26 March 2026
EMADOC-1700519818-2976092
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hetronifly

International non-proprietary name: Serplulimab

Procedure No. EMA/VR/0000284402

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

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ADR	Adverse drug reaction
ASP	Aspartate aminotransferase
BIL	Bilirubin
BMI	Body mass index
BNP	Brain natriuretic peptide
BOIN	Bayesian Optimal Interval
BOR	Best overall response
BSA	Body surface area
ChT	Chemotherapy
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
C_{max}	Peak concentration
COVID-19	Coronavirus disease 2019
CPS	Combined positive score
CR	Complete response
CRCL	Creatinine or creatinine clearance
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration
dMMR	Mismatch repair deficient
DCO	Data cut-off date
DCR	Disease control rate
DLT	Dose-limiting toxicity
EAC	Esophageal adenocarcinoma

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-OES18	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Esophageal Cancer Module
ESCC	Esophageal Squamous Cell Carcinoma
ESMO	European Society for Medical Oncology
ES-SCLC	Extensive-stage small cell lung cancer
EOS	End of study
EOT	End of treatment
EU	European Union
FDA	Food and Drug Administration
FIH	First-in-human
GCP	Good clinical practice
HCC	Hepatocellular carcinoma
HR	Hazard ratio
HXL10	Serplulimab
IC	Immune cells
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
iPD	Progressive disease assessed by iRECIST
irAE	Immune-related adverse event
IRR	Infusion-related reaction
IRRC	Independent Radiology Review Committee
iRECIST	immune Response Evaluation Criteria in Solid Tumors
ITT	Intention-to-treat
IWRS	Interactive web response system
IV	Intravenous

LVEF	Left ventricular ejection fraction
MAA	Marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMR	Mismatch repair
MMRM	Mixed-effect model for repeated measures
MRI	Magnetic resonance imaging
MSH	Microsatellite instability
MSI-H	Microsatellite instability-high
MSH-L	Microsatellite instability-low
MSS	Microsatellite stable
MTD	Maximum tolerated dose
NAb	Neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMPA	National Medical Products Administration (China)
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
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
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	Stable disease/standard deviation
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SS	Safety set
TAP	Tumor area positivity
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TMB	Tumor mutational burden
TPS	Tumor proportion score
ULN	Upper limit of normal

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 02 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, in combination with fluoropyrimidine- and platinum-based chemotherapy, the first-line treatment of adult patients with unresectable, locally advanced/recurrent or metastatic oesophageal squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1 for HETRONIFLY, based on results from study HLX10-007-EC301; this is a randomized, double-blind, multi-center, phase III clinical study comparing the clinical efficacy and safety of HLX10 or placebo combined with chemotherapy in first-line treatment of locally advanced/metastatic esophageal squamous cell carcinoma (ESCC) patients. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.2 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 No. EMA/PE/0000258486 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 and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Eva Skovlund

Timetable	Actual dates
Submission date	2 July 2025
Start of procedure:	19 July 2025
CHMP Rapporteur's preliminary assessment report circulated on:	12 September 2025
PRAC Rapporteur AR	16 September 2025
PRAC RMP advice and assessment overview adopted by PRAC	2 October 2025
Updated CHMP Rapporteur AR	9 October 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	16 October 2025
MAH's responses submitted to the CHMP on:	28 November 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 December 2025
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	29 January 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 March 2026
Updated CHMP Rapporteur AR	19 March 2026
CHMP Outcome	26 March 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Esophageal cancer is a malignant tumor that originates from the epithelial cells of the esophageal tract. The major pathological types include esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) (Yang, 2024). The distribution of pathological types varies in different regions. Around 90% of worldwide cases are ESCC, which has particularly high incidence

in South America and Asia. In contrast, EAC is more prevalent in Europe and North America (Deboever, 2024). The 2022 global cancer statistics showed that esophageal cancer is the 11th most commonly diagnosed cancer and the seventh leading cause of cancer death worldwide, with an estimated 511,000 new cases and 445,000 deaths in 2022 (Bray, 2024).

State the claimed therapeutic indication

The originally proposed indication was as follows: "Hetronifly in combination with fluoropyrimidine- and platinum-based chemotherapy is indicated for the first-line treatment of adult patients with unresectable, locally advanced/recurrent or metastatic oesophageal squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1."

The proposed dose is 3.0 mg/kg serplulimab every 2 weeks until disease progression or unacceptable toxicity.

Epidemiology and risk factors

Esophageal cancer (EC) is among the most common cancers and causes of cancer-related death worldwide. It can be categorised into 2 main histological subtypes: esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (AC). ESCC is the most common histology of esophageal cancer seen globally, while AC is the most common subtype in high-income countries, with the highest incidence rates observed in Northern Europe, North America, and Oceania.

Worldwide, the incidence of EC varies significantly. The highest incidence rates are observed in Eastern Asia as well as Southern and Eastern Africa (including Malawi and Swaziland), whereas the lowest incidence rates are reported in Northern and Western Africa as well as Central America. Although EC is relatively rare in Europe (annual incidence approximately 1 per 13,300, according to Orphanet 2013), it remains a highly fatal disease and a major cause of cancer-related mortality.

Approximately 70% of EC diagnoses occur in men, with an approximately 2 to 3-fold difference in incidence and mortality rates between the men and women. Incidence rates are higher in developing versus developed countries for men, while rates are more comparable for women (ESMO-guideline, 2022).

In the highest-risk areas, stretching from Northern Iran through Central Asia republics to North-Central China (often referred to as the "esophageal cancer belt"), 90 percent of cases are esophageal ESCC. The major risk factors in these areas are not well understood, but are thought to include poor nutritional status, low intake of fruits and vegetables, and consumption of beverages at high temperatures. By contrast, in lower-risk areas for ESCC, such as the United States and other Western countries, smoking and excessive alcohol consumption account for approximately 90% of cases.

ESCC remains the most common histological subtype worldwide and is increasing in certain Asian countries, such as Taiwan, likely reflecting increases in tobacco and alcohol consumption. Infection with human papillomavirus (HPV) may also contribute to the development of ESCC. Familial aggregation of EC has been reported in regions with a high incidence of ESCC, such as China suggesting hereditary factors contribute to the risk of ESCC.

Biologic features, aetiology and pathogenesis

The majority of ESCCs are located in the mid-esophagus. ESCC invades the submucosa at an early stage and extends along the esophagus wall. Local lymph node invasion occurs early because the

lymphatics in the esophagus are located in the lamina propria. The tumor spreads to regional lymph nodes along the esophagus, the celiac area, and adjacent to the aorta.

Distant metastases to the liver, bone, and lung are seen in nearly 30% of patients.

Clinical presentation and diagnosis

ESCC is usually asymptomatic until an advanced disease stage with common presenting symptoms being dysphagia and weight loss. Consequently, diagnosis is often made late in the disease course, particularly in settings where screening programs for early detection are not implemented or are impractical due to low incidence rates. The diagnosis of EC requires a histologic examination of tumor tissue. A diagnostic biopsy may be obtained by upper endoscopy or, if metastases are present, by image-guided biopsy of a metastatic site.

Management

Patients with EC that is metastatic or unresectable and cannot be treated with curative-intent chemoradiotherapy have a poor prognosis. Survival in clinical trials has historically been <1 year; however, the use of immune checkpoint inhibitors in combination with chemotherapy has recently improved survival for this patient group (ESMO guideline, 2022).

According to the ESMO guideline (2022), first-line chemotherapy (ChT) with a platinum-fluoropyrimidine doublet is recommended as a standard treatment for advanced untreated esophageal SCC. Dose-reduced oxaliplatin-capecitabine is an alternative option for patients who are unsuitable for full-dose chemotherapy.

However, in recent years, clinical trials have demonstrated the efficacy of immune checkpoint inhibitors in combination with chemotherapy. Consequently, updated ESMO recommendations (2022, updated February 2025) include chemo-immunotherapy as first-line treatment in patients with PD-L1 positive disease, while chemotherapy remains standard option for PD-L1 negative or unknown populations.

ESCC is a severe and life-threatening condition and there remains a need for additional treatment options, including for patients with tumours characterised by different levels of PD-L1 expression.

2.1.2. About the product

Serplulimab is a recombinant humanized IgG4 monoclonal antibody 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 in the EU on 03 February 2025 (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).

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

No scientific advice has been sought by the MAH for the applied indication ESCC.

2.1.4. General comments on compliance with GCP

Two clinical trials support the current extension of the indication to ESCC:

- The pivotal phase 3 efficacy and safety clinical study ASTRUM-007 (HLX10-007-EC301) was carried out exclusively in China. There were 71 study sites opened in China, of which 5 sites did not enrol participants.
- The phase 1 dose finding and dose expansion study (HLX10-001) which was carried out exclusively in Taiwan.

The MAH included a statement that both trials which were carried out outside the EU and met the ethical requirements of Directive 2001/20/EC.

The CSR for the study HLX10-001 includes a statement that the study was conducted in accordance with national and international ethical principles, including the Helsinki Declaration, the International Coordinating Conference on the Registration of Medicines (ICH) Guidelines, the Practice for the Administration of Clinical Trials of Medicines (GCP) and all other applicable regulations and policies.

The CSR for study HLX10-007-EX301 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 other applicable regulatory requirements.

In addition, GCP inspections were carried out in 2023 at two sites in China by the NMPA (National Medical Products Administration in China) with positive outcome.

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.

2.3. Clinical aspects

2.3.1. Introduction

2.3.2. GCP

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

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.

The pivotal study, HLX10-007-EC301 (ASTRUM-007), involved 66 clinical trial sites which enrolled a total of 551 participants. Two clinical trial sites underwent GCP inspection by the China National Medical Products Administration (NMPA) with positive outcome, and five clinical trial sites were audited. The inspections were carried out on 13-15th February 2023 and 6–8th March 2023 respectively. No other regulatory authority carried out inspections for this study.

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	HLX10-007-EC301 (ASTRUM-007)	A randomised double blind multicentre Phase III clinical study to evaluate serplulimab (recombinant humanised 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 oesophageal squamous cell carcinoma (ESCC)	China

2.3.3. 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 on Day 1 of each cycle. The proposed dosage of serplulimab for the intended indication is 3 mg/kg administered once every 2 weeks (Q2W).

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 is included 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 ESCC 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 tumors 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. **HLX10-007-EC301**: A randomized, double-blind, multicenter, phase III clinical study to evaluate serplulimab (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 oesophageal squamous cell carcinoma (ESCC).

PK sampling: Within 24 hours before dosing in Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter. Additionally, within 0.5 hr post-dose in Cycles 1 and 8 during the treatment period, at the termination visit and 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 14687 serplulimab serum concentration measurements from 2110 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

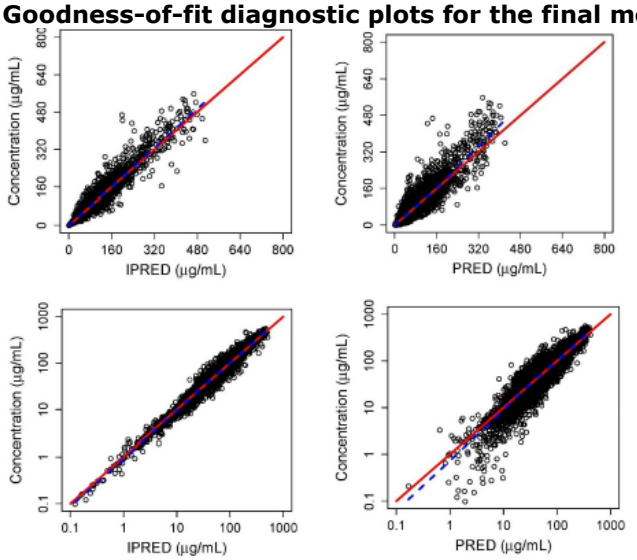
A summary of the final population parameters is in Table 5.

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%)	
	Esophageal squamous cell carcinoma	0.178 (1.98%)	
	Other tumor 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%)	
	Esophageal squamous cell carcinoma	3.48 (1.51%)	
	Other tumor 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 tumor burden on CL		0.0548 (20.8%)	—
Influence of tumor burden on V_p		0.107 (24.6%)	—
Covariance (CL, V_c)		0.0140 (11%)	—
Residual errors (%)		17.6 (1.75%)	—

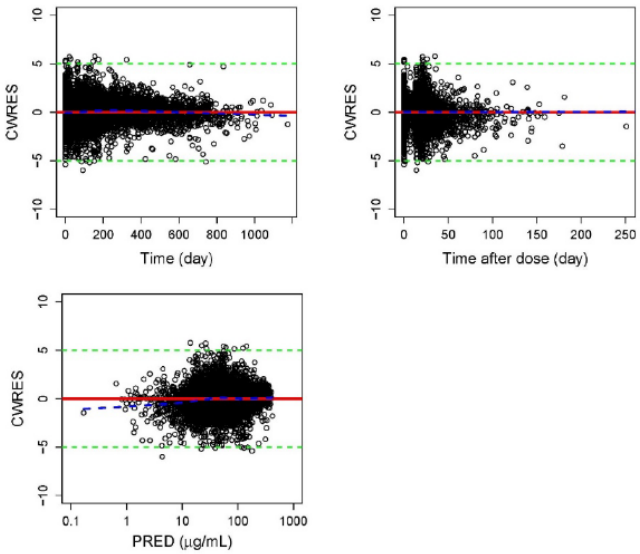
Model evaluation

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

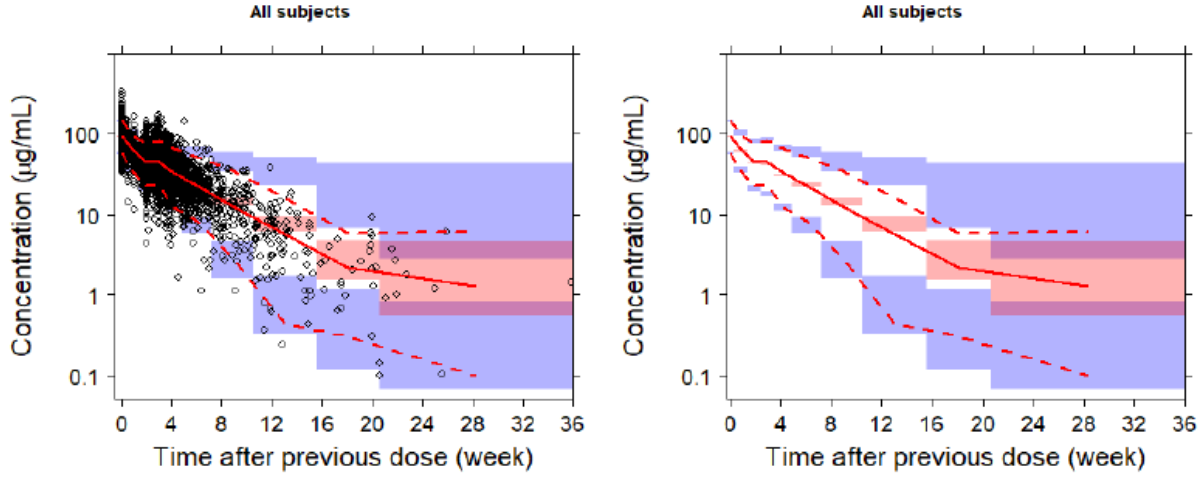
Table 6. Comparison of final model of serplulimab estimates and bootstrap results

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 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

2.3.3.1. Absorption

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

2.3.3.1.1. 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.

2.3.3.1.2. Elimination

As a protein product, serplulimab is expected to be catabolised into amino acids by general protein 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.

2.3.3.1.3. 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)

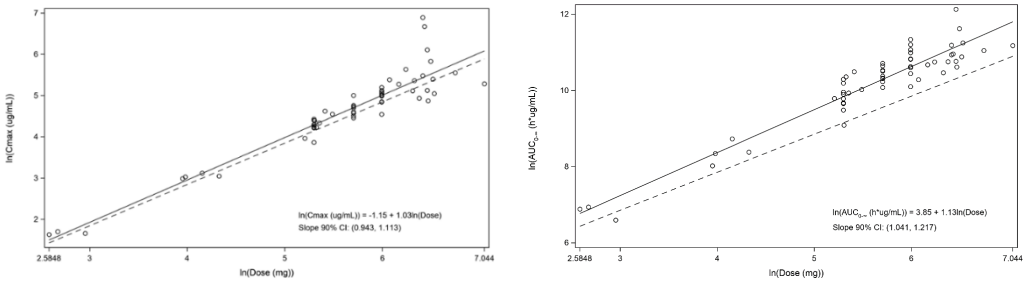
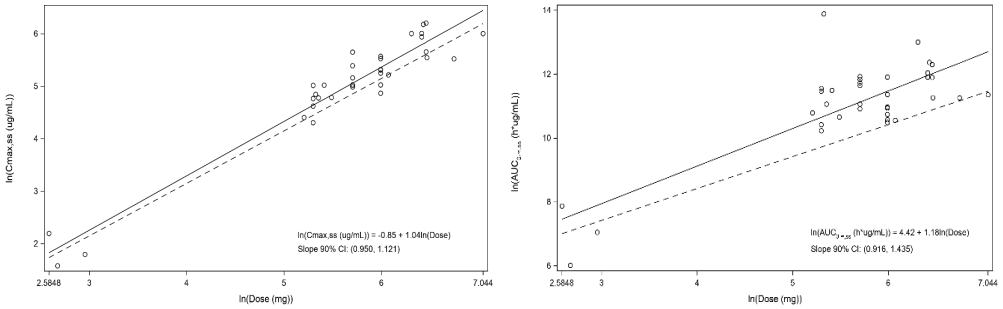


Figure 5. Statistical assessment of dose proportionality for serplulimab after multiple doses (power model) (PK data set)



Target populations

For subjects who received serplulimab + chemotherapy throughout the study HLX10-007-EC301, the mean serum serplulimab concentration after the first dose and the eighth dose are in Table 10.

Table 10. Summary of Serplulimab PK Parameters (HLX10-007-EC301 pivotal study)

PK parameters	Received serplulimab + chemotherapy throughout (N=371)		Subjects with alternated medication (N=8)	
	Number of subjects (n)	Arithmetic mean ± standard deviation (% CV)	Number of subjects (n)	Arithmetic mean ± standard deviation (% CV)
C1-C_{max} (μg/mL)	367	54.030±20.263 (37.50)	8	81.641±43.942 (53.82)
C2-C_{trough} (μg/mL)	350	16.776±7.118 (42.43)	7	26.293±11.775 (44.78)
C8-C_{max} (μg/mL)	221	101.730±33.425 (32.86)	3	113.110±53.179 (47.02)
C8-C_{trough} (μg/mL)	215	51.947±20.136 (38.76)	3	44.013±9.307 (21.15)
R_{ac_Cmax}	216	4.583±37.917 (827.35)	3	2.178±0.060 (2.76)
$R_{ac\_Ctrough}$	212	3.599±4.014 (111.54)	3	2.322±0.708 (30.47)

Note: The summary of PK parameters of serplulimab is based on all subjects who received serplulimab, including subjects who received serplulimab + chemotherapy throughout and subjects with alternated medication.
C1-C_{max} = concentration after the first dose, C2-C_{trough} = concentration before the second dose, C8-C_{max} = concentration after the eighth dose, C8-C_{trough} = concentration before the eighth dose.
R_{ac_Cmax} = concentration after the eighth dose/concentration after the first dose, $R_{ac\_Ctrough}$ = concentration before the eighth dose/concentration before the second dose.

PopPK in the target population

All studied subjects were cancer patients. HLX10-007-EC301 is the pivotal trial to evaluate the efficacy and safety of serplulimab for the targeted patient population, locally advanced/metastatic

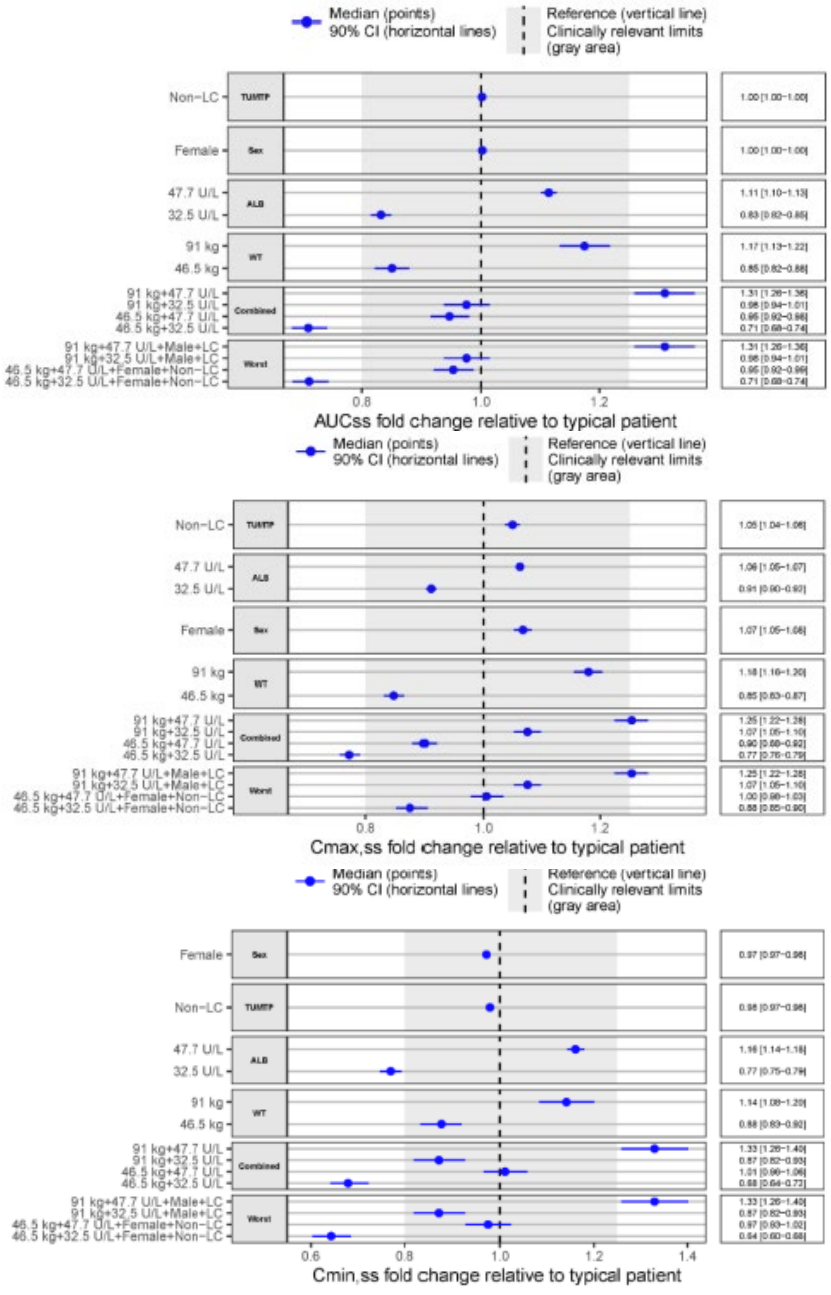
ESCC patients. In the population PK analysis, tumour type was tested as covariate, but it was considered clinically not relevant.

2.3.3.2. 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.

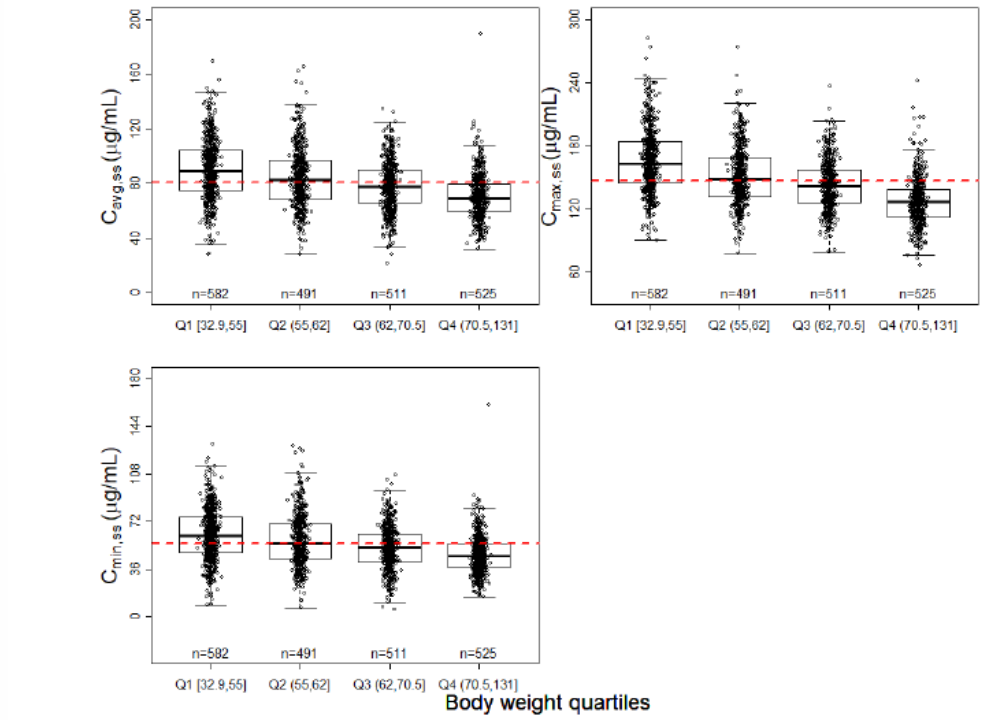
Figure 6. Model-predicted impact of covariates on exposures



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

Body weight

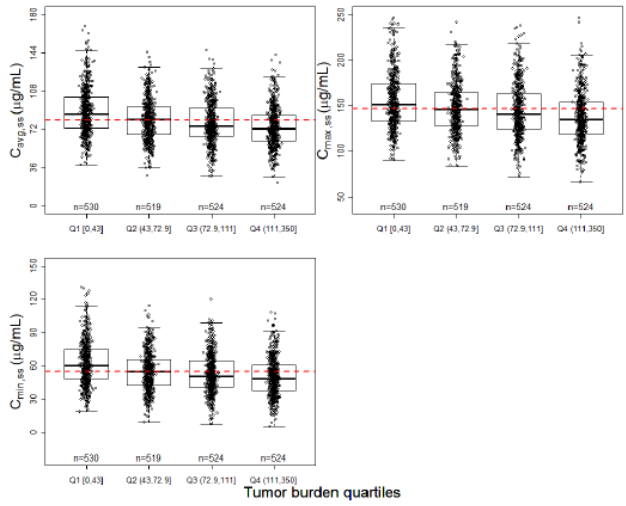
Figure 7. Impact of body weight on steady state exposure of serplulimab



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 burden on exposure

Figure 8. 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.

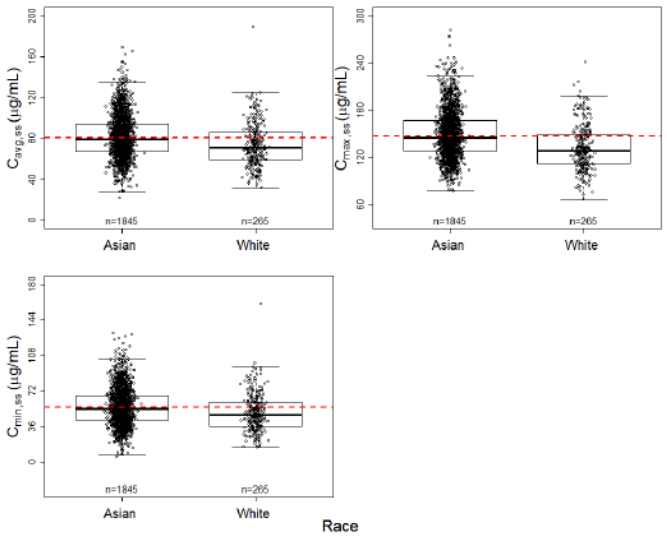
Impact of ethnicity on exposure

Table 11. 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.

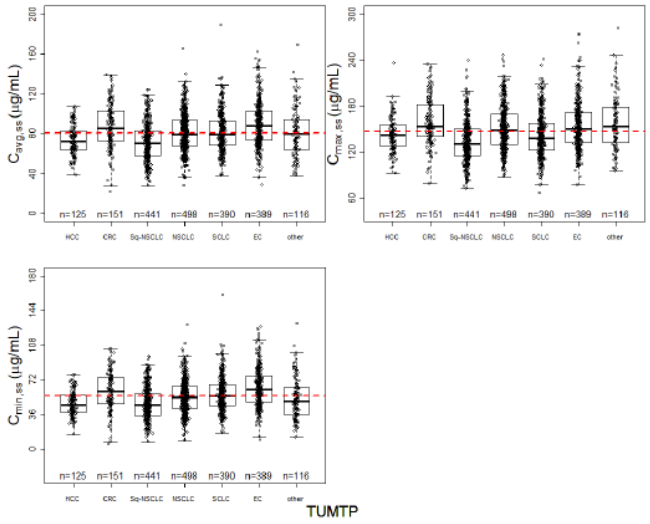
Figure 9. Impact of ethnicity on steady state exposure of serplulimab



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 10. Impact of tumor 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.

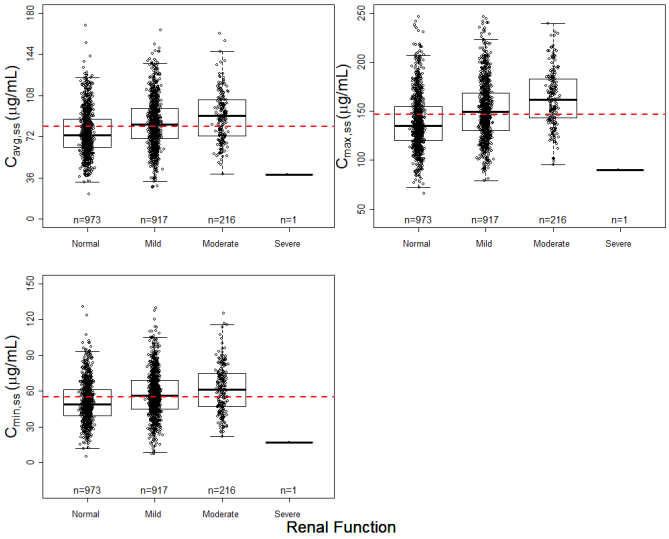
Table 12 - Impact of tumor type on geometric mean (%CV) steady state exposure of HLX10

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.

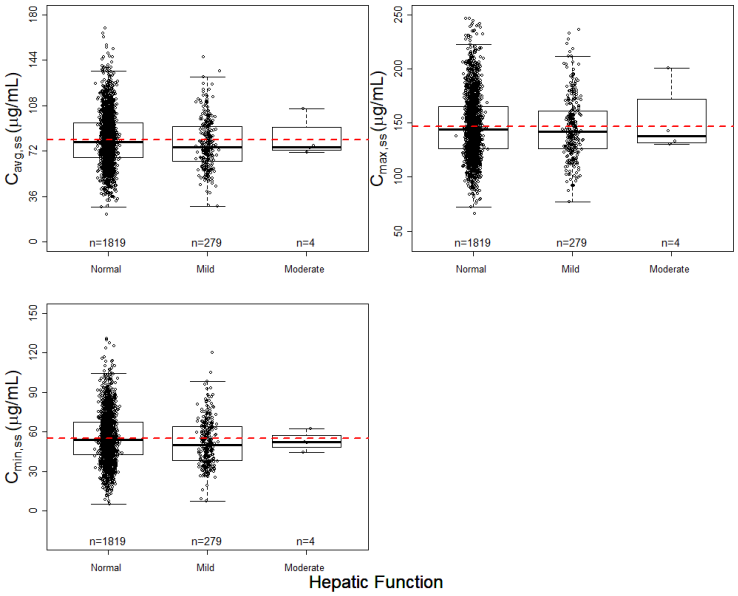
2.3.3.2.1. Impaired renal functions

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



2.3.3.2.2. Impaired hepatic function

Figure 12. 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 13. Concentration-time profiles of different dosing regimens

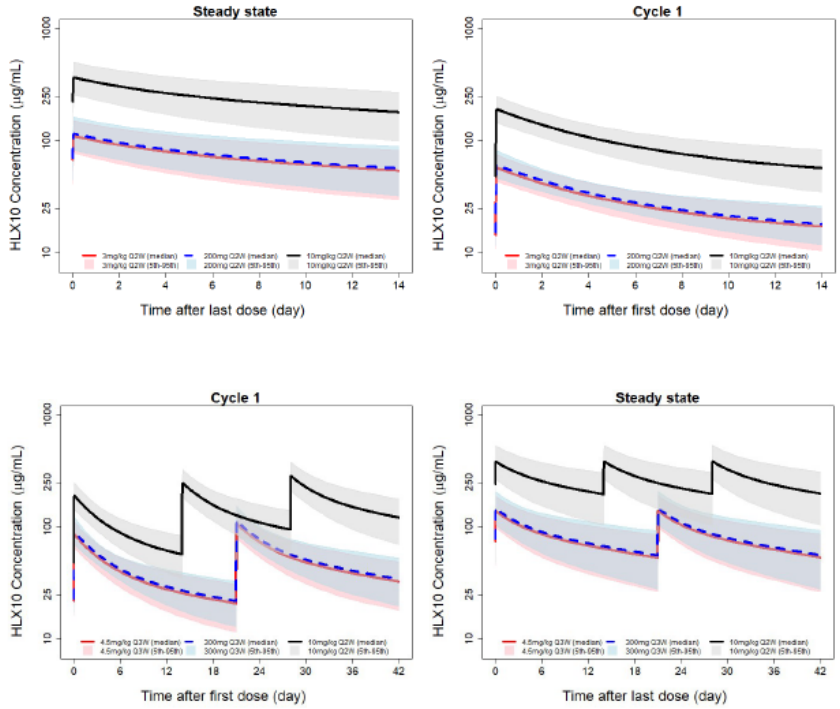


Table 13. Summary of serplulimab exposures following 3 mg/kg Q2W and 200 mg Q2W dosing - stratified by body weight quartiles (geometric mean [CV])

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 14. 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)		1575.92 (27.5)	1779.72 (27.4)		1633.01 (24.7)	1640.66 (24.7)		1798.71 (23.5)	1493.87 (24.3)	
$C_{max,ss}$ (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)	33.9	719.33 (16.4)	812.36 (16.3)	12.93	777.9 (15.5)	781.54 (15.3)	0.47	867.33 (15.4)	720.33 (15.1)	-16.95
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.

2.3.4. 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.

2.3.5. 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 derived from 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 ESCC were conducted exclusively in Asian populations.

While the PK data are derived from 11 studies, the evaluation relevant to the extension of indication to patients with locally advanced or metastatic ESCC, primarily relies 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, while study HLX10-007-EC301 is the pivotal study for the extension of indication to ESCC 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 (Caucasians 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 HLX10-007-EC301, 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 ESCC 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 CL0 and Vc for subjects with oesophageal squamous cell carcinoma was 0.178 L/day and 3.48 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.

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.

Body weight, race, and tumour burden are covariates of specific interest in the current application.

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 was required to provide exposure data (AUC, Cavg, Cmax, and Cmin) presented in boxplots stratified by 10 kg weight bands, spanning from 30 kg to 140 kg and a comprehensive table summarizing all exposure data, including minimum and maximum values for each parameter using the appropriate dosing regimen. The MAH has provided the requested plots and table under the correct dosing regimen and no further action is required on this matter as the issue is considered resolved.

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, in this application, all patients with ESCC are Asians, and 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.

2.3.6. Conclusions on clinical pharmacology

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

2.4.1. Dose response study

The phase 1 clinical study HLX10-001 was an open label dose-finding and dose-expansion study enrolling 66 participants to investigate the safety, tolerability and to determine the maximum tolerated dose and recommended phase II dose of HLX10 in patients with advanced solid tumours.

The study included a dose-finding cohort assessing intravenous administration of 0.3, 1, 3 and 10 mg/kg every 2 weeks (Q2W), as well as a dose-expansion cohort assessing 200 mg Q2W, 300 mg every 3 weeks (Q3W), 400 mg every 4 weeks (Q4W) and 600 mg every 6 weeks (Q6W).

Serplulimab was considered safe and tolerable across the dose range 0.3 to 10 mg/kg with no clinically relevant differences observed between dose cohorts.

The selection of the serplulimab dose (3 mg/kg every 2 weeks) was based on in vitro pharmacology, in vivo mice tumour model, clinical study results and PopPK analysis. Data from other authorised PD-1 inhibitors with similar mechanism of action were also taken into account.

2.4.2. Main study

ASTRUM-007

Methods

In ASTRUM-007 eligible subjects were randomised at a 2:1 ratio to Group A (serplulimab + chemotherapy [cisplatin + 5-FU]) or Group B (placebo + chemotherapy [cisplatin + 5-FU]) for treatment up to 2 years or until loss of clinical benefit, death, intolerable toxicity, withdrawal of informed consent or other protocol-specified reasons, whichever occurred first.

Randomisation was stratified by PD-L1 expression level (1 ≤ combined positive score [CPS] < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and disease status (locally advanced vs. metastatic disease).

The study included three periods: screening period (28 days), treatment period, and follow-up period (including safety and survival follow-up). Safety follow-up was performed at 30 days after the last dose (at the study site) and at 90 days (by telephone) while patients were followed for survival every 12 weeks.

The study was performed exclusively in China.

CT or MRI test was to be performed at screening, every 6 weeks (± 7 days) in the first 48 weeks after randomised medication, and every 12 weeks (± 7 days) after 48 weeks.

MRI or CT of the brain (MRI was preferred) was performed at baseline and subsequently as clinically indicated at baseline and during treatment. An independent radiology review committee (IRRC) was established to develop a standardised imaging acquisition method based on protocol. The investigator and the IRRC were to separately assess the radiological results per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (the frequency of tumor assessments could be increased by the investigator as clinically indicated). The investigator was to determine subsequent treatment based on his/her efficacy assessment.

During the study, patients were allowed to continue treatment beyond first progressive disease (PD) as per RECIST v1.1, subject to predefined clinical criteria and re-consent.

Patients continuing treatment beyond progression underwent repeated radiological assessment after 4–8 weeks to confirm progression according to iRECIST, after which treatment was discontinued if progression was confirmed.

An Independent Data Monitoring Committee (IDMC) was established to oversee the interim analysis and monitor safety and efficacy.

2.4.3. Study participants

Key inclusion criteria

1. Adult patients (aged 18–75 years) with histologically confirmed, unresectable locally advanced, recurrent or distantly metastatic ESCC.
2. Patients had not received prior systemic anti-tumour therapy for advanced disease; prior neoadjuvant/adjuvant or chemoradiotherapy was permitted if completed ≥6 months before relapse
3. Patients were required to have at least one measurable lesion according to RECIST version 1.1, PD-L1-positive tumours (CPS ≥1), and an ECOG performance status of 0–1.

Key exclusion criteria

1. Patients at high risk of gastrointestinal perforation or fistulae within 6 months prior to the first dose of the study drug, including tumour invasion into adjacent critical structures.
2. Patients with uncontrolled effusions (pleural, pericardial or ascites)
3. Patients previously treating with PD-1/PD-L1 inhibitors or with recent anticancer treatment
4. Patients with unresolved toxicities from prior anticancer therapy
5. Patients with central nervous system metastases
6. Patients with active autoimmune disease or requiring systemic immunosuppressive therapy
7. Patients with clinically significant cardiovascular disease or severe/uncontrolled infections
8. Patients with interstitial lung disease or a history of pneumonitis
9. Patients with active infections, including tuberculosis or hepatitis B
10. Patients with a history of other malignancies within 5 years (with exceptions for low-risk cancers)

2.4.4. Treatments

Dosing sequence for combination therapy: serplulimab or placebo, cisplatin, and 5-FU were administered sequentially, with 2 weeks (14 days) as one cycle.

Investigational product or comparator drug: serplulimab (HLX10) or placebo

3 mg/kg, intravenous infusion (IV), administered on Day 1 of each cycle, once every 2 weeks (14 days), with no reduction in dose for up to 2 years or until loss of clinical benefit, intolerable toxicity, discontinuation decided by the subject or physician, death, withdrawal of informed consent, pregnancy or other reasons specified in the protocol (whichever occurred first).

Other study drugs: combination of chemotherapy: cisplatin and 5-fluorouracil (5-FU)

Cisplatin: 50 mg/m^2, IV, once every 2 weeks (14 days), administered on Day 1 of each cycle, for up to 8 cycles, or progressive disease or unacceptable toxicity, whichever occurred first.

5-FU: at a total dose of 2400 mg/m^2, continuous IV for 44–48 hours in each cycle, once every 2 weeks (14 days), for up to 12 cycles, or progressive disease or unacceptable toxicity, whichever occurred first.

2.4.5. Objectives

Primary objective

- To evaluate the clinical efficacy of serplulimab versus placebo in combination with chemotherapy as first-line therapy in patients with locally advanced or metastatic ESCC.

Secondary objective

- To evaluate the safety and tolerability of serplulimab versus placebo in combination with chemotherapy as first-line therapy in patients with locally advanced or metastatic ESCC.

2.4.6. Outcomes/endpoints

Primary endpoints

PFS and OS were dual primary endpoints.

