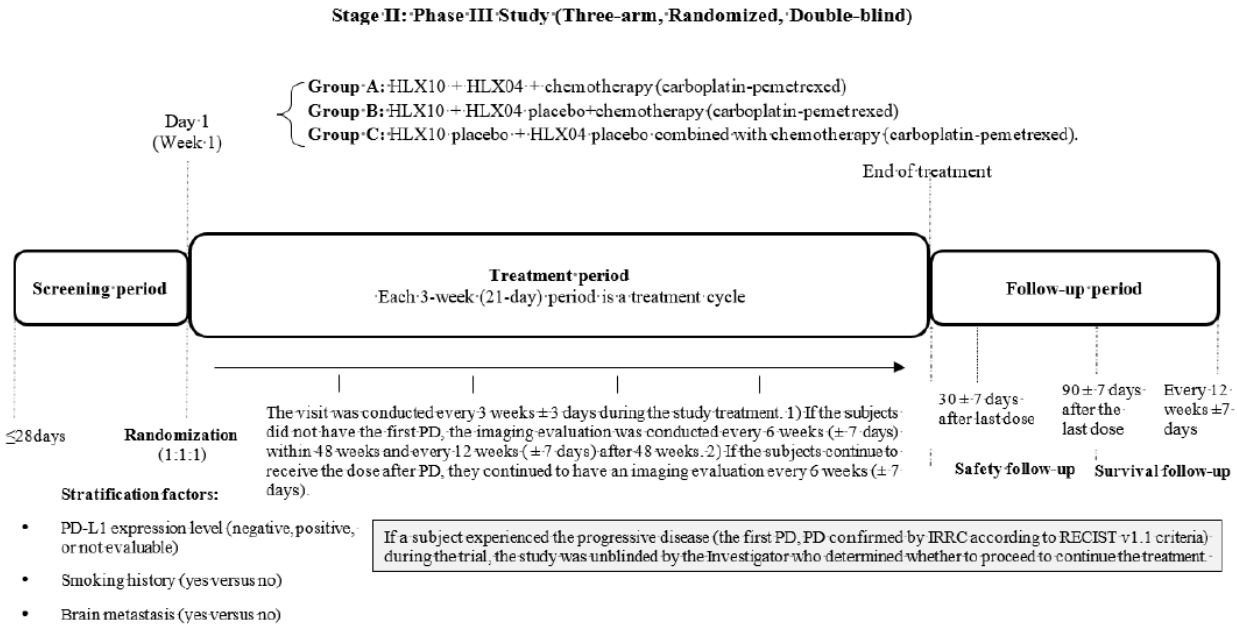
Study HLX10-002-NSCLC301 consisted of two stages, where stage I was a single-arm, safety run-in period. Stage II of the study was a randomized, three-arm, double-blind, multicenter, phase III study of serplulimab (HLX10) combined with Carboplatin-Pemetrexed chemotherapy versus serplulimab in combination with bevacizumab (HLX04) and Carboplatin-Pemetrexed chemotherapy versus Carboplatin-Pemetrexed chemotherapy in subjects with non-squamous NSCLC who had not previously received systemic treatment for advanced NSCLC. Study design is shown in the figures below.

Figure 13 - Study Design Schematic in Stage I



1. After the completion of the first cycle of study treatment for all subjects, a preliminary safety and tolerability analysis was performed.
2. If a subject experiences the progressive disease (the first PD, PD confirmed by IRRC according to RECIST v1.1 criteria) during the study, the Investigator determined whether to proceed to continue treatment.

Figure 14. Stage II study design



Methods

Study participants

Key inclusion criteria

- Adult (aged ≥ 18 years and ≤ 75 years) patients with histologically or cytologically confirmed unresectable or radiographically ineligible stage IIIB, IIIC, or IV (American Joint Committee on Cancer [AJCC] 8th edition) non-squamous NSCLC that could not be treated with surgery or radiotherapy

- No sensitizing mutation in epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) or ROS proto-oncogene 1 (ROS1) rearrangement
- No previous histories of systemic treatment for stage IIIB, IIIC, or IV NSCLC
- ≥1 measurable lesion assessed by IRRC as per RECIST v1.1 within 4 weeks prior to randomization
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1

Key exclusion criteria

- With active/suspected autoimmune diseases
- Subjects with known or found active metastases to the central nervous system (CNS) and/or carcinomatous meningitis at screening. However, the following subjects were allowed to be enrolled: 1) subjects with asymptomatic brain metastases, 2) subjects whose brain metastases had been stable for at least 1 month after the treatment for the brain metastases
- Subjects with spinal cord compression that could not be radically treated by surgery and/or radiotherapy
- Subjects who experienced myocardial infarction or poorly controlled arrhythmia within half a year prior to the first dose of the study drug
- With class III to IV cardiac insufficiency according to the New York Heart Association (NYHA) classification or a left ventricular ejection fraction (LVEF) < 50% by cardiac Doppler ultrasound
- Subjects with previous or current interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis, or severe lung function impairment
- Subjects with known active or suspected autoimmune diseases
- Subjects requiring treatment with systemic corticosteroids
- Subjects who received radical radiotherapy within 3 months prior to the first dose of the study drugs
- Subjects who had previously received other antibodies/drugs against immune checkpoints, such as PD-1, PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)

Treatments

Patients were randomised to 3 groups:

Group A: Serplulimab (HLX10) in combination with bevacizumab (HLX04) and chemotherapy (carboplatin-pemetrexed);

Group B: Serplulimab in combination with the bevacizumab placebo and chemotherapy (carboplatin-pemetrexed);

Group C: Serplulimab placebo in combination with bevacizumab placebo and chemotherapy (carboplatin-pemetrexed).

In group C, after the subject experienced the first PD, chemotherapy would be discontinued and changed to treatment with a combination of serplulimab and bevacizumab.

The study drugs were administered in a treatment cycle of 21 days (3 weeks).

Investigational products/Comparators

Serplulimab was administered at 4.5 mg/kg via intravenous infusion within 30–90 min on Day 1 of each cycle (3 weeks, i.e., 21 days). The treatment was continued until loss of clinical benefits, or completion of 2-year treatment (35 dosing cycles), after which Investigator assessed whether the subject would continue to receive the investigational product.

Bevacizumab was administered at 15 mg/kg via intravenous infusion.

The dosages of serplulimab or placebo and bevacizumab or placebo were calculated based on the body weight of the subjects before each dose. If the body weight change was > 10%, the dosage should be re-calculated based on the newly measured body weight, which was used as the baseline for subsequent body weight measurements.

Other study drugs: Chemotherapy

Pemetrexed was administered at 500 mg/m2 via intravenous infusion for more than 10 min. The administration was performed on Day 1 of each cycle (3 weeks, i.e., 21 days). The treatment was continued until loss of clinical benefits or completion of 2-year treatment (35 dosing cycles), after which whether the subject would continue to receive the study drugs was assessed by Investigator. The dosage of pemetrexed was calculated based on body surface area.

Carboplatin (AUC = 5) was administered at a maximum dosage of no more than 800 mg via intravenous infusion on Day 1 of each cycle (3 weeks, i.e., 21 days) for up to 4 cycles. The dose of carboplatin should be calculated using the Calvert formula as follows:

The dosages of chemotherapies were calculated based on the body weight of the subjects.

Objectives

Stage I: Single-Arm Study (Safety Run-In Phase)

Primary objective

- To evaluate the safety and tolerability of serplulimab + bevacizumab combined with chemotherapy as first-line treatment in patients with advanced non-squamous NSCLC

Secondary objective

- To evaluate the preliminary clinical efficacy of serplulimab+ bevacizumab combined with chemotherapy as first line treatment in patients with advanced non-squamous NSCLC

Stage II: Phase III, three-arm, randomised, double-blind, multicentre clinical trial

Primary objective

- To evaluate the clinical efficacy of serplulimab combined with chemotherapy versus serplulimab + bevacizumab combined with chemotherapy as first-line treatment in patients with advanced non-squamous non-small cell lung cancer

Secondary objective

- To evaluate the safety and tolerability of serplulimab combined with chemotherapy versus serplulimab + bevacizumab combined with chemotherapy as first-line treatment in patients with advanced non-squamous non-small cell lung cancer

Outcomes/endpoints

Stage I endpoints

Primary endpoint

- Safety and tolerability of the first cycle of study treatment

Secondary endpoints

- Incidence rates of adverse events (AEs) and serious adverse events (TESAEs)
- Overall survival (OS)
- Progression-free survival (PFS) (assessed by IRRC and the investigator as per RECIST v1.1, respectively)
- Objective response rate (ORR, assessed by IRRC and the investigator as per RECIST v1.1)
- Duration of response (DOR, assessed by IRRC and the investigator as per RECIST v1.1)
- Pharmacokinetics (PK): serum HLX10/HLX04 concentration
- Immunogenicity assessment: positive rate of anti-drug antibody (ADA)
- Relationship between PD-L1 expression level, MSI, TMB in tumour tissues and efficacy
- Quality of life assessment

Stage II endpoints

Primary endpoint

- Progression-free survival (PFS, assessed by IRRC as per RECIST v1.1)

Secondary endpoints

- Overall survival (OS), as a key secondary endpoint in this study
- Progression-free survival (PFS, assessed by the investigator as per RECIST v1.1)
- Objective response rate (ORR, assessed by IRRC and the investigator as per RECIST v1.1)
- Duration of response (DOR, assessed by IRRC and the investigator as per RECIST v1.1)

Sample size

Assuming that the median PFS of the control group receiving placebo + chemotherapy (carboplatin-pemetrexed) was 6 months, the HR of serplulimab + chemotherapy compared with the control group was 0.69, the enrolment duration was 24 months, the study duration was 30 months, and the type I error rate (α) was 0.05 (two-sided), it was estimated that at least 264 PFS events should be observed to obtain a power of 85%. Assuming a 15% drop-out rate, a total of 400 subjects were enrolled in the 2 groups (200 per group).

Assuming that the median PFS of serplulimab in combination with chemotherapy was 8.7 months, the HR of the serplulimab + bevacizumab + chemotherapy group compared to the serplulimab + chemotherapy group was 0.67, and other parameters were the same as those for the comparison between the serplulimab + chemotherapy group and the control group, it was calculated that a total of 404 subjects should be enrolled in the 2 groups (202 per group). In summary,

approximately 606 subjects were required to be enrolled in stage II of the study, and at least 396 PFS events should be observed.

For the key secondary endpoint OS, assuming that the median OS of the control group (placebo +chemotherapy [carboplatin-pemetrexed]) was 10.7 months, and the HR of serplulimab +chemotherapy group to the control group was 0.7, a group sequential design was adopted with an O'Brien-Fleming-like α-spending function using the Lan-DeMets algorithm to control an overall type I error rate (α) of 0.05 (two-sided). Assuming that the enrolment duration was 24 months, and the study duration was 46 months, it was calculated that at least 288 OS events should be observed to obtain a power of 85%.

Assuming that the median OS of serplulimab + chemotherapy (carboplatin-pemetrexed) group was 15.2 months, the HR of the serplulimab + HLX04 + chemotherapy group compared to the serplulimab + chemotherapy group was 0.68, other parameters and calculation methods were the same as those for the comparison between the serplulimab + chemotherapy group and the control group, and the number of potential dropouts, events and required enrolled subjects for the serplulimab + HLX04 + chemotherapy group were the same as those for other treatment groups, it was calculated that a total of about 630 patients should be enrolled in stage II of the study and at least 432 OS events should be observed.

Considering the sample size required for PFS and OS evaluations, a total of 630 subjects (210 each in the serplulimab+ chemotherapy group, serplulimab + HLX04+ chemotherapy group, and control group) was planned to be enrolled in stage II of this study.

Randomisation

In stage two of the trial eligible subjects were randomly allocated using an interactive web/voice response system (IWRS/IVRS) in a 1:1:1 ratio to:
Group A: patients received serplulimab 4.5 mg/kg, bevacizumab 15 mg/kg, carboplatin (AUC=5, up to 800 mg, for up to four cycles), and pemetrexed (500 mg/m²) every three weeks until disease progression or unacceptable toxicity. Patients randomized to Arm B and Arm C received treatments as shown in Table 16. Randomisation was stratified by PD-L1 expression measured by PD-L1 IHC 22C3 pharmDx kit (negative [CPS<1] versus positive [CPS≥1] versus indeterminate), smoking history (yes versus no), and brain metastasis (yes versus no).

Table 16. Intravenous treatment regimens

Treatment regimen	Induction (Four 21-Day Cycles)	Maintenance (21-Day Cycles)
B	Serplulimab (4.5 mg/kg) [a] + placebo (15 mg/kg) [a] + carboplatin (AUC=5, up to 800 mg) [b] + pemetrexed (500 mg/m^2) [a]	Serplulimab (4.5 mg/kg) [a] + placebo (15 mg/kg) [a] + pemetrexed (500 mg/m^2) [a]
C	Placebo (4.5 mg/kg) [a] + placebo (15 mg/kg) [a] + carboplatin (AUC=5, up to 800 mg) [b] + pemetrexed (500 mg/m^2) [a]	Placebo (4.5 mg/kg) [a] + placebo (15 mg/kg) [a] + pemetrexed (500 mg/m^2) [a,c]

a. Serplulimab and pemetrexed were administered until disease progression or unacceptable toxicity.

b. Carboplatin was administered until completion of 4 cycles, or progressive disease or unacceptable toxicity, whichever occurred first.

c. Crossover was allowed from arm C to receive serplulimab 4.5 mg/kg every 3 weeks and bevacizumab treatment 15 mg/kg every 3 weeks.

Blinding (masking)

An injection that is visually indistinguishable and does not contain any active ingredient of HLX10 or HLX04 was used as placebo control.

During the study, the subjects, the investigator, the sponsor, and the designees are not aware of the randomized allocation, with the exception of the need for emergency unblinding or the initiation of treatment after disease progression.

Statistical methods

Analysis sets

Intention-To-Treat (ITT) All subjects randomized into the study. Primary analysis population for efficacy based on randomized groups.

Per Protocol Set (PPS) Consists of all randomized subjects who have received at least one post-treatment tumour assessment without any major protocol deviation that can significantly affect the primary efficacy. Analysis based on the PPS will serve as a support of ITT analyses. The population of the PPS will be determined in the blinded data review meeting prior to database lock.

Safety Set (SS) All subjects who have received at least one dose of investigational product. The primary analysis population for safety assessment, based on actual treatment groups.

Pharmacokinetic Set (PKS)All subjects who have received at least one dose of HLX10 or HLX04 and have at least one post-dose concentration measurement at scheduled PK time points, without any major protocol deviations that can obviously affect the PK assessment. PKS will be used for PK analysis.

Main analysis methods for primary and key secondary endpoints

Primary endpoint and estimand

Population: Patients receiving first-line treatment for advanced non-squamous non-small cell lung cancer (NSCLC) who meet the inclusion and exclusion criteria.

Variable: Progression-free survival (PFS) assessed by IRRC as per RECIST v1.1 defined as the time from randomization to the first documentation of PD or death due to any reason (whichever occurs first).

Treatment: HLX10/placebo + HLX04/placebo combined with chemotherapy (carboplatin-pemetrexed), with every 3 weeks (21 days) as a treatment cycle.

Intercurrent events and handling strategies: Initiation of new anti-tumour therapy (subsequent systemic therapy for NSCLC) before PD or death was handled by a hypothetical strategy. Interruption or dose modification was handled by a treatment policy strategy.

Population-level summary: hazard ratio

The inter-group comparison of PFS was performed using the stratified log-rank test using the randomization stratification factors collected by IWRS, with treatment group as the only fixed effect, and the two-sided P-value will be reported. The median and its 95% CI (Brookmeyer-Crowley method based on log-log transformation) was estimated using the Kaplan-Meier method, and the Kaplan-Meier curve plotted. The HR and its 95% CI (Efron method) was estimated using the stratified Cox proportional hazards model.

In addition, sensitivity and supplementary analyses were performed on the primary efficacy endpoint.

Subjects were censored at date of randomization if they lack baseline, or if they lack all post-baseline tumour assessments and they did not die, in which case they were not censored. Subjects were also censored at the date of last tumour assessment if they initiated new anti-tumour therapy.

Multiplicity control

A gate keeping strategy over the two comparisons of PFS and OS, Group B *vs* C and PFS and OS in Group A *vs* B, and a group sequential design using a Lan-DeMets approximation to the O'Brien-Fleming boundary for OS over interim analyses, was used to control the type I error at 5% two-sided.

Final analysis of PFS was planned to be conducted when the target number (about 396 PFS events) was observed. At this time an interim analysis of OS was planned with 72% of the total number of events predicted. The alpha significance level of the interim/final analysis of OS was adjusted based on the actual number events achieved at the analysis time point using the specified α-spending function.

Table 17 Efficacy Boundaries for the Interim and Final Analyses of OS

Analysis	**Number of events (%)**	**HR boundary**	**Z value**	***P* value**
Group B (HLX10 + chemotherapy) vs. Group C (placebo + chemotherapy)				
Interim analysis	213（74.0%）	0.723	2.36	0.0183
Final analysis	288（100%）	0.788	2.01	0.0445
Group A (HLX10 + HLX04 + chemotherapy group) vs. Group B (HLX10 + chemotherapy group)				
Interim analysis	200（69.4%）	0.686	2.45	0.0142
Final analysis	288（100%）	0.774	2.00	0.0457

Data cut-off date: June 15, 2023

Sensitivity or supplementary analyses

For PFS sensitivity analyses included censoring events after 2 or more consecutive missing tumour assessments or unblinding, with actual stratification factors instead of randomization stratification factors, and unstratified analysis. A supplementary analysis using the PPS was performed.

Key secondary endpoint and estimand

The key secondary efficacy endpoint of this study was OS, defined as the time from randomization to death due to any reason.

The statistical analysis method for OS was the same as that for the primary efficacy endpoint. Patients were censored in case of loss to follow-up.

Sensitivity analyses and supplementary analysis performed on OS. included rank-preserving structural failure time model (RPSFTM) to adjust for treatment switch for the placebo + chemotherapy group to HLX10 + HLX04 (or other drugs in the same class), using actual stratification factors as adjustment variables for inter-group comparisons or statistical models, and an unstratified analysis. A supplementary analysis in the PPS was performed.

Secondary endpoints and estimands

Objective response rate (ORR)

Objective response rate (ORR) was defined as the percentage of subjects whose best overall response (BOR) is complete response (CR) or partial response (PR). Subjects without post-baseline tumour assessments will be considered non-responders. BOR is defined as the best result of overall tumour response assessment during study treatment (respectively assessed by the IRRC and the investigator as per RECIST v1.1) as per the following priority levels in order: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The interval between the date of randomization and SD should be no less than 6 weeks (42 days). If the time from randomization to the best overall response of SD was less than 6 weeks, it was not to be counted as SD.

Unconfirmed ORR and confirmed ORR were analysed separately, and subjects with confirmed BOR of complete response (CR) or partial response (PR) were to be re-assessed at least 4 weeks later for confirmation.

For unconfirmed ORR and confirmed ORR, the stratified Cochran-Mantel-Haenszel (CMH) method was used to test the difference in ORR between the two groups, and the odds ratio and its 95% CI estimated. The stratification factors were as per the randomization. A 95% CI in an individual treatment group were calculated using the Clopper-Pearson method. The number and percentage of subjects who achieve best overall response as assessed by the IRRC and the investigator was summarized.

A sensitivity analysis not considering the stratification factors in inter-group comparison was performed and a supplementary analysis in the PPS performed.

Duration of response (DOR)

The DOR was analysed only for subjects whose best overall response is evaluated as CR or PR. The median and its 95% CI was estimated using the Kaplan-Meier method, and the Kaplan-Meier curve plotted. Patients were censored if they did not experience PD or death before endo of follow-up, lacked tumour assessments and did not die, or initiated new anti-tumour therapy, after the first documented CR.

A supplementary analysis based on the PPS was performed.

Planned subgroup analyses

Subgroup analyses included the subgroups defined by stratification factors and by biomarker, if the subgroup population was at least 5% of the ITT population, and included presenting the subgroup results in forest plots. Subgroup analyses were based on the efficacy results assessed by the IRRC, in the ITT.

The planned subgroup analyses include:

- Age: <65 vs.≥65 years
- ECOG performance score: 0 vs.1
- Sex: male vs. female
- Smoking history: yes vs. no
- Brain metastasis: yes vs. no
- PD-L1 expression level: negative vs. positive vs. not evaluable
- PD-L1 expression level: CPS<1 vs.1 ≤ CPS≤9 vs. CPS≥10
- PD-L1 expression level: TPS<1% vs. 1%≤TPS<50% vs.TPS≥50%

- Tumour status: locally advanced (stage IIIB/IIIC) vs. distant metastasis (stage IV)
- MSI: MSS/MSI-Low vs. MSI-High
- TMB: < 10 muts/Mb vs. ≥ 10 muts/Mb

Error probabilities, adjustment for multiplicity and interim analyses

All statistical tests in the study were performed using the two-sided tests, with a significance level of α=0.05 overall (See also *Interim Analysis*).

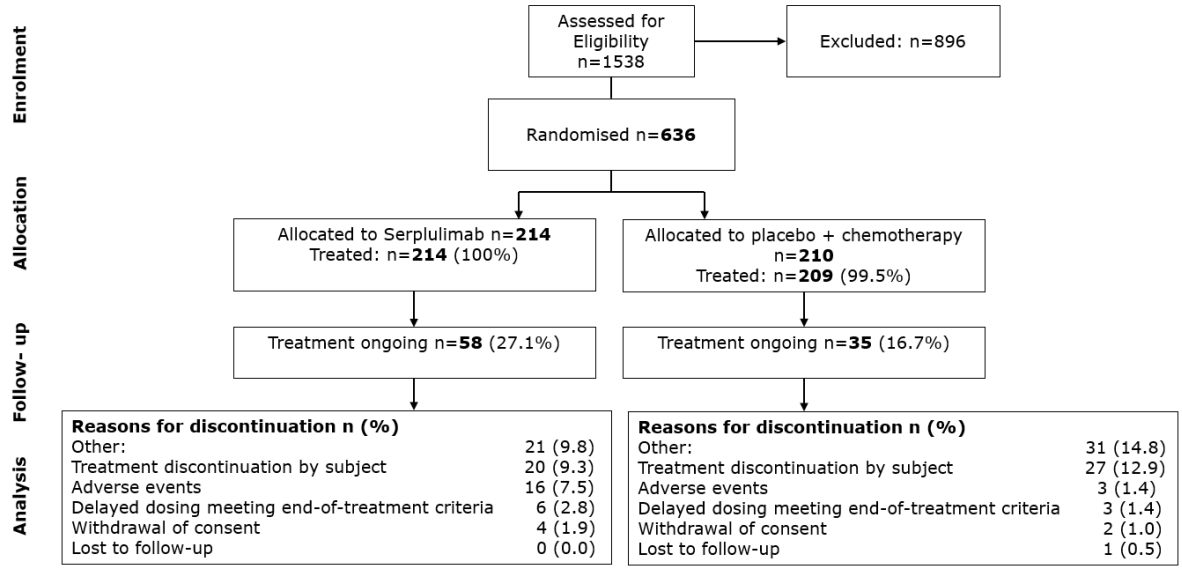
Changes from protocol-specified analyses

The study protocol was amended 6 times from version 1.0 to version 7.0 before the cutoff date for the interim analysis (June 15, 2023).

Results

Participant flow

Figure 15 Participant flow



Recruitment

The first patient (first signed informed consent) was enrolled 25 November 2019. The last patient was enrolled 15 June 2022.

The study was initiated at 92 study sites. A total of 1538 subjects were screened at 75 study sites, of which 896 (58.3%) failed the screening and 642 (41.7%) were enrolled at 72 study sites. All study sites were located in China.

The results presented here have DCO of 15 Jun 2023, which corresponds to the final PFS analysis and an interim OS analysis.

Conduct of the study

Table 18 Protocol amendments

Protocol amendment	Most relevant changes

02 (3 April 2019)	Stage I safety run-in phase added. The safety and tolerability of serplulimab and bevacizumab combined with chemotherapy were to be evaluated first, followed by stage II of the study. Number of subjects in stage I added, primary endpoints and efficacy and safety analyses of phase I and II defined based on revisions to objectives and study design.
03 (10 January 2020)	Patients with locally advanced NSCLC were enrolled in the study, which was adjusted based on the population. The requirements for the infusion duration and interval of the investigational product were supplemented according to the drug management procedures. The PD-L1 expression level as a stratification factor was uniformly revised to must be collected. An interim analysis for sample-size re-assessment was added.
04 (28 June 2020)	Safety event settings and safety assessment criteria for stage I supplemented. Description of adverse events adjusted according to new version of GCP in 2020. Requirement for gene mutation added.
05 (25 December 2020)	Revised OS as a key secondary endpoint and added PFS2 as a secondary endpoint. Sample size calculated by considering PFS and OS, based on revision of OS as key secondary endpoint. Updated the statistical processing of primary efficacy endpoint and secondary efficacy endpoints due to revision of OS as a key secondary endpoint and addition of PFS2 as a secondary endpoint. Interim analysis plan updated due to revision of OS as key secondary endpoint.
06 (24 January 2022)	Updated the duration of treatment with reference to the latest study data of the competitive product pembrolizumab. Updated and supplemented the statistical hypotheses for investigational product arms. Cancelled the second interim analysis of PFS and supplemented the statistical analysis of PFS and the interim analysis of OS.
07 (28 November 2022)	Deleted PFS2 secondary endpoint. Deleted definition of PFS2. Deleted time point for unblinding.

Table 19 Summary of Major Protocol Deviations (ITT Set)

	HLX10 + HLX04 + Chemotherapy (N = 212) n (%)	HLX10 + Chemotherapy (N = 214) n (%)	Placebo + Chemotherapy (N = 210) n (%)	Total (N = 636) n (%)
Subjects with any major protocol deviations	101 (47.6)	88 (41.1)	88 (41.9)	277 (43.6)
Informed Consent	2 (0.9)	4 (1.9)	3 (1.4)	9 (1.4)
SAE	3 (1.4)	4 (1.9)	5 (2.4)	12 (1.9)
Inclusion Criteria	2 (0.9)	2 (0.9)	6 (2.9)	10 (1.6)
Exclusion Criteria	3 (1.4)	4 (1.9)	1 (0.5)	8 (1.3)
Criteria for Discontinuation	4 (1.9)	2 (0.9)	3 (1.4)	9 (1.4)
Treatment Regimen	3 (1.4)	5 (2.3)	3 (1.4)	11 (1.7)
Treatment Compliance	17 (8.0)	12 (5.6)	12 (5.7)	41 (6.4)
Disallowed Medications/Treatments	17 (8.0)	9 (4.2)	11 (5.2)	37 (5.8)
Study Visit	50 (23.6)	36 (16.8)	35 (16.7)	121 (19.0)
Stratified Randomization Procedures	8 (3.8)	2 (0.9)	8 (3.8)	18 (2.8)
Imaging Procedures	27 (12.7)	21 (9.8)	29 (13.8)	77 (12.1)
Drug Randomization/Usage (Maintenance of Blinding)	9 (4.2)	8 (3.7)	7 (3.3)	24 (3.8)

Note: Subjects with multiple major protocol deviations were counted once in the summary.

Baseline data

Table 20 Demographics and baseline data (ITT set)

	Serplulimab + HLX04 + Chemotherapy (N=212)	Serplulimab + Chemotherapy (N=214)	Placebo + Chemotherapy (N=210)	Total (N=636)
Age (years)				
n	212	214	210	636
Mean (SD)	60.8 (8.73)	60.6 (9.05)	59.8 (8.33)	60.4 (8.71)
Median	61.5	62.0	61.0	61.0
Min − Max	27 - 74	29 - 75	33 - 75	27 - 75
Sex, n (%)				
Male	152 (71.7)	157 (73.4)	156 (74.3)	465 (73.1)
Female	60 (28.3)	57 (26.6)	54 (25.7)	171 (26.9)
Ethnicity, n (%)				
Han	199 (93.9)	200 (93.5)	200 (95.2)	599 (94.2)
Other	13 (6.1)	14 (6.5)	10 (4.8)	37 (5.8)
Height (cm)				
n	211	214	210	635
Mean (SD)	165.45 (7.866)	164.73 (7.700)	165.74 (7.952)	165.30 (7.838)
Median	166.00	165.00	166.00	165.00
Min − Max	145 - 188	138 - 180	140 - 185	138 - 188
Weight (kg)				
n	212	214	210	636
Mean (SD)	62.85 (10.959)	61.31 (11.079)	62.14 (9.940)	62.10 (10.677)
Median	62.00	60.00	62.00	61.00
Min − Max	41 - 94.2	35 - 94	38 - 93.5	35 - 94.2
BMI (kg/m^2)[1]				
n	211	214	210	635
Mean (SD)	22.91 (3.210)	22.54 (3.469)	22.60 (3.183)	22.68 (3.289)
Median	23.00	22.60	22.50	22.70
Min − Max	15.9 - 34.4	14.5 - 30.5	15.2 - 32.6	14.5 - 34.4
LVEF (%)				
n	212	214	209	635
Mean (SD)	64.390 (4.8988)	65.202 (5.0148)	64.601 (4.7571)	64.733 (4.8969)
Median	64.000	65.000	64.000	64.000
Min − Max	52 - 83	51 - 81.3	51 - 78	51 - 83
Echocardiography, n (%)				
Normal	49 (23.1)	53 (24.8)	58 (27.6)	160 (25.2)
Abnormal - not clinically significant	149 (70.3)	146 (68.2)	139 (66.2)	434 (68.2)
Abnormal - clinically significant	14 (6.6)	15 (7.0)	12 (5.7)	41 (6.4)
Not done	0	0	1 (0.5)	1 (0.2)
ECOG performance score, n (%)				
0	53 (25.0)	60 (28.0)	58 (27.6)	171 (26.9)
1	158 (74.5)	154 (72.0)	152 (72.4)	464 (73.0)

Missing	1 (0.5)	0	0	1 (0.2)
PD-L1 expression level, n (%)				
Positive (CPS ≥ 1)	166 (78.3)	166 (77.6)	164 (78.1)	496 (78.0)
Negative (CPS < 1)	43 (20.3)	44 (20.6)	43 (20.5)	130 (20.4)
Not evaluable	3 (1.4)	4 (1.9)	3 (1.4)	10 (1.6)
Smoking history, n (%)				
Yes	142 (67.0)	143 (66.8)	140 (66.7)	425 (66.8)
No	70 (33.0)	71 (33.2)	70 (33.3)	211 (33.2)
History of brain metastasis, n (%)				
Yes	40 (18.9)	41 (19.2)	38 (18.1)	119 (18.7)
No	172 (81.1)	173 (80.8)	172 (81.9)	517 (81.3)
PD-L1 expression level at randomization, n (%)				
Positive (CPS ≥ 1)	166 (78.3)	166 (77.6)	163 (77.6)	495 (77.8)
Negative (CPS < 1)	43 (20.3)	44 (20.6)	44 (21.0)	131 (20.6)
Not evaluable	3 (1.4)	4 (1.9)	3 (1.4)	10 (1.6)
Smoking history at randomization, n (%)				
Yes	142 (67.0)	143 (66.8)	140 (66.7)	425 (66.8)
No	70 (33.0)	71 (33.2)	70 (33.3)	211 (33.2)
History of brain metastasis at randomization, n (%)				
Yes	39 (18.4)	41 (19.2)	39 (18.6)	119 (18.7)
No	173 (81.6)	173 (80.8)	171 (81.4)	517 (81.3)

Note: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group performance status score. [1] BMI = weight (kg)/ height $(m)^2$.

