EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Hetronifly (serplulimab)
Treatment of small cell lung cancer
EU/3/22/2731

Sponsor: Henlius Europe GmbH

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance	Serplulimab
Other names	Hetronifly, Serplulimab
International Non-Proprietary Name	Serplulimab
Tradename	Hetronifly
Orphan condition	Treatment of small cell lung cancer
Sponsor's details:	Henlius Europe GmbH Sternstraße 67 Pempelfort 40479 Duesseldorf North Rhine-Westphalia Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Henlius Europe GmbH
COMP opinion	10 November 2022
EC decision	09 December 2022
EC registration number	EU/3/22/2731
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Eva Skovlund / Aaron Sosa Mejia
Applicant	Henlius Europe GmbH
Application submission	02 March 2023
Procedure start	23 March 2023
Procedure number	EMA/H/C/006170/0000
Invented name	Hetronifly
Therapeutic indication	Hetronifly in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) Further information can be found in the European public assessment report (EPAR) on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Hetronifly
CHMP opinion	19 September 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Brigitte Schwarzer-Daum
Sponsor's report submission	12 October 2023
COMP discussion and adoption of list of questions	10-12 September 2024
Oral explanation	09 October 2024
COMP opinion (adoption via written procedure)	23 October 2024
Appeal to the COMP opinion procedural history	
COMP rapporteur(s)	Jana Mazelova / Bozenna Dembowska-Baginska
Appeal submission	15 November 2024

Appeal oral explanation	03 December 2024
COMP final opinion	05 December 2024

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2022 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing serplulimab was considered justified based on clinical data from patients affected by the condition which indicate improved survival of the proposed product in combination with chemotherapy;
- the condition is chronically debilitating and life threatening due to its rapid progression and the development of widespread metastases, with a poor 5-year overall survival;
- the condition was estimated to be affecting approximately 1.2 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing serplulimab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data in treatment-naïve patients with extensive stage small cell lung cancer indicating a higher rate of responses and improved survival when combined with other chemotherapeutic agents authorised for the condition (cisplatin, etoposide). Indirect comparison to additional authorised treatments (atezolizumab and durvalumab) also compare favourably with respect to overall response rate and survival. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing serplulimab as an orphan medicinal product for the orphan condition: treatment of small cell lung cancer.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Small-cell lung cancer (SCLC) is an aggressive neuroendocrine carcinoma known for its rapid growth, poor differentiation, and poor prognosis. Representing about 15% of all lung cancers (Wéber et al 2023), it is linked to tobacco exposure with up to 9 in 10 cases being caused by smoking (Wéber et al

2023). Genetic mutations, particularly the loss of function in tumour suppressor genes (TP53 and RB1) and MYC oncogene amplification, drive aggressiveness, leading to rapid tumour growth, poor genomic stability, and replication stress (Rudin et al., 2021; Saltos et al., 2020). Environmental factors have also been suggested as risk factors, though evidence remains limited (Rudin et al., 2021). Pathophysiologically, SCLC is characterized by rapid growth, high metastatic potential, and resistance to apoptosis, often associated with paraneoplastic syndromes. It overexpresses VEGF, promoting angiogenesis and a poor prognosis (Montanino et al., 2021). Histologically, SCLC appears as irregular masses in the central lung with distinctive features like cytoplasmic globules and the Azzopardi effect (Raso et al., 2021).

The World Health Organization (WHO) classifies SCLC as a "small cell carcinoma" within the neuroendocrine carcinoma category. The tumour-node-metastasis (TNM) staging system further classifies SCLC into "limited stage" (LS), "extensive stage" (ES), and "recurrent," based on tumour size, lymph node involvement, and distant metastasis (Arriola et al., 2022; Dingemans et al., 2021). In addition to the TNM staging system, the Veterans Administration Lung Study Group (VALG) staging system is used due to its simplicity and clinical utility. According to the European Society for Medical Oncology (ESMO) guidelines, SCLC is divided into two histological subtypes: pure SCLC (P-SCLC) and combined SCLC (C-SCLC), with the latter involving additional non-small cell lung cancer (NSCLC) components (Li et al., 2022).

Clinically, SCLC typically presents with centrally located tumours in the major airways and extensive metastatic spread. Patients often remain asymptomatic until advanced disease stages due to the rapid growth of the tumour. If symptoms are present, they are typically recent and may include cough, dyspnoea, haemoptysis, wheezing, upper body oedema, and laryngeal nerve compression leading to vocal cord paralysis (Rudin et al., 2021). The 2021 ESMO guidelines recommend a diagnostic approach involving smoking history, physical examination, blood tests, and imaging studies (Dingemans et al., 2021).

For the context of this application, SCLC has been recognized as a distinct subtype of lung cancer characterized by its rapid progression, unique genetic alterations, and specific clinical and histopathological features. However, without implications to the sponsor, a shift in classification for future applications has occurred following the 2022 World Health Organization (WHO) classification of Epithelial Neuroendocrine Neoplasms by anatomic site. The COMP now considers both Small Cell Lung Carcinoma (SCLC) and Large Cell Neuroendocrine Carcinoma (LCNEC) of the lung as poorly differentiated neuroendocrine carcinomas (NECs). Consequently, new applications for orphan designation will be grouped under the broader category of "Pulmonary Neuroendocrine Carcinoma."

The proposed therapeutic indication “Hetronifly in combination with carboplatin and etoposide is indicated for the first -line treatment of adult patients with extensive -stage small cell lung cancer (ES-SCLC)” falls within the scope of the designated orphan condition “Treatment of small cell lung cancer”.

Intention to diagnose, prevent or treat

The medical plausibility is confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor discusses the condition to be life threatening characterized by aggressive growth and early metastasis to distant sites, resulting in most patients being diagnosed with extensive-stage disease. The median overall survival (mOS) of SCLC is just 18.4 months, despite available treatments

(Jones et al., 2020). Patients with limited stage (LS) SCLC, as defined by the tumour, node, metastasis (TNM) staging system, have a 5-year OS rate of 20-25%, whereas patients with extensive stage (ES) have a 5-year OS rate of only 2% (Arriola et al., 2022; Tsiouprou et al., 2019). Stage II and III SCLC patients also have an increased risk of death compared to patients with Stage I (Zeng et al., 2021).

Although not mentioned specifically by the sponsor, SCLC is known to be chronically debilitating due to paraneoplastic syndromes.

The COMP considers that the condition is chronically debilitating and life threatening due to its rapid progression and the development of widespread metastases, with a poor 5-year overall survival.

Number of people affected or at risk

At the time of maintenance of the orphan designation in 2022, the COMP concluded that the condition was estimated to be affecting approximately 1.5 per 10,000 persons in the European Union (EU).

The sponsor uses two conservative methods to estimate the prevalence of small cell lung cancer (SCLC) in the EU to support the maintenance of the orphan designation. Both methods focus on calculating the number of living SCLC patients in 2023.

Method 1 calculates prevalence based on the incidence rate of SCLC and overall survival (OS) rates. The EU-27 lung cancer incidence rate in 2022 is reported as 71.5 per 100,000 people (ECIS). Given that SCLC comprises about 13% of lung cancer cases, the incidence rate for SCLC is calculated at 9.3 per 100,000. The 1-year and 3-year relative survival rates for SCLC are 36.66% and 16.47%, respectively. Using these rates, the sponsor estimates the number of new SCLC cases from 2019 to 2023 by multiplying the EU population (448.4 million, EUROSTAT 2023) by the SCLC incidence rate, yielding approximately 41,701 new cases annually. To estimate the prevalence, the sponsor considers survivors from different time periods: those diagnosed from 2019-2020 are projected to have a 3-year survival rate of 16.47%, resulting in 13,736 survivors; those from 2021-2022 are calculated using a 1-year survival rate of 36.66%, leading to 30,575 survivors; and all 41,701 patients diagnosed in 2023 are assumed to be alive for a conservative estimate. Adding these groups, the estimated total prevalence reaches 86,012, equating to 1.9 cases per 10,000 people in the EU.

Method 2 relies on the number of new cases and deaths from lung cancer. In 2022, there were 319,236 new lung cancer cases and 252,582 deaths in the EU, leaving an estimated 66,654 new lung cancer survivors each year (ECIS). With SCLC representing 13% of lung cancer cases, the estimated annual number of new SCLC survivors is 8,665. Given that the 5-year OS rate for SCLC is under 10%, the total number of surviving SCLC patients would be significantly less than 43,325 (8,665 × 5). This results in a prevalence estimate of approximately 1 per 10,000 people.

Both methods estimate the SCLC prevalence in the EU to be well below the threshold for orphan drug designation, which is 5 per 10,000 people. Method 1 estimates a prevalence of 1.9 per 10,000, while Method 2 suggests a prevalence of around 1 per 10,000. The prevalence estimate presented by the sponsor is based on comparable data sources, but with a focus on more recent data, to those used in the estimation accepted for the orphan designation 2022.

The COMP therefore came to the same conclusion for this procedure, that SCLC affects approximately 1.5 in 10,000 people in the EU, a figure that lies in between the two new estimates provided by the sponsor.

Note: Due to the recent shift in classification by the 2022 World Health Organization (WHO) for Epithelial Neuroendocrine Neoplasms by anatomic site, the accepted condition for classification purposes will change. Small Cell Lung Carcinoma (SCLC) and Large Cell Neuroendocrine Carcinoma

(LCNEC) of the lung are now considered poorly differentiated neuroendocrine carcinomas (NECs) and are grouped under the broader category of "Pulmonary Neuroendocrine Carcinoma." As a result, for future orphan designation applications, the calculation of disease prevalence will need to reflect this updated classification, encompassing all relevant subtypes within the "Pulmonary Neuroendocrine Carcinoma" category.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Several products have been authorised for the treatment of small cell lung cancer (SCLC), including etoposide, cisplatin, carboplatin, atezolizumab, durvalumab, cyclophosphamide, topotecan, doxorubicin, and vincristine (Table 1).