- Progression-free survival (PFS) (assessed by Independent Radiology Review Committee [IRRC] as per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1)

Definition: the time from randomisation to the first record of PD or death due to any cause (whichever occurred first).

- Overall survival (OS)

Definition: the time from randomisation to death due to any cause.

The analysis based on the ITT set was the primary analysis.

Secondary endpoints

- PFS (assessed by IRRC as per immune-modified RECIST [iRECIST], and assessed by Investigator as per RECIST v1.1 and iRECIST);
- ORR (assessed by IRRC and Investigator as per RECIST v1.1 and iRECIST);

Definition: the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR). Subjects without post-baseline tumor assessments were to be counted as non-responders in calculating the ORR.

- Relationship between PD-L1 expression of tumor tissues and efficacy;
- Duration of response (DOR) (assessed by IRRC and Investigator as per RECIST v1.1 and iRECIST);

Definition: the time from the first record response (CR or PR) to the first record of PD or death (whichever occurred first).

- Incidence of adverse events (AEs) and serious adverse events (SAEs);

- PK: concentration of HLX10 in serum;
- Immunogenicity evaluation: positive rate of anti-drug antibody (ADA)/neutralizing antibody (NAb);
- Relationship between microsatellite instability (MSI), tumor mutational burden (TMB) and efficacy;

Quality of life assessment: Subjects were assessed for quality of life using three instruments: European Quality of Life Five-Dimension Five-Level Scale (EQ-5D-5L), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Esophageal Cancer Module (EORTC QLQ-OES18), and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30).

PD-L1 analysis method

The PD-L1 expression of tissue samples was detected in the Sponsor's contracted bioanalytical laboratory using a validated quantitative analysis method. According to the MAH, PD-L1 expression was detected using a methodologically validated immunohistochemistry method. Validation was performed to assess sensitivity, precision, specificity, and sample stability. PD-L1 expression in slices was interpreted using the Dako 22C3 pharmDx companion diagnostic product.

Primary estimand PFS

Population: Patients with locally advanced/metastatic ESCC

Treatment: serplulimab/placebo combined with chemotherapy (cisplatin + 5-FU), with every 2 weeks (14 days) as a treatment cycle

Variable: Time from randomisation to the first documented progressive disease (PD) or death due to any cause, whichever occurs first, as assessed by the IRRC according to RECIST v1.1.

Population-level summary: Hazard ratio (HR)

Intercurrent events and handling strategies are presented below:

Table 15 Intercurrent events and handling strategies:

#	Intercurrent events	Handling strategies and description
1	No PD/death prior to the initiation of new anti-tumor therapy for ESCC Emergency unblinding or accidental unblinding due to other reasons	**Hypothetical strategy:** The subjects with intercurrent events are assumed to have the same risk of disease progression or death as those without intercurrent events. PFS data will be censored on the date of the last tumor imaging before the intercurrent event. Since the independent radiological review committee (IRRC) can make independent judgment without interference from other information and will not communicate with the investigator's information, the PFS assessed by IRRC will not be affected by emergency unblinding of the investigator or accidental unblinding for other reasons, and only the PFS assessed by the investigator will be censored on the date of the last tumor imaging examination before emergency unblinding or accidental unblinding for other reasons.

2	Death prior to PD	**Composite strategy**: Death directly reflects the loss of clinical benefit of patients, so death and PD are jointly used as the target endpoints of PFS.
3	Temporary treatment interruption Treatment discontinuation due to adverse events or other non-progressive disease reasons Use of rescue medications	**Treatment policy strategy**: Temporary treatment interruption, treatment discontinuation due to adverse events or other reasons, and use of rescue medications reflect clinical practice, so the treatment policy strategy is adopted to continue to collect imaging assessment data of patients until PD/death.

PD or death after missing ≥2 consecutive scheduled imaging follow-ups was to be censored at last observation prior to missing assessment.

Primary estimand OS

Population: Patients with locally advanced/metastatic ESCC

Treatment: HLX10/placebo combined with chemotherapy (cisplatin + 5-FU), with every 2 weeks (14 days) as a treatment cycle

Variable: Time from randomisation to death due to any cause.

Population-level summary: Hazard ratio (HR)

Intercurrent events and handling strategies

Table S1: Intercurrent events and handling strategies:

#	Intercurrent events	Handling strategies and description
1	Initiation of new anti-tumor therapy for ESCC Temporary treatment interruption Treatment discontinuation Use of rescue medications	**Treatment policy strategy**: The initiation of new anti-tumor therapy for ESCC, temporary treatment interruption, treatment discontinuation, and the use of rescue medications reflect clinical practice and do not affect the objectivity of OS, so the treatment policy strategy is used to continue to collect survival follow-up data of patients until death.

Sample size

This study employs PFS and OS as dual primary endpoints. To control the overall type I errors, α is assigned as follows:

PFS: α = 0.005 (one-sided)

OS: α = 0.02 (one-sided)

Considering the sample size required for PFS and OS evaluation, a total of 540 patients (360 in the HLX10 group and 180 in the control group) were enrolled in this study.

2.4.7. Randomisation

This is a randomised, double-blind study. Eligible subjects are randomised 2:1 into serplulimab or control groups using an Interactive Web Response System/Interactive Voice Response System (IWRS/IVRS).

Randomisation is stratified by: PD-L1 expression level (1 ≤ CPS < 10 versus CPS ≥ 10), age (≥ 65 years versus < 65 years), and tumor state (locally advanced versus distant metastasis).

2.4.8. Blinding (masking)

Subjects, the investigator, the sponsor, and the designees were not aware of the randomised allocation. Unblinding was only to be performed in cases of emergency medical situations (where knowledge of the randomised treatment is necessary for urgent medical care) or upon request by regulatory authorities; otherwise, the blind had to be maintained.

2.4.9. Statistical methods

Statistical analysis sets

Intention to treat (ITT) set

ITT set is defined as all subjects randomised to the study. The ITT population is the primary analysis population for the efficacy analysis of this study. Analysis for the ITT population is conducted based on randomised treatment groups.

Modified intention to treat (mITT) set

It was recommended to exclude the efficacy data of subjects with drug dispensing errors from the ITT set, defining the mITT set that was used for sensitivity analysis.

Per protocol set (PPS)

Subset of ITT include all randomised subjects without major protocol deviations significantly affecting the primary efficacy evaluation. S

Safety set (SS)

SS is defined as all subjects who have received at least one dose of study drug.

Pharmacokinetic set (PKS)

All subjects who have received at least one dose of serplulimab, and have at least one post-dose detectable concentration at planned PK time point and have no major protocol deviations that may impact the PK evaluation significantly., .

Statistical analysis methods

Interim analysis and multiplicity control

Table 16 Significance levels at each analysis time point

Scenario	Progression-free survival (PFS)				Overall survival (OS)			
Analysis time point	Before update		After update		Before update		After update	
	Z value	*P* value[1]	Z value	*P* value[1]	Z value	*P* value[1]	Z value	*P* value[1]
Superiority is not achieved in the final analysis of PFS and the interim analysis of OS								
Interim analysis[2]	2.580	0.010	/	/	2.580	0.010	/	/
Final analysis	—	—	—	—	2.086	0.037	/	/
Superiority is achieved in the final analysis of PFS, but not in the interim analysis of OS (the α assigned to PFS is reallocated to OS and the test boundary is updated)								
Interim analysis[2]	2.580	0.010	/	/	2.580	0.010	2.470	0.014
Final analysis	—	—	—	—	2.086	0.037	1.997	0.046
Superiority is not achieved in the final analysis of PFS, but is achieved in the interim analysis of OS (the α assigned to OS is reallocated PFS and the test boundary is updated)								
Interim analysis[2]	2.580	0.010	1.960	0.020	2.580	0.010	/	/
Final analysis	—	—	—	—	/	/	/	/
Superiority is achieved in the final analysis of PFS and the interim analysis of OS								
Interim analysis[2]	2.580	0.010	/	/	2.580	0.010	/	/
Final analysis	—	—	—	—	/	/	/	/

Notes:

[1] The *P* value in the table represents the nominal significance level (two-sided);

[2] The final analysis of PFS will be performed when the target number of events (339 PFS events) is reached, and the interim analysis of OS will be performed simultaneously with the final analysis of PFS. The final analysis of OS will be performed when the target number of events (388 OS events) is reached. Therefore, the interim analysis in the table represents the final analysis of PFS and the interim analysis of OS, and the final analysis represents the final analysis of OS.

Primary analyses

For the primary analyses of PFS and OS a stratified Log-Rank test was employed. The hazard ratio (HR) and its 95% confidence interval (CI) was to be estimated using a stratified Cox proportional hazards model. Median PFS and its 95% CI were calculated using the Kaplan-Meier method, with standard error estimated via Greenwood's formula and confidence intervals based on the log-log transformation (Brookmeyer-Crowley method), and Kaplan-Meier curves were to be plotted. The Kaplan-Meier method was also be used to calculate the 6-, 9-, and 12-month PFS rates and their 95% CIs.

Sensitivity and supplementary analyses

A total of 8 sensitivity and 2 supplementary analyses were preplanned for PFS including use of alternative population sets described above. For OS 5 sensitivity and two supplemental analyses were preplanned. The sensitivity and supplementary analyses were planned to test underlying assumptions related to the analyses and the impact on protocol violations. Details are found in the SAP.

Secondary endpoints

The secondary endpoint ORR was to be tested using the stratified Cochran-Mantel-Haenszel (CMH) method to test the difference in ORR between the two groups and its 95% CI. The collected values

of the true stratification factors were to be used for analysis. 95% CI in individual treatment groups were to be calculated using the Clopper-Pearson method.

Disease control rate (DCR) was also be analysed. DCR is defined as the proportion of subjects with best overall response (BOR) of CR, PR, or SD as assessed by IRRC.

DOR was to be analysed similar to PFS and OS.

Sensitivity and supplemental analyses were preplanned for the secondary endpoints assessing robustness of results dependent on assumptions.

Quality of Life

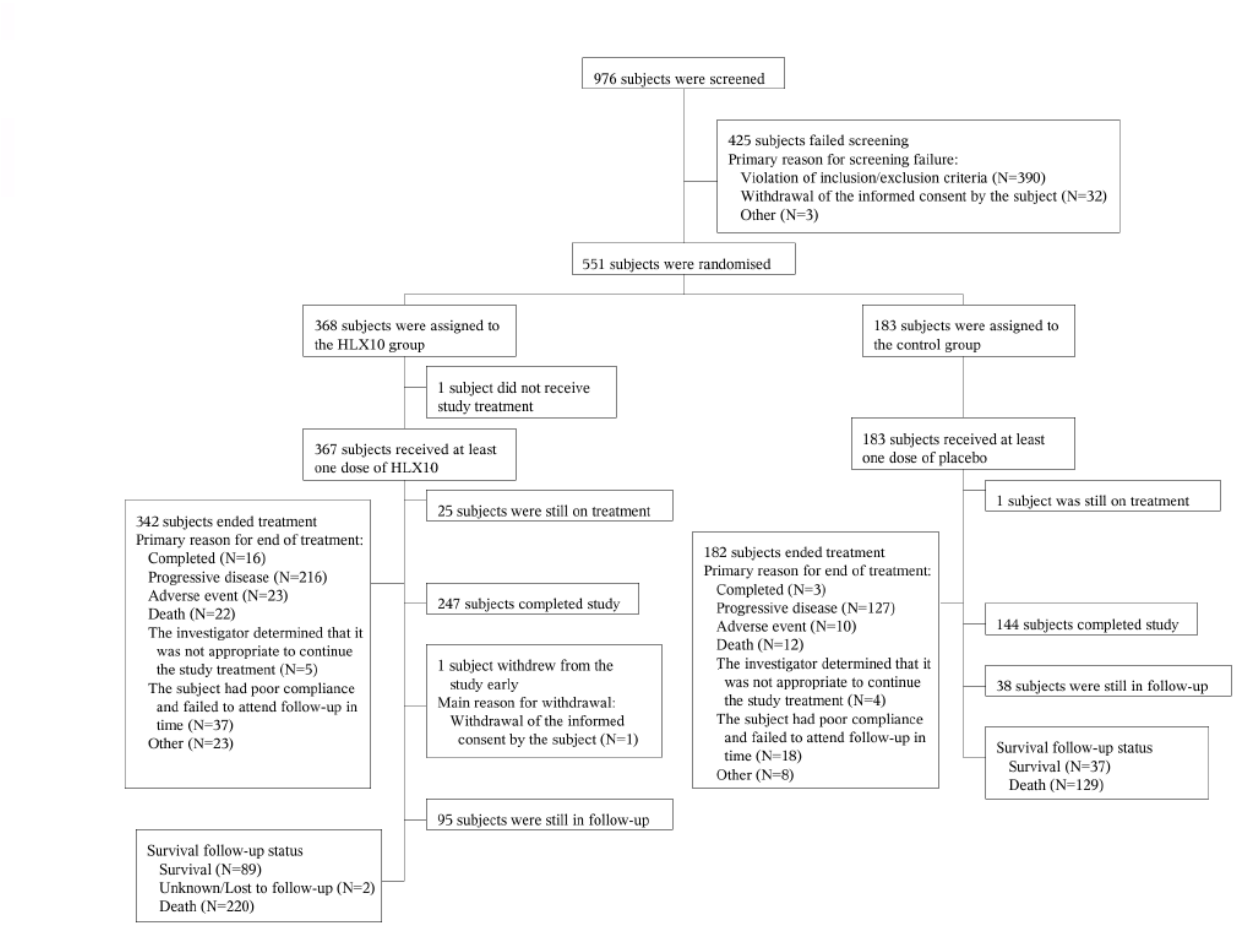
The quality of life (QoL) instruments EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-OES18 were collected at baseline and at each visit. Changes in each item of EQ-5D-5L and VAS scores were to be described by visit, and quality of life questionnaire index scores for EORTC QLQ-C30 and EORTC QLQ-OES18 were to be calculated by dimension (Fayers et. al., 2001). The baseline and post-baseline scores for each EQ-5D-5L item were to be described in terms of number and percentage. Descriptive statistics (number of subjects, mean, standard deviation, median, maximum, and minimum) were to be calculated for the dimensions of each scale at baseline and post-baseline, as well as for the changes from baseline, between the two control groups by visit.

Results

2.4.10. Participant flow

Subject disposition is summarised in the figure below.

Figure 14. Subject Distribution Flowchart (All Subjects) – DCO 09 January 2023



2.4.11. Recruitment

A total of 71 study sites were initiated in China, of which 66 study sites enrolled subjects.

Date of the first subject signing the informed consent form: June 19, 2019.

Date of the last subject enrolment: December 17, 2021.

The submission included clinical data from the interim analysis (data cut-off date: April 15, 2022; database lock date: May 17, 2022) and clinical data from the updated analysis (database lock date: November 22, 2023; data cut-off date: January 09, 2023).

2.4.12. Conduct of the study

Protocol amendments

The protocol was amended three times from the initiation of the study, with revised versions 2.0 (version date: October 29, 2019), 3.0 (version date: February 28, 2021), and 4.0 (version date:

June 26, 2021). The major changes were submitted and assessed with this procedure but not included in this report.

The statistical analysis plan (SAP) version 1.0 was finalised and implemented on May 11, 2022. During the study, the SAP was amended one time.

Protocol deviations

Table 17. Major protocol deviations (ITT)

	HLX10 group (N=368)	Control group (N=183)	Total (N=551)
Subjects with at least one major protocol deviation	224 (60.9%)	91 (49.7%)	315 (57.2%)
Deviation from Study Procedure	211 (57.3%)	88 (48.1%)	299 (54.3%)
Laboratory measurement missing	108 (29.3%)	56 (30.6%)	164 (29.8%)
Imaging examination missing	69 (18.8%)	19 (10.4%)	88 (16.0%)
Imaging examination out of window	48 (13.0%)	12 (6.6%)	60 (10.9%)
Randomization error	36 (9.8%)	15 (8.2%)	51 (9.3%)
Out-of-window laboratory measurements	24 (6.5%)	6 (3.3%)	30 (5.4%)
Inconsistent/unqualified imaging examination methods	8 (2.2%)	6 (3.3%)	14 (2.5%)
Missing visit	1 (0.3%)	0	1 (0.2%)
Out-of-window visit	0	1 (0.5%)	1 (0.2%)
Study Treatment-related Deviation	52 (14.1%)	18 (9.8%)	70 (12.7%)
Use of study treatment (HLX10/Placebo) not according to dose/dosing regimen/dosing time specified in the protocol	41 (11.1%)	10 (5.5%)	51 (9.3%)
Not meeting the requirement for dosing, but dosed	12 (3.3%)	8 (4.4%)	20 (3.6%)
Use of study treatment (chemotherapy) at a dose/dosing regimen/time not specified in the protocol	2 (0.5%)	0	2 (0.4%)
Deviation from Inclusion/Exclusion Criteria	4 (1.1%)	0	4 (0.7%)
Not meeting the inclusion criteria, but included in the study	3 (0.8%)	0	3 (0.5%)
Meeting the exclusion criteria, but included in this study	1 (0.3%)	0	1 (0.2%)
Deviation from Criteria for Discontinuation/Withdrawal	2 (0.5%)	1 (0.5%)	3 (0.5%)
Meeting any of the criteria for discontinuation/withdrawal specified in the protocol, but continuing study treatment or participation	2 (0.5%)	1 (0.5%)	3 (0.5%)
Deviation from Informed Consent	0	1 (0.5%)	1 (0.2%)
ICF missing/incomplete	0	1 (0.5%)	1 (0.2%)

Data cut-off date: 2023-01-09

2.4.13. Baseline data

The demographic characteristics of subjects in the ITT set are summarised in the table below.

Table 18. Summary of demographic characteristics (ITT)

	HLX10 group (N=368)	Control group (N=183)	Total (N=551)
Age (years)			
N	368	183	551
Mean (SD)	61.8 (7.96)	62.3 (7.51)	61.9 (7.81)
Median	64.0	64.0	64.0
Min, Max	34, 75	37, 75	34, 75
< 65 years	199 (54.1%)	98 (53.6%)	297 (53.9%)
≥ 65 years	169 (45.9%)	85 (46.4%)	254 (46.1%)
Gender			
Total	368	183	551
Male	317 (86.1%)	153 (83.6%)	470 (85.3%)
Female	51 (13.9%)	30 (16.4%)	81 (14.7%)
Height (cm)			
N	368	183	551
Mean (SD)	166.45 (7.551)	166.25 (7.519)	166.38 (7.534)
Median	168.00	167.00	167.00
Min, Max	145.0, 185.0	141.0, 183.0	141.0, 185.0
Weight (kg)			
N	368	183	551
Mean (SD)	58.903 (9.155)	59.072 (9.377)	58.959 (9.221)
Median	58.000	59.000	58.000
Min, Max	40.00, 92.00	34.10, 84.00	34.10, 92.00
BMI (kg/m^2)			
N	368	183	551
Mean (SD)	21.236 (2.818)	21.330 (2.865)	21.267 (2.832)
Median	20.721	20.755	20.741
Min, Max	15.590, 29.675	16.219, 29.102	15.590, 29.675
Baseline ECOG PS			
Total	368	183	551
0	92 (25.0%)	53 (29.0%)	145 (26.3%)
1	276 (75.0%)	130 (71.0%)	406 (73.7%)
PD-L1 expression level			
Total	368	183	551
1 < CPS < 10	206 (56.0%)	104 (56.8%)	310 (56.3%)
CPS ≥ 10	162 (44.0%)	79 (43.2%)	241 (43.7%)
Tumor status			
Total	368	183	551
Locally advanced	46 (12.5%)	29 (15.8%)	75 (13.6%)
Distant metastasis	322 (87.5%)	154 (84.2%)	476 (86.4%)

Notes: ECOG PS = ECOG Performance Status
The denominator of the percentage was the total number of subjects in the corresponding HLX10 group for each parameter
Data cut-off date: 2023-01-09

Table 19. Summary of demographic characteristics of patients with CPS < 5 and CPS ≥ 5

	CPS < 5		CPS ≥ 5	
	HLX10 N=138	Placebo N=70	HLX10 N=230	Placebo N=113
Age (years)				
N	138	70	230	113
Mean (SD)	61.3 (8.17)	62.0 (7.51)	62.0 (7.84)	62.5 (7.54)
Median	62	62	64	64
Min, Max	34 , 75	37 , 75	34 , 75	46 , 74
< 65 years	80 (58.0%)	40 (57.1%)	119 (51.7%)	58 (51.3%)
≥ 65 years	58 (42.0%)	30 (42.9%)	111 (48.3%)	55 (48.7%)
Gender				
Total	138	70	230	113
Male	118 (85.5%)	58 (82.9%)	199 (86.5%)	95 (84.1%)
Female	20 (14.5%)	12 (17.1%)	31 (13.5%)	18 (15.9%)
Height (cm)				
N	138	70	230	113
Mean (SD)	166.23 (7.446)	167.54 (7.818)	166.58 (7.627)	165.46 (7.248)
Median	168	168.5	168	165
Min, Max	148.0 , 183.0	145.0 , 183.0	145.0 , 185.0	141.0 , 181.0
Weight (kg)				
N	138	70	230	113
Mean (SD)	59.34 (9.968)	59.58 (9.933)	58.642 (8.642)	58.755 (9.047)
Median	57.75	60	58	58
Min, Max	42.5 , 92.0	34.1 , 82.0	40.00 , 81.00	38.00 , 84.00
BMI (kg/m^2)				
N	138	70	230	113
Mean (SD)	21.428 (2.973)	21.143 (2.751)	21.121 (2.722)	21.446 (2.940)
Median	20.709	21.007	20.757	20.617
Min, Max	17.175 , 28.720	16.219 , 29.053	15.590 , 29.675	16.797 , 29.102
Baseline ECOG PS				
Total	138	70	230	113
0	33 (23.9%)	22 (31.4%)	59 (25.7%)	31 (27.4%)
1	105 (76.1%)	48 (68.6%)	171 (74.3%)	82 (72.6%)
PD-L1 expression level				
Total	138	70	230	113
1≤CPS<10	138 (100%)	70 (100%)	68 (29.6%)	34 (30.1%)
CPS≥10	0	0	162 (70.4%)	79 (69.9%)
Tumour status				
Total	138	70	230	113
Locally advanced	18 (13.0%)	9 (12.9%)	28 (12.2%)	20 (17.7%)
Distant metastasis	120 (87.0%)	61 (87.1%)	202 (87.8%)	93 (82.3%)

Table 20. Diagnosis of Esophageal Squamous Cell Carcinoma (ITT)

	HLX10 group (N=368)	Control group (N=183)	Total (N=551)
Time from initial diagnosis to informed consent (months) [1]			
N	368	183	551
Mean (SD)	11.68 (21.535)	9.45 (15.971)	10.94 (19.874)
Median	0.60	0.70	0.60
Min, Max	0.0 , 140.9	0.0 , 83.8	0.0 , 140.9
Histopathological type at initial diagnosis			
Total	368	183	551
Adenocarcinoma	0	0	0
Squamous cell carcinoma	368 (100.0%)	183 (100.0%)	551 (100.0%)
Adenosquamous cell carcinoma	0	0	0
Undifferentiated carcinoma	0	0	0
Other	0	0	0
Differentiation grade			
Total	368	183	551
Gx - Grade cannot be assessed	131 (35.6%)	73 (39.9%)	204 (37.0%)
G1 - Well differentiated	19 (5.2%)	1 (0.5%)	20 (3.6%)
G2 - Moderately differentiated	76 (20.7%)	46 (25.1%)	122 (22.1%)
G3 - Poorly differentiated	73 (19.8%)	26 (14.2%)	99 (18.0%)
Other	69 (18.8%)	37 (20.2%)	106 (19.2%)
Location of primary tumour at the initial diagnosis (multiple selections allowed)			
Total	368	183	551
Location of single primary tumour			
Total	275 (74.7%)	141 (77.0%)	416 (75.5%)
Cervical segment	18 (4.9%)	5 (2.7%)	23 (4.2%)
Upper thoracic segment	40 (10.9%)	17 (9.3%)	57 (10.3%)
Middle thoracic segment	102 (27.7%)	53 (29.0%)	155 (28.1%)
Lower thoracic segment (excluding esophagogastric junction)	84 (22.8%)	43 (23.5%)	127 (23.0%)
Esophagogastric junction	20 (5.4%)	15 (8.2%)	35 (6.4%)
Not evaluable	11 (3.0%)	8 (4.4%)	19 (3.4%)
Locations of multiple primary tumours (≥ 2)			
Total	93 (25.3%)	42 (23.0%)	135 (24.5%)
Middle thoracic segment,Lower thoracic segment	50 (13.6%)	26 (14.2%)	76 (13.8%)
Upper thoracic segment,Middle thoracic segment	18 (4.9%)	6 (3.3%)	24 (4.4%)
Lower thoracic segment,Esophagogastric junction	6 (1.6%)	2 (1.1%)	8 (1.5%)
Upper thoracic segment,Middle thoracic segment,Lower thoracic segment	5 (1.4%)	1 (0.5%)	6 (1.1%)
Cervical segment,Upper thoracic segment	3 (0.8%)	1 (0.5%)	4 (0.7%)
Middle thoracic segment,Esophagogastric junction	0	3 (1.6%)	3 (0.5%)
Upper thoracic segment,Lower thoracic segment	2 (0.5%)	1 (0.5%)	3 (0.5%)
Cervical segment,Upper thoracic segment,Middle thoracic segment	2 (0.5%)	0	2 (0.4%)
Cervical segment,Esophagogastric junction	1 (0.3%)	0	1 (0.2%)
Cervical segment,Lower thoracic segment	0	1 (0.5%)	1 (0.2%)
Cervical segment,Middle thoracic segment	1 (0.3%)	0	1 (0.2%)
Cervical segment,Middle thoracic segment,Esophagogastric junction	0	1 (0.5%)	1 (0.2%)
Cervical segment,Middle thoracic segment,Lower thoracic segment	1 (0.3%)	0	1 (0.2%)
Cervical segment,Upper thoracic segment,Lower thoracic segment	1 (0.3%)	0	1 (0.2%)
Middle thoracic segment,Lower thoracic segment,Esophagogastric junction	1 (0.3%)	0	1 (0.2%)
Upper thoracic segment,Esophagogastric junction	1 (0.3%)	0	1 (0.2%)
Upper thoracic segment,Lower thoracic segment,Esophagogastric junction	1 (0.3%)	0	1 (0.2%)

Initial TNM stage			
Primary tumour			
Total	368	183	551
Tx	102 (27.7%)	68 (37.2%)	170 (30.9%)
T0	1 (0.3%)	0	1 (0.2%)
Tis	0	0	0
T1	9 (2.4%)	3 (1.6%)	12 (2.2%)
T1a	2 (0.5%)	2 (1.1%)	4 (0.7%)
T1b	4 (1.1%)	5 (2.7%)	9 (1.6%)
T2	40 (10.9%)	16 (8.7%)	56 (10.2%)
T3	155 (42.1%)	67 (36.6%)	222 (40.3%)
T4	31 (8.4%)	9 (4.9%)	40 (7.3%)
T4a	9 (2.4%)	8 (4.4%)	17 (3.1%)
T4b	12 (3.3%)	2 (1.1%)	14 (2.5%)
Missing	3 (0.8%)	3 (1.6%)	6 (1.1%)
Regional lymph node			
Total	368	183	551
Nx	107 (29.1%)	64 (35.0%)	171 (31.0%)
N0	56 (15.2%)	25 (13.7%)	81 (14.7%)
N1	66 (17.9%)	25 (13.7%)	91 (16.5%)
N2	76 (20.7%)	39 (21.3%)	115 (20.9%)
N3	60 (16.3%)	27 (14.8%)	87 (15.8%)
Missing	3 (0.8%)	3 (1.6%)	6 (1.1%)
Distant metastasis			
Total	368	183	551
M0	151 (41.0%)	80 (43.7%)	231 (41.9%)
M1	213 (57.9%)	100 (54.6%)	313 (56.8%)
Missing	4 (1.1%)	3 (1.6%)	7 (1.3%)
Clinical staging at initial diagnosis			
Total	368	183	551
Stage 0	1 (0.3%)	0	1 (0.2%)
Stage I	10 (2.7%)	8 (4.4%)	18 (3.3%)
Stage II	42 (11.4%)	15 (8.2%)	57 (10.3%)
Stage III	63 (17.1%)	30 (16.4%)	93 (16.9%)
Stage IVA	26 (7.1%)	24 (13.1%)	50 (9.1%)
Stage IVB	205 (55.7%)	89 (48.6%)	294 (53.4%)
Unknown	21 (5.7%)	17 (9.3%)	38 (6.9%)
TNM stage at the time of ICF signing			
Primary tumour			
Total	368	183	551
Tx	165 (44.8%)	98 (53.6%)	263 (47.7%)
T0	0	0	0
Tis	0	0	0
T1	4 (1.1%)	2 (1.1%)	6 (1.1%)
T1a	1 (0.3%)	0	1 (0.2%)
T1b	2 (0.5%)	2 (1.1%)	4 (0.7%)
T2	23 (6.3%)	7 (3.8%)	30 (5.4%)
T3	113 (30.7%)	52 (28.4%)	165 (29.9%)
T4	39 (10.6%)	12 (6.6%)	51 (9.3%)
T4a	9 (2.4%)	7 (3.8%)	16 (2.9%)
T4b	12 (3.3%)	3 (1.6%)	15 (2.7%)
Regional lymph node			
Total	368	183	551
Nx	139 (37.8%)	81 (44.3%)	220 (39.9%)
N0	24 (6.5%)	11 (6.0%)	35 (6.4%)
N1	51 (13.9%)	25 (13.7%)	76 (13.8%)
N2	84 (22.8%)	32 (17.5%)	116 (21.1%)

N3	70 (19.0%)	34 (18.6%)	104 (18.9%)
Distant metastasis			
Total	368	183	551
M0	46 (12.5%)	29 (15.8%)	75 (13.6%)
M1	322 (87.5%)	154 (84.2%)	476 (86.4%)
Clinical stage at the time of ICF signing			
Total	368	183	551
Stage 0	0	0	0
Stage I	0	0	0
Stage II	2 (0.5%)	0	2 (0.4%)
Stage III	24 (6.5%)	11 (6.0%)	35 (6.4%)
Stage IVA	18 (4.9%)	15 (8.2%)	33 (6.0%)
Stage IVB	322 (87.5%)	154 (84.2%)	476 (86.4%)
Unknown	2 (0.5%)	3 (1.6%)	5 (0.9%)
Tumour status at study entry			
Total	368	183	551
Locally advanced	46 (12.5%)	29 (15.8%)	75 (13.6%)
Distant metastasis	322 (87.5%)	154 (84.2%)	476 (86.4%)
Unknown	0	0	0
Time from metastasis to informed consent (months) [2]			
N	280	138	418
Mean (SD)	0.53 (1.546)	0.36 (0.591)	0.47 (1.312)
Median	0.20	0.20	0.20
Min, Max	-0.4 , 16.9	-0.4 , 3.8	-0.4 , 16.9
Metastasized location(s) (multiple selections allowed)			
Total	322	154	476
Single metastasized location			
Total	196 (60.9%)	93 (60.4%)	289 (60.7%)
Lung metastasis	32 (9.9%)	8 (5.2%)	40 (8.4%)
Liver metastasis	15 (4.7%)	5 (3.2%)	20 (4.2%)
Bone metastasis	6 (1.9%)	0	6 (1.3%)
Skin metastasis	0	0	0
Brain metastasis	0	0	0
Lymph nodes metastasis	135 (41.9%)	74 (48.1%)	209 (43.9%)
Other metastases	8 (2.5%)	6 (3.9%)	14 (2.9%)
Multiple metastasized locations			
Total	126 (39.1%)	61 (39.6%)	187 (39.3%)
Lung,Lymph nodes	29 (9.0%)	11 (7.1%)	40 (8.4%)
Liver,Lymph nodes	16 (5.0%)	14 (9.1%)	30 (6.3%)
Lymph nodes,Other	11 (3.4%)	5 (3.2%)	16 (3.4%)
Bone,Lymph nodes	12 (3.7%)	2 (1.3%)	14 (2.9%)
Lung,Liver,Lymph nodes	8 (2.5%)	3 (1.9%)	11 (2.3%)
Liver,Bone,Lymph nodes	7 (2.2%)	3 (1.9%)	10 (2.1%)
Lung,Other	6 (1.9%)	4 (2.6%)	10 (2.1%)
Lung,Liver	6 (1.9%)	2 (1.3%)	8 (1.7%)
Lung,Liver,Bone,Lymph nodes	5 (1.6%)	3 (1.9%)	8 (1.7%)
Lung,Lymph nodes,Other	1 (0.3%)	5 (3.2%)	6 (1.3%)
Bone,Lymph nodes,Other	3 (0.9%)	1 (0.6%)	4 (0.8%)
Bone,Other	3 (0.9%)	1 (0.6%)	4 (0.8%)
Liver,Lymph nodes,Other	4 (1.2%)	0	4 (0.8%)
Lung,Bone	2 (0.6%)	2 (1.3%)	4 (0.8%)
Liver,Bone	3 (0.9%)	0	3 (0.6%)
Liver,Other	2 (0.6%)	1 (0.6%)	3 (0.6%)
Lung,Bone,Lymph nodes	2 (0.6%)	1 (0.6%)	3 (0.6%)
Lung,Bone,Lymph nodes,Other	1 (0.3%)	1 (0.6%)	2 (0.4%)
Lung,Liver,Bone,Other	1 (0.3%)	1 (0.6%)	2 (0.4%)
Liver,Bone,Lymph nodes,Other	1 (0.3%)	0	1 (0.2%)

Lung,Liver,Bone	1 (0.3%)	0	1 (0.2%)
Lung,Liver,Bone,Lymph nodes,Other	1 (0.3%)	0	1 (0.2%)
Lung,Liver,Other	1 (0.3%)	0	1 (0.2%)
Lung,Lymph nodes,Skin,Other	0	1 (0.6%)	1 (0.2%)
Was there a recurrence			
Total	368	183	551
Yes	131 (35.6%)	64 (35.0%)	195 (35.4%)
No	237 (64.4%)	119 (65.0%)	356 (64.6%)
Time from last recurrence to informed consent (months) [3]			
N	130	64	194
Mean (SD)	0.59 (1.163)	0.51 (0.957)	0.56 (1.098)
Median	0.20	0.20	0.20
Min, Max	0.0 , 10.5	0.0 , 5.3	0.0 , 10.5

Notes:[1] Time from initial diagnosis to informed consent (months) = (Date of signing informed consent form - Date of initial diagnosis of esophageal squamous cell carcinoma) / 30.4375.
[2] Time from initial diagnosis of metastasis to informed consent (months) = (Date of signing informed consent form - Date of initial diagnosis of metastasis) / 30.4375. For some subjects, the value was negative due to metastasis confirmed by imaging examination of the study site after signing the informed consent form.
[3] Time from last recurrence to informed consent (months) = (Date of signing informed consent form - Date of last recurrence) / 30.4375. For some subjects, the value was negative due to recurrence confirmed by imaging examination of the study site after signing the informed consent form.
Data cut-off date: 2023-01-09

ESCC history of patients with CPS < 5 and CPS ≥ 5 is summarised in the table below:

Table 21. Diagnosis of ESCC of patients with CPS < 5 and CPS ≥ 5

	CPS < 5		CPS ≥ 5	
	HLX10 (N=138)	Control (N=70)	HLX10 (N=230)	Control (N=113)
Time from initial diagnosis to informed consent (months)				
N	138	70	230	113
Mean (SD)	12.01 (20.860)	10.36 (17.029)	11.49 (21.972)	8.88 (15.330)
Median	0.55	0.6	0.6	0.7
Min, Max	0.0 , 106.7	0.0 , 70.1	0.0 , 140.9	0.0 , 83.8
Histopathological type at initial diagnosis				
Total	138	70	230	113
Squamous cell carcinoma	138 (100.0%)	70 (100.0%)	230 (100.0%)	113 (100.0%)
Clinical stage at the time of ICF signing				
Total	138	70	230	113
Stage III	9 (6.5%)	3 (4.3%)	15 (6.5%)	8 (7.1%)
Stage IVA	8 (5.8%)	5 (7.1%)	10 (4.3%)	10 (8.8%)
Stage IVB	120 (87.0%)	61 (87.1%)	202 (87.8%)	93 (82.3%)
Tumour status at study entry				
Total	138	70	230	113
Locally advanced	18 (13.0%)	9 (12.9%)	28 (12.2%)	20 (17.7%)
Distant metastasis	120 (87.0%)	61 (87.1%)	202 (87.8%)	93 (82.3%)
Unknown	0	0	0	0
Was there a recurrence				
Total	138	70	230	113
Yes	52 (37.7%)	26 (37.1%)	79 (34.3%)	38 (33.6%)
No	86 (62.3%)	44 (62.9%)	151 (65.7%)	75 (66.4%)
Tumour burden at baseline (mm)				
n	138	70	230	113
Mean (SD)	50.5 (39.11)	56.5 (42.37)	45.7 (31.29)	47.9 (31.60)
Median	41	48	39	40
Min, Max	11.0, 250.0	10.0, 261.0	11.0, 238.0	15.0, 151.0

Prior treatment for ESCC

In the ITT set, 120 (32.6%) subjects in the HLX10 group and 60 (32.8%) subjects in the control group previously received surgery for ESCC; among them, 119 (32.3%) subjects and 59 (32.2%) subjects received radical therapy, respectively.

A total of 41 (11.1%) subjects and 11 (6.0%) subjects in the two groups previously received radiotherapy for ESCC; among them, 20 (5.4%) subjects and 5 (2.7%) subjects received adjuvant radiotherapy, and 17 (4.6%) subjects and 5 (2.7%) subjects received radical radiotherapy.

A total of 86 (23.4%) subjects and 37 (20.2%) subjects in the two groups previously received systemic therapy for ESCC; all of them previously received chemotherapy, including 81 (22.0%) subjects and 34 (18.6%) subjects treated with platinum compounds, and 58 (15.8%) subjects and 33 (18.0%) subjects treated with taxanes in the respective group.

The MAH clarified that in the ITT set, 131 (35.6%) subjects in the serplulimab group and 63 (34.4%) subjects in the control group received prior anti-ESCC therapy and experienced a recurrence more than 6 months from previous treatment.