Table 21 Baseline tumour diagnoses (ITT set)

	HLX10 + HLX04 + Chemotherapy (N = 212) n (%)	HLX10 + Chemotherapy (N = 214) n (%)	Placebo + Chemotherapy (N = 210) n (%)	Total (N = 636) n (%)
Time from initial diagnosis of NSCLC to informed consent (months)				
n	212	214	210	636
Mean (SD)	1.9979 (7.5146)	2.1375 (7.6779)	3.0033 (10.8323)	2.3769 (8.7952)
Median	0.4600	0.4600	0.5257	0.4764
Min − Max	0.0329 - 73.4620	−0.0657 - 61.8645	0.0329 - 92.0575	−0.0657 - 92.0575
Time from diagnosis of stage IIIB/IIIC or stage IV NSCLC to informed consent (months)				
n	212	214	210	636
Mean (SD)	0.5291 (1.4204)	0.4056 (0.9063)	0.6616 (4.7690)	0.5313 (2.9056)
Median	0.2300	0.1643	0.1643	0.1971
Min − Max	−1.3142 - 12.1889	−0.7228 - 7.1622	−0.9528 - 68.8624	−1.3142 - 68.8624
Time from the most recent pathological diagnosis to informed consent (months)				
n	212	214	210	636
Mean (SD)	0.5097 (1.2569)	0.6192 (2.6356)	0.9169 (6.4760)	0.6810 (4.0851)
Median	0.2628	0.2300	0.2300	0.2628
Min − Max	−0.9199 - 12.1889	−0.8871 - 36.3696	−1.3799 - 92.0575	−1.3799 - 92.0575
Pathological diagnosis method, n (%)				
Histology	206 (97.2)	207 (96.7)	204 (97.1)	617 (97.0)
Cytology	6 (2.8)	7 (3.3)	6 (2.9)	19 (3.0)
Pathological type, n (%)				
Adenocarcinoma	210 (99.1)	207 (96.7)	208 (99.0)	625 (98.3)
Large cell carcinoma	0	3 (1.4)	0	3 (0.5)
Other	2 (0.9)	4 (1.9)	2 (1.0)	8 (1.3)
TNM stage and clinical stage at the time of ICF signing, n (%)				
Primary tumor (T)				
TX	3 (1.4)	9 (4.2)	13 (6.2)	25 (3.9)
T0	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.5)
Tis	0	0	0	0
T1	27 (12.7)	32 (15.0)	29 (13.8)	88 (13.8)
T2	56 (26.4)	47 (22.0)	46 (21.9)	149 (23.4)
T3	41 (19.3)	29 (13.6)	45 (21.4)	115 (18.1)
T4	84 (39.6)	96 (44.9)	76 (36.2)	256 (40.3)
Regional lymph nodes (N)				
Nx	7 (3.3)	5 (2.3)	8 (3.8)	20 (3.1)
N0	19 (9.0)	27 (12.6)	20 (9.5)	66 (10.4)
N1	7 (3.3)	11 (5.1)	2 (1.0)	20 (3.1)
N2	77 (36.3)	59 (27.6)	66 (31.4)	202 (31.8)
N3	102 (48.1)	112 (52.3)	114 (54.3)	328 (51.6)
Distant metastasis (M)				
MX	1 (0.5)	1 (0.5)	4 (1.9)	6 (0.9)
M0	39 (18.4)	29 (13.6)	28 (13.3)	96 (15.1)
M1a	48 (22.6)	52 (24.3)	57 (27.1)	157 (24.7)
M1b	27 (12.7)	28 (13.1)	25 (11.9)	80 (12.6)
M1c	97 (45.8)	104 (48.6)	96 (45.7)	297 (46.7)
Clinical stage				
IA1	0	0	0	0
IA2	0	0	0	0
IA3	0	0	0	0
IB	0	0	0	0
IIA	0	0	0	0
IIB	0	0	0	0
IIIA	0	0	0	0
IIIB	29 (13.7)	18 (8.4)	20 (9.5)	67 (10.5)
IIIC	11 (5.2)	12 (5.6)	11 (5.2)	34 (5.3)
IVA	75 (35.4)	80 (37.4)	82 (39.0)	237 (37.3)
IVB	97 (45.8)	104 (48.6)	97 (46.2)	298 (46.9)
Not evaluable	0	0	0	0
Tumor status, n (%)				
Locally advanced (stage IIIB/IIIC)	40 (18.9)	30 (14.0)	31 (14.8)	101 (15.9)
Distant metastasis (stage IV)	172 (81.1)	184 (86.0)	179 (85.2)	535 (84.1)

Numbers analysed

Table 22 Analysis populations

	HLX10 + HLX04 + Chemotherapy n (%)	HLX10 + Chemotherapy n (%)	Placebo + Chemotherapy n (%)	Total n (%)
Subjects screened				1538
Screen failed[1]				896 (58.3)
Reason for screen failed				
Stage I: Subjects in the safety run-in period of the single-arm study	6			6
Stage II: Phase III study				
Subjects randomized	212	214	210	636
Subjects who had received at least one dose of the study drugs	211 (99.5)	214 (100)	209 (99.5)	634 (99.7)
Analysis sets[3]				
Intent-to-treat (ITT) set	212 (100)	214 (100)	210 (100)	636 (100)
Per-protocol set (PPS)	202 (95.3)	208 (97.2)	195 (92.9)	605 (95.1)
Safety set (SS)	211 (99.5)	214 (100)	209 (99.5)	634 (99.7)
Pharmacokinetics set (PKS)	211 (99.5)	213 (99.5)	72 (34.3)	496 (78.0)

Number of subjects still in follow-up at data cut-off date = total number of subjects − number of subjects who have completed the study – number of subjects who prematurely discontinued study.
[1] The percentage of screen failed was calculated based on the number of subjects who signed the informed consent form. All other percentages were calculated based on the number of subjects randomized.
[2] Subjects who had completed the treatment referred to the subjects who discontinued the treatment after progressive disease (PD) confirmed by the Independent Radiology Review Committee (IRRC), subject death, or subjects who discontinued the study treatment as assessed by Investigator after 2 years of treatment (35 cycles).
[3] Intent-to-treat (ITT) set: All subjects were randomized into the study. Per-protocol set (PPS): A subset of ITT, in which all randomized subjects who received at least one post-treatment tumour assessment and had no major protocol deviation that significantly affected the primary efficacy were included. Safety set (SS): All subjects who received at least one dose of the study drug. Pharmacokinetics set (PKS): All subjects who received at least one dose of HLX10 or HLX04, with at least one post-dose concentration measured at scheduled PK time points, and without any major
protocol deviations that may markedly affect the PK assessment.

Reasons for exclusion from the PPS were submitted and assessed with this procedure but not included in this report.

Outcomes and estimation

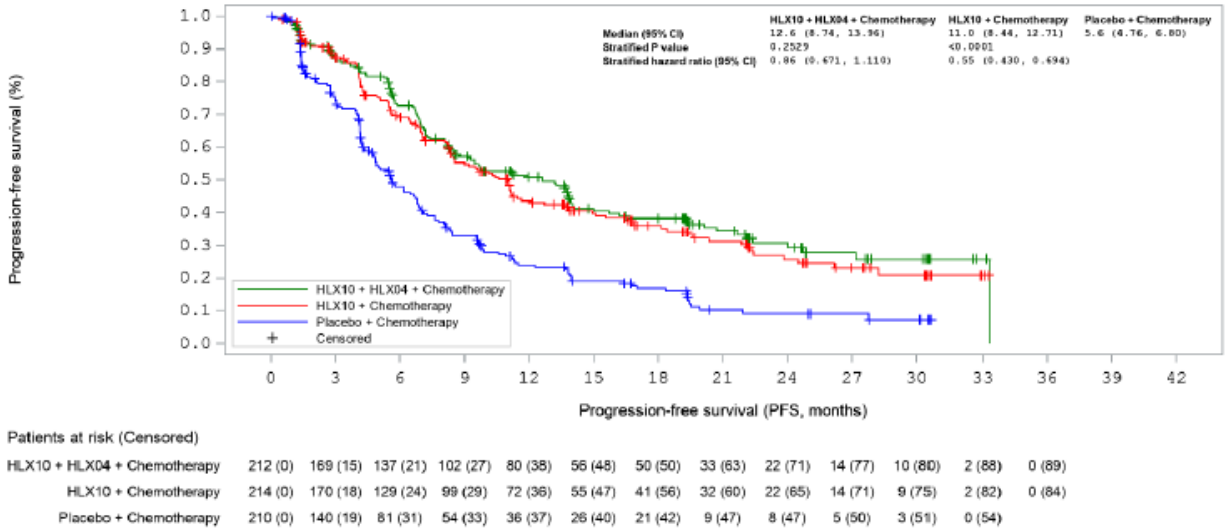
Primary endpoint – PFS assessed by IRRC per RECIST v1.1:

Table 23 Summary of PFS assessed by IRRC per RECIST v1.1 (ITT set), DCO 15-Jun-2023

	HLX10 + HLX04 + Chemotherapy (N = 212)	HLX10 + Chemotherapy (N = 214)	Placebo + Chemotherapy (N = 210)
Subject status, n (%)			
Number of subjects with events	123 (58.0)	130 (60.7)	156 (74.3)
Progressive disease	89 (42.0)	110 (51.4)	133 (63.3)
Death without PD	34 (16.0)	20 (9.3)	23 (11.0)
Number of subjects with censors	89 (42.0)	84 (39.3)	54 (25.7)
No baseline tumor assessment	0	0	0
No post-baseline tumor assessment and no death	1 (0.5)	1 (0.5)	3 (1.4)
No post-baseline tumor assessment and death after the start of a new anti-tumor therapy	1 (0.5)	0	2 (1.0)
At least one post-baseline tumor assessment and no PD or death before the start of a new anti-tumor therapy	27 (12.7)	26 (12.1)	26 (12.4)
At least one post-baseline tumor assessment and no PD or death before the end of follow-up	60 (28.3)	57 (26.6)	23 (11.0)
Progression-free survival (PFS, month)			
n	212	214	210
25% percentile	5.7	5.1	3.0
Median (95% CI)[1]	12.6 (8.74, 13.96)	11.0 (8.44, 12.71)	5.6 (4.76, 6.80)
75% percentile	33.3	24.5	11.3
Stratified *P* value[2]	0.2529	< 0.0001	
Stratified hazard ratio (95% CI)[3]	0.86 (0.671, 1.110)	0.55 (0.430, 0.694)	
Unstratified *P* value[2]	0.4216	< 0.0001	
Unstratified hazard ratio (95% CI)[3]	0.90 (0.705, 1.157)	0.54 (0.428, 0.685)	
PFS rate and 95% CI (%)[4]			
6 months	72.8 (65.96, 78.42)	69.0 (62.01, 74.99)	47.9 (40.51, 54.90)
9 months	57.1 (49.80, 63.80)	55.3 (47.95, 62.07)	33.0 (26.12, 39.95)
12 months	50.8 (43.37, 57.67)	43.6 (36.35, 50.70)	24.0 (17.79, 30.63)
15 months	41.2 (33.77, 48.45)	39.7 (32.51, 46.85)	19.2 (13.53, 25.58)
18 months	38.2 (30.84, 45.55)	35.9 (28.72, 43.15)	16.8 (11.45, 23.12)

Note: RECIST = Response Evaluation Criteria in Solid Tumors; the time from randomization to the first documented PD or death from any cause, whichever occurred first. PFS was calculated as follows: PFS (months) = (min [Date of first documented PD, Date of death] – Randomization date + 1)/30.4375;
[1] The Kaplan-Meier method was used to estimate the median and 95% CI were estimated using the (stratified/unstratified) Cox proportional hazards model (Efron method).
[2] The (stratified/unstratified) Log-Rank test was used to compare PFS between two groups based on the stratification factors of PD-L1 expression level (negative/positive/not evaluable), smoking history (yes/no), and brain metastases (yes/no).
[3] HR and its 95% CI were estimated using the (stratified/unstratified) Cox proportional hazards model (Efron method).
[4] Kalbfleisch-Prentice method with log-log transformation was utilized.

Figure 16 K-M Curve of Progression-Free Survival (PFS) Assessed by IRRC per RECIST v1.1 (ITT Set), DCO 15-Jun-2023



Sensitivity analysis 1

In the ITT set, subjects who developed PD or death after 2 or more consecutive missing tumour assessments, or PD after unblinding (PD or death after consecutive missing tumour assessments, or PD censoring after unblinding), were censored to the date of the last imaging examination before the missing imaging and the date of the last imaging examination before unblinding, respectively.

As of June 15, 2023, the median PFS in the serplulimab + HLX04 + chemotherapy group, the serplulimab + chemotherapy group, and the placebo + chemotherapy group was 13.2 months (95% CI: 8.74, 15.70), 11.1 months (95% CI: 8.48, 14.95), and 5.6 months (95% CI: 4.73, 6.80).

Sensitivity analysis 2

In the ITT set, the actual stratification factors were used for inter-group comparison or used as adjustment variables in the statistical model.

As of June 15, 2023, the median PFS in the HLX10 + HLX04 + chemotherapy group, the HLX10 + chemotherapy group, and the placebo + chemotherapy group was 12.6 months (95% CI: 8.74, 13.96), 11.0 months (95% CI: 8.44, 12.71), and 5.6 months (95% CI: 4.76, 6.80).

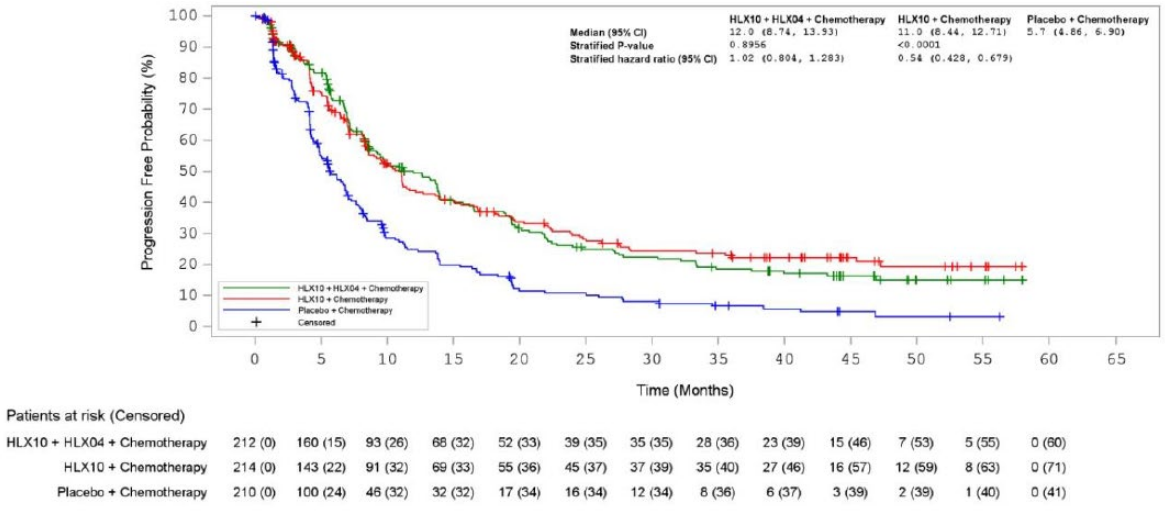
Updated PFS analysis, DCO 7-Aug-2025

Table 24: Summary of PFS assessed by IRRC per RECIST v1.1 (ITT Set), DCO 07-Aug-2025

	HLX10 + HLX04 + Chemotherapy (N = 212)	HLX10 + Chemotherapy (N = 214)	Placebo + Chemotherapy (N = 210)	Total (N = 636)
Subject status, n (%)				
Number of subjects with events	152 (71.7)	143 (66.8)	169 (80.5)	464 (73.0)
Progressive disease	112 (52.8)	119 (55.6)	141 (67.1)	372 (58.5)
Death without PD	40 (18.9)	24 (11.2)	28 (13.3)	92 (14.5)
Number of subjects with censors	60 (28.3)	71 (33.2)	41 (19.5)	172 (27.0)
No baseline tumor assessment	0	0	0	0
No post-baseline tumor assessment and no death	1 (0.5)	1 (0.5)	3 (1.4)	5 (0.8)
No post-baseline tumor assessment and death after the start of a new anti-tumor therapy	1 (0.5)	0	2 (1.0)	3 (0.5)
At least one post-baseline tumor assessment and no PD or death before the start of a new anti-tumor therapy	29 (13.7)	30 (14.0)	28 (13.3)	87 (13.7)
At least one post-baseline tumor assessment and no PD or death before the end of follow-up	29 (13.7)	40 (18.7)	8 (3.8)	77 (12.1)
Progression-free survival (PFS, month)				
n	212	214	210	636
25% percentile	5.7	5.1	3.0	4.2
Median (95% CI)[1]	12.0 (8.74, 13.93)	11.0 (8.44, 12.71)	5.7 (4.86, 6.90)	8.5 (8.08, 9.76)
75% percentile	24.7	28.3	11.5	21.9
Stratified P-value[2]	0.8956	< 0.0001		
Stratified hazard ratio (95% CI)[3]	1.02 (0.804, 1.283)	0.54 (0.428, 0.679)		
Unstratified P-value[2]	0.6984	< 0.0001		
Unstratified hazard ratio (95% CI)[3]	1.05 (0.832, 1.315)	0.53 (0.422, 0.663)		
PFS rate and 95% CI (%)[4]				
6 months	72.9 (66.08, 78.50)	69.0 (62.01, 74.99)	49.0 (41.66, 55.93)	63.9 (59.82, 67.63)
9 months	56.8 (49.46, 63.44)	55.3 (47.95, 62.07)	34.0 (27.22, 40.97)	49.0 (44.78, 53.03)
12 months	49.5 (42.12, 56.37)	43.9 (36.60, 50.89)	24.9 (18.71, 31.48)	39.7 (35.58, 43.76)
15 months	40.6 (33.46, 47.66)	40.4 (33.24, 47.42)	19.9 (14.28, 26.18)	33.9 (29.95, 37.95)
18 months	37.0 (30.02, 44.06)	36.9 (29.88, 43.88)	16.8 (11.59, 22.80)	30.5 (26.65, 34.47)
24 months	26.2 (19.90, 32.88)	29.4 (22.86, 36.30)	10.8 (6.59, 16.15)	22.4 (18.88, 26.08)
36 months	18.5 (13.05, 24.75)	23.0 (16.94, 29.57)	6.7 (3.45, 11.36)	16.2 (13.12, 19.63)

Note: RECIST = Response Evaluation Criteria in Solid Tumors; the time from randomization to the first documented PD or death from any cause, whichever occurred first. PFS was calculated as follows: PFS (months) = (min [Date of first documented PD, Date of death] – Randomization date + 1)/30.4375;
[1] The Kaplan-Meier method was used to estimate the median and 95% CI were estimated using the (stratified/unstratified) Cox proportional hazards model (Efron method).
[2] The (stratified/unstratified) Log-Rank test was used to compare PFS between two groups based on the stratification factors of PD-L1 expression level (negative/positive/not evaluable), smoking history (yes/no), and brain metastases (yes/no).
[3] HR and its 95% CI were estimated using the (stratified/unstratified) Cox proportional hazards model (Efron method).
[4] Kalbfleisch-Prentice method with log-log transformation was utilized.

Figure 17: KM curve of PFS assessed by IRRC per RECIST v1.1 (ITT Set), DCO 07-Aug-2025



Patients at risk (Censored)

HLX10 + HLX04 + Chemotherapy	212 (0)	160 (15)	93 (26)	68 (32)	52 (33)	39 (35)	35 (35)	28 (36)	23 (39)	15 (46)	7 (53)	5 (55)	0 (60)
HLX10 + Chemotherapy	214 (0)	143 (22)	91 (32)	69 (33)	55 (36)	45 (37)	37 (39)	35 (40)	27 (46)	16 (57)	12 (59)	8 (63)	0 (71)
Placebo + Chemotherapy	210 (0)	100 (24)	46 (32)	32 (32)	17 (34)	16 (34)	12 (34)	8 (36)	6 (37)	3 (39)	2 (39)	1 (40)	0 (41)

Key secondary endpoint – OS

Table 25 Summary of OS (ITT set), DCO 15-Jun-2023

	HLX10 + HLX04 + Chemotherapy (N = 212)	HLX10 + Chemotherapy (N = 214)	Placebo + Chemotherapy (N = 210)
Subject status, n (%)			
Death	98 (46.2)	102 (47.7)	111 (52.9)
Censored	114 (53.8)	112 (52.3)	99 (47.1)
Alive	110 (51.9)	105 (49.1)	91 (43.3)
Withdrawal of the Informed Consent	2 (0.9)	4 (1.9)	3 (1.4)
Lost to follow-up	2 (0.9)	3 (1.4)	5 (2.4)
Overall survival (OS, months)			
n	212	214	210
25% percentile	11.8	11.7	8.0
Median (95% CI)[1]	23.7 (20.57, -)	25.0 (20.44, 28.68)	20.4 (16.39, 24.18)
75% percentile	-	-	-
Stratified *P* value[2]	0.8817	0.1234	
Stratified hazard ratio (95% CI)[3]	0.98 (0.740, 1.295)	0.81 (0.615, 1.060)	
Unstratified *P* value[2]	0.8333	0.1110	
Unstratified hazard ratio (95% CI)[3]	0.97 (0.735, 1.281)	0.80 (0.614, 1.052)	
Overall survival rate and 95% CI (%)[4]			
6 months	88.1 (82.89, 91.79)	91.0 (86.23, 94.15)	83.5 (77.70, 87.92)
12 months	73.7 (67.15, 79.12)	74.5 (68.05, 79.92)	65.3 (58.32, 71.37)
18 months	61.6 (54.43, 68.03)	63.6 (56.41, 69.88)	53.8 (46.52, 60.50)
24 months	49.8 (41.80, 57.25)	51.8 (43.89, 59.04)	42.7 (34.85, 50.33)
Follow-up time[5]			
n	212	214	210
Mean (SD)	17.2595 (8.7870)	17.2752 (8.8227)	15.5749 (9.2303)
Median	17.3963	17.1006	15.0965
Min – Max	0.0986 - 36.8953	0.1314 - 37.5195	0.0657 - 36.5667
Median follow-up time (95% CI)[6]	23.4 (21.59, 24.87)	23.1 (21.39, 25.56)	23.0 (20.73, 25.56)

Note: The time from randomization to death from any cause. OS was calculated as follows: OS (months) = (Date of death – Randomization date + 1)/30.4375.

[1] The Kaplan-Meier method was used to estimate the median and 95% CI (Brookmeyer-Crowley method based on log-log transformation).

[2] The (stratified/unstratified) Log-Rank test was used to compare OS between two groups based on the stratification factors of PD-L1 expression level (negative/positive/not evaluable), smoking history (yes/no), and brain metastases (yes/no).

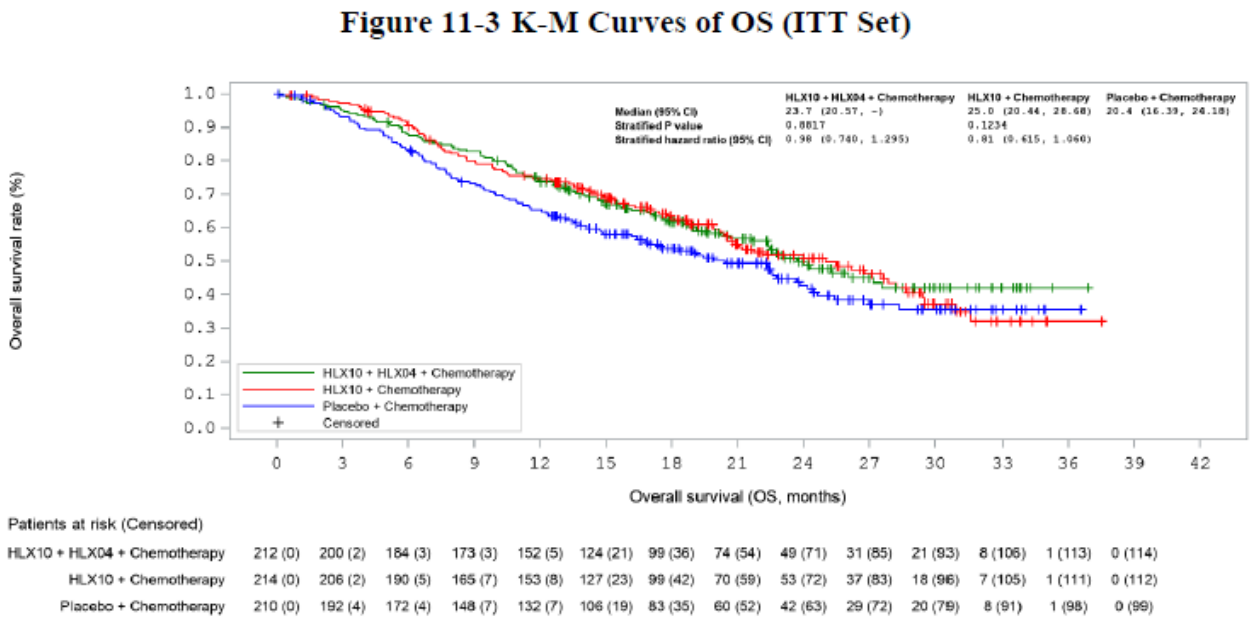
[3] HR and its 95% CI were estimated using the (stratified/unstratified) Cox proportional hazards model (Efron method).

[4] Kalbfleisch-Prentice method with log-log transformation was adopted.

[5] It was defined as the time from randomization to the last follow-up (survival follow-up) visit, calculated as: (Date of the last follow-up visit –Randomization date + 1)/30.4375.

[6] The Kaplan-Meier method was used to estimate the median follow-up time and its 95% CI (Brookmeyer-Crowley method based on log-log transformation).

Figure 18 K-M Curves of OS (ITT set), DCO 15-Jun-2023



Sensitivity analysis 1

At the primary analysis, 72 (34.3%) subjects in the placebo + chemotherapy group had received serplulimab in combination with HLX04 after PD. The deviation of OS efficacy evaluation in this group was adjusted using RPSFTM.

At data cut-off date, 15 June 2023, in the ITT set, the adjusted median OS of the placebo + chemotherapy group was 18.9 months (95% CI: 14.59, 24.48).

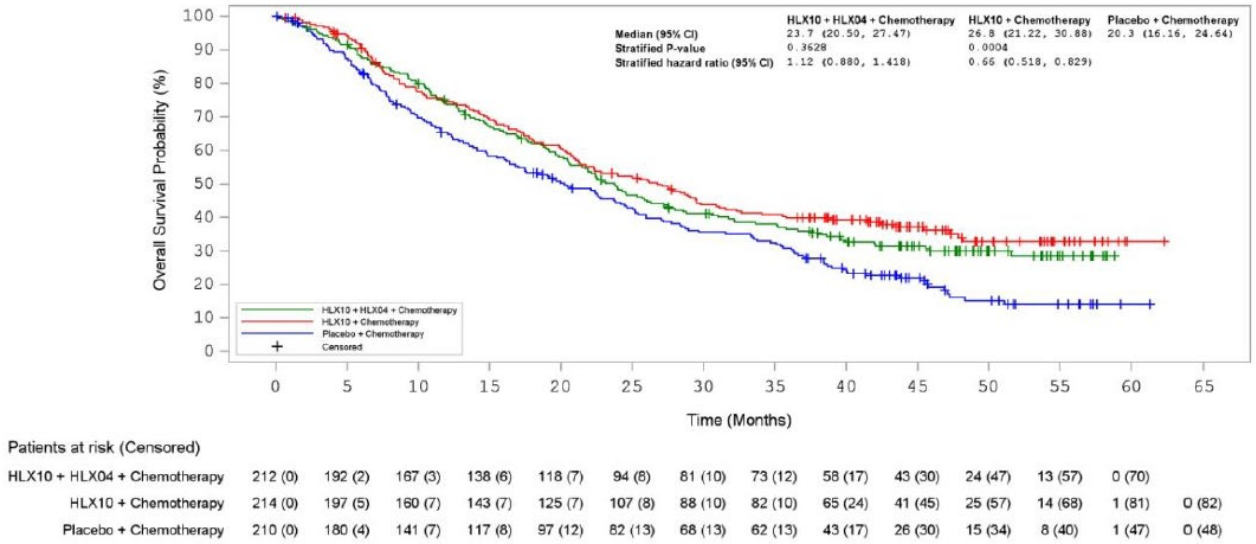
Updated OS analysis, DCO 7-Aug-2025

Table 26: Summary of OS (ITT set), DCO 07-Aug-2025

	HLX10 + HLX04 + Chemotherapy (N = 212)	HLX10 + Chemotherapy (N = 214)	Placebo + Chemotherapy (N = 210)	Total (N = 636)
Subject status, n (%)				
Death	142 (67.0)	132 (61.7)	162 (77.1)	436 (68.6)
Censored	70 (33.0)	82 (38.3)	48 (22.9)	200 (31.4)
Alive	57 (26.9)	71 (33.2)	36 (17.1)	164 (25.8)
Withdrawal of the Informed Consent	2 (0.9)	4 (1.9)	3 (1.4)	9 (1.4)
Lost to follow-up	11 (5.2)	7 (3.3)	9 (4.3)	27 (4.2)
Overall survival (OS, months)				
n	212	214	210	636
25% percentile	11.8	11.7	8.0	10.4
Median (95% CI)[1]	23.7 (20.50, 27.47)	26.8 (21.22, 30.88)	20.3 (16.16, 24.64)	22.8 (20.90, 25.69)
75% percentile	-	-	39.0	-
Stratified P-value[2]	0.3628	0.0004		
Stratified hazard ratio (95% CI)[3]	1.12 (0.880, 1.418)	0.66 (0.518, 0.829)		
Unstratified P-value[2]	0.3512	0.0005		
Unstratified hazard ratio (95% CI)[3]	1.12 (0.883, 1.420)	0.67 (0.529, 0.839)		
Overall survival rate and 95% CI (%)[4]				
6 months	88.1 (82.89, 91.79)	91.0 (86.23, 94.15)	83.5 (77.70, 87.92)	87.6 (84.72, 89.91)
12 months	73.7 (67.15, 79.12)	74.6 (68.06, 79.92)	65.3 (58.32, 71.37)	71.2 (67.49, 74.61)
18 months	62.0 (55.00, 68.19)	63.4 (56.47, 69.56)	53.3 (46.22, 59.91)	59.6 (55.64, 63.38)
24 months	48.7 (41.68, 55.30)	52.8 (45.74, 59.30)	44.5 (37.51, 51.24)	48.7 (44.66, 52.57)
36 months	36.5 (29.89, 43.10)	39.9 (33.14, 46.49)	30.9 (24.55, 37.42)	35.8 (31.98, 39.63)
48 months	30.0 (23.60, 36.54)	34.0 (27.00, 41.07)	16.2 (10.80, 22.53)	26.9 (23.17, 30.78)
60 months	- (-, -)	32.8 (25.74, 40.04)	14.0 (8.80, 20.39)	25.3 (21.47, 29.27)
Follow-up time[5]				
n	212	214	210	636
Mean (SD)	26.0583 (17.3729)	26.9569 (17.5502)	22.3966 (16.6967)	25.1516 (17.2987)
Median	22.4394	24.5092	18.3162	21.8316
Min – Max	0.0986 - 58.8419	0.1314 - 62.3244	0.0657 - 61.3060	0.0657 - 62.3244
Median follow-up time (95% CI)[6]	48.4 (45.86, 49.94)	45.4 (43.27, 49.05)	45.7 (43.56, 51.71)	47.0 (45.04, 49.05)

Note: The time from randomization to death from any cause. OS was calculated as follows: OS (months) = (Date of death – Randomization date + 1)/30.4375.
[1] The Kaplan-Meier method was used to estimate the median and 95% CI (Brookmeyer-Crowley method based on log-log transformation).
[2] The (stratified/unstratified) Log-Rank test was used to compare OS between two groups based on the stratification factors of PD-L1 expression level (negative/positive/not evaluable), smoking history (yes/no), and brain metastases (yes/no).
[3] HR and its 95% CI were estimated using the (stratified/unstratified) Cox proportional hazards model (Efron method).
[4] Kalbfleisch-Prentice method with log-log transformation was adopted.
[5] It was defined as the time from randomization to the last follow-up (survival follow-up) visit, calculated as: (Date of the last follow-up visit –Randomization date + 1)/30.4375.
[6] The Kaplan-Meier method was used to estimate the median follow-up time and its 95% CI (Brookmeyer-Crowley method based on log-log transformation).