Table 1. List of medicines for the treatment of SCLC according to ESMO 2021 and their marketing authorisation status in the EU

Medicinal product	Authorisation status for the treatment of SCLC in the EU
Cisplatin	Authorised
Carboplatin	Authorised
Etoposide	Authorised
Atezolizumab	Authorised
Durvalumab	Authorised
Topotecan	Authorised
Irinotecan	Not authorised specifically for the treatment of SCLC*
Gemcitabine	Not authorised specifically for the treatment of SCLC*
Cyclofosfamide	Authorised
Doxorubicin	Authorised
Vincristine	Authorised
Lurbinectedin	Not authorised specifically for the treatment of SCLC*

*According to current internal information available at time of submission

According to clinical guidelines (Dómine et al., 2020; Früh et al., 2013), the preferred first-line chemotherapy regimen is cisplatin or carboplatin plus etoposide (with options for atezolizumab, durvalumab, irinotecan, gemcitabine, or topotecan). For second-line and subsequent treatments, the approach depends on the timing of relapse:

- Relapse >3 months: Reinduction with the same regimen is preferred.
- Relapse <3 months: Switch to topotecan or a combination of cyclophosphamide/doxorubicin/vincristine.
- For patients whose disease progresses during treatment or within three months, inclusion in clinical trials is recommended.

PD-L1 Inhibitors for ES-SCLC

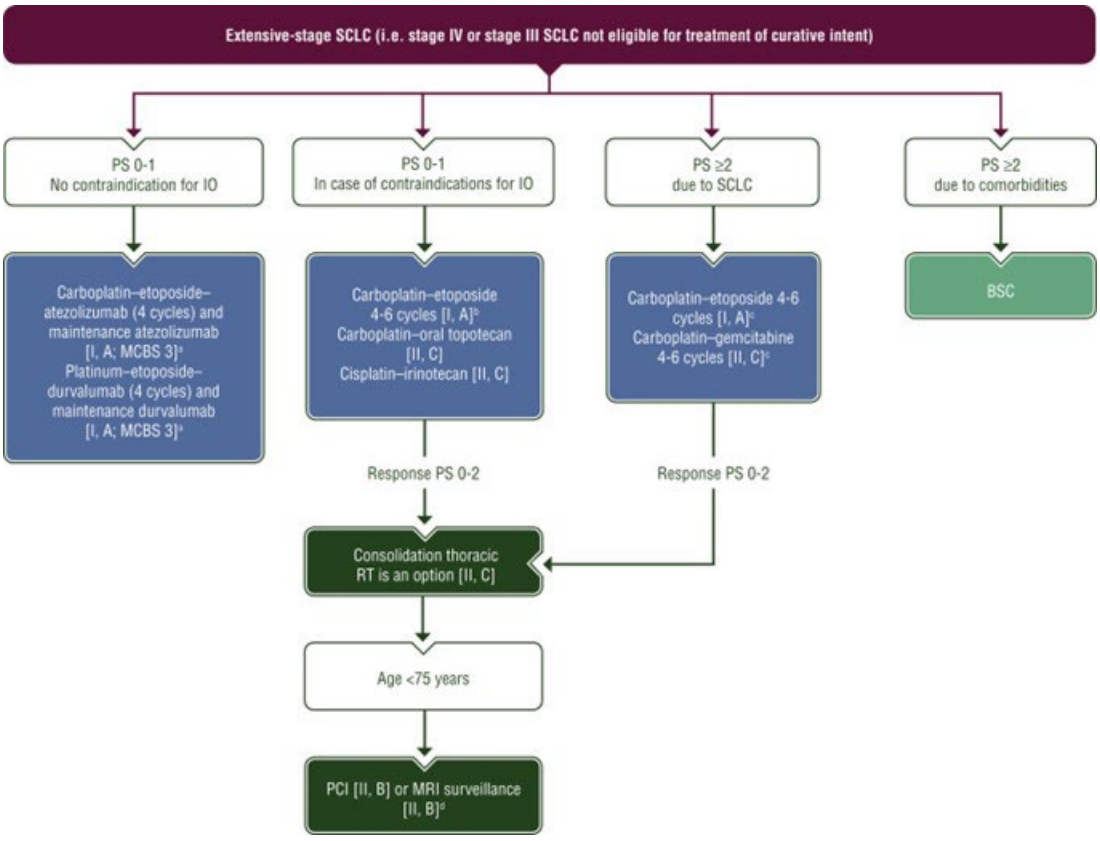
Atezolizumab (Tecentriq) and durvalumab (Imfinzi) are two PD-L1 inhibitors authorised for the treatment of extensive-stage SCLC (ES-SCLC):

- Tecentriq: In combination with carboplatin and etoposide for first-line treatment of adult patients with ES-SCLC.
- Imfinzi: In combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with ES-SCLC.

The sponsor positions the product for treatment-naïve adult ES-SCLC patients. As outlined in the ESMO Clinical Practice Guidelines (Figure 1), the standard of care for first-line treatment of ES-SCLC includes platinum chemotherapy (carboplatin or cisplatin) with etoposide, potentially combined with Atezolizumab (Tecentriq) or durvalumab (Imfinzi) (NCCN guidelines version 1.2023).

In conclusion, cisplatin, carboplatin, etoposide, atezolizumab and durvalumab are all considered satisfactory methods of treatment relevant for a discussion on significant benefit of serplulimab in the target SCLC patient population. In contrast, topotecan monotherapy, is indicated for the treatment of patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate. Therefore, it is not defined as satisfactory method and the demonstration of significant benefit is not required. Similarly, cyclophosphamide, doxorubicin, and vincristine are also deemed non-satisfactory methods at the present time as their use is limited to the second-line treatment settings rather than the first-line setting relevant to serplulimab.

Figure 1. ESMO Clinical Practice Guidelines for the diagnosis, treatment, and follow-up of ES-SCLC patients, detailing the recommended standard-of-care approaches (Dingemans et al., 2021).



Significant benefit

The sponsor did not seek protocol assistance from EMA regarding the evidence needed to demonstrate significant benefit of serplulimab over satisfactory methods of treatment for adult patients with extensive-stage small cell lung cancer (ES-SCLC).

The claim of significant benefit is based on the results from a Phase III study HLX10-005-SCLC301 (ASTRUM-005) to investigate efficacy and safety of serplulimab (HLX10) in combination with chemotherapy (Carboplatin- Etoposide) in previously untreated patients with ES-SCLC. A total of 585 subjects were randomized 2:1 to either HLX10 (4.5 mg/kg) + carboplatin (AUC=5) + etoposide (100 mg/m2), or placebo + carboplatin (AUC=5) + etoposide (100 mg/m2). Efficacy endpoints included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), duration of response (DOR).

The sponsor pursued two different approaches to establish the significant benefit of serplulimab over satisfactory methods of treatment:

- A comparative analysis against the combination of carboplatin and etoposide based on clinical data from the pivotal study HLX10-005-SCLC301 (Direct Comparison).
- Matching-adjusted indirect comparisons (MAIC) of efficacy outcomes (OS, PFS) across clinical studies, between participants treated with serplulimab in study HLX10-005-SCLC301 (ASTRUM-005) and participants treated with additional authorised treatments atezolizumab and durvalumab in their respective registrational studies (IMPOWER133 and CASPIAN) (Indirect Comparsions).

Direct comparison against carboplatin and etoposide

The overall survival (OS) analysis for the ITT population showed that, by database lock October 22, 2021, the HLX10 group had a median OS of 15.38 months (95% CI: 13.273, NA) compared to 10.91 months (95% CI: 9.955, 14.324) in the placebo group, with a hazard ratio (HR) of 0.63 (95% CI: 0.489, 0.818; p<0.001), indicating a 37% reduction in the risk of death for the HLX10 group. Progression-free survival (PFS) also favoured HLX10 (median 5.72 months vs. 4.34 months for placebo; HR 0.48, 95% CI: 0.383, 0.590; p<0.001).

The updated analysis with a longer follow-up duration (median 19.75 months) by June 13, 2022, confirmed these findings, showing a median OS of 15.80 months (95% CI: 14.127, 17.577) for the HLX10 group and 11.10 months (95% CI: 9.955, 12.353) for placebo, with a HR of 0.62 (95% CI: 0.496, 0.763; p<0.001) (Table 2, Figure 2). This represents a 38% reduction in the risk of death. The ORR and DOR also improved significantly with HLX10, confirming its clinical benefit.

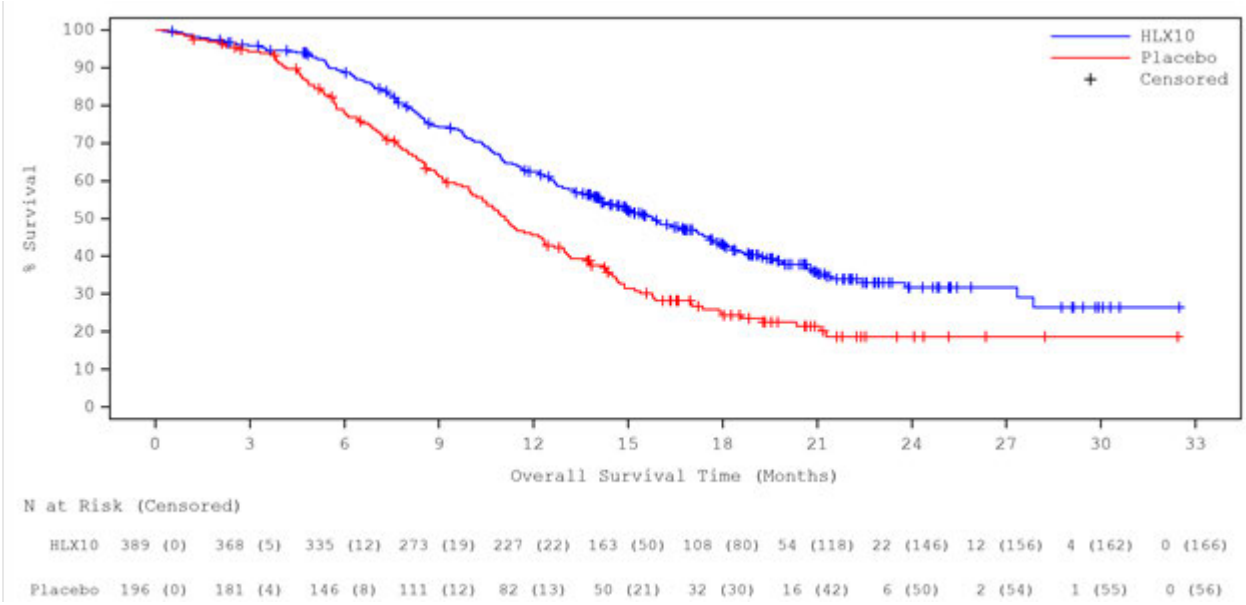
Subset analysis in the non-Asian population showed similar trends, with the HLX10 group consistently demonstrating longer OS and improved response rates compared to the placebo group, further supporting the efficacy of HLX10 in combination with chemotherapy for patients with ES-SCLC.