Post-hoc analyses of PFS of patients who received and not received prior anti-cancer treatment are summarised in the table below. The corresponding Kaplan-Meier plots are shown in Figure A (assessed by IRRC) and B (assessed by Investigator) below:

Table 22 PFS of patients who received and not received prior anti-cancer treatment – ITT (data cutoff [DCO]: 2023-01-09)

		Median (95%CI), Months		Stratified HR (95%CI)	p value
		HLX10	Placebo		
IRRC	Primary analysis submitted previously (ITT)	N=368	N=183	0.58 (0.465, 0.716)	<0.0001
		6.5 (5.75, 7.10)	5.3 (4.30, 5.55)		
	Received prior anti-cancer treatment	N=131	N=63	0.53 (0.365, 0.787)	0.0011
		7.0 (5.78, 8.67)	4.6 (3.84, 5.62)		
	Not Received prior anti-cancer treatment	N=237	N=120	0.53 (0.400, 0.696)	<0.0001
		5.8 (5.59, 6.97)	5.5 (4.30, 5.62)		
Investigator	Primary analysis submitted previously (ITT)	N=368	N=183	0.54 (0.442, 0.671)	<0.0001
		6.9 (6.41, 7.16)	5.4 (4.34, 5.59)		
	Received prior anti-cancer treatment	N=131	N=63	0.62 (0.427, 0.901)	0.0102
		7.0 (5.75, 9.23)	5.5 (4.17, 5.78)		
	Not Received prior anti-cancer treatment	N=237	N=120	0.47 (0.357, 0.610)	<0.0001
		6.9 (5.82, 7.23)	5.4 (4.21, 5.65)		

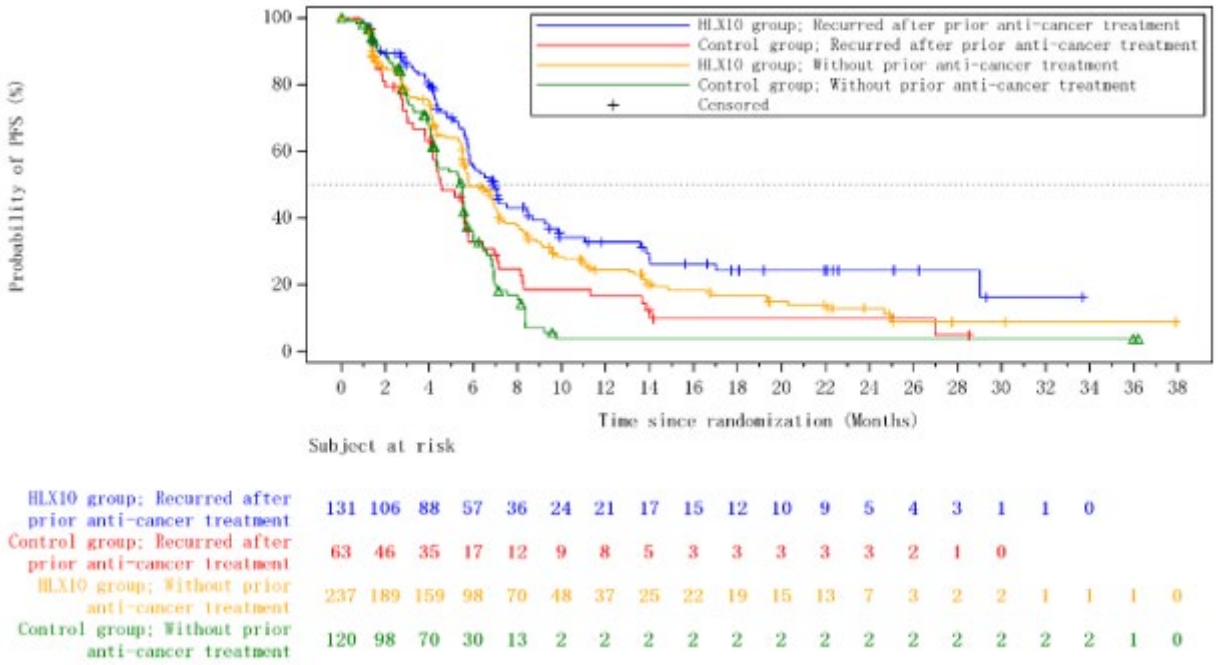


Figure 15 PFS of patients who received and not received prior anti-cancer treatment by IRRC - ITT (DCO: 2023-01-09)

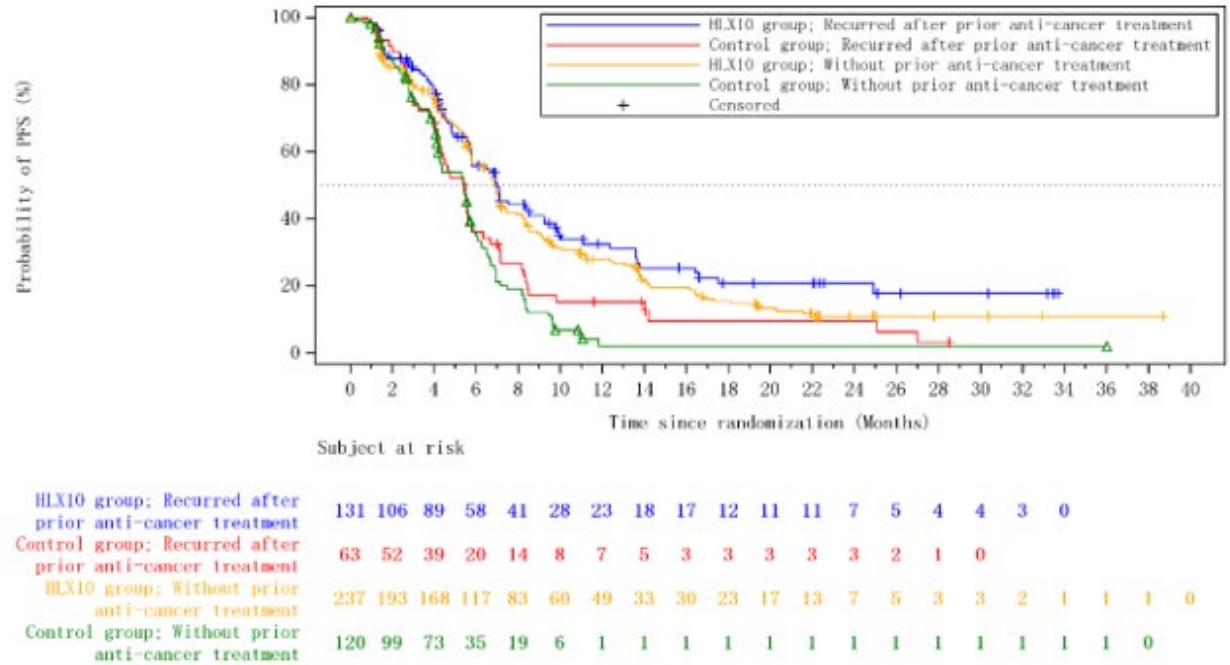


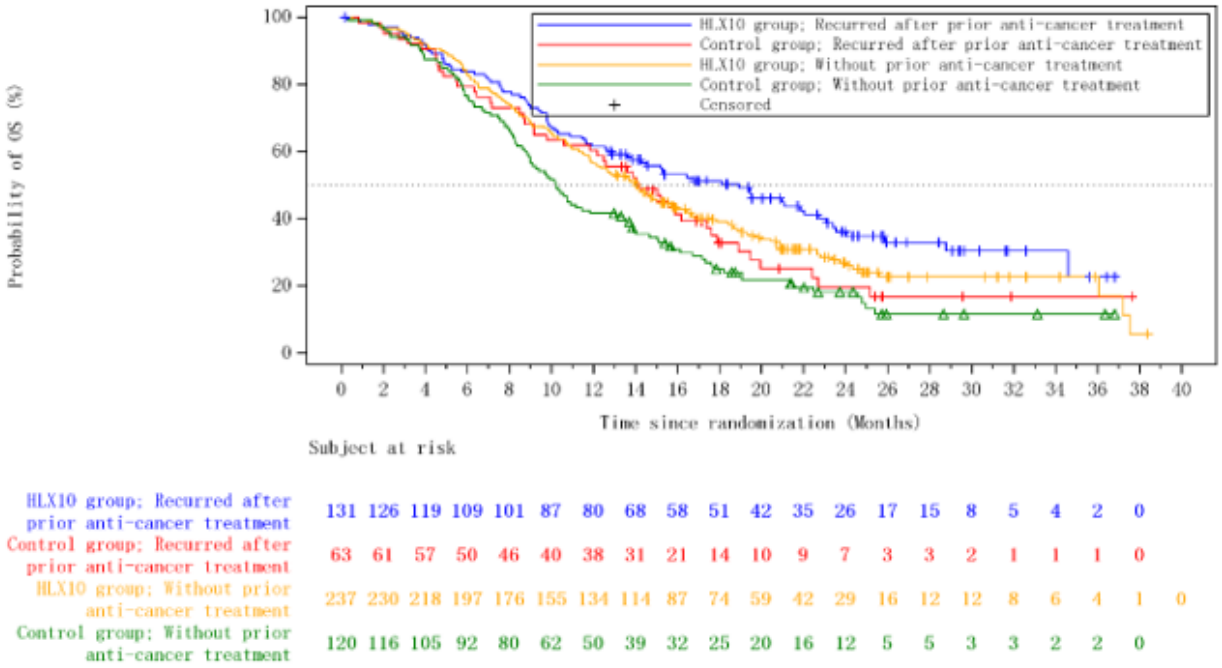
Figure 16 PFS of patients who received and not received prior anti-cancer treatment by investigator - ITT (DCO: 2023-01-09)

Post-hoc analyses of OS of patients who received and not received prior anti-cancer treatment are summarised in the table and shown in the Kaplan-Meier plot below.

Table 23 OS of patients who received and not received prior anti-cancer treatment - ITT (DCO: 2023-01-09)

	Median (95%CI), Months		Stratified HR (95%CI)	p value
	HLX10	Placebo		
Primary analysis submitted previously (ITT)	**N=368**	**N=183**	0.70 (0.568, 0.862)	0.0007
	14.8 (13.11, 16.66)	11.2 (9.69, 13.86)		
Received prior anti-cancer treatment	**N=131**	**N=63**	0.69 (0.471, 1.008)	0.0497
	18.9 (13.60, 22.77)	14.2 (10.58, 17.38)		
Not Received prior anti-cancer treatment	**N=237**	**N=120**	0.66 (0.512, 0.854)	0.0013
	14.1 (11.93, 15.80)	10.2 (8.84, 13.08)		

Figure 17 OS of patients who received and not received prior anti-cancer treatment - ITT (DCO: 2023-01-09)



CORTICOSTEROIDS FOR SYSTEMIC USE	195 (53.0%)	91 (49.7%)	286 (51.9%)
DEXAMETHASONE SODIUM PHOSPHATE	135 (36.7%)	61 (33.3%)	196 (35.6%)
DEXAMETHASONE	31 (8.4%)	20 (10.9%)	51 (9.3%)
METHYLPREDNISOLONE SODIUM SUCCINATE	34 (9.2%)	14 (7.7%)	48 (8.7%)
DEXAMETHASONE ACETATE	16 (4.3%)	13 (7.1%)	29 (5.3%)
PREDNISONE ACETATE	21 (5.7%)	5 (2.7%)	26 (4.7%)
METHYLPREDNISOLONE	14 (3.8%)	3 (1.6%)	17 (3.1%)
PREDNISONE	10 (2.7%)	0	10 (1.8%)
PREDNISOLONE	5 (1.4%)	3 (1.6%)	8 (1.5%)
BETAMETHASONE SODIUM PHOSPHATE	4 (1.1%)	3 (1.6%)	7 (1.3%)
HYDROCORTISONE	2 (0.5%)	0	2 (0.4%)
HYDROCORTISONE ACETATE	2 (0.5%)	0	2 (0.4%)
HYDROCORTISONE SODIUM SUCCINATE	1 (0.3%)	1 (0.5%)	2 (0.4%)
BETAMETHASONE DIPROPIONATE;BETAMETHASONE SODIUM PHOSPHATE	0	1 (0.5%)	1 (0.2%)
BETAMETHASONE PHOSPHATE	0	1 (0.5%)	1 (0.2%)
CORTISONE ACETATE	1 (0.3%)	0	1 (0.2%)

Subsequent treatment for ESCC

Subjects' subsequent anti-cancer therapy is shown in the table below. Of note, the complete original table is not shown as therapies used by only 1 or 2 patients in either of the two groups are not included here.

Table 24. Subsequent systemic anti-cancer therapy (ITT)

ATC level Preferred name (PN)	HLX10 group (N=368)	Control group (N=183)	Total (N=551)
Any subsequent systemic anti-cancer therapy			
Yes	158 (42.9%)	97 (53.0%)	255 (46.3%)
No	210 (57.1%)	86 (47.0%)	296 (53.7%)
Time from first dose to subsequent systemic anti-cancer therapy (months) [1]			
N	158	97	255
Mean (SD)	7.76 (5.351)	6.45 (3.433)	7.26 (4.749)
Median	6.85	5.90	6.20
Min, Max	1.1 , 32.6	1.2 , 19.7	1.1 , 32.6
Treatment type [2][3]			
Total	158 (42.9%)	97 (53.0%)	255 (46.3%)
Chemotherapy	90 (24.5%)	47 (25.7%)	137 (24.9%)
Targeted therapy	19 (5.2%)	11 (6.0%)	30 (5.4%)
Immunotherapy	11 (3.0%)	10 (5.5%)	21 (3.8%)
Chemotherapy + Immunotherapy	51 (13.9%)	39 (21.3%)	90 (16.3%)
Immunotherapy + Targeted therapy	15 (4.1%)	8 (4.4%)	23 (4.2%)
Chemotherapy + Targeted therapy	13 (3.5%)	12 (6.6%)	25 (4.5%)
Other	6 (1.6%)	4 (2.2%)	10 (1.8%)
Reason for changing treatment [2]			
Total	158 (42.9%)	97 (53.0%)	255 (46.3%)
AE	3 (0.8%)	2 (1.1%)	5 (0.9%)
PD	143 (38.9%)	87 (47.5%)	230 (41.7%)
Intolerable drug toxicity	4 (1.1%)	3 (1.6%)	7 (1.3%)
Other	25 (6.8%)	18 (9.8%)	43 (7.8%)
Duration of systemic treatment (days) [4]			
N	158	97	255
Mean (SD)	283.9 (271.79)	246.3 (229.18)	269.6 (256.61)
Median	192.5	196.0	196.0
Min, Max	1 , 1018	1 , 915	1 , 1018
TAXANES	116 (31.5%)	80 (43.7%)	196 (35.6%)
PACLITAXEL NANOPARTICLE ALBUMIN-BOUND	71 (19.3%)	52 (28.4%)	123 (22.3%)
PACLITAXEL	31 (8.4%)	19 (10.4%)	50 (9.1%)
DOCETAXEL	18 (4.9%)	11 (6.0%)	29 (5.3%)
PACLITAXEL LIPOSOME	4 (1.1%)	4 (2.2%)	8 (1.5%)
PD-1/PDL-1 (PROGRAMMED CELL DEATH PROTEIN 1/DEATH LIGAND 1) INHIBITORS	70 (19.0%)	55 (30.1%)	125 (22.7%)
CAMRELIZUMAB	48 (13.0%)	39 (21.3%)	87 (15.8%)
SINTILIMAB	13 (3.5%)	8 (4.4%)	21 (3.8%)
TISLELIZUMAB	4 (1.1%)	7 (3.8%)	11 (2.0%)
PEMBROLIZUMAB	5 (1.4%)	2 (1.1%)	7 (1.3%)
ENVAFOLIMAB	1 (0.3%)	0	1 (0.2%)
NIVOLUMAB	1 (0.3%)	0	1 (0.2%)
PENPULIMAB	1 (0.3%)	0	1 (0.2%)
PUCOTENLIMAB	1 (0.3%)	0	1 (0.2%)
SCT I10A	1 (0.3%)	0	1 (0.2%)
SERPLULIMAB	0	1 (0.5%)	1 (0.2%)
TORIPALIMAB	0	1 (0.5%)	1 (0.2%)
TQ B2450	1 (0.3%)	0	1 (0.2%)
PLATINUM COMPOUNDS	76 (20.7%)	46 (25.1%)	122 (22.1%)
NEDAPLATIN	41 (11.1%)	22 (12.0%)	63 (11.4%)
CARBOPLATIN	15 (4.1%)	12 (6.6%)	27 (4.9%)
CISPLATIN	15 (4.1%)	11 (6.0%)	26 (4.7%)
OXALIPLATIN	9 (2.4%)	3 (1.6%)	12 (2.2%)
LOBAPLATIN	2 (0.5%)	0	2 (0.4%)

PYRIMIDINE ANALOGUES	50 (13.6%)	21 (11.5%)	71 (12.9%)
GIMERACIL;OTERACIL POTASSIUM;TEGAFUR	30 (8.2%)	14 (7.7%)	44 (8.0%)
FLUOROURACIL	15 (4.1%)	7 (3.8%)	22 (4.0%)
CAPECITABINE	9 (2.4%)	3 (1.6%)	12 (2.2%)
GEMCITABINE HYDROCHLORIDE	1 (0.3%)	1 (0.5%)	2 (0.4%)
OTHER PROTEIN KINASE INHIBITORS	26 (7.1%)	18 (9.8%)	44 (8.0%)
CATEQUENTINIB	19 (5.2%)	14 (7.7%)	33 (6.0%)
CATEQUENTINIB HYDROCHLORIDE	5 (1.4%)	4 (2.2%)	9 (1.6%)
AL 2846	1 (0.3%)	0	1 (0.2%)
REGORAFENIB	1 (0.3%)	0	1 (0.2%)
TOPOISOMERASE 1 (TOP1) INHIBITORS	13 (3.5%)	13 (7.1%)	26 (4.7%)
IRINOTECAN	11 (3.0%)	10 (5.5%)	21 (3.8%)
IRINOTECAN HYDROCHLORIDE	2 (0.5%)	3 (1.6%)	5 (0.9%)
VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR (VEGFR) TYROSINE KINASE INHIBITORS	13 (3.5%)	8 (4.4%)	21 (3.8%)
RIVOCERANIB MESYLATE	9 (2.4%)	5 (2.7%)	14 (2.5%)
RIVOCERANIB	4 (1.1%)	3 (1.6%)	7 (1.3%)
FRUQUINTINIB	1 (0.3%)	0	1 (0.2%)
OTHER ANTINEOPLASTIC AGENTS	6 (1.6%)	2 (1.1%)	8 (1.5%)
OTHER ANTINEOPLASTIC AGENTS	5 (1.4%)	1 (0.5%)	6 (1.1%)
OH2	1 (0.3%)	1 (0.5%)	2 (0.4%)
ANTINEOPLASTIC AGENTS	5 (1.4%)	2 (1.1%)	7 (1.3%)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	5 (1.4%)	2 (1.1%)	7 (1.3%)
EGFR (EPIDERMAL GROWTH FACTOR RECEPTOR) INHIBITORS	3 (0.8%)	4 (2.2%)	7 (1.3%)
NIMOTUZUMAB	2 (0.5%)	2 (1.1%)	4 (0.7%)

Notes: WHO Drug Dictionary Version 202309
[1] If a subject had multiple records of subsequent systemic anti-cancer therapy, the record closest to the first dose was included in the summary. Time from the first dose to subsequent systemic anti-cancer therapy (months) = (Start date of first documented subsequent systemic anti-cancer systemic therapy - Date of first dose +1)/30.4375.
[2] If a subject had multiple records of subsequent systemic anti-cancer systemic therapy, the subject was included in the summary for each relevant category but was counted only once within the same category.
[3] "Chemotherapy", "targeted therapy", and "immunotherapy" referred to cases where only one same type of prior treatment was used.
[4] If a subject had multiple records of subsequent systemic anti-cancer therapy, the duration of treatment was calculated as the total duration of subsequent systemic anti-cancer therapy received by the subject, using the following formula: Duration of treatment (days) = End date of the last systemic therapy- Start date of the first systemic therapy+1. The summary was made only for subjects without missing start date. If the end date was missing, it was imputed with the analysis cut-off date.
Data cut-off date: 2023-01-09
Reference Listing: L16_02_01_11_03_F; Reference ADaM Data: ADSL,ADCM.

In the ITT set, 59 (16.0%) subjects in the HLX10 group and 37 (20.2%) subjects in the control group received subsequent radiotherapy for ESCC; and the median time from the first administration of investigational product to the subsequent radiotherapy for ESCC was 7.622 months (range: 1.643–21.585 months) and 5.979 months (range: 1.873–25.363 months), respectively.

Table 25. Histories of smoking, alcohol use and drug dependence (ITT)

	HLX10 group (N=368)	Control group (N=183)	Total (N=551)
Smoking status			
Total	368	183	551
Never	135 (36.7%)	68 (37.2%)	203 (36.8%)
Current	135 (36.7%)	60 (32.8%)	195 (35.4%)
Former	98 (26.6%)	55 (30.1%)	153 (27.8%)
Duration of smoking (years)			
N	221	108	329
Mean (SD)	31.8 (11.07)	31.2 (10.87)	31.6 (10.99)
Median	30.0	30.0	30.0
Min, Max	2 , 60	2 , 50	2 , 60
Quantity of consumed cigarettes (cigarette/day)			
N	223	110	333
Mean (SD)	19.51 (10.241)	20.55 (12.691)	19.85 (11.102)
Median	20.00	20.00	20.00
Min, Max	1 , 60	1 , 80	1 , 80
Alcohol status			
Total	368	183	551
Never	147 (39.9%)	73 (39.9%)	220 (39.9%)
Current	123 (33.4%)	55 (30.1%)	178 (32.3%)
Former	98 (26.6%)	55 (30.1%)	153 (27.8%)
Duration of alcohol use (years)			
N	202	94	296
Mean (SD)	29.0 (11.82)	30.6 (9.83)	29.5 (11.23)
Median	30.0	30.0	30.0
Min, Max	1 , 60	10 , 50	1 , 60
Any histories of drug allergy			
Total	368	183	551
Yes	16 (4.3%)	11 (6.0%)	27 (4.9%)
No	352 (95.7%)	172 (94.0%)	524 (95.1%)
Any histories of other allergies			
Total	368	183	551
Yes	6 (1.6%)	2 (1.1%)	8 (1.5%)
No	362 (98.4%)	181 (98.9%)	543 (98.5%)
Any histories of addictive drug dependence			
Total	368	183	551
Yes	0	0	0
No	368 (100%)	183 (100%)	551 (100%)

Data cut-off date: 2023-01-09

Biomarkers

The examination of biomarkers at screening is summarised in the table below.

Table 26. Biomarkers test at screening (ITT)

	HLX10 group (N=368)	Control group (N=183)	Total (N=551)
PD-L1			
CPS			
N	368	183	551
Mean (SD)	20.7 (28.07)	18.4 (26.42)	19.9 (27.53)
Median	6.5	5.0	6.0
Min, Max	1, 100	1, 100	1, 100
1≤CPS<10	206 (56.0%)	104 (56.8%)	310 (56.3%)
CPS≥10	162 (44.0%)	79 (43.2%)	241 (43.7%)
TPS(%)			
N	368	183	551
Mean (SD)	16.9 (27.63)	14.6 (25.68)	16.1 (27.00)
Median	2.0	1.0	2.0
Min, Max	0, 100	0, 98	0, 100
IC(%)			
N	20	8	28
Mean (SD)	10.5 (12.48)	8.8 (9.42)	10.0 (11.54)
Median	5.0	7.5	5.0
Min, Max	1, 50	1, 30	1, 50
MIDS Score			
N	348	175	523
Mean (SD)	4.1 (4.88)	3.8 (4.53)	4.0 (4.77)
Median	2.0	2.0	2.0
Min, Max	1, 50	1, 30	1, 50
MIDS Bin			
N	348	175	523
Mean (SD)	2.7 (0.74)	2.7 (0.66)	2.7 (0.71)
Median	3.0	3.0	3.0
Min, Max	1, 4	1, 4	1, 4
MSI/MMR			
Total	368	183	551
MSS/MSI-L	35 (9.5%)	26 (14.2%)	61 (11.1%)
MSI-H	0	2 (1.1%)	2 (0.4%)
Missing	333 (90.5%)	155 (84.7%)	488 (88.6%)
TMB (mutations/Mb)			
N	35	28	63
Mean (SD)	4.643 (4.490)	3.855 (1.841)	4.293 (3.562)
Median	3.630	3.435	3.540
Min, Max	0.70, 25.95	0.76, 10.04	0.70, 25.95
< 10	33 (9.0%)	27 (14.8%)	60 (10.9%)
≥ 10	2 (0.5%)	1 (0.5%)	3 (0.5%)
Missing	333 (90.5%)	155 (84.7%)	488 (88.6%)

Notes: PD-L1: programmed cell death-ligand 1, CPS: combined positive score, TPS: tumor proportion score, IC: immune cell, MIDS score: mononuclear immune-cell density score, MSI/MMR: microsatellite instability/mismatch repair, TMB: tumor mutational burden, MSS/MSI-L: Microsatellite stable or microsatellite instability-low, MSI-H: Microsatellite instability-high.
Data cut-off date: 2023-01-09

2.4.14. Numbers analysed

The analysis sets are summarised in the table below.

Table 27. Analysis sets (all randomised subjects)

	HLX10 group	Control group	Subjects with alternated medication [1]	Total
Intent-to-treat (ITT) set	368 (66.8%)	183 (33.2%)		551 (100%)
Subjects excluded from the ITT set	0	0		0
Subjects not randomized	0	0		0
Modified intent-to-treat (mITT) set	368 (66.8%)	168 (30.5%)		536 (97.3%)
Subjects excluded from the mITT set	0	15 (2.7%)		15 (2.7%)
Subjects not randomized	0	0		0
Subjects with drug dispensing error after randomization [1]	0	15 (2.7%)		15 (2.7%)
Per protocol set (PPS)	367 (66.6%)	168 (30.5%)		535 (97.1%)
Subjects excluded from the PPS	1 (0.2%)	15 (2.7%)		16 (2.9%)
Subjects not randomized	0	0		0
Subjects who did not use HLX10/placebo	1 (0.2%)	0		1 (0.2%)
Subjects without post-dose tumor assessment or survival data	0	0		0
Subjects with poor overall medication compliance	0	0		0
Subjects with drug dispensing error after randomization [1]	0	15 (2.7%)		15 (2.7%)
Subjects with other major protocol deviations affecting the primary efficacy evaluation	0	0		0
Safety set (SS)	374 (67.9%)	168 (30.5%)	8	550 (99.8%)
Subjects excluded from the SS	1 (0.2%)	0		1 (0.2%)
Subjects who did not use HLX10/placebo	1 (0.2%)	0		1 (0.2%)
Pharmacokinetics set (PKS)	364 (66.1%)	15 (2.7%)		379 (68.8%)
Subjects excluded from the PKS	4 (0.7%)	168 (30.5%)		172 (31.2%)
Subjects who did not use HLX10	1 (0.2%)	168 (30.5%)		169 (30.7%)
Subjects without HLX10 post-dose concentration	3 (0.5%)	0		3 (0.5%)
Subjects with other major protocol deviations affecting PK assessment	0	0		0

Notes: Percentage was calculated using the number of enrolled subjects in each group at each site as denominator.
[1] On April 26, 2020, the IWRS system administrator received a reminder email regarding the need for unblinding due to an SAE in a subject and found that a subject randomized to the control group was receiving HLX10 in combination with chemotherapy. Later, an internal review revealed that in the drug settings of the IWRS system, subjects in the control group with a weight of 33.3 kg < weight ≤ 66.6 kg were mistakenly assigned to the HLX10 group. As of April 26, 2020, a total of 51 subjects were enrolled in this weight group, resulting in some subjects in the control group being mistakenly treated with HLX10 in combination with chemotherapy. This issue was reported to the Ethics Committee of all study sites, regulatory authorities, and Independent Data Monitoring Committee (IDMC) in a timely manner upon discovery. Therefore, the safety analysis was performed in 5 groups: "a. received placebo + chemotherapy throughout. b. received HLX10 + chemotherapy throughout. c. subjects with alternated medication. d. received HLX10 (b and c combined). e. total".
Data cut-off date: 2023-01-09

2.4.15. Outcomes and estimation

Primary endpoints

ASTRUM-007 had dual primary endpoints; OS and PFS. After observing the target number (at least 339) of PFS events, the MAH conducted an interim analysis with 348 PFS events actually observed. The IDMC indicated that the interim analysis results met the pre-specified superiority criteria for the primary endpoints as defined in the protocol. Consequently, the MAH performed a database lock (database lock date: May 17, 2022; data cut-off date: April 15, 2022), unblinded the study and conducted statistical analyses to evaluate serplulimab versus placebo combined with chemotherapy.

To evaluate the long-term efficacy and safety in each treatment group, the MAH performed an updated analysis after observing the target number (at least 388) of OS events. The data cut-off

date was January 09, 2023, with a total of 391 OS events actually observed. The OS endpoint was then fully mature.

Outcomes ITT population

2.4.15.1. Overall survival (OS)

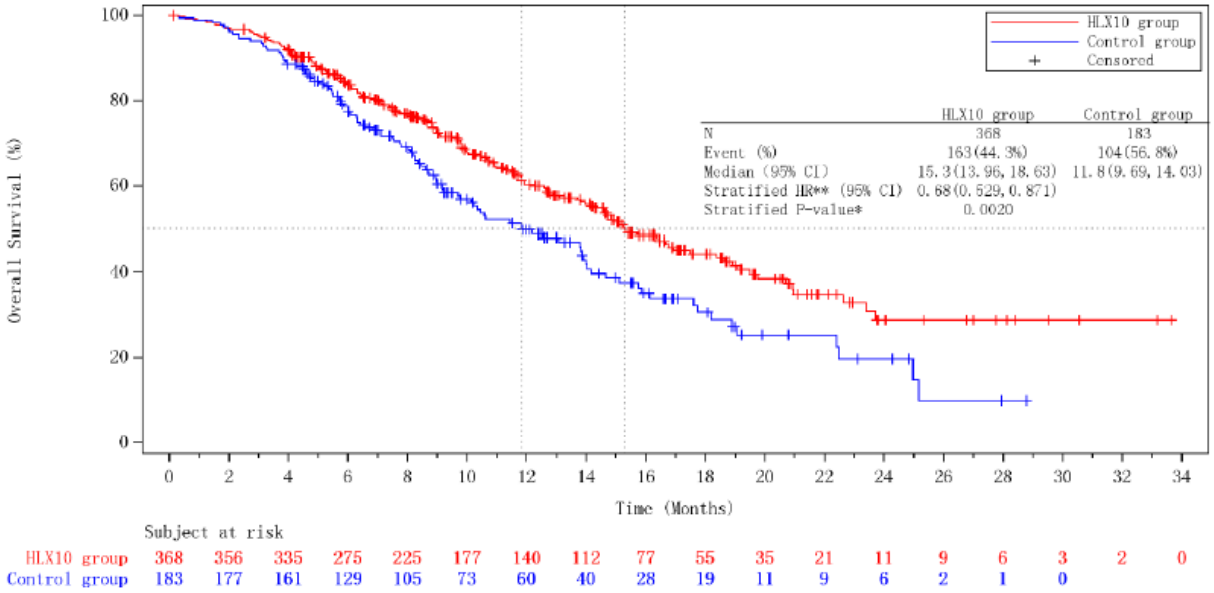
Primary analysis (ITT) of OS - DCO 15 April 2022

Table 28. OS (ITT) - DCO 15 April 2022

	HLX10 group (N=368)	Control group (N=183)
Number of deaths, n (%)	163 (44.3%)	104 (56.8%)
Number of Censor, n (%)	205 (55.7%)	79 (43.2%)
Alive by end of study/analysis cut-off date	204 (55.4%)	79 (43.2%)
Lost to follow-up	0	0
Early withdrawal due to reasons other than lost to follow-up	1 (0.3%)	0
Overall survival (OS, months)		
Median (95% CI) [1]	15.3 (13.96, 18.63)	11.8 (9.69, 14.03)
Min, Max	0.16+, 33.64+	0.33, 28.78+
6-Month survival rate (%) (95% CI) [1]	83.9 (79.68, 87.38)	78.6 (71.79, 83.96)
12-Month survival rate (%) (95% CI) [1]	60.4 (54.46, 65.75)	49.7 (41.44, 57.41)
18-Month survival rate (%) (95% CI) [1]	44.3 (37.63, 50.80)	30.6 (22.00, 39.64)
24-Month survival rate (%) (95% CI) [1]	28.8 (20.33, 37.81)	19.7 (10.88, 30.33)
12-Month restricted mean survival time	10.0 (9.66, 10.33)	9.3 (8.77, 9.78)
P value	0.0197	
24-Month restricted mean survival time	15.3 (14.41, 16.25)	13.1 (11.88, 14.38)
P value	0.0053	
Stratified log-rank test *P* value [2]	0.0020	
Stratified HR (95% CI) [3]	0.68 (0.529, 0.871)	
Unstratified log-rank test *P* value [4]	0.0027	
Unstratified HR (95% CI) [5]	0.69 (0.538, 0.882)	
Max-Combo test [6]	0.0060	
Follow-up time (months)		
Median (95% CI)	14.9 (13.44, 15.77)	
Min, Max	0.16, 33.64	

Notes: HR: hazard ratio. CI: confidence interval. NR: not reached, NE: not evaluable.
[1] The 95% CI of median OS was calculated using the Brookmeyer-Crowley method based on log-log transformation. The 95% CI of survival rate was calculated using the pointwise method based on log-log transformation.
[2] The two-sided *P* value was based on the stratified log-rank test, with stratification factors being PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced vs. distant metastasis).
[3] The HR and its CI were estimated using a stratified Cox proportional hazards model, with treatment group as the fixed effect and the randomization stratification factors being PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced vs. distant metastasis). The collected true stratification factor values were used for analysis. This study used two primary endpoints, PFS and OS.
[4] Two-sided *P* value was based on the unstratified log-rank test.
[5] HR and its CI were estimated using the unstratified Cox proportional hazards model, with only the treatment group as a fixed effect. This study used two primary endpoints, PFS and OS.
[6] The Max-Combo test was based on four Fleming-Harrington (FH) weights, i.e., FH (0, 0), FH (0, 1), FH (1, 0), and FH (1, 1).
Data cut-off date: 2022-04-15

Figure 18. Kaplan-Meier curve of OS (ITT) - DCO 15 April 2022



*: *P* value was based on the Log-rank test, **: HR (hazard ratio) was based on the Cox proportional hazards model.
Data cut-off date: 2022-04-15

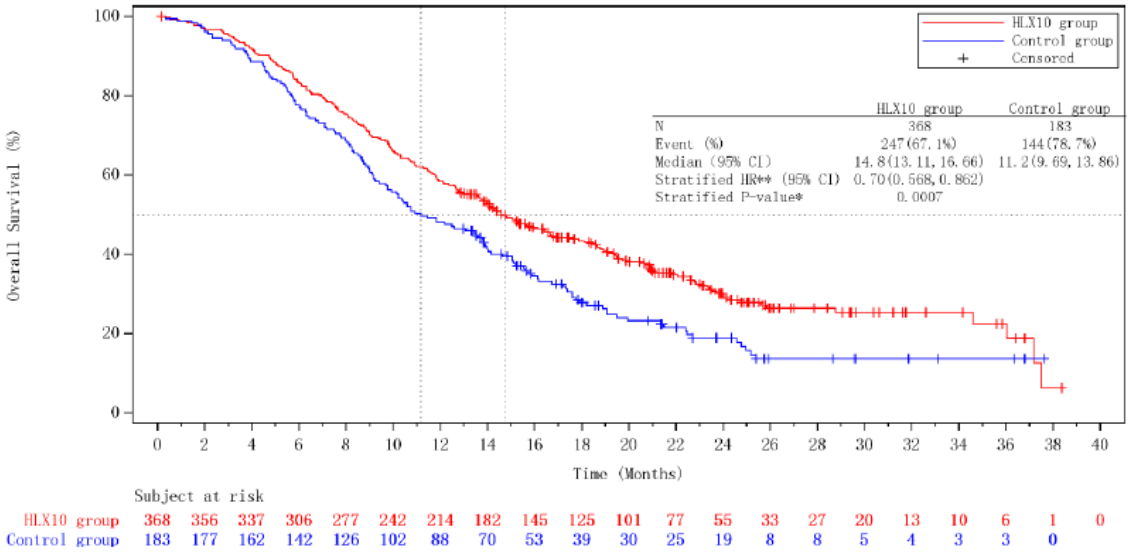
Updated OS analysis – DCO January 09, 2023

Table 29. OS (ITT) updated analysis (DCO: 09 January 2023)

	HLX10 group (N=368)	Control group (N=183)
Number of deaths, n (%)	247 (67.1%)	144 (78.7%)
Number of Censor, n (%)	121 (32.9%)	39 (21.3%)
Alive by end of study/analysis cut-off date	120 (32.6%)	39 (21.3%)
Lost to follow-up	0	0
Early withdrawal due to reasons other than lost to follow-up	1 (0.3%)	0
Overall survival (OS, months)		
Median (95% CI) [1]	14.8 (13.11, 16.66)	11.2 (9.69, 13.86)
Min, Max	0.16+, 38.37+	0.33, 37.62+
6-Month survival rate (%) (95% CI) [1]	83.4 (79.16, 86.82)	77.6 (70.84, 82.98)
12-Month survival rate (%) (95% CI) [1]	58.3 (53.09, 63.16)	48.1 (40.69, 55.10)
18-Month survival rate (%) (95% CI) [1]	43.5 (38.22, 48.58)	27.8 (21.24, 34.70)
24-Month survival rate (%) (95% CI) [1]	30.1 (24.91, 35.44)	18.8 (12.96, 25.58)
12-Month restricted mean survival time	9.9 (9.57, 10.22)	9.2 (8.75, 9.73)
P value	0.0281	
24-Month restricted mean survival time	15.1 (14.28, 15.89)	12.9 (11.83, 14.00)
P value	0.0016	
Stratified log-rank test *P* value [2]	0.0007	
Stratified HR (95% CI) [3]	0.70 (0.568, 0.862)	
Unstratified log-rank test *P* value [4]	0.0012	
Unstratified HR (95% CI) [5]	0.71 (0.581, 0.878)	
Max-Combo test [6]	0.0028	
Follow-up time (months)		
Median (95% CI)	24.3 (23.13, 25.30)	
Min, Max	0.16, 38.37	

Notes: HR: hazard ratio. CI: confidence interval. NR: not reached, NE: not evaluable.
[1] The 95% CI of median OS was calculated using the Brookmeyer-Crowley method based on log-log transformation. The 95% CI of survival rate was calculated using the pointwise method based on log-log transformation.
[2] The two-sided *P* value was based on the stratified log-rank test, with stratification factors being PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced vs. distant metastasis).
[3] The HR and its CI were estimated using a stratified Cox proportional hazards model, with treatment group as the fixed effect and the randomization stratification factors being PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced vs. distant metastasis). The collected true stratification factor values were used for analysis. This study used two primary endpoints, PFS and OS.
[4] Two-sided *P* value was based on the unstratified log-rank test.
[5] HR and its CI were estimated using the unstratified Cox proportional hazards model, with only the treatment group as a fixed effect. This study used two primary endpoints, PFS and OS.
[6] The Max-Combo test was based on four Fleming-Harrington (FH) weights, i.e., FH (0, 0), FH (0, 1), FH (1, 0), and FH (1, 1).
Data cut-off date: 2023-01-09

Figure 19. Kaplan-Meier curve of OS (ITT) updated analysis (DCO: 09 January 2023)



*: *P* value was based on the Log-rank test, **: HR (hazard ratio) was based on the Cox proportional hazards model.
Data cut-off date: 2023-01-09

2.4.15.2. Progression-free survival (PFS)

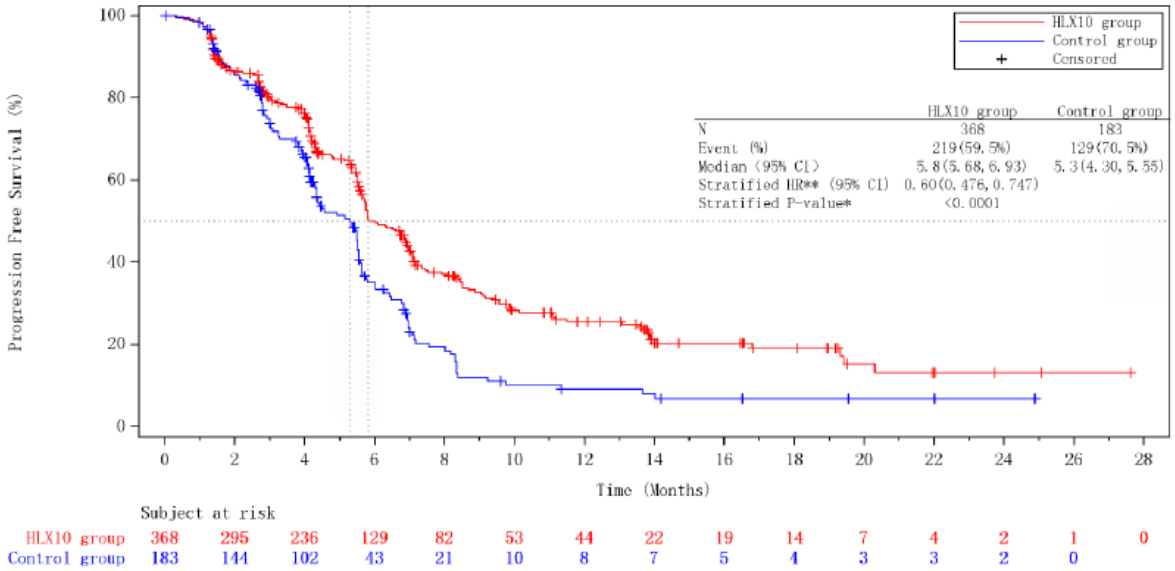
Primary analysis as assessed by IRRC based on RECIST v1.1 – DCO 15 April 2022

Table 30. PFS Assessed by IRRC Based on RECIST v1.1 (ITT) – DCO 15 April 2022

	HLX10 group (N=368)	Control group (N=183)
Number of events, n (%)	219 (59.5%)	129 (70.5%)
Progressive disease (PD)	194 (52.7%)	106 (57.9%)
Death	25 (6.8%)	23 (12.6%)
Number of censor, n (%)	149 (40.5%)	54 (29.5%)
No PD prior to initiation of new anti-tumor therapy	47 (12.8%)	22 (12.0%)
PD or death after missing ≥ 2 consecutive scheduled imaging visits	13 (3.5%)	10 (5.5%)
No PD or death by the end of study/analysis cut-off date/dropout	88 (23.9%)	21 (11.5%)
No post-baseline imaging examination	1 (0.3%)	1 (0.5%)
Major protocol deviation that affected efficacy assessment	0	0
Progression-free survival (PFS, months)		
Median (95% CI) [1]	5.8 (5.68, 6.93)	5.3 (4.30, 5.55)
Min, Max	0.03+, 27.63+	0.03+, 24.90+
6-month PFS rate (%) (95% CI) [1]	50.0 (44.08, 55.55)	35.0 (27.17, 42.89)
9-month PFS rate (%) (95% CI) [1]	32.8 (27.06, 38.55)	12.0 (6.89, 18.60)
12-month PFS rate (%) (95% CI) [1]	25.5 (20.08, 31.25)	9.1 (4.66, 15.24)
6-month restricted mean survival time	4.8 (4.63, 4.99)	4.4 (4.16, 4.68)
P value	0.0166	
12-month restricted mean survival time	6.9 (6.43, 7.29)	5.4 (4.88, 5.88)
P value	< 0.0001	
Stratified log-rank test *P* value [2]	< 0.0001	
Stratified HR (95% CI) [3]	0.60 (0.476, 0.747)	
Unstratified log-rank test *P* value [4]	< 0.0001	
Unstratified HR (95% CI) [5]	0.63 (0.507, 0.788)	
Max-Combo test [6]	< 0.0001	

Notes: HR: hazard ratio. CI: confidence interval.
[1] The 95% CI of median PFS was calculated using the Brookmeyer-Crowley method based on log-log transformation. The 95% CI of PFS rate was calculated using the pointwise method based on log-log transformation.
[2] The two-sided *P* value was based on the stratified log-rank test, with stratification factors being PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced vs. distant metastasis).
[3] HR and its 95% CI were estimated using the stratified Cox proportional hazards model, with randomization stratification factors being PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced vs. distant metastasis).
[4] Two-sided *P* value was based on the unstratified log-rank test.
[5] HR and its 95% CI were estimated using the unstratified Cox proportional hazards model.
[6] The Max-Combo test was based on four Fleming-Harrington (FH) weights, i.e., FH (0, 0), FH (0, 1), FH (1, 0), and FH (1, 1).
Data cut-off date: 2022-04-15

Figure 20. Kaplan-Meier curve of PFS assessed by IRRC based on RECIST v1.1 (ITT) – DCO 15 April 2022



*: *P* value was based on the Log-rank test, **: HR (hazard ratio) was based on the Cox proportional hazards model.
Data cut-off date: 2022-04-15

Updated analysis as assessed by IRRC based on RECIST v1.1 – DCO 09 January 2023

Summary of PFS assessed by IRRC based on RECIST v1.1 in the ITT set is presented in the table below, and the Kaplan-Meier curve of PFS is presented in the figure below.