Figure 19: K-M Curves of OS (ITT set), DCO 07-Aug-2025



Secondary efficacy endpoints

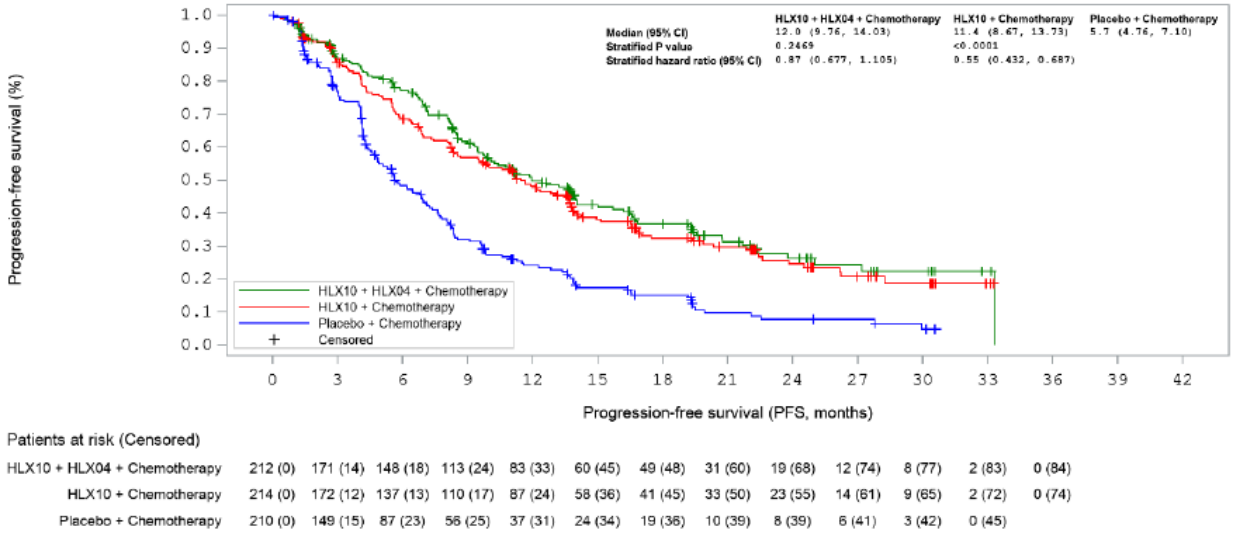
Table 27 Summary of PFS as Assessed by Investigator per RECIST v1.1 (ITT Set), DCO 15-Jun-2023

	HLX10 + HLX04 + Chemotherapy (N = 212)	HLX10 + Chemotherapy (N = 214)	Placebo + Chemotherapy (N = 210)
Subject status, n (%)			
Number of subjects with events	128 (60.4)	140 (65.4)	165 (78.6)
Progressive disease	96 (45.3)	121 (56.5)	143 (68.1)
Death without PD	32 (15.1)	19 (8.9)	22 (10.5)
Number of subjects with censors	84 (39.6)	74 (34.6)	45 (21.4)
No baseline tumor assessment	0	0	0
No post-baseline tumor assessment and no death	1 (0.5)	1 (0.5)	3 (1.4)
No post-baseline tumor assessment and death after the start of a new anti-tumor therapy	0	0	2 (1.0)
At least one post-baseline tumor assessment and no PD or death before the start of a new anti-tumor therapy	25 (11.8)	16 (7.5)	19 (9.0)
At least one post-baseline tumor assessment and no PD or death before the end of follow-up	58 (27.4)	57 (26.6)	21 (10.0)
Progression-free survival (PFS, month)			
n	212	214	210
25% percentile	6.7	5.1	3.1
Median (95% CI)[1]	12.0 (9.76, 14.03)	11.4 (8.67, 13.73)	5.7 (4.76, 7.10)
75% percentile	25.0	23.8	11.5
Stratified *P* value[2]	0.2469	< 0.0001	
Stratified hazard ratio (95% CI)[3]	0.87 (0.677, 1.105)	0.55 (0.432, 0.687)	
Unstratified *P* value[2]	0.3979	< 0.0001	
Unstratified hazard ratio (95% CI)[3]	0.90 (0.708, 1.146)	0.54 (0.426, 0.672)	
PFS rate and 95% CI (%)[4]			
6 months	77.0 (70.55, 82.28)	68.5 (61.63, 74.43)	48.3 (41.09, 55.21)
9 months	61.6 (54.38, 68.07)	56.8 (49.66, 63.35)	32.0 (25.38, 38.78)
12 months	49.8 (42.40, 56.70)	48.2 (41.06, 55.00)	24.1 (18.12, 30.65)
15 months	42.6 (35.19, 49.72)	38.1 (31.14, 45.07)	17.4 (12.12, 23.58)
18 months	36.7 (29.44, 44.02)	32.3 (25.47, 39.39)	15.2 (10.15, 21.19)

Note: RECIST = Response Evaluation Criteria in Solid Tumors. The time from randomization to the first documented PD or death from any cause, whichever occurred first. PFS was calculated as follows: PFS (months) = (min [Date of first documented PD, Date of death] – Randomization date + 1)/30.4375.
[1] The Kaplan-Meier method was used to estimate the median and 95% CI (Brookmeyer-Crowley method based on log-log transformation).
[2] The (stratified/unstratified) Log-Rank test was used to compare PFS between two groups based on the stratification factors of PD-L1 expression level (negative/positive/not evaluable), smoking history (yes/no), and brain metastases (yes/no).

[3] HR and its 95% CI were estimated using the (stratified/unstratified) COX proportional hazards model (Efron method).
[4] Kalbfleisch-Prentice method with log-log transformation was adopted.

Figure 20 K-M Curves of PFS Assessed by Investigator per RECIST v1.1 (ITT Set), DCO 15-Jun-2023



ORR

Table 28 - Summary of Confirmed ORR Assessed by IRRC per RECIST v1.1 (ITT Set), DCO 15-Jun-2023

	HLX10 + HLX04 + Chemotherapy (N = 212) n (%)	HLX10 + Chemotherapy (N = 214) n (%)	Placebo + Chemotherapy (N = 210) n (%)
Best overall response (BOR)			
Complete response (CR)	2 (0.9)	2 (0.9)	2 (1.0)
Partial response (PR)	114 (53.8)	111 (51.9)	56 (26.7)
Stable disease (SD)	68 (32.1)	72 (33.6)	94 (44.8)
Progressive disease (PD)	13 (6.1)	19 (8.9)	38 (18.1)
Not evaluable (NE)	15 (7.1)	10 (4.7)	20 (9.5)
Objective response rate (ORR)			
CR + PR	116 (54.7)	113 (52.8)	58 (27.6)
95% CI[1]	47.75, 61.55	45.88, 59.65	21.69, 34.19
Odds ratio (OR) (95% CI)	1.07 (0.73, 1.58)	2.84 (1.90, 4.23)	
Stratified *P* value[2]	0.7139	< 0.0001	
Unstratified rate difference (95% CI)	1.91 (−7.55, 11.38)	25.18 (16.17, 34.20)	
Unstratified *P* value[3]	0.6921	< 0.0001	

Note: RECIST = Response Evaluation Criteria in Solid Tumors
Note: Objective response rate (ORR): the proportion of subjects with the Best overall response of Complete response (CR) or Partial response (PR). Confirmed complete response (CR) or partial response (PR) must be re-assessed at least 4 weeks later for confirmation.
[1] 95% CI in an individual treatment group was calculated using the Clopper-Pearson method.
[2] The stratified Cochran-Mantel-Haenszel (CMH) method was used to test the inter-group difference in ORR and estimate the odds ratio and its 95% CI. Stratification factors: PD-L1 expression level (negative/positive/not evaluable), smoking history (yes/no), and brain metastases (yes/no).
[3] The chi-square test was used to test the inter-group difference in ORR and estimate the odds ratio and its 95% CI.

Table 29: Summary of Confirmed ORR Assessed by IRRC per RECIST v1.1 (ITT Set), DCO 07-Aug-2025

	HLX10 + HLX04 + Chemotherapy (N = 212) n (%)	HLX10 + Chemotherapy (N = 214) n (%)	Placebo + Chemotherapy (N = 210) n (%)	Total (N = 636) n (%)
Best overall response (BOR)				
Complete response (CR)	5 (2.4)	2 (0.9)	2 (1.0)	9 (1.4)
Partial response (PR)	110 (51.9)	111 (51.9)	56 (26.7)	277 (43.6)
Stable disease (SD)	69 (32.5)	72 (33.6)	95 (45.2)	236 (37.1)
Progressive disease (PD)	13 (6.1)	19 (8.9)	37 (17.6)	69 (10.8)
Not evaluable (NE)	15 (7.1)	10 (4.7)	20 (9.5)	45 (7.1)
Objective response rate (ORR)				
CR + PR	115 (54.2)	113 (52.8)	58 (27.6)	286 (45.0)
95% CI[1]	47.28, 61.09	45.88, 59.65	21.69, 34.19	41.05, 48.93
Odds ratio (OR) (95% CI)	1.05 (0.72, 1.55)	2.85 (1.91, 4.26)		
Stratified *P* value[2]	0.7881	< 0.0001		
Unstratified rate difference (95% CI)	1.44 (-8.03, 10.91)	25.18 (16.17, 34.20)		
Unstratified *P* value[3]	0.7655	< 0.0001		

Note: RECIST = Response Evaluation Criteria in Solid Tumors.
Note: Objective response rate (ORR): the proportion of subjects with the Best overall response of Complete response (CR) or Partial response (PR). Confirmed complete response (CR) or partial response (PR) must be re-assessed at least 4 weeks later for confirmation.
[1] 95% CI in an individual treatment group was calculated using the Clopper-Pearson method.
[2] The stratified Cochran-Mantel-Haenszel (CMH) method was used to test the inter-group difference in ORR and estimate the odds ratio and its 95% CI. Stratification factors: PD-L1 expression level (negative/positive/not evaluable), smoking history (yes/no), and brain metastases (yes/no).
[3] The chi-square test was used to test the inter-group difference in ORR and estimate the odds ratio and its 95% CI.

DOR

At data cut-off date, June 15, 2023, in the ITT set, there were 56, 57, and 42 subjects with DOR events in the HLX10 + HLX04 + chemotherapy group, the HLX10 + chemotherapy group, and the placebo + chemotherapy group, respectively The confirmed median DOR was 18.3 months (95% CI: 11.17, 29.14), 15.4 months (95% CI: 11.04, 21.16), and 9.7 months (95% CI: 5.52, 13.93) in the three treatment groups, respectively.

At the data cut-off date of Aug 7, 2025, in the ITT set, there were 115, 113, and 58 subjects achieving confirmed CR or PR as assessed by IRRC according to RECIST v1.1 in the HLX10 + HLX04 + chemotherapy group, the HLX10 + chemotherapy group, and the placebo + chemotherapy group. There were 77, 68 and 48 patients with DOR events in the respective groups. The confirmed median DOR was 16.0 months (95% CI: 11.17, 19.45), 15.4 months (95% CI: 11.07, 23.72), and 8.3 months (95% CI: 5.45, 12.52) in the three treatment groups.

Analyses of quality of life

Quality of life data using the EuroQol 5 Dimension 5 Level Questionnaire (EQ-5D-5L), the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30); and the EORTC Quality of Life 13-item lung cancer-specific questionnaire module (EORTC QLQ-LC13) was also provided as a secondary endpoint.

Ancillary analyses

Subgroup analysis primary efficacy endpoint

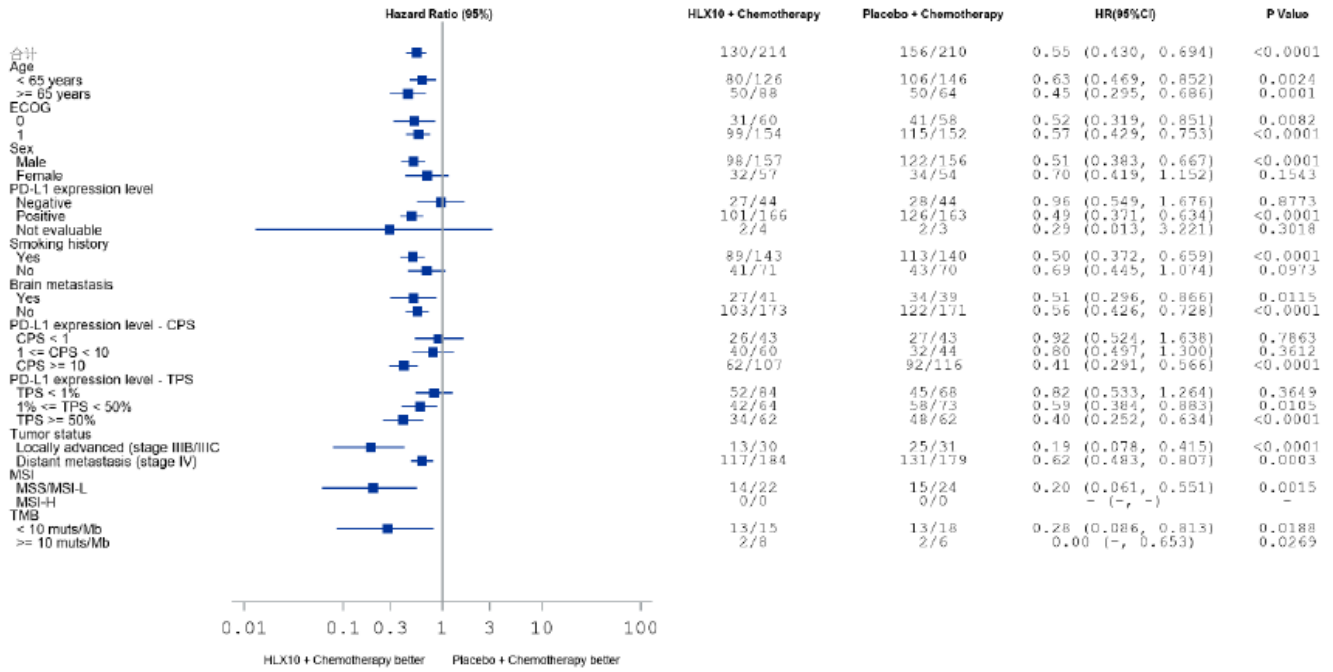
HLX10 + Chemotherapy Group vs. Placebo + Chemotherapy Group

Table 30 Subgroup Analysis of PFS Assessed by IRRC per RECIST v1.1 (HLX10 + Chemotherapy Group vs. Placebo + Chemotherapy Group) (ITT Set), DCO 15-Jun-2023

	HLX10 + Chemotherapy (N = 214)				Placebo + Chemotherapy (N = 210)				Stratified hazard ratio (HR)[2]	
Subgroup	n	Number of events	Median (months)[1]	95% CI	n	Number of events	Median (months)[1]	95% CI	(95% CI)	*P* Value
Age										
< 65 years	126	80	8.5	(7.06, 11.10)	146	106	5.6	(4.24, 6.87)	0.63 (0.469, 0.852)	0.0024
≥ 65 years	88	50	12.7	(9.59, 19.61)	64	50	5.8	(4.37, 7.62)	0.45 (0.295, 0.686)	0.0001
ECOG										
0	60	31	12.7	(9.00, -)	58	41	6.2	(4.76, 9.63)	0.52 (0.319, 0.851)	0.0082
1	154	99	9.6	(7.10, 11.43)	152	115	5.6	(4.21, 6.87)	0.57 (0.429, 0.753)	< 0.0001
Sex										
Male	157	98	9.0	(7.10, 11.66)	156	122	4.9	(4.21, 6.18)	0.51 (0.383, 0.667)	< 0.0001
Female	57	32	11.1	(9.59, 20.34)	54	34	8.3	(5.59, 13.67)	0.70 (0.419, 1.152)	0.1543
PD-L1 expression level										
Negative	44	27	11.4	(4.07, 19.61)	44	28	7.0	(4.17, 16.39)	0.96 (0.549, 1.676)	0.8773
Positive	166	101	10.4	(8.28, 12.12)	163	126	5.6	(4.37, 6.80)	0.49 (0.371, 0.634)	< 0.0001
Not evaluable	4	2	-	(-, -)	3	2	-	(-, -)	- (-, -)	-
Smoking history										
Yes	143	89	10.4	(8.08, 12.71)	140	113	4.9	(4.17, 5.78)	0.50 (0.372, 0.659)	< 0.0001
No	71	41	11.1	(8.28, 16.56)	70	43	8.1	(5.59, 11.50)	0.69 (0.445, 1.074)	0.0973
Brain metastasis										
Yes	41	27	8.1	(6.41, 11.04)	39	34	4.1	(2.99, 5.68)	0.51 (0.296, 0.866)	0.0115
No	173	103	11.2	(9.00, 15.08)	171	122	6.2	(5.03, 7.06)	0.56 (0.426, 0.728)	< 0.0001
CPS										
CPS < 1	43	26	12.7	(4.30, 19.61)	43	27	7.0	(4.37, 16.39)	0.92 (0.524, 1.638)	0.7863
1 ≤ CPS < 10	60	40	7.1	(5.49, 9.59)	44	32	6.2	(4.83, 8.08)	0.80 (0.497, 1.300)	0.3612
CPS ≥ 10	107	62	11.2	(9.72, 18.40)	116	92	5.4	(4.21, 6.70)	0.41 (0.291, 0.566)	< 0.0001
TPS										
TPS < 1%	84	52	8.5	(5.55, 13.90)	68	45	6.2	(4.60, 9.76)	0.82 (0.533, 1.264)	0.3649
1% ≤ TPS < 50%	64	42	10.3	(8.08, 15.54)	73	58	6.8	(4.90, 8.08)	0.59 (0.384, 0.883)	0.0105
TPS ≥ 50%	62	34	12.1	(9.49, -)	62	48	4.4	(3.98, 5.78)	0.40 (0.252, 0.634)	< 0.0001
Tumor status										
Locally advanced (stage IIIB/IIIC)	30	13	20.3	(8.54, -)	31	25	5.6	(4.01, 6.64)	0.19 (0.078, 0.415)	< 0.0001
Distant metastasis (stage IV)	184	117	10.3	(8.21, 11.43)	179	131	5.6	(4.60, 7.06)	0.62 (0.483, 0.807)	0.0003
MSI										
MSS/MSI-L	22	14	18.2	(6.97, 23.82)	24	15	4.6	(2.10, 9.56)	0.20 (0.061, 0.551)	0.0015
MSI-H	0	0	-	(-, -)	0	0	-	(-, -)	- (-, -)	-
TMB										
< 10 muts/Mb	15	13	12.1	(5.42, 22.34)	18	13	4.6	(2.10, 6.80)	0.28 (0.086, 0.813)	0.0188
≥ 10 muts/Mb	8	2	-	(15.54, -)	6	2	9.6	(1.41, -)	0.00 (-, 0.653)	0.0269

[1] Median was Product-Limit (Kaplan-Meier) estimates, n = Number of subjects in each subgroup category
[2] The hazard ratio and its 95% CI were estimated by (unstratified) Cox proportional hazards model. Efron's method was used to handle ties.

Figure 21 Forest Plot of Subgroup Analysis of IRRC-assessed PFS (HLX10 + Chemotherapy Group vs. Placebo + Chemotherapy Group) (ITT Set), DCO 15-Jun-2023



Note: RECIST = Response Evaluation Criteria in Solid Tumors
[1] HR and its 95%confidence interval (CI) were estimated using the stratified Cox proportional hazards model (Efron method).

Subgroup analysis key secondary endpoint

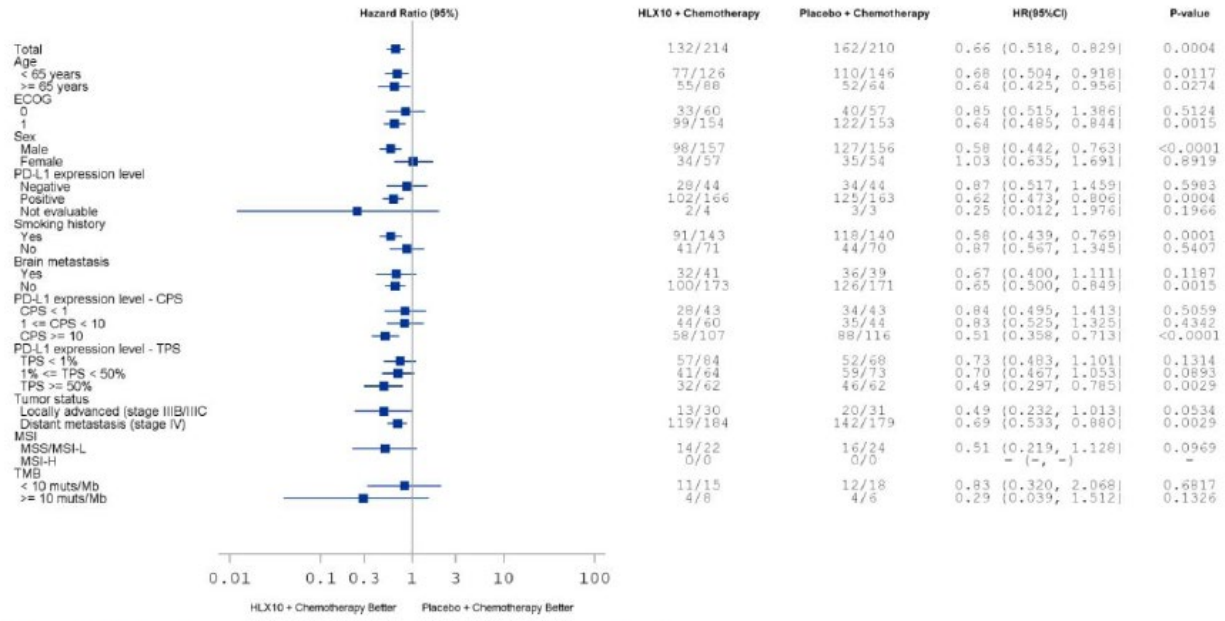
Updated subgroup analysis key secondary efficacy endpoint

Table 31: Subgroup analysis of OS (HLX10+chemotherapy group vs placebo + chemotherapy group, ITT set, DCO 07-Aug-2025)

	HLX10 + Chemotherapy (N = 214)				Placebo + Chemotherapy (N = 210)					
Subgroup	n	Events	Median (months)[1]	95% CI	n	Events	Median (months)[1]	95% CI	Stratified hazard ratio (HR)[2](95% CI)	P-value
Age										
< 65 years	126	77	27.6	(20.90, 32.66)	146	110	20.3	(14.82, 25.43)	0.68 (0.504, 0.918)	0.0117
≥ 65 years	88	55	24.0	(20.17, 41.43)	64	52	20.4	(12.39, 25.99)	0.64 (0.425, 0.956)	0.0274
ECOG										
0	60	33	27.6	(19.88, -)	57	40	28.9	(24.64, 38.41)	0.85 (0.515, 1.386)	0.5124
1	154	99	26.2	(20.70, 30.88)	153	122	16.4	(12.85, 20.44)	0.64 (0.485, 0.844)	0.0015
Sex										
Male	157	98	24.0	(20.17, 31.54)	156	127	16.4	(12.85, 22.41)	0.58 (0.442, 0.763)	< 0.0001
Female	57	34	28.2	(20.70, -)	54	35	33.3	(20.44, 47.11)	1.03 (0.635, 1.691)	0.8919
PD-L1 expression level										
Negative	44	28	22.3	(12.71, 32.66)	44	34	19.9	(11.50, 25.99)	0.87 (0.517, 1.459)	0.5983
Positive	166	102	27.5	(21.26, 34.10)	163	125	20.8	(16.00, 25.43)	0.62 (0.473, 0.806)	0.0004
Not evaluable	4	2	-	(-, -)	3	3	-	(-, -)	- (-, -)	-
Smoking history										
Yes	143	91	26.1	(20.90, 31.54)	140	118	16.2	(12.39, 19.94)	0.58 (0.439, 0.769)	0.0001
No	71	41	27.6	(18.73, -)	70	44	33.3	(23.69, 45.17)	0.87 (0.567, 1.345)	0.5407
Brain metastasis										
Yes	41	32	21.7	(13.86, 29.50)	39	36	13.2	(8.80, 22.54)	0.67 (0.400, 1.111)	0.1187
No	173	100	28.4	(21.26, 35.81)	171	126	22.4	(16.79, 27.17)	0.65 (0.500, 0.849)	0.0015
CPS										
CPS < 1	43	28	22.3	(12.71, 32.66)	43	34	19.1	(11.50, 25.99)	0.84 (0.495, 1.413)	0.5059
1 ≤ CPS < 10	60	44	20.5	(11.70, 27.50)	44	35	20.4	(11.60, 33.45)	0.83 (0.525, 1.325)	0.4342
CPS ≥ 10	107	58	31.5	(26.09, 48.20)	116	88	22.4	(14.85, 27.01)	0.51 (0.358, 0.713)	< 0.0001
TPS										
TPS < 1%	84	57	21.2	(15.41, 29.50)	68	52	18.3	(11.50, 23.69)	0.73 (0.483, 1.101)	0.1314
1% ≤ TPS < 50%	64	41	25.5	(17.38, 29.50)	73	59	20.3	(14.85, 33.77)	0.70 (0.467, 1.053)	0.0893
TPS ≥ 50%	62	32	45.4	(26.09, -)	62	46	23.8	(13.17, 36.30)	0.49 (0.297, 0.785)	0.0029
Tumor status										
Locally advanced (stage IIIB/IIIC)	30	13	-	(18.76, -)	31	20	34.7	(9.43, 41.36)	0.49 (0.232, 1.013)	0.0534
Distant metastasis (stage IV)	184	119	25.5	(20.76, 29.50)	179	142	19.2	(14.82, 24.18)	0.69 (0.533, 0.880)	0.0029
MSI										
MSS/MSI-L	22	14	29.5	(25.49, -)	24	16	25.4	(22.41, 38.41)	0.51 (0.219, 1.128)	0.0969
MSI-H	0	0	-	(-, -)	0	0	-	(-, -)	- (-, -)	-
TMB										
< 10 muts/Mb	15	11	27.6	(18.73, 30.88)	18	12	27.8	(7.69, 40.05)	0.83 (0.320, 2.068)	0.6817
≥ 10 muts/Mb	8	4	46.4	(24.02, -)	6	4	24.0	(9.72, -)	0.29 (0.039, 1.512)	0.1326

[1] The Kaplan-Meier method was used to estimate the median and 95% CI (Brookmeyer-Crowley method based on log-log transformation).
[2] HR and its 95% CI were estimated using the stratified Cox proportional hazards model (Efron method).

Figure 22: Forest Plot of Subgroup Analysis of OS (HLX10+chemotherapy group vs placebo + chemotherapy group), ITT Set, DCO 07-Aug-2025.



Note: RECIST = Response Evaluation Criteria in Solid Tumors
1] HR and its 95% confidence interval (CI) were estimated using the stratified COX proportional hazards model Efron method).

Subgroup analyses for primary and key secondary efficacy endpoints based on PD-L1 levels (DCO 07-Aug-2025)

Table 32: PFS Assessed by the IRRC and investigator (INV) per RECIST v1.1 – PD-L1 TPS Subgroup Analysis (HLX10 plus Chemotherapy vs. Placebo plus Chemotherapy), DCO 07-Aug-2025

	PD-L1 subgroups (TPS)	Treatment	Patients number	Interim analysis (DCO: 15 JUN 2023)			Final analysis (DCO: 07 AUG 2025)		
				mPFS (months)	Unstratified HR (95% CI)	P value	mPFS (months)	Unstratified HR (95% CI)	P value
IRRC	TPS<1%	HLX10+Chem	84	8.5 (5.55, 13.90)	0.75 (0.504, 1.127)	0.1635	8.5 (5.55, 13.90)	0.73 (0.501, 1.068)	0.1019
		Placebo+Chem	68	6.2 (4.60, 9.76)			6.8 (4.60, 9.76)		
	TPS≥1%	HLX10+Chem	126	11.1 (9.00, 15.08)	0.46 (0.342, 0.621)	<0.0001	11.1 (9.00, 15.54)	0.45 (0.338, 0.602)	<0.0001
		Placebo+Chem	135	5.6 (4.27, 6.87)			5.6 (4.37, 7.06)		
	1%≤TPS<50%	HLX10+Chem	64	10.3 (8.08, 15.54)	0.59 (0.390, 0.872)	0.0082	10.3 (8.08, 15.54)	0.61 (0.414, 0.898)	0.0118
		Placebo+Chem	73	6.8 (4.90, 8.08)			6.9 (5.09, 8.41)		
	TPS <50%	HLX10+Chem	148	9.2 (8.08, 11.43)	0.67 (0.506, 0.888)	0.0051	9.2 (8.08, 11.43)	0.67 (0.516, 0.882)	0.0038
		Placebo+Chem	141	6.6 (5.09, 7.62)			6.8 (5.52, 7.92)		
	TPS ≥50%	HLX10+Chem	62	12.1 (9.49, -)	0.36 (0.227, 0.558)	<0.0001	12.1 (9.49, 45.44)	0.33 (0.210, 0.510)	<0.0001
		Placebo+Chem	62	4.4 (3.98, 5.78)			4.4 (3.98, 5.78)		
INV	TPS<1%	HLX10+Chem	84	8.3 (5.49, 13.08)	0.70 (0.477, 1.018)	0.0586	8.3 (5.49, 11.89)	0.76(0.531, 1.090)	0.1306
		Placebo+Chem	68	5.7 (4.17, 7.66)			5.7 (4.17, 7.66)		
	TPS≥1%	HLX10+Chem	126	13.6 (10.58, 14.95)	0.47 (0.347, 0.626)	<0.0001	13.6 (10.58, 16.53)	0.47 (0.353, 0.619)	<0.0001
		Placebo+Chem	135	5.8 (4.83, 7.62)			6.4 (4.86, 7.72)		
	1%≤TPS<50%	HLX10+Chem	64	11.1 (6.87, 13.86)	0.62 (0.417, 0.921)	0.0177	11.1 (6.87, 14.03)	0.63 (0.432, 0.919)	0.0159
		Placebo+Chem	73	7.1 (5.32, 9.10)			7.3 (5.32, 9.59)		
	TPS <50%	HLX10+Chem	148	9.9 (6.87, 12.85)	0.66 (0.504, 0.868)	0.0027	9.9 (6.87, 12.19)	0.70 (0.544, 0.911)	0.0073
		Placebo+Chem	141	6.8 (5.29, 7.72)			6.9 (5.29, 7.79)		
	TPS ≥50%	HLX10+Chem	62	14.0 (11.10, 17.48)	0.35 (0.227, 0.549)	<0.0001	14.9 (11.10, 22.60)	0.34 (0.220, 0.516)	<0.0001
		Placebo+Chem	62	4.9 (4.11, 6.90)			4.9 (4.11, 6.90)		

Table 33 IRRC assessed PFS by PD-L1 expression (data cut-off date: 07 August 2025)

	Arm B (Serplulimab + carboplatin + pemetrexed)		**Arm C (Placebo + carboplatin + pemetrexed)**		
PD-L1 expression	Events /N (%)	Median (months, 95% CI)	Events /N (%)	Median (months, 95% CI)	Stratified hazard ratio (95% CI)

	Arm B (Serplulimab + carboplatin + pemetrexed)		Arm C (Placebo + carboplatin + pemetrexed)		
TPS < 1%	59/84 (70.2%)	8.5 (5.6, 13.9)	51/68 (75.0%)	6.8 (4.6, 9.8)	0.83 (0.55, 1.26)
1% ≤ TPS < 50%	45/64 (70.3%)	10.3 (8.1, 15.5)	62/73 (84.9%)	6.9 (5.1, 8.4)	0.63 (0.43, 0.94)
TPS ≥ 50%	37/62 (59.7%)	12.1 (9.5, 45.4)	51/62 (82.3%)	4.4 (4.0, 5.8)	0.36 (0.23, 0.57)

Table 34: Overall Survival (OS) - PD-L1 TPS Subgroup Analysis (HLX10 plus Chemotherapy vs. Placebo plus Chemotherapy), DCO 07-Aug-2025

PD-L1 subgroups (TPS)	Treatment	Patients number	Interim analysis (DCO: 15 JUN 2023)			Final analysis (DCO: 07 AUG 2025)		
			mOS (months)	Unstratified HR (95% CI)	P value	mOS (months)	Unstratified HR (95% CI)	P value
TPS<1%	HLX10+Chem	84	20.2 (15.41, 29.50)	0.83 (0.541, 1.280)	0.3953	21.2 (15.41, 29.50)	0.76 (0.522, 1.112)	0.1540
	Placebo+Chem	68	19.1 (11.50, 22.77)			18.3 (11.50, 23.69)		
TPS≥1%	HLX10+Chem	126	26.2 (21.06, 31.54)	0.80 (0.561, 1.146)	0.2275	28.9 (22.34, 45.44)	0.61 (0.454, 0.826)	0.0013
	Placebo+Chem	135	23.8 (16.79, -)			22.5 (16.79, 31.54)		
1%≤TPS<50%	HLX10+Chem	64	24.0 (18.73, 28.25)	1.05 (0.643, 1.698)	0.8550	25.5 (17.38, 29.50)	0.72 (0.481, 1.072)	0.1078
	Placebo+Chem	73	24.2 (14.85, -)			20.3 (14.85, 33.77)		
TPS <50%	HLX10+Chem	148	21.2 (18.00, 28.25)	0.94 (0.683, 1.298)	0.7130	22.3 (17.81, 28.68)	0.76 (0.575, 0.991)	0.0423
	Placebo+Chem	141	19.9 (14.85, 24.48)			19.6 (14.85, 24.64)		
TPS ≥50%	HLX10+Chem	62	27.6 (20.76, -)	0.61 (0.354, 1.029)	0.0629	45.4 (26.09, -)	0.54 (0.338, 0.839)	0.0061
	Placebo+Chem	62	22.5 (13.17, -)			23.8 (13.17, 36.30)		

Table 35: Progression-Free Survival (PFS) Assessed by the IRRC and investigator(INV) per RECIST v1.1 – PD-L1 CPS Subgroup Analysis (HLX10 plus Chemotherapy vs. Placebo plus Chemotherapy), DCO 07-Aug-2025