Table 2. Analysis of Overall Survival (ITT) (Data cut-off 13 June 2022)

Characteristic	**HLX10 (N=389)**	**Placebo (N=196)**	**Total (N=585)**
Number of Event (Deaths), n (%)	223 (57.3)	140 (71.4)	363 (62.1)
Number of Censor, n (%)	166 (42.7)	56 (28.6)	222 (37.9)
Alive	142 (36.5)	43 (21.9)	185 (31.6)
Lost to Follow-up	24 (6.2)	13 (6.6)	37 (6.3)
Overall Survival (Months)			
Median (95% CI) [1]	15.80 (14.127, 17.577)	11.10 (9.955, 12.353)	13.86 (12.649, 14.949)
Min, Max	0.2, 32.5	0.4, 32.4	0.2, 32.5
Stratified [2]			
Hazard Ratio (95% CI) [3]	0.62 (0.496, 0.763)		
p-Value [4]	<0.001		
Unstratified			
Hazard Ratio (95% CI) [3]	0.61 (0.497, 0.760)		
p-Value [4]	<0.001		
Survival Rate up to [5]			
3 Months	0.959 (0.933, 0.974)	0.944 (0.900, 0.968)	0.954 (0.933, 0.968)
6 Months	0.890 (0.854, 0.917)	0.780 (0.714, 0.832)	0.853 (0.821, 0.880)
9 Months	0.742 (0.695, 0.783)	0.611 (0.538, 0.677)	0.699 (0.659, 0.735)
12 Months	0.625 (0.573, 0.672)	0.456 (0.383, 0.526)	0.569 (0.527, 0.609)
15 Months	0.521 (0.469, 0.571)	0.314 (0.247, 0.383)	0.453 (0.410, 0.494)
18 Months	0.432 (0.378, 0.485)	0.251 (0.188, 0.319)	0.372 (0.330, 0.415)
21 Months	0.353 (0.297, 0.409)	0.215 (0.153, 0.284)	0.307 (0.264, 0.351)
24 Months	0.317 (0.256, 0.379)	0.187 (0.125, 0.259)	0.273 (0.227, 0.322)
27 Months	0.317 (0.256, 0.379)	0.187 (0.125, 0.259)	0.273 (0.227, 0.322)
30 Months	0.264 (0.184, 0.351)	0.187 (0.125, 0.259)	0.234 (0.173, 0.301)

[1] The Brookmeyer-Crowley method was used to construct the 95% CI for the median OS.
[2] Stratification factor: PD-L1 expression level (TPS < 1%, TPS ≥ 1%, not evaluable/ not available), brain metastasis (yes versus no), and age (≥ 65 years versus < 65 years).
[3] The hazard ratio and its 95% CI were estimated by (stratified/unstratified) Cox proportional hazards model. Efron's method was used to handle ties.
[4] The comparison of OS between the two arms was performed by a two-sided stratified/unstratified log-rank test.
[5] The standard error of the survival rate was calculated using Greenwood's formula.
The OS for patient 11009001 is censored since the month of death date is missing.

Figure 2. Kaplan-Meier Curve of Overall Survival. (Data cut-off 13 June 2022)



These findings can be considered sufficient to support the basis of significant benefit of serplulimab based on a clinically relevant advantage in terms of improved efficacy in comparison to the authorised combination chemotherapy (cisplatin, carboplatin, etoposide) regimen in ES-SCLC treatment naive patients.

Indirect comparison against atezolizumab and durvalumab

The sponsor conducted indirect comparisons of serplulimab efficacy against two authorized treatments for extensive-stage small cell lung cancer (ES-SCLC): atezolizumab and durvalumab. In these comparisons, individual patient data from the ASTRUM-005 trial are compared to aggregate data from either the IMPOWER133 (atezolizumab) or CASPIAN (durvalumab) trials, which studied anti-PD-L1 antibodies combined with platinum-based chemotherapy as first-line treatments for ES-SCLC.

- Study selection and design

The trials were selected since they were performed in a similar setting: similar: ES-SCLC indication, first-line therapy combining checkpoint inhibitors with chemotherapy, subjects aged >18 years with ECOG performance score 0 or 1, no prior systemic ES-SCLC treatment, and normal major organ functions. The selected studies, IMPOWER133 (atezolizumab) and CASPIAN (durvalumab), were randomized and included OS and PFS as primary endpoints. Serplulimab efficacy data comes from the ASTRUM-005 study, a Phase III, double-blinded trial where serplulimab plus chemotherapy significantly improved OS (HR 0.62, 95% CI: 0.496, 0.763).

- Outcome measures and methodology

The key outcome measures compared were OS and investigator-assessed PFS. Indirect treatment comparisons (ITC) were performed using both an anchored and an unanchored matching-adjusted indirect comparison (MAIC) methodology. The study populations were matched based on inclusion criteria, such as age, ECOG status, and disease characteristics, to handle cross-trial heterogeneity. The weights were computed according to the approach of Signorovitch et al. (2012). The estimated hazard ratios (HRs) for OS and PFS were then compared between the weighted individual patient data (IPD)

from ASTRUM-005 and the comparator aggregate data (AgD) from IMpower133 and CASPIAN, respectively, using the Bucher method (Bucher et al., 1997).

Baseline Characteristics differences between studies were adjusted for by re-weighting individual patient data (IPD) from ASTRUM-005 to match aggregated data from IMPOWER133 and CASPIAN. Seven baseline characteristics were considered: sex, age group, ECOG score, smoking status, brain metastasis, liver metastases, and race. While these seven covariates were generally considered relevant, not all of them were used as covariates in the ITCs. Further analyses refined the covariates to balance effective sample size and treatment effect modifiers.

- Results: primary and sensitivity analyses

Atezolizumab analysis (ASTRUM-005 vs. IMPOWER133): After matching, five characteristics were adjusted: age group, ECOG status, smoking status, brain metastasis, and liver metastases. Post-matching, PFS for serplulimab vs. atezolizumab showed HR 0.73 (95% CI: 0.53, 0.99), and OS showed HR 0.72 (95% CI: 0.51, 1.01) (Table 3). For sensitivity analysis using the non-anchored MAIC approach, similar trends were observed (Table 4).

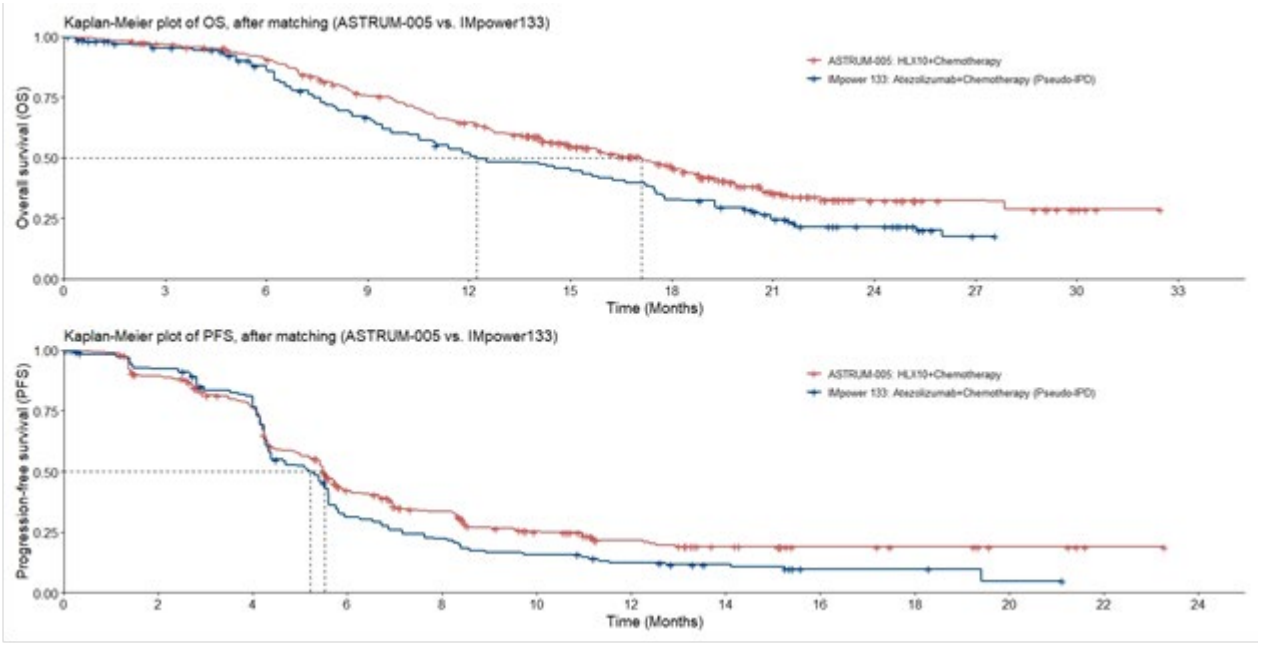
Table 3. Outcome Comparison in Anchored MAIC (ASTRUM-005 vs. IMpower133)