Table 31. PFS Assessed by IRRC Based on RECIST v1.1 (ITT) – DCO 09 January 2023

	HLX10 group (N=368)	Control group (N=183)
Number of Events, n (%)	244 (66.3%)	139 (76.0%)
Progressive disease (PD)	215 (58.4%)	115 (62.8%)
Death	29 (7.9%)	24 (13.1%)
Number of Censor, n (%)	124 (33.7%)	44 (24.0%)
No PD prior to initiation of new anti-tumor therapy	54 (14.7%)	26 (14.2%)
PD or death after missing ≥ 2 consecutive scheduled imaging visits	19 (5.2%)	10 (5.5%)
No PD or death by the end of study/analysis cut-off date/dropout	50 (13.6%)	7 (3.8%)
No post-baseline imaging examination	1 (0.3%)	1 (0.5%)
Major protocol deviation that affected efficacy evaluation	0	0
Progression-free survival (PFS, months)		
Median (95% CI) [1]	6.5 (5.75, 7.10)	5.3 (4.30, 5.55)
Min, Max	0.03+, 37.91+	0.03+, 36.21+
6-month PFS rate (95% CI) [1]	51.7 (46.05, 57.02)	34.3 (26.83, 41.94)
9-month PFS rate (95% CI) [1]	35.1 (29.66, 40.53)	11.8 (6.94, 17.95)
12-month PFS rate (95% CI) [1]	27.2 (22.10, 32.57)	9.1 (4.88, 14.92)
6-month restricted mean survival time	4.8 (4.66, 5.01)	4.4 (4.17, 4.69)
P value	0.0119	
12-month restricted mean survival time	7.0 (6.59, 7.43)	5.4 (4.91, 5.87)
P value	< 0.0001	
Stratified log-rank test *P* value [2]	< 0.0001	
Stratified HR (95% CI) [3]	0.58 (0.465, 0.716)	
Unstratified log-rank test *P* value [4]	< 0.0001	
Unstratified HR (95% CI) [5]	0.60 (0.489, 0.746)	
Max-Combo test [6]	< 0.0001	

Notes: HR: hazard ratio. CI: confidence interval.

[1] The 95% CI of median PFS was calculated using the Brookmeyer-Crowley method based on log-log transformation. The 95% CI of PFS rate was calculated using the pointwise method based on log-log transformation.

[2] The two-sided *P* value was based on the stratified log-rank test, with stratification factors being PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced vs. distant metastasis).

[3] HR and its 95% CI were estimated using the stratified Cox proportional hazards model, with randomization stratification factors being PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced vs. distant metastasis).

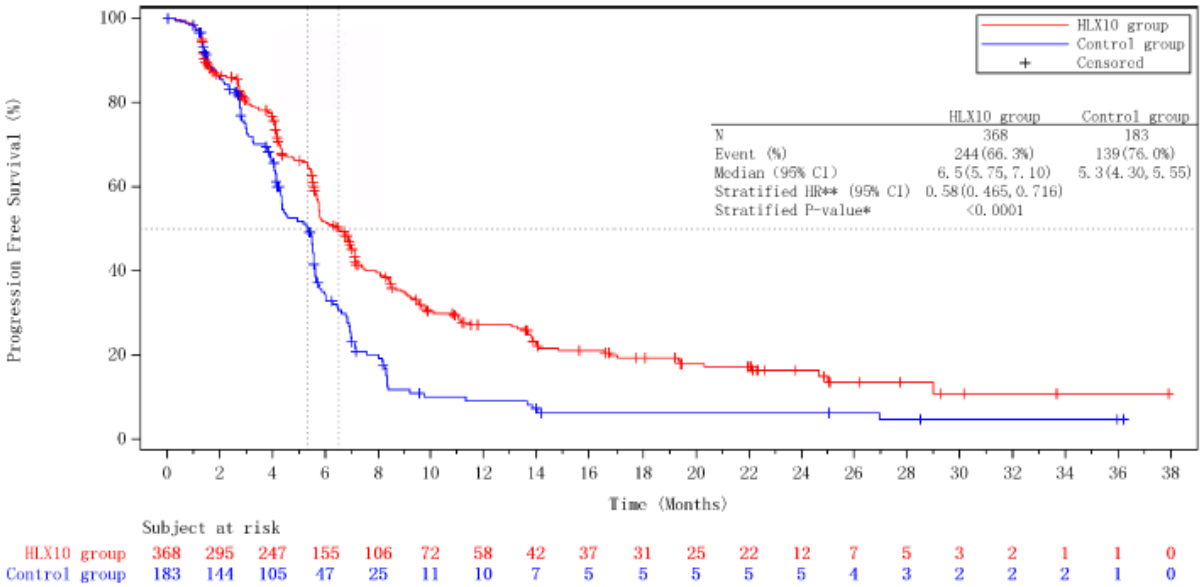
[4] Two-sided *P* value was based on the unstratified log-rank test.

[5] HR and its 95% CI were estimated using the unstratified Cox proportional hazards model.

[6] The Max-Combo test was based on four Fleming-Harrington (FH) weights, i.e., FH (0, 0), FH (0, 1), FH (1, 0), and FH (1, 1).

Data cut-off date: 2023-01-09

Figure 21. Kaplan-Meier curve of PFS assessed by IRRC based on RECIST v1.1 (ITT) – DCO 09 January 2023



*: *P* value was based on the Log-rank test, **: HR (hazard ratio) was based on the Cox proportional hazards model.
Data cut-off date: 2023-01-09

2.4.15.3. Secondary efficacy endpoints

PFS assessed by Investigator based on RECIST v1.1 - primary analysis (DCO 15 April 2022)

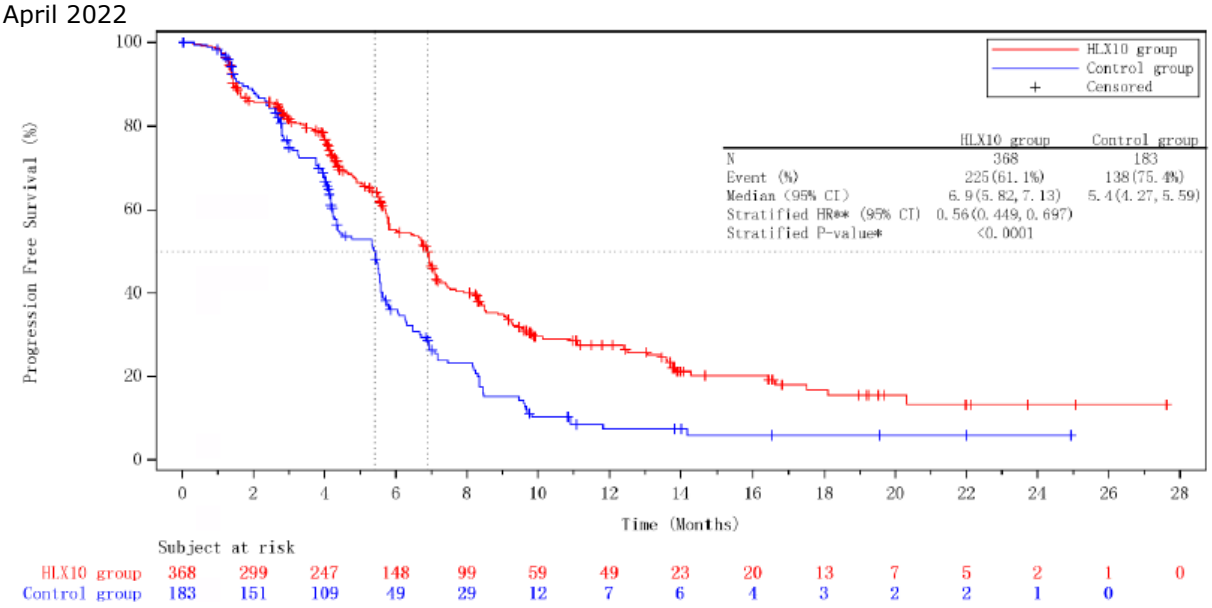
Table 32. PFS Assessed by Investigator Based on RECIST v1.1 (ITT) – DCO 15 April 2022

	HLX10 group (N=368)	Control group (N=183)
Number of Events, n (%)	225 (61.1%)	138 (75.4%)
Progressive disease (PD)	195 (53.0%)	118 (64.5%)
Death	30 (8.2%)	20 (10.9%)
Number of Censor, n (%)	143 (38.9%)	45 (24.6%)
No PD prior to initiation of new anti-tumor therapy	26 (7.1%)	11 (6.0%)
Emergency unblinding or accidental unblinding due to SAE/special or urgent event/other	2 (0.5%)	5 (2.7%)
PD or death after missing ≥ 2 consecutive scheduled imaging visits	14 (3.8%)	9 (4.9%)
No PD or death by the end of study/analysis cut-off date/dropout	100 (27.2%)	19 (10.4%)
No post-baseline imaging examination	1 (0.3%)	1 (0.5%)
Major protocol deviation that affected efficacy evaluation	0	0
Progression-free survival (PFS, months)		
Median (95% CI) [1]	6.9 (5.82, 7.13)	5.4 (4.27, 5.59)
Min, Max	0.03+, 27.63+	0.03+, 24.94+
6-month PFS rate (95% CI) [1]	55.3 (49.47, 60.64)	36.0 (28.39, 43.64)
9-month PFS rate (95% CI) [1]	34.9 (29.28, 40.63)	15.1 (9.69, 21.74)
12-month PFS rate (95% CI) [1]	27.5 (22.12, 33.15)	7.4 (3.59, 12.96)
6-month restricted mean survival time	4.9 (4.70, 5.06)	4.5 (4.25, 4.74)
P value	0.0143	
12-month restricted mean survival time	7.1 (6.66, 7.51)	5.5 (5.06, 6.03)
P value	< 0.0001	
Stratified log-rank test *P* value [2]	< 0.0001	
Stratified HR (95% CI) [3]	0.56 (0.449, 0.697)	
Unstratified log-rank test *P* value [4]	< 0.0001	
Unstratified HR (95% CI) [5]	0.60 (0.484, 0.743)	
Max-Combo test [6]	< 0.0001	

Notes: HR: hazard ratio. CI: confidence interval. NR: not reached, NE: not evaluable.
[1] The 95% CI of median PFS was calculated using the Brookmeyer-Crowley method based on log-log transformation. The 95% CI of PFS rate was calculated using the pointwise method based on log-log transformation.
[2] The two-sided *P* value was based on the stratified log-rank test, with stratification factors being PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced vs. distant metastasis).
[3] HR and its 95% CI were estimated using the stratified Cox proportional hazards model, with randomization stratification factors being PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced vs. distant metastasis).
[4] Two-sided *P* value was based on the unstratified log-rank test.
[5] HR and its 95% CI were estimated using the unstratified Cox proportional hazards model.

[6] The Max-Combo test was based on four Fleming-Harrington (FH) weights, i.e., FH (0, 0), FH (0, 1), FH (1, 0), and FH (1, 1).
Data cut-off date: 2022-04-15

Figure 22. Kaplan-Meier Curve of PFS Assessed by Investigator Based on RECIST v1.1 (ITT) – DCO 15 April 2022



*: *P* value was based on the Log-rank test, **: HR (hazard ratio) was based on the Cox proportional hazards model.
Data cut-off date: 2022-04-15

Analysis of PFS based on iRECIST

As immunotherapy can lead to pseudo-progression, PFS assessed by IRRC and by Investigator based on iRECIST was implemented as secondary endpoints. Data from these analyses are not shown in the Assessment Report.

Overall tumor response (ORR)

Of note, for ORR, the MAH has submitted results for both confirmed and unconfirmed data. However, in this Assessment Report, only confirmed data are presented.

ORR assessed by IRRC based on RECIST v1.1 – primary analysis - DCO 15 April 2022

Table 33. Confirmed Overall Tumour Response assessed by IRRC as per RECIST v1.1 (ITT) – DCO 15 April 2022

Key parameter	HLX10 group (N=368)	Control group (N=183)
Best overall response (BOR) [1]		
Complete response (CR)	50 (13.6%)	12 (6.6%)
Partial response (PR)	162 (44.0%)	65 (35.5%)
Stable disease (SD) [2]	81 (22.0%)	62 (33.9%)
Progressive disease (PD)	49 (13.3%)	28 (15.3%)
Not evaluable (NE) or not applicable (NA)	26 (7.1%)	16 (8.7%)
Objective response rate (ORR) [3]		
CR+PR	212 (57.6%)	77 (42.1%)
95% CI [4]	52.4%, 62.7%	34.8%, 49.6%
ORR odds ratio (95% CI) [5]	1.85 (1.29, 2.65)	
P value [5]	0.0007	
Disease control rate (DCR) [6]		
CR+PR+SD	293 (79.6%)	139 (76.0%)
95% CI [4]	75.1%, 83.6%	69.1%, 82.0%
DCR odds ratio (95% CI) [5]	1.26 (0.83, 1.92)	
P value [5]	0.2785	

Notes: [1] Best overall response was defined as the best assessed response after treatment, i.e., the best response among all efficacy evaluations (excluding tumour response assessments after PD and after the initiation of new anti-tumour treatments).
[2] The confirmation period for the best overall response of stable disease (SD) was 42 days. Subjects with SD were not counted if the time from randomisation to the best overall response of SD was < 42 days.
[3] ORR was defined as the proportion of subjects with confirmed best overall response of complete response (CR) or partial response (PR) as per RECIST 1.1.
[4] 95% CI in individual treatment groups was calculated using the Clopper-Pearson exact method.
[5] Calculated using the stratified Cochran-Mantel-Haenszel (CMH) test, with the treatment group as the fixed effect and the stratification factors being PD-L1 expression level (CPS < 10 vs. CPS >= 10), age (>= 65 years vs. < 65 years), and tumour status (locally advanced vs. distant metastasis). The collected actual stratification factor values were used for analysis.
[6] DCR was defined as the proportion of subjects with confirmed best overall response of complete response (CR), partial response (PR), or stable disease (SD) as per RECIST 1.1.
Data cut-off date: 2022-04-15

2.4.16. Updated analysis – DCO 09 January 2023

Table 34. Confirmed Overall Tumor Response assessed by IRRC based on RECIST v1.1 (ITT) – DCO 09 January 2023

Characteristic parameters	HLX10 group (N=368)	Control group (N=183)
Best overall response (BOR) [1]		
Complete response (CR)	48 (13.0%)	12 (6.6%)
Partial response (PR)	168 (45.7%)	65 (35.5%)
Stable disease (SD) [2]	77 (20.9%)	62 (33.9%)
Progressive disease (PD)	49 (13.3%)	28 (15.3%)
Not evaluable (NE) or not applicable (NA)	26 (7.1%)	16 (8.7%)
Objective response rate (ORR) [3]		
CR+PR	216 (58.7%)	77 (42.1%)
95% CI [4]	53.5%, 63.8%	34.8%, 49.6%
ORR odds ratio (95% CI) [5]	1.94 (1.35, 2.77)	
P value [5]	0.0003	
Disease control rate (DCR) [6]		
CR+PR+SD	293 (79.6%)	139 (76.0%)
95% CI [4]	75.1%, 83.6%	69.1%, 82.0%
DCR odds ratio (95% CI) [5]	1.26 (0.83, 1.92)	
P value [5]	0.2785	

Notes: [1] Best overall response was defined as the best assessed response after treatment, i.e., the best response among all efficacy evaluations (excluding tumor response assessments after PD and after the initiation of new anti-tumor treatments).
[2] The confirmation period for the best overall response of stable disease (SD) was 42 days. Subjects with SD were not counted if the time from randomization to the best overall response of SD was < 42 days.
[3] ORR was defined as the proportion of subjects with confirmed best overall response of complete response (CR) or partial response (PR).
[4] 95% CI in individual treatment groups was calculated using the Clopper-Pearson exact method.
[5] Calculated using the stratified Cochran–Mantel–Haenszel (CMH) test, with the treatment group as the fixed effect and the stratification factors being PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced vs. distant metastasis).
[6] DCR was defined as the proportion of subjects with confirmed best overall response of complete response (CR), partial response (PR), or stable disease (SD).
Data cut-off date: 2023-01-09

2.4.17. Duration of response (DOR)

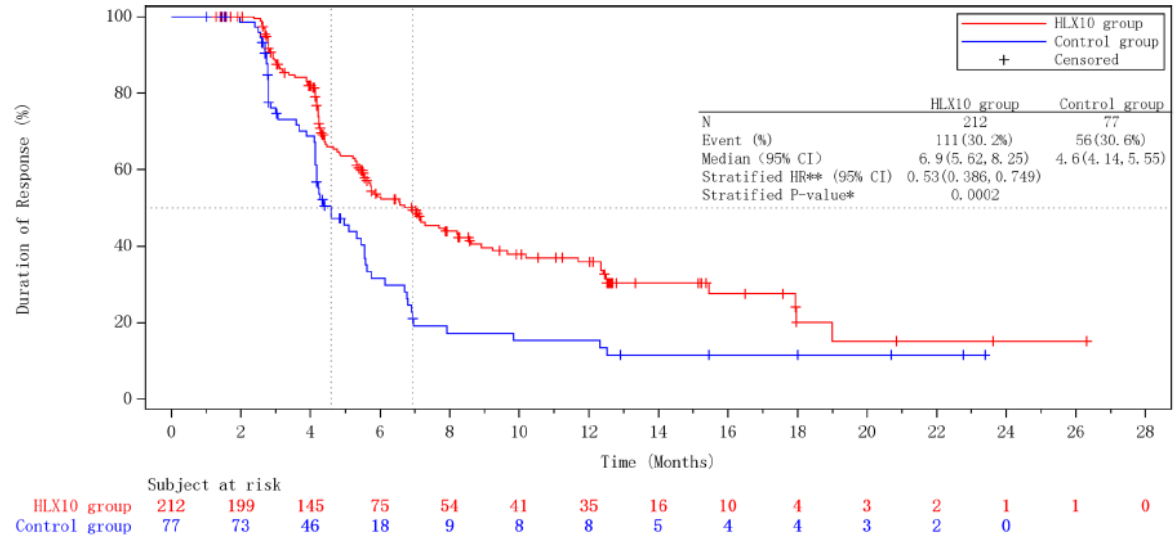
As for ORR, the MAH has submitted results for both confirmed and unconfirmed data of DOR as well. However, in this Assessment Report, only the confirmed data are presented.

Table 35. Confirmed Duration of Response (DOR) assessed by IRRC as per RECIST v1.1 (ITT) – DCO 15 April 2022

	HLX10 group (N=368)	Control group (N=183)
Number of subjects with objective response (CR or PR) [1]	212 (57.6%)	77 (42.1%)
Number of Events	111 (30.2%)	56 (30.6%)
Progressive disease (PD)	107 (29.1%)	51 (27.9%)
Death	4 (1.1%)	5 (2.7%)
Number of Censor	101 (27.4%)	21 (11.5%)
No PD prior to initiation of new anti-tumour therapy	21 (5.7%)	5 (2.7%)
PD or death after missing ≥ 2 consecutive scheduled imaging visits	4 (1.1%)	3 (1.6%)
No PD or death by the end of study/analysis cut-off date/dropout	76 (20.7%)	13 (7.1%)
Major protocol deviation that affected efficacy evaluation	0	0
Duration of response (DOR)/months		
Median (95% CI) [2]	6.9 (5.62, 8.25)	4.6 (4.14, 5.55)
Min, Max	1.28+, 26.32+	1.02+, 23.39+
6-month DOR rate (95% CI) [2]	53.0 (45.07, 60.23)	31.5 (20.46, 43.22)
9-month DOR rate (95% CI) [2]	39.6 (31.70, 47.45)	17.2 (8.84, 27.90)
12-month DOR rate (95% CI) [2]	35.9 (27.98, 43.84)	15.3 (7.43, 25.76)
18-month DOR rate (95% CI) [2]	20.1 (10.41, 32.01)	11.5 (4.81, 21.32)
24-month DOR rate (95% CI) [2]	15.1 (5.65, 28.72)	NE (NE, NE)
Stratified log-rank test P value [3]	0.0002	
Stratified hazard ratio (HR) (95% CI) [4]	0.53 (0.386, 0.749)	
Unstratified log-rank test P value [5]	0.0003	
Unstratified hazard ratio (HR) (95% CI) [6]	0.55 (0.403, 0.771)	

Notes: NR: not reached, NE: not evaluable [1] Objective response was defined as the proportion of subjects with confirmed best overall response of complete response (CR) or partial response (PR) as per RECIST 1.1.
[2] The 95% CI of the median duration of response was calculated using the Brookmeyer-Crowley method (log-log transformation).
[3] Two-sided P value of the stratified log-rank test. Stratification factors: PD-L1 expression level (CPS < 10 vs. CPS >= 10), age (>= 65 years vs. < 65 years), and tumour status (locally advanced vs. distant metastasis). The collected actual stratification factor values were used for analysis.
[4] HR and 95% CI were estimated using the stratified Cox proportional hazards model, with the treatment group as a fixed effect. Randomisation stratification factors included: PD-L1 expression level (CPS < 10 vs. CPS >= 10), age (>= 65 years vs. < 65 years), and tumour status (locally advanced versus distant metastasis). The collected actual stratification factor values were used for analysis.
[5] Two-sided P value of the unstratified log-rank test.
[6] HR and 95% CI were estimated using the unstratified Cox proportional hazards model, with treatment group as the fixed effect only.
Data cut-off date: 2022-04-15

Figure 23. Kaplan-Meier curve of confirmed Duration of Response (DOR) assessed by IRRC as per RECIST v1.1 (ITT) – DCO15 April 2022



Note: The Kaplan-Meier method and the Brookmeyer-Crowley method (using log-log transformation) were used to estimate the median and 95% CI. NR: not reached, NE: not evaluable. two-sided P value for the stratified log-rank test. HR and 95% CI were determined using the stratified Cox proportional hazards model. Stratification factors: PD-L1 expression level (CPS < 10 vs. CPS >= 10), age (>= 65 years vs. < 65 years), and tumour status (locally advanced vs. distant metastasis).
Data cut-off date: 2022-04-15

DOR - updated analysis - DCO 09 January 2023

Table 36. Confirmed DOR assessed by IRRC based on RECIST v1.1 (ITT) – DCO 09 January 2023

	HLX10 group (N=368)	Control group (N=183)
Number of subjects with objective response (CR or PR) [1]	216 (58.7%)	77 (42.1%)
Number of Events, n (%)	134 (36.4%)	62 (33.9%)
Progressive disease (PD)	127 (34.5%)	57 (31.1%)
Death	7 (1.9%)	5 (2.7%)
Number of Censor, n (%)	82 (22.3%)	15 (8.2%)
No PD prior to initiation of new anti-tumor therapy	27 (7.3%)	6 (3.3%)
PD or death after missing ≥ 2 consecutive scheduled imaging visits	7 (1.9%)	4 (2.2%)
No PD or death by the end of study/analysis cut-off date/dropout	48 (13.0%)	5 (2.7%)
Major protocol deviation that affected efficacy evaluation	0	0
Duration of response (DOR)/months		
Median (95% CI) [2]	7.1 (5.75, 8.61)	4.6 (4.17, 5.55)
Min, Max	1.28+, 36.60+	1.02+, 34.76+
6-month DOR rate (95% CI) [2]	54.5 (47.19, 61.22)	33.0 (22.35, 44.09)

	HLX10 group (N=368)	Control group (N=183)
9-month DOR rate (95% CI) [2]	41.8 (34.55, 48.89)	17.0 (9.10, 27.08)
12-month DOR rate (95% CI) [2]	36.3 (29.20, 43.50)	15.3 (7.82, 25.17)
18-month DOR rate (95% CI) [2]	25.0 (18.15, 32.38)	11.9 (5.40, 21.24)
24-month DOR rate (95% CI) [2]	19.2 (11.57, 28.37)	11.9 (5.40, 21.24)
Stratified log-rank test *P* value [3]	< 0.0001	
Stratified HR (95% CI) [4]	0.52 (0.384, 0.718)	
Unstratified log-rank test *P* value [5]	< 0.0001	
Unstratified HR (95% CI) [6]	0.54 (0.403, 0.740)	

NR: not reached, NE: not evaluable

Notes: [1] Objective response was defined as the proportion of subjects with confirmed best overall response of complete response (CR) or partial response (PR).

[2] The 95% CI of the median duration of response was calculated using the Brookmeyer-Crowley method (log-log transformation).

[3] Two-sided *P* value of the stratified log-rank test. Stratification factors: PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced vs. distant metastasis).

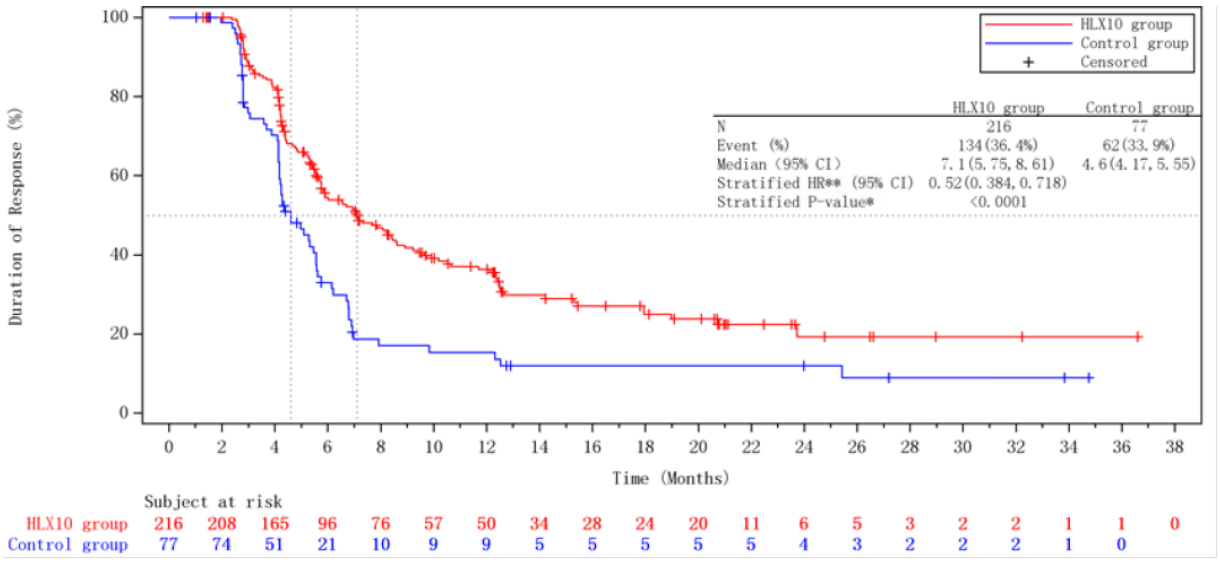
[4] HR and 95% CI were estimated using the stratified Cox proportional hazards model, with the treatment group as a fixed effect. Randomization stratification factors included: PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced versus distant metastasis).

[5] Two-sided *P* value of the unstratified log-rank test.

[6] HR and 95% CI were estimated using the unstratified Cox proportional hazards model, with treatment group as the fixed effect only.

Data cut-off date: 2023-01-09

Figure 24. Kaplan-Meier curve of confirmed DOR assessed by IRRC based on RECIST v1.1 (ITT) – DCO 09 January 2023



NR: not reached, NE: not evaluable.

Note: The Kaplan-Meier method and the Brookmeyer-Crowley method (using log-log transformation) were used to estimate the median and 95% CI. Two-sided *P* value for the stratified log-rank test. HR and 95% CI were determined using the stratified Cox proportional hazards model. Stratification factors: PD-L1 expression level (CPS < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and tumor status (locally advanced vs. distant metastasis).

2.4.18. Quality of life analyses

EQ-5D-5L

The MAH concluded that overall health status in the serplulimab group was comparable to the control group. As the follow-up period extended, the summary utility index in both groups showed no obvious changes.

EORTC QLQ-OES18

The MAH concluded that treatment with serplulimab improved dysphagia scale and choking item compared with the control group. For the remaining scales and items, no obvious differences in quality of life were observed between the serplulimab group and the control group.

EORTC QLQ-C30

The MAH concluded that there were no obvious differences in overall quality of life between the two groups across the overall health status, five function subscales (physical, role, emotional, cognitive, and social), and nine symptom subscales/items (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties).

2.4.18.1. Subgroup analyses

2.4.19. Overall survival - OS

Primary analysis – DCO 15 April 2022

Subgroup analysis of OS in the ITT set is summarised in the table below.

Table 37. Subgroup analysis of Overall Survival (OS) (ITT) – DCO 15 April 2022

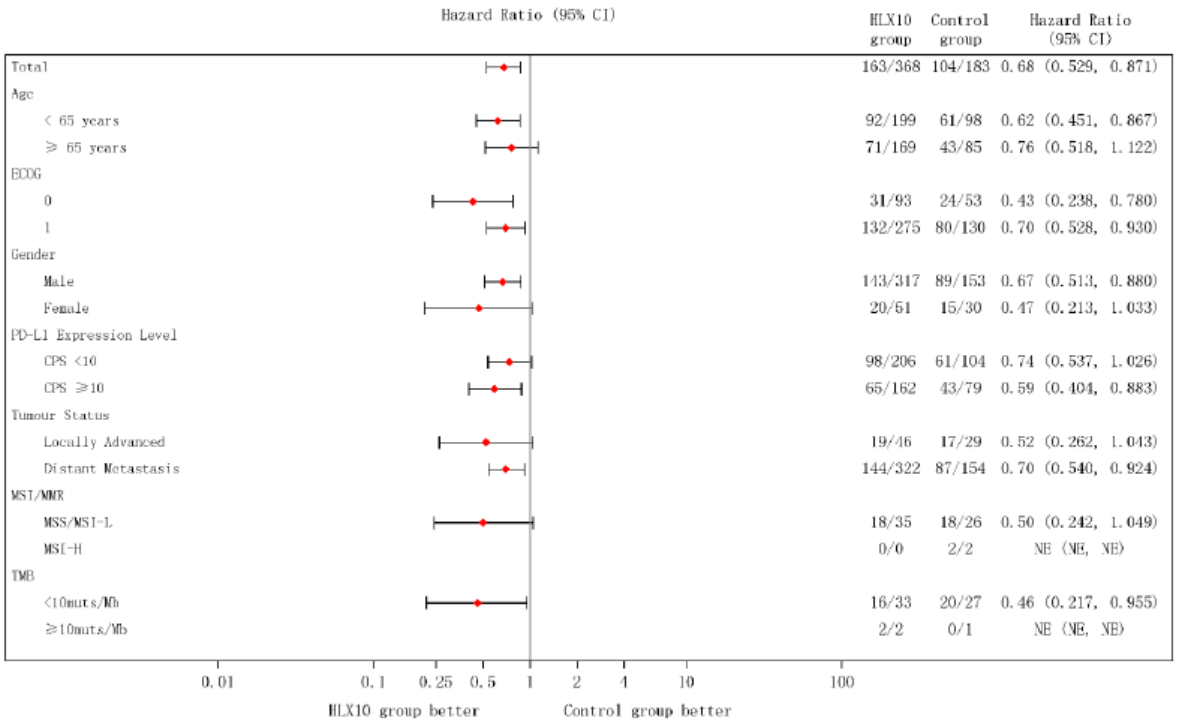
Subgroup	HLX10 group (N=368)	Control group (N=183)
Age		
< 65 years		
N	199 (54.1%)	98 (53.6%)
Events	92 (46.2%)	61 (62.2%)
Median (95% CI) [1]	15.3 (12.68, 18.92)	9.8 (8.34, 13.83)
Hazard ratio (HR) (95% CI) [2]	0.62 (0.451, 0.867)	
Log-rank test P value [3]	0.0042	
≥ 65 years		
N	169 (45.9%)	85 (46.4%)
Events	71 (42.0%)	43 (50.6%)
Median (95% CI) [1]	15.7 (13.11, 20.70)	13.9 (10.45, 18.89)
Hazard ratio (HR) (95% CI) [2]	0.76 (0.518, 1.122)	
Log-rank test P value [3]	0.1574	
ECOG PS		
0		
N	93 (25.3%)	53 (29.0%)
Events	31 (33.3%)	24 (45.3%)
Median (95% CI) [1]	21.0 (16.79, NE)	15.7 (10.61, 22.47)
Hazard ratio (HR) (95% CI) [2]	0.43 (0.238, 0.780)	
Log-rank test P value [3]	0.0041	
1		
N	275 (74.7%)	130 (71.0%)
Events	132 (48.0%)	80 (61.5%)
Median (95% CI) [1]	13.8 (11.66, 15.31)	10.2 (8.18, 13.08)
Hazard ratio (HR) (95% CI) [2]	0.70 (0.528, 0.930)	
Log-rank test P value [3]	0.0123	
Gender		
Male		
N	317 (86.1%)	153 (83.6%)

Events	143 (45.1%)	89 (58.2%)
Median (95% CI) [1]	15.2 (12.78, 18.63)	10.6 (8.97, 14.00)
Hazard ratio (HR) (95% CI) [2]	0.67 (0.513, 0.880)	
Log-rank test P value [3]	0.0034	
Female		
N	51 (13.9%)	30 (16.4%)
Events	20 (39.2%)	15 (50.0%)
Median (95% CI) [1]	17.5 (12.88, NE)	13.1 (9.23, 17.61)
Hazard ratio (HR) (95% CI) [2]	0.47 (0.213, 1.033)	
Log-rank test P value [3]	0.0553	
PD-L1 expression level		
CPS <10		
N	206 (56.0%)	104 (56.8%)
Events	98 (47.6%)	61 (58.7%)
Median (95% CI) [1]	14.2 (11.47, 15.31)	11.4 (9.17, 14.00)
Hazard ratio (HR) (95% CI) [2]	0.74 (0.537, 1.026)	
Log-rank test P value [3]	0.0658	
CPS ≥10		
N	162 (44.0%)	79 (43.2%)
Events	65 (40.1%)	43 (54.4%)
Median (95% CI) [1]	18.6 (15.28, 20.93)	13.9 (8.25, 18.20)
Hazard ratio (HR) (95% CI) [2]	0.59 (0.404, 0.883)	
Log-rank test P value [3]	0.0082	
Tumour status		
Locally advanced		
N	46 (12.5%)	29 (15.8%)
Events	19 (41.3%)	17 (58.6%)
Median (95% CI) [1]	18.4 (13.70, NE)	9.2 (7.10, 18.89)
Hazard ratio (HR) (95% CI) [2]	0.52 (0.263, 1.043)	
Log-rank test P value [3]	0.0576	
Distant metastasis		
N	322 (87.5%)	154 (84.2%)
Events	144 (44.7%)	87 (56.5%)
Median (95% CI) [1]	15.2 (12.88, 17.48)	12.6 (9.76, 14.16)
Hazard ratio (HR) (95% CI) [2]	0.70 (0.540, 0.924)	
Log-rank test P value [3]	0.0100	

Notes: HR: hazard ratio. CI: confidence interval. NR: not reached, NE: not evaluable.
[1] The 95% CI of median OS was calculated using the Brookmeyer-Crowley method based on log-log transformation. The 95% CI of survival rate was calculated using the pointwise method based on log-log transformation.
[2] HR and 95% CI were estimated using the stratified Cox proportional hazards model. The analysis was only performed in subgroups with corresponding characteristics, with the treatment group as the fixed effect and the stratification factors being PD-L1 expression level (CPS < 10 vs. CPS >= 10), age (>= 65 years vs. < 65 years), and tumour status (locally advanced vs. distant metastasis). The collected actual stratification factor values were used for analysis. If the subgroup factor itself was one of the randomisation stratification factors, then this model was equivalent to a Cox model or Log-Rank test stratified by the remaining randomisation stratification factors.
[3] The two-sided P value was based on the stratified log-rank test and was only analysed in subgroups with corresponding characteristics, with the treatment group as the fixed effect and the stratification factors being PD-L1 expression level (CPS < 10 vs. CPS >= 10), age (>= 65 years vs. < 65 years), and tumour status (locally advanced vs. distant metastasis). The collected actual stratification factor values were used for analysis. If the subgroup factor itself was one of the randomisation stratification factors, then this model was equivalent to a Cox model or Log-Rank test stratified by the remaining randomisation stratification factors.
Data cut-off date: 2022-04-15

The subgroup forest plot of OS subgroups is presented in the figure below.