	PD-L1 subgroups (CPS)	Treatment	Patients number	Interim analysis (DCO: 15 JUN 2023)			Final analysis (DCO: 07 AUG 2025)		
				mPFS (months)	Unstratified HR (95% CI)	P value	mPFS (months)	Unstratified HR (95% CI)	P value
IRRC	**CPS<1**	HLX10+Chem	43	12.7 (4.30, 19.61)	0.82 (0.472, 1.410)	0.4595	12.7 (4.30, 19.61)	0.84 (0.512, 1.391)	0.5008
		Placebo+Chem	43	7.0 (4.37, 16.39)			7.6 (4.37, 16.39)		
	CPS≥1	HLX10+Chem	167	10.4 (8.28, 11.66)	0.50 (0.383, 0.651)	<0.0001	10.4 (8.28, 12.12)	0.48 (0.374, 0.626)	<0.0001
		Placebo+Chem	160	5.6 (4.76, 6.80)			5.6 (4.83, 6.87)		
	1≤CPS<10	HLX10+Chem	60	7.1 (5.49, 9.59)	0.80 (0.504, 1.287)	0.3536	7.1 (5.49, 9.59)	0.80 (0.507, 1.255)	0.3197
		Placebo+Chem	44	6.2 (4.83, 8.08)			6.2 (4.83, 8.08)		
	CPS <10	HLX10+Chem	103	8.4 (5.68, 11.10)	0.81 (0.568, 1.150)	0.2313	8.4 (5.68, 11.10)	0.80 (0.576, 1.118)	0.1897
		Placebo+Chem	87	6.8 (4.83, 8.08)			6.8 (4.90, 9.56)		
	CPS ≥10	HLX10+Chem	107	11.2 (9.72, 18.40)	0.40 (0.285, 0.552)	<0.0001	11.2 (9.72, 20.34)	0.39 (0.283, 0.539)	<0.0001
		Placebo+Chem	116	5.4 (4.21, 6.70)			5.5 (4.21, 6.80)		
INV	**CPS<1**	HLX10+Chem	43	9.9 (4.07, 16.92)	0.76 (0.459, 1.262)	0.2871	8.3 (4.07, 16.36)	0.84 (0.525, 1.352)	0.4736
		Placebo+Chem	43	5.9 (4.37, 8.34)			5.9 (4.37, 8.38)		
	CPS≥1	HLX10+Chem	167	11.7 (9.49, 13.80)	0.50 (0.386, 0.650)	<0.0001	11.9 (9.49, 13.86)	0.51 (0.400, 0.657)	<0.0001
		Placebo+Chem	160	5.6 (4.76, 7.13)			5.6 (4.76, 7.26)		
	1≤CPS<10	HLX10+Chem	60	6.9 (5.59, 11.10)	0.74 (0.469, 1.162)	0.1805	6.9 (5.59, 11.10)	0.82 (0.536, 1.271)	0.3683
		Placebo+Chem	44	6.2 (4.83, 7.66)			6.2 (4.83, 7.79)		
	CPS <10	HLX10+Chem	103	6.9 (5.65, 11.43)	0.75 (0.538, 1.050)	0.0902	6.9 (5.65, 11.10)	0.83 (0.610, 1.146)	0.2594
		Placebo+Chem	87	6.2 (4.83, 7.66)			6.2 (4.83, 7.79)		
	CPS ≥10	HLX10+Chem	107	13.8 (11.20, 17.48)	0.40 (0.290, 0.557)	<0.0001	13.9 (11.20, 19.52)	0.40 (0.290, 0.544)	<0.0001
		Placebo+Chem	116	5.5 (4.24, 7.62)			5.5 (4.24, 7.62)		

Table 36: Overall Survival (OS) - PD-L1 CPS Subgroup Analysis (HLX10 plus Chemotherapy vs. Placebo plus Chemotherapy), DCO 07-Aug-2025

PD-L1 subgroups (CPS)	Treatment	Patients number	Interim analysis (DCO: 15 JUN 2023)			Final analysis (DCO: 07 AUG 2025)		
			mOS (months)	Unstratified HR (95% CI)	P value	mOS (months)	Unstratified HR (95% CI)	P value
CPS<1	HLX10+Chem	43	18.1 (12.71, -)	0.89 (0.494, 1.575)	0.6776	22.3 (12.71, 32.66)	0.77 (0.460, 1.264)	0.2983
	Placebo+Chem	43	19.9 (11.50, 24.64)			19.1 (11.50, 25.99)		
CPS≥1	HLX10+Chem	167	25.0 (20.70, 28.25)	0.82 (0.597, 1.113)	0.1975	27.5 (21.26, 34.10)	0.66 (0.506, 0.856)	0.0017
	Placebo+Chem	160	22.4 (16.16, 27.01)			22.1 (16.16, 27.01)		
1≤CPS<10	HLX10+Chem	60	20.2 (11.70, 27.86)	1.14 (0.668, 1.999)	0.6303	20.5 (11.70, 27.50)	0.88 (0.567, 1.385)	0.5835
	Placebo+Chem	44	20.4 (11.60, -)			20.4 (11.60, 33.45)		
CPS <10	HLX10+Chem	103	18.1 (14.23, 28.68)	1.02 (0.691, 1.512)	0.9217	20.9 (14.23, 27.50)	0.83 (0.599, 1.162)	0.2820
	Placebo+Chem	87	19.9 (13.83, 24.64)			19.9 (13.83, 25.99)		
CPS ≥10	HLX10+Chem	107	26.8 (21.75, -)	0.67 (0.448, 0.979)	0.0388	31.5 (26.09, 48.20)	0.55 (0.393, 0.764)	0.0003
	Placebo+Chem	116	22.5 (14.85, 27.01)			22.4 (14.85, 27.01)		

Summary of main study(ies)

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 37 Summary of Efficacy for trial: HLX10-002-NSCLC301, DCO 15-Jun-2023

Title: A Three Arm, Randomized, Double-blind, Multicenter, Phase III Clinical Study to Evaluate HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Pemetrexed) Versus HLX10 + HLX04 (Recombinant Humanized Anti-VEGF Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Pemetrexed) Versus Chemotherapy (Carboplatin-Pemetrexed) as First-line Therapy for Advanced Non-squamous Non-small Cell Lung Cancer (NSCLC)		
Study identifier	NCT03952403	
Design	It's a three arm, randomized, double-blind, multicenter, phase III clinical study to compare the clinical efficacy, safety, and tolerability of HLX10 (recombinant humanized anti-PD-1 monoclonal antibody injection) in combination with chemotherapy versus HLX10 + HLX04 (recombinant humanized anti-VEGF monoclonal antibody injection) in combination with chemotherapy versus chemotherapy in patients with previously untreated non-squamous NSCLC.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	November 25, 2019-present November 25, 2019- March 5, 2020 Not applicable
Hypothesis	Superiority	
Treatments groups	HLX10+HLX04 + chemotherapy group	HLX10 + HLX04 + chemotherapy (carboplatin-pemetrexed) N = 212 Subjects received the study drugs every 3 weeks until loss of clinical benefit, death, intolerable toxicity, withdrawal of informed consent, or other reasons specified in the protocol (whichever occurred first).
	HLX10 + chemotherapy group	HLX10 + HLX04 placebo + chemotherapy (carboplatin-pemetrexed) N = 214 Subjects received the study drugs every 3 weeks until loss of clinical benefit, death, intolerable toxicity, withdrawal of informed consent, or other reasons specified in the protocol (whichever occurred first).
	Placebo + chemotherapy group	HLX10 placebo +HLX04 placebo + chemotherapy (carboplatin-pemetrexed) N = 210 Subjects received the study drugs every 3 weeks until loss of clinical benefit, death, intolerable toxicity, withdrawal of informed consent, or other reasons specified in the protocol (whichever occurred first).

Endpoints and definitions	Primary endpoint	PFS by IRRC	PFS assessed by IRRC per RECIST v1.1
	Key secondary endpoint	OS	Defined as the time from randomization to death by any cause.
	Other secondary endpoint	PFS by Investigator	PFS assessed by Investigator per RECIST v1.1
	Other secondary endpoint	Confirmed ORR	Confirmed ORR assessed by IRRC and Investigator per RECIST v1.1
	Other secondary endpoint	Confirmed DOR	Confirmed DOR assessed by IRRC and Investigator per RECIST v1.1
Database lock	August 1, 2023		
Results and Analysis			
Analysis description	**Interim Analysis**		
Analysis population and time point description	Intent-to-treat set: Defined as the primary analysis population for efficacy analysis in the study.		
Descriptive statistics and estimate variability	Treatment group	HLX10 + chemotherapy group	Placebo + chemotherapy group
	Number of subjects	214	210
	PFS by IRRC (Median)	11.0	5.6
	95% confidence interval	8.44, 12.71	4.76, 6.80
	OS (Median)	25.0	20.4
	95% confidence interval	20.44, 28.68	16.39, 24.18
	Adjusted OS using RPSFTM method (Median)	-	18.9
	95% confidence interval	-	14.59, 24.48
	PFS by Investigator (Median)	11.4	5.7
	95% confidence interval	8.67, 13.73	4.76, 7.10
	Confirmed ORR by IRRC	52.8%	27.6%
	95% confidence interval (%)	45.88%, 59.65%	21.69%, 34.19%
	Confirmed ORR by Investigator	52.3%	28.6%
	95% confidence interval (%)	45.42%, 59.19%	22.57%, 35.19%
	Confirmed DOR by IRRC (Median)	15.4	9.7
	95% confidence interval (%)	11.04, 21.16	5.52, 13.93
	Confirmed DOR by Investigator (Median)	15.2	10.9
	95% confidence interval (%)	11.20, 21.16	5.78, 12.45
Effect estimates per comparison	PFS by IRRC	Comparison groups	HLX10 + chemotherapy group vs. placebo + chemotherapy group

		Stratified Hazard Ratio	0.55
		95% confidence interval	0.430, 0.694
		Stratified P-value	< 0.0001
	OS	Comparison groups	HLX10 + chemotherapy group vs. placebo + chemotherapy group
		Stratified Hazard Ratio	0.81
		95% confidence interval	0.615, 1.060
		Stratified P-value	0.1234
	Adjusted OS using RPSFTM method	Comparison groups	HLX10 + chemotherapy group vs. placebo + chemotherapy group
		Stratified Hazard Ratio	0.68
		95% confidence interval	0.511, 0.913
		Stratified P-value	0.0097
	PFS by Investigator	Comparison groups	HLX10 + chemotherapy group vs. placebo + chemotherapy group
		Stratified Hazard Ratio	0.55
		95% confidence interval	0.432, 0.687
		Stratified P-value	< 0.0001
	Confirmed ORR by IRRC	Comparison groups	HLX10 + chemotherapy group vs. placebo + chemotherapy group
		Odds ratio	2.84
		95% confidence interval	1.90, 4.23
		Stratified P-value	< 0.0001
	Confirmed ORR by Investigator	Comparison groups	HLX10 + chemotherapy group vs. placebo + chemotherapy group
		Odds ratio	2.75
		95% confidence interval	1.84, 4.11
		Stratified P-value	<0.0001
	Confirmed DOR by IRRC	Comparison groups	HLX10 + chemotherapy group vs. placebo + chemotherapy group
		Stratified Hazard Ratio	0.57
		95% confidence interval	0.372, 0.881
		Stratified P-value	0.0096
	Confirmed DOR by Investigator	Comparison groups	HLX10 + chemotherapy group vs. placebo + chemotherapy group
		Stratified Hazard Ratio	0.57
		95% confidence interval	0.377, 0.869
		Stratified P-value	0.0075

2.4.3. Discussion on clinical efficacy

The current application is based on pivotal trial HLX10-002-NSCLC301 and the originally proposed indication was in combination with chemotherapy (carboplatin-pemetrexed) as first-line treatment of adult patients with locally advanced or metastatic nonsquamous NSCLC without EGFR or ALK positive mutations. The applicant has revised the indication in the course of the procedure to reflect the exclusion of patients with ROS1 rearrangement and the restriction to patients not eligible for surgery or radiotherapy.

Design and conduct of clinical studies

The pivotal study HLX10-002-NSCLC301 consisted of two stages, where stage I was a single-arm, safety run-in period designed to evaluate the safety, tolerability, and preliminary efficacy of serplulimab combined with bevacizumab and chemotherapy (carboplatin + pemetrexed) as first-line treatment for advanced non-squamous NSCLC. Stage II was a three-arm, randomised, double-blind, multicentre, Phase III clinical study to evaluate serplulimab (HLX10), a recombinant humanized anti-PD-1 monoclonal antibody, in combination with chemotherapy (carboplatin-pemetrexed) versus serplulimab (HLX10) + HLX04 (recombinant humanized anti-VEGF monoclonal antibody) in combination with chemotherapy (carboplatin-pemetrexed) versus chemotherapy (carboplatin-pemetrexed) as first-line therapy for advanced non-squamous non-small cell lung cancer (NSCLC). The MAH has stated that since the triple combination of serplulimab, HLX04, and chemotherapy failed to demonstrate statistically significant efficacy compared to serplulimab plus chemotherapy, this regimen will not be pursued for marketing approval. Therefore, throughout the assessment report, the focus will be on the serplulimab plus chemotherapy and chemotherapy arms.

Study population

The inclusion and exclusion criteria are overall considered acceptable. The pivotal study included adult patients no older than 75 years of age, with ECOG score of 0 or 1, with histologically or cytologically confirmed stage IIIB, IIIC, or IV non-squamous NSCLC that could not be treated with surgery or radiotherapy, who had no sensitizing mutations in epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) or ROS proto-oncogene 1 (ROS1) rearrangement and with no prior history of systemic treatment for stage IIIB, IIIC, or IV NSCLC.

The originally proposed indication wording did not reflect the exclusion of patients with ROS1 rearrangement, but this was corrected in the course of the procedure. Similarly, the initially proposed indication wording was modified in the course of the procedure to also reflect a restriction in patients who are not candidates for surgery or radiotherapy, in line with the inclusion criteria.

Patients older than 75 years of age were excluded from the pivotal trial, which is not considered reflective of the target population in the indication. Information has been included in section 4.8 on the lack of data in this age group and this is acknowledged. Subjects with active metastases to the CNS and/or carcinomatous meningitis were excluded.

Treatments

The dosing of serplulimab in the current pivotal study was the same as that employed in the pivotal study for the MAA, HLX10-005-SCLC301, namely 4.5 mg/kg Q3W, and is based on the same dose-finding study, HLX10-001. At the time of the initial marketing authorisation application, the dose-exposure-response relationship for serplulimab was not considered well characterised, and it was noted that the relationship between IL-2 secretion/receptor occupancy and efficacy was not established, with a large discrepancy between the lowest dose needed to achieve a high level of PD1 receptor occupancy and the pivotal study dose, which is 11 to 12 times higher than the

receptor occupancy dose. However, it was considered that the exposure-response analyses suggested that efficacy and safety were similar across the range of exposure achieved following a 4.5 mg/kg Q3W dose.

The treatment in the control arm, with pemetrexed and carboplatin, is no longer standard of care for first-line advanced or metastatic nonsquamous NSCLC, where it has been replaced by combination treatment with platinum-based chemotherapy plus PD-1/PDL1 blockade for patients with ECOG 0-1 and molecular tests negative. The trial was initiated in November 2019, shortly after the approvals of pembrolizumab and atezolizumab (with and without bevacizumab) in combination with chemotherapy in this indication. The ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of metastatic NSCLC which were in effect at the time, updated in Oct 2018, recommended, in the absence of contraindications and conditioned by the registration of accessibility of anti-PD(L)1 combinations with platinum-based ChT, this strategy over platinum-based chemotherapy in patients with PS 0-1 and PD-L1<50%. Thus, an updated control arm with PD-1/PD-L1 blockade in combination with chemotherapy would have been preferred.

After the first PD, patients in the control arm (group C) could receive treatment with a combination of serplulimab and bevacizumab. A substantial proportion of patients in this arm (79 patients, 37.6% at the updated analysis) did in fact receive this combination post-progression.

Endpoints

The objectives and endpoints in the study are acceptable. PFS assessed by IRRC as per RECIST v1.1 was chosen as the primary endpoint, with OS as a key secondary endpoint. Further secondary endpoints included PFS by investigator per RECIST v1.1, ORR, DOR, ADA rate, QoL assessment and the relationship between PD-L1 expression level, MSI, TMB in tumour tissues and efficacy.

Statistics

The primary estimand for the primary endpoint (PFS) includes all randomized patients, which can be supported. However, it employs a hypothetical strategy with regards to handling of initiation of new anti-tumour therapy (censoring progression after), which is not the analysis preferred by guidelines. In the course of the procedure, the MAH provided sensitivity analyses to address this concern, including PFS by treatment policy strategy for intercurrent events "violations, end of treatment or change of therapy" and a sensitivity analysis for PFS where start of new anti-cancer therapy is considered an event. Overall, the results of the provided analyses are in line with the primary PFS analysis submitted.

The study employed a gate keeping strategy to control the type I error at 5% (two-sided) over the two comparisons of PFS and OS, Group B vs C and PFS and OS in Group A vs B, and a group sequential design using a Lan-DeMets approximation to the O'Brien-Fleming boundary for OS over interim analyses. PFS analysis occurred after a pre-planned number of events, at which time an OS interim analysis was conducted. This is an acceptable method for study-wise Type-I error control. Some amendments to the protocol and SAP during the conduct of the study concern specification of the order of the statistical testing in the gate-keeping procedure, and the interim analyses, which is acceptable.

An interim analysis was performed when about 2/3 of planned subjects had been enrolled with the purpose of the IDMC re-assessing the sample size in a blinded manner. Based on observed blinded PFS and OS medians, and estimates from updated literature values, the IDMC recommended to not change the sample size.

Study conduct

The first patient was enrolled on 25 November 2019 and the last patient was enrolled on 15 June 2022. The study was initiated at 92 study sites, all in China. A total of 1538 subjects were screened at 75 study sites, with a high proportion of screened patients (896, 58.3%) failing the screening and 642 (41.7%) enrolling at 72 study sites. The results presented here have a DCO of 15 Jun 2023, which corresponds to the final PFS analysis and an interim OS analysis. In the course of the procedure, the results of the final OS analysis (DCO 07-Aug-2025) were also provided, along with an updated CSR from this data cut-off.

Of the 896 subjects who failed screening, 492 (32% of the total subjects screened) failed inclusion criterion 4, which required patients not to have EGFR-sensitivity mutation, ALK gene rearrangement, or ROS1 gene rearrangement. While the percentage of patients who did not meet this inclusion criterion appears high, it is overall in line with the mutation/gene rearrangement rate that might be expected in an Asian population, where the rate of EGFR mutations in nonsquamous NSCLC is known to be higher, up to 50% (Stanzione et al., 2025).

Another frequent reason for screening failure included not meeting inclusion criterion 1 (74 patients, 4.8%), which specified that subjects should voluntarily participate in the study; fully understand and have been informed about the study; should have signed the informed consent form (ICF) and be willing to follow and able to complete all study procedures. In the course of the procedure, the MAH clarified that the primary reason for these screening failures was patient unwillingness. While the number of subjects who failed this inclusion criterion is still considered high, and more detailed reasons for the high rate of patient unwillingness are not given, the information provided by the MAH is acknowledged and the issue will not be further pursued as it is not expected that any further, more detailed information is available.

A further 45 patients (2.9%) failed on exclusion criterion 5, which excluded subjects with active metastases to the CNS and/or carcinomatous meningitis, a failure rate which can be understood in this population.

There was a total of 7 protocol versions, and the protocol amendments are overall acceptable. In protocol version 6, the treatment durations for serplulimab and HLX04 were amended, such that patients could be treated beyond two years at the discretion of the investigator. it was clarified that 12 out of 214 subjects (5.6%) in the HLX10+chemotherapy group and 3 out of 210 subjects (1.4%) in the placebo + chemotherapy group received treatment beyond two years. While the percentage receiving this extended treatment duration is not very large, it is considered to provide some support for the sought posology, which specifies an unlimited treatment duration. Further, while no data has been provided on the benefit of serplulimab in these patients treated beyond two years, it is assumed that the continued treatment reflects a continued response and some degree of benefit in these patients.

A large proportion of patients had major protocol deviations that were generally balanced between arms. The majority of the deviations were related to study visits and imaging procedures. In the course of the procedure, the MAH clarified that most of the study visit deviations were due to out-of-window visits, most of which were due to COVID-19 restrictions. As it appears that this protocol deviation is largely balanced between arms, the issue was not further pursued. As for imaging procedure-related deviations, these were largely due to missed or unqualified imaging assessments. Again, given that these deviations also appear to relatively evenly distributed between the two arms, the issue will not be further pursued. The large proportion of major protocol deviations remains an uncertainty.

The demographics and baseline characteristics were generally balanced between the three arms. In the total study population, the median age was 61 (min-max: 27-75), 73.1% male, median weight

61kg, 26.9% with ECOG performance status (PS) 0 and 73.0% with ECOG PS 1, 66.8% with smoking history at randomisation, 18.7% with history of brain metastasis at randomisation. All patients enrolled were Chinese and the baseline characteristics are not fully representative for a Caucasian population. Of note, the median age in the study population (61 years), is considered low, with an average age closer to 70 at diagnosis expected (Simeone et al., 2019). The proportion (33.2%) without a smoking history is also high relative to what would be expected in a Caucasian patient population, where a number around 10% might be expected (Simeone et al., 2019).

No Caucasians were included in the study and the MAH was requested to provide a discussion regarding the adequacy of extrapolating the efficacy results in Asian patients to a Caucasian population. The risk factors and disease characteristics in non-squamous NSCLC can overall be considered similar between regions, although the proportion of non-smokers, where the aetiology is potentially different than in smokers, is higher than would be expected in a European population (as discussed above).

The MAH provided a PopPK analysis, indicating that race did not have a statistically significant impact on the exposures of serplulimab. The absence of clinical data in Caucasian patients remains a key uncertainty as extrapolation of efficacy and safety is not supported by PK alone.

However, given the breadth of experience with PD-1/PD-L1-axis targeting treatments in this indication, the absence of data in the European population can be accepted.

The MAH states that no dedicated study in a Caucasian NSQ NSCLC population is currently planned, but that routine pharmacovigilance activities will monitor outcomes. However, pharmacovigilance activities are not designed to detect differences in efficacy and therefore provide limited reassurance regarding extrapolation.

In terms of tumour PD-L1 expression, which was assessed using the PD-L1 IHC 22C3 pharmDx kit, 77.8% were positive (CPS≥1) for PD-L1 at randomisation and 20.6% negative (CPS<1) at randomisation, with 1.6% not evaluable for PD-L1. In the serplulimab +chemotherapy arm, 84/214 (39.3%) patients had TPS<1% , 64/214 (29.9%) patients had 1%≤TPS<50% and 62/214 (29.0%) patients had TPS ≥50%, while in the chemotherapy arm, 68/210 (32.4%) patients had TPS<1%, 73/210 (34.8%) patients had 1%≤TPS<50% and 62/210 (29.5%) patients had TPS ≥50%. In general, the TPS distribution in these arms was comparable. A substantial proportion of patients thus had low TPS (<1%), in both arms.

In terms of baseline tumour diagnoses, the vast majority (98.3% in the total population) had adenocarcinoma and most patients had stage IV NSCLC (84.1% in the total population), with a smaller percentage (15.9% in the total population) with stage IIIB/IIIC.

Efficacy data and additional analyses

The primary analysis set was the ITT, which had 214 patients in the serplulimab +chemotherapy arm and 210 patients in the chemotherapy arm. The PPS, which consisted of all randomized subjects who had received at least one post-treatment tumour assessment without any major protocol deviation that could significantly affect the primary efficacy, consisted of 208 patients in the serplulimab +chemotherapy arm and 195 patients in the chemotherapy arm. The MAH has listed the reasons for exclusion from the PPS, with the majority of exclusions being due to lacking post-baseline tumour assessments.

The median PFS was 12.6 months (95% CI: 8.74, 13.96) in the serplulimab + bevacizumab + chemotherapy group, 11.0 months (95% CI: 8.44, 12.71) in the serplulimab + chemotherapy group and 5.6 months (95% CI: 4.76, 6.80) in the chemotherapy group. Using a stratified Cox

proportional hazards model, comparing the serplulimab + chemotherapy group vs the placebo + chemotherapy group, the HR was 0.55 (95% CI: 0.430, 0.694, P < 0.0001). This met the superiority criterion prespecified in the protocol. No significant difference in PFS between the serplulimab + chemotherapy group and the serplulimab + bevacizumab + chemotherapy group was observed.

The results from the sensitivity analyses for PFS were overall in line with the results from the main analysis.

PFS assessed by the investigator per RECIST v1.1 was a secondary endpoint. These results were overall similar to those by IRRC, with a median PFS per investigator of 12.0 months (95% CI: 9.76, 14.03) in the serplulimab + HLX04 + chemotherapy group, 11.4 months (95% CI: 8.67, 13.73) in the serplulimab + chemotherapy group and 5.7 months (95% CI: 4.76, 7.10) in the chemotherapy group.

The key secondary endpoint was OS. Median OS was 23.7 months (95% CI: 20.57, -) in the serplulimab + HLX04 + chemotherapy group, 25.0 months (95% CI: 20.44, 28.68) in the serplulimab + chemotherapy group and 20.4 months (95% CI: 16.39, 24.18) in the chemotherapy group. Using a stratified Cox proportional hazards model, comparing the serplulimab + chemotherapy group vs the placebo + chemotherapy group, the HR was 0.81 (95% CI: 0.615, 1.060), with p=0.1234 when the serplulimab + chemotherapy group was compared with the placebo + chemotherapy group. The OS analysis was not statistically significant at this interim analysis, and therefore statistical testing of remaining endpoints in the hierarchy does not take place. Although the main OS analysis was not statistically significant, the OS results appear overall positive, with a numerical improvement in the serplulimab + chemotherapy arm versus the chemotherapy arm.

In a sensitivity analysis where the deviation of OS efficacy in the patients receiving serplulimab and bevacizumab after PD in the control arm was corrected using the RPSFTM method provide some support for the primary analysis.

Further secondary endpoints included ORR and DOR and the results provide support for the primary endpoint.

Quality of life data using the EuroQol 5 Dimension 5 Level Questionnaire (EQ-5D-5L), the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30); and the EORTC Quality of Life 13-item lung cancer-specific questionnaire module (EORTC QLQ-LC13) was also provided as a secondary endpoint. Side-by-side comparisons of QoL data for treatment arms B and C by treatment cycle were also provided. The percentage of missing patients at each cycle has been provided, but not the number of eligible patients at each time point, hence the response rate cannot be determined. In the absence of a clearer presentation, the QoL data is challenging to interpret. However, as the requested data has in principle largely been provided, and no obvious detriment in QoL is evident, the issue will not be further pursued, but remains an uncertainty.

The efficacy observed in most of the prespecified subgroups, both in terms of PFS and OS, is generally consistent with that in the overall population. However, a few subgroups showed indications of lower efficacy.

Bearing in mind the limitations of subgroup analyses, the data available indicated poorer PFS and OS results in the patient groups with low PD-L1 expression levels and additional analyses of treatment efficacy (PFS and OS), including KM plots, in the following subgroups: TPS<1%, TPS≥1%, 1%≤TPS<50%, TPS<50%, TPS≥50%, CPS <1%, CPS≥1%, 1%≤CPS<10%, CPS<10%,

CPS≥10% were provided, based on an updated analysis with DCO 07-Aug-2025. As expected, and as also observed in the interim analysis, there was a clear trend towards less benefit of addition of serplulimab to chemotherapy in subgroups with lower levels of PD-L1 expression, both per TPS and CPS.

A general positive trend in both PFS and OS in the low PD-L1 groups was nonetheless observed, and was more pronounced at the final analysis as compared to the data from the interim analysis. While the 95% confidence intervals of the hazard ratios in the low PD-L1 groups span one, the width of the intervals implies reasonably well estimated hazard ratios and they largely overlap the confidence interval for the overall results and are therefore seen as consistent. When looking at stratified analyses, the hazard ratios in the low PD-L1 groups (TPS, CPS<1%) are less favourable, but still considered generally consistent with the overall population. Given the totality of analyses provided, it can be agreed that a degree of clinical benefit is observed both in terms of PFS and OS also in the subgroups with low PD-L1 expression levels, and that a restriction of the indication based on PD-L1 levels is not required. However, the stratified HRs, including 95% confidence intervals, for PFS for PD-L1 subgroups (TPS<1%, 1%≤TPS<50%, and TPS≥50%) from the updated analysis (DCO 07-Aug-2025) were included in section 5.1 of the SmPC to inform the prescriber regarding the trend in efficacy across these subgroups .

The relationship between PD-L1 expression level, MSI, TMB in tumour tissues and efficacy was also a secondary endpoint. However, given that MSI and TMB results are available only for a small minority of patients, any impact of these factors on efficacy are uninterpretable in the current study.

In the primary analysis (DCO 15-Jun-2023), in the subgroups females and non-smokers, there were indications of reduced OS benefit of add-on serplulimab. While much less pronounced, a similar pattern appeared to be present also for PFS subgroup analysis. While the MAH had not discussed the results in these subgroups, there could be several potential explanations, including a possible degree of overlap between patient populations in these subgroups, with a common underlying confounding variable. Different post-progression therapies in the treatment arm versus the control arm in these groups could potentially also impact OS results. In the course of the procedure, the MAH submitted data on the degree of overlap between the female, non-smoker and low PD-L1 groups, as well as Kaplan-Meier curves of OS in the female and non-smoking patient groups. There is a large degree of overlap between the female and non-smoker groups with 111 females, 141 non-smokers and 102 non-smoking females, with the overlapping group constituting 72.3% of the total non-smoker population and 91.9% of the total female population. The proportion of patients with low PD-L1 levels (<1% and <50% TPS) was similar in the female subgroup, non-smoker subgroup and overall population.

While in final OS analysis (DCO Aug-07-2025), the OS results in these subgroups were numerically improved as compared to the interim analysis, there was still apparently reduced efficacy in these subgroups as compared to the overall population. However, given that there is no indication of a detrimental effect on OS in these subgroups, and the PFS results in the female and non-smoker subgroups are more favourable (at the DCO of 07-Aug-2025, the PFS HR was 0.67 [95%CI: 0.414, 1.084] in the female subgroup, and 0.64 [0.423, 0.973] in the non-smoker subgroup), the issue was not further pursued.

In the course of the procedure, an updated CSR with a data cutoff-date of Aug-07-2025 was provided. Overall, the results for the primary and secondary endpoints were consistent with those from the primary analysis.

2.4.4. Conclusions on the clinical efficacy

HLX10-002-NSCLC301 met its primary endpoint, PFS, assessing the addition of serplulimab to carboplatin and pemetrexed in the first line treatment of patients with locally advanced or metastatic NSQ-NSCLC. Results for OS, which was the key secondary endpoint, appeared favourable, though not statistically significant, at the primary analysis, and were numerically improved at the final OS analysis. Secondary endpoints ORR and DOR supported the benefits of added serplulimab. There is a trend towards poorer efficacy results in patients with lower PD-L1 expression, but results in all subgroups can be considered generally in line with the overall population The uncertainty regarding the adequacy of extrapolation of the results to a Caucasian population is considered to be overcome by the breadth of experience with PD-1/PD-L1-axis targeting treatments in this indication.

2.5. Clinical safety

Introduction

The safety analyses of serplulimab (HLX10) for the first-line treatment of advanced non-squamous non-small cell lung cancer (NSCLC) were based primarily on the pivotal Phase III trial HLX10-002-NSCLC301 (NCT03952403), which evaluated serplulimab in combination with carboplatin-pemetrexed versus serplulimab + HLX04 (anti-VEGF antibody, bevacizumab) combined with the same chemotherapy versus chemotherapy alone, N = 634. The safety profile was primarily derived from the serplulimab in combination with chemotherapy group.

In order to fully evaluate the safety of serplulimab, safety data collected from a total of ten clinical studies (including the pivotal study HLX10-002-NSCLC301) in subjects with various types of solid tumours were pooled for analyses. The pooled safety population included all subjects in these studies who received at least one dose of serplulimab (N=2086), regardless of the amount of treatment administered. Details of the ten studies included in the pooled safety dataset are listed in the table below.