	Before Matching	**After Matching**
Interim Analysis Data (Cut-off Date: 22 October 2021)		
PFS		
HR (95% CI)	0.75 (0.56, 1.01)	0.73 (0.53, 0.99)
Updated Data (Cut-off Date: 13 June 2022)		
OS		
HR (95% CI)	0.81 (0.59, 1.11)	0.72 (0.51, 1.01)

Table 4. Outcome Comparison in Non-Anchored MAIC (ASTRUM-005 vs. IMpower133)

	Before Matching	**After Matching**
PFS		
HR (95% CI)	0.75 (0.56, 1.01)	Non-Anchored MAIC: 0.79 (0.64, 0.98)
OS		
HR (95% CI)	0.81 (0.59, 1.11)	Non-Anchored MAIC: 0.71 (0.56, 0.91)

Figure 3. Pseudo-IPD plot of OS/PFS, after matching (ASTRUM-005 vs. IMpower133) (unanchored MAIC)



Durvalumab analysis (ASTRUM-005 vs. CASPIAN): Four characteristics were adjusted: ECOG status, smoking status, brain metastasis, and liver metastases. Post-matching, PFS for serplulimab vs. durvalumab showed HR 0.70 (95% CI: 0.53, 0.94), and OS showed HR 0.78 (95% CI: 0.57, 1.05) (Table 5). For sensitivity analysis using the non-anchored MAIC approach, similar trends were observed (Table 6).

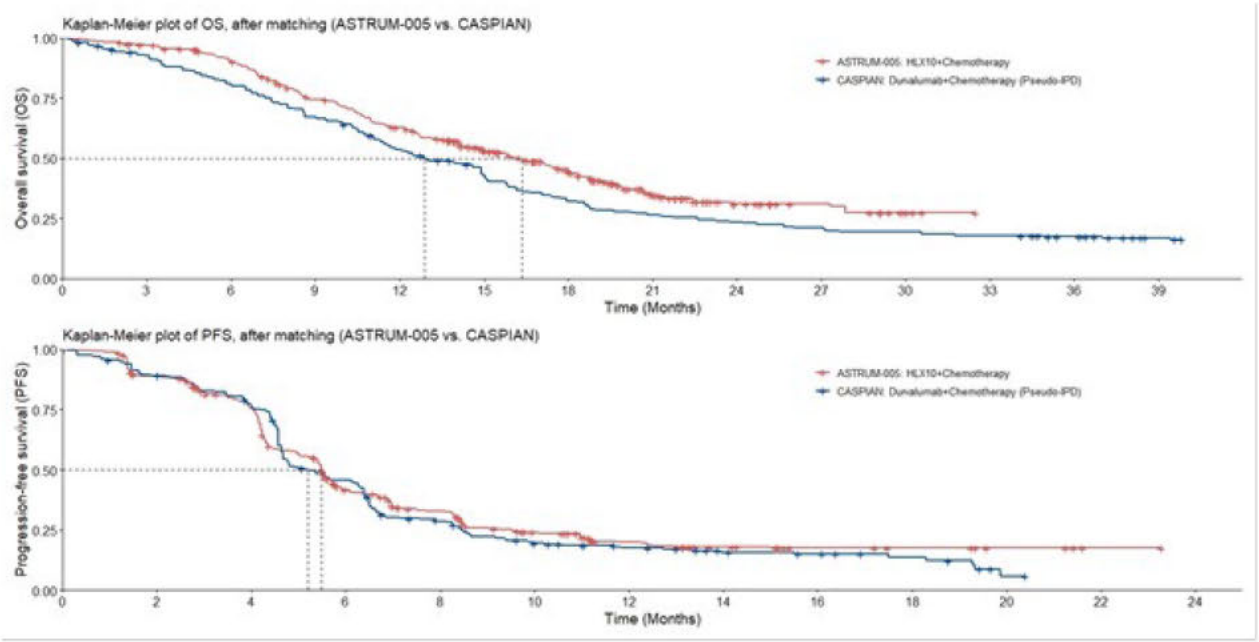
Table 5. Outcome Comparison in Anchored MAIC(ASTRUM-005 vs. CASPIAN)

	Before Matching	After Matching
Interim Analysis Data (Cut off Date: 22 October 2021)		
PFS		
HR (95% CI)	0.74 (0.57, 0.97)	0.70 (0.53, 0.94)
Updated Data (Cut-off Date: 13 June 2022)		
OS		
HR (95% CI)	0.87 (0.66, 1.15)	0.78 (0.57, 1.05)

Table 6. Outcome Comparison in Non-Anchored MAIC(ASTRUM-005 vs. CASPIAN)

	Before Matching	After Matching
PFS		
HR (95% CI)	0.74 (0.57, 0.97)	Non-Anchored MAIC: 0.94 (0.77, 1.15)
OS		
HR (95% CI)	0.87 (0.66, 1.15)	Non-Anchored MAIC: 0.75 (0.60, 0.92)

Figure 4. Pseudo-IPD plot of OS/PFS, after matching (ASTRUM-005 vs. CASPIAN) (unanchored MAIC).



Overall, the indirect comparisons between the ASTRUM-005 trial and the comparator studies IMpower133 and CASPIAN raise several methodological questions that need to be addressed in order to allow the interpretability and reliability of the findings. Key concerns include the lack of a comprehensive discussion of the difference between baseline characteristics in the selected trials, insufficient rationale for the chosen methodologies, and inadequate explanation of the statistical methods employed.

A primary concern is the incomplete reporting of baseline characteristics for the comparisons between ASTRUM-005 and both IMpower133 and CASPIAN. Providing a comprehensive table of these characteristics, both before and after the matching process, is essential for assessing the impact of adjustments. The absence of such information limits the ability to evaluate the comparability of the study populations and to understand potential sources of bias. Additionally, there is ambiguity in the handling of covariates, such as race, which is defined and utilized inconsistently across studies. Specifically, the categorization and handling of the Asian versus non-Asian variable, given that the majority of participants in ASTRUM-005 are Asian, lack sufficient justification. Moreover, the exclusion of pre-matching baseline characteristics and the choice of an Effective Sample Size (ESS) threshold of 60%, which is still considered low, are not well-supported by the provided documentation and require further explanation.

The methodological description is also insufficient as the combination of the Signorovitch and Bucher methods is not adequately explained and requires further justification. The rationale for using a non-anchored MAIC approach to derive pseudo-individual patient data (IPD) remains also unclear. Additionally, there is no discussion on the distribution of weights among matched subjects, which is critical to understanding the generalizability and robustness of the results.

In summary, the lack of comprehensive methodological details, clear justification for methodological choices, and the lack of thorough presentation of baseline characteristics raises concerns about the validity and reliability of the indirect comparison results between ASTRUM-005 and the comparator studies.

The COMP asked the sponsor to provide a detailed explanation of the methodology and data handling for the indirect comparison studies (ASTRUM-005 vs. IMPOWER133 and ASTRUM-005 vs. CASPIAN). This should include a more comprehensive presentation and discussion of the baseline characteristics

of the study populations, both before and after matching. Additionally, the sponsor is asked to provide a side-by-side comparison of all baseline characteristics for all three studies.

The sponsor is also asked to clarify the rationale behind the decision to combine the Signorovitch and Bucher methods for indirect comparisons. A detailed explanation of the assumptions underlying these indirect comparisons, and the sensitivity analyses is required, including a justification for selecting a non-anchored Matching-Adjusted Indirect Comparison approach.

Furthermore, additional justification is needed regarding the exclusion of pre-matching results and the chosen threshold for Effective Sample Size. The sponsor should also provide a detailed discussion on the weight distribution of matched subjects and its potential impact on the robustness and generalizability of the outcomes.

The sponsor provided additional data to address the COMP's concerns regarding the significant benefit.

Comments on sponsor's response to the COMP list of issues

Information provided by the company

The sponsor has presented clinical evidence from a Phase III randomized, double-blind, placebo-controlled trial demonstrating that Hetronifly (serplulimab), in combination with chemotherapy, significantly improves overall survival (OS) in in previously untreated patients with extensive-stage small cell lung cancer (ES-SCLC) as compared to chemotherapy alone (placebo). A total of 585 subjects were randomized 2:1 to either HLX10 (4.5 mg/kg) + carboplatin (AUC=5) + etoposide (100 mg/m2), or placebo + carboplatin (AUC=5) + etoposide (100 mg/m2). In the updated analysis, the trial showed a median OS of 15.80 months for Hetronifly compared to 11.10 months in the placebo group, with a hazard ratio (HR) of 0.62 (95% CI: 0.496, 0.763), confirming the efficacy of Hetronifly in this population. Forest plots document consistent survival benefits across a number of relevant subgroups defined by baseline characteristics including comparable effects between Asian and non-Asian patients. Secondary endpoints of PFS, ORR and DOR supported the claim of a positive effect of adding Hetronifly to chemotherapy in the respective indication.

There are two other checkpoint inhibitors, atezolizumab and durvalumab, approved in combination with chemotherapy for extensive-stage small cell lung cancer. Atezolizumab is combined with carboplatin and etoposide, while durvalumab is combined with etoposide and either carboplatin or cisplatin. In absence of head-to-head randomised controlled trials (RCTs), the sponsor used the following indirect comparison methodologies for the main comparisons of Hetronifly against atezolizumab and durvalumab: Bucher indirect treatment comparison (ITC), Anchored Matching-Adjusted Indirect Comparison (MAIC), and Non-Anchored MAIC. These methods were applied to compare the clinical endpoint progression-free survival (PFS) and overall survival (OS) - the latter was the primary endpoint in the clinical study, and it is considered the most relevant for comparison purposes.