Figure 25. OS - subgroup forest plot (ITT) DCO 15 April 2022



Data cut-off date: 2022-04-15

Updated analysis – DCO 09 January 2023

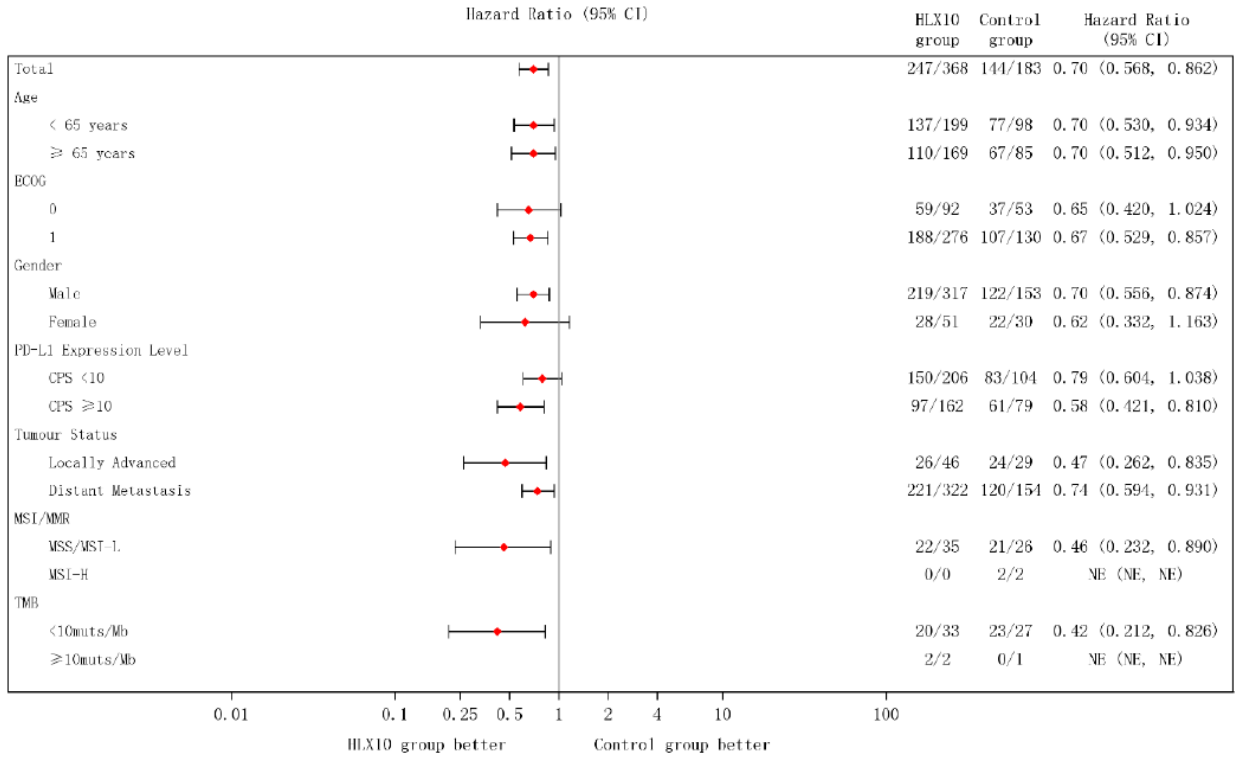
Table 38. Subgroup analysis of Overall Survival (OS) (ITT) – DCO 09 January 2023

Subgroup	HLX10 group (N=368)	Control group (N=183)
Age		
< 65 years		
N	199 (54.1%)	98 (53.6%)
Events	137 (68.8%)	77 (78.6%)
Median (95% CI) [1]	14.3 (12.16, 16.79)	10.2 (8.94, 13.54)
Hazard ratio (HR) (95% CI) [2]	0.70 (0.530, 0.934)	
Log-rank test P value [3]	0.0137	
≥ 65 years		
N	169 (45.9%)	85 (46.4%)
Events	110 (65.1%)	67 (78.8%)
Median (95% CI) [1]	14.8 (12.65, 18.66)	13.6 (9.40, 15.51)
Hazard ratio (HR) (95% CI) [2]	0.70 (0.512, 0.950)	
Log-rank test P value [3]	0.0202	
ECOG PS		
0		
N	92 (25.0%)	53 (29.0%)
Events	59 (64.1%)	37 (69.8%)
Median (95% CI) [1]	19.3 (15.21, 22.64)	16.7 (13.80, 19.06)
Hazard ratio (HR) (95% CI) [2]	0.66 (0.423, 1.026)	
Log-rank test P value [3]	0.0603	
1		
N	276 (75.0%)	130 (71.0%)
Events	188 (68.1%)	107 (82.3%)
Median (95% CI) [1]	13.8 (11.43, 15.24)	9.8 (8.18, 11.43)
Hazard ratio (HR) (95% CI) [2]	0.67 (0.529, 0.857)	
Log-rank test P value [3]	0.0011	
Gender		
Male		
N	317 (86.1%)	153 (83.6%)

Events	219 (69.1%)	122 (79.7%)
Median (95% CI) [1]	14.3 (12.58, 16.46)	10.6 (9.00, 13.83)
Hazard ratio (HR) (95% CI) [2]	0.70 (0.556, 0.874)	
Log-rank test P value [3]	0.0016	
Female		
N	51 (13.9%)	30 (16.4%)
Events	28 (54.9%)	22 (73.3%)
Median (95% CI) [1]	18.4 (12.88, NE)	13.6 (9.40, 17.38)
Hazard ratio (HR) (95% CI) [2]	0.62 (0.332, 1.163)	
Log-rank test P value [3]	0.1380	
PD-L1 expression level		
CPS <10		
N	206 (56.0%)	104 (56.8%)
Events	150 (72.8%)	83 (79.8%)
Median (95% CI) [1]	12.4 (10.71, 14.82)	10.8 (9.17, 13.83)
Hazard ratio (HR) (95% CI) [2]	0.79 (0.604, 1.038)	
Log-rank test P value [3]	0.0867	
CPS ≥10		
N	162 (44.0%)	79 (43.2%)
Events	97 (59.9%)	61 (77.2%)
Median (95% CI) [1]	18.6 (14.42, 22.83)	12.2 (8.71, 15.87)
Hazard ratio (HR) (95% CI) [2]	0.58 (0.421, 0.810)	
Log-rank test P value [3]	0.0010	
Tumour status		
Locally advanced		
N	46 (12.5%)	29 (15.8%)
Events	26 (56.5%)	24 (82.8%)
Median (95% CI) [1]	18.5 (13.70, NE)	9.0 (7.16, 17.38)
Hazard ratio (HR) (95% CI) [2]	0.47 (0.262, 0.835)	
Log-rank test P value [3]	0.0083	
Distant metastasis		
N	322 (87.5%)	154 (84.2%)
Events	221 (68.6%)	120 (77.9%)
Median (95% CI) [1]	14.2 (12.65, 16.46)	12.3 (10.22, 14.03)
Hazard ratio (HR) (95% CI) [2]	0.74 (0.594, 0.931)	
Log-rank test P value [3]	0.0090	

Notes: HR: hazard ratio. CI: confidence interval. NR: not reached, NE: not evaluable.
[1] The 95% CI of median OS was calculated using the Brookmeyer-Crowley method based on log-log transformation. The 95% CI of survival rate was calculated using the pointwise method based on log-log transformation.
[2] HR and 95% CI were estimated using the stratified Cox proportional hazards model. The analysis was only performed in subgroups with corresponding characteristics, with the treatment group as the fixed effect and the stratification factors being PD-L1 expression level (CPS < 10 vs. CPS >= 10), age (>= 65 years vs. < 65 years), and tumour status (locally advanced vs. distant metastasis). The collected actual stratification factor values were used for analysis. If the subgroup factor itself was one of the randomisation stratification factors, then this model was equivalent to a Cox model or Log-Rank test stratified by the remaining randomisation stratification factors.
[3] The two-sided P value was based on the stratified log-rank test and was only analysed in subgroups with corresponding characteristics, with the treatment group as the fixed effect and the stratification factors being PD-L1 expression level (CPS < 10 vs. CPS >= 10), age (>= 65 years vs. < 65 years), and tumour status (locally advanced vs. distant metastasis). The collected actual stratification factor values were used for analysis. If the subgroup factor itself was one of the randomisation stratification factors, then this model was equivalent to a Cox model or Log-Rank test stratified by the remaining randomisation stratification factors.
Data cut-off date: 2023-01-09

Figure 26. OS - Subgroup Forest Plot (ITT) – DCO 09 January 2023



Data cut-off date: 2023-01-09

Subgroup PD-L1 expression

Figure 27. Kaplan-Meier plots of OS for patients with 1 ≤ CPS < 10 (DCO: 2023-01-09)

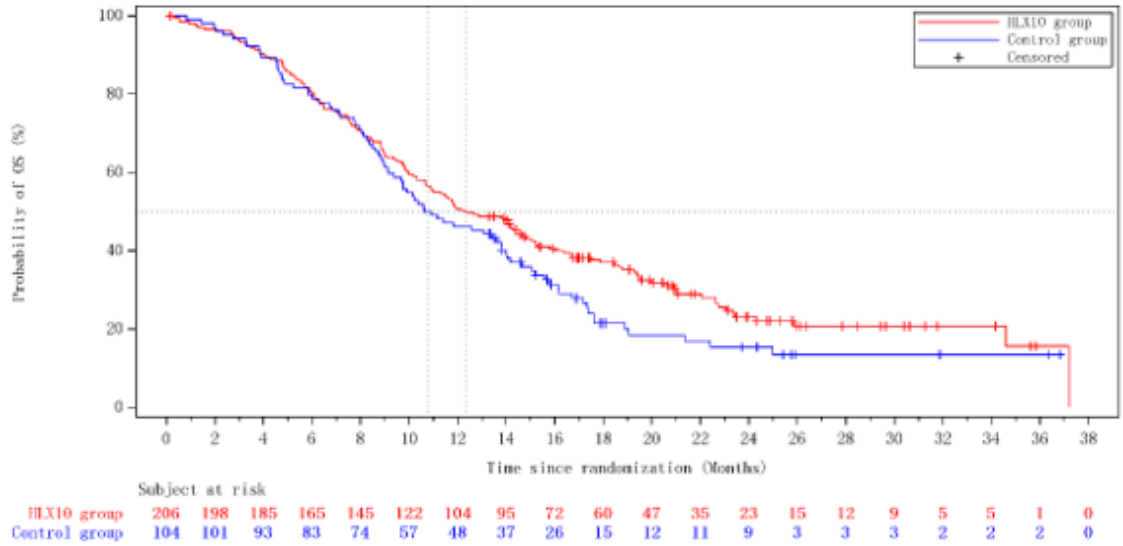
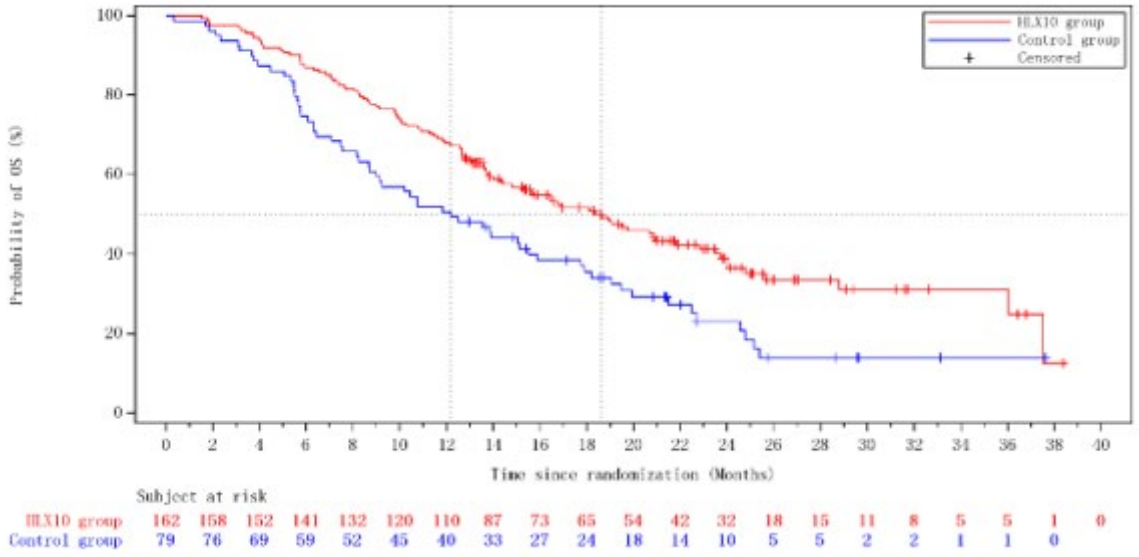


Figure 28. Kaplan-Meier plots of OS for patients with CPS ≥ 10 (DCO: 2023-01-09)



Progression-free survival - PFS

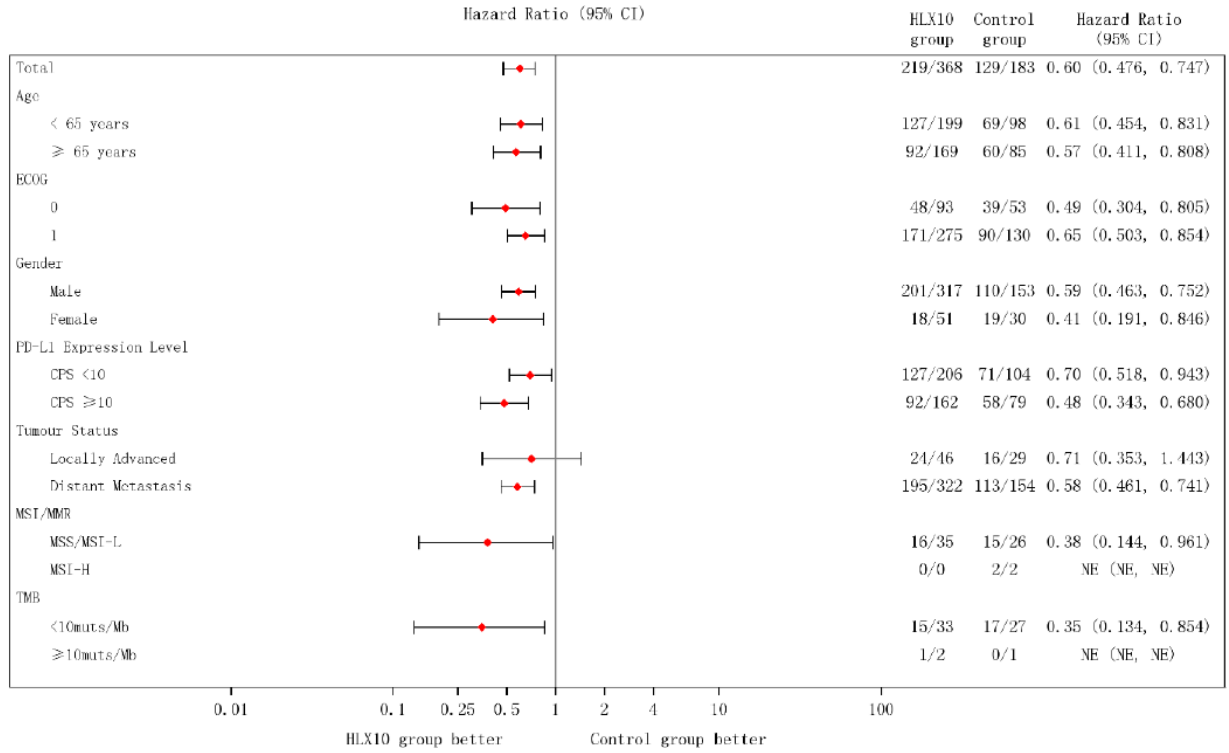
Primary analysis – DCO 15 April 2022

Table 39. Subgroup Analysis of Progression-Free Survival (PFS) assessed by IRRC as per RECIST v1.1 (ITT) – DCO 15 April 2022

Subgroup	HLX10 group (N=368)	Control group (N=183)
Age		
< 65 years		
N	199 (54.1%)	98 (53.6%)
Events	127 (63.8%)	69 (70.4%)
Median (95% CI) [1]	5.7 (5.49, 6.74)	4.6 (4.07, 5.55)
Hazard ratio (HR) (95% CI) [2]	0.61 (0.454, 0.831)	
Log-rank test P value [3]	0.0013	
≥ 65 years		
N	169 (45.9%)	85 (46.4%)
Events	92 (54.4%)	60 (70.6%)
Median (95% CI) [1]	6.9 (5.72, 8.67)	5.3 (4.27, 6.90)
Hazard ratio (HR) (95% CI) [2]	0.57 (0.411, 0.809)	
Log-rank test P value [3]	0.0012	
ECOG PS		
0		
N	93 (25.3%)	53 (29.0%)
Events	48 (51.6%)	39 (73.6%)
Median (95% CI) [1]	7.1 (5.52, 9.92)	5.3 (4.11, 5.75)
Hazard ratio (HR) (95% CI) [2]	0.50 (0.305, 0.806)	
Log-rank test P value [3]	0.0037	
1		
N	275 (74.7%)	130 (71.0%)
Events	171 (62.2%)	90 (69.2%)
Median (95% CI) [1]	5.8 (5.62, 6.87)	5.3 (4.17, 5.55)
Hazard ratio (HR) (95% CI) [2]	0.65 (0.503, 0.854)	
Log-rank test P value [3]	0.0016	
Gender		
Male		
N	317 (86.1%)	153 (83.6%)
Events	201 (63.4%)	110 (71.9%)
Median (95% CI) [1]	5.7 (5.59, 6.87)	4.4 (4.14, 5.49)
Hazard ratio (HR) (95% CI) [2]	0.59 (0.463, 0.752)	
Log-rank test P value [3]	<0.0001	
Female		
N	51 (13.9%)	30 (16.4%)
Events	18 (35.3%)	19 (63.3%)
Median (95% CI) [1]	10.1 (5.78, NE)	6.8 (5.49, 7.10)
Hazard ratio (HR) (95% CI) [2]	0.41 (0.191, 0.846)	
Log-rank test P value [3]	0.0136	
PD-L1 expression level		
CPS <10		
N	206 (56.0%)	104 (56.8%)
Events	127 (61.7%)	71 (68.3%)
Median (95% CI) [1]	5.7 (5.49, 6.34)	5.3 (4.17, 5.55)
Hazard ratio (HR) (95% CI) [2]	0.70 (0.518, 0.943)	
Log-rank test P value [3]	0.0174	
CPS ≥10		
N	162 (44.0%)	79 (43.2%)
Events	92 (56.8%)	58 (73.4%)
Median (95% CI) [1]	7.1 (5.75, 9.10)	5.3 (4.14, 6.01)
Hazard ratio (HR) (95% CI) [2]	0.48 (0.343, 0.680)	
Log-rank test P value [3]	<0.0001	
Tumour status		
Locally advanced		
N	46 (12.5%)	29 (15.8%)
Events	24 (52.2%)	16 (55.2%)
Median (95% CI) [1]	7.4 (5.45, 9.86)	6.9 (4.14, 9.23)
Hazard ratio (HR) (95% CI) [2]	0.71 (0.353, 1.443)	
Log-rank test P value [3]	0.3354	
Distant metastasis		
N	322 (87.5%)	154 (84.2%)
Events	195 (60.6%)	113 (73.4%)
Median (95% CI) [1]	5.8 (5.59, 6.87)	5.2 (4.17, 5.52)
Hazard ratio (HR) (95% CI) [2]	0.58 (0.461, 0.741)	
Log-rank test P value [3]	<0.0001	

Notes: NR: not reached, NE: not evaluable, ECOG PS: ECOG Performance Status, MSS/MSI-L: Microsatellite stability or microsatellite instability-low, MSI-H: Microsatellite instability-high.
[1] The 95% CI of median PFS was calculated using the Brookmeyer-Crowley method based on log-log transformation.
[2] HR and 95% CI were estimated using the stratified Cox proportional hazards model. The analysis was only performed in subgroups with corresponding characteristics, with treatment group as a fixed effect and stratification factors being PD-L1 expression level (CPS < 10 vs. CPS >= 10), age (>= 65 years vs. < 65 years), and tumour status (locally advanced vs. distant metastasis). The collected actual stratification factor values were used for analysis. If the subgroup factor itself was one of the randomisation stratification factors, then this model was equivalent to a Cox model or Log-Rank test stratified by the remaining randomisation stratification factors.
[3] The two-sided P value was based on the stratified log-rank test and was only analysed in subgroups with corresponding characteristics, with treatment group as a fixed effect and stratification factors being PD-L1 expression level (CPS < 10 vs. CPS >= 10), age (>= 65 years vs. < 65 years), and tumour status (locally advanced vs. distant metastasis). The collected actual stratification factor values were used for analysis. If the subgroup factor itself was one of the randomisation stratification factors, then this model was equivalent to a Cox model or Log-Rank test stratified by the remaining randomisation stratification factors.
Data cut-off date: 2022-04-15

Figure 29. PFS assessed by IRRC based on RECIST v1.1 - Subgroup Forest Plot (ITT) – DCO 15 April 2022



Data cut-off date: 2022-04-15

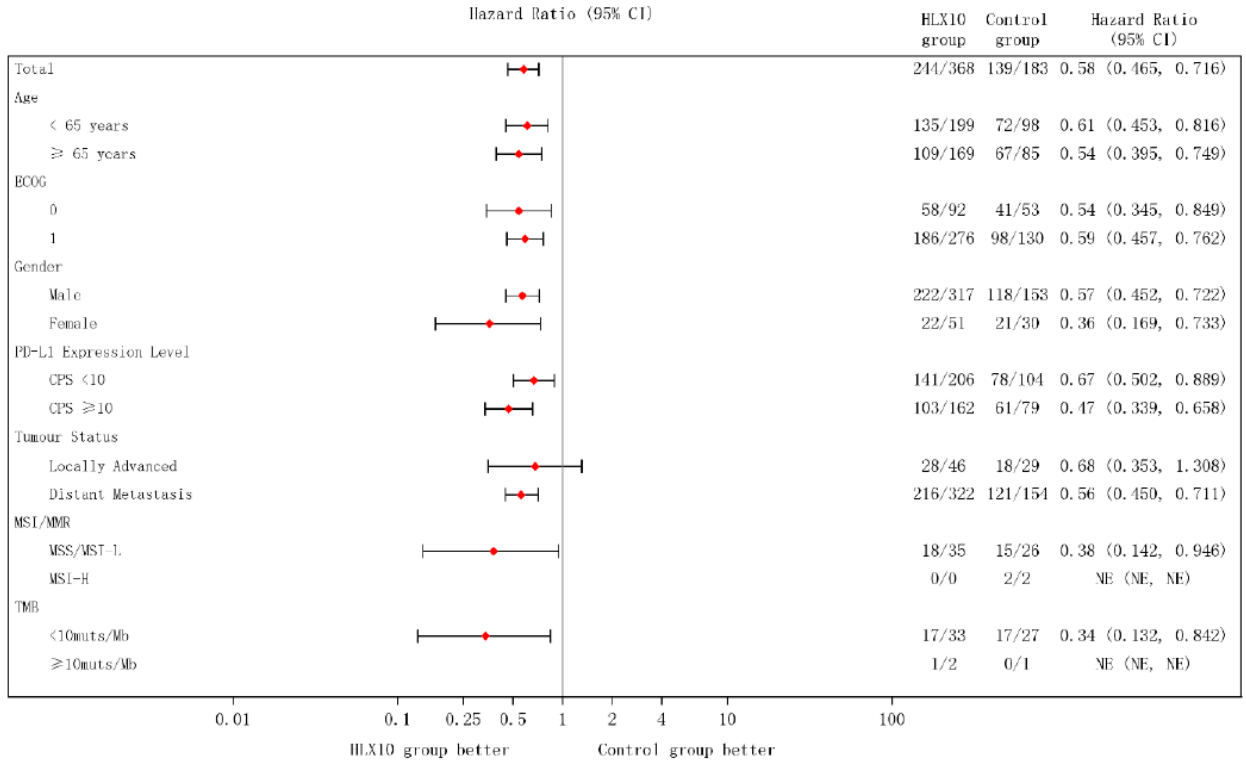
Updated analysis – DCO 09 January 2023

Table 40. Subgroup analysis of Progression-Free Survival (PFS) assessed by IRRC as per RECIST v1.1 (ITT) – DCO 09 January 2023

Subgroup	HLX10 group (N=368)	Control group (N=183)
Age		
< 65 years		
N	199 (54.1%)	98 (53.6%)
Events	135 (67.8%)	72 (73.5%)
Median (95% CI) [1]	5.8 (5.55, 6.97)	4.6 (4.07, 5.55)
Hazard ratio (HR) (95% CI) [2]	0.61 (0.453, 0.816)	
Log-rank test P value [3]	0.0007	
≥ 65 years		
N	169 (45.9%)	85 (46.4%)
Events	109 (64.5%)	67 (78.8%)
Median (95% CI) [1]	7.0 (5.78, 8.51)	5.3 (4.30, 6.60)
Hazard ratio (HR) (95% CI) [2]	0.54 (0.396, 0.749)	
Log-rank test P value [3]	0.0001	
ECOG PS		
0		
N	92 (25.0%)	53 (29.0%)
Events	58 (63.0%)	41 (77.4%)
Median (95% CI) [1]	7.1 (5.52, 8.51)	5.3 (4.11, 5.65)
Hazard ratio (HR) (95% CI) [2]	0.54 (0.346, 0.849)	
Log-rank test P value [3]	0.0064	
1		
N	276 (75.0%)	130 (71.0%)
Events	186 (67.4%)	98 (75.4%)
Median (95% CI) [1]	6.1 (5.75, 6.97)	5.3 (4.30, 5.55)
Hazard ratio (HR) (95% CI) [2]	0.59 (0.457, 0.762)	
Log-rank test P value [3]	<0.0001	
Gender		
Male		
N	317 (86.1%)	153 (83.6%)
Events	222 (70.0%)	118 (77.1%)
Median (95% CI) [1]	5.8 (5.62, 6.90)	4.4 (4.14, 5.49)
Hazard ratio (HR) (95% CI) [2]	0.57 (0.452, 0.722)	
Log-rank test P value [3]	<0.0001	
Female		
N	51 (13.9%)	30 (16.4%)
Events	22 (43.1%)	21 (70.0%)
Median (95% CI) [1]	10.9 (7.13, NE)	6.8 (5.49, 7.56)
Hazard ratio (HR) (95% CI) [2]	0.36 (0.169, 0.733)	
Log-rank test P value [3]	0.0040	
PD-L1 expression level		
CPS <10		
N	206 (56.0%)	104 (56.8%)
Events	141 (68.4%)	78 (75.0%)
Median (95% CI) [1]	5.7 (5.52, 6.51)	5.3 (4.27, 5.55)
Hazard ratio (HR) (95% CI) [2]	0.67 (0.502, 0.889)	
Log-rank test P value [3]	0.0050	
CPS ≥10		
N	162 (44.0%)	79 (43.2%)
Events	103 (63.6%)	61 (77.2%)
Median (95% CI) [1]	7.9 (6.51, 9.56)	5.5 (4.14, 6.44)
Hazard ratio (HR) (95% CI) [2]	0.47 (0.339, 0.658)	
Log-rank test P value [3]	<0.0001	
Tumour status		
Locally advanced		
N	46 (12.5%)	29 (15.8%)
Events	28 (60.9%)	18 (62.1%)
Median (95% CI) [1]	7.4 (5.45, 9.82)	6.5 (4.14, 9.23)
Hazard ratio (HR) (95% CI) [2]	0.68 (0.353, 1.308)	
Log-rank test P value [3]	0.2369	
Distant metastasis		
N	322 (87.5%)	154 (84.2%)
Events	216 (67.1%)	121 (78.6%)
Median (95% CI) [1]	6.0 (5.72, 6.97)	5.2 (4.27, 5.55)
Hazard ratio (HR) (95% CI) [2]	0.56 (0.450, 0.711)	
Log-rank test P value [3]	<0.0001	

Notes: NR: not reached, NE: not evaluable, ECOG PS: ECOG Performance Status, MSS/MSI-L: Microsatellite stability or microsatellite instability-low, MSI-H: Microsatellite instability-high.
[1] The 95% CI of median PFS was calculated using the Brookmeyer-Crowley method based on log-log transformation.
[2] HR and 95% CI were estimated using the stratified Cox proportional hazards model. The analysis was only performed in subgroups with corresponding characteristics, with treatment group as a fixed effect and stratification factors being PD-L1 expression level (CPS < 10 vs. CPS >= 10), age (>= 65 years vs. < 65 years), and tumour status (locally advanced vs. distant metastasis). The collected actual stratification factor values were used for analysis. If the subgroup factor itself was one of the randomisation stratification factors, then this model was equivalent to a Cox model or Log-Rank test stratified by the remaining randomisation stratification factors.
[3] The two-sided P value was based on the stratified log-rank test and was only analysed in subgroups with corresponding characteristics, with treatment group as a fixed effect and stratification factors being PD-L1 expression level (CPS < 10 vs. CPS >= 10), age (>= 65 years vs. < 65 years), and tumour status (locally advanced vs. distant metastasis). The collected actual stratification factor values were used for analysis. If the subgroup factor itself was one of the randomisation stratification factors, then this model was equivalent to a Cox model or Log-Rank test stratified by the remaining randomisation stratification factors.
Data cut-off date: 2023-01-09

Figure 30. PFS Assessed by IRRC Based on RECIST v1.1 - Subgroup Forest Plot (ITT) – DCO 09 January 2023



Data cut-off date: 2023-01-09

Additional post-hoc subgroup analyses of baseline PD-L1 expression with cut-off 5%

2.4.20. Ancillary analyses

Additional post-hoc subgroup analyses of baseline PD-L1 expression with cut-off 5%:

Table 41. Subgroup analyses of OS by baseline PD-L1 expression with CPS cut-off at 5 (DCO: 2023-01-09)

	Median (95%CI), Months		Stratified HR (95%CI)	p value
	HLX10	Placebo		
ITT	N=368	N=183	0.70 (0.568, 0.862)	0.0007
	14.8 (13.11, 16.66)	11.2 (9.69, 13.86)		
CPS<5	N=138	N=70	0.88 (0.637, 1.241)	0.4702
	12.0 (9.99, 14.82)	12.8 (9.76, 15.05)		
CPS>=5	N=230	N=113	0.60 (0.460, 0.786)	0.0002
	16.5 (13.83, 19.48)	10.7 (8.67, 13.90)		
5≤CPS<10	N=68	N=34	0.61 (0.381, 1.006)	0.0459
	13.8 (9.86, 18.46)	8.9 (6.28, 13.80)		

Figure 31. Kaplan-Meier plots of OS for patients with CPS<5 (DCO: 2023-01-09)

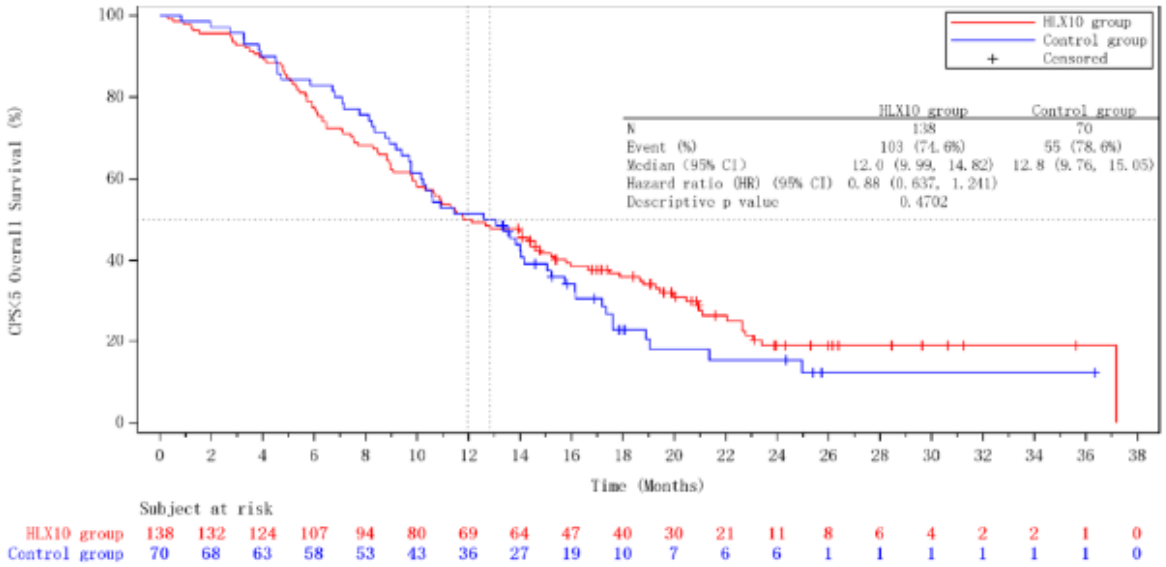


Figure 32. Kaplan-Meier plots of OS for patients with CPS≥5 (DCO: 2023-01-09)

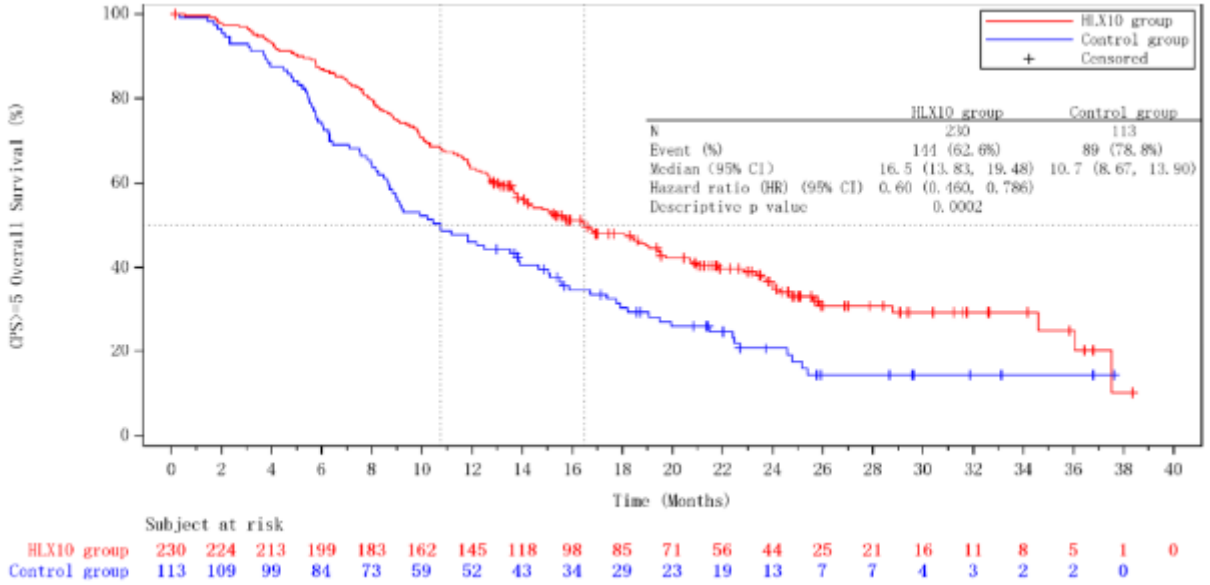
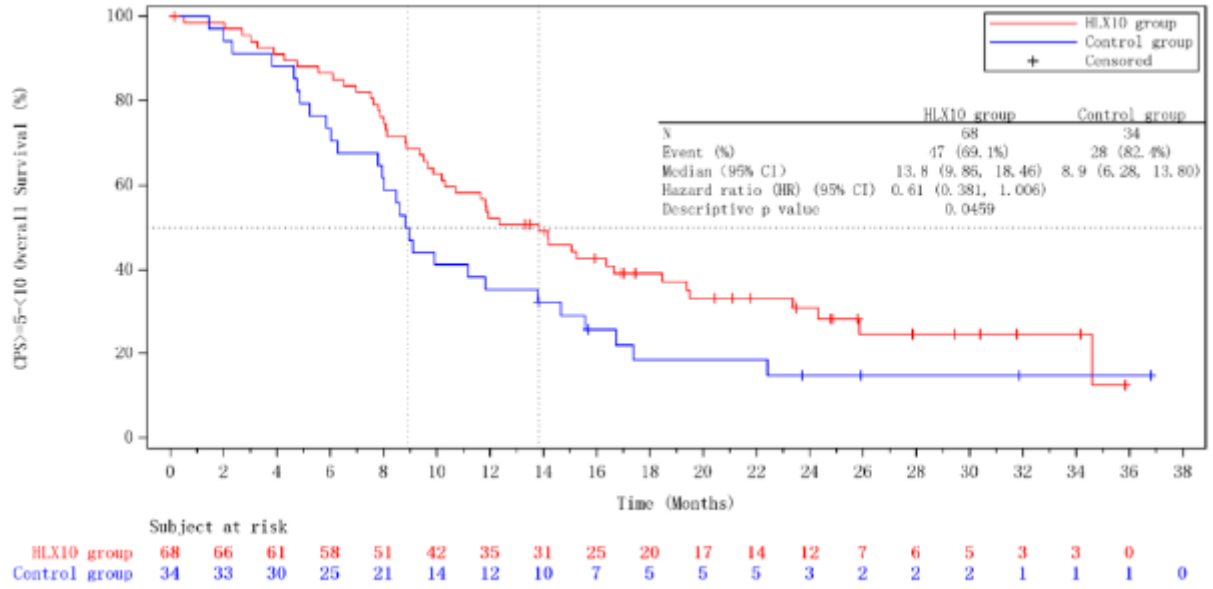


Figure 33. Kaplan-Meier plots of OS for patients with 5≤CPS<10 (DCO: 2023-01-09)



To further inform on the efficacy of serplulimab by baseline PD-L1 status, additional subgroup PFS analyses by baseline PD-L1 expression status (corresponding to CPS < 5, CPS ≥ 5 and 5 ≤ CPS < 10) were conducted.

Table 42. Subgroup analyses of PFS by baseline PD-L1 expression with CPS cut-off at 5 (DCO: 2023-01-09)

		Median (95%CI), Months		Stratified HR (95%CI)	p value
		HLX10	Placebo		
IRRC	ITT	N=368	N=183	0.58 (0.465, 0.716)	< 0.0001
		6.5 (5.75, 7.10)	5.3 (4.30, 5.55)		
	CPS<5	N=138	N=70	0.60 (0.424, 0.855)	0.0039
		5.8 (5.32, 6.93)	4.6 (4.11, 5.62)		
	CPS≥5	N=230	N=113	0.57 (0.435, 0.752)	<0.0001
		6.9 (5.75, 8.08)	5.3 (4.14, 5.78)		
	5≤CPS<10	N=68	N=34	0.87 (0.517, 1.505)	0.6069
		5.6 (4.34, 6.74)	5.3 (3.81, 6.28)		
Investigator	ITT	N=368	N=183	0.54 (0.442, 0.671)	< 0.0001
		6.9 (6.41, 7.16)	5.4 (4.34, 5.59)		
	CPS<5	N=138	N=70	0.68 (0.491, 0.958)	0.0251
		5.7 (4.80, 6.93)	5.5 (4.17, 5.62)		
	CPS≥5	N=230	N=113	0.48 (0.366, 0.624)	<0.0001
		7.1 (6.90, 9.03)	5.4 (4.21, 5.65)		
	5≤CPS<10	N=68	N=34	0.51 (0.311, 0.837)	0.0063
		6.4 (5.52, 7.52)	4.2 (3.75, 5.55)		

Figure 34. Kaplan-Meier plots of PFS in patients with CPS < 5 by IRRC

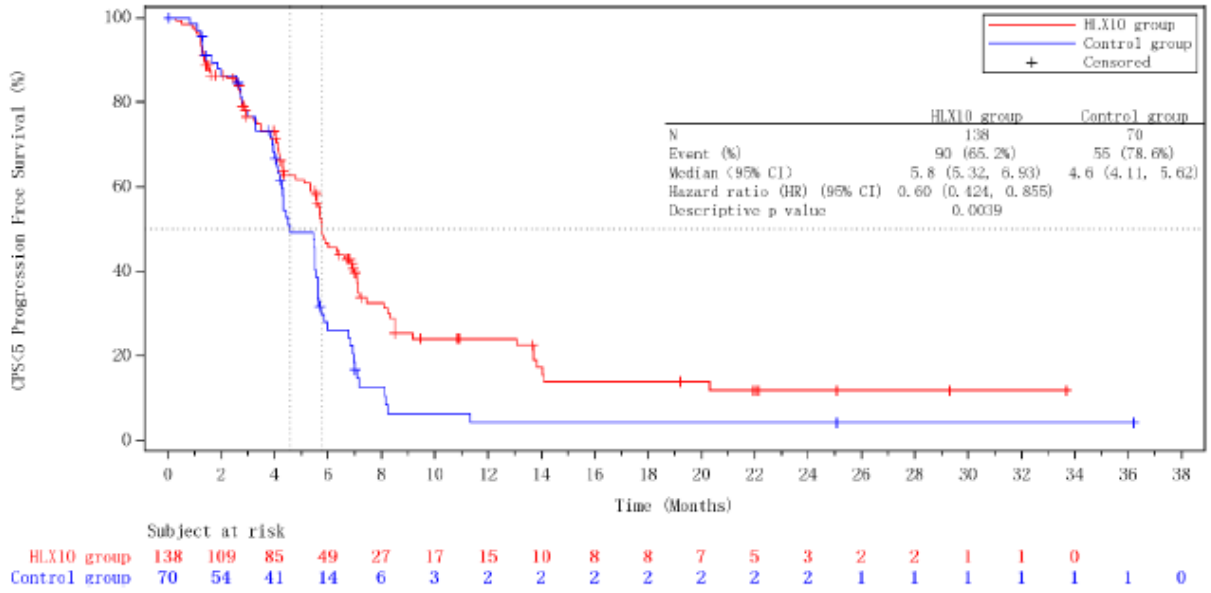
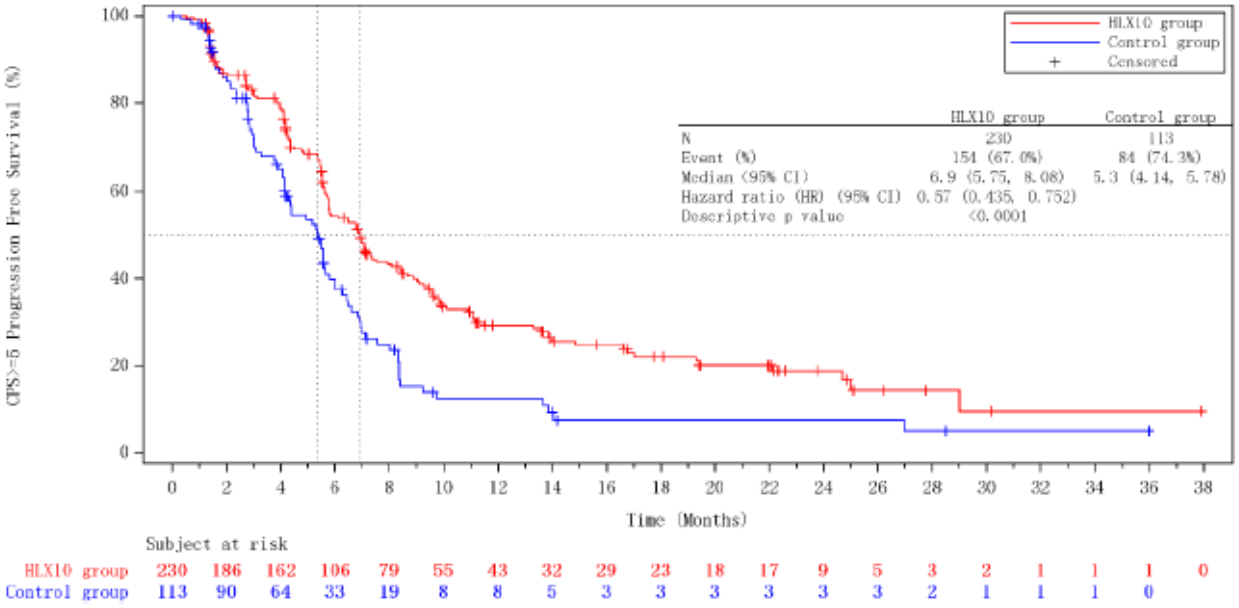


Figure 35. Kaplan-Meier plots of PFS in patients with CPS ≥ 5 by IRRC



ORR

Table 43. 13 Subgroup analyses of ORR by baseline PD-L1 expression with CPS cut-off at 5 (DCO: 2023-01-09)