Table 38 Overview of the Ten Clinical Trials Pooled in Safety Evaluations for Serplulimab

Study No.	Title	Study Treatment	Control	Serplulimab Dose	No. of Subjects in Analysis [a]	Study Status	Cutoff Date for Safety Data
HLX10-002-NSCLC301 (Pivotal study for targeted indication)	A three-arm, randomized, double-blind, multicenter, phase III clinical study to evaluate HLX10 (recombinant humanized anti-PD-1 monoclonal antibody injection) in combination with chemotherapy (carboplatin-pemetrexed) versus HLX10 + HLX04 (recombinant anti-VEGF humanized monoclonal antibody injection) in combination with chemotherapy (carboplatin-pemetrexed) versus chemotherapy (carboplatin-pemetrexed) as first-line treatment of advanced non-squamous non-small cell lung cancer (NSCLC)	Serplulimab with carboplatin-pemetrexed or serplulimab plus HLX04 with carboplatin-pemetrexed	Placebo with carboplatin-pemetrexed	4.5 mg/kg, Q3W	Stage I: Serplulimab + HLX04+chemotherapy: 6. Stage II: Serplulimab + chemotherapy: 214; Serplulimab + HLX04 + chemotherapy: 211; Placebo + chemotherapy swithching to serplulimab + HLX04: 72. Total: 503	Ongoing	June 15, 2023
HLX10-001	A prospective open-label dose-escalation phase I study to investigate the safety and tolerability, and to determine the maximum tolerated dose and recommended phase II dose, of HLX10 in patients with advanced solid tumors	Serplulimab monotherapy	None	0.3 mg/kg Q2W, 1 mg/kg Q2W, 3 mg/kg Q2W, 10 mg/kg Q2W 200 mg Q2W, 300 mg Q3W, 400 mg Q4W, 600 mg Q6W.	3 4 6 16 9 9 10 9 Total: 66	Completed	January 05, 2024
HLX10HLX04-001	A phase I clinical study to evaluate the safety, tolerability and pharmacokinetics of recombinant anti-PD-1 humanized monoclonal antibody injection (HLX10) in combination with recombinant anti-VEGF humanized monoclonal antibody injection (HLX04) in patients with advanced solid tumors	Serplulimab with HLX04 combination therapy	None	1 mg/kg Q2W, 3 mg/kg Q2W, 10 mg/kg Q2W	3 3 20 Total: 26	Completed	October 11, 2022
HLX10HLX07-001	A multiple-center, open-label, phase II clinical trial to evaluate the efficacy and safety of HLX10 in combination with HLX07 in patients with advanced head and neck tumors	Serplulimab with HLX07 combination therapy	None	3 mg/kg, Q2W	13	Completed	September 16, 2022
HLX10-010-MSI201	A single-arm, multi-center, phase II clinical study to evaluate the HLX10 monotherapy for the treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that failed to respond to standard therapy	Serplulimab monotherapy	None	3 mg/kg, Q2W	108	Completed	July 10, 2021

Study No.	Title	Study Treatment	Control	Serplulimab Dose	No. of Subjects in Analysis [a]	Study Status	Cutoff Date for Safety Data
HLX10-011-CC201	A single-arm, open-label, multicenter, phase II clinical study to evaluate efficacy and safety of HLX10 (recombinant humanized anti-PD-1 monoclonal antibody injection) combined with albumin-bound paclitaxel in patients with advanced cervical cancer who have progressive disease or intolerable toxicity after first-line standard chemotherapy	Serplulimab with paclitaxel combination therapy	None	4.5 mg/kg, Q3W	21	Completed	September 22, 2022
HLX10-008-HCC201	A single-arm, open, multicenter, phase II clinical study evaluating the use of HLX10 (recombinant anti-PD-1 humanized monoclonal antibody injection) in combination with HLX04 (recombinant anti-VEGF humanized monoclonal antibody injection) for the treatment of advanced hepatocellular carcinoma (HCC) patients	Serplulimab monotherapy or serplulimab with HLX04 combination therapy	None	3 mg/kg, Q2W	Monotherapy: 21 Combination therapy: 102 Total: 123	Completed	February 07, 2023
HLX10-005-SCLC301	A randomized, double-blind, multicenter, phase III study to evaluate HLX10 in combination with chemotherapy (carboplatin-etoposide) in previously untreated patients with extensive stage small cell lung cancer (ES-SCLC)	Serplulimab with carboplatin and etoposide combination therapy	Placebo with carboplatin and etoposide	4.5 mg/kg, Q3W	Serplulimab: 389	Completed	May 07, 2024
HLX10-004-NSCLC303	A randomized, double-blind, multicenter, phase III clinical study of HLX10 + chemotherapy (carboplatin and nab-paclitaxel) vs placebo + chemotherapy (carboplatin and nab-paclitaxel) as first-line therapy for locally advanced or metastatic squamous NSCLC	Serplulimab with carboplatin and nab-paclitaxel combination therapy	Placebo with carboplatin and nab-paclitaxel	4.5 mg/kg, Q3W	Serplulimab: 358/455 [b]	Completed	January 31, 2023
HLX10-007-EC301	A randomized, double-blind, multicenter, phase III clinical study to evaluate HLX10 (recombinant humanized anti-PD-1 monoclonal antibody injection) versus placebo in combination with chemotherapy (cisplatin + 5-FU) as first-line therapy in patients with locally advanced/metastatic esophageal squamous cell carcinoma (ESCC)	Serplulimab with cisplatin and 5-FU combination therapy	Placebo with cisplatin and 5-FU	3 mg/kg, Q2W	Serplulimab: 382	Completed	January 09, 2023

Abbreviations: NSCLC=non-small cell lung cancer, Q2W=once every 2 weeks, Q3W=once every 3 weeks, Q4W=once every 4 weeks, Q6W=once every 6 weeks.
b In the HLX10-004-NSCLC303 study, subjects randomized to the placebo group either ended treatment or were allowed to crossover to receive serplulimab after the first progressive disease. As of the cutoff date, 97 subjects in the placebo group crossed over to receive serplulimab monotherapy. Therefore, 455 subjects received serplulimab (serplulimab + chemotherapy: 358 subjects, serplulimab monotherapy: 97 subjects).

Table 39 Grouping Structure of the Pooled Safety Dataset

Dose Category	Treatment
< RP2D/3D [a]: • 0.3 mg/kg Q2W • 1 mg/kg Q2W	Monotherapy
	Other Combination
≥ RP2D/3D: • 3 mg/kg Q2W • 4.5 mg/kg Q3W • 10 mg/kg Q2W • 200 mg Q2W • 300 mg Q3W • 400 mg Q4W • 600 mg Q6W	Monotherapy
	Chemotherapy Combination
	Other Combination

Abbreviations: RP2D/3D = recommended phase II/III dose, Q2W = once every 2 weeks, Q3W = once every 3 weeks, Q4W = once every 4 weeks, Q6W = once every 6 weeks.
a In the < RP2D/3D group, no subjects received serplulimab in combination with chemotherapy

Patient exposure

Pivotal trial – study HLX10-002-NSCLC301

See Table 20 Demographics and baseline data (ITT set)

Pooled safety population

Table 40 Pooled Safety Population: Summary of Demographic Characteristics

	<RP2D/3D			≥RP2D/3D				Total population (N=2086)
	Monotherapy (N=7)	Other Combination (N=3)	Total (N=10)	Monotherapy (N=285)	Chemotherapy Combination (N=1364)	Other Combination (N=427)	Total (N=2076)	
Treated subjects	7	3	10	285	1364	427	2076	2086
Age (year)								
n	7	3	10	285	1364	427	2076	2086
Mean (SD)	60.3 (2.69)	46.3 (13.28)	56.1 (9.46)	57.4 (11.24)	61.4 (8.42)	58.6 (9.70)	60.3 (9.26)	60.3 (9.27)
Median	60.0	54.0	58.5	58.0	63.0	59.0	62.0	61.5
Q1, Q3	57, 63	31, 54	54, 61	52, 65	56, 68	53, 66	55, 67	55, 67
Age Group								
<65	7 (100)	3 (100)	10 (100)	210 (73.7)	794 (58.2)	298 (69.8)	1302 (62.7)	1312 (62.9)
≥65	0	0	0	75 (26.3)	570 (41.8)	129 (30.2)	774 (37.3)	774 (37.1)
Sex								
Male	4 (57.1)	1 (33.3)	5 (50.0)	205 (71.9)	1123 (82.3)	328 (76.8)	1656 (79.8)	1661 (79.6)
Female	3 (42.9)	2 (66.7)	5 (50.0)	80 (28.1)	241 (17.7)	99 (23.2)	420 (20.2)	425 (20.4)
Height (cm)								
n	7	3	10	284	1359	426	2069	2079
Mean (SD)	158.50 (6.817)	164.00 (8.544)	160.15 (7.366)	165.12 (7.868)	166.66 (8.070)	165.91 (7.532)	166.29 (7.950)	166.26 (7.957)
Median	160.00	163.00	160.50	165.50	168.00	167.00	167.00	167.00
Q1, Q3	150.0, 164.0	156.0, 173.0	156.0, 164.0	160.0, 170.0	161.0, 172.0	160.0, 171.0	160.0, 172.0	160.0, 172.0
Missing	0	0	0	1	5	1	7	7
Weight (kg)								
n	7	3	10	285	1363	427	2075	2085
Mean (SD)	57.34 (10.951)	85.20 (5.897)	65.70 (16.393)	62.21 (12.613)	64.14 (13.480)	62.84 (10.229)	63.61 (12.774)	63.62 (12.790)
Median	53.50	82.90	63.85	61.00	62.00	62.00	62.00	62.00
Q1, Q3	48.3, 64.0	80.8, 91.9	52.0, 80.8	54.0, 68.5	55.0, 71.0	55.0, 69.0	55.0, 70.0	55.0, 70.0
Missing	0	0	0	0	1	0	1	1
BMI (kg/m^2)								
n	7	3	10	284	1358	426	2068	2078
Mean (SD)	22.99 (5.337)	31.70 (1.321)	25.61 (6.089)	22.73 (3.833)	23.01 (4.034)	22.79 (3.082)	22.93 (3.829)	22.94 (3.845)

Median	22.84	31.20	23.87	22.37	22.49	22.87	22.54	22.55
Q1, Q3	19.3, 24.1	30.7, 33.2	20.3, 31.2	20.2, 24.8	20.1, 25.2	20.5, 24.8	20.2, 25.1	20.2, 25.1
Missing	0	0	0	1	6	1	8	8
ECOG at Baseline								
0	3 (42.9)	1 (33.3)	4 (40.0)	104 (36.5)	301 (22.1)	143 (33.5)	548 (26.4)	552 (26.5)
1	3 (42.9)	2 (66.7)	5 (50.0)	179 (62.8)	1063 (77.9)	283 (66.3)	1525 (73.5)	1530 (73.3)
2	1 (14.3)	0	1 (10.0)	2 (0.7)	0	0	2 (0.1)	3 (0.1)
Missing	0	0	0	0	0	1 (0.2)	1 (<0.1)	1 (<0.1)
Disease Stage								
I	0	0	0	1 (0.4)	1 (0.1)	1 (0.2)	3 (0.1)	3 (0.1)
II	0	0	0	1 (0.4)	4 (0.3)	8 (1.9)	13 (0.6)	13 (0.6)
III	0	0	0	33 (11.6)	205 (15.0)	74 (17.3)	312 (15.0)	312 (15.0)
IV	7 (100)	3 (100)	10 (100)	249 (87.4)	1100 (80.6)	330 (77.3)	1679 (80.9)	1689 (81.0)
Missing	0	0	0	1 (0.4)	54 (4.0)	14 (3.3)	69 (3.3)	69 (3.3)

< RP2D/3D: Doses of serplulimab included 0.3 mg/kg/2 week and 1 mg/kg/2 week. ≥ RP2D/3D: Doses of 3 mg/kg/2 week, 4.5 mg/kg/3 week, 10 mg/kg/2 week, 200 mg/2 week, 300 mg/3 week, 400 mg/4 week and 600 mg/6 week. Total subjects included all the subjects treated at least one dose with serplulimab; other combination included all other kinds of combinations with serplulimab except chemotherapy combination with serplulimab. BMI (kg/m^2) = Weight (kg)/(Height [cm]/100)^2.

Table 41 Pooled Safety Population: Summary of Exposure to Serplulimab

	<RP2D/3D			≥RP2D/3D				
	Monotherapy (N=7)	Other Combination (N=3)	Total (N=10)	Monotherapy (N=285)	Chemotherapy Combination (N=1364)	Other Combination (N=427)	Total (N=2076)	Total population (N=2086)
Treated subjects	7	3	10	285	1364	427	2076	2086
Duration of treatment (Month)								
N	7	3	10	285	1364	427	2076	2086
Mean (SD)	2.05 (1.867)	8.47 (2.957)	3.97 (3.726)	5.73 (6.736)	9.34 (9.498)	8.63 (7.851)	8.70 (8.922)	8.68 (8.910)
Median	1.41	9.69	3.06	2.79	6.00	6.28	5.55	5.55
Q1, Q3	0.49, 3.25	5.09, 10.61	0.95, 5.32	0.99, 8.28	3.27, 12.68	2.10, 13.17	2.45, 12.45	2.43, 12.42
Min, Max	0.0, 5.3	5.1, 10.6	0.0, 10.6	0.0, 30.2	0.0, 52.7	0.0, 34.1	0.0, 52.7	0.0, 52.7
≥3 months	2 (28.6%)	3 (100%)	5 (50.0%)	133 (46.7%)	1043 (76.5%)	294 (68.9%)	1470 (70.8%)	1475 (70.7%)
≥ 6 months	0	2 (66.7%)	2 (20.0%)	90 (31.6%)	682 (50.0%)	220 (51.5%)	992 (47.8%)	994 (47.7%)
≥ 9 months	0	2 (66.7%)	2 (20.0%)	66 (23.2%)	464 (34.0%)	162 (37.9%)	692 (33.3%)	694 (33.3%)
Number of administrations								
N	7	3	10	285	1364	427	2076	2086
Mean (SD)	5.1 (3.80)	19.0 (6.08)	9.3 (7.92)	10.6 (11.64)	14.0 (13.00)	13.4 (12.03)	13.4 (12.68)	13.4 (12.66)
Median	4.0	22.0	7.0	6.0	9.0	9.0	9.0	9.0
Q1, Q3	2.0, 7.0	12.0, 23.0	3.0, 12.0	3.0, 12.0	5.0, 19.0	4.0, 19.0	4.0, 19.0	4.0, 19.0
Min, Max	1, 12	12, 23	1, 23	1, 47	1, 73	1, 53	1, 73	1, 73
Cumulative dose (mg)								
N	7	3	10	285	1364	427	2076	2086
Mean (SD)	147.49 (79.566)	1551.20 (411.524)	568.60 (708.250)	2631.99 (3022.934)	3792.39 (4041.754)	3498.33 (3409.802)	3572.61 (3810.846)	3558.21 (3807.642)
Median	130.00	1733.60	165.00	1400.00	2346.00	2450.00	2250.00	2244.00
Q1, Q3	91.00, 173.00	1080.00, 1840.00	126.40, 1080.00	600.00, 3600.00	1203.00, 5016.00	1051.00, 5096.00	1050.00, 4821.75	1043.00, 4800.00
Min, Max	52.0, 303.0	1080.0, 1840.0	52.0, 1840.0	135.0, 26994.3	129.0, 33561.0	135.0, 29818.0	129.0, 33561.0	52.0, 33561.0
Drug Compliance (%)								
N	7	3	10	285	1364	427	2076	2086
Mean (SD)	100.66 (3.987)	100.00 (0.000)	100.46 (3.271)	99.94 (0.859)	99.92 (0.800)	99.88 (0.678)	99.91 (0.785)	99.91 (0.813)
Median	101.12	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Q1, Q3	96.11, 104.00	100.00, 100.00	100.00, 104.00	100.00, 100.00	100.00, 100.00	99.93, 100.00	100.00, 100.00	100.00, 100.00
Min, Max	94.7, 104.7	100.0, 100.0	94.7, 104.7	86.5, 102.6	89.2, 109.1	92.9, 102.1	86.5, 109.1	86.5, 109.1
Relative Dose Intensity (%)								
N	7	3	10	285	1364	427	2076	2086
Mean (SD)	99.81 (4.664)	100.00 (0.000)	99.87 (3.809)	98.66 (3.563)	97.54 (4.365)	98.35 (3.559)	97.86 (4.130)	97.87 (4.130)
Median	101.12	100.00	100.00	100.00	99.75	99.88	99.92	99.93
Q1, Q3	94.69, 104.00	100.00, 100.00	100.00, 101.92	98.25, 100.00	96.42, 100.00	98.13, 100.00	96.92, 100.00	96.92, 100.00
Min, Max	92.3, 104.7	100.0, 100.0	92.3, 104.7	73.7, 113.5	67.7, 109.1	70.0, 103.7	67.7, 113.5	67.7, 113.5

< RP2D/3D: Doses of serplulimab included 0.3 mg/kg/2 week and 1 mg/kg/2 week. ≥RP2D/3D: Doses of 3 mg/kg/2 week, 4.5 mg/kg/3 week, 10 mg/kg/2 week, 200 mg/2 week, 300 mg/3 week, 400 mg/4 week and 600 mg/6 week.

Adverse events

Adverse events - pivotal trial

Table 42 Summary of Adverse Events (SS)

	HLX10 + HLX04 + Chemotherapy (N = 211) n (%)	HLX10 + Chemotherapy (N = 214) n (%)	Placebo + Chemotherapy (N = 209) n (%)	Placebo + Chemotherapy switching to HLX10 + HLX04 (N = 72) n (%)	Total (N = 634) n (%)
All AEs during the study	210 (99.5)	212 (99.1)	208 (99.5)	62 (86.1)	630 (99.4)
All treatment-emergent adverse events (TEAEs) [1]	210 (99.5)	212 (99.1)	208 (99.5)	59 (81.9)	630 (99.4)
Related to HLX10/placebo	195 (92.4)	192 (89.7)	163 (78.0)	50 (69.4)	550 (86.8)
Related to HLX04/placebo	198 (93.8)	180 (84.1)	159 (76.1)	53 (73.6)	537 (84.7)
Related to pemetrexed	207 (98.1)	210 (98.1)	206 (98.6)	20 (27.8)	623 (98.3)
Related to carboplatin	207 (98.1)	209 (97.7)	205 (98.1)	10 (13.9)	621 (97.9)
Related to any study drugs[2]	208 (98.6)	212 (99.1)	206 (98.6)	55 (76.4)	626 (98.7)
Severe TEAEs (CTCAE Grade ≥ 3)	164 (77.7)	153 (71.5)	142 (67.9)	27 (37.5)	459 (72.4)
Related to HLX10/placebo	97 (46.0)	87 (40.7)	63 (30.1)	14 (19.4)	247 (39.0)
Related to HLX04/placebo	100 (47.4)	75 (35.0)	64 (30.6)	10 (13.9)	239 (37.7)
Related to pemetrexed	137 (64.9)	135 (63.1)	119 (56.9)	3 (4.2)	391 (61.7)
Related to carboplatin	125 (59.2)	124 (57.9)	116 (55.5)	1 (1.4)	365 (57.6)
Related to any study drugs	149 (70.6)	142 (66.4)	119 (56.9)	16 (22.2)	410 (64.7)
Serious TEAEs	106 (50.2)	96 (44.9)	85 (40.7)	24 (33.3)	287 (45.3)
Related to HLX10/placebo	70 (33.2)	62 (29.0)	34 (16.3)	11 (15.3)	166 (26.2)
Related to HLX04/placebo	56 (26.5)	47 (22.0)	35 (16.7)	10 (13.9)	138 (21.8)
Related to pemetrexed	64 (30.3)	65 (30.4)	51 (24.4)	2 (2.8)	180 (28.4)
Related to carboplatin	49 (23.2)	58 (27.1)	41 (19.6)	0	148 (23.3)
Related to any study drugs	82 (38.9)	79 (36.9)	51 (24.4)	14 (19.4)	212 (33.4)
TEAEs leading to death	32 (15.2)	18 (8.4)	28 (13.4)	9 (12.5)	78 (12.3)
Related to HLX10/placebo	8 (3.8)	5 (2.3)	4 (1.9)	2 (2.8)	17 (2.7)
Related to HLX04/placebo	7 (3.3)	4 (1.9)	4 (1.9)	2 (2.8)	15 (2.4)
Related to pemetrexed	6 (2.8)	4 (1.9)	7 (3.3)	0	17 (2.7)
Related to carboplatin	4 (1.9)	3 (1.4)	5 (2.4)	0	12 (1.9)
Related to any study drugs	10 (4.7)	5 (2.3)	7 (3.3)	2 (2.8)	22 (3.5)
TEAEs leading to the interruption of HLX10/placebo	141 (66.8)	126 (58.9)	80 (38.3)	26 (36.1)	347 (54.7)
HLX10/placebo-related TEAEs leading to the interruption of HLX10/placebo	100 (47.4)	73 (34.1)	41 (19.6)	19 (26.4)	214 (33.8)
TEAEs leading to the interruption of HLX04/placebo	140 (66.4)	115 (53.7)	79 (37.8)	23 (31.9)	334 (52.7)
HLX04/placebo-related TEAEs leading to the interruption of HLX04/placebo	93 (44.1)	58 (27.1)	38 (18.2)	12 (16.7)	189 (29.8)
TEAEs leading to the interruption of any chemotherapy drugs	141 (66.8)	119 (55.6)	73 (34.9)	3 (4.2)	333 (52.5)
TEAEs leading to dose modification of HLX04/placebo	13 (6.2)	3 (1.4)	5 (2.4)	1 (1.4)	21 (3.3)
TEAEs leading to dose modification of any chemotherapy drugs	51 (24.2)	36 (16.8)	38 (18.2)	0	125 (19.7)
TEAEs leading to the discontinuation of HLX10/placebo	35 (16.6)	23 (10.7)	12 (5.7)	5 (6.9)	70 (11.0)
HLX10/placebo-related TEAEs leading to the discontinuation of HLX10/placebo	29 (13.7)	18 (8.4)	5 (2.4)	5 (6.9)	52 (8.2)
TEAEs leading to the discontinuation of HLX04/placebo	37 (17.5)	27 (12.6)	16 (7.7)	7 (9.7)	80 (12.6)
HLX04/placebo-related TEAEs leading to the discontinuation of HLX04/placebo	27 (12.8)	17 (7.9)	9 (4.3)	5 (6.9)	53 (8.4)
TEAEs leading to the discontinuation of any chemotherapy drugs	39 (18.5)	30 (14.0)	22 (10.5)	1 (1.4)	91 (14.4)
Adverse events of special interest (AESI) [3]	70 (33.2)	65 (30.4)	28 (13.4)	15 (20.8)	163 (25.7)
Immune-related TEAEs (irAEs)	67 (31.8)	65 (30.4)	26 (12.4)	15 (20.8)	158 (24.9)
Serious Immune-related TEAEs (irAEs)	25 (11.8)	21 (9.8)	3 (1.4)	5 (6.9)	49 (7.7)
Infusion-related reactions	3 (1.4)	0	1 (0.5)	0	4 (0.6)
Serious infusion-related reactions	0	0	1 (0.5)	0	1 (0.2)

[1] Treatment-emergent adverse event (TEAE) included any AE that occurred or was worsened on or after the first dose of the study drugs, till 90 days after the last dose of the study drugs or the start of a new anti-tumour therapy (whichever occurred first), as well as TESAEs related to HLX10/HLX04 that were recorded after the start of a new anti-tumour therapy. Drug-related TEAEs were defined as TEAEs with a relationship to the study drugs categorized as (related, possibly related, and unable to determine) or TEAEs with missing relationship status. The placebo + chemotherapy column did not include TEAEs that occurred after crossing over from placebo + chemotherapy to HLX10 + HLX04. [2] Related to any study drug referred to adverse events related to any of the following: HLX10/placebo, HLX04/placebo, pemetrexed, and carboplatin. [3] AESIs in this study included infusion-related reactions and immune-related adverse events (irAEs).

Pooled safety population

Table 43 - Pooled Safety Population: Summary of Adverse Events

	< RP2D/3D			≥ RP2D/3D				
	Monotherapy (N=7)	Other Combination (N=3)	Total (N=10)	Monotherapy (N=285)	Chemotherapy Combination (N=1364)	Other Combination (N=427)	Total (N=2076)	Total population (N=2086)
All adverse events	7 (100%)	3 (100%)	10 (100%)	272 (95.4%)	1347 (98.8%)	415 (97.2%)	2034 (98.0%)	2044 (98.0%)
TEAEs	7 (100%)	3 (100%)	10 (100%)	270 (94.7%)	1342 (98.4%)	415 (97.2%)	2027 (97.6%)	2037 (97.7%)
CTCAE Grade ≥ 3	5 (71.4%)	2 (66.7%)	7 (70.0%)	127 (44.6%)	1059 (77.6%)	273 (63.9%)	1459 (70.3%)	1466 (70.3%)
Serplulimab-related TEAEs	6 (85.7%)	3 (100%)	9 (90.0%)	199 (69.8%)	1073 (78.7%)	369 (86.4%)	1641 (79.0%)	1650 (79.1%)
CTCAE Grade ≥ 3	2 (28.6%)	1 (33.3%)	3 (30.0%)	58 (20.4%)	496 (36.4%)	159 (37.2%)	713 (34.3%)	716 (34.3%)
Drug-related TEAEs	6 (85.7%)	3 (100%)	9 (90.0%)	206 (72.3%)	1321 (96.8%)	399 (93.4%)	1926 (92.8%)	1935 (92.8%)
CTCAE Grade ≥ 3	2 (28.6%)	2 (66.7%)	4 (40.0%)	58 (20.4%)	928 (68.0%)	233 (54.6%)	1219 (58.7%)	1223 (58.6%)
TESAEs	5 (71.4%)	0	5 (50.0%)	92 (32.3%)	601 (44.1%)	173 (40.5%)	866 (41.7%)	871 (41.8%)
CTCAE Grade ≥ 3	4 (57.1%)	0	4 (40.0%)	74 (26.0%)	500 (36.7%)	145 (34.0%)	719 (34.6%)	723 (34.7%)
Serplulimab-related TESAEs	2 (28.6%)	0	2 (20.0%)	35 (12.3%)	298 (21.8%)	96 (22.5%)	429 (20.7%)	431 (20.7%)
CTCAE Grade ≥ 3	1 (14.3%)	0	1 (10.0%)	30 (10.5%)	229 (16.8%)	77 (18.0%)	336 (16.2%)	337 (16.2%)
TEAEs leading to serplulimab discontinuation	3 (42.9%)	0	3 (30.0%)	32 (11.2%)	150 (11.0%)	57 (13.3%)	239 (11.5%)	242 (11.6%)
CTCAE Grade ≥ 3	3 (42.9%)	0	3 (30.0%)	26 (9.1%)	104 (7.6%)	45 (10.5%)	175 (8.4%)	178 (8.5%)
Serplulimab-related	1 (14.3%)	0	1 (10.0%)	14 (4.9%)	94 (6.9%)	41 (9.6%)	149 (7.2%)	150 (7.2%)
TEAEs leading to serplulimab interruption	5 (71.4%)	2 (66.7%)	7 (70.0%)	86 (30.2%)	732 (53.7%)	227 (53.2%)	1045 (50.3%)	1052 (50.4%)
CTCAE Grade ≥ 3	3 (42.9%)	0	3 (30.0%)	39 (13.7%)	436 (32.0%)	123 (28.8%)	598 (28.8%)	601 (28.8%)
Serplulimab-related	3 (42.9%)	0	3 (30.0%)	54 (18.9%)	433 (31.7%)	161 (37.7%)	648 (31.2%)	651 (31.2%)
TEAEs leading to death	2 (28.6%)	0	2 (20.0%)	38 (13.3%)	155 (11.4%)	51 (11.9%)	244 (11.8%)	246 (11.8%)
CTCAE Grade ≥ 3	2 (28.6%)	0	2 (20.0%)	38 (13.3%)	155 (11.4%)	51 (11.9%)	244 (11.8%)	246 (11.8%)
Serplulimab-related	1 (14.3%)	0	1 (10.0%)	9 (3.2%)	28 (2.1%)	12 (2.8%)	49 (2.4%)	50 (2.4%)
All serious adverse events	5 (71.4%)	0	5 (50.0%)	92 (32.3%)	603 (44.2%)	174 (40.7%)	869 (41.9%)	874 (41.9%)
AESIs	1 (14.3%)	3 (100%)	4 (40.0%)	93 (32.6%)	487 (35.7%)	151 (35.4%)	731 (35.2%)	735 (35.2%)
CTCAE Grade ≥ 3	0	1 (33.3%)	1 (10.0%)	24 (8.4%)	127 (9.3%)	38 (8.9%)	189 (9.1%)	190 (9.1%)
IRRs	0	0	0	3 (1.1%)	25 (1.8%)	7 (1.6%)	35 (1.7%)	35 (1.7%)
CTCAE Grade ≥ 3	0	0	0	0	5 (0.4%)	0	5 (0.2%)	5 (0.2%)
irAEs	1 (14.3%)	3 (100%)	4 (40.0%)	91 (31.9%)	473 (34.7%)	146 (34.2%)	710 (34.2%)	714 (34.2%)
CTCAE Grade ≥ 3	0	1 (33.3%)	1 (10.0%)	24 (8.4%)	122 (8.9%)	38 (8.9%)	184 (8.9%)	185 (8.9%)

CTCAE: Common Terminology Criteria for Adverse Events. < RP2D/3D: Doses of serplulimab included 0.3 mg/kg/2 week and 1 mg/kg/2 week. ≥ RP2D/3D: Doses of 3 mg/kg/2 week, 4.5 mg/kg/3 week, 10 mg/kg/2 week, 200 mg/2 week, 300 mg/3 week, 400 mg/4 week and 600 mg/6 week. Total patients included all the patients treated at least one dose with serplulimab; other combinations included all other kinds of combinations with serplulimab except chemotherapy combination with serplulimab. Percentage was based on the safety population as denominator. TEAEs were AEs that developed or worsened during the on-treatment period. CTCAE 4.03 version was used in HLX10-001, HLX10HLX04-001 and HLX10-007-EC301, CTCAE 5.0 version was used in other studies.

Treatment emergent adverse events (TEAEs) – Pivotal trial

Table 44 . Summary of TEAEs with Incidence ≥ 20% in Any Group by SOC and PT (Safety Set) - Pivotal trial

System Organ Class Preferred Term	Serplulimab + HLX04 + Chemotherapy (N=211) n (%) E	Serplulimab + Chemotherapy (N=214) n (%) E	Placebo + Chemotherapy (N=209) n (%) E	Placebo + Chemotherapy Switching to Serplulimab + HLX04 (N=72) n (%) E	Total (N=634) n (%) E
Investigations					
Neutrophil count decreased	171 (81.0) 761	175 (81.8) 743	160 (76.6) 594	7 (9.7) 25	506 (79.8) 2098
White blood cell count decreased	163 (77.3) 725	170 (79.4) 740	153 (73.2) 583	7 (9.7) 33	486 (76.7) 2048
Platelet count decreased	120 (56.9) 346	104 (48.6) 273	99 (47.4) 235	7 (9.7) 9	323 (50.9) 854
Alanine aminotransferase increased	107 (50.7) 239	110 (51.4) 253	86 (41.1) 186	10 (13.9) 17	303 (47.8) 678
Aspartate aminotransferase increased	122 (57.8) 320	101 (47.2) 250	79 (37.8) 180	17 (23.6) 28	302 (47.6) 750
Weight decreased	46 (21.8) 59	44 (20.6) 52	37 (17.7) 39	10 (13.9) 14	127 (20.0) 150
Gamma-glutamyltransferase increased	51 (24.2) 75	45 (21.0) 71	26 (12.4) 36	8 (11.1) 8	122 (19.2) 182
Weight increased	27 (12.8) 33	45 (21.0) 62	29 (13.9) 35	3 (4.2) 3	101 (15.9) 130
Blood and lymphatic system disorders					
Anaemia	161 (76.3) 441	165 (77.1) 413	167 (79.9) 346	15 (20.8) 31	493 (77.8) 1200
Metabolism and nutrition disorders					
Decreased appetite	84 (39.8) 158	78 (36.4) 115	50 (23.9) 72	9 (12.5) 11	212 (33.4) 345
Hypoalbuminaemia	71 (33.6) 151	65 (30.4) 141	55 (26.3) 93	22 (30.6) 44	191 (30.1) 385
Hypercholesterolaemia	50 (23.7) 115	50 (23.4) 116	42 (20.1) 72	8 (11.1) 9	142 (22.4) 303
Hypokalaemia	48 (22.7) 81	46 (21.5) 84	30 (14.4) 51	11 (15.3) 25	124 (19.6) 216
Gastrointestinal disorders					
Nausea	89 (42.2) 217	85 (39.7) 237	71 (34.0) 161	8 (11.1) 11	245 (38.6) 615
Constipation	74 (35.1) 120	75 (35.0) 130	61 (29.2) 93	7 (9.7) 15	210 (33.1) 343
Vomiting	55 (26.1) 90	54 (25.2) 139	49 (23.4) 81	8 (11.1) 9	158 (24.9) 310
Diarrhoea	46 (21.8) 71	31 (14.5) 48	18 (8.6) 24	7 (9.7) 17	95 (15.0) 143
General disorders and administration site conditions					
Asthenia	75 (35.5) 131	67 (31.3) 98	48 (23.0) 76	6 (8.3) 6	190 (30.0) 305

System Organ Class Preferred Term	Serplulimab + HLX04 + Chemotherapy (N=211) n (%) E	Serplulimab + Chemotherapy (N=214) n (%) E	Placebo + Chemotherapy (N=209) n (%) E	Placebo + Chemotherapy Switching to Serplulimab + HLX04 (N=72) n (%) E	Total (N=634) n (%) E
Pyrexia	43 (20.4) 67	37 (17.3) 50	26 (12.4) 32	11 (15.3) 16	106 (16.7) 149
Renal and urinary disorders					
Proteinuria	69 (32.7) 117	35 (16.4) 56	22 (10.5) 37	16 (22.2) 25	126 (19.9) 210
Vascular disorders					
Hypertension	47 (22.3) 65	11 (5.1) 32	11 (5.3) 15	6 (8.3) 6	69 (10.9) 112

Notes: TEAEs were coded according to MedDRA 26.0.
Treatment-emergent adverse event (TEAE) included any AE that occurred or was worsened on or after the first dose of the study drugs, till 90 days after the last dose of the study drugs or the start of a new anti-tumor therapy (whichever occurred first), as well as SAEs related to serplulimab/HLX04 that were recorded after the start of a new anti-tumor therapy.