MAIC is used in situations where individual patient data (IPD) are available for one trial and aggregate data for the comparators. This approach allows to adjust for differences between patient populations in the trials by re-weighting the patients in the trial with available IPD to match the aggregate distribution of selected baseline characteristics in the trial with aggregate data. Additionally, using the placebo arm from both the trial with and without IPD as an anchor (hence "anchored" comparison), the approach compares the relative effects of Hetronifly vs placebo with the relative effects of atezolizumab / durvalumab vs placebo. This aims to ensures that differences in prognostic variables between the trials, even if the respective variables are not used for the re-weighting, do not bias the indirectly estimated effect of Hetronifly compared to atezolizumab / durvalumab. Ultimately, the anchored MAIC estimates the relative effect of Hetronifly compared to atezolizumab / durvalumab in

the population of the trials without bias, if all the relevant predictive variables are included in the adjustment.

The Bucher ITC and the unanchored MAIC both rely on stronger assumptions, namely that the populations do not differ regarding prognostic and predictive variables (Bucher) or that all relevant prognostic and predictive variables have been included in the adjustment (unanchored) MAIC. Consequently, the anchored MAIC is considered the most appropriate method of the approaches presented by the sponsor for conducting an indirect treatment comparison.

The results of these indirect comparisons are provided. In Tables 7, 8, 9, 10, and 11 the sponsor provides a range of the indirect comparisons between Hetronifly and existing therapies - atezolizumab (based on the IMpower133 trial) and durvalumab (based on the CASPIAN trial) that use different sets of baseline variables for adjustment.

Additionally, the sponsor has provided a detailed methodological description of the selection of adjustment variables, including clinically relevant factors such as age, smoking status, ECOG performance status, and metastatic sites (brain and liver). Several analyses based in different sets of matching variables were presented as sensitivity analyses, and the distributions of baseline variables after the adjustment for the main analyses were presented (a complete list of the baseline characteristics of the ASTRUM-005 trial before and after matching that can be seen in Tables 12 and 13 below).

For variables not included in the main analysis (combination 1 of the adjustment variables), the table shows imbalances in the following variables: sex, race, disease stage, and tumour mutational burden. Sensitivity analyses including sex and disease stage were conducted, showing results consistent with the main analysis. For race, a sensitivity analysis including the variable resulted in a strongly reduced effective sample size (ESS), raising questions about the interpretability of the comparison. However, since the overall survival outcomes were comparable in the Asian and Non-Asian population, based on the results of the ASTRUM-005 trial, matching for race was not considered critical.

Table 7 (Table 11 from the sponsor responses to the List of Questions): Results of Indirect Comparison.

	Standard ITC	Anchored MAIC (primary analysis)	Non-Anchored MAIC (supplementary analysis)
ASTRUM-005 vs. IMpower133			
PFS (per Investigator)			
HR (95% CI)	0.75 (0.56, 1.01)	0.73 (0.53, 0.99)	0.79 (0.64, 0.98)
OS			
HR (95% CI)	0.81 (0.59, 1.11)	0.72 (0.51, 1.01)	0.71 (0.56, 0.91)
ASTRUM-005 vs. CASPIAN			
PFS (per Investigator)			
HR (95% CI)	0.74 (0.57, 0.97)	0.70 (0.53, 0.94)	0.94 (0.77, 1.15)
OS			
HR (95% CI)	0.87 (0.66, 1.15)	0.78 (0.57, 1.05)	0.75 (0.60, 0.92)

Note: Standard ITC used Bucher's standard indirect comparison method, while Anchored MAIC and Non-Anchored MAIC used Signorovitch's MAIC method.

Table 8 (Table 9 from the sponsor responses to the List of Questions): Summary of Effective Sample Size (ESS) in Sensitivity Analysis (ASTRUM-005 vs. CASPIAN).

Treatment Group	CASPIAN	ASTRUM-005 pre-matching	ASTRUM-005 post-matching
Combination 1 (Original primary analysis)			
Active	268	389	256 (65.8%)
Control	269	196	134 (68.4%)
Combination 2 (Smoking Status, Brain Metastatic, Liver Metastatic)			
Active	268	389	316 (81.2%)
Control	269	196	163 (83.2%)
Combination 3 (Race, ECOG, Smoking Status, Brain Metastatic, Liver Metastatic)			
Active	268	389	133 (34.2%)
Control	269	196	60 (30.6%)
Combination 4 (Sex, ECOG, Smoking Status, Brain Metastatic, Liver Metastatic)			
Active	268	389	174 (44.7%)
Control	269	196	77 (39.3%)
Combination 5: (Age Group, ECOG, Smoking Status, Brain Metastatic, Liver Metastatic)			
Active	268	389	256 (65.8%)
Control	269	196	134 (68.4%)

Table 9 (Table 10 from the sponsor responses to the List of Questions): Results of Sensitivity Analysis using Anchored MAIC (ASTRUM-005 vs. CASPIAN).

	Anchored MAIC, HR (95% CI)	
	PFS (per Investigator)	OS
Combination 1 (Original primary analysis)	0.70 (0.53,0.94)	0.78 (0.57,1.05)
Combination 2	0.75 (0.57,0.98)	0.84 (0.63,1.12)
Combination 3	0.79 (0.56,1.12)	0.64 (0.43,0.93)
Combination 4	0.68 (0.50,0.93)	0.77 (0.56,1.07)
Combination 5	0.70 (0.53,0.94)	0.77 (0.57,1.05)

Table 10 (Table 7 from the sponsor responses to the List of Questions): Summary of Effective Sample Size (ESS) in Sensitivity Analysis (ASTRUM-005 vs. IMpower133).

Treatment Group	IMpower133	ASTRUM-005 pre-matching	ASTRUM-005 post-matching
Combination 1 (Original primary analysis)			
Active	201	389	240 (61.7%)
Control	202	196	126 (64.3%)
Combination 2 (Age Group, Smoking Status, Brain Metastatic, Liver Metastatic)			
Active	201	389	301 (77.4%)
Control	202	196	151 (77.0%)
Combination 3 (Age Group, Race, ECOG, Smoking Status, Brain Metastatic, Liver Metastatic)			
Active	201	389	127 (32.6%)
Control	202	196	58 (29.6%)
Combination 4 (Age Group, Sex, ECOG, Smoking Status, Brain Metastatic, Liver Metastatic)			
Active	201	389	117 (30.1%)
Control	202	196	58 (29.6%)

Table 11 (Table 8 from the sponsor responses to the List of Questions): Results of Sensitivity Analysis using Anchored MAIC (ASTRUM-005 vs. IMpower133).

	Anchored MAIC, HR (95% CI)	
	PFS (per Investigator)	OS
Combination 1 (Original primary analysis)	0.73 (0.53,0.99)	0.72 (0.51,1.01)
Combination 2	0.77 (0.57,1.04)	0.78 (0.56,1.08)
Combination 3	0.80 (0.55,1.16)	0.57 (0.38,0.86)
Combination 4	0.70 (0.50,0.99)	0.70 (0.48,1.02)

Table 12 (Table 1 from sponsor responses after the Oral Explanation): Distribution of Baseline Characteristics Before and After Weighting.

ASTRUM-005 vs. IMpower133							
Baseline Variables	Matching / adjustment variable	ASTRUM-005, Serplulimab Arm (N = 389)	ASTRUM-005, Control Arm (N = 196)	ASTRUM-005, adjusted Serplulimab Arm (ESS = 240)[1]	ASTRUM-005, adjusted Control Arm (ESS = 126)[1]	IMpower133, Control Arm (N = 202)	IMpower133, Atezolizumab Arm (N = 201)
Age Group, n (%)	Yes						
≥ 65 years		154 (39.6)	77 (39.3)	108 (44.8)	60 (47.5)	96 (47.5)	90 (44.8)
< 65 years		235 (60.4)	119 (60.7)	132 (55.2)	66 (52.5)	106 (52.5)	111 (55.2)
Sex, n (%)	No						
Male		317 (81.5)	164 (83.7)	216 (90.2)	117 (92.9)	132 (65.3)	129 (64.2)
Female		72 (18.5)	32 (16.3)	24 (9.8)	9 (7.1)	70 (34.7)	72 (35.8)
Race, n (%)	No						
Asian		262 (67.4)	139 (70.9)	150 (62.6)	84 (66.4)	36 (17.8)	33 (16.4)
Non-Asian		127 (32.6)	57 (29.1)	90 (37.4)	42 (33.6)	166 (82.2)	168 (83.6)
Disease Stage, n (%)[2]	No						
IV		318 (81.7)	155 (79.1)	204 (84.8)	100 (79.3)	Not Reported	Not Reported
III or other		71 (18.3)	41 (20.9)	36 (15.2)	26 (20.7)	Not Reported	Not Reported
ECOG, n (%)	Yes						
PS 1		318 (81.7)	164 (83.7)	153 (63.7)	84 (66.8)	135 (66.8)	128 (63.7)
PS 0		71 (18.3)	32 (16.3)	87 (36.3)	42 (33.2)	67 (33.2)	73 (36.3)
Smoking Status, n (%)	Yes						
Current/former smoker		308 (79.2)	161 (82.1)	229 (95.5)	124 (98.5)	199 (98.5)	192 (95.5)
Never		81 (20.8)	35 (17.9)	11 (4.5)	2 (1.5)	3 (1.5)	9 (4.5)
Brain Metastasis, n (%)	Yes						
Yes		50 (12.9)	28 (14.3)	20 (8.5)	11 (8.9)	18 (8.9)	17 (8.5)
No		339 (87.1)	168 (85.7)	220 (91.5)	115 (91.1)	184 (91.1)	184 (91.5)
Liver Metastasis, n (%)	Yes						
Yes		99 (25.4)	51 (26.0)	92 (38.3)	45 (35.6)	72 (35.6)	77 (38.3)
No		290 (74.6)	145 (74.0)	148 (61.7)	81 (64.4)	130 (64.4)	124 (61.7)
Tumor Mutational Burden, n (%)[3]	No						
≥10 mutations/Mb		22/195 (11.3)	4/110 (3.6)	13/120 (10.5)	2/71 (2.7)	110/178 (61.8)	102/173 (59.0)
<10 mutations/Mb		173/195 (88.7)	106/110 (96.4)	107/120 (89.5)	69/71 (97.3)	68/178 (38.2)	71/173 (41.0)
Previous Anticancer Treatments, n (%)	No						
Yes		10 (2.6)	5 (2.6)	6 (2.4)	3 (2.0)	65 (32.2)	66 (32.8)
No		379 (97.4)	191 (97.4)	234 (97.6)	123 (98.0)	137 (67.8)	135 (67.2)
ASTRUM-005 vs. CASPIAN							
Baseline Variables	Matching / adjustment variable	ASTRUM-005, Serplulimab Arm (N = 389)	ASTRUM-005, Control Arm (N = 196)	ASTRUM-005, adjusted Serplulimab Arm (ESS = 256)[1]	ASTRUM-005, adjusted Control Arm (ESS = 134)[1]	CASPIAN, Control Arm (N = 269)	CASPIAN, Durvalumab Arm (N = 268)
Age Group, n (%)	No						
≥ 65 years		154 (39.6)	77 (39.3)	93 (36.5)	52 (38.5)	112(41.6)	101 (37.7)
< 65 years		235 (60.4)	119 (60.7)	163 (63.5)	82 (61.5)	157 (58.4)	167 (62.3)
Sex, n (%)	No						
Male		317 (81.5)	164 (83.7)	228 (89.1)	122 (91.0)	184 (68.4)	190 (70.9)
Female		72 (18.5)	32 (16.3)	28 (10.9)	12 (9.0)	85 (31.6)	78 (29.1)
Race, n (%)	No						