		ORR (95%CI)		ORR odds ratio (95% CI)	p value
		HLX10	Placebo		
IRRC	ITT	N=368	N=183	1.94 (1.35, 2.77)	0.0003
		58.7% (53.5%, 63.8%)	42.1% (34.8%, 49.6%)		
	CPS<5	N=138	N=70	1.09 (0.61, 1.94)	0.7708
		47.8% (39.3%, 56.5%)	45.7% (33.7%, 58.1%)		
	CPS≥5	N=230	N=113	2.80 (1.76, 4.45)	<0.0001
		65.2% (58.7%, 71.4%)	39.8% (30.7%, 49.5%)		
	5≤CPS<10	N=68	N=34	2.49 (1.07, 5.80)	0.0259
		57.4% (44.8%, 69.3%)	35.3% (19.7%, 53.5%)		
Investigator	ITT	N=368	N=183	1.86 (1.29, 2.68)	0.0008
		53.5% (48.3%, 58.7%)	38.3% (31.2%, 45.7%)		
	CPS<5	N=138	N=70	1.20 (0.66, 2.18)	0.5496
		42.0% (33.7%, 50.7%)	37.1% (25.9%, 49.5%)		
	CPS≥5	N=230	N=113	2.38 (1.50, 3.78)	0.0002
		60.4% (53.8%, 66.8%)	38.9% (29.9%, 48.6%)		
	5≤CPS<10	N=68	N=34	2.90 (1.21, 6.92)	0.0138
		55.9% (43.3%, 67.9%)	29.4% (15.1%, 47.5%)		

2.4.21. 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 44 Summary of efficacy for trial HLX10-007-EC301 (ASTRUM-007)

Title: A Randomised, 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 or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)		
Study identifier	NCT03958890	
Design	Randomised, double-blind, multicenter, phase Ⅲ clinical study to compare the efficacy and safety of HLX10 versus placebo in combination with chemotherapy as first-line therapy in patients with locally advanced, metastatic ESCC.	
	Duration of main phase:	June 19, 2019–May 14, 2025
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable

Hypothesis	Superiority		
Treatments groups	HLX10 group		HLX10 + chemotherapy (cisplatin and 5-FU) N = 368 HLX10 was administered for a maximum of 2 years, cisplatin was administered for a maximum of 8 cycles, 5-FU was administered for a maximum of 12 cycles. Subjects were treated with HLX10 in combination with chemotherapy once every 2 weeks, until loss of clinical benefit, intolerable toxicity, discontinuation decided by the subject or physician, death, withdrawal of informed consent, pregnancy or other reasons specified in the protocol (whichever occurred first).
	Control group		Placebo + chemotherapy (cisplatin and 5-FU) N = 183 Placebo was administered for a maximum of 2 years, cisplatin was administered for a maximum of 8 cycles, 5-FU was administered for a maximum of 12 cycles. Subjects were treated with placebo in combination with chemotherapy once every 2 weeks, until loss of clinical benefit, intolerable toxicity, discontinuation decided by the subject or physician, death, withdrawal of informed consent, pregnancy or other reasons specified in the protocol (whichever occurred first).
Endpoints and definitions	Dual primary endpoint	PFS by IRRC	PFS assessed by IRRC as per RECIST v1.1.
	Dual primary endpoint	OS	Defined as the time from randomization to death due to any cause.
	Secondary endpoint	PFS by IRRC	PFS assessed by IRRC as per iRECIST.
	Secondary endpoint	PFS by Investigator	PFS assessed by Investigator as per RECIST v1.1 and iRECIST.
	Secondary endpoint	ORR by IRRC	ORR assessed by IRRC as per RECIST v1.1.
	Secondary endpoint	ORR by Investigator	ORR assessed by Investigator as per RECIST v1.1.
	Secondary endpoint	DOR by IRRC	DOR assessed by IRRC as per RECIST v1.1.
	Secondary endpoint	DOR by Investigator	DOR assessed by Investigator as per RECIST v1.1.
Results and Analysis			
Analysis description	**Primary Analysis (DCO 15 April 2022)**		

Database lock	May 17, 2022		
Analysis population and time point description	Intent-to-treat (ITT) set. The ITT set was defined as all subjects randomized in the study.		
Descriptive statistics and estimate variability	Treatment group	HLX10 group	Control group
	Number of subjects	368	183
	PFS assessed by IRRC as per RECIST v1.1 (Median)	5.8	5.3
	95% confidence interval	5.68, 6.93	4.30, 5.55
	OS (Median)	15.3	11.8
	95% confidence interval	13.96, 18.63	9.69, 14.03
	PFS assessed by Investigator as per RECIST v1.1 (Median)	6.9	5.4
	95% confidence interval	5.82, 7.13	4.27, 5.59
	Confirmed ORR assessed by IRRC as per RECIST v1.1 (%)	57.6	42.1
	95% confidence interval	52.4, 62.7	34.8, 49.6
	Confirmed DOR assessed by IRRC as per RECIST v1.1 (Median)	6.9	4.6
	95% confidence interval	5.62, 8.25	4.14, 5.55

Effect estimates per comparison	PFS assessed by IRRC as per RECIST v1.1	Comparison groups	HLX10 group vs control group
		Stratified Hazard Ratio	0.60
		95% confidence interval	0.476, 0.747
		P-value (By a two-sided stratified log-rank test)	< 0.0001
	OS	Comparison groups	HLX10 group vs control group
		Stratified Hazard Ratio	0.68
		95% confidence interval	0.529, 0.871
		P-value (By a two-sided stratified log-rank test)	0.0020
	PFS assessed by Investigator as per RECIST v1.1	Comparison groups	HLX10 group vs control group
		Stratified Hazard Ratio	0.56

		95% confidence interval	0.449, 0.697
		P-value (By a two-sided stratified log-rank test)	< 0.0001
	Confirmed ORR assessed by IRRC as per RECIST v1.1	Comparison groups	HLX10 group vs control group
		Odds Ratio	1.85
		95% confidence interval	1.29, 2.65
		P-value	0.0007
	Confirmed DOR assessed by IRRC as per RECIST v1.1	Comparison groups	HLX10 group vs control group
		Stratified Hazard Ratio	0.53
		95% confidence interval	0.386, 0.749
		P-value (By a two-sided stratified log-rank test)	0.0002

Notes	The dual primary endpoints both reached prespecified statistical significance (alpha = 0.01 [two-sided]) in the interim analysis. HLX10 in combination with cisplatin and 5-FU for first-line treatment of ESCC significantly reduced the risk of PD or death compared to standard chemotherapy (median PFS: 5.8 months vs. 5.3 months, HR = 0.60, 95% CI: 0.476, 0.747, *P* < 0.0001; median OS: 15.3 months vs. 11.8 months, HR = 0.68, 95% CI: 0.529, 0.871, *P* = 0.0020), prolonging both PFS and OS.		
Analysis description	**Updated Analysis (DOC 09 January 2023)**		
Database lock	November 22, 2023		
Analysis population and time point description	ITT set. The ITT set was defined as all subjects randomized in the study.		
Descriptive statistics and estimate variability	Treatment group	HLX10 group	Control group
	Number of subjects	368	183
	PFS assessed by IRRC as per RECIST v1.1 (Median)	6.5	5.3
	95% confidence interval	5.75, 7.10	4.30, 5.55
	OS (Median)	14.8	11.2
	95% confidence interval	13.11, 16.66	9.69, 13.86
	PFS assessed by Investigator as per RECIST v1.1 (Median)	6.9	5.4
	95% confidence interval	6.41, 7.16	4.34, 5.59
Effect estimates per comparison		Comparison groups	HLX10 group vs control group

	PFS assessed by IRRC as per RECIST v1.1	Stratified Hazard Ratio	0.58
		95% confidence interval	0.465, 0.716
	OS	Comparison groups	HLX10 group vs control group
		Stratified Hazard Ratio	0.70
		95% confidence interval	0.568, 0.862
	PFS assessed by Investigator as per RECIST v1.1	Comparison groups	HLX10 group vs control group
		Stratified Hazard Ratio	0.54
		95% confidence interval	0.442, 0.671

2.4.22. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH applied for an extension of indication of serplulimab in combination with fluoropyrimidine- and platinum-based chemotherapy as first-line treatment of adult patients with unresectable, locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) whose tumours express PD-L1 with a CPS ≥ 1.

The primary evidence supporting the efficacy of serplulimab in the target indication is derived from the pivotal study ASTRUM-007, which included 551 patients.

Study design

ASTRUM-007 is a phase 3, randomised, placebo-controlled, multicenter, double-blind study comparing the efficacy and safety of serplulimab (combined with cisplatin + 5-FU) to placebo (combined with cisplatin + 5-FU) as first-line treatment. The trial was designed to show superiority using 2:1 allocation of patients to the serplulimab and placebo groups, respectively.

Stratification factors were PD-L1 expression level (1 ≤ combined positive score [CPS] < 10 vs. CPS ≥ 10), age (≥ 65 years vs. < 65 years), and disease status (locally advanced vs. distant metastasis).

Patients had the option to continue treatment after first PD if predefined criteria were fulfilled. From a methodological perspective, continuation of treatment beyond progression may introduce heterogeneity and potential bias. In addition, there is a potential risk of unblinding. Furthermore, continuation of treatment beyond progression may obscure the magnitude of efficacy in 1L setting.

Study population

Overall, the inclusion and exclusion criteria largely reflect the target population. However, patients > 75 years were excluded and only patients with ECOG 0 or 1 were eligible, which limits the representativeness of the study population, considering that a substantial proportion of patients with ESCC are ≥ 65 years of age (Lester et al, 2017).

Study participants had histologically confirmed ESCC with locally advanced, recurrent or metastatic disease that was not resectable or curable by chemoradiotherapy. Histology was evaluated by local investigator only. Patients were required to have at least one evaluable lesion based on central imaging per RECIST v1.1 and be PD-L1 positive (CPS ≥ 1).

Patients were generally required to be treatment-naïve in the advanced setting; however, patients with prior therapy could be included if relapse occurred ≥6 months after prior treatment. Inclusion of such patients may complicate the interpretation of study outcomes, as prior treatment could impact prognosis. Preferably, prior treatment for recurrent disease should have been implemented as a stratification factor.

A total of 22.3% had received prior systemic anti-cancer therapy. Post-hoc subgroup analyses did not indicate a reduced treatment effect in patients who had received prior treatment compared with those who had not. 35.2% of patients received prior anti-cancer treatment including surgery, radiotherapy and systemic anti-cancer therapy before enrolment in this study.

Treatments

Serplulimab was administered at a dose of 3 mg/kg every 2 weeks. This dose regimen is considered acceptable from a dose-exposure perspective.

The comparator was cisplatin + 5-FU which is recommended by ESMO (2022) for patients who are PD-L1 negative or low expression. However, given that ASTRUM-007 was initiated before PD-L1 inhibitors such as pembrolizumab and nivolumab had received marketing authorisation in this setting, the choice of comparator is considered acceptable.

Endpoints

The dual primary efficacy endpoints were PFS (assessed by IRRC per RECIST v1.1) and OS in the ITT population. Secondary endpoints were Investigator-assessed PFS, ORR as well as analyses based on iRECIST and according to PD-1 expression, DOR (both assessed by IRRC and Investigator as per RECIST v1.1 and per iRECIST), and relationship between PDOS is considered the most clinically relevant endpoint and is an appropriate primary endpoint.

Statistics

The primary estimand for OS used a treatment policy strategy, which is considered appropriate. The primary estimand for PFS used a hypothetical strategy for start of next line treatment prior to documented progression or death. In addition, patients with two or more consecutive missing assessments prior to documented progression or death were censored at the last observation prior to the missing visits. This approach is not in line with EMA guidance, where a treatment policy is preferred. The MAH was requested to provide PFS estimates based on treatment policy strategy, which were provided by the MAH (see results below).

An interim analysis was planned, and the multiplicity control strategy and propagation of alpha was in principle acceptable controlling type 1 error. Both primary endpoints were met at interim, and the trial was unblinded.

For the primary analyses of PFS and OS a stratified Log-Rank test was employed. The hazard ratio (HR) and its 95% confidence interval (CI) was to be estimated using a stratified Cox proportional hazards model. The analyses were based on the ITT set. Sensitivity and supplementary analyses as well as relevant subgroup analyses (e.g. age, gender, PD-L1 expression level and ECOG) were preplanned.

Study conduct

A higher number of major protocol deviations were observed in the serplulimab group compared with control group (224 [60.9%] vs. 91 [49.7%], respectively). These were mainly related to deviations from study procedures (57.3% vs. 48.1%, respectively) and were primarily driven by "Imaging examination missing" (serplulimab group 69 [18.8%] vs. control group 19 [10.4%]) and

"Imaging examination out of window" (serplulimab group 48 [13.0%] vs. control group 12 [6.6%]). While the large number of missing imaging examinations might have influenced the PFS estimate, it is not expected to impact the OS results. Therefore, this issue is not considered to affect the overall benefit-risk conclusion.

A total of 976 patients were screened, 551 patients were included and randomly assigned (ratio 2:1) to either serplulimab + cisplatin + 5-FU group (n=368) or the control group i.e., placebo + cisplatin + 5-FU (n=183). Per DCO 09 January 2023, 6.8% of patients in the serplulimab group was still on treatment vs. 0.5% of patients in the control group.

The most common reason for study discontinuation was disease progression, with the higher rate in the control group (69.4% vs. 58.7% in the serplulimab group). The proportion of patients still in follow-up (included both safety and survival follow-up) was 25.8% in the serplulimab group vs. 20.8% in the control group. No patients in either treatment group were reported lost to follow-up during the study. Concerning survival follow-up, 2 patients in the serplulimab group were reported as lost to follow up/unknown.

Baseline and disease characteristics

Overall, demographic and baseline disease characteristics were balanced between the two treatment arms. The study population was predominantly male (85.3%) with a median age of 64.0 years (range 34 - 75). Considering that esophageal cancer diagnoses are much more common in males, the imbalance in gender is not unexpected. As only 46% of the included patients were ≥ 65 years, the age distribution of the study population is not considered fully representative considering that esophageal cancer is more prevalent in elderly people (in their 70s and 80s). According to the inclusion criteria, the study allowed participation of patients only until the age of 75 years. This is reflected in section 5.1 of the SmPC. Over 70% of the included patients had ECOG performance status 1, indicating a relatively fit patient population than would be expected in clinical practice.

All of the patients had ESCC, and the majority had distant metastases with tumour status IVB at study entry (86.4%). The distribution of patients in the two PD-L1 expression levels categories (1 ≤ CPS < 10 vs. CPS ≥ 10) was balanced between the two treatment groups. A total of 56.3% of the patients had a PD-L1 expression level of 1<CPS<10 and around 44% had CPS ≥ 10.

With regards to patients whose tumors expressed PD-L1 CPS <5 and CPS ≥ 5, the baseline demographic and disease characteristics were considered to be generally similar between the serplulimab + ChT group and the control group for each of the two subgroups and also overall consistent with the ITT population.

One of the secondary objectives was to study the relationship of efficacy between microsatellite instability (MSI) and tumor mutational burden (TMB), respectively. However, due to a very high proportion of missing data (in total 88.6%) in these two biomarker groups and that nearly no patients had MSI-H or ≥10 mutations/Mb, no meaningful evaluations could be made.

All patients were recruited in China. Published meta-analyses (Peng et al, 2020 and Ren et al, 2025) have suggested an improved survival benefit of PD-1/PD-L1 inhibitors in Asian patients compared to non-Asian patients. However, these analyses are subject to methodological issues and no definitive conclusions can be drawn.

It is acknowledged that treatment standards are broadly similar, with both the National Comprehensive Cancer Network (NCCN, 2025) and European Society for Medical Oncology (ESMO, 2022 with update in February 2025) recommending PD-1/PD-L1 inhibitors in combination with chemotherapy as first-line therapy for advanced ESCC.

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

It is acknowledged that for other PD-1/PD-L1 inhibitors approved for ESCC, pivotal studies included mainly Asian patients, although some data were available for non-Asian patients. The lack of data in a European ESCC population for serplulimab remains an uncertainty in terms of the generalisability of the efficacy study results. However, given the consistent class effect of PD-1/PD-L1 inhibitors and the overall evidence, this uncertainty is not considered to preclude approval.

The MAH stated that no studies in European patients are 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.

Efficacy data and additional analyses

Results

The primary analysis had a data cut-off date of 15 April 2022 as well as an updated analysis with data cut-off date of 09 January 2023. The MAH confirmed that the clinical studies for ESCC were completed and that the final analysis was included with this application.

OS outcomes (ITT population)

In the primary analysis (DCO 15 April 2022), the median duration of follow-up was 14.9 months.

The median OS for the overall population was 15.3 months (95% CI: 13.96, 18.63) in the serplulimab group and 11.8 months (95% CI: 9.69, 14.03) in the control group, with HR (stratified Cox proportional hazards model) of 0.68 (95% CI:0.529, 0.871), p = 0.0020.

The increase in median OS of 3.5 months in favour of the serplulimab group is considered clinically meaningful for the intended population. Notably, the Kaplan-Meier survival curves demonstrated a separation after ~ 4 months of treatment in favour of the serplulimab group. This suggests a relatively early onset of efficacy following add-on immunotherapy with serplulimab.

In the updated analysis (DCO 09 January 2023) the median duration of follow-up was 24.3 months.

The median OS for the overall population was 14.8 months (95% CI: 13.11, 16.66) in the serplulimab group and 11.2 months (95% CI: 9.69, 13.86) in the control group, with HR (stratified Cox proportional hazards model) of 0.70 (95% CI: 0.568, 0.862). These results thus confirmed the results reported from the primary analysis.

Notwithstanding the inherent limitations and risk of bias when comparing results across trials, the observed OS benefit for serplulimab in combination with ChT was in the same order of magnitude or somewhat lower than reported for other PD-L1/PD-1-inhibitors (combined with ChT) intended for use in a similar target population (based on EPAR data from: toripalimab, tislelizumab, nivolumab and pembrolizumab). For serplulimab all patients had to be PD-L1 positive (CPS ≥ 1).

As already mentioned, several patients received subsequent systemic anti-cancer therapy (ca. 43% in the serplulimab group [19% PD-1/PDl-1 inhibitors] and 53% in the control group [ca. 30% PD-1/PDl-1 inhibitors]). This lends uncertainty in the estimation of the true effect of serplulimab on OS. Patients had the possibility to continue the original treatment after first PD, which further

complicates the evaluation of the OS results. Overall, the available analyses are not conclusive regarding the impact of subsequent treatments or continuation of serplulimab beyond PD on OS.

The various sensitivity analyses and the supplementary analysis (performed in the per-protocol-set) were consistent with the results from the primary analysis of OS (ITT-set).

PFS outcomes (ITT population)

The primary analysis (DCO 15 April 2022) showed a median PFS as assessed by IRRC (per RECIST v1.1) of 5.8 months (95% CI: 5.68, 6.93) for the serplulimab group compared with 5.3 months (95% CI: 4.30, 5.55) for the control group with HR (stratified Cox proportional hazards model) of 0.60 (95% CI: 0.476, 0.747, $P < 0.0001$). The observed difference in median PFS was very small (0.5 months in favour of serplulimab).

The updated analysis (DCO 09 January 2023) showed a median PFS as assessed by IRRC (per RECIST v1.1) of 6.5 months (95% CI: 5.75, 7.10) for the serplulimab group compared with 5.3 months (95% CI: 4.30, 5.55) in the control group with HR (stratified Cox proportional hazards model) of 0.58 (95% CI: 0.465, 0.716).

Compared to the primary analysis, the updated analysis showed a PFS gain of 1.2 months favouring serplulimab. As mentioned above for OS, comparisons across studies should be interpreted with caution. It is noted that relatively small gains in PFS have been reported for studies in ESCC with other PD-L1/PD-1 inhibitors.

Several sensitivity analyses (including those based on iRECIST) in addition to supplementary analyses in the per-protocol population, were performed for PFS. Overall, the results of these analyses were consistent with the main analysis (i.e., PFS as assessed by IRRC based on RECIST v1.1). A supplementary analysis of PFS using the treatment policy strategy was consistent with the primary analysis both for the IRRC-assessed PFS and investigator-assessed PFS, which is reassuring.

Secondary outcomes (ITT population)

PFS assessed by Investigator based on RECIST v1.1

The primary analysis (DCO 15 April 2022) showed a median PFS of 6.9 months (95% CI: 5.82, 7.13) in the serplulimab group vs. 5.4 months (95% CI: 4.27, 5.59) in the control group. HR was 0.56, 95% CI: 0.449, 0.697. The updated analysis (DCO 09 January 2023) showed consistency with this result (gain in PFS 1.5 months, stratified HR 0.54, 95% CI: 0.442, 0.671).

PFS assessed by IRRC and by Investigator based on immune-modified RECIST (iRECIST) – ITT set

Overall, the PFS analyses assessed by IRRC and by Investigator based on iRECIST in the various analysis sets were in line with the corresponding analyses when based on RECIST v1.1. This was valid both for the primary analysis (DCO 15 April 2022) and the updated analysis (DCO 09 January 2023).

ORR

The primary analysis (DCO 15 April 2022) of confirmed ORR assessed by IRRC (based on RECIST v1.1) demonstrated higher tumour response rates in the serplulimab group than in the control group (ORR: 57.6% vs. 42.1%, respectively). The results from the updated analysis (DCO 09 January 2023) pointed in the same direction, 58.7% (53.5% - 63.8%) in the serplulimab group compared with 42.1% (34.8% - 49.6%) in the control group.

Moreover, both the primary analysis and the updated analysis of ORR assessed by Investigator, also showed higher response rates for patients in the serplulimab group as compared with the control group, although slightly lower than seen in the analysis assessed by IRRC.

DOR

The primary analysis (DCO 15 April 2022) of confirmed DOR assessed by IRRC (based on RECIST v1.1) showed a more durable (although rather small) tumour response in the serplulimab group than in the control group (6.9 months vs. 4.6 months, respectively). The results from the updated analysis (DCO 09 January 2023) were in support of the results observed in the primary analysis, 7.1 (5.75, 8.61) months in in the serplulimab group compared with 4.6 (4.17, 5.55) months in the control group.

The results were supported by the analyses when assessed by Investigator (an overall higher median DOR was observed for the serplulimab group compared to the assessment made by IRRC).

In conclusion, the results of the secondary endpoints were generally in support of the outcomes of the primary endpoints.

Subgroups

Efficacy by PD-L1 expression status

The MAH initially sought approval for an indication restricted to patients whose tumours express PD-L1 with a CPS ≥ 1. Efficacy results by PD-L1 expression in several large phase 3 studies such as KEYNOTE-590 (pembrolizumab), CheckMate 648 (nivolumab) and RATIONALE-306 (tislelizumab) all suggested a positive correlation between PD-L1 expression level and the efficacy of PD-1 blockade in combination with chemotherapy.

OS

The results for the subgroups PD-L1 expression level 1≤CPS<10 and CPS ≥10 demonstrated an OS gain favouring the serplulimab group for both levels. However, a trend of lower benefit in the subgroup 1 ≤ CPS < 10 was observed in both the primary analysis (2.8 months vs. 4.7 months for CPS ≥10) and the updated analysis (1.6 months vs. 6.4 months for CPS ≥10). The primary analysis showed a HR of 0.74 (95% CI: 0.537, 1.026) for 1≤CPS<10 vs. HR 0.59 (95% CI: 0.404, 0.883) for CPS ≥ 10.

The number of patients in the CPS ≥ 10 group was more limited compared to the 1≤CPS<10 group. Due to fewer events in the CPS ≥ 10 subgroup (particularly in the serplulimab group), rendering the estimate of HR less accurate, it was difficult to draw definite conclusions and make direct comparisons between the two subgroups. In addition, due to the 2:1 randomisation, the control group became even smaller.

In order to gain further insight on the efficacy of serplulimab in relation to PD-L1 expression level, additional post-hoc subgroup analyses of CPS < 5, CPS ≥ 5 and 5 ≤ CPS <10 were requested by CHMP. For the subgroup of CPS < 5 there was no clear OS benefit for the serplulimab group (12.0 months) compared to the control group (12.8 months), HR 0.88 (95% CI: 0.637, 1.241). In contrast, the subgroup CPS ≥ 5 showed a clear OS benefit with a difference in median OS of 5.8 months favouring the serplulimab group, HR 0.60 (95% CI: 0.460, 0.786).

Based on these results, it is apparent that the benefit in median OS observed in the ITT population is primarily driven by patients with CPS ≥ 5.

The MAH conducted landmark analyses at 6 and 12 months, excluding early events. The results showed that for patients with CPS <5 who survived beyond 6 months, serplulimab reduced the

subsequent risk of death by 24% (Landmark HR=0.76, 95% CI: 0.52, 1.12). For those surviving beyond 12 months, the risk reduction reached 38% (Landmark HR=0.62, 95% CI: 0.35, 1.09). However, landmark analyses are prone to bias, and the observed effects were only slightly lower compared to the randomised OS analyses. Therefore, greater weight is given to the randomised OS analyses.

In addition, the MAH provided two supplemental analyses concerning the subgroup of patients with CPS <5; one excluding patients who had received subsequent immunotherapy and another analysis where patients were divided by immune checkpoint inhibitor (ICI) exposure (including also serplulimab and post-study exposure for ICI). These analyses showed HRs of 0.76 and 0.72 (both with 95% CIs including 1), respectively, which were not very different from the HRs resulting from the comparison of the randomised groups (acknowledging the limitations and biases of these analyses).

Given the biological plausibility of a target-dependent response, the net advantage of serplulimab as add-on to chemotherapy does not appear convincing in patients with CPS <5. Therefore, the indication is restricted to ESCC patients whose tumours express PD-L1 with a CPS ≥5.

Other subgroups

Age: There was no difference in efficacy for subjects <65 years compared to those ≥ 65 years, as indicated by overlapping 95% CI in the updated analysis (DCO 09 January 2023).

For the subgroups gender, ECOG performance and tumor status, the number of patients within each subgroup was imbalanced limiting the interpretability of the results. For MSI/MMR (MSS/MSI-I or MSI-H) and TMB (< 10 muts/Mb or ≥ 10 muts/Mb) the proportion of missing data was very high (approximately 90%). Hence, no meaningful evaluations are possible.

PFS

Similarly, as observed in the subgroup analysis for OS, a trend for a lower gain in PFS (as assessed by IRRC based on RECIST v1.1) in favour of the serplulimab group was seen in the 1≤CPS<10 group compared to the CPS ≥ 10 group. In the primary analysis, the HR was 0.48 (95% CI: 0.343, 0.680) for CPS ≥ 10 vs. 0.70 (95% CI: 0.518, 0.943) for 1 ≤ CPS < 10. The 95% CIs partly overlapped but neither included 1.

Additional post-hoc subgroup analyses of PFS by CPS <5%, CPS ≥ 5 and 5≤ CPS <10% were submitted. The results for IRRC-assessed PFS showed the same trends as observed for OS. A larger benefit in median PFS, in favour of serplulimab, was seen in the subgroup of CPS ≥ 5 (1.6 months, HR 0.57; 95% CI: 0.435, 0.752). For the other subgroups the difference in median PFS in favour of serplulimab was smaller; 1.2 months for CPS <5; HR 0.60 (95% CI: 0.424, 0.855) and only 0.3 month in 5 ≤ CPS <10; HR 0.87 (95% CI: 0.517, 1.505).

Overall, the PFS benefit for serplulimab + ChT is modest both in the ITT population and across PD-L1 expression subgroups.

Other subgroups

For the analyses of age, gender, ECOG score 1 and tumor status, the results pointed in the same direction as seen for OS. Likewise, for the subgroups MSI/MMR (MSS/MSI-I or MSI-H) and TMB (< 10 muts/Mb or ≥ 10 muts/Mb), it is not possible to conclude due to incomplete and missing data.

ORR

Regarding ORR, the results of the subgroup analyses as assessed by IRRC (based on RECIST v1.1) pointed in the same direction as those for PFS. Additional post-hoc subgroup analyses by CPS

<5%, CPS ≥5% and 5≤ CPS <10% were submitted for ORR. The same pattern as seen for OS was observed for ORR (IRRC-assessed). The largest difference in favour of serplulimab was shown in subgroup CPS ≥ 5 (25.4% compared to the control group), while in the subgroup 5 ≤ CPS < 10 the difference was 22.1% and in the subgroup CPS <5 it was negligible (2.1%).

2.4.23. Conclusions on the clinical efficacy

The primary efficacy analysis (DCO 15 April 2022) showed a statistically significant and clinically relevant OS benefit favouring serplulimab as add-on to chemotherapy in the first-line treatment of adult patients with unresectable, locally advanced, recurrent or metastatic ESCC.

However, the results for patients in the CPS <5 category (constituting around 40% of the study population), showed no clinically relevant benefit. The PFS benefit did not demonstrate a clinically meaningful effect and was coupled with no relevant effect in ORR and no clear OS benefit.

The limitations of post-hoc subgroup analyses are acknowledged; however, the approach is considered to be in line with previous decisions for other PD-L1/PD-1 inhibitors approved for ESCC.

Given the biological plausibility of a target-dependent response, the benefit of serplulimab as add-on to chemotherapy is not established in patients with CPS <5. The indication is therefore restricted to ESCC patients whose tumours express PD-L1 with a CPS ≥5.

2.5. Clinical safety

Introduction

The proposed dose of serplulimab is 3 mg/kg every 2 weeks (Q2W) until disease progression or unacceptable toxicity.

The safety data of serplulimab are based on the updated analysis (DCO January 09, 2023) of the pivotal study ASTRUM-007 in locally advanced, recurrent or metastatic ESCC, in combination with cisplatin + 5-FU. In total, 382 patients received serplulimab in this study.

Supportive safety data was provided by pooled safety data (pooled safety dataset) from 10 clinical studies (including the pivotal study HLX10-007-EC301) in subjects with various types of solid tumors. Included studies had a data cut-off within 4 years prior to submission of the current EOI application. 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.

All adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system version 26.1

Table 45 - Overview of the Clinical Trials Pooled in Safety Evaluations for Serplulimab

Study No.	Title	Study Treatment	Control	Serplulimab Dose	Number of Subjects in Analysis [a]	Study Status	Cutoff Date for Safety Data
HLX10-007-EC301 (Pivotal study for targeted indication)	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
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
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
HLX10-002-NSCLC301	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 switching to serplulimab + HLX04: 72. Total: 503	Ongoing	June 15, 2023
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

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. a Data Source: Table 2.7.4.1.1. 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).

Patient exposure in pivotal trial – Study ASTRUM-007

Pooled safety population

Table 46: Pooled Safety Population: Summary of Demographic Characteristics

	<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
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/m2) = Weight (kg)/(Height [cm]/100)2.

Table 47: 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

Overall safety evaluation plan

HLX10-007-EC301

Safety analyses were based on all treated patients.

Pooled Safety Population

Safety analyses were focused on patients receiving doses relevant to the proposed indication.

Table 48: 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

Table 49: Summary of Adverse Events (Safety Set, SS) in HLX10-007-EC301

	a. Received placebo + chemotherapy throughout (N=168)		b. Received HLX10 + chemotherapy throughout (N=374)		c. Subjects with alternated medication [1] (N=8)		d. Received HLX10 (b and c combined) (N=382)		e. Total (N=550)	
	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)
Treatment-emergent adverse events (TEAEs) [2]	3645	167 (99.4%)	10671	372 (99.5%)	395	8 (100%)	11066	380 (99.5%)	14711	547 (99.5%)
TEAEs with Grade ≥ 3 [3]	282	103 (61.3%)	751	241 (64.4%)	19	6 (75.0%)	770	247 (64.7%)	1052	350 (63.6%)
HLX10/placebo-related TEAEs [4]	1084	131 (78.0%)	4396	312 (83.4%)	110	8 (100%)	4506	320 (83.8%)	5590	451 (82.0%)
HLX10/placebo-related TEAEs with Grade ≥ 3 [3][4]	100	47 (28.0%)	321	133 (35.6%)	6	3 (37.5%)	327	136 (35.6%)	427	183 (33.3%)
Other drug-related TEAEs [4]										
Cisplatin-related	2494	165 (98.2%)	6599	368 (98.4%)	218	8 (100%)	6817	376 (98.4%)	9311	541 (98.4%)
5-FU-related	2559	165 (98.2%)	6890	370 (98.9%)	242	8 (100%)	7132	378 (99.0%)	9691	543 (98.7%)
Any drug-related TEAEs [4]	2785	165 (98.2%)	8040	370 (98.9%)	276	8 (100%)	8316	378 (99.0%)	11101	543 (98.7%)
Any drug-related TEAEs with Grade ≥ 3 [3][4]	201	82 (48.8%)	535	196 (52.4%)	11	6 (75.0%)	546	202 (52.9%)	747	284 (51.6%)
Serious TEAEs (TESAEs)	100	54 (32.1%)	343	146 (39.0%)	11	4 (50.0%)	354	150 (39.3%)	454	204 (37.1%)
Grade ≥ 3 TESAEs [3]	74	43 (25.6%)	212	111 (29.7%)	7	3 (37.5%)	219	114 (29.8%)	293	157 (28.5%)
HLX10/placebo-related TESAEs [4]	32	22 (13.1%)	157	76 (20.3%)	1	1 (12.5%)	158	77 (20.2%)	190	99 (18.0%)
HLX10/placebo-related TESAEs with Grade ≥ 3 [3][4]	23	18 (10.7%)	89	53 (14.2%)	0	0	89	53 (13.9%)	112	71 (12.9%)
Other drug-related TESAEs [4]										
Cisplatin-related	45	29 (17.3%)	184	82 (21.9%)	7	3 (37.5%)	191	85 (22.3%)	236	114 (20.7%)
5-FU-related	44	27 (16.1%)	177	81 (21.7%)	7	3 (37.5%)	184	84 (22.0%)	228	111 (20.2%)
Any drug-related TESAEs [4]	48	30 (17.9%)	225	99 (26.5%)	7	3 (37.5%)	232	102 (26.7%)	280	132 (24.0%
Any drug-related TESAEs with Grade ≥ 3 [3][4]	32	23 (13.7%)	121	70 (18.7%)	3	2 (25.0%)	124	72 (18.8%)	156	95 (17.3%
TEAEs leading to death	22	22 (13.1%)	47	38 (10.2%)	0	0	47	38 (9.9%)	69	60 (10.9%
Drug-related TEAEs leading to death [4]	3	3 (1.8%)	20	12 (3.2%)	0	0	20	12 (3.1%)	23	15 (2.7%)
HLX10/placebo-related	2	2 (1.2%)	19	11 (2.9%)	0	0	19	11 (2.9%)	21	13 (2.4%)
Cisplatin-related	3	3 (1.8%)	11	7 (1.9%)	0	0	11	7 (1.8%)	14	10 (1.8%)
5-FU-related	3	3 (1.8%)	10	7 (1.9%)	0	0	10	7 (1.8%)	13	10 (1.8%)
TEAEs leading to drug interruption	212	80 (47.6%)	717	212 (56.7%)	18	7 (87.5%)	735	219 (57.3%)	947	299 (54.4%
Grade ≥ 3 TEAEs leading to drug interruption [3]	63	38 (22.6%)	194	112 (29.9%)	7	4 (50.0%)	201	116 (30.4%)	264	154 (28.0%
HLX10/placebo-related TEAEs leading to drug interruption [4]	91	40 (23.8%)	408	135 (36.1%)	5	2 (25.0%)	413	137 (35.9%)	504	177 (32.2%
HLX10/placebo-related Grade ≥ 3 TEAEs leading to drug interruption [3][4]	25	20 (11.9%)	111	64 (17.1%)	1	1 (12.5%)	112	65 (17.0%)	137	85 (15.5%
HLX10/placebo-related TEAEs leading to [4]										
HLX10/placebo interruption	83	36 (21.4%)	382	129 (34.5%)	5	2 (25.0%)	387	131 (34.3%)	470	167 (30.4%
Cisplatin interruption	67	30 (17.9%)	255	92 (24.6%)	0	0	255	92 (24.1%)	322	122 (22.2%
5-FU interruption	76	35 (20.8%)	309	107 (28.6%)	2	1 (12.5%)	311	108 (28.3%)	387	143 (26.0%

TEAEs leading to drug discontinuation	47	30 (17.9%)	111	79 (21.1%)	0	0	111	79 (20.7%)	158	109 (19.8%)
Grade ≥ 3 TEAEs leading to drug discontinuation [3]	16	11 (6.5%)	41	36 (9.6%)	0	0	41	36 (9.4%)	57	47 (8.5%)
HLX10/placebo-related TEAEs leading to drug discontinuation [4]	16	11 (6.5%)	46	37 (9.9%)	0	0	46	37 (9.7%)	62	48 (8.7%)
HLX10/placebo-related Grade ≥ 3 TEAEs leading to drug discontinuation [3][4]	8	5 (3.0%)	18	16 (4.3%)	0	0	18	16 (4.2%)	26	21 (3.8%)
HLX10/placebo-related TEAEs leading to [4]										
HLX10/placebo discontinuation	8	5 (3.0%)	23	21 (5.6%)	0	0	23	21 (5.5%)	31	26 (4.7%)
Cisplatin discontinuation	7	4 (2.4%)	24	19 (5.1%)	0	0	24	19 (5.0%)	31	23 (4.2%)
5-FU discontinuation	8	7 (4.2%)	21	19 (5.1%)	0	0	21	19 (5.0%)	29	26 (4.7%)
Adverse events of special interest (AESIs)	60	33 (19.6%)	397	137 (36.6%)	14	5 (62.5%)	411	142 (37.2%)	471	175 (31.8%)
Infusion-related reactions (IRRs)	4	3 (1.8%)	12	4 (1.1%)	0	0	12	4 (1.0%)	16	7 (1.3%)
Immune-related adverse events (irAEs)	57	32 (19.0%)	388	137 (36.6%)	14	5 (62.5%)	402	142 (37.2%)	459	174 (31.6%)
AESIs with Grade ≥ 3 [3]	8	6 (3.6%)	61	34 (9.1%)	0	0	61	34 (8.9%)	69	40 (7.3%)
IRRs with Grade ≥ 3 [3]	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
irAEs with Grade ≥ 3 [3]	7	5 (3.0%)	61	34 (9.1%)	0	0	61	34 (8.9%)	68	39 (7.1%)
Serious AESIs	4	3 (1.8%)	52	29 (7.8%)	0	0	52	29 (7.6%)	56	32 (5.8%)
Serious IRRs	0	0	0	0	0	0	0	0	0	0
Serious irAEs	4	3 (1.8%)	52	29 (7.8%)	0	0	52	29 (7.6%)	56	32 (5.8%)
Serious AESIs with Grade ≥ 3 [3]	4	3 (1.8%)	34	21 (5.6%)	0	0	34	21 (5.5%)	38	24 (4.4%)
Serious IRRs with Grade ≥ 3 [3]	0	0	0	0	0	0	0	0	0	0
Serious irAEs with Grade ≥ 3 [3]	4	3 (1.8%)	34	21 (5.6%)	0	0	34	21 (5.5%)	38	24 (4.4%)
TEAEs with an incidence ≥ 1%	3508	166 (98.8%)	10154	372 (99.5%)	383	8 (100%)	10537	380 (99.5%)	14045	546 (99.3%)
Grade ≥ 3 TEAEs with an incidence ≥ 1% [3]	231	92 (54.8%)	609	218 (58.3%)	15	6 (75.0%)	624	224 (58.6%)	855	316 (57.5%)
TESAEs with an incidence ≥ 1%	64	38 (22.6%)	206	104 (27.8%)	9	3 (37.5%)	215	107 (28.0%)	279	145 (26.4%)
TESAEs with Grade ≥ 3 and an incidence ≥ 1% [3]	45	31 (18.5%)	109	68 (18.2%)	2	1 (12.5%)	111	69 (18.1%)	156	100 (18.2%)
HLX10/placebo-related TEAEs with an incidence ≥ 1% [4]	1016	126 (75.0%)	4067	305 (81.6%)	109	8 (100%)	4176	313 (81.9%)	5192	439 (79.8%)
HLX10/placebo-related Grade ≥ 3 TEAEs with an incidence ≥ 1% [3][4]	68	34 (20.2%)	222	100 (26.7%)	6	3 (37.5%)	228	103 (27.0%)	296	137 (24.9%)
HLX10/placebo-related TESAEs with an incidence ≥ 1% [4]	18	11 (6.5%)	74	40 (10.7%)	1	1 (12.5%)	75	41 (10.7%)	93	52 (9.5%)
HLX10/placebo-related TESAEs with Grade ≥ 3 and an incidence ≥ 1% [3][4]	11	9 (5.4%)	37	26 (7.0%)	0	0	37	26 (6.8%)	48	35 (6.4%)
Any drug-related TEAEs with an incidence ≥ 1% [4]	2697	163 (97.0%)	7719	369 (98.7%)	272	8 (100%)	7991	377 (98.7%)	10688	540 (98.2%)
Any drug-related Grade ≥ 3 TEAEs with an incidence ≥ 1% [3][4]	166	74 (44.0%)	432	169 (45.2%)	10	6 (75.0%)	442	175 (45.8%)	608	249 (45.3%)
Any drug-related TESAEs with an incidence ≥ 1% [4]	30	17 (10.1%)	129	65 (17.4%)	7	3 (37.5%)	136	68 (17.8%)	166	85 (15.5%)
Any drug-related Grade ≥ 3 TESAEs with an incidence ≥ 1% [3][4]	16	12 (7.1%)	57	39 (10.4%)	0	0	57	39 (10.2%)	73	51 (9.3%)