Treatment emergent adverse events (TEAEs) – Pooled Safety Population

Treatment related TEAEs – Pivotal trial

Table 45 Summary of HLX10/Placebo-related TEAEs with an incidence ≥ 10% by SOC and PT (SS)

System Organ Class Preferred Term	HLX10 + HLX04 + Chemotherapy (N = 211) n (%) E	HLX10 + Chemotherapy (N = 214) n (%) E	Placebo + Chemotherapy (N = 209) n (%) E	Placebo + Chemotherapy switching to HLX10 + HLX04 (N = 72) n (%) E	Total (N = 634) n (%) E
Investigations					
Neutrophil count decreased	77 (36.5) 266	71 (33.2) 286	66 (31.6) 232	7 (9.7) 24	214 (33.8) 784
Alanine aminotransferase increased	77 (36.5) 158	77 (36.0) 178	58 (27.8) 109	7 (9.7) 11	212 (33.4) 445
Aspartate aminotransferase increased	90 (42.7) 225	67 (31.3) 175	49 (23.4) 111	12 (16.7) 21	206 (32.5) 511
White blood cell count decreased	73 (34.6) 249	65 (30.4) 303	67 (32.1) 226	7 (9.7) 33	205 (32.3) 778
Platelet count decreased	59 (28.0) 133	45 (21.0) 104	47 (22.5) 102	5 (6.9) 7	151 (23.8) 339
Gamma-glutamyltransferase increased	33 (15.6) 49	28 (13.1) 44	15 (7.2) 22	5 (6.9) 5	76 (12.0) 115
Blood creatinine increased	32 (15.2) 69	20 (9.3) 42	10 (4.8) 15	0	62 (9.8) 126
Weight decreased	23 (10.9) 28	12 (5.6) 13	14 (6.7) 14	2 (2.8) 3	49 (7.7) 55
Metabolism and nutrition disorders					
Decreased appetite	46 (21.8) 78	37 (17.3) 53	21 (10.0) 32	5 (6.9) 5	104 (16.4) 163
Hypoalbuminaemia	32 (15.2) 71	34 (15.9) 93	22 (10.5) 40	15 (20.8) 34	88 (13.9) 204
Hypercholesterolaemia	23 (10.9) 59	28 (13.1) 71	17 (8.1) 26	5 (6.9) 6	68 (10.7) 156
Hypokalaemia	27 (12.8) 41	16 (7.5) 30	15 (7.2) 22	6 (8.3) 14	58 (9.1) 93
Hypertriglyceridaemia	23 (10.9) 51	15 (7.0) 40	11 (5.3) 29	3 (4.2) 4	49 (7.7) 120
Blood and lymphatic system disorders					
Anaemia	76 (36.0) 189	76 (35.5) 176	76 (36.4) 147	8 (11.1) 22	228 (36.0) 512
Gastrointestinal disorders					
Nausea	31 (14.7) 72	33 (15.4) 130	33 (15.8) 84	5 (6.9) 8	97 (15.3) 286
Constipation	31 (14.7) 50	27 (12.6) 52	21 (10.0) 29	5 (6.9) 9	79 (12.5) 131
Vomiting	18 (8.5) 35	26 (12.1) 91	25 (12.0) 50	5 (6.9) 6	69 (10.9) 176
Diarrhoea	21 (10.0) 30	13 (6.1) 17	12 (5.7) 16	5 (6.9) 7	46 (7.3) 63
General disorders and administration site conditions					
Asthenia	42 (19.9) 80	38 (17.8) 52	25 (12.0) 44	4 (5.6) 4	105 (16.6) 176

Skin and subcutaneous tissue disorders					
Rash	27 (12.8) 34	16 (7.5) 18	10 (4.8) 20	1 (1.4) 2	53 (8.4) 72
Renal and urinary disorders					
Proteinuria	27 (12.8) 46	16 (7.5) 21	14 (6.7) 27	7 (9.7) 10	57 (9.0) 94
Endocrine disorders					
Hypothyroidism	26 (12.3) 39	28 (13.1) 37	9 (4.3) 14	9 (12.5) 11	63 (9.9) 90
Vascular disorders					
Hypertension	21 (10.0) 24	2 (0.9) 3	2 (1.0) 2	1 (1.4) 1	25 (3.9) 29

Notes: TEAEs were coded according to MedDRA 26.0. Treatment-emergent adverse event (TEAE) included any AE that occurred or was worsened on or after the first dose of the study drugs, till 90 days after the last dose of the study drugs or the start of a new anti-tumour therapy (whichever occurred first), as well as TESAEs related to HLX10/HLX04 that were recorded after the start of a new anti-tumour therapy.

Adverse events by severity – Pivotal trial

As of June 15, 2023, the incidence of CTCAE Grade ≥ 3 TEAEs in the, serplulimab + chemotherapy group, placebo + chemotherapy group was 71.5% and 67.9% respectively.

CTCAE Grade ≥ 3 TEAEs with incidence ≥ 5% in any group by PT included neutrophil count decreased (serplulimab + chemotherapy group vs. placebo + chemotherapy group (43.9% vs. 35.9%), white blood cell count decreased (22.4% vs. 19.6%), anaemia (22.4% vs. 21.5%), platelet count decreased (14.0% vs. 15.8%), hypertension (2.8% vs. 2.4%), lymphocyte count decreased (2.8% vs. 3.8%), disease progression (4.7% vs. 7.7%), and hypokalaemia (2.3% vs. 2.9%).

The incidence of serplulimab/placebo-**related** CTCAE Grade ≥ 3 TEAEs in the serplulimab + chemotherapy group was 40.7% and in the placebo + chemotherapy group 30.1%.

The serplulimab/placebo-related CTCAE Grade ≥ 3 TEAEs with incidence ≥ 5% in any group by PT included neutrophil count decreased (serplulimab + chemotherapy group vs. placebo + chemotherapy group): 18.2% vs. 15.3%), platelet count decreased (7.0% vs. 8.1%), white blood cell count decreased (10.7% vs. 8.6%), and anaemia (8.9% vs. 9.1%).

Adverse drug reactions (ADRs)

The section 4.8 of the SmPC was updated to include the nsqNSCLC population into the safety pooled data, which includes the small cell lung cancer (ES-SCLC) (EMEA/H/C/006170), non-small cell lung cancer (NSCLC) (EMA/VR/0000282407) and ESCC indication (EMA/VR/0000284402, which concluded at the same time). Therefore, the changes included in section 4.8 of the current procedure represent the most updated safety pool and a consolidated version.

ADRs Based on All-cause AE Frequency

The frequencies of ADRs listed in the serplulimab plus chemotherapy column are based on all-cause AE frequency identified in 985 subjects from three studies: in ASTRUM-005, ASTRUM-002, and ASTRUM-007.

The most common adverse reactions were anaemia (78.6%), neutropenia (72.9%), leukopenia (69.9%), thrombocytopenia (50.7%), nausea (48.5%), decreased appetite (36.5%), hypoproteinaemia (33.4%), vomiting (31.2%), constipation (29.0%), and asthenia (29.0%).

The most common Grade ≥ 3 adverse reactions were neutropenia (42.7%), leukopenia (22.5%), anaemia (21.5%), thrombocytopenia (13.7%), hyponatraemia (7.4%), and hypokalaemia (5.2%).

The most common serious adverse reactions were thrombocytopenia (8.3%), leukopenia (5.6%), neutropenia (5.6%), pneumonia (4.7%), anaemia (4.1%), and pneumonitis (3.4%).

The most common immune-mediated adverse reactions were hypothyroidism (12.6%), hyperthyroidism (8.7%), immune-mediated skin adverse reactions (6.8%), immune-mediated lung disease (4.9%), abnormal liver function (3.1%), immune-mediated nephritis and renal dysfunction (3.1%), and immune-mediated colitis (1.5%).

Serplulimab was discontinued due to adverse reactions in 6.6% of patients. The most common adverse reaction leading to treatment discontinuation was pneumonitis (1.3%).

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 46. Adverse reactions in patients treated with serplulimab*

	Serplulimab in combination with chemotherapy
Infections and infestations	
Very common	pneumonia [a]
Common	urinary tract infection [b], respiratory tract infection [c], skin infection
Uncommon	septic shock, gastrointestinal infection, meningoencephalitis herpetic
Blood and lymphatic system disorders	
Very common	neutropenia, leukopenia, anaemia, thrombocytopenia, lymphopenia
Common	coagulation function test abnormal [d], granulocytopenia, febrile neutropenia
Uncommon	lymphadenitis
Immune system disorders	
Uncommon	infusion-related reaction [e], anaphylactic reaction
Endocrine disorders	
Very common	hypothyroidism [f], hyperthyroidism [g], hyperglycaemia or type 1 diabetes mellitus [h]
Common	thyroiditis [i], adrenal insufficiency [j]
Uncommon	other thyroid disorder [k], hyperadrenocorticism, hypophysitis, thyroid function test abnormal [l], hypoparathyroidism
Metabolism and nutrition disorders	
Very common	hyperlipidaemia, decreased appetite, hypoproteinaemia, hyperuricaemia, electrolyte imbalance [m], weight decreased
Common	hypoglycaemia, lipoprotein abnormal
Psychiatric disorders	
Very common	insomnia
Nervous system disorders	
Common	paraesthesia, headache, dizziness, neuropathy peripheral [n], vertigo
Uncommon	immune-mediated encephalitis [o], neurotoxicity, motor dysfunction, cerebral infarction, taste disorder, memory impairment

	Serplulimab in combination with chemotherapy
Rare	myasthenia gravis, myasthenic syndrome
Eye disorders	
Uncommon	vision blurred, keratitis, conjunctivitis
Cardiac disorders	
Very common	arrhythmia [p]
Common	sinus tachycardia, conduction defects [q], sinus bradycardia, cardiac failure [r], troponin increased, myocardial injury
Uncommon	cardiomyopathy, myocardial ischaemia, pericardial effusion, myocarditis
Vascular disorders	
Common	hypertension, vasculitis, hypotension
Uncommon	venous thrombosis
Respiratory, thoracic and mediastinal disorders	
Very common	cough, chest pain
Common	pneumonitis [s], dyspnoea, dysphonia, pulmonary embolism
Uncommon	respiratory failure
Gastrointestinal disorders	
Very common	nausea, constipation, diarrhoea, vomiting
Common	dysphagia, abdominal pain, flatulence, gastrointestinal disorder [t], stomatitis, dyspepsia, dry mouth
Uncommon	enteritis [u], gastritis, immune-mediated pancreatitis, gingival bleeding, oesophagitis, gastric ulcer
Hepatobiliary disorders	
Very common	alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased
Common	hyperbilirubinaemia, liver injury [v]
Skin and subcutaneous tissue disorders	
Very common	rash [w], alopecia
Common	pruritus, dermatitis [x], pigmentation disorder
Uncommon	psoriasis, dry skin, hyperhidrosis
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain
Uncommon	myositis [y], arthritis
Renal and urinary disorders	
Very common	protein urine present, blood creatinine increased
Common	blood urea increased, haematuria, renal injury [z]
Uncommon	dysuria, pollakiuria
General disorders and administration site conditions	
Very common	pyrexia, asthenia

	Serplulimab in combination with chemotherapy
Common	malaise, oedema
Uncommon	chills
Investigations	
Common	blood alkaline phosphatase increased, myoglobin blood increased, blood creatine phosphokinase increased, amylase increased, lipase increased

[*] Adverse reaction frequencies presented in the table may not be fully attributable to serplulimab alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.
The following terms represent a group of related events that describe a medical condition rather than a single event:

a. Includes pneumonia, lung abscess.
b. Includes urinary tract infection, asymptomatic bacteriuria, white blood cells urine positive.
c. Includes upper respiratory tract infection, pharyngotonsillitis, tonsillitis, influenza-like illness, lower respiratory tract infection.
d. Includes activated partial thromboplastin time prolonged, activated partial thromboplastin time, activated partial thromboplastin time shortened, international normalised ratio decreased, prothrombin level increased, coagulopathy, hypercoagulation.
e. Includes drug hypersensitivity, infusion-related reaction.
f. Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroxine free decreased, thyroxine decreased, central hypothyroidism, tri-iodothyronine decreased, tri-iodothyronine free decreased.
g. Includes hyperthyroidism, blood thyroid stimulating hormone decreased, thyroxine increased, tri-iodothyronine increased, tri-iodothyronine free increased, thyroxine free increased.
h. Includes hyperglycaemia, type 1 diabetes mellitus, blood glucose increased, impaired fasting glucose, diabetic ketoacidosis, blood ketone body increased, glucose tolerance impaired, ketoacidosis, glycosuria.
i. Includes thyroid disorder, thyroiditis.
j. Includes adrenal insufficiency, cortisol decreased.
k. Includes euthyroid sick syndrome, ultrasound thyroid abnormal.
l. Includes anti-thyroid antibody positive, thyroglobulin increased.
m. Includes hyponatraemia, hypocalcaemia, hypokalaemia, hypomagnesaemia, hypophosphataemia, hypochloraemia, hyperphosphataemia, hyperkalaemia, hypermagnesaemia, hypercalcaemia.
n. Includes neuropathy peripheral, peripheral sensorimotor neuropathy, immune-mediated neuropathy.
o. Includes immune-mediated encephalitis, encephalitis autoimmune.
p. Includes supraventricular extrasystoles, supraventricular tachycardia, arrhythmia, ventricular extrasystoles, arrhythmia supraventricular, atrial fibrillation, atrial tachycardia, bradyarrhythmia, early repolarisation syndrome, ventricular arrhythmia, palpitations, electrocardiogram abnormal.
q. Includes atrioventricular block first degree, bundle branch block right, atrial conduction time prolongation, bundle branch block left, defect conduction intraventricular.
r. Includes cardiac failure, cardiac failure acute, left ventricular failure, N terminal prohormone brain natriuretic peptide increased.
s. Includes immune-mediated lung disease, pneumonitis, interstitial lung disease.
t. Includes acquired trachea-oesophageal fistula, gastrointestinal haemorrhage, gastrointestinal disorder, intestinal obstruction.
u. Includes enteritis, enteritis infectious, immune-mediated enterocolitis [**].
v. Includes hepatic function abnormal, drug-induced liver injury, liver injury, immune-mediated hepatitis, immune-mediated hepatic disorder [**], hepatic failure [**].
w. Includes rash, rash maculo-papular, eczema, drug eruption, erythema, skin toxicity, palmar-plantar erythrodysaesthesia syndrome.
x. Includes autoimmune dermatitis, dermatitis, dermatitis allergic, dermatitis bullous, seborrhoeic dermatitis.
y. Includes myositis [**], immune-mediated myositis.
z. Includes acute kidney injury, renal failure, renal impairment, renal injury, chronic kidney disease, creatinine renal clearance decreased, immune-mediated nephritis.

[**] Post-marketing event.

The following ADRs were added to the SmPC in the context of this procedure or EMA/VR/0000284402:

- Febrile neutropenia, adrenal insufficiency, hypoglycaemia, hypotension , dysphonia, pulmonary embolism amylase increased, lipase increased (with frequency: common)

- Cerebral infarction, taste disorder, memory impairment, keratitis, conjunctivitis, venous thrombosis, respiratory failure, oesophagitis, gastric ulcer, dysuria, pollakiuria (with frequency: uncommon)

The following ADRs frequencies were updated:

- Skin infection, adrenal insufficiency lipoprotein abnormal, vertigo dry mouth, pigmentation disorder from uncommon to common
- Weight decreased chest pain from common to very common
- Abdominal pain. blood urea increased, haematuria, renal injury, blood alkaline phosphatase increased from very common to common
- Infusion related reaction, thyroid function test abnormal, hyperhidrosis from common to uncommon

Lip infection was grouped under the term skin infection and enteritis infectious was grouped under the term enteritis

Myocardial necrosis marker increased was renamed myocardial injury and frequency updated from uncommon to common

Fatigue was grouped with asthenia

Arthralgia, pain in extremity, and musculoskeletal discomfort were grouped under musculoskeletal pain.

Serious adverse event/deaths/other significant events

Deaths – Pivotal study

Table 47 Summary of TEAEs Leading to Death by SOC and PT (Safety Set)

System Organ Class Preferred Term	Serplulimab + HLX04 + Chemotherapy (N=211) n (%) E	Serplulimab + Chemotherapy (N=214) n (%) E	Placebo + Chemotherapy (N=209) n (%) E	Placebo + Chemotherapy Switching to Serplulimab + HLX04 (N=72) n (%) E	Total (N=634) n (%) E
All TEAEs leading to death	32 (15.2) 35	18 (8.4) 18	28 (13.4) 32	9 (12.5) 10	78 (12.3) 85
General disorders and administration site conditions	19 (9.0) 19	13 (6.1) 13	19 (9.1) 19	7 (9.7) 7	51 (8.0) 51

Disease progression	12 (5.7) 12	10 (4.7) 10	16 (7.7) 16	7 (9.7) 7	38 (6.0) 38
Death	4 (1.9) 4	3 (1.4) 3	2 (1.0) 2	0	9 (1.4) 9
Multiple organ dysfunction syndrome	1 (0.5) 1	0	0	0	1 (0.2) 1
Pyrexia	0	0	1 (0.5) 1	0	1 (0.2) 1
Sudden cardiac death	1 (0.5) 1	0	0	0	1 (0.2) 1
Sudden death	1 (0.5) 1	0	0	0	1 (0.2) 1
Respiratory, thoracic and mediastinal disorders	5 (2.4) 6	2 (0.9) 2	2 (1.0) 2	2 (2.8) 2	9 (1.4) 10
Respiratory failure	2 (0.9) 2	2 (0.9) 2	1 (0.5) 1	2 (2.8) 2	5 (0.8) 5
Haemoptysis	1 (0.5) 1	0	0	0	1 (0.2) 1
Interstitial lung disease	1 (0.5) 1	0	0	0	1 (0.2) 1
Pneumonitis	1 (0.5) 1	0	0	0	1 (0.2) 1
Pneumothorax	1 (0.5) 1	0	0	0	1 (0.2) 1
Pulmonary embolism	0	0	1 (0.5) 1	0	1 (0.2) 1
Infections and infestations	3 (1.4) 3	2 (0.9) 2	2 (1.0) 2	1 (1.4) 1	7 (1.1) 7
Pneumonia	1 (0.5) 1	1 (0.5) 1	0	0	2 (0.3) 2
COVID-19	0	1 (0.5) 1	0	0	1 (0.2) 1
Gastrointestinal infection	0	0	1 (0.5) 1	0	1 (0.2) 1
Influenza	1 (0.5) 1	0	0	0	1 (0.2) 1
Septic shock	1 (0.5) 1	0	0	1 (1.4) 1	1 (0.2) 1
Soft tissue infection	0	0	1 (0.5) 1	0	1 (0.2) 1

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Cardiac disorders	4 (1.9) 4	0	2 (1.0) 2	0	6 (0.9) 6
Myocardial infarction	1 (0.5) 1	0	1 (0.5) 1	0	2 (0.3) 2
Arteriosclerosis coronary artery	1 (0.5) 1	0	0	0	1 (0.2) 1
Cardiac failure	1 (0.5) 1	0	0	0	1 (0.2) 1
Cardiovascular disorder	0	0	1 (0.5) 1	0	1 (0.2) 1
Myocarditis	1 (0.5) 1	0	0	0	1 (0.2) 1
Nervous system disorders	1 (0.5) 1	0	1 (0.5) 1	0	2 (0.3) 2
Cerebrovascular accident	0	0	1 (0.5) 1	0	1 (0.2) 1
Epilepsy	1 (0.5) 1	0	0	0	1 (0.2) 1
Vascular disorders	1 (0.5) 1	0	1 (0.5) 1	0	2 (0.3) 2
Circulatory collapse	0	0	1 (0.5) 1	0	1 (0.2) 1
Embolism	1 (0.5) 1	0	0	0	1 (0.2) 1
Injury, poisoning and procedural complications	0	0	1 (0.5) 1	0	1 (0.2) 1
Road traffic accident	0	0	1 (0.5) 1	0	1 (0.2) 1
Investigations	0	0	1 (0.5) 3	0	1 (0.2) 3
Neutrophil count decreased	0	0	1 (0.5) 1	0	1 (0.2) 1

Platelet count decreased	0	0	1 (0.5) 1	0	1 (0.2) 1
White blood cell count decreased	0	0	1 (0.5) 1	0	1 (0.2) 1
Metabolism and nutrition disorders	0	0	1 (0.5) 1	0	1 (0.2) 1
Tumour lysis syndrome	0	0	1 (0.5) 1	0	1 (0.2) 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.5) 1	0	0	1 (0.2) 1
Plasma cell myeloma	0	1 (0.5) 1	0	0	1 (0.2) 1
Psychiatric disorders	1 (0.5) 1	0	0	0	1 (0.2) 1
Completed suicide	1 (0.5) 1	0	0	0	1 (0.2) 1

Notes: TEAEs were coded according to MedDRA 26.0. Treatment-emergent adverse event (TEAE) included any AE that occurred or was worsened on or after the first dose of the study drugs, till 90 days after the last dose of the study drugs or the start of a new anti-tumour therapy (whichever occurred first), as well as TESAEs related to serplulimab/HLX04 that were recorded after the start of a new anti-tumour therapy.

Deaths considered treatment related

Table 48 Summary of TEAEs Related to Serplulimab/Placebo Leading to Death by SOC and PT (Safety Set)

System Organ Class Preferred Term	Serplulimab + HLX04 + Chemotherapy (N=211) n (%) E	Serplulimab + Chemotherapy (N=214) n (%) E	Placebo + Chemotherapy (N=209) n (%) E	Placebo + Chemotherapy Switching to Serplulimab + HLX04 (N=72) n (%) E	Total (N=634) n (%) E
All serplulimab/placebo-related TEAEs leading to death	8 (3.8) 10	5 (2.3) 5	4 (1.9) 5	2 (2.8) 3	17 (2.7) 20
Cardiac disorders	3 (1.4) 3	0	1 (0.5) 1	0	4 (0.6) 4
Cardiac failure	1 (0.5) 1	0	0	0	1 (0.2) 1
Cardiovascular disorder	0	0	1 (0.5) 1	0	1 (0.2) 1
Myocardial infarction	1 (0.5) 1	0	0	0	1 (0.2) 1
Myocarditis	1 (0.5) 1	0	0	0	1 (0.2) 1
General disorders and administration site conditions	1 (0.5) 1	2 (0.9) 2	1 (0.5) 1	0	4 (0.6) 4
Death	0	2 (0.9) 2	1 (0.5) 1	0	3 (0.5) 3
Sudden cardiac death	1 (0.5) 1	0	0	0	1 (0.2) 1

Respiratory, thoracic and mediastinal disorders	3 (1.4) 4	1 (0.5) 1	0	2 (2.8) 2	4 (0.6) 5
Respiratory failure	2 (0.9) 2	1 (0.5) 1	0	2 (2.8) 2	3 (0.5) 3
Interstitial lung disease	1 (0.5) 1	0	0	0	1 (0.2) 1
Pneumonitis	1 (0.5) 1	0	0	0	1 (0.2) 1
Infections and infestations	1 (0.5) 1	1 (0.5) 1	1 (0.5) 1	1 (1.4) 1	3 (0.5) 3
Pneumonia	0	1 (0.5) 1	0	0	1 (0.2) 1
Septic shock	1 (0.5) 1	0	0	1 (1.4) 1	1 (0.2) 1
Soft tissue infection	0	0	1 (0.5) 1	0	1 (0.2) 1
Nervous system disorders	1 (0.5) 1	0	1 (0.5) 1	0	2 (0.3) 2
Cerebrovascular accident	0	0	1 (0.5) 1	0	1 (0.2) 1
Epilepsy	1 (0.5) 1	0	0	0	1 (0.2) 1
Metabolism and nutrition disorders	0	0	1 (0.5) 1	0	1 (0.2) 1
Tumour lysis syndrome	0	0	1 (0.5) 1	0	1 (0.2) 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.5) 1	0	0	1 (0.2) 1
Plasma cell myeloma	0	1 (0.5) 1	0	0	1 (0.2) 1

Notes: TEAEs were coded according to MedDRA 26.0. Treatment-emergent adverse event (TEAE) includes any AE that occurred or was worsened on or after the first dose of the study drugs, till 90 days after the last dose of the study drugs or the start of a new anti-tumour therapy (whichever occurred first), as well as TESAEs related to serplulimab/HLX04 that were recorded after the start of a new anti-tumour therapy.

Deaths considered treatment related

Table 49 Pooled Safety Population: Summary of Serplulimab-related TEAEs Leading to Death

	< RP2D/3D			≥ RP2D/3D				
SOC PT	Monotherapy (N = 7)	Other Combination (N = 3)	Total (N = 10)	Monotherapy (N = 285)	Chemotherapy Combination (N = 1364)	Other Combination (N = 427)	Total (N = 2076)	Total population (N = 2086)
At least one serplulimab-related TEAE leading to death	1 (14.3%)	0	1 (10.0%)	9 (3.2%)	28 (2.1%)	12 (2.8%)	49 (2.4%)	50 (2.4%)
Combined TEAE	1 (14.3%)	0	1 (10.0%)	7 (2.5%)	23 (1.7%)	11 (2.6%)	41 (2.0%)	42 (2.0%)
Pneumonitis	0	0	0	0	7 (0.5%)	2 (0.5%)	9 (0.4%)	9 (0.4%)
Immune-mediated lung disease	0	0	0	0	6 (0.4%)	0	6 (0.3%)	6 (0.3%)
Pneumonitis	0	0	0	0	1 (< 0.1%)	1 (0.2%)	2 (< 0.1%)	2 (< 0.1%)
Interstitial lung disease	0	0	0	0	0	1 (0.2%)	1 (< 0.1%)	1 (< 0.1%)
Respiratory failure	0	0	0	1 (0.4%)	4 (0.3%)	4 (0.9%)	9 (0.4%)	9 (0.4%)
Respiratory failure	0	0	0	0	4 (0.3%)	4 (0.9%)	8 (0.4%)	8 (0.4%)
Acute respiratory failure	0	0	0	1 (0.4%)	0	0	1 (< 0.1%)	1 (< 0.1%)
Septic shock	0	0	0	0	3 (0.2%)	2 (0.5%)	5 (0.2%)	5 (0.2%)
Septic shock	0	0	0	0	3 (0.2%)	2 (0.5%)	5 (0.2%)	5 (0.2%)
Myocarditis	0	0	0	1 (0.4%)	2 (0.1%)	1 (0.2%)	4 (0.2%)	4 (0.2%)
Immune-mediated myocarditis	0	0	0	0	2 (0.1%)	0	2 (< 0.1%)	2 (< 0.1%)
Myocarditis	0	0	0	1 (0.4%)	0	1 (0.2%)	2 (< 0.1%)	2 (< 0.1%)
Pneumonia	0	0	0	2 (0.7%)	2 (0.1%)	0	4 (0.2%)	4 (0.2%)
Pneumonia	0	0	0	2 (0.7%)	1 (< 0.1%)	0	3 (0.1%)	3 (0.1%)
Lung abscess	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Liver injury	0	0	0	2 (0.7%)	0	1 (0.2%)	3 (0.1%)	3 (0.1%)

Table 49 Pooled Safety Population: Summary of Serplulimab-related TEAEs Leading to Death

	< RP2D/3D			≥ RP2D/3D				
SOC PT	Monotherapy (N = 7)	Other Combination (N = 3)	Total (N = 10)	Monotherapy (N = 285)	Chemotherapy Combination (N = 1364)	Other Combination (N = 427)	Total (N = 2076)	Total population (N = 2086)
Hepatic failure	0	0	0	1 (0.4%)	0	1 (0.2%)	2 (< 0.1%)	2 (< 0.1%)
Hepatitis acute	0	0	0	1 (0.4%)	0	0	1 (< 0.1%)	1 (< 0.1%)
Myocardial infarction	0	0	0	1 (0.4%)	1 (< 0.1%)	1 (0.2%)	3 (0.1%)	3 (0.1%)
Myocardial infarction	0	0	0	1 (0.4%)	0	1 (0.2%)	2 (< 0.1%)	2 (< 0.1%)
Acute coronary syndrome	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Thrombocytopenia	1 (14.3%)	0	1 (10.0%)	0	1 (< 0.1%)	1 (0.2%)	2 (< 0.1%)	3 (0.1%)
Platelet count decreased	0	0	0	0	1 (< 0.1%)	1 (0.2%)	2 (< 0.1%)	2 (< 0.1%)
Thrombocytopenia	1 (14.3%)	0	1 (10.0%)	0	0	0	0	1 (< 0.1%)
Cardiac failure	0	0	0	0	1 (< 0.1%)	1 (0.2%)	2 (< 0.1%)	2 (< 0.1%)
Cardiac failure	0	0	0	0	0	1 (0.2%)	1 (< 0.1%)	1 (< 0.1%)
Cardiopulmonary failure	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Colitis	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Immune-mediated enterocolitis	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Dermatitis	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Immune-mediated dermatitis	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Epilepsy	0	0	0	0	0	1 (0.2%)	1 (< 0.1%)	1 (< 0.1%)
Epilepsy	0	0	0	0	0	1 (0.2%)	1 (< 0.1%)	1 (< 0.1%)
Gastrointestinal disorder	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)

Table 49 Pooled Safety Population: Summary of Serplulimab-related TEAEs Leading to Death

	< RP2D/3D			≥ RP2D/3D				
SOC PT	Monotherapy (N = 7)	Other Combination (N = 3)	Total (N = 10)	Monotherapy (N = 285)	Chemotherapy Combination (N = 1364)	Other Combination (N = 427)	Total (N = 2076)	Total population (N = 2086)
Upper gastrointestinal haemorrhage	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Ileus	0	0	0	1 (0.4%)	0	0	1 (< 0.1%)	1 (< 0.1%)
Intestinal obstruction	0	0	0	1 (0.4%)	0	0	1 (< 0.1%)	1 (< 0.1%)
Immune-mediated encephalitis	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Immune-mediated encephalitis	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Pancreatitis	0	0	0	1 (0.4%)	0	0	1 (< 0.1%)	1 (< 0.1%)
Pancreatitis acute	0	0	0	1 (0.4%)	0	0	1 (< 0.1%)	1 (< 0.1%)
Pulmonary haemorrhage	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Pulmonary haemorrhage	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Pyrexia	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Pyrexia	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Sepsis	0	0	0	1 (0.4%)	0	0	1 (< 0.1%)	1 (< 0.1%)
Sepsis	0	0	0	1 (0.4%)	0	0	1 (< 0.1%)	1 (< 0.1%)
Other TEAE	0	0	0	3 (1.1%)	6 (0.4%)	2 (0.5%)	11 (0.5%)	11 (0.5%)
General disorders and administration site conditions	0	0	0	2 (0.7%)	5 (0.4%)	2 (0.5%)	9 (0.4%)	9 (0.4%)
Death	0	0	0	0	4 (0.3%)	0	4 (0.2%)	4 (0.2%)
Disease progression	0	0	0	2 (0.7%)	0	1 (0.2%)	3 (0.1%)	3 (0.1%)
Multiple organ dysfunction syndrome	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)

Table 49 Pooled Safety Population: Summary of Serplulimab-related TEAEs Leading to Death

	< RP2D/3D			≥ RP2D/3D				
SOC PT	Monotherapy (N = 7)	Other Combination (N = 3)	Total (N = 10)	Monotherapy (N = 285)	Chemotherapy Combination (N = 1364)	Other Combination (N = 427)	Total (N = 2076)	Total population (N = 2086)
Sudden cardiac death	0	0	0	0	0	1 (0.2%)	1 (< 0.1%)	1 (< 0.1%)
Hepatobiliary disorders	0	0	0	1 (0.4%)	0	0	1 (< 0.1%)	1 (< 0.1%)
Cholangitis acute	0	0	0	1 (0.4%)	0	0	1 (< 0.1%)	1 (< 0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)
Plasma cell myeloma	0	0	0	0	1 (< 0.1%)	0	1 (< 0.1%)	1 (< 0.1%)

< RP2D/3D: Doses of serplulimab included 0.3 mg/kg/2 week and 1 mg/kg/2 week.
≥ RP2D/3D: Doses of 3 mg/kg/2 week, 4.5 mg/kg/3 week, 10 mg/kg/2 week, 200 mg/2 week, 300 mg/3 week, 400 mg/4 week and 600 mg/6 week.
Total patients included all the patients treated at least one dose with serplulimab; other combination included all other kinds of combinations with serplulimab except chemotherapy combination with serplulimab.
Percentage was based on the safety population as denominator.
MedDRA Version 27.0
TEAEs were AEs that developed or worsened during the on-treatment period.

Adverse Events of Special Interest (AESI)

AESIs included infusion-related reactions (IRRs) and immune-related adverse events (irAEs). An irAE referred to an AE that was related to drug exposure and consistent with immune mediated mechanism of action without any other definitive pathological factor. Serological, immunological, and histological (biopsy) data had to be used to support diagnosis of irAE when appropriate. Appropriate methods were used to exclude pathological factors of irAEs such as tumour, infection, metabolism, toxin.