Asian		262 (67.4)	139 (70.9)	159 (62.1)	88 (65.9)	42 (15.6)	36 (13.4)
Non-Asian		127 (32.6)	57 (29.1)	97 (37.9)	46 (34.1)	227 (84.4)	232 (86.6)
Disease Stage, n (%)[2]	No						
IV		318 (81.7)	155 (79.1)	217 (84.9)	106 (79.4)	245 (91.1)	240 (89.6)
III or other		71 (18.3)	41 (20.9)	39 (15.1)	28 (20.6)	24 (8.9)	28 (10.4)
ECOG, n (%)	Yes						
PS 1		318 (81.7)	164 (83.7)	162 (63.1)	89 (66.5)	179 (66.5)	169 (63.1)
PS 0		71 (18.3)	32 (16.3)	94 (36.9)	45 (33.5)	90 (33.5)	99 (36.9)
Smoking Status, n (%)	Yes						
Current/former smoker		308 (79.2)	161 (82.1)	235 (91.8)	126 (94.4)	254 (94.4)	246 (91.8)
Never		81 (20.8)	35 (17.9)	21 (8.2)	8 (5.6)	15 (5.6)	22 (8.2)
Brain Metastasis, n (%)	Yes						
Yes		50 (12.9)	28 (14.3)	27 (10.4)	13 (10.0)	27 (10.0)	28 (10.4)
No		339 (87.1)	168 (85.7)	229 (89.6)	121 (90.0)	242 (90.0)	240 (89.6)
Liver Metastasis, n (%)	Yes						
Yes		99 (25.4)	51 (26.0)	103 (40.3)	52 (38.7)	104 (38.7)	108 (40.3)
No		290 (74.6)	145 (74.0)	153 (59.7)	82 (61.3)	165 (61.3)	160 (59.7)
Tumor Mutational Burden, n (%)[2,3]	No						
≥10 mutations/Mb		22 (11.3)	4 (3.6)	14/128 (10.8)	2/75 (3.0)	Not Reported	Not Reported
<10 mutations/Mb		173 (88.7)	106 (96.4)	114/128 (89.2)	73/75 (97.0)	Not Reported	Not Reported
Previous Anticancer Treatments, n (%)[2]	No						
Yes		10 (2.6)	5 (2.6)	6 (2.5)	4 (2.8)	Not Reported	Not Reported
No		379 (97.4)	191 (97.4)	250 (97.5)	130 (97.2)	Not Reported	Not Reported

Table 13 (Table 2 from sponsor responses after the Oral Explanation): 2 Distribution of Baseline Characteristics Before and After Weighting (Add Disease Stage)

ASTRUM-005 vs. IMpower133 (Stage IV in "Disease Stage" was imputed to be 100%)							
Baseline Variables	Matching / adjustment variable	ASTRUM-005, Serplulimab Arm (N = 389)	ASTRUM-005, Control Arm (N = 196)	ASTRUM-005, adjusted Serplulimab Arm (ESS = 210)[1]	ASTRUM-005, adjusted Control Arm (ESS = 100)[1]	IMpower133, Control Arm (N = 202)	IMpower133, Atezolizumab Arm (N = 201)
Age Group, n (%)	Yes						
≥ 65 years		154 (39.6)	77 (39.3)	94 (44.8)	48 (47.5)	96 (47.5)	90 (44.8)
< 65 years		235 (60.4)	119 (60.7)	116 (55.2)	52 (52.5)	106 (52.5)	111 (55.2)
Sex, n (%)	No						
Male		317 (81.5)	164 (83.7)	193 (91.9)	92 (91.7)	132 (65.3)	129 (64.2)
Female		72 (18.5)	32 (16.3)	17 (8.1)	8 (8.3)	70 (34.7)	72 (35.8)
Race, n (%)	No						
Asian		262 (67.4)	139 (70.9)	125 (59.5)	65 (65.4)	36 (17.8)	33 (16.4)
Non-Asian		127 (32.6)	57 (29.1)	85 (40.5)	35 (34.6)	166 (82.2)	168 (83.6)
Disease Stage, n (%)[2]	Yes						
IV		318 (81.7)	155 (79.1)	210 (100.0)	100 (100.0)	202 (100.0)	201 (100.0)
III or other		71 (18.3)	41 (20.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ECOG, n (%)	Yes						
PS 1		318 (81.7)	164 (83.7)	134 (63.7)	67 (66.8)	135 (66.8)	128 (63.7)
PS 0		71 (18.3)	32 (16.3)	76 (36.3)	33 (33.2)	67 (33.2)	73 (36.3)
Smoking Status, n (%)	Yes						
Current/former smoker		308 (79.2)	161 (82.1)	201 (95.5)	98 (98.5)	199 (98.5)	192 (95.5)
Never		81 (20.8)	35 (17.9)	9 (4.5)	2 (1.5)	3 (1.5)	9 (4.5)
Brain Metastasis, n (%)	Yes						

Yes		50 (12.9)	28 (14.3)	18 (8.5)	9 (8.9)	18 (8.9)	17 (8.5)
No		339 (87.1)	168 (85.7)	192 (91.5)	91 (91.1)	184 (91.1)	184 (91.5)
Liver Metastasis, n (%)	Yes						
Yes		99 (25.4)	51 (26.0)	80 (38.3)	36 (35.6)	72 (35.6)	77 (38.3)
No		290 (74.6)	145 (74.0)	130 (61.7)	64 (64.4)	130 (64.4)	124 (61.7)
Tumor Mutational Burden, n (%)[3]	No						
≥10 mutations/Mb		22/195 (11.3)	4/110 (3.6)	10/105 (9.3)	1/56 (2.3)	110/178 (61.8)	102/173 (59.0)
<10 mutations/Mb		173/195 (88.7)	106/110 (96.4)	95/105 (90.7)	55/56 (97.7)	68/178 (38.2)	71/173 (41.0)
Previous Anticancer Treatments, n (%)	No						
Yes		10 (2.6)	5 (2.6)	5 (2.6)	2 (2.4)	65 (32.2)	66 (32.8)
No		379 (97.4)	191 (97.4)	205 (97.4)	98 (97.6)	137 (67.8)	135 (67.2)
ASTRUM-005 vs. IMpower133 (Stage IV in "Disease Stage" was imputed using the CASPIAN study proportion)							
Baseline Variables	Matching / adjustment variable	ASTRUM-005, Serplulimab Arm (N = 389)	ASTRUM-005, Control Arm (N = 196)	ASTRUM-005, adjusted Serplulimab Arm (ESS = 236)[1]	ASTRUM-005, adjusted Control Arm (ESS = 116)[1]	IMpower133, Control Arm (N = 202)	IMpower133, Atezolizumab Arm (N = 201)
Age Group, n (%)	Yes						
≥ 65 years		154 (39.6)	77 (39.3)	106 (44.8)	55 (47.5)	96 (47.5)	90 (44.8)
< 65 years		235 (60.4)	119 (60.7)	130 (55.2)	61 (52.5)	106 (52.5)	111 (55.2)
Sex, n (%)	No						
Male		317 (81.5)	164 (83.7)	214 (90.7)	107 (92.2)	132 (65.3)	129 (64.2)
Female		72 (18.5)	32 (16.3)	22 (9.3)	9 (7.8)	70 (34.7)	72 (35.8)
Race, n (%)	No						
Asian		262 (67.4)	139 (70.9)	145 (61.6)	76 (65.8)	36 (17.8)	33 (16.4)
Non-Asian		127 (32.6)	57 (29.1)	91 (38.4)	40 (34.2)	166 (82.2)	168 (83.6)
Disease Stage, n (%)[2]	Yes						
IV		318 (81.7)	155 (79.1)	211 (89.6)	106 (91.1)	184 (91.1)	180 (89.6)
III or other		71 (18.3)	41 (20.9)	25 (10.4)	10 (8.9)	18 (8.9)	21 (10.4)
ECOG, n (%)	Yes						
PS 1		318 (81.7)	164 (83.7)	150 (63.7)	77 (66.8)	135 (66.8)	128 (63.7)
PS 0		71 (18.3)	32 (16.3)	86 (36.3)	39 (33.2)	67 (33.2)	73 (36.3)
Smoking Status, n (%)	Yes						
Current/former smoker		308 (79.2)	161 (82.1)	225 (95.5)	114 (98.5)	199 (98.5)	192 (95.5)
Never		81 (20.8)	35 (17.9)	11 (4.5)	2 (1.5)	3 (1.5)	9 (4.5)
Brain Metastasis, n (%)	Yes						
Yes		50 (12.9)	28 (14.3)	20 (8.5)	10 (8.9)	18 (8.9)	17 (8.5)
No		339 (87.1)	168 (85.7)	216 (91.5)	106 (91.1)	184 (91.1)	184 (91.5)
Liver Metastasis, n (%)	Yes						
Yes		99 (25.4)	51 (26.0)	90 (38.3)	41 (35.6)	72 (35.6)	77 (38.3)
No		290 (74.6)	145 (74.0)	146 (61.7)	75 (64.4)	130 (64.4)	124 (61.7)
Tumor Mutational Burden, n (%)[3]	No						
≥10 mutations/Mb		22/195 (11.3)	4/110 (3.6)	12/118 (10.1)	2/65 (2.5)	110/178 (61.8)	102/173 (59.0)
<10 mutations/Mb		173/195 (88.7)	106/110 (96.4)	106/118 (89.9)	63/65 (97.5)	68/178 (38.2)	71/173 (41.0)
Previous Anticancer Treatments, n (%)	No						
Yes		10 (2.6)	5 (2.6)	6 (2.5)	3 (2.2)	65 (32.2)	66 (32.8)
No		379 (97.4)	191 (97.4)	230 (97.5)	113 (97.8)	137 (67.8)	135 (67.2)
ASTRUM-005 vs. CASPIAN							