TEAEs with an incidence ≥ 5%	3051	163 (97.0%)	8881	372 (99.5%)	348	8 (100%)	9229	380 (99.5%)	12280	543 (98.7%)
Grade ≥ 3 TEAEs with an incidence ≥ 5% [3]	139	62 (36.9%)	352	149 (39.8%)	10	5 (62.5%)	362	154 (40.3%)	501	216 (39.3%)
TESAEs with an incidence ≥ 5%	12	7 (4.2%)	60	38 (10.2%)	1	1 (12.5%)	61	39 (10.2%)	73	46 (8.4%)
TESAEs with Grade ≥ 3 and an incidence ≥ 5% [3]	4	4 (2.4%)	20	19 (5.1%)	0	0	20	19 (5.0%)	24	23 (4.2%)
HLX10/placebo-related TEAEs with an incidence ≥ 5% [4]	825	117 (69.6%)	3236	297 (79.4%)	104	8 (100%)	3340	305 (79.8%)	4165	422 (76.7%)
HLX10/placebo-related Grade ≥ 3 TEAEs with an incidence ≥ 5% [3][4]	45	24 (14.3%)	129	64 (17.1%)	6	3 (37.5%)	135	67 (17.5%)	180	91 (16.5%)
HLX10/placebo-related TESAEs with an incidence ≥ 5% [4]	0	0	0	0	0	0	0	0	0	0
HLX10/placebo-related TESAEs with Grade ≥ 3 and an incidence ≥ 5% [3][4]	0	0	0	0	0	0	0	0	0	0
Any drug-related TEAEs with an incidence ≥ 5% [4]	2408	163 (97.0%)	6636	367 (98.1%)	258	8 (100%)	6894	375 (98.2%)	9302	538 (97.8%)
Any drug-related Grade ≥ 3 TEAEs with an incidence ≥ 5% [3][4]	118	56 (33.3%)	261	121 (32.4%)	7	4 (50.0%)	268	125 (32.7%)	386	181 (32.9%)
Any drug-related TESAEs with an incidence ≥ 5% [4]	4	2 (1.2%)	40	25 (6.7%)	1	1 (12.5%)	41	26 (6.8%)	45	28 (5.1%)
Any drug-related Grade ≥ 3 TESAEs with an incidence ≥ 5% [3][4]	0	0	0	0	0	0	0	0	0	0
TEAEs with an incidence ≥ 10%	2752	162 (96.4%)	7796	369 (98.7%)	325	8 (100%)	8121	377 (98.7%)	10873	539 (98.0%)
Grade ≥ 3 TEAEs with an incidence ≥ 10% [3]	120	56 (33.3%)	275	132 (35.3%)	8	4 (50.0%)	283	136 (35.6%)	403	192 (34.9%)
TESAEs with an incidence ≥ 10%	0	0	0	0	0	0	0	0	0	0
TESAEs with Grade ≥ 3 and an incidence ≥ 10% [3]	0	0	0	0	0	0	0	0	0	0
HLX10/placebo-related TEAEs with an incidence ≥ 10% [4]	683	103 (61.3%)	2528	274 (73.3%)	96	8 (100%)	2624	282 (73.8%)	3307	385 (70.0%)
HLX10/placebo-related Grade ≥ 3 TEAEs with an incidence ≥ 10% [3][4]	17	17 (10.1%)	42	38 (10.2%)	0	0	42	38 (9.9%)	59	55 (10.0%)
HLX10/placebo-related TESAEs with an incidence ≥ 10% [4]	0	0	0	0	0	0	0	0	0	0
HLX10/placebo-related TESAEs with Grade ≥ 3 and an incidence ≥ 10% [3][4]	0	0	0	0	0	0	0	0	0	0
Any drug-related TEAEs with an incidence ≥ 10% [4]	2270	161 (95.8%)	6058	367 (98.1%)	245	8 (100%)	6303	375 (98.2%)	8573	536 (97.5%)
Any drug-related Grade ≥ 3 TEAEs with an incidence ≥ 10% [3][4]	118	56 (33.3%)	261	121 (32.4%)	7	4 (50.0%)	268	125 (32.7%)	386	181 (32.9%)
Any drug-related TESAEs with an incidence ≥ 10% [4]	0	0	0	0	0	0	0	0	0	0
Any drug-related Grade ≥ 3 TESAEs with an incidence ≥ 10% [3][4]	0	0	0	0	0	0	0	0	0	0

Notes: AEs were coded according to MedDRA 26.1 [1] On April 26, 2020, the IWRS system administrator received a reminder email regarding the need for unblinding due to an SAE in a subject and found that a subject randomized to the control group was receiving HLX10 in combination with chemotherapy. Later, an internal review revealed that in the drug settings of the IWRS system, subjects in the control group with a weight of 33.3 kg < weight ≤ 66.6 kg were mistakenly assigned to the HLX10 group. As of April 26, 2020, a total of 51 subjects were enrolled in this weight group, resulting in some subjects in the control group being mistakenly treated with HLX10 in combination with chemotherapy. This issue was reported to the Ethics Committee of all study sites, regulatory authorities, and Independent Data Monitoring Committee (IDMC) in a timely manner upon discovery. A total of xx subjects finally received both the treatments of the HLX10 group and the control group, therefore, the safety analysis was performed in 5 groups: "a. received placebo + chemotherapy throughout. b. received HLX10 + chemotherapy throughout. c. subjects with alternated medication. d. received HLX10 (b and c combined). e. total". [2] Treatment-emergent adverse event (TEAE) was defined as an AE that occurred or was worsened on or after the first dose of the study drug (C1D1), till 90 days after the last dose of the study drug or the start of a new anti-tumor therapy (whichever occurred first). [3] The highest CTCAE grade, defined

as the highest CTCAE grade of all TEAEs that occurred in one subject, was only used for calculation for the subject. [4] A drug-related AE was defined as an AE whose relationship to the study drug was (1 = related, 2 = possibly related, and 5 = unknown) or missing. Data cut-off date: 2023-01-09

Pooled safety population

A summary of adverse events reported in the pooled safety population is given below.

Table 50: 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 (ASTRUM-007)

Table 51: HLX10-007-EC301: Summary of TEAEs with Incidence ≥ 10% in Any Group by SOC and PT (SS)

System organ class (SOC) Preferred term (PT)	a. Received placebo + chemotherapy throughout (N=168)		b. Received serplulimab + chemotherapy throughout (N=374)		c. Subjects with alternated medication (N=8)		d. Received serplulimab (b and c combined) (N=382)		e. Total (N=550)	
	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)
TEAEs with an incidence ≥ 10% [1]	2752	162 (96.4%)	7796	369 (98.7%)	325	8 (100%)	8121	377 (98.7%)	10873	539 (98.0%)
Investigations	1129	137 (81.5%)	3109	326 (87.2%)	117	8 (100%)	3226	334 (87.4%)	4355	471 (85.6%)
White blood cell count decreased	398	103 (61.3%)	1029	222 (59.4%)	38	5 (62.5%)	1067	227 (59.4%)	1465	330 (60.0%)
Neutrophil count decreased	363	90 (53.6%)	906	212 (56.7%)	34	6 (75.0%)	940	218 (57.1%)	1303	308 (56.0%)
Platelet count decreased	166	69 (41.1%)	512	171 (45.7%)	20	5 (62.5%)	532	176 (46.1%)	698	245 (44.5%)
Weight decreased	75	50 (29.8%)	192	127 (34.0%)	3	2 (25.0%)	195	129 (33.8%)	270	179 (32.5%)
Blood creatinine increased	35	22 (13.1%)	147	65 (17.4%)	1	1 (12.5%)	148	66 (17.3%)	183	88 (16.0%)
Aspartate aminotransferase increased	20	13 (7.7%)	88	59 (15.8%)	6	3 (37.5%)	94	62 (16.2%)	114	75 (13.6%)
Lymphocyte count decreased	54	17 (10.1%)	162	46 (12.3%)	10	2 (25.0%)	172	48 (12.6%)	226	65 (11.8%)
Alanine aminotransferase increased	18	11 (6.5%)	73	47 (12.6%)	5	3 (37.5%)	78	50 (13.1%)	96	61 (11.1%)
Blood and lymphatic system disorders	324	134 (79.8%)	812	316 (84.5%)	25	7 (87.5%)	837	323 (84.6%)	1161	457 (83.1%)
Anaemia	324	134 (79.8%)	812	316 (84.5%)	25	7 (87.5%)	837	323 (84.6%)	1161	457 (83.1%)
Gastrointestinal disorders	664	128 (76.2%)	1572	308 (82.4%)	50	8 (100%)	1622	316 (82.7%)	2286	444 (80.7%)
Nausea	358	108 (64.3%)	878	245 (65.5%)	30	6 (75.0%)	908	251 (65.7%)	1266	359 (65.3%)
Vomiting	214	75 (44.6%)	444	169 (45.2%)	11	5 (62.5%)	455	174 (45.5%)	669	249 (45.3%)
Constipation	62	39 (23.2%)	167	111 (29.7%)	7	3 (37.5%)	174	114 (29.8%)	236	153 (27.8%)
Diarrhoea	30	23 (13.7%)	83	55 (14.7%)	2	2 (25.0%)	85	57 (14.9%)	115	80 (14.5%)
Metabolism and nutrition disorders	435	118 (70.2%)	1656	303 (81.0%)	80	6 (75.0%)	1736	309 (80.9%)	2171	427 (77.6%)
Decreased appetite	147	67 (39.9%)	458	167 (44.7%)	33	5 (62.5%)	491	172 (45.0%)	638	239 (43.5%)
Hyponatraemia	75	46 (27.4%)	250	127 (34.0%)	10	4 (50.0%)	260	131 (34.3%)	335	177 (32.2%)
Hypoalbuminaemia	77	40 (23.8%)	282	127 (34.0%)	18	4 (50.0%)	300	131 (34.3%)	377	171 (31.1%)
Hypokalaemia	48	29 (17.3%)	176	85 (22.7%)	9	2 (25.0%)	185	87 (22.8%)	233	116 (21.1%)
Hypercholesterolaemia	18	13 (7.7%)	124	49 (13.1%)	2	1 (12.5%)	126	50 (13.1%)	144	63 (11.5%)
Hyperglycaemia	19	13 (7.7%)	103	44 (11.8%)	8	2 (25.0%)	111	46 (12.0%)	130	59 (10.7%)
	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)
Hypomagnesaemia	23	15 (8.9%)	97	42 (11.2%)	0	0	97	42 (11.0%)	120	57 (10.4%)
Hyperuricaemia	20	12 (7.1%)	107	43 (11.5%)	0	0	107	43 (11.3%)	127	55 (10.0%)
Hypocalcaemia	8	7 (4.2%)	59	38 (10.2%)	0	0	59	38 (9.9%)	67	45 (8.2%)
General disorders and administration site conditions	134	70 (41.7%)	370	157 (42.0%)	37	5 (62.5%)	407	162 (42.4%)	541	232 (42.2%)
Asthenia	90	58 (34.5%)	272	127 (34.0%)	35	5 (62.5%)	307	132 (34.6%)	397	190 (34.5%)
Pyrexia	44	20 (11.9%)	98	53 (14.2%)	2	1 (12.5%)	100	54 (14.1%)	144	74 (13.5%)
Endocrine disorders	18	14 (8.3%)	116	71 (19.0%)	4	3 (37.5%)	120	74 (19.4%)	138	88 (16.0%)
Hypothyroidism	18	14 (8.3%)	116	71 (19.0%)	4	3 (37.5%)	120	74 (19.4%)	138	88 (16.0%)
Renal and urinary disorders	22	13 (7.7%)	109	63 (16.8%)	6	2 (25.0%)	115	65 (17.0%)	137	78 (14.2%)
Proteinuria	22	13 (7.7%)	109	63 (16.8%)	6	2 (25.0%)	115	65 (17.0%)	137	78 (14.2%)
Respiratory, thoracic and mediastinal disorders	26	20 (11.9%)	52	41 (11.0%)	6	2 (25.0%)	58	43 (11.3%)	84	63 (11.5%)
Cough	26	20 (11.9%)	52	41 (11.0%)	6	2 (25.0%)	58	43 (11.3%)	84	63 (11.5%)

Notes: AEs were coded according to MedDRA 26.1 [1] TEAE was defined as an AE that occurred or was worsened on or after the first dose of the study drug (C1D1), till 90 days after the last dose of the study drug or the start of a new anti-tumor therapy (whichever occurred first). Data cut-off date: 2023-01-09

Table 52: Summary of HLX10/Placebo-related TEAEs with an Incidence ≥ 10% by SOC and PT (SS) in ASTRUM-007

System organ class (SOC) Preferred term (PT)	a. Received placebo + chemotherapy throughout (N=168)		b. Received HLX10 + chemotherapy throughout (N=374)		c. Subjects with alternated medication (N=8)		d. Received HLX10 (b and c combined) (N=382)		e. Total (N=550)	
	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)
HLX10/placebo-related TEAEs with an incidence ≥ 10% [1][2]	683	103 (61.3%)	2528	274 (73.3%)	96	8 (100%)	2624	282 (73.8%)	3307	385 (70.0%)
Investigations	330	53 (31.5%)	1334	185 (49.5%)	54	4 (50.0%)	1388	189 (49.5%)	1718	242 (44.0%)
White blood cell count decreased	133	34 (20.2%)	494	114 (30.5%)	22	4 (50.0%)	516	118 (30.9%)	649	152 (27.6%)
Neutrophil count decreased	114	29 (17.3%)	414	111 (29.7%)	18	4 (50.0%)	432	115 (30.1%)	546	144 (26.2%)
Platelet count decreased	63	25 (14.9%)	283	97 (25.9%)	13	3 (37.5%)	296	100 (26.2%)	359	125 (22.7%)
Blood creatinine increased	13	10 (6.0%)	87	41 (11.0%)	1	1 (12.5%)	88	42 (11.0%)	101	52 (9.5%)
Aspartate aminotransferase increased	7	6 (3.6%)	56	38 (10.2%)	0	0	56	38 (9.9%)	63	44 (8.0%)
Blood and lymphatic system disorders	113	50 (29.8%)	336	148 (39.6%)	6	3 (37.5%)	342	151 (39.5%)	455	201 (36.5%)
Anaemia	113	50 (29.8%)	336	148 (39.6%)	6	3 (37.5%)	342	151 (39.5%)	455	201 (36.5%)
Gastrointestinal disorders	126	37 (22.0%)	392	105 (28.1%)	2	2 (25.0%)	394	107 (28.0%)	520	144 (26.2%)
Nausea	79	34 (20.2%)	242	91 (24.3%)	2	2 (25.0%)	244	93 (24.3%)	323	127 (23.1%)
Vomiting	47	20 (11.9%)	150	62 (16.6%)	0	0	150	62 (16.2%)	197	82 (14.9%)
General disorders and administration site conditions	44	29 (17.3%)	146	77 (20.6%)	20	4 (50.0%)	166	81 (21.2%)	210	110 (20.0%)
Asthenia	44	29 (17.3%)	146	77 (20.6%)	20	4 (50.0%)	166	81 (21.2%)	210	110 (20.0%)
Metabolism and nutrition disorders	37	24 (14.3%)	137	63 (16.8%)	4	2 (25.0%)	141	65 (17.0%)	178	89 (16.2%)
Decreased appetite	37	24 (14.3%)	137	63 (16.8%)	4	2 (25.0%)	141	65 (17.0%)	178	89 (16.2%)
Endocrine disorders	18	14 (8.3%)	109	66 (17.6%)	4	3 (37.5%)	113	69 (18.1%)	131	83 (15.1%)
Hypothyroidism	18	14 (8.3%)	109	66 (17.6%)	4	3 (37.5%)	113	69 (18.1%)	131	83 (15.1%)
Renal and urinary disorders	15	8 (4.8%)	74	43 (11.5%)	6	2 (25.0%)	80	45 (11.8%)	95	53 (9.6%)
Proteinuria	15	8 (4.8%)	74	43 (11.5%)	6	2 (25.0%)	80	45 (11.8%)	95	53 (9.6%)

Notes: AEs were coded according to MedDRA 26.1 [1] Treatment-emergent adverse event (TEAE) was defined as an AE that occurred or was worsened on or after the first dose of the study drug (C1D1), till 90 days after the last dose of the study drug or the start of a new anti-tumor therapy (whichever occurred first). [2] A drug-related AE was defined as an AE whose relationship to

HLX10/placebo was (1 = related, 2 = possibly related, and 5 = unknown) or missing. Data cut-off date: 2023-01-09

Adverse Events of Special Interest

AESIs included infusion-related reactions (IRRs) and immune-related adverse events (irAEs).

Table 53: Summary of irAEs by SOC and PT (SS)

System organ class (SOC) Preferred term (PT)	a. Received placebo + chemotherapy throughout (N=168)		b. Received HLX10 + chemotherapy throughout (N=374)		c. Subjects with alternated medication (N=8)		d. Received HLX10 (b and c combined) (N=382)		e. Total (N=550)	
	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)
Immune-related adverse events (irAEs)	57	32 (19.0%)	388	137 (36.6%)	14	5 (62.5%)	402	142 (37.2%)	459	174 (31.6%)
Endocrine disorders	12	9 (5.4%)	104	66 (17.6%)	7	4 (50.0%)	111	70 (18.3%)	123	79 (14.4%)
Hypothyroidism	6	5 (3.0%)	65	40 (10.7%)	3	2 (25.0%)	68	42 (11.0%)	74	47 (8.5%)
Hyperthyroidism	4	4 (2.4%)	21	16 (4.3%)	4	2 (25.0%)	25	18 (4.7%)	29	22 (4.0%)
Immune-mediated hypothyroidism	1	1 (0.6%)	3	3 (0.8%)	0	0	3	3 (0.8%)	4	4 (0.7%)
Immune-mediated adrenal insufficiency	0	0	3	3 (0.8%)	0	0	3	3 (0.8%)	3	3 (0.5%)
Thyroid disorder	0	0	3	3 (0.8%)	0	0	3	3 (0.8%)	3	3 (0.5%)
Hypopituitarism	0	0	2	2 (0.5%)	0	0	2	2 (0.5%)	2	2 (0.4%)
Immune-mediated hyperthyroidism	0	0	2	2 (0.5%)	0	0	2	2 (0.5%)	2	2 (0.4%)
Immune-mediated hypophysitis	0	0	2	2 (0.5%)	0	0	2	2 (0.5%)	2	2 (0.4%)
Autoimmune thyroiditis	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Euthyroid sick syndrome	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Immune-mediated thyroiditis	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Secondary adrenocortical insufficiency	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)

Investigations	16	10 (6.0%)	106	36 (9.6%)	3	2 (25.0%)	109	38 (9.9%)	125	48 (8.7%)
Blood creatinine increased	5	3 (1.8%)	14	8 (2.1%)	1	1 (12.5%)	15	9 (2.4%)	20	12 (2.2%)
Alanine aminotransferase increased	1	1 (0.6%)	12	7 (1.9%)	0	0	12	7 (1.8%)	13	8 (1.5%)
Aspartate aminotransferase increased	1	1 (0.6%)	8	6 (1.6%)	0	0	8	6 (1.6%)	9	7 (1.3%)
Amylase increased	1	1 (0.6%)	12	4 (1.1%)	0	0	12	4 (1.0%)	13	5 (0.9%)
Protein urine present	1	1 (0.6%)	8	4 (1.1%)	0	0	8	4 (1.0%)	9	5 (0.9%)
Bilirubin conjugated increased	0	0	4	4 (1.1%)	0	0	4	4 (1.0%)	4	4 (0.7%)
Neutrophil count decreased	0	0	4	3 (0.8%)	2	1 (12.5%)	6	4 (1.0%)	6	4 (0.7%)
Platelet count decreased	0	0	9	4 (1.1%)	0	0	9	4 (1.0%)	9	4 (0.7%)
Blood thyroid stimulating hormone increased	0	0	5	3 (0.8%)	0	0	5	3 (0.8%)	5	3 (0.5%)
Blood urea increased	0	0	3	2 (0.5%)	0	0	3	2 (0.5%)	3	2 (0.4%)
Glucose urine present	1	1 (0.6%)	2	1 (0.3%)	0	0	2	1 (0.3%)	3	2 (0.4%)
Lipase increased	1	1 (0.6%)	4	1 (0.3%)	0	0	4	1 (0.3%)	5	2 (0.4%)
Thyroxine free increased	0	0	2	2 (0.5%)	0	0	2	2 (0.5%)	2	2 (0.4%)
White blood cell count decreased	0	0	2	2 (0.5%)	0	0	2	2 (0.5%)	2	2 (0.4%)
Albumin urine present	2	1 (0.6%)	0	0	0	0	0	0	2	1 (0.2%)
Angiotensin converting enzyme increased	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Bile acids increased	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Blood alkaline phosphatase increased	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Blood bilirubin increased	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Blood creatine phosphokinase MB increased	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Blood creatine phosphokinase increased	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)

Blood thyroid stimulating hormone decreased	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Cardiac function test abnormal	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Gamma-glutamyltransferase increased	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Glomerular filtration rate decreased	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Myocardial necrosis marker increased	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Myoglobin blood increased	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Thyroxine increased	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Tri-iodothyronine free decreased	0	0	2	1 (0.3%)	0	0	2	1 (0.3%)	2	1 (0.2%)
Tri-iodothyronine increased	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Troponin T increased	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Urinary occult blood positive	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Weight decreased	0	0	2	1 (0.3%)	0	0	2	1 (0.3%)	2	1 (0.2%)
Skin and subcutaneous tissue disorders	7	5 (3.0%)	57	31 (8.3%)	0	0	57	31 (8.1%)	64	36 (6.5%)
Rash	4	4 (2.4%)	28	18 (4.8%)	0	0	28	18 (4.7%)	32	22 (4.0%)
Pruritus	1	1 (0.6%)	10	8 (2.1%)	0	0	10	8 (2.1%)	11	9 (1.6%)
Immune-mediated dermatitis	1	1 (0.6%)	7	3 (0.8%)	0	0	7	3 (0.8%)	8	4 (0.7%)
Vitiligo	1	1 (0.6%)	2	2 (0.5%)	0	0	2	2 (0.5%)	3	3 (0.5%)
Rash maculo-papular	0	0	3	2 (0.5%)	0	0	3	2 (0.5%)	3	2 (0.4%)
Dermatitis	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Drug eruption	0	0	3	1 (0.3%)	0	0	3	1 (0.3%)	3	1 (0.2%)
Dry skin	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Psoriasis	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Skin hypopigmentation	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Renal and urinary disorders	8	5 (3.0%)	18	14 (3.7%)	4	1 (12.5%)	22	15 (3.9%)	30	20 (3.6%)
Proteinuria	3	2 (1.2%)	13	9 (2.4%)	4	1 (12.5%)	17	10 (2.6%)	20	12 (2.2%)
Immune-mediated renal disorder	1	1 (0.6%)	2	2 (0.5%)	0	0	2	2 (0.5%)	3	3 (0.5%)
Nephropathy toxic	2	1 (0.6%)	1	1 (0.3%)	0	0	1	1 (0.3%)	3	2 (0.4%)
Immune-mediated nephritis	2	1 (0.6%)	0	0	0	0	0	0	2	1 (0.2%)
Renal impairment	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Renal injury	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)

Respiratory, thoracic and mediastinal disorders	2	2 (1.2%)	23	16 (4.3%)	0	0	23	16 (4.2%)	25	18 (3.3%)
Immune-mediated lung disease	2	2 (1.2%)	22	16 (4.3%)	0	0	22	16 (4.2%)	24	18 (3.3%)
Respiratory disorder	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Gastrointestinal disorders	1	1 (0.6%)	22	13 (3.5%)	0	0	22	13 (3.4%)	23	14 (2.5%)
Diarrhoea	1	1 (0.6%)	5	3 (0.8%)	0	0	5	3 (0.8%)	6	4 (0.7%)
Nausea	0	0	3	3 (0.8%)	0	0	3	3 (0.8%)	3	3 (0.5%)
Abdominal discomfort	0	0	4	2 (0.5%)	0	0	4	2 (0.5%)	4	2 (0.4%)
Immune-mediated enterocolitis	0	0	3	2 (0.5%)	0	0	3	2 (0.5%)	3	2 (0.4%)
Abdominal pain	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Dry mouth	0	0	2	1 (0.3%)	0	0	2	1 (0.3%)	2	1 (0.2%)
Mouth ulceration	0	0	2	1 (0.3%)	0	0	2	1 (0.3%)	2	1 (0.2%)
Pancreatitis	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Upper gastrointestinal haemorrhage	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Cardiac disorders	3	2 (1.2%)	21	10 (2.7%)	0	0	21	10 (2.6%)	24	12 (2.2%)
Supraventricular extrasystoles	1	1 (0.6%)	4	3 (0.8%)	0	0	4	3 (0.8%)	5	4 (0.7%)
Immune-mediated myocarditis	1	1 (0.6%)	4	2 (0.5%)	0	0	4	2 (0.5%)	5	3 (0.5%)
Atrial fibrillation	1	1 (0.6%)	1	1 (0.3%)	0	0	1	1 (0.3%)	2	2 (0.4%)
Myocardial injury	0	0	5	2 (0.5%)	0	0	5	2 (0.5%)	5	2 (0.4%)
Atrial tachycardia	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Sinus bradycardia	0	0	3	1 (0.3%)	0	0	3	1 (0.3%)	3	1 (0.2%)
Sinus tachycardia	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Ventricular extrasystoles	0	0	2	1 (0.3%)	0	0	2	1 (0.3%)	2	1 (0.2%)
Metabolism and nutrition disorders	4	4 (2.4%)	12	6 (1.6%)	0	0	12	6 (1.6%)	16	10 (1.8%)
Decreased appetite	2	2 (1.2%)	5	2 (0.5%)	0	0	5	2 (0.5%)	7	4 (0.7%)
Hyperglycaemia	1	1 (0.6%)	5	2 (0.5%)	0	0	5	2 (0.5%)	6	3 (0.5%)
Glucose tolerance impaired	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Hyperuricaemia	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Hypophosphataemia	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
General disorders and administration site conditions	1	1 (0.6%)	6	6 (1.6%)	0	0	6	6 (1.6%)	7	7 (1.3%)
Asthenia	1	1 (0.6%)	3	3 (0.8%)	0	0	3	3 (0.8%)	4	4 (0.7%)
Pyrexia	0	0	3	3 (0.8%)	0	0	3	3 (0.8%)	3	3 (0.5%)

Infections and infestations	2	1 (0.6%)	7	5 (1.3%)	0	0	7	5 (1.3%)	9	6 (1.1%)
Pneumonia	2	1 (0.6%)	4	3 (0.8%)	0	0	4	3 (0.8%)	6	4 (0.7%)
Herpes zoster	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Septic shock	0	0	2	1 (0.3%)	0	0	2	1 (0.3%)	2	1 (0.2%)
Musculoskeletal and connective tissue disorders	0	0	4	4 (1.1%)	0	0	4	4 (1.0%)	4	4 (0.7%)
Arthritis	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Immune-mediated arthritis	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Muscular weakness	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Rhabdomyolysis	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Blood and lymphatic system disorders	0	0	4	3 (0.8%)	0	0	4	3 (0.8%)	4	3 (0.5%)
Anaemia	0	0	4	3 (0.8%)	0	0	4	3 (0.8%)	4	3 (0.5%)
Hepatobiliary disorders	0	0	2	2 (0.5%)	0	0	2	2 (0.5%)	2	2 (0.4%)
Hepatic function abnormal	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Immune-mediated hepatitis	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Immune system disorders	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Reactive capillary endothelial proliferation	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Nervous system disorders	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Immune-mediated neuropathy	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Vascular disorders	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Hypotension	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)

Notes: AEs were coded according to MedDRA 26.1 Data cut-off date: 2023-01-09

Infusion-related Reactions (IRRs)

Table 54 - Summary of Grade ≥3 IRRS by SOC and PT (SS)

System organ class (SOC) Preferred term (PT)	a. Received placebo + chemotherapy throughout (N=168)		b. Received HLX10 + chemotherapy throughout (N=374)		c. Subjects with alternated medication (N=8)		d. Received HLX10 (b and c combined) (N=382)		e. Total (N=550)	
	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)
IRRs with Grade ≥ 3	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
General disorders and administration site conditions	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Pyrexia	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)

Notes: AEs were coded according to MedDRA 26.1
Data cut-off date: 2023-01-09

Adverse drug reactions

The MAH has updated section 4.8 of the SmPC to include the population of ESCC into the 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). Therefore, the changes included in section 4.8 of the current procedure represent the most updated safety pool and a consolidated version.

Table 55 - Adverse reactions reported in clinical trial and in post marketing experience are listed by system organ class and frequency 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 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
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
Uncommon	cardiomyopathy, myocardial ischaemia, pericardial effusion, myocardial injury, myocarditis
Vascular disorders	
Common	hypertension, vasculitis, hypotension,
Respiratory, thoracic and mediastinal disorders	
Very common	cough
Common	pneumonitis [s], dyspnoea, chest pain, dysphonia, pulmonary embolism
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]
General disorders and administration site conditions	

Very common	pyrexia, asthenia
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 Table 2 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:

Includes pneumonia, lung abscess.

Includes urinary tract infection, asymptomatic bacteriuria, white blood cells urine positive.

Includes upper respiratory tract infection, pharyngotonsillitis, tonsillitis, influenza-like illness, lower respiratory tract infection.

Includes activated partial thromboplastin time prolonged, activated partial thromboplastin time, activated partial thromboplastin time shortened, international normalised ratio decreased, prothrombin level increased, coagulopathy, hypercoagulation.

Includes drug hypersensitivity, infusion-related reaction.

Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroxine free decreased, thyroxine decreased, central hypothyroidism, tri-iodothyronine decreased, tri-iodothyronine free decreased.

Includes hyperthyroidism, blood thyroid stimulating hormone decreased, thyroxine increased, tri-iodothyronine increased, tri-iodothyronine free increased, thyroxine free increased.

Includes hyperglycaemia, diabetes mellitus, blood glucose increased, impaired fasting glucose, diabetic ketoacidosis, blood ketone body increased, glucose tolerance impaired, ketoacidosis, glycosuria.

Includes thyroid disorder, thyroiditis.

Includes adrenal insufficiency, cortisol decreased.

Includes euthyroid sick syndrome, ultrasound thyroid abnormal.

Includes anti-thyroid antibody positive, thyroglobulin increased.

Includes hyponatraemia, hypocalcaemia, hypokalaemia, hypomagnesaemia, hypophosphataemia, hypochloraemia, hyperphosphataemia, hyperkalaemia, hypermagnesaemia, hypercalcaemia.

Includes neuropathy peripheral, peripheral sensorimotor neuropathy, immune-mediated neuropathy.

Includes immunemediated encephalitis, encephalitis autoimmune.

Includes supraventricular extrasystoles, supraventricular tachycardia, arrhythmia, ventricular extrasystoles, arrhythmia supraventricular, atrial fibrillation, atrial tachycardia, bradyarrhythmia, early repolarisation syndrome, ventricular arrhythmia, palpitations, electrocardiogram abnormal.

Includes atrioventricular block first degree, bundle branch block right, atrial conduction time prolongation, bundle branch block left, defect conduction intraventricular.

Includes cardiac failure, cardiac failure acute, left ventricular failure, N terminal prohormone brain natriuretic peptide increased.

Includes immune-mediated lung disease, pneumonitis, interstitial lung disease.

Includes acquired trachea-oesophageal fistula, gastrointestinal haemorrhage, gastrointestinal disorder, intestinal obstruction.

Includes enteritis, enteritis infectious, immune-mediated enterocolitis **.

Includes hepatic function abnormal, drug-induced liver injury, liver injury, immune-mediated hepatitis, immune-mediated hepatic disorder **, hepatic failure **.

Includes rash, rash maculo-papular, eczema, drug eruption, erythema, skin toxicity, palmar-plantar erythrodysaesthesia syndrome.

Includes autoimmune dermatitis, dermatitis, dermatitis allergic, dermatitis bullous, seborrhoeic dermatitis.

Includes myositis **, immune-mediated myositis.

Includes acute kidney injury, renal failure, renal impairment, renal injury, chronic kidney disease, creatinine renal clearance decreased, immune-mediated nephritis.

** Post-marketing event.

Analysis of AESI by SOC and PT

Immune-related TEAEs

A total of 714 (34.2%) subjects experienced at least one irAE.

Among the subjects who experienced irAEs, 154 (7.4%) subjects received high dose corticosteroids.

Infusion-related Reactions

IRRs were reported in 35 (1.7%) subjects. Most of the events were Grade 1 or Grade 2 in severity. Five (0.2%) subjects experienced Grade ≥ 3 IRRs.

Analysis of AESI by SMQ and PT

Immune-related TEAEs

Immune-mediated lung disease

Immune-mediated lung disease occurred in 4.9% of subjects, including Grade 3, 4 or 5 in 1.2%, 0.2%, and 0.3% of subjects, respectively. 2.5% of subjects received high-dose corticosteroid treatment. Immune-mediated lung disease led to discontinuation in 1.3% of subjects. 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 related lung disease led to discontinuation in 1.3% of patients.

Immune-mediated Colitis

Immune-mediated colitis occurred in 2.0% of subjects, including Grade 3 in 0.6% of subjects and Grade 5 in < 0.1% of subjects. 0.7% of subjects received high-dose corticosteroid treatment. Immune-mediated colitis led to discontinuation in 0.2% of subjects. 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 related colitis led to discontinuation in 0.2% of patients.

Immune-mediated Hepatitis

Hepatitis occurred in 0.8% of subjects, including Grade 3 in 0.3% of subjects, Grade 4 in 0.1% of subjects, and Grade 5 in 0.1% of subjects. 0.4% of subjects received high-dose corticosteroid treatment. 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. Hepatitis led to discontinuation in 0.3% of subjects. Abnormal liver function led to discontinuation in 0.2% of patients.

Immune-mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis and renal dysfunction occurred in 3.0% of subjects, including Grade 3 in 0.3% of subjects and Grade 4 in < 0.1% of subjects. 0.4% of subjects received high-dose corticosteroid treatment. Immune-mediated nephritis and renal dysfunction led to discontinuation in 0.2% of subjects.

Immune-mediated Endocrinopathies

Hypothyroidism

Hypothyroidism occurred in 11.7% of subjects, including Grade 3 in 0.2% of subjects. 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. 6.7% of subjects received thyroid hormone replacement therapy. < 0.1% subjects discontinued serplulimab due to hypothyroidism.

Hyperthyroidism

Hyperthyroidism occurred in 6.7% of subjects, 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 subjects 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.

Diabetes mellitus/hyperglycaemia

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. Diabetes mellitus/hyperglycaemia led to discontinuation in < 0.1% of patients.

Immune-mediated Skin Adverse Reactions

Immune-mediated skin adverse reactions occurred in 7.8% of subjects, including Grade 3 in 0.8% of subjects, Grade 4 in < 0.1% of subjects, and Grade 5 in < 0.1% of subjects. 1.2% of subjects received high-dose corticosteroid treatment. 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 adverse reactions led to discontinuation in 0.5% of subjects.

Immune related pancreatitis

Immune related 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 related pancreatitis led to discontinuation in 0.2% of patients.

Immune related myocarditis

Immune related 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 related myocarditis led to discontinuation in 0.3% of patients.

Immune related uveitis

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

Other immune related adverse reactions

Other clinically significant immune related adverse reactions reported in patients who received serplulimab were as follows. Severe or fatal cases have been reported for some of these adverse reactions.

Blood and lymphatic system: anaemia, leukopenia, thrombocytopenia, neutropenia.

Nervous system: immune mediated encephalitis, neuropathy peripheral, epilepsy, encephalopathy, peripheral sensorimotor neuropathy.

Eye disorders: vision blurred.

Cardiac/vascular: acute coronary syndrome, myocardial infarction, cardiac failure, cardiotoxicity, troponin increased, cardiac function test abnormal.

Respiratory, thoracic and mediastinal: dyspnoea, chronic obstructive pulmonary disease, respiratory failure.

Gastrointestinal: mouth ulceration, vomiting, proctitis, upper gastrointestinal haemorrhage.

General disorders and administration site conditions: asthenia, fatigue, pyrexia.

Other: panic disorder, abnormal behaviour, cholangitis acute, sepsis, peritonitis, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, n-terminal prohormone brain natriuretic peptide increased, blood cholesterol increased, electrolyte imbalance, chronic kidney disease, urinary tract inflammation.

Infusion-related Reactions

Infusion-related reactions occurred in 1.7% of subjects, including Grade 3 in 0.1% of subjects and Grade 4 in 0.1% of subjects. 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 subjects discontinued serplulimab due to infusion-related reactions.

Laboratory Abnormalities

Grade ≥ 3 laboratory abnormality were infrequent. 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.

Adverse drug reactions (ADRs)

ADRs Based on All-cause AE Frequency

The frequencies of ADRs listed are based on all causality assessment for AE frequency, identified in 985 subjects from HLX10-005-SCLC301 & HLX10-002-NSCLC301 & HLX10-007-EC301 studies.

The most common ADRs (incidence ≥ 10%, maximum 10 PTs) based on all-cause AE frequency 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 hyperlipidaemia (27.4%).

The most common Grade ≥ 3 ADRs (incidence ≥ 5%) based on all-cause AE frequency were neutropenia (42.7%), leukopenia (22.5%), anaemia (21.5%), thrombocytopenia (13.7%), hyponatraemia (7.4%), and hypokalaemia (5.2%). hThe most common serious ADRs (incidence ≥ 2%) based on all-cause AE frequency were thrombocytopenia (8.3%), leukopenia (5.6%), neutropenia (5.6%), pneumonia (4.7%), anaemia (4.1%), and pneumonitis (3.4%). hThe most common immune-mediated ADRs (incidence ≥ 1.5%) based on all-cause AE frequency 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%). (ADRs leading to

discontinuation of serplulimab based on all-cause AE frequency occurred in 6.6% of subjects. The most common ADR leading to treatment discontinuation (incidence ≥ 1.0%) was pneumonitis (1.3%). (ADRs Based on Serplulimab-related AE Frequency

The frequencies of ADRs are based on serplulimab-related AE frequency identified in 985 subjects from HLX10-005-SCLC301 & HLX10-002-NSCLC301 & HLX10-007-EC301 studies.

The most common ADRs (incidence ≥ 10%) based on serplulimab-related AE frequency were anaemia (32.5%), neutropenia (29.1%), leukopenia (28.5%), thrombocytopenia (22.0%), hypothyroidism (20.1%), nausea (18.1%), alanine aminotransferase increased (16.2%), aspartate aminotransferase increased (14.6%), asthenia (14.4%), decreased appetite (14.4%), hyperthyroidism (12.9%), vomiting (11.8%) hyperlipidaemia (10.9%), and hypoproteinaemia (10.6%).

The most common Grade ≥ 3 ADRs (incidence ≥ 5%) based on serplulimab-related AE frequency were neutropenia (14.7%), leukopenia (9.0%), anaemia (8.2%), and thrombocytopenia (5.6%).

ADRs leading to discontinuation of serplulimab based on serplulimab-related AE frequency occurred in 6.2% of subjects. The most common ADR leading to treatment discontinuation (incidence ≥ 1.0%) was pneumonitis (1.3%).