Immune-related AEs (irAEs) – Pivotal trial

Table 50 Summary of serious immune-related Adverse Events by SOC and PT – Safety Set

System Organ Class Preferred Term	HLX10 + HLX04 + Chemotherapy (N=211) n (%) E	HLX10 + Chemotherapy (N=214) n (%) E	Placebo + Chemotherapy (N=209) n (%) E	Placebo + Chemotherapy switching to HLX10 + HLX04 (N=72) n (%) E	Total (N=634) n (%) E
All serious immune-related adverse events	25 (11.8) 32	21 (9.8) 24	3 (1.4) 3	5 (6.9) 6	49 (7.7) 59
Respiratory, thoracic and mediastinal disorders	7 (3.3) 7	11 (5.1) 11	1 (0.5) 1	1 (1.4) 1	19 (3.0) 19
Immune-mediated lung disease	5 (2.4) 5	8 (3.7) 8	0	1 (1.4) 1	13 (2.1) 13
Interstitial lung disease	2 (0.9) 2	2 (0.9) 2	0	0	4 (0.6) 4
Chronic obstructive pulmonary disease	0	1 (0.5) 1	0	0	1 (0.2) 1
Pneumonitis	0	0	1 (0.5) 1	0	1 (0.2) 1
Cardiac disorders	5 (2.4) 6	2 (0.9) 2	0	1 (1.4) 1	7 (1.1) 8
Immune-mediated myocarditis	3 (1.4) 3	1 (0.5) 1	0	0	4 (0.6) 4
Cardiac failure	1 (0.5) 1	0	0	0	1 (0.2) 1
Myocardial injury	1 (0.5) 1	0	0	1 (1.4) 1	1 (0.2) 1
Myocarditis	1 (0.5) 1	0	0	0	1 (0.2) 1
Sinus bradycardia	0	1 (0.5) 1	0	0	1 (0.2) 1
Gastrointestinal disorders	3 (1.4) 4	3 (1.4) 3	1 (0.5) 1	2 (2.8) 2	7 (1.1) 8
Immune-mediated enterocolitis	2 (0.9) 3	0	1 (0.5) 1	1 (1.4) 1	3 (0.5) 4
Diarrhoea	0	2 (0.9) 2	0	1 (1.4) 1	2 (0.3) 2
Abdominal pain	1 (0.5) 1	0	0	0	1 (0.2) 1
Immune-mediated pancreatitis	0	1 (0.5) 1	0	0	1 (0.2) 1
Investigations	3 (1.4) 4	3 (1.4) 3	0	1 (1.4) 2	6 (0.9) 7
Alanine aminotransferase increased	1 (0.5) 1	1 (0.5) 1	0	0	2 (0.3) 2
Aspartate aminotransferase increased	1 (0.5) 1	0	0	0	1 (0.2) 1
Blood creatinine increased	0	1 (0.5) 1	0	0	1 (0.2) 1
N-terminal prohormone brain natriuretic peptide increased	1 (0.5) 1	0	0	0	1 (0.2) 1
Platelet count decreased	1 (0.5) 1	0	0	0	1 (0.2) 1
Troponin I increased	0	1 (0.5) 1	0	0	1 (0.2) 1
Amylase increased	0	0	0	1 (1.4) 1	0
Lipase increased	0	0	0	1 (1.4) 1	0
General disorders and administration site conditions	2 (0.9) 2	1 (0.5) 1	1 (0.5) 1	0	4 (0.6) 4
Asthenia	2 (0.9) 2	1 (0.5) 1	0	0	3 (0.5) 3
Pyrexia	0	0	1 (0.5) 1	0	1 (0.2) 1
Hepatobiliary disorders	2 (0.9) 2	1 (0.5) 1	0	0	3 (0.5) 3
Drug-induced liver injury	1 (0.5) 1	0	0	0	1 (0.2) 1
Immune-mediated hepatitis	1 (0.5) 1	0	0	0	1 (0.2) 1
Liver injury	0	1 (0.5) 1	0	0	1 (0.2) 1
Infections and infestations	1 (0.5) 1	1 (0.5) 1	0	0	2 (0.3) 2
Peritonitis	1 (0.5) 1	0	0	0	1 (0.2) 1
Pneumonia fungal	0	1 (0.5) 1	0	0	1 (0.2) 1
Metabolism and nutrition disorders	2 (0.9) 2	0	0	0	2 (0.3) 2
Decreased appetite	1 (0.5) 1	0	0	0	1 (0.2) 1
Hyperglycaemia	1 (0.5) 1	0	0	0	1 (0.2) 1

Renal and urinary disorders	1 (0.5) 1	1 (0.5) 1	0	0	2 (0.3) 2
Chronic kidney disease	1 (0.5) 1	0	0	0	1 (0.2) 1
Urinary tract inflammation	0	1 (0.5) 1	0	0	1 (0.2) 1
Endocrine disorders	1 (0.5) 1	0	0	0	1 (0.2) 1
Hypothyroidism	1 (0.5) 1	0	0	0	1 (0.2) 1
Nervous system disorders	1 (0.5) 1	0	0	0	1 (0.2) 1
Epilepsy	1 (0.5) 1	0	0	0	1 (0.2) 1
Psychiatric disorders	1 (0.5) 1	0	0	0	1 (0.2) 1
Abnormal behaviour	1 (0.5) 1	0	0	0	1 (0.2) 1
Skin and subcutaneous tissue disorders	0	1 (0.5) 1	0	0	1 (0.2) 1
Drug eruption	0	1 (0.5) 1	0	0	1 (0.2) 1

Data source: Listing 16.2.7.2, 16.2.7.7.
Notes: TEAEs were coded according to MedDRA 26.0
Treatment-emergent adverse event (TEAE) include any AE that occurred or was worsened on or after the first dose of the study drugs, till 90 days after the last dose of the study drugs or the start of a new anti-tumor therapy (whichever occurred first), as well as SAEs related to HLX10/HLX04 that were recorded after the start of a new anti-tumor therap

Immune-related AEs (irAEs) – Pooled safety population

Serplulimab is associated with immune-mediated adverse reactions. The data for the following immune-mediated adverse reactions are based on 2 086 patients who received serplulimab monotherapy (n=292) or in combination with other medicinal products (n=1 794) across nine doses (0.3, 1, 3, 10 mg/kg every 2 weeks, 4.5 mg/kg every 3 weeks, 200 mg every 2 weeks, 300 mg every 3 weeks, 400 mg every 4 weeks, or 600 mg every 6 weeks) in ten clinical trials.

Immune-mediated lung disease

Immune-mediated lung disease occurred in 4.9% of patients, including Grade 3, 4 or 5 in 1.2%, 0.2%, and 0.3% of patients, respectively. The median time to onset was 4.40 months (range: 0.03 34.53 months). The median duration was 1.76 months (range: 0.10 13.34 months). 2.5% of patients received high dose corticosteroid treatment. Immune-mediated lung disease led to discontinuation in 1.3% of patients.

Immune-mediated colitis

Immune-mediated colitis occurred in 2.0% of patients, including Grade 3 in 0.6% of patients and Grade 5 in < 0.1% of patients. The median time to onset was 3.35 months (range: 0.03 30.55 months). The median duration was 0.43 months (range: 0.03 8.94 months). 0.7% of patients received high dose corticosteroid treatment. Immune-mediated colitis led to discontinuation in 0.2% of patients.

Immune mediated hepatitis

Hepatitis occurred in 0.8% of patients, including Grade 3 in 0.3% of patients, Grade 4 in 0.1% of patients, and Grade 5 in 0.1% of patients. The median time to onset was 2.48 months (range: 0.36 26.78 months). The median duration was 0.95 months (range: 0.10 8.48 months). 0.4% of patients received high dose corticosteroid treatment. Hepatitis led to discontinuation in 0.3% of patients. Abnormal liver function occurred in 3.7% of patients, including Grade 3 in 0.8% of patients, and Grade 4 in 0.1% of patients. The median time to onset was 2.30 months (range: 0.07 45.31 months). The median duration was 1.31 months (range: 0.26 17.54 months). 0.5% of patients received high dose corticosteroid treatment. Abnormal liver function led to discontinuation in 0.2% of patients.

Immune-mediated nephritis and renal insufficiency

Immune-mediated nephritis and renal insufficiency occurred in 3.0% of patients, including Grade 3 in 0.3% of patients and Grade 4 in < 0.1% of patients. The median time to onset was 2.83 months (range: 0.23 17.77 months). The median duration was 1.48 months (range: 0.13 17.94 months). 0.4% of patients received high dose corticosteroid treatment. Immune-mediated nephritis and renal insufficiency led to discontinuation in 0.2% of patients.

Immune-mediated endocrinopathies

Hypothyroidism

Hypothyroidism occurred in 11.7% of patients, including Grade 3 in 0.2% of patients. The median time to onset was 3.83 months (range: 0.46 34.10 months). The median duration was 2.73 months (range: 0.13 29.08 months). 6.7% of patients received thyroid hormone replacement therapy. < 0.1% patients discontinued serplulimab due to hypothyroidism.

Hyperthyroidism

Hyperthyroidism occurred in 6.7% of patients, and there were no Grade ≥ 3 hyperthyroidism. The median time to onset was 2.73 months (range: 0.62 31.18 months). The median duration was 1.45 months (range: 0.07 17.77 months). No patients discontinued serplulimab due to hyperthyroidism.

Thyroiditis

Thyroiditis occurred in 0.7% of patients, and there were no Grade ≥ 3 thyroiditis. The median time to onset was 6.64 months (range: 0.99 13.50 months). The median duration was 1.30 months (range: 0.56 11.30 months). 0.2% of patients received thyroid hormone replacement therapy. No patients discontinued serplulimab due to thyroiditis.

Adrenal gland disorders

Adrenal gland disorders occurred in 0.5% of patients, including Grade 3 in 0.1% of patients. The median time to onset was 6.24 months (range: 3.55 21.45 months). The median duration was 4.60 months. < 0.1% of patients received high dose corticosteroid treatment. No patients discontinued serplulimab due to adrenal gland disorders.

Pituitary disorders

Pituitary disorders occurred in 0.8% of patients, including Grade 3 in 0.1% of patients. The median time to onset was 6.72 months (range: 1.41 20.53 months). The median duration was 3.25 months. 0.2% of patients received high dose corticosteroid treatment. Pituitary disorders led to discontinuation in 0.1% of patients.

Type 1 diabetes mellitus/hyperglycaemia

Type 1 diabetes mellitus/hyperglycaemia occurred in 0.9% of patients, including Grade 3 in 0.4% of patients and Grade 4 in 0.1% of patients. The median time to onset was 4.34 months (range: 0.69 40.28 months). The median duration was 3.48 months (range: 0.53-10.68). 0.5% of patients received insulin replacement therapy. Type 1 diabetes mellitus/hyperglycaemia led to discontinuation in < 0.1% of patients.

Immune-mediated skin reactions

Immune mediated skin reactions occurred in 7.8% of patients, including Grade 3 in 0.8% of patients, Grade 4 in < 0.1% of patients, and Grade 5 in < 0.1% of patients. The median time to onset was 2.96 months (range: 0.03 30.52 months). The median duration was 1.56 months

(range: 0.07 19.06 months). 1.2% of patients received high dose corticosteroid treatment. Immune mediated skin reactions led to discontinuation in 0.5% of patients.

Immune-mediated pancreatitis

Immune-mediated pancreatitis occurred in 1.0% of patients, including Grade 3 in 0.3% of patients, Grade 4 in 0.1% of patients and Grade 5 in < 0.1% of patients. The median time to onset was 2.86 months (range: 0.23 13.67 months). The median duration was 0.76 months (range: 0.16 10.12 months). 0.1% of patients received high dose corticosteroid treatment. Immune-mediated pancreatitis led to discontinuation in 0.2% of patients.

Immune mediated myocarditis

Immune-mediated myocarditis occurred in 0.7% of patients, including Grade 3 in 0.1% of patients, Grade 4 in < 0.1% of patients and Grade 5 in 0.2% of patients. The median time to onset was 1.71 months (range: 0.26 20.70 months). The median duration was 0.79 months (range: 0.30 5.72 months). 0.5% of patients received high dose corticosteroid treatment. Immune-mediated myocarditis led to discontinuation in 0.3% of patients.

Immune-mediated uveitis

Immune-mediated uveitis occurred in < 0.1% of patients, which was Grade 1. The time to onset was 6.90 months. The duration of immune-mediated uveitis was 1.35 months. The event resolved for the patient.

Infusion related reactions

Infusion related reactions occurred in 1.7% of patients, including Grade 3 in 0.1% of patients and Grade 4 in 0.1% of patients. The median time to onset was 1.74 months (range: 0.03 34.04 months). The median duration was 0.07 months (range: 0.03 6.70 months). No patients discontinued serplulimab due to infusion related reactions.

Laboratory findings

Laboratory Abnormalities: Pooled Safety Population

The proportions of patients who experienced a shift from baseline to a Grade ≥ 3 laboratory abnormality were as follows: 0.5% for platelet count decreased, 0.3% for neutrophil count decreased, 0.2% for blood creatine phosphokinase increased, 0.1% for white blood cell count decreased, 0.1% for troponin I increased.

Haematology: Pivotal trial

TEAEs with incidence ≥ 5% in any group in haematology variables by PT were neutrophil count decreased (serplulimab + chemotherapy group vs. placebo + chemotherapy group vs. 81.8% vs. 76.6%), white blood cell count decreased (79.4% vs. 73.2%), platelet count decreased (48.6% vs. 47.4%), lymphocyte count decreased (13.1% vs. 15.3%), and white blood cell count increased (5.1% vs. 6.7%).

Haematology: Pooled Safety Population

Haematology parameters with shifts from normal or abnormal with no clinical significance at baseline to clinically significant post-baseline observed in > 10% of subjects included: neutrophils (64.8%), leukocytes (62.5%), haemoglobin (55.5%), platelets (46.9%), erythrocytes (45.8%), neutrophils/leukocytes (22.7%), and lymphocytes (14.8%).

Serum chemistry: Pivotal Study

TEAEs with incidence ≥ 5% were aspartate aminotransferase increased (serplulimab + chemotherapy group vs. placebo + chemotherapy group) 47.2% vs. 37.8%, alanine aminotransferase increased (51.4% vs. 41.1%), gamma-glutamyltransferase increased (21.0% vs. 12.4%), blood creatinine increased (13.1% vs. 7.2%), blood lactate dehydrogenase increased (13.6% vs. 9.6%), blood alkaline phosphatase increased (10.3% vs. 12.4%), blood urea increased (5.1% vs. 2.4%), blood bilirubin increased (6.5% vs. 4.8%), blood glucose increased (4.7% vs. 3.3%), blood creatine phosphokinase increased (6.5% vs. 2.4%), and bilirubin conjugated increased (3.7% vs. 2.9%).

Blood Chemistry: Pooled Safety Population

Blood chemistry parameters with shifts from normal or abnormal with no clinical significance at baseline to clinically significant post-baseline observed in > 10% of subjects included: aspartate aminotransferase (27.3%), alanine aminotransferase (26.5%), albumin (23.3%), potassium (19.8%), sodium (17.4%), cholesterol (15.5%), glucose (14.9%), creatinine (13.6%), protein (10.6%), and calcium (10.3%).

Coagulation Function: **Pivotal study**

TEAEs with incidence ≥ 1% were fibrin D dimer increased (serplulimab + chemotherapy group vs. placebo + chemotherapy group: 2.3% vs. 3.8%, blood fibrinogen increased (0.5% vs. 1.9%), prothrombin time prolonged (0.5% vs. 1.0%), activated partial thromboplastin time prolonged (0 vs. 1.0%), antithrombin III decreased (0 vs. 0.5%), fibrin degradation products increased (0 vs. 0.5%), and prothrombin time ratio increased (0 vs. 0.5%)

Coagulation Function: Pooled Safety Population

Coagulation function parameters with shifts from normal or abnormal with no clinical significance at baseline to clinically significant post-baseline were observed in less than 5% of subjects.

Urinalysis: Pivotal study

TEAEs with incidence ≥ 1% in any group in urinalysis variables under the SOC of Investigations by PT were urinary occult blood positive (serplulimab + chemotherapy group vs. placebo + chemotherapy group: 1.9% vs. 3.3%), white blood cells urine positive (1.4% vs. 1.4%), protein urine present (3.3% vs. 3.8%), urobilinogen urine increased (1.4% vs. 0.5%), protein urine (0.5% vs. 1.4%), red blood cells urine positive (0.5% vs. 0.5%), urine ketone body present (0 vs. 0.5%), and urine bilirubin increased (0.9% vs. 0.5%)

Urinalysis: Pooled Safety Population

Urinalysis parameter with shifts from normal or abnormal with no clinical significance at baseline to clinically significant post-baseline observed in > 10% of subjects was urine protein (14.7%).

Thyroid Function: Pivotal study

TEAEs with incidence ≥ 1% in any group in thyroid function variables under the SOC of Investigations by PT were blood thyroid stimulating hormone increased (serplulimab + chemotherapy group vs. placebo + chemotherapy group: 7.0% vs. 3.8%), tri-iodothyronine decreased (1.9% vs. 1.0%), blood thyroid stimulating hormone decreased (2.8% vs. 1.0%), thyroxine increased (3.7% vs. 1.4%), tri-iodothyronine free decreased (2.3% vs. 0), tri-iodothyronine free increased (1.9% vs. 0.5%), and tri-iodothyronine increased (1.9% vs. 0), thyroxine free increased (0.9% vs. 1.4%)

Thyroid Function: Pooled Safety Population

Thyroid function parameters with shifts from normal or abnormal with no clinical significance at baseline to clinically significant post-baseline observed in > 10% of subjects included: thyrotropin (19.4%), free triiodothyronine (13.1%) and free thyroxine (12.8%).

Myocardial enzymes: Pivotal study

TEAEs with incidence ≥ 1% in any group in myocardial enzyme were N-terminal prohormone brain natriuretic peptide increased (serplulimab + chemotherapy group vs. placebo + chemotherapy group: 7.5% vs. 4.8%), brain natriuretic peptide increased (3.3% vs. 1.0%), troponin I increased (1.4% vs. 0.5%), troponin T increased (0.9% vs. 1.0%), and troponin increased (1.4% vs. 1.0%)

VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Electrocardiogram – Pivotal study

12-lead ECG: HLX10-002-NSCLC301

TEAEs with incidence ≥ 1% in any group in 12-lead ECG variables under the SOC of Investigations by PT were electrocardiogram QT prolonged (serplulimab + chemotherapy group vs. placebo + chemotherapy group: 1.4% vs. 0.5%, electrocardiogram Q wave abnormal (0 vs. 0.5% vs), electrocardiogram ST segment abnormal (1.9% vs. 0 vs.), and electrocardiogram T wave abnormal (1.4% vs. 1.0%), and electrocardiogram T wave amplitude decreased (0.5% vs. 1.0%).

Electrocardiogram: Pooled Safety Population

In the pooled safety population, the mean (SD) worst change (largest increase) in QTcF interval on treatment was 28.84 (34.704) msec. The proportion of subjects with the worst QTcF > 500 msec was 2.5%. The proportion of subjects with the largest QTcF increases between > 30 and ≤ 60 msec was 26.2%. The proportion of subjects with the largest QTcF increase of > 60 msec was 10.6%.

Safety in special populations

Pooled studies

Intrinsic Factors

Paediatric Use

The safety of serplulimab has not been established in paediatric patients.

Geriatric Use

Table 51 Safety Profile by Age Group

MedDRA Terms	Age < 65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)
Total TEAEs	1284 (97.9%)	715 (97.5%)	37 (92.5%)	1 (100%)
TESAEs – Total	489 (37.3%)	365 (49.8%)	16 (40.0%)	1 (100%)
-Fatal	132 (10.1%)	108 (14.7%)	5 (12.5%)	1 (100%)
-Hospitalization/prolong existing hospitalization	414 (31.6%)	313 (42.7%)	13 (32.5%)	1 (100%)
-Life-threatening	56 (4.3%)	52 (7.1%)	4 (10.0%)	1 (100%)
-Disability/incapacity	5 (0.4%)	1 (0.1%)	0	0
-Other (medically significant)	19 (1.4%)	9 (1.2%)	0	0

MedDRA Terms	Age < 65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)
AE leading to drop-out	135 (10.3%)	103 (14.1%)	3 (7.5%)	1 (100%)
Psychiatric disorders	154 (11.7%)	102 (13.9%)	4 (10.0%)	0
Nervous system disorders	265 (20.2%)	168 (22.9%)	10 (25.0%)	0
Accidents and injuries	47 (3.6%)	39 (5.3%)	2 (5.0%)	1 (100%)
Cardiac disorders	277 (21.1%)	196 (26.7%)	7 (17.5%)	1 (100%)
Vascular disorders	177 (13.5%)	106 (14.5%)	7 (17.5%)	1 (100%)
Cerebrovascular disorders	26 (2.0%)	16 (2.2%)	1 (2.5%)	0
Infections and infestations	455 (34.7%)	280 (38.2%)	12 (30.0%)	1 (100%)
Anticholinergic syndrome	319 (24.3%)	215 (29.3%)	9 (22.5%)	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	83 (6.3%)	77 (10.5%)	2 (5.0%)	0
Other AE appearing more frequently in older patients	1161 (88.5%)	678 (92.5%)	37 (92.5%)	1 (100%)
Decreased appetite	362 (27.6%)	286 (39.0%)	12 (30.0%)	1 (100%)
Anaemia	813 (62.0%)	539 (73.5%)	26 (65.0%)	0
White blood cell count decreased	638 (48.6%)	429 (58.5%)	14 (35.0%)	0
Neutrophil count decreased	629 (47.9%)	421 (57.4%)	14 (35.0%)	0
Platelet count decreased	468 (35.7%)	358 (48.8%)	12 (30.0%)	0
Nausea	429 (32.7%)	292 (39.8%)	12 (30.0%)	0
Alanine aminotransferase increased	395 (30.1%)	139 (19.0%)	10 (25.0%)	0
Dyspnoea	89 (6.8%)	52 (7.1%)	10 (25.0%)	0
Asthenia	253 (19.3%)	183 (25.0%)	8 (20.0%)	0
Cough	156 (11.9%)	102 (13.9%)	8 (20.0%)	0
Neutropenia	125 (9.5%)	96 (13.1%)	7 (17.5%)	0
Leukopenia	106 (8.1%)	75 (10.2%)	6 (15.0%)	0
Fatigue	84 (6.4%)	49 (6.7%)	6 (15.0%)	0
Constipation	290 (22.1%)	208 (28.4%)	5 (12.5%)	0
Pruritus	76 (5.8%)	59 (8.0%)	5 (12.5%)	0
Protein urine present	44 (3.4%)	18 (2.5%)	3 (7.5%)	0

MedDRA Version 27.0
AEs leading to drop-out are TEAES leading to permanent treatment discontinuation.
The "Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures" included the PTs of Orthostatic hypotension, Fall, Loss of consciousness, Syncope, Dizziness, Ataxia, and the HLGT of Fractures.
The following AE categories have been analysed by MedDRA SMQs (broad and narrow): Accidents and injuries (SMQ: Accidents and Injuries), Cerebrovascular disorders (SMQ: Central nervous system vascular disorders), and Anticholinergic syndrome (SMQ: Anticholinergic syndrome).
> 5% difference between the < 65, 65-74, 75-84 and ≥ 85 age categories.

Renal impairment

No effect of CRCL (Cockcroft-Gault) was found on serplulimab CL based on a popPK analysis in patients with mild (CRCL=60-89 mL/min; n=917), moderate (CRCL=30-59 mL/min; n=216), and severe (CRCL=15-29 mL/min; n=1) renal impairment, and normal renal function (CRCL ≥ 90 mL/min, n=973). There are insufficient data in patients with severe renal impairment for dosing recommendations.

Hepatic impairment

No effect of ALT, AST or total BIL was found on serplulimab CL based on a popPK analysis in patients with mild (BIL ≤ ULN and AST > ULN or BIL > 1 to 1.5 × ULN and any AST; n=279) and moderate (BIL > 1.5 to 3 × ULN and any AST; n=4) hepatic impairment, and normal (BIL ≤ ULN and AST ≤ ULN; n=1819) hepatic function. There are insufficient data in patients with moderate

hepatic impairment for dosing recommendations. Serplulimab has not been studied in patients with severe (BIL > 3 × ULN and any AST) hepatic impairment.

Extrinsic Factors

No specific safety analyses based on factors associated with patient environment (medical environment, use of other drugs, use of tobacco, use of alcohol, and food habits) were conducted in the pivotal study HLX10-002-NSCLC301 and the pooled ten studies.

Immunological events

Table 52: Summary of immunogenicity results for serplulimab by study

ADA category	HLX10-001 (N=66)	HLX10 HLX04-001 (N=26)	HLX10-010-MSI201 (N=108)	HLX10-008-HCC201 (N=123)	HLX10-011-CC201 (N=21)	HLX10 HLX07-001 (N=13)	HLX10-004-NSCLC303 (N=455)	HLX10-005-SCLC301 (N=389)	HLX10-002-NSCLC301 (N=503)	HLX10-007-EC301 (N=382)	Total (N=2086)
ADA positive at baseline only	2 (3.0%)	0	2 (1.9%)	1 (0.8%)	0	0	2 (0.4%)	1 (0.3%)	5 (1.0%)	2 (0.5%)	15 (0.7%)
ADA positive at any visit	13 (19.7%)	1 (3.8%)	7 (6.5%)	3 (2.4%)	0	1 (7.7%)	15 (3.3%)	8 (2.1%)	22 (4.4%)	24 (6.3%)	94 (4.5%)
Treatment-emergent ADA positive	11 (16.7%)	1 (3.8%)	5 (4.6%)	2 (1.6%)	0	1 (7.7%)	13 (2.9%)	7 (1.8%)	17 (3.4%)	22 (5.8%)	79 (3.8%)
Treatment-boosted ADA	0	0	0	0	0	0	0	0	0	0	0
Treatment-induced ADA	8 (12.1%)	1 (3.8%)	3 (2.8%)	2 (1.6%)	0	0	12 (2.6%)	6 (1.5%)	15 (3.0%)	15 (3.9%)	62 (3.0%)
Persistent positive ADA	6 (9.1%)	0	2 (1.9%)	1 (0.8%)	0	1 (7.7%)	3 (0.7%)	2 (0.5%)	4 (0.8%)	8 (2.1%)	27 (1.3%)
Transient positive ADA	5 (7.6%)	1 (3.8%)	3 (2.8%)	1 (0.8%)	0	0	10 (2.2%)	5 (1.3%)	14 (2.8%)	14 (3.7%)	53 (2.5%)
NAb positive at any visit	0	NA	0	0	NA	NA	0	0	2 (0.4%)	1 (0.3%)	3 (0.1%)

Note: NA: not applicable. NAb testing was not performed in this study. Definitions for the different categories of ADA-positive patients are as follows:
Treatment-emergent ADA positive is defined as at least one post-baseline ADA positive.
Treatment-induced ADA is defined as baseline negative ADA, post-baseline ADA positive.
Treatment-boosted ADA is defined as baseline positive ADA titer that was boosted to ≥4 fold during the study period. If the titer test value is less than 10, it will be calculated as 10.
Persistently positive is defined as having at least 2 post-baseline ADA positive measurements with at least 16 weeks between the first and last positive measurements, or an ADA positive result at the last available assessment, including patients meeting these criteria who are ADA positive at baseline.
Transiently positive is defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive, including patients meeting these criteria who are ADA positive at baseline.
For subjects who switched from placebo to serplulimab, baseline is defined as the last observation before serplulimab treated.

Table 53: Summary of immunogenicity results for serplulimab by dose and combination

ADA category	<RP2D/3D			≥RP2D/3D				Total population (N=2086)
	Monotherapy (N=7)	Other Combination (N=3)	Total (N=10)	Monotherapy (N=285)	Chemotherapy Combination (N=1364)	Other Combination (N=427)	Total (N=2076)	
ADA positive at baseline only	0	0	0	4 (1.4%)	8 (0.6%)	3 (0.7%)	15 (0.7%)	15 (0.7%)
ADA positive at any visit	1 (14.3%)	1 (33.3%)	2 (20.0%)	21 (7.4%)	55 (4.0%)	16 (3.7%)	92 (4.4%)	94 (4.5%)
Treatment-emergent ADA positive	1 (14.3%)	1 (33.3%)	2 (20.0%)	17 (6.0%)	47 (3.4%)	13 (3.0%)	77 (3.7%)	79 (3.8%)
Treatment-boosted ADA	0	0	0	0	0	0	0	0
Treatment-induced ADA	1 (14.3%)	1 (33.3%)	2 (20.0%)	12 (4.2%)	37 (2.7%)	11 (2.6%)	60 (2.9%)	62 (3.0%)
Persistent positive ADA	0	0	0	8 (2.8%)	15 (1.1%)	4 (0.9%)	27 (1.3%)	27 (1.3%)
Transient positive ADA	1 (14.3%)	1 (33.3%)	2 (20.0%)	9 (3.2%)	32 (2.3%)	10 (2.3%)	51 (2.5%)	53 (2.5%)
NAb positive at any visit	0	0	0	0	2 (0.1%)	1 (0.2%)	3 (0.1%)	3 (0.1%)

Note: Definitions for the different categories of ADA-positive patients are as follow.
Treatment-emergent ADA positive is defined as at least one post-baseline ADA positive.
Treatment-induced ADA is defined as baseline negative ADA, post-baseline ADA positive.
Treatment-boosted ADA is defined as baseline positive ADA titer that was boosted to ≥4 fold during the study period. If the titer test value is less than 10, it will be calculated as 10.
Persistently positive is defined as having at least 2 post-baseline ADA positive measurements with at least 16 weeks between the first and last positive measurements, or an ADA positive result at the last available assessment, including patients meeting these criteria who are ADA positive at baseline.
Transiently positive is defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive, including patients meeting these criteria who are ADA positive at baseline.

For subjects who switched from placebo to serplulimab, baseline is defined as the last observation before serplulimab treated.

HLX10-002-NSCLC301

In this study, ADA samples were collected within 7 days before dosing in Cycle 1, within 3 days before dosing in Cycles 2, 4, 6, 8, and every 4 cycles thereafter, at the termination visit and/or during the safety follow-up. ADAs were measured using an ACL immunoassay, method AP-HLX10ADA02 and Nabs were measured by ELISA, method APHLX10NAb01. ADA samples were collected and sent to the central laboratory for evaluation.

At the 5-Jun-2023 data cut-off, in the safety population (n=503), 5 (1.0%) patients were ADA positive at baseline only, 22 (4.4%) patients were ADA positive at any visit and 17 (3.4%) of patients were treatment-emergent ADA positive, defined as at least one post-baseline ADA positive. There was no treatment-boosted ADA, defined as baseline positive ADA titer that was boosted to ≥4 fold during the study period (if titer test value <10, it will be calculated as 10). There was 15 (3.0%) treatment-induced ADA, defined as baseline negative ADA, post-baseline ADA positive.

Immunogenicity results per arm in the safety set of study HLX10-002-NSCLC301 were presented with a May 31, 2023 data cut-off. Here, six (2.8%) subjects in the HLX10 + HLX04 + chemotherapy group were detected positive for HLX10 ADA at least once at visits after administration, with negative NAb detected in the further test. Seven (3.3%) subjects in the HLX10 + chemotherapy group were detected positive for serplulimab ADAs at least once at visits after administration, of which 1 (0.5%) subject was detected positive for NAb at least once at visits. In the placebo + chemotherapy switching to HLX10 + HLX04 after PD group, 4 (5.6%) subjects tested positive for serplulimab ADAs at least once at visits after administration, of which 1 (1.4%) subject tested positive for NAbs at least once at visits.

Pooled safety population

In the ten studies where the immunogenicity of serplulimab was studied, the overall treatment-induced ADA positive rate was 3.0% (62/2086). From the 2086 evaluable subjects, 94 (4.5%) subjects were ADA positive at any visit. 79 (3.8%) patients had treatment-emergent ADA (defined as at least one post-baseline ADA positive). 27 (1.3%) were persistently positive for ADA, defined as having at least 2 post-baseline ADA positive measurements with at least 16 weeks between the first and last positive measurements, or an ADA positive result at the last available assessment, including patients meeting these criteria who are ADA positive at baseline. 53 (2.5%) patients were transiently positive for ADA, defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive, including patients meeting these criteria who are ADA positive at baseline. No patients had treatment-boosted ADA, defined as baseline positive ADA titer that was boosted to ≥4 fold during the study period (for titer test value <10, it will be calculated as 10). Three patients (0.1%) patients had neutralising antibodies. Nabs were tested in 7 of the 10 studies included in the ISI.

The immunogenicity of serplulimab was evaluated in all 2086 patients who were treated with serplulimab with dose ranging from 0.3 mg/kg Q2W to 10 mg/kg Q2W. 2076 of them were administrated with doses greater than RP2D or 3D (including 3 mg/kg Q2W, 4.5 mg/kg Q3W, 10 mg/kg Q2W, 200 mg Q2W, 300 mg Q3W, 400 mg Q4W, 600 mg Q6W). 285 patients with doses greater than RP2D or 3D (N=2076) were treated with serplulimab monotherapy, 1364 patients received serplulimab co-administered with chemotherapy and 427 patients received serplulimab co-administered with other anticancer agents, in whom the treatment-emergent ADA positive rates were 6.0% (17/285), 3.4% (47/1364) and 3.0% (13/427), respectively.