Baseline Variables	Matching / adjustment variable	ASTRUM-005, Serplulimab Arm (N = 389)	ASTRUM-005, Control Arm (N = 196)	ASTRUM-005, adjusted Serplulimab Arm (ESS = 253)[1]	ASTRUM-005, adjusted Control Arm (ESS = 125)[1]	CASPIAN, Control Arm (N = 269)	CASPIAN, Durvalumab Arm (N = 268)
Age Group, n (%)	No						
≥ 65 years		154 (39.6)	77 (39.3)	93 (36.9)	49 (39.4)	112(41.6)	101 (37.7)
< 65 years		235 (60.4)	119 (60.7)	160 (63.1)	76 (60.6)	157 (58.4)	167 (62.3)
Sex, n (%)	No						
Male		317 (81.5)	164 (83.7)	227 (89.6)	113 (90.3)	184 (68.4)	190 (70.9)
Female		72 (18.5)	32 (16.3)	26 (10.4)	12 (9.7)	85 (31.6)	78 (29.1)
Race, n (%)	No						
Asian		262 (67.4)	139 (70.9)	155 (61.3)	82 (65.5)	42 (15.6)	36 (13.4)
Non-Asian		127 (32.6)	57 (29.1)	98 (38.7)	43 (34.5)	227 (84.4)	232 (86.6)
Disease Stage, n (%)[2]	Yes						
IV		318 (81.7)	155 (79.1)	227 (89.6)	114 (91.1)	245 (91.1)	240 (89.6)
III or other		71 (18.3)	41 (20.9)	26 (10.4)	11 (8.9)	24 (8.9)	28 (10.4)
ECOG, n (%)	Yes						
PS 1		318 (81.7)	164 (83.7)	160 (63.1)	83 (66.5)	179 (66.5)	169 (63.1)
PS 0		71 (18.3)	32 (16.3)	93 (36.9)	42 (33.5)	90 (33.5)	99 (36.9)
Smoking Status, n (%)	Yes						
Current/former smoker		308 (79.2)	161 (82.1)	232 (91.8)	118 (94.4)	254 (94.4)	246 (91.8)
Never		81 (20.8)	35 (17.9)	21 (8.2)	7 (5.6)	15 (5.6)	22 (8.2)
Brain Metastasis, n (%)	Yes						
Yes		50 (12.9)	28 (14.3)	26 (10.4)	13 (10.0)	27 (10.0)	28 (10.4)
No		339 (87.1)	168 (85.7)	227 (89.6)	112 (90.0)	242 (90.0)	240 (89.6)
Liver Metastasis, n (%)	Yes						
Yes		99 (25.4)	51 (26.0)	102 (40.3)	48 (38.7)	104 (38.7)	108 (40.3)
No		290 (74.6)	145 (74.0)	151 (59.7)	77 (61.3)	165 (61.3)	160 (59.7)
Tumor Mutational Burden, n (%)[2,3]	No						
≥10 mutations/Mb		22/195 (11.3)	4/110 (3.6)	13/127 (10.3)	2/70 (2.8)	Not Reported	Not Reported
<10 mutations/Mb		173/195 (88.7)	106/110 (96.4)	114/127 (89.7)	68/70 (97.2)	Not Reported	Not Reported
Previous Anticancer Treatments, n (%)[2]	No						
Yes		10 (2.6)	5 (2.6)	7 (2.6)	4 (3.1)	Not Reported	Not Reported
No		379 (97.4)	191 (97.4)	246 (97.4)	121 (96.9)	Not Reported	Not Reported

Note:

1. **"n" in the ESS column represents the theoretical effective sample size with certain characteristics, calculated as ESS * Proportion** or **ESS * Available Sample Size / Total Sample Size * Proportion (only for Tumor Mutational Burden), rather than the actual sample size.**
2. "Disease Stage" were not reported in the IMpower133 study, "Tumor Mutational Burden" and "Previous Anticancer Treatments" were not reported in the CASPIAN study.
3. In the ASTRUM-005 study, Tumor Mutational Burden was tested in 195 patients in the Serplulimab Arm and 110 patients in the Control Arm; in the IMpower133 study, it was tested in 173 patients in the Atezolizumab Arm and 178 patients in the Control Arm.

COMP discussion

The results of that indirect comparison were not considered convincing enough to overcome the uncertainties around the presented estimates and to overcome the inherent biases from such cross-trial comparisons. Especially the characteristics of populations included were not comparable and several favoured Hetronifly, particularly the high rate of non-smokers. The magnitude of OS estimates may have been affected. With so many differences at baseline and heterogenous study populations, it is questioned whether this can be fully addressed by a complete matching, or whether there are other covariaties and prognostic factors that could have played role with this selected patients' population. As noted by the CHMP in the benefit-risk assessment, there are uncertainties identified regarding the study design and conduct might have impacted the magnitude of the effect observed.

Currently, two anti-PD-L1 immune checkpoint inhibitors, atezolizumab and durvalumab, are approved in the EU for this indication, while no anti-PD-1 antibodies have been approved for the claimed indication. Both PD-1 and PD-L1 inhibitors— Hetronifly (a PD-1 inhibitor) and PD-L1 inhibitors atezolizumab and durvalumab—target the same immune pathway that suppresses the immune response against cancer cells. Hetronifly, by inhibiting PD-1, blocks its interaction with both PD-L1 and

PD-L2. PD-L1 inhibitors, such as atezolizumab and durvalumab, specifically block the PD-L1/PD-1 interaction. Overall, it was considered that there is no biological rationale why Hetronifly would demonstrate significant benefit over the other immune checkpoint inhibitors. In other study in ES-SCLC and in other cancer types (e.g. NSCLC), no difference was found regarding efficacy and toxicity among PD1 and PD-L1 inhibitors (see eg. Wang et al, BMC cancer 2023, 2023) 23:1196 and Pilae et al., Cancer. 2018 Jan 15;124(2):271-277)., and there is no reason why this would not also apply for Hetronifly in ES-SCL. It is not excluded that the outcomes of the indirect comparisons that were provided are influenced by the selected study population.

The applicant performed an indirect comparison of their results with the data from the pivotal trial with atezolizumab + carboplatin + etoposide versus placebo + carboplatin + etoposide which showed OS (median) of 12.3 months vs. 10.3 months, and also an indirect comparison to the pivotal trial for Durvalumab + Platinum + Etoposide versus Placebo + Platinum + Etoposide which showed OS (median) of 12.9 months vs. 10.5 months.

A recent meta-analysis has documented a significantly improved survival benefit in Asian versus non-Asian patients receiving a checkpoint inhibitor-based therapy across a range of tumour histologies (Peng L, Qin BD, Xiao K, Xu S, Yang JS, Zang YS, Stebbing J, Xie LP. A meta-analysis comparing responses of Asian versus non-Asian cancer patients to PD-1 and PD-L1 inhibitor-based therapy. Oncoimmunology. 2020 Jun 26;9(1):1781333.) So, it is unclear if the apparent improvement of OS in the indirect comparison also holds for the non-Asian population.

Also, the sponsor has not provided a *direct* comparison with these other approved combination therapies, atezolizumab and durvalumab.

According to the Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03), the significant benefit should include a quantitative element that allows the COMP to measure magnitude of effect as compared with an already authorised product. Any advantage of the designated orphan product will be considered in the context of experience with authorised products in the orphan condition, even if comparative clinical studies are not possible. In exceptional cases, if it is not possible to generate a sample big enough to provide sufficient comparative evidence, alternative methods (e.g. indirect comparisons with external data) may be used. The COMP does not consider this an exceptional case.

Overall, the COMP considers that the claim that Hetronifly is of significant benefit over atezolizumab and durvalumab has not been established.