Serious adverse event/deaths/other significant events

Deaths – Pivotal study (ASTRUM-007)

Table 56: HLX10-007-EC301: Summary of TEAEs Leading to Death by SOC and PT (SS)

System organ class (SOC) Preferred term (PT)	a. Received placebo + chemotherapy throughout (N = 168)		b. Received serplulimab + chemotherapy throughout (N = 374)		c. Subjects with alternated medication (N = 8)		d. Received serplulimab (b and c combined) (N = 382)		e. Total (N = 550)	
	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)
TEAEs leading to death [1]	22	22 (13.1%)	47	38 (10.2%)	0	0	47	38 (9.9%)	69	60 (10.9%)
General disorders and administration site conditions	7	7 (4.2%)	13	13 (3.5%)	0	0	13	13 (3.4%)	20	20 (3.6%)
Disease progression	3	3 (1.8%)	7	7 (1.9%)	0	0	7	7 (1.8%)	10	10 (1.8%)
Death	3	3 (1.8%)	5	5 (1.3%)	0	0	5	5 (1.3%)	8	8 (1.5%)
Sudden cardiac death	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Sudden death	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8	8 (4.8%)	6	6 (1.6%)	0	0	6	6 (1.6%)	14	14 (2.5%)
Malignant neoplasm progression	7	7 (4.2%)	3	3 (0.8%)	0	0	3	3 (0.8%)	10	10 (1.8%)
Neoplasm progression	0	0	2	2 (0.5%)	0	0	2	2 (0.5%)	2	2 (0.4%)
Tumour haemorrhage	1	1 (0.6%)	1	1 (0.3%)	0	0	1	1 (0.3%)	2	2 (0.4%)

Respiratory, thoracic and mediastinal disorders	1	1 (0.6%)	8	7 (1.9%)	0	0	8	7 (1.8%)	9	8 (1.5%)
Immune-mediated lung disease	0	0	4	3 (0.8%)	0	0	4	3 (0.8%)	4	3 (0.5%)
Respiratory failure	0	0	2	2 (0.5%)	0	0	2	2 (0.5%)	2	2 (0.4%)
Choking	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Pneumonitis	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Pulmonary embolism	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Infections and infestations	2	2 (1.2%)	6	5 (1.3%)	0	0	6	5 (1.3%)	8	7 (1.3%)
Pneumonia	2	2 (1.2%)	2	2 (0.5%)	0	0	2	2 (0.5%)	4	4 (0.7%)
Septic shock	0	0	4	3 (0.8%)	0	0	4	3 (0.8%)	4	3 (0.5%)
Cardiac disorders	1	1 (0.6%)	6	5 (1.3%)	0	0	6	5 (1.3%)	7	6 (1.1%)
Cardiopulmonary failure	1	1 (0.6%)	2	2 (0.5%)	0	0	2	2 (0.5%)	3	3 (0.5%)
Immune-mediated myocarditis	0	0	3	2 (0.5%)	0	0	3	2 (0.5%)	3	2 (0.4%)
Myocardial infarction	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Gastrointestinal disorders	2	2 (1.2%)	4	4 (1.1%)	0	0	4	4 (1.0%)	6	6 (1.1%)
Gastrointestinal haemorrhage	1	1 (0.6%)	1	1 (0.3%)	0	0	1	1 (0.3%)	2	2 (0.4%)
Upper gastrointestinal haemorrhage	0	0	2	2 (0.5%)	0	0	2	2 (0.5%)	2	2 (0.4%)
Haematemesis	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Oesophageal fistula	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Nervous system disorders	1	1 (0.6%)	1	1 (0.3%)	0	0	1	1 (0.3%)	2	2 (0.4%)
Cerebral haemorrhage	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Cerebral infarction	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Metabolism and nutrition disorders	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Acidosis	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Skin and subcutaneous tissue disorders	0	0	2	1 (0.3%)	0	0	2	1 (0.3%)	2	1 (0.2%)
Immune-mediated dermatitis	0	0	2	1 (0.3%)	0	0	2	1 (0.3%)	2	1 (0.2%)

Notes: AEs were coded according to MedDRA 26.1 [1] TEAE was defined as an AE that occurred or was worsened on or after the first dose of the study drug (C1D1), till 90 days after the last dose of the study drug or the start of a new anti-tumor therapy (whichever occurred first). Data cut-off date: 2023-01-09

Deaths considered treatment related

Table 57: HLX10-007-EC301: Summary of Serplulimab/Placebo-related TEAEs Leading to Death by SOC and PT (SS)

System organ class (SOC) Preferred term (PT)	a. Received placebo + chemotherapy throughout (N=168)		b. Received serplulimab + chemotherapy throughout (N=374)		c. Subjects with alternated medication (N=8)		d. Received serplulimab (b and c combined) (N=382)		e. Total (N=550)	
	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)
Serplulimab/placebo-related TEAEs leading to death [1][2]	2	2 (1.2%)	19	11 (2.9%)	0	0	19	11 (2.9%)	21	13 (2.4%)
Respiratory, thoracic and mediastinal disorders	0	0	6	5 (1.3%)	0	0	6	5 (1.3%)	6	5 (0.9%)
Immune-mediated lung disease	0	0	4	3 (0.8%)	0	0	4	3 (0.8%)	4	3 (0.5%)
Pneumonitis	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Respiratory failure	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Cardiac disorders	0	0	4	3 (0.8%)	0	0	4	3 (0.8%)	4	3 (0.5%)
Immune-mediated myocarditis	0	0	3	2 (0.5%)	0	0	3	2 (0.5%)	3	2 (0.4%)
Cardiopulmonary failure	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
General disorders and administration site conditions	1	1 (0.6%)	2	2 (0.5%)	0	0	2	2 (0.5%)	3	3 (0.5%)
Death	1	1 (0.6%)	2	2 (0.5%)	0	0	2	2 (0.5%)	3	3 (0.5%)
Infections and infestations	0	0	4	3 (0.8%)	0	0	4	3 (0.8%)	4	3 (0.5%)
Septic shock	0	0	4	3 (0.8%)	0	0	4	3 (0.8%)	4	3 (0.5%)
Gastrointestinal disorders	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Upper gastrointestinal haemorrhage	0	0	1	1 (0.3%)	0	0	1	1 (0.3%)	1	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Tumour haemorrhage	1	1 (0.6%)	0	0	0	0	0	0	1	1 (0.2%)
Skin and subcutaneous tissue disorders	0	0	2	1 (0.3%)	0	0	2	1 (0.3%)	2	1 (0.2%)
Immune-mediated dermatitis	0	0	2	1 (0.3%)	0	0	2	1 (0.3%)	2	1 (0.2%)

[1] TEAE was defined as an AE that occurred or was worsened on or after the first dose of the study drug (C1D1), till 90 days after the last dose of the study drug or the start of a new anti-tumor therapy (whichever occurred first). [2] A drug-related AE was defined as an AE whose relationship to serplulimab/placebo was (1 = related, 2 = possibly related, and 5 = unknown) or missing. Data cut-off date: 2023-01-09

Table 58: Pooled Safety Population: Summary of Serplulimab-related TEAEs Leading to Death (part of table 2.5-19)

SOC PT	< RP2D/3D Monotherapy (N=7)	< RP2D/3D Other Combination (N=3)	< RP2D/3D Total (N=10)	≥ RP2D/3D Monotherapy (N=285)	≥ RP2D/3D Chemotherapy Combination (N=1364)	≥ RP2D/3D Other Combination (N=427)	≥ RP2D/3D 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%)

TESAEs

Table 59: HLX10-007-EC301: Summary of HLX10/Placebo-related TESAEs with an Incidence ≥ 1% by SOC and PT (SS)

System organ class (SOC) Preferred term (PT)	a. Received placebo + chemotherapy throughout (N=168)		b. Received serplulimab + chemotherapy throughout (N=374)		c. Subjects with alternated medication (N=8)		d. Received serplulimab (b and c combined) (N=382)		e. Total (N=550)	
	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)
Serplulimab/placebo-related TESAEs with an incidence ≥ 1% [1][2]	18	11 (6.5%)	74	40 (10.7%)	1	1 (12.5%)	75	41 (10.7%)	93	52 (9.5%)
Investigations	7	3 (1.8%)	51	24 (6.4%)	1	1 (12.5%)	52	25 (6.5%)	59	28 (5.1%)
Platelet count decreased	1	1 (0.6%)	30	18 (4.8%)	1	1 (12.5%)	31	19 (5.0%)	32	20 (3.6%)
White blood cell count decreased	1	1 (0.6%)	12	12 (3.2%)	0	0	12	12 (3.1%)	13	13 (2.4%)
Neutrophil count decreased	5	2 (1.2%)	9	9 (2.4%)	0	0	9	9 (2.4%)	14	11 (2.0%)
Blood and lymphatic system disorders	5	3 (1.8%)	10	10 (2.7%)	0	0	10	10 (2.6%)	15	13 (2.4%)
Anaemia	5	3 (1.8%)	10	10 (2.7%)	0	0	10	10 (2.6%)	15	13 (2.4%)
Respiratory, thoracic and mediastinal disorders	0	0	11	8 (2.1%)	0	0	11	8 (2.1%)	11	8 (1.5%)
Immune-mediated lung disease	0	0	11	8 (2.1%)	0	0	11	8 (2.1%)	11	8 (1.5%)
Infections and infestations	2	2 (1.2%)	2	2 (0.5%)	0	0	2	2 (0.5%)	4	4 (0.7%)
Pneumonia	2	2 (1.2%)	2	2 (0.5%)	0	0	2	2 (0.5%)	4	4 (0.7%)
Cardiac disorders	2	2 (1.2%)	0	0	0	0	0	0	2	2 (0.4%)
Cardiac failure	2	2 (1.2%)	0	0	0	0	0	0	2	2 (0.4%)
Gastrointestinal disorders	2	2 (1.2%)	0	0	0	0	0	0	2	2 (0.4%)
Oesophageal fistula	2	2 (1.2%)	0	0	0	0	0	0	2	2 (0.4%)

Notes: AEs were coded according to MedDRA 26.1 [1] TEAE was defined as an AE that occurred or was worsened on or after the first dose of the study drug (C1D1), till 90 days after the last dose of the study drug or the start of a new anti-tumor therapy (whichever occurred first). [2] A drug-

related AE was defined as an AE whose relationship to HLX10/placebo was (1 = related, 2 = possibly related, and 5 = unknown) or missing. Data cut-off date: 2023-01-09

Laboratory findings

Haematology

Haematological and biochemical laboratory abnormalities were observed, including decreases in white blood cells, neutrophils, platelets and haemoglobin, as well as increases in liver enzymes and creatinine.

Urinalysis

Urinalysis abnormalities were observed, including proteinuria.

Thyroid Function

Thyroid function abnormalities were observed.

Cardiac Marker

Increases in cardiac markers were observed.

Pancreatic Enzyme

Increases in pancreatis enzyme were observed.

Vital Signs

No clinically relevant changes in vital signs were observed between the two groups.

Physical Examination

No clinically relevant finding for physical examination were reported.

Electrocardiogram

12-lead ECG

QT prolongation was reported infrequently.

Electrocardiogram: Pooled Safety Population

In the pooled safety population, QTcF prolongation was observed, with 2.5% of subjects having > 500 ms and 10.6% showing increases >60 ms from baseline.

Safety in special populations

Intrinsic Factors

Paediatric Use

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

Geriatric Use

Table 60 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
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 analyzed 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 creatinine or creatinine clearance (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 alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin was found on serplulimab CL based on a popPK analysis in patients with mild (bilirubin [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.

Immunological events

HLX10-001

The first-in-human (FIH) study HLX10-001 was dose-finding and dose expansion study initiated in 2018 which included an evaluation of immunogenicity. The study included a dose-finding cohort assessing intravenous administration of 0.3 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg Q2W doses as well as a dose-expansion cohort assessing 200mg Q2W, 300mg Q3W, 400mg Q4W and 600mg Q6W administered intravenously. In the HLX10-001 study, the assay used to detect ADAs was an electrochemiluminescence immunoassay (BTM-2497) which had an assay sensitivity of 37.9 ng/mL.

Table 61. Summary of the number and percentage of patients with at least one positive ADA by dose level. (Interim analysis)

Study	Treatment Group	ADA positive n (%)
Dose finding cohorts	0.3 mg/kg Q2W (N = 3)	1 (33.3)
	1 mg/kg Q2W (N = 4)	0
	3 mg/kg Q2W (N = 6)	0
	10 mg/kg Q2W (N = 16)	0
	Total (N = 29)	1 (3.4)
Dose expansion cohorts	200 mg Q2W (N = 9)	2 (22.2)
	300 mg Q3W (N = 9)	7 (77.8)
	400 mg Q4W (N = 10)	10 (100)
	Total (N = 28)	19 (67.9)

Table 62. Summary of the number and percentage of treatment-emergent ADA positive patients (Interim analysis)

Study	Treatment Group	ADA positive n (%)
Dose finding cohorts	0.3 mg/kg Q2W (N = 3)	1 (33.3)
	1 mg/kg Q2W (N = 4)	0
	3 mg/kg Q2W (N = 6)	0
	10 mg/kg Q2W (N = 16)	0
	Total (N = 29)	1 (3.4)
Dose expansion cohorts	200 mg Q2W (N = 9)	2 (22.2)
	300 mg Q3W (N = 9)	4 (44.4)
	400 mg Q4W (N = 10)	4 (40.0)
	Total (N = 28)	10 (35.71)

According to the clinical overview, a small number of subjects developed ADA status across these cohorts.

ADA responses were transient. No neutralising antibodies were detected. Clearance and PK values were similar for subjects with and without ADAs.

Table 63: Summary of the number and percentage of subjects with at least one positive ADA by dose level. (Final analysis)

Study	Treatment Group	ADA positive n (%)
Dose finding cohorts	0.3 mg/kg Q2W (N = 3)	1 (33.3)
	1 mg/kg Q2W (N = 4)	0
	3 mg/kg Q2W (N = 6)	0
	10 mg/kg Q2W (N = 16)	0
	Total (N = 29)	1 (3.4)
Dose expansion cohorts	200 mg Q2W (N = 9)	1 (11.1)
	300 mg Q3W (N = 9)	4 (44.4)
	400 mg Q4W (N = 10)	5 (50.0)
	600 mg Q6W (N=9)	2 (22.2)
	Total (N = **37**)	12 (32.4)

Table 64: Summary of the number and percentage of treatment-emergent ADA positive subjects (Final analysis)

Study	Treatment Group	ADA positive n (%)
Dose finding cohorts	0.3 mg/kg Q2W (N = 3)	1 (33.3)
	1 mg/kg Q2W (N = 4)	0
	3 mg/kg Q2W (N = 6)	0
	10 mg/kg Q2W (N = 16)	0
	Total (N = 29)	1 (3.4)
Dose expansion cohorts	200 mg Q2W (N = 9)	1 (11.1)
	300 mg Q3W (N = 9)	4 (44.4)
	400 mg Q4W (N = 10)	1 (10.0)
	600 mg Q6W(N=9)	1 (11.1)
	Total (N = **37**)	7 (18.9)

At the time of the interim analysis, a provisional ADA assay cut point was applied, which was subsequently updated and validated using in-study patient samples for the final analysis.

Differences in ADA incidence between the interim and final analyses were attributable to the application of a final, validated in-study ADA assay cut points.

HLX10-007-EC301

A subject's ADA status was defined as treatment emergent if at least one of the subject's samples was positive for ADA or NAb after receiving serplulimab treatment. Overall, the ADA positive rate and NAb positive rate after the administration of serplulimab were 5.8% (22/382) and 0.3% (1/382), respectively.

No apparent impact of immunogenicity on safety was observed.

Immunogenicity - Pooled Safety Population

Table 65: Summary of immunogenicity results for serplulimab in pooled safety population

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.

Immunological Status – Pivotal study HLX10-007-EC301

In the serplulimab group, a total of 22 (5.8%) subjects tested positive for ADA after serplulimab treatment. The safety profile of ADA-positive patients was comparable to that of the overall serplulimab-treated population.

Safety related to drug-drug interactions and other interactions

Serplulimab is a humanised monoclonal antibody and 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

Table 66: Summary of Adverse Events Leading to Drug Discontinuation

	a. Received placebo + chemotherapy throughout (N=168)		b. Received HLX10 + chemotherapy throughout (N=374)		c. Subjects with alternated medication [1] (N=8)		d. Received HLX10 (b and c combined) (N=382)		e. Total (N=550)	
	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)
TEAEs leading to drug discontinuation	47	30 (17.9%)	111	79 (21.1%)	0	0	111	79 (20.7%)	158	109 (19.8%)
Grade ≥ 3 TEAEs leading to drug discontinuation [3]	16	11 (6.5%)	41	36 (9.6%)	0	0	41	36 (9.4%)	57	47 (8.5%)
HLX10/placebo-related TEAEs leading to drug discontinuation [4]	16	11 (6.5%)	46	37 (9.9%)	0	0	46	37 (9.7%)	62	48 (8.7%)
HLX10/placebo-related Grade ≥ 3 TEAEs leading to drug discontinuation [3][4]	8	5 (3.0%)	18	16 (4.3%)	0	0	18	16 (4.2%)	26	21 (3.8%)
HLX10/placebo-related TEAEs leading to [4]										
HLX10/placebo discontinuation	8	5 (3.0%)	23	21 (5.6%)	0	0	23	21 (5.5%)	31	26 (4.7%)
Cisplatin discontinuation	7	4 (2.4%)	24	19 (5.1%)	0	0	24	19 (5.0%)	31	23 (4.2%)
5-FU discontinuation	8	7 (4.2%)	21	19 (5.1%)	0	0	21	19 (5.0%)	29	26 (4.7%)

Pooled safety population

TEAEs leading to serplulimab discontinuation in the pooled safety population TEAEs leading to serplulimab discontinuation occurred in 242 (11.6%) subjects.

A total of 150 (7.2%) subjects experienced serplulimab-related TEAEs leading to serplulimab discontinuation.

Discontinuations were mainly associated pneumonitis.

TEAEs Leading to Dose Modification

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

Adverse Events Leading to Drug Interruption

Pivotal ASTRUM-007 study

A total of 299 (54.4%) subjects experienced TEAEs leading to drug interruption, including 219 (57.3%) subjects in the serplulimab group and 80 (47.6%) subjects in the control group. Grade ≥ 3 TEAEs leading to drug interruption, occurred in 116 (30.4%) subjects in the serplulimab group and 38 (22.6%) subjects in the control group. Interruptions were mainly associated with haematological toxicities and immune-related adverse events, including immune-mediated lung disease.

Pooled safety population

TEAEs leading to serplulimab interruption occurred in 1052 (50.4%) subjects.

A total of 651 (31.2%) subjects experienced serplulimab-related TEAEs leading to the serplulimab interruption. Interruptions were mainly associated with haematological toxicities.

Post marketing experience

Serplulimab was first authorised in China on 30 March 2022 for indications in NSCLC, SCLC and ESCC combined with chemotherapy. Serplulimab has been approved in the EU for ES-SCLC in combination with carboplatin and etoposide on February 3, 2025 (EU/1/24/1870/001).

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

Adverse Events from Marketing Experience

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

2.5.1. Discussion on clinical safety

The safety of serplulimab for the targeted indication is based primarily on the safety data from the pivotal trial ASTRUM-007 with 382 patients exposed to serplulimab. The study was conducted in China and enrolled only Asian patients.

Supportive pooled safety data from a total of 10 clinical trials with serplulimab in subjects with 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.

The dose of serplulimab given in the pivotal ASTRUM-007 study was 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Adverse drug reactions were handled by treatment interruption or discontinuation and/or symptomatic treatment (e.g., glucocorticoids).

Immune-related adverse events (irAEs) and infusion related reactions (IRRs) were adverse events of special interest (AESI) for serplulimab. The total incidence of immune-related TEAEs is in line with the overall results in the pooled safety population (irAEs: 34.2%, see below). The most common irAEs by PT were hypothyroidism, hyperthyroidism and rash.

In the pooled safety population, 7.4% received high-dose corticosteroids to treat irAEs. In the pivotal study, however, the use of high-dose corticosteroids to handle adverse reactions was not stated, however given upon request to be 7.1% in the serplulimab arm compared to 1.8% in the placebo arm. The high-dose corticosteroid use in serplulimab-treated patients were mainly driven by immune-mediated lung disease (2.6% vs. 0.6%) and abnormal liver function (1.0% vs 0), and the median duration of high-dose corticosteroid treatment was 1.22 months vs. 0.46 months in the serplulimab and placebo groups, respectively.

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

In the pivotal study, IRRs were reported more frequently in placebo treated patients (1.8%) than patients receiving serplulimab (1.0%), however overall, the incidence was low, consistent with the pooled safety population (1.7%; ≥Grade 3: 0.2%).

The MAH has submitted a consolidated SmPC based on the consolidated safety database from variation procedures EMA/VR/0000284402 and EMA/VR/0000282407.

In the pivotal ASTRUM-007 study, almost all (~99.5%) of the patients reported at least one TEAE, of which the majority were considered serplulimab/placebo-related (serplulimab: 83.8% vs. placebo: 78.0%). The rates of Grade ≥3 TEAEs were 64.7% and 61.3% (serplulimab/placebo-related: 35.6% and 28.0%), respectively.

The overall safety profiles for the two treatment groups in the pivotal study are quite similar, with only somewhat higher frequencies of TESAEs (39.3% vs 32.1%) and Grade ≥3 TESAEs (29.8% vs 25.6%). There were more patients with TESAEs related to any study drug (26.7% vs 17.9%) in the serplulimab treated patients, and the difference was in part caused by SAEs considered related to serplulimab/placebo (20.2% vs 13.1%), however, cisplatin and 5-FU contributed, as well (TESAEs cisplatin-related: 22.3% vs. 17.3%, and TESAEs 5-FU-related: 22.0% vs. 16.1%).

There were slightly more TEAEs leading to permanent discontinuation in serplulimab treated patients than in the placebo treated patients (20.7% vs. 17.9%, considered serplulimab/placebo-related in 9.7% vs. 6.5%, respectively). Serplulimab/placebo-related TEAEs led to serplulimab/placebo discontinuation almost twice as frequent (5.5%) in serplulimab treated patients compared to the placebo treated patients (3.0%).

There were also more TEAEs leading to drug interruptions in serplulimab treated patients than in placebo treated patients (57.3% vs. 47.6%, serplulimab/placebo-related: 35.9% vs. 23.8%, respectively). Almost all cases of serplulimab/placebo interruption were due to serplulimab/placebo-related TEAEs (34.3% vs. 21.4%, respectively), however, serplulimab/placebo-related TEAEs also led to interruption of the chemotherapy treatment (cisplatin: 24.1% vs. 17.9% and 5-FU: 28.3% vs. 20.8%). The large proportion of TEAEs reported as related to serplulimab in placebo treated patients (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.

There were more TEAEs reported as leading to death in the control arm (13.1%) than in the serplulimab arm (9.9%); however, a higher proportion of deaths were considered treatment-related in serplulimab arm [2.9% (11 patients) vs 1.2% (2 patients)], mostly driven by immune-related AEs (in 6 of 11 cases in the serplulimab arm).

There is no apparent trend in the cause of death due to AEs in the pivotal trial. The MAH has confirmed that none of the additional fatal cases were considered related to serplulimab/placebo.

The most common TEAEs were haematological events which occurred more frequently in the serplulimab arm and were often considered treatment-related. TEAEs considered attributable to serplulimab included hypothyroidism, hyperthyroidism and rash, which are common immune-mediated AEs reported for serplulimab and other immune checkpoint inhibitors.

The SAEs with incidence ≥2% occurring at a similar rate or more frequently in the serplulimab arm than the placebo arm were platelet count decreased (6.8% vs. 1.8%), anaemia (5.0% vs. 2.4%), white blood cell count decreased (4.5% vs. 0.6%), pneumonia (4.2% vs. 3.6%), neutrophil count decreased (3.9% vs. 2.4%), pneumonitis (2.1% vs. 1.2%), and immune-mediated lung disease (2.1% vs. 0).

QT prolongation

No dedicated QT studies were performed, which is acceptable for monoclonal antibodies with low potential for direct ion channel interactions. In the pivotal trial, small imbalances in QT-related events were observed; however, the absolute numbers were low. No SAEs that were related to increases in QTc were identified. Arrythmia is already listed as a very common ADR in section 4.8 of the SmPC.

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 were ≥ 65 years. In this population, higher frequencies of Grade ≥3 TEAEs, SAEs and deaths were observed compared to patients <65 years. The incidence of irAEs was similar between age groups (35.4% vs 32.2%). Some of the observed

differences could be related to the chemotherapy backbone (e.g. haematological toxicities). No dose adjustments are considered necessary in elderly patients, based on PK analyses. A statement has been added in section 5.1 of the SmPC clarifying that data for patients ≥ 75 of age are too limited to draw conclusions on this population.

Gender

No dedicated gender analysis has been submitted for the pivotal trial or the updated pooled safety population. Available data from the MAA indicated no consistent or robust differences in safety profile between men and women across analyse. No further analyses are considered necessary.

Immunogenicity

Anti-drug antibodies (ADA) were assessed in both the phase 1 HLX10-001 and pivotal phase 3 study HLX10-007-EC301.

Differences in ADA incidence between interim and final analyses were attributed to the use of the updated validated assay cut-points.

The immunogenicity of serplulimab was evaluated in 382 patients treated with serplulimab at 3 mg/kg Q2W in the ASTRUM-007 trial. A total of 24 patients (6.3%) were ADA positive at any visit, of whom 22 patients (5.8%) were treatment-emergent ADA positive, defined as at least one post-baseline ADA positive. 19 (5.1%) subjects that received serplulimab + chemotherapy throughout the study were detected positive for ADA at least once at visits after administration, and 1 (0.3%) subject was detected positive for NAb at least once; 3 (37.5%) subjects with alternated medication were detected positive for ADA at least once at visits after administration, with negative NAb detected in the further test.

In dose escalation and dose expansion study HLX10-001, the overall percentage of treatment-emergent ADA for dose finding cohorts and dose expansion cohorts were 3.4% and 18.9% respectively. All the ADA positive samples were detected with negative NAbs.

Serplulimab showed a low potential immunogenicity risk. There were no apparent altering or clinically meaningful differences in PK, pharmacodynamics and safety profiles in individuals that were ADA positive compared to ADA negative. However, data is still limited.

2.5.2. Conclusions on clinical safety

The reported safety profile is overall consistent with the known safety profile of serplulimab and comparable to other PD-1/PD-L1 inhibitors. The observed safety profile reflects the contribution of both the chemotherapy backbone (predominantly haematological toxicities) and serplulimab (immune-related events). In general, irAEs were of low-grade nature and manageable with dose interruptions or corticosteroids. An increased incidence of serious adverse events, treatment discontinuations and treatment-related events was observed in the serplulimab arm, including events related to immune-mediated toxicity; however, the overall safety profile is considered manageable and in line with the class effects.

Overall, the safety profile of serplulimab in combination with cisplatin and 5-FU 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.

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.

Safety concerns

Table 67 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:

No significant changes have been made to the package leaflet. The variation is intended to extend the already existing marketing authorisation of Hetronifly (serplulimab) with a new indication.

Accordingly, package leaflet is amended. The changes do not affect key messages for the safe use of the medicinal product. The design, layout and format of the package leaflet will not be affected.

Thus, the justification for not performing a full user testing is considered acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication is serplulimab in combination with fluoropyrimidine- and platinum-based chemotherapy, for the first-line treatment of adult patients with unresectable, locally advanced, recurrent or metastatic oesophageal squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 5.

The proposed dose is 3.0 mg/kg serplulimab every 2 weeks until disease progression or unacceptable toxicity. Dose escalation or reduction of serplulimab is not recommended.

3.1.2. Available therapies and unmet medical need

Patients with esophageal cancer that is metastatic or unresectable and cannot be treated with curative-intent chemoradiotherapy have a poor prognosis. Survival in clinical trials has historically been <1 year; however, the use of immune checkpoint inhibitors with chemotherapy has recently improved survival for this patient group (ESMO guideline, 2022).

According to the ESMO Clinical Practice Guideline on esophageal cancer (2022), first-line chemotherapy (ChT) with a platinum- fluoropyrimidine doublet is recommended as a standard treatment for advanced untreated esophageal SCC. Dose-reduced oxaliplatin-capecitabine is an alternative option for patients who are unsuitable for full-dose chemotherapy. However, in recent years, new trials of immune checkpoint inhibitors have confirmed their efficacy in combination with chemotherapy. Consequently, ESMO (2022, with update from February 2025) now recommends first-line treatment with a platinum-fluoropyrimidine doublet for patients who are PD-L1 negative, low or unknown. For the first-line treatment of PD-L1 positive patients the recommended treatment is pembrolizumab-ChT for PD-L1 CPS ≥ 10; nivolumab-ChT or nivolumab-ipilimumab (lower grade of recommendation compared with nivolumab-ChT due to risk of early progression and death for patients treated without ChT) for PD-L1 TPS ≥1% and tislelizumab-ChT for PD-L1 TAP score ≥5%. Even though also toripalimab-ChT has been authorised in the EU, ESMO does not, at present, provide any recommendation due to the treatment being evaluated in Chinese patients only.

ESCC is a severe and life-threatening condition and there remains a need for additional treatment options, including for patients with tumours characterised by different levels of PD-L1 expressions.

3.1.3. Main clinical studies

The MAH has provided one pivotal study called ASTRUM-007 (HLX10-007-EC301) to support the current application.

ASTRUM-007 was a randomised (2:1), placebo-controlled, multicenter, double-blind phase 3 clinical trial comparing the efficacy and safety of treatment with serplulimab in combination with cisplatin + 5-FU versus placebo in combination with cisplatin + 5-FU when given as first-line treatment in adult patients with unresectable, locally advanced, recurrent or metastatic ESCC.

The trial included 551 patients recruited in China, with 368 patients randomised to serplulimab in combination with chemotherapy and 183 patients to placebo in combination with chemotherapy.

The dual primary endpoints were PFS assessed by IRRC according to RECIST v1.1 and OS. Secondary endpoints included ORR, DOR and safety.

Randomisation was stratified by PD-L1 expression level (1 ≤ CPS < 10 vs. CPS ≥10), age (≥ 65 years vs. < 65 years), and disease status (locally advanced vs. distant metastasis).

The data presented within this application were based on a primary analysis with data cut-off date of 15 April 2022 as well as an updated analysis with data cut-off date of 09 January 2023. The study is completed.

3.2. Favourable effects

Patients whose tumours expressed PD-L1 with a CPS ≥ 5 (DCO 09 January 2023), based on post-hoc analysis:

For OS the stratified HR was 0.60 (95% CI: 0.460, 0.786). Median OS was 16.5 months (95% CI: 13.83, 19.48) for serplulimab in combination with cisplatin + 5-FU vs. 10.7 months (95% CI: 8.67, 13.90) for placebo in combination with cisplatin +5-FU.

Median IRRC-assessed PFS according to RECIST v.1.1 was 6.9 months (95% CI: 5.75, 8.08) for serplulimab in combination with cisplatin + 5-FU vs. 5.3 months (95% CI: 4.14, 5.78) for placebo in combination with cisplatin + 5-FU, stratified HR was 0.57 (95% CI: 0.435, 0.752).

Results for the ITT population are presented for context:

- Primary analysis (DCO 15 April 2022)

The dual primary endpoint OS was met with a stratified HR of 0.68 (95% CI: 0.529 – 0.871, p = 0.0020). Median OS was 15.3 months (95% CI: 13.96, 18.63) for serplulimab in combination with cisplatin + 5-FU vs. 11.8 months (95% CI: 9.69, 14.03) for placebo in combination with cisplatin + 5-FU.

The dual primary endpoint IRRC-assessed PFS (per RECIST v.1.1) was also met with a stratified HR of 0.60 (95% CI: 0.476, 0.747, *P* < 0.0001). Median PFS was 5.8 months (95% CI: 5.68, 6.93) for serplulimab in combination with cisplatin + 5-FU vs. 5.3 months (95% CI: 4.30, 5.55) for placebo in combination with cisplatin + 5-FU.

- Updated analysis (DCO 09 January 2023)

For OS the stratified HR was 0.70 (95% CI: 0.568 – 0.862). Median OS was 14.8 months (95% CI: 13.11, 16.66) for serplulimab in combination with cisplatin + 5-FU vs. 11.2 months (95% CI: 9.69, 13.86) for placebo in combination with cisplatin + 5-FU.

Median IRRC-assessed PFS (per RECIST v.1.1) was 6.5 months (95% CI: 5.75, 7.10) for serplulimab in combination with cisplatin + 5-FU vs. 5.3 months (95% CI: 4.30, 5.55) for placebo in combination with cisplatin + 5-FU, stratified HR 0.58 (95% CI: 0.465, 0.716).

Results of the main secondary endpoints (PFS by Investigator, ORR and DOR) were supportive of the primary endpoint.

3.3. Uncertainties and limitations about favourable effects

- Only patients enrolled in China were included in the study; therefore, generalisability of the study results to the European population remains uncertain.
- Patients > 75 years were excluded from the study; therefore, no efficacy data are available in this population. A sentence has been added in section 5.1 of the SmPC stating that data for patients ≥ 75 years of age are too limited to draw conclusions on this population.

- The primary analysis for the ITT population was based on patients with CPS ≥1 while the results in the agreed indication (patients with CPS ≥5) were based on post-hoc subgroup analyses.

3.4. Unfavourable effects

Almost all patients reported at least one TEAE in both treatment groups. Grade ≥ 3 TEAEs occurred in 64.7% of patients in the serplulimab group and 61.3% in the placebo group.

TEAEs leading to death were reported more frequently in the control arm (13.1%) than in the serplulimab arm (9.9%). However, a higher proportion of these were considered related to study treatment in the serplulimab group (2.9%) compared to the control arm (1.2%), mainly driven by immune-related AEs.

Serious TEAEs were reported more frequently in the serplulimab arm than in the control arm (39.3% vs. 32.1%). Similarly, serious TEAEs considered related to study treatment occurred more often in the serplulimab treated patients than in the control group (26.7% vs 17.9%).

TEAEs leading to treatment discontinuation were reported more frequently in the serplulimab group than in the control group (20.7% vs. 17.9%), including TEAEs considered related to study treatment (5.5% vs 3.0%).

TEAEs leading to treatment interruption occurred more frequently in the serplulimab arm than in the control arm (57.3% vs. 47.6%), mainly due to serplulimab associated adverse events.

The most frequently reported adverse events were consistent with the known safety profile of the chemotherapy backbone and included haematological and gastrointestinal toxicities.

Immune-related adverse events (irAEs), which are expected with PD-1 inhibitors, were reported more frequently in the serplulimab arm than in the control arm (37.2% vs 19.0%). Infusion related reactions (IRR) were uncommon in both treatment groups.

The pooled safety database including 2086 patients did not reveal new safety concerns, and the safety profile of serplulimab was consistent with that observed in the pivotal study and with the known class effects of PD-1 inhibitors.

3.5. Uncertainties and limitations about unfavourable effects

3.6. Effects Table

Table 68 Effects Table for serplulimab in combination with fluoropyrimidine- and platinum-based chemotherapy for the first-line treatment of adult patients with unresectable, locally advanced, recurrent or metastatic esophageal squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 5

Effect	Short description	Unit	Serplulimab + cisplatin + 5-FU	Placebo + cisplatin + 5-FU	Uncertainties / Strength of evidence	References
Favourable Effects (PD-L1 CPS ≥5; N= 343, data cut-off 09 January 2023)						
OS	Duration of survival from randomisation to death	Months (median) (95% CI)	16.5 (13.83, 19.48)	10.7 (8.67, 3.90)	Data only from Asian patients	ASTRUM-007- study

Effect	Short description	Unit	Serplulimab + cisplatin + 5-FU	Placebo + cisplatin + 5-FU	Uncertainties / Strength of evidence	References
	regardless of cause				No efficacy data from patients > 75 years Double-blind study Updated analysis consistent with primary analysis Supplemental PFS analysis based on treatment policy supports the primary PFS analysis	CSR
		HR (95% CI)	0.60 (0.460, 0.786)			
PFS - by IRRC RECIST v1.1.	Duration of survival without progression from randomisation to first record of PD or death (whichever occurred first)	Months (median) (95% CI)	6.9 (5.75, 8.08)	5.3 (4.14, 5.78)		
		HR (95% CI)	0.57 (0.435, 0.752)			
Unfavourable Effects (treatment emergent adverse events, all-cause incidences) **ASTRUM-007 (DCO 09 Jan 2023) – Safety set, n=550**						
		Unit	**Ser+CFU N=382**	**PLA+CFU N=168**	>99% experienced AEs in both arms	
Anaemia		%	84.6	79.8	The majority of these adverse events are likely related to chemotherapy, taking into consideration the quite similar incidences in the two treatment arms and the known safety profile of the	
Nausea		%	65.7	64.3		
White blood cell count decreased		%	59.4	61.3		

Effect	Short description	Unit	Serplulimab + cisplatin + 5-FU	Placebo + cisplatin + 5-FU	Uncertainties / Strength of evidence	References
					chemotherapy backbone.	
Immune-mediated TEAEs		%	37.2	19.6		
SAEs		%	39.3	32.1		
Grade 3/4 AEs		%	64.7	61.3		
TEAEs leading to death		%	9.9	13.1		
Ser-related TEAEs leading to death		%	2.9	1.2		
TEAEs leading to drug interruption		%	57.3	47.6		
tr TEAE leading to ser/PLA interruption		%	34.3	21.4		
TEAEs leading to drug discontinuation		%	20.7	17.9		
tr TEAEs leading to Ser/PLA discontinuation		%	5.5	3.0		

Abbreviations: Ser: Serplulimab, CFU: cisplatin and 5-fluorouracil, PLA: placebo, 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

Initially the MAH sought approval for an indication restricted to patients whose tumours express PD-L1 with a CPS ≥ 1.

Post-hoc subgroup analyses of OS and PFS according to PD-L1 CPS did not demonstrate a clear OS benefit for patients with CPS < 5 (difference in median OS of 0.8 months in favour of the control group; HR 0.88, 95% CI: 0.64, 1.24). In this subgroup, the Kaplan-Meier curves did not separate in favour of the serplulimab group until approximately 14 months.

In contrast, for patients with CPS ≥ 5, a clinically relevant improvement in OS was observed, with a difference in median OS of 5.8 months (HR 0.60, 95% CI: 0.460, 0.786) in favour of serplulimab + ChT. In this subgroup, the Kaplan-Meier curves separated in favour of the serplulimab group.

These findings indicate that the benefit in OS observed in the overall ITT population is primarily driven by patients having the highest PD-L1 CPS.

Of note, the primary efficacy analysis (DCO 15 April 2022) of the ASTRUM-007 study showed a statistically significant OS benefit of 3.5 months (HR 0.68, 95% CI: 0.529 – 0.871) in favour of serplulimab + ChT as first line treatment of adult patients with unresectable, locally advanced, recurrent or metastatic ESCC expressing PD-L1 with a CPS ≥ 1.

The updated analysis (DCO 09 January 2023) confirmed this result (gain of 3.6 months in favour of serplulimab + ChT; HR 0.70, 95% CI: 0.568 – 0.862).

The OS results were supported by the statistically significant dual primary endpoint PFS (assessed by IRRC, based on RECIST v1.1). However, the magnitude of the PFS benefit was limited (median difference 0.5 months in the primary analysis [HR 0.60, 95% CI: 0.476, 0.747] and 1.2 months in the updated analysis [HR 0.58, 95% CI: 0.465, 0.716].

The higher number of missing imaging examinations in the serplulimab group compared with the control group, together with the handling of intercurrent events using a hypothetical strategy, may have influenced the estimation of PFS relative to the more robust OS estimate. A supplementary sensitivity analysis applying a treatment policy strategy supported the primary PFS analysis, which is considered reassuring. In addition, it is noted that relatively small gains in PFS have been also reported in ESCC studies with other PD-L1/PD-1 inhibitors.

The results for patients with CPS<5 (representing approximately 40% of the study population), showed an overall limited clinical efficacy. While the limitations of post-hoc subgroup analyses are acknowledged, the approach is considered consistent with previous CHMP decisions for other PD-L1/PD-1 inhibitors in ESCC (Tevimbra**,** EMEA/H/C/005919/II/0003; Opdivo, EMEA/H/C/003985/II/010) and with the principles outlined in the relevant guideline on subgroup analyses (Guideline on the investigation of subgroups in confirmatory clinical trials).

Furthermore, given the biological plausibility of a PD-L1-dependent treatment effect, the benefit of serplulimab in combination with chemotherapy is considered insufficiently demonstrated in patients with CPS <5. Therefore, the indication is restricted to ESCC patients whose tumours express PD-L1 with a CPS ≥5.

The study population was enrolled in China only, which introduces uncertainty regarding the generalisability of the results to the European population. Considering that the incidence of ESCC is substantially lower in Western countries compared to Asia, clinical experience in European patients is limited. However, when taking into account the extensive experience with PD-1/PD-L1 inhibitors in this indication, the absence of data in European patients is not considered to preclude the applicability of the study results to the target population.

The safety profile of serplulimab is consistent with that of other PD-1/PD-L1 inhibitors approved for the same indication. Immune-related AEs, which are known class effects, can be serious and potentially life-threatening; however, they are generally manageable and adequately addressed through warnings and precautions in the SmPC, including treatment interruption and discontinuation. No new safety signals were identified.

The pooled safety data were mainly obtained in an Asian population, with only Asian patients included in the pivotal study in ESCC. 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

Based on the available efficacy data showing a statistically significant and clinical relevant PFS and OS benefit, and the reported safety profile of serplulimab, which is consistent with other immune checkpoint inhibitors used for the same indication and considered manageable, the benefit-risk is considered positive in the agreed indication for the first-line treatment of adult patients with unresectable, locally advanced, recurrent or metastatic esophageal squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 5.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit-risk of serplulimab in combination with fluoropyrimidine- and platinum-based chemotherapy for the first-line treatment of adult patients with unresectable, locally advanced, recurrent or metastatic oesophageal squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 5 is positive.

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 changes:

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, in combination with fluoropyrimidine- and platinum-based chemotherapy, the first-line treatment of adult patients with unresectable, locally advanced, recurrent or metastatic oesophageal squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 5 for HETRONIFLY, based on results from study HLX10-007-EC301; this is a randomized, double-blind, multi-center, phase III clinical study comparing the clinical efficacy and safety of HLX10 or placebo combined with chemotherapy in first-line treatment of locally advanced/metastatic esophageal squamous cell carcinoma (ESCC) patients. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.

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.