An overview of AEs by ADA status are shown in Table 54.

Table 54: Overview of AEs by ADA

Number of subjects experiencing	Subjects with at least one positive ADA (n=94)	Subjects without positive ADA (n=1992)	Total (n=2086)
At least one adverse event	90 (95.7%)	1947 (97.7%)	2037 (97.7%)
At least one adverse event with CTCAE Grade >=3	55 (58.5%)	1411 (70.8%)	1466 (70.3%)
At least one serplulimab related adverse event with CTCAE Grade >=3	31 (33.0%)	685 (34.4%)	716 (34.3%)
At least one serious adverse event	34 (36.2%)	837 (42.0%)	871 (41.8%)
At least one irAE	30 (31.9%)	684 (34.3%)	714 (34.2%)
At least one AESI	30 (31.9%)	705 (35.4%)	735 (35.2%)

Safety related to drug-drug interaction and other interactions

Serplulimab is a humanised monoclonal antibody and thus has not been investigated for PK interactions with other drugs. Monoclonal antibodies are not metabolised by Cytochrome P450 enzymes or other drug metabolic enzymes. The inhibitory effect or induction of the concomitant drugs on these enzymes was not expected to affect the PK profile of serplulimab.

Before treatment with serplulimab is started, systemic corticosteroids or other immunosuppressants should be avoided, as they may interfere with the pharmacodynamic activity of serplulimab. Systemic corticosteroids and other immunosuppressants can be used for treatment of immune-related adverse reactions after the treatment with this product is started.

Discontinuation due to adverse events

Adverse Events Leading to Treatment Discontinuation : Pivotal trial

The number of subjects who experienced TEAEs leading to the discontinuation of serplulimab/placebo, was 23 (10.7%) subjects in the serplulimab + chemotherapy group and 12 (5.7%) subjects in the placebo + chemotherapy group.

TEAEs leading to the discontinuation of serplulimab/placebo with incidence ≥ 1% by PT (in descending order of incidence) included immune-mediated lung disease (4 [1.9%] subjects) in the serplulimab + chemotherapy group; disease progression (3 [1.4%] subjects) and pneumonitis (2 [1.0%] subjects) in the placebo + chemotherapy group.

The number of subjects who experienced serplulimab/placebo-related TEAEs leading to the discontinuation of serplulimab/placebo was 18 (8.4%) subjects in the serplulimab + chemotherapy group and 5 (2.4%) subjects in the placebo + chemotherapy group.

The serplulimab/placebo-related TEAEs leading to the discontinuation of serplulimab/placebo with incidence ≥ 1% by PT (in descending order of incidence) included immune-mediated lung disease (4 [1.9%] subjects) in the serplulimab + chemotherapy group and pneumonitis (2 [1.0%] subjects) in the placebo + chemotherapy group.

Pooled safety population

TEAEs leading to serplulimab discontinuation occurred in 242 (11.6%) subjects. In the ≥ RP2D/3D dose group, 11.2% of the subjects who received serplulimab monotherapy discontinued serplulimab due to TEAEs, compared to 11.0% of the subjects who received serplulimab in combination with chemotherapy, and 13.3% of the subjects who received serplulimab in combination with other drugs.

For the grouped categories, TEAEs leading to serplulimab discontinuation with an incidence ≥ 0.5% in the total population were pneumonitis (1.3%), pneumonia (1.0%), thrombocytopenia (0.6%), liver injury (0.6%), and renal injury (0.5%).

For the ungrouped PTs, TEAEs leading to serplulimab discontinuation with incidence ≥ 0.5% in the total population was disease progression (0.7%).

A total of 150 (7.2%) subjects experienced serplulimab-related TEAEs leading to serplulimab discontinuation. In the ≥ RP2D/3D dose group, 4.9% of the subjects who received serplulimab monotherapy discontinued serplulimab due to serplulimab-related TEAEs, compared to 6.9% of the subjects who received serplulimab in combination with chemotherapy, and 9.6% of the subjects who received serplulimab in combination with other drugs.

For the grouped categories, serplulimab-related TEAE leading to serplulimab discontinuation with an incidence ≥ 0.5% in the total population was pneumonitis (1.3%). No serplulimab-related TEAEs leading to serplulimab discontinuation had an incidence ≥ 0.5% by ungrouped PT.

TEAEs Leading to Dose Modification

Dose modification of serplulimab/placebo was not allowed in this study.

Adverse Events Leading to Treatment Interruption

Pivotal study

TEAEs leading to serplulimab/placebo interruption

As of June 15, 2023, 126 (58.9%) subjects in the serplulimab + chemotherapy group, 80 (38.3%) subjects in the placebo + chemotherapy group experienced TEAEs leading to the interruption of serplulimab/placebo, respectively.

In the serplulimab + chemotherapy group, TEAEs leading to the interruption of serplulimab/placebo with incidence ≥ 10% by PT (in descending order of incidence) included neutrophil count decreased (29 [13.6%] subjects), COVID-19 (28 [13.1%] subjects), and white blood cell count decreased (24 [11.2%] subjects).

In the placebo + chemotherapy group, TEAEs leading to the interruption of serplulimab/placebo with incidence ≥ 10% by PT was anaemia (21 [10.0%] subjects).

Serplulimab/Placebo-related TEAEs Leading to Serplulimab/Placebo Interruption

As of June 15, 2023, 73 (34.1%) subjects in the serplulimab + chemotherapy group, 41 (19.6%) subjects in the placebo + chemotherapy group experienced serplulimab/placebo-related TEAEs leading to the interruption of serplulimab/placebo, respectively.

In the serplulimab + chemotherapy group, serplulimab/placebo-**related** TEAEs leading to the interruption of serplulimab/placebo with incidence ≥ 5% by PT (in descending order of incidence) included alanine aminotransferase increased (16 [7.5%] subjects), aspartate aminotransferase increased (13 [6.1%] subjects), and platelet count decreased (12 [5.6%] subjects).

In the placebo + chemotherapy group, serplulimab/placebo-**related** TEAEs leading to the interruption of serplulimab/placebo with incidence ≥ 5% by PT was platelet count decreased (12 [5.7%] subjects).

Pooled safety population

TEAEs leading to serplulimab interruption occurred in 1052 (50.4%) subjects. In the ≥ RP2D/3D dose group, 30.2% of the subjects who received serplulimab monotherapy serplulimab interruption due to TEAEs, compared to 53.7% of the subjects who received serplulimab in combination with chemotherapy, and 53.2% of the subjects who received serplulimab in combination with other drugs.

For the grouped categories, TEAEs leading to serplulimab interruption with an incidence ≥ 5% in the total population were neutropenia (15.2%), thrombocytopenia (13.8%), leukopenia (10.8%), anaemia (8.1%), and COVID-19 (5.1%).

No TEAEs leading to serplulimab interruption had an incidence ≥ 5% by ungrouped PT.

A total of 651 (31.2%) subjects experienced serplulimab-related TEAEs leading to the serplulimab interruption. In the ≥ RP2D/3D dose group, 18.9% of the subjects who received serplulimab monotherapy interrupted serplulimab due to serplulimab related TEAEs, compared to 31.7% of the subjects who received serplulimab in combination with chemotherapy, and 37.7% of the subjects who received serplulimab in combination with other drugs.

For the grouped categories, serplulimab-related TEAEs leading to the serplulimab interruption with an incidence ≥ 5% in the total population were thrombocytopenia (7.4%), neutropenia (6.4%), and leukopenia (5.1%).

No serplulimab-related TEAEs leading to serplulimab interruption had an incidence ≥ 5% by ungrouped PT.

Post marketing experience

Serplulimab was approved by National Medical Products Administration (NMPA) of China with the trade name Hansizhuang on March 22, 2022 and marketed in China on March 30, 2022 and is authorized for indications in NSCLC, SCLC and ESCC combined with chemotherapy. Serplulimab was authorised in EU for ES-SCLC in combination with carboplatin and etoposide on February 3, 2025 (EMEA/H/C/006170). This indication is also approved in Indonesia, Cambodia and Thailand.

Cumulatively, it was estimated that 93 899 patients used serplulimab injection.

Adverse Events from Marketing Experience

As of March 21, 2025, 1554 valid individual case safety reports (ICSRs) were collected which included 2712 AEs (2641 ADRs). 1500 ICSRs were collected from spontaneous reports, which included 2593 AEs (2528 ADRs). And the rest of 54 ICSRs were collected from solicited source, which included 119 AEs (113 ADRs).

No new significant safety risks have been identified so far. Neither the regulatory authorities nor Henlius have taken any actions for safety issues of serplulimab.

2.5.1. Discussion on clinical safety

The safety of serplulimab for the targeted indication, in combination with carboplatin and pemetrexed is for the first-line treatment of adult patients with locally advanced or metastatic non-

squamous non-small cell lung carcinoma is based primarily on interim results from study HLX10-002-NSCLC30.

Supportive pooled safety data from a total of 10 clinical trials with serplulimab in subjects with various types of solid tumours is available including a total of 2086 serplulimab treated patients. Of these, only 268 patients are non-Asian. The safety database is considered large enough to sufficiently describe the safety profile of serplulimab. As of the cut-off of 9 January 2023, in this pooled safety population, 70.7%, 47.7%, and 33.3% of subjects had serplulimab exposure for at least 3 months, 6 months, and 9 months, respectively.

Immune-related adverse events (irAEs) and **infusion related reactions (IRRs)** were adverse events of special interest (AESI) for serplulimab. In the pivotal study, immune-related TEAEs occurred in 30.4% and 12.4 % of the patients in the serplulimab and placebo arm, respectively, which is in line with the overall results in the pooled safety population (irAEs: 34.2%, see below). The majority were non-serious in both arms (serious irAEs: 9.8% vs. 1.4%).

The most common irAEs by PT were hypothyroidism (serplulimab vs placebo), hypothyroidism, (hyperthyroidism, rash, immune-mediated lung disease.

In the pooled safety population, 7.4% received high-dose corticosteroids to treat irAEs. In the pivotal study, 7.9% of the patients treated with serplulimab were treated with a high-dose corticosteroid to handle immune-related AEs.

Adequate description of how to manage immune-mediated adverse reactions are included in section 4.4 of the SmPC .

There were no **infusion-related reactions (IRRs)** in the serplulimab arm and 1 (0.5%) IRR in the control arm, which was a CTCAE grade 4 infusion reaction.

A consolidated SmPC based on the consolidated safety database of the concomitant type II variation procedures (EMA/VR/0000284402, EMA/VR/0000282407) was provided.

In the pivotal study, as of June 15, 2023, almost all (99.1% in the serplulimab arm and 99.5% in the placebo arm) reported at least one **TEAE**, of which the majority were considered serplulimab/placebo-related (serplulimab: 89.7% vs. placebo: 78.0%). The rates of **≥Grade 3 TEAEs** were 71.5% and 67.9% (serplulimab/placebo-related: 40.7% and 30.1%), respectively. The large proportion of TEAEs reported as related to serplulimab in the placebo arm (78.0%) indicates that most of the TEAEs are not related to the study drug, or they are caused by the chemotherapy backbone in both study arms.

The most common TEAEs that occurred in at least 20% in the serplulimab group were neutrophil count decreased, white blood cell count decreased, platelet count decreased, alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased, gamma-glutamyltransferase increased, weight increased, anaemia, decreased appetite, hypoalbuminemia, hypercholesterolaemia, hypokalaemia, nausea, constipation, vomiting and asthenia).

The overall safety profiles of the two treatment arms in the pivotal study are quite similar, with only slightly higher frequencies of **TESAEs** (44.9% vs 40.7%). There are more TESAES reported in the Respiratory SOC for the serplulimab arm compared to the placebo arm. This is mainly driven by the event immune-mediated lung disease which was reported more frequently in the serplulimab-arm (8 subjects, 3.7%) vs in the placebo-arm (0). In the SOC Infections and infestation there was a similar imbalance, mainly driven by the event 'pneumonia' (6 subjects [2.8%] vs 1 [0.5]). The reporting of TESAEs is of a similar size in both arms when it comes to the other SOCs (GI, renal, nervous system, endocrine, musculoskeletal)

Serplulimab/placebo-**related TEAEs lead to serplulimab/placebo discontinuation** were three times as frequent (8.4%) in subjects in the serplulimab arm compared to the placebo arm (2.4%).

There were also more TEAEs leading to **drug interruptions** in the serplulimab arm than in the placebo arm (53.7 % vs 37.8%, serplulimab/placebo-related: 34.1% vs 19.6 %, respectively).

TEAEs leading to death: 8.4% in the serplulimab arm and 13.4% in the placebo arm experienced TEAEs leading to death, of which the majority was considered not related. Five (5) subjects vs 4 subjects experienced TEAEs considered related. Although the numbers are balanced, 2 of the fatal cases in the serplulimab arm and 1 case in the placebo arm were coded with "death" which according to further information showed to be caused by cancer disease in two of the cases and the latter the cause of death could not be determined.

Race

The majority of the patients in the clinical trials were Asian. In the pooled safety population, 1818 subjects were Asian and 268 were non-Asian. Despite the limited number of non-Asians, the safety profile was considered overall comparable between Asian and non-Asians. However, the frequencies of the TEAEs were generally lower in the non-Asian subset. *Age*

In the pooled safety set, 37% of the patients are ≥ 65 years. In this population, there are generally more TEAEs Grade ≥3, TESAEs and deaths in patients ≥65 years than in patients <65 years. The <65 age group had a numerically higher incidence of irAEs (35.4% vs 32.2%), which is not unexpected. Some of the TEAEs that appear more frequently in the older patients in the pooled safety population could be related to the chemotherapy backbone, e.g. anaemia, leukopenia, neutropenia, platelet count decreased, and decreased appetite. Considering the toxicity profile reported for serplulimab in general, high age may not be a hindrance for treatment if the patient is considered fit for chemotherapy. Furthermore, based on pharmacokinetic analysis no special precautions are warranted in the elderly; this information has been included in section 4.8 of the SmPC.

Gender

Neither has a gender analysis from the pivotal trial been submitted, nor has the MAH submitted a new gender analysis with the upgraded and expanded pooled population. From the MAA, the following was formulated in the safety discussion: "(…) Based on the pooled safety population, the safety profile seems slightly worse in men than in women. However, based on the pivotal trial, the opposite tendency is seen, (with an exception for TEAEs leading to death). This might be caused by the specific combination of serplulimab and chemotherapy, with women being less tolerant to chemotherapy. Based on the provided data, the impression is that Caucasian women seem to tolerate the treatment better than the Asian women, in line with previous findings that Asians are more sensitive to certain anticancer treatments than Caucasians. (…)". This is found acceptable, and no further analysis is deemed necessary.

Immunogenicity

The MAH has provided an integrated summary of immunogenicity (ISI) in section 2.7.2.4.1 with results from the ten studies where the immunogenicity of serplulimab was studied and this is acknowledged. At the time of the MAA, the issue of lacking cross validation of the four ADA methods used in the different studies was raised. The applicant has not provided any cross validation in the current submission either. Thus, direct comparisons of immunogenicity results across studies are not possible.

Bearing this uncertainty in mind, it appears that the overall rate of ADA incidence is low. From the 2086 evaluable subjects, 94 (4.5%) subjects were ADA positive at any visit and 62 patients (3.0%) had treatment-induced ADAs, defined as baseline negative ADA, post-baseline ADA positive. 27 patients (1.3%) were persistently positive for ADA, defined as having at least 2 post-baseline ADA positive measurements with at least 16 weeks between the first and last positive measurements, or an ADA positive result at the last available assessment, including patients meeting these criteria who are ADA positive at baseline. Three patients (0.1%) had neutralising antibodies (Nabs). It should be noted that Nabs were only tested in 7 of the 10 studies included in the ISI. Overall, the ISI did not show any evidence for ADA impact on PK, safety or efficacy in these ten studies.

In the pivotal study HLX10-002-NSCLC301, as of the 5-Jun-2023 data cut-off, in the safety population (n=503), 22 (4.4%) patients were ADA positive at any visit, 5 (1.0%) patients were ADA positive at baseline only, and 17 (3.4%) of patients were treatment-emergent ADA positive, defined as at least one post-baseline ADA positive. There were 15 patients (3.0%) with treatment-induced ADA, defined as baseline negative ADA, post-baseline ADA positive.

There may be a trend towards more immunogenicity in patients treated with serplulimab monotherapy. In the ≥RP2D/3D group of the pooled safety population (n=2076), 7.4% of those treated with serplulimab monotherapy were ADA positive at any visit, as compared to 4.0% in the group treated with serplulimab in combination with chemotherapy, and 3.7% in the group treated with serplulimab in combination with other medications. A similar trend is seen in study HLX10-002-NSCLC301, where 6 (2.8%) subjects in Arm A, 7 (3.3%) subjects in Arm B, and 4 (5.6%) subjects in Arm C (who received serplulimab and bevacizumab treatment after PD, without receiving concomitant chemotherapy), were ADA-positive at least once at visits after administration. Given the proposed posology as combination treatment with chemotherapy in the current indication, the issue of potential higher ADA levels with monotherapy treatment will not be further pursued.

Two patients were Nab-positive in study HLX10-002-NSCLC301, one the serplulimab + chemotherapy group (arm B) and one in the placebo + chemotherapy switching to HLX10 + HLX04 after PD group in arm C.

Overall, the immunogenicity in the pivotal study in NSQ NSCLC was in line with that observed in the pivotal study for the MAA, HLX10-005-SCLC301 and in the overall safety population. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed.

Immunogenicity in dose-finding study HLX10-001 was presented and assessed in the original application and no further data has been provided in this submission. This is acknowledged. The final CSR for the study was submitted in the course of the procedure. Briefly, 13 out of 66 patients (19.7%) in the dose finding and dose expansion parts of study HLX10-001 were found to be ADA positive at any time, 3.4% (1/29) in the dose finding cohorts and 32.4% (12/37) in the dose expansion cohorts. No patients were found to be Nab positive. Though data was very limited, no evidence of ADA impact on pharmacokinetics, efficacy or safety was observed.

2.5.2. Conclusions on clinical safety

The dossier for serplulimab in this EoI application on nsq-NSCLC provides data from a population large enough to assess the safety of serplulimab and identify the most common adverse drug reactions. The reported safety profile is overall consistent with the known safety profile of serplulimab and comparable to the other anti-PD1/PD-L1 antibodies qualitatively. There is an increased incidence of TESAEs, grade ≥3 AEs, TEAEs leading to drug discontinuation and drug interruption compared to a standard of care regimen including chemotherapy but the increase is

modest and indicative of an additive effect. No new safety concerns were identified. Overall, the safety profile of serplulimab in combination with carboplatin and pemetrexed is considered acceptable.

2.5.3. PSUR cycle

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 Direct Healthcare Professional Communication

2.6. Risk management plan

The MAH submitted an updated RMP version 2.0 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

Safety concerns

Table 55 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Immune-mediated adverse reactions • Severe infusion reactions
Important potential risks	• None
Missing information	• Long-term safety in immunocompromised patients

Pharmacovigilance plan

No routine pharmacovigilance activities are planned beyond adverse reactions reporting and signal detection.

Risk minimisation measures

No update to the risk minimisation measures was introduced with this procedure.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. 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:

The variation is intended to add a new indication to the already existing marketing authorisation of Hetronifly (serplulimab). The changes to the package leaflet are minimal and do not require user consultation with target patient groups. They do not affect key messages for the safe use of the medicinal product.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication is as follows:

HETRONIFLY in combination with carboplatin and pemetrexed is indicated for the first-line treatment of adult non-squamous NSCLC patients with no EGFR, ALK or ROS1 positive mutations and who have:

- locally advanced NSCLC who are not candidates for surgery or radiotherapy, or
- metastatic NSCLC.

3.1.2. Available therapies and unmet medical need

Prior to the advent of immune checkpoint-inhibitor-based therapy, platinum-based doublet chemotherapy was the traditional first-line treatment regimen for patients with metastatic non-squamous NSCLC. With the rise and development of immunotherapy, anti-programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) inhibitors have become the standard first-line treatment regimen for stage IV non-squamous NSCLC without driver gene mutations.

According to the current ESMO guidelines (Hendriks et al., 2025)[1], for patients with stage IV NSQ NSCLC, PS 0-1, regardless of tumour PD-L1 status and without contraindication for ICI, a combination of platinum-based chemotherapy (ChT) plus programmed cell death protein 1 (PD-1)/PDL1 blockade is the most common treatment approach. For the subset of patients with PD-L1 >50%, monotherapy with ICIs could also be relevant. Several combination regimens have successfully demonstrated improved overall survival (OS) compared with ChT alone and are recommended according to the ESMO guidelines for patients with stage IV NSQ NSCLC, PS 0-1, regardless of tumour PD-L1 status and without contraindication for ICI. These have included platinum-based ChT plus: pembrolizumab, atezolizumab with or without bevacizumab, nivolumab and ipilimumab, cemiplimab, sugemalimab, and durvalumab-tremelimumab.

Concerning patients with locally advanced (stage IIIB or IIIC) disease that are not candidates for platinum-based chemoradiation or surgery, the usual approach is the same as for patients with metastatic disease.

[1] Hendriks L, Cortiula F, Martins-Branco D
Updated treatment recommendations for systemic treatment: from the ESMO non-oncogene-addicted metastatic NSCLC Living Guideline
Annals of Oncology, 2025; 36, 1223-1227

3.1.3. Main clinical studies

The main evidence of efficacy submitted is HLX10-002-NSCLC301, a three arm, randomised, double-blind, multicentre, Phase III clinical study to evaluate HLX10 (serplulimab, recombinant humanized anti-PD-1 monoclonal antibody) in combination with carboplatin-pemetrexed chemotherapy (n=214) versus HLX10 + HLX04 (recombinant humanized anti-VEGF monoclonal antibody) in combination with carboplatin-pemetrexed chemotherapy (n=212) versus carboplatin-pemetrexed chemotherapy (n=210) as first-line therapy for advanced non-squamous non-small cell lung cancer (NSCLC). The applicant has stated that since the triple combination of serplulimab, HLX04, and chemotherapy failed to demonstrate statistically significant efficacy compared to serplulimab plus chemotherapy, this regimen will not be pursued for marketing approval. Consequently, throughout the assessment report, the focus will be on the serplulimab plus chemotherapy and chemotherapy arms.

Patients were only enrolled in China. The primary endpoint was PFS assessed by IRRC (per RECIST v1.1). Overall survival was a key secondary endpoint. Other secondary endpoints included, among others, ORR and DOR.

Stratification factors for randomisation were PD-L1 expression level (negative/positive/not evaluable), smoking history (yes/no), and brain metastases (yes/no).

The data originally presented were based on a data cut-off date of June 15, 2023, which corresponded to the final analysis for PFS, and an interim analysis for OS. An updated CSR, with the final OS analysis, with a DCO of 07-Aug-2025, was provided in the course of the procedure.

3.2. Favourable effects

At the primary analysis (DCO 15-Jun-2023), the median PFS was 11.0 months (95% CI: 8.44, 12.71) in the serplulimab + chemotherapy group and 5.6 months (95% CI: 4.76, 6.80) in the chemotherapy group, with an HR of 0.55 (95% CI: 0.430, 0.694, P < 0.0001) using a stratified Cox proportional hazards model. Thus, the primary endpoint was met.

The key secondary endpoint was OS, where the median OS was 25.0 months (95% CI: 20.44, 28.68) in the serplulimab + chemotherapy group and 20.4 months (95% CI: 16.39, 24.18) in the chemotherapy group, with an HR of 0.81 (95% CI: 0.615, 1.060), p=0.1234, using a stratified Cox proportional hazards model. While the OS analysis was not statistically significant at this interim analysis, the OS results appear overall positive, with a numerical improvement in the serplulimab + chemotherapy arm versus the chemotherapy arm.

Secondary endpoints ORR and DOR are supportive of the primary endpoint. The confirmed ORR was 52.8% (95% CI: 45.88%, 59.65%) in the HLX10 + chemotherapy group and 27.6% (95% CI: 21.69%, 34.19%) in the chemotherapy group. The confirmed median DOR was 15.4 months (95% CI: 11.04, 21.16) in the serplulimab + chemotherapy group, and 9.7 months (95% CI: 5.52, 13.93) in the chemotherapy arm.

The final OS analysis was carried out with a DCO of 07-Aug-2025 and an updated CSR was provided. Efficacy results at this DCO were generally in line with those from the primary analysis. OS results were slightly improved at this DCO, with a median OS of 26.8 months (95% CI: 21.22, 30.88) in the serplulimab + chemotherapy arm, and 20.3 months (95% CI: 16.16, 24.64) in the chemotherapy arm, with a stratified HR of 0.66 (95% CI: 0.518, 0.829).

3.3. Uncertainties and limitations about favourable effects

Study Design

Only patients enrolled in China were included in the study; therefore, generalisability of the study results to the European population remains uncertain. However, given the breadth of experience with PD-1/PD-L1-axis targeting treatments in this indication, the absence of data in the European population can be accepted.

Patients > 75 years were excluded from the study; therefore, no efficacy data are available in this population. This exclusion criterion is reflected in section 5.1 of the SmPC

Efficacy Results

In both updated (07-Aug-2025) and interim analyses, there was a trend towards less benefit of addition of serplulimab to chemotherapy in subgroups with lower levels of PD-L1 expression, both per TPS and CPS. However, even in the groups with the lowest level of PD-L1 expression (TPS<1%, CPS <1%), there appears to be a degree of clinical benefit (both in terms of PFS and OS) from the addition of serplulimab. A restriction of the indication based on PD-L1 levels is thus not considered required, but the trend in efficacy across PD-L1 levels is reflected in Section 5.1 of the SmPC to inform the prescriber.

3.4. Unfavourable effects

As of the cut-off date June 15, 2023, almost all (>99%) of the patients reported at least one TEAE in the pivotal study HLX10-002-NSCLC301 with the majority of TEAEs considered related to serplulimab or placebo: 89.7% in the serplulimab + chemotherapy arm and 78.0% in the placebo + chemotherapy group.

In general, the rate of all-cause and related Grade ≥ 3 TEAEs (71.5% vs. 67.9% and 40.7% vs. 30.1%, respectively), TESAEs (44.9% vs. 40.7% and 29% vs. 16.3%), TEAEs leading to drug interruption (53.7% vs. 37.8% and 27.1% vs. 18.2%) and discontinuation (10.7% vs. 5.7% and 8.4% vs. 2.4%) was higher in the serplulimab + chemotherapy arm compared to the placebo + chemotherapy arm. In the pivotal study, 8.4% in the serplulimab arm and 13.4% in the placebo arm experienced TEAEs leading to death, of which 5 subjects vs 4 subjects, respectively, experienced TEAEs considered related.

The majority of the common TEAEs (≥20%) were typical of chemotherapy treatment, i.e. affecting the blood/lymphatic and hepatobiliary system, however, were generally reported with higher frequency in the serplulimab + chemotherapy arm.

Consistent with the known safety profile of serplulimab and other PD-1/PD-L1 inhibitors, serplulimab add-on treatment led to higher rates of irAEs (30.4% vs. 12.4%), particularly endocrinopathies such as hypothyroidism and hyperthyroidism.

In the immunogenicity safety population (n=503), 22 (4.4%) patients were ADA positive at any visit, and 15 patients (3.0%) had treatment-induced ADA, defined as baseline negative ADA, post-baseline ADA positive.

Safety data from the pooled safety population, including the occurrence of ADAs, was generally consistent with the safety data from the pivotal study.

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Effects Table

Table 56: Effects Table for serplulimab in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced non-squamous non-small cell lung cancer (NSCLC) (data cut-off: 15 June 2023)

Effect	Short description	Unit	Serplulimab +pemetrexed + carboplatin	Placebo + pemetrexed + carboplatin	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS by IRRC per RECIST v1.1 (primary endpoint)	Time from randomisation to the first documentation of PD or death due to any reason (whichever occurs first).	Months (median) (95% CI)	11.0 (8.44, 12.71)	5.6 (4.76, 6.80)	Data only in Asian patients Lower efficacy in patients with lower PD-L1 levels Potential lower efficacy in females and non-smokers High rate of major protocol deviations Double-blinded, randomised study	ASTRUM-002
		HR (95% CI)	0.55 (0.430, 0.694), p<0.0001			
OS (key secondary endpoint)	Duration of survival from randomisation to death regardless of cause	Months (median) (95% CI)	25.0 (20.44, 28.68)	20.4 (16.39, 24.18)		
		HR (95% CI)	0.81 (0.615, 1.060), p=0.1234			
Unfavourable Effects (treatment emergent adverse events, all-cause incidences) **– Safety set, n=634**						
Anaemia		%	77.1	79.9	The majority of these adverse events are likely related to chemotherapy, taking into consideration the similar incidences in the two treatment arms and the known safety profile of the chemotherapy backbone.	
Nausea		%	39.7	34.0		
White blood cell count decreased		%	79.4	73.2		
Immune-mediated TEAEs (irAEs)		%	30.4	12.4		
TESAEs (related)		%	44.9 (29.0)	40.7 (16.3)		
Grade 3/4 TEAEs (related)		%	71.5 (40.7)	67.9 (30.1)		
TEAEs leading to death (related)		%	8.4 (2.3)	13.4 (1.9)		

Effect	Short description	Unit	Serplulimab +pemetrexed + carboplatin	Placebo + pemetrexed + carboplatin	Uncertainties / Strength of evidence	References
TEAEs leading to drug interruption		%	58.9	38.3		
trTEAEs leading to SER/PLA interruption		%	34.1	19.6		
TEAEs leading to drug discontinuation		%	10.7	5.7		
tr TEAEs leading to Ser/PLA discontinuation		%	8.4	2.4		

Abbreviations: Ser/HLX10: Serplulimab, HLX04: bevacizumab, CP: carboplatin and pemetrexed, tr: treatment-related (i.e. here: serplulimab/placebo-related)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In study HLX10-002-NSCLC301, the addition of serplulimab to chemotherapy (carboplatin + pemetrexed) as first line treatment of locally advanced or metastatic nonsquamous NSCLC prolonged progression-free survival significantly and led to a numerical increase in OS at the interim analysis. This is considered clinically relevant. Other immune checkpoint inhibitors (e.g. pembrolizumab, cemiplimab, tislelizumab) are already approved for this setting, and serplulimab appears to give comparable efficacy results to the already approved options. The comparator used is no longer standard-of-care in this setting, and an updated control arm with PD-1/PD-L1 blockade in combination with chemotherapy would have been preferred.

A few uncertainties remain pertaining to the interpretation of the efficacy estimates. First, the age distribution and smoking status in the study population, which is Chinese, is not considered fully representative for the Caucasian target population. However, given the breadth of experience with PD-1/PD-L1-axis targeting treatments in this indication, the absence of data in the European population can be accepted. Although all subgroups investigated are considered to be generally in line with the overall population, there is a trend towards lower efficacy in patients with lower PD-L1 levels, this finding is reflected in section 5.1 of the SmPC.

The safety profile of serplulimab is consistent with the known safety profile of a PD1-inhibitor. There is an increased incidence of TESAEs, grade ≥3 AEs, TEAEs leading to drug discontinuation and drug interruption compared to a standard of care regime including chemotherapy but the increase is modest and indicative of an additive effect. No new safety concerns were identified.

The safety data is mainly obtained in an Asian population. However, the safety profile of serplulimab is not expected to be significantly different in the non-Asian patient population.

3.7.2. Balance of benefits and risks

The improvement of median PFS by 5.4 months in patients who received add-on serplulimab can be considered clinically relevant for locally advanced or metastatic NSQ-NSCLC patients who have a poor prognosis.

The safety profile is consistent with the safety profile of a PD1-inhibitor, and no new safety concerns were identified.

The benefit-risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Hetronifly (serplulimab) is positive for the extension of the indication to include serplulimab, in combination with carboplatin and pemetrexed, as first-line treatment of adult non-squamous non-small cell lung carcinoma patients with no EGFR, ALK or ROS1 positive mutations and who have either locally advanced NSCLC and are not candidates for surgery or radiotherapy or metastatic NSCLC.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I, and IIIB

Extension of indication to include HETRONIFLY in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung carcinoma who do not have EGFR or ALK positive mutations based on results from study HLX10-002-NSCLC301. As a consequence, sections 4.1, 4.2, 4,4, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been approved.

The variation leads to amendments to the annex(es) I and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

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

- **Risk management plan (RMP)**

The 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.

In addition, 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

The MAH shall ensure that in each Member State where HETRONIFLY is marketed, all patients/caregivers who use HETRONIFLY are provided with the patient educational material.

- **Composition of educational material package:**
    - Summary of product characteristics/package leaflet (will be voluntarily provided)
    - Patient card
- **Risks covered by the educational material:**
    - Immune-mediated adverse reactions
    - Severe infusion reactions

The Education Material includes information on the signs and symptoms of immune-related adverse reactions and infusion-related reactions, as well as the guidance for the importance of patient monitoring and the clinical management of these events. The material will be distributed to relevant HCPs as a package and patients will receive their materials through the HCP.