4. COMP position adopted on 23 October 2024

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of small cell lung cancer (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life threatening due to its rapid progression and the development of widespread metastases, with a poor 5-year overall survival;
- in view of the fact that satisfactory methods for the treatment of the condition have been authorised in the European Union, the existence of significant benefit over the authorised methods of treatment should be established at the stage of the granting of marketing authorisation;
- the claim that Hetronifly is of significant benefit over other satisfactory methods to those affected by the orphan condition has not been established;
- the sponsor has provided indirect matched comparisons with other checkpoint inhibitors that are approved for this condition. However, the results of these matched indirect comparisons were not convincing enough to overcome the uncertainties around the presented estimates and their clinical relevance, and to overcome the inherent biases from such cross-trial comparisons. There are concerns whether matching can be complete as the prognostic factors differed significantly among study populations and were more favourable for Hetronifly;
- in addition, in certain exceptional cases, where it is not feasible to generate direct comparative clinical data, indirect comparisons may be considered as an alternative. However, this particular case is not viewed as one of those exceptional cases. Consequently, the indirect comparisons submitted do not provide sufficient evidence to demonstrate a significant benefit for Hetronifly over other approved therapies for the same condition;
- moreover, there is no clear biological rationale to suggest that Hetronifly would offer a meaningful advantage over other checkpoint inhibitors with comparable mechanisms of action.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are not satisfied.

The Committee for Orphan Medicinal Products, by 16 out of 25 votes, did not reach a two-thirds majority in favour of finding significant benefit over other satisfactory methods to those affected by the orphan condition for Hetronifly. Therefore, the COMP has recommended that Hetronifly, serplulimab for treatment of small cell lung cancer (EU/3/22/2731) is removed from the Community Register of Orphan Medicinal Products.

5. Appeal to the negative opinion adopted on 15 November 2024

Grounds for appeal

The sponsor presented detailed grounds for appeal EMA/OD/0000237657 on 15 November 2024.

Please refer to the sponsor's appeal documents in the case *Input from industry* folder.

The detailed grounds for appeal were further addressed by the sponsor at an oral explanation before the COMP on 03 December 2024

Comments on the grounds of appeal

Ground #1. Distinctive mechanism of action of serplulimab

In the written responses and at the oral explanation, the sponsor argued that serplulimab despite its unique mechanism of action, has the potential to block interactions with both PD-L1 and PD-L2 expressed in the surface of tumoral cells unlike the other two approved anti-PD-L1 antibodies atezolizumab and durvalumab. Existing literature indicated anti-PD-L1 agents specifically inhibit PD-L1/PD-1 and PD-L1/B7-1 interactions, thereby enhancing tumour specific T-cell immunity (Herbst RS, et al. 2014). With the additional blockage of PD-1 and PD-L2 interaction, anti-PD-1 agents like serplulimab may exhibit stronger anti-tumour activity compared to anti-PD-L1 agents (Chen L, et al. 2015). This singularity may contribute to explain the additional clinical benefits observed in clinical trials and the sponsor's analyses.

COMP discussion

The COMP agreed that serprulimab could offer broader immune checkpoint blockade, as it inhibits PD-1's interaction with both PD-L1 and PD-L2. This could potentially lead to more comprehensive immune reactivation, but it may come with an increased risk of immune-related adverse events (irAEs). At this stage the safety data are limited to conclude on the increased risks. In addition, the COMP considered that the mechanism per se cannot justify the significant benefit of serprulimab versus atezolizumab and durvalumab.

Nevertheless, irrespective of these mechanistic differences, the indirect comparison between Hetronifly and the PD-L1 inhibitors demonstrated a better overall survival outcome for Hetronifly in the ASTRUM-005 trial regardless of race, with a median OS of 15.8 months compared to 12.3 months and 12.9 months for atezolizumab and durvalumab, respectively.

Ground #2. The difficulties of conducting direct comparisons with atezolizumab and durvalumab

In the written responses and at the oral explanation the sponsor argued that any direct comparisons with atezolizumab and durvalumab used in the first-line treatment of extensive-stage small cell lung cancer (ES-SCLC) were unfeasible due to the mismatch in the timelines of marketing authorisation and commercialisation of these agents and the design and execution of serplulimab's pivotal trial.

Explicitly, the European commission granted the approval of atezolizumab and durvalumab for ES-SCLC in September 2019 and September 2020, respectively. The reimbursement decisions were issued in European countries from 2020 for atezolizumab and from 2021 for durvalumab. The marketing availability timeline is an average of 526 days across EU countries, and a median of 469 days (Figure 5) for oncology products (EFPIA Patients W.A.I.T. Indicator 2023 Survey), which means that the anti-PD-L1 antibodies were not available on the market until at least several months after the initiation of the pivotal phase III study, by which time most patients had been enrolled. The pivotal global Phase

III study (HLX10-005-SCLC301, also called ASTRUM-005) of serplulimab was initiated in March 2019; the protocol version 1.0 was finalised on 4 March 2019 (Figure 6).

Figure 5 Oncology median time to availability in EU

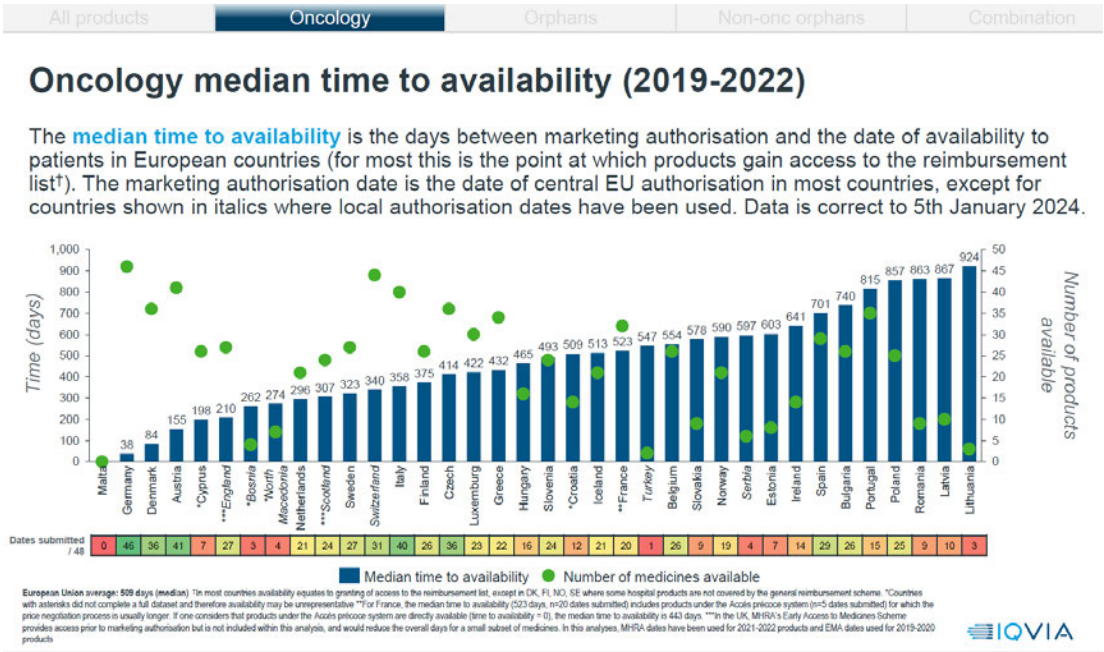
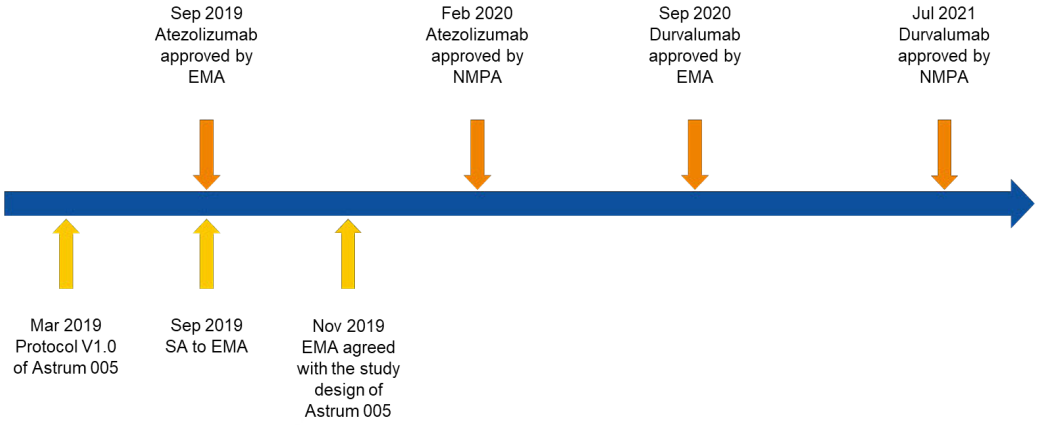


Figure 6. Timeline of approval of atezolizumab and durvalumab and the conduct of ASTRUM-005 study



A separate head-to-head trial comparing serplulimab with atezolizumab or durvalumab would have required about 1000 patients to generate statistically significant evidence within the available time frame. This was considered unfeasible and would have delayed EU patients' access to effective treatments, leaving indirect comparison methods as the only feasible option.

The sponsor also argued that the choice of comparator and overall protocol design and endpoints were discussed with the European Medicines Agency (EMA) during scientific advice (SA) requested by Henlius in September 2019. The Agency's feedback, which was received by November 2019, was broadly favourable with regard to the proposed study design including the treatment of control group, major patient selection criteria, dosage regimen.

COMP discussion

The COMP agreed with the sponsor that it was not feasible for the sponsor to conduct a separate head-to-head trial comparing serplulimab with atezolizumab or durvalumab due to the mismatch in the timelines of marketing authorisation of atezolizumab or durvalumab.

Ground #3. Clinically significant results of indirect comparison

In the written responses and at the oral explanation the sponsor arguments were as follows:

- Significant benefit vs atezolizumab

a) Race considerations

Besides the previously submitted sensitivity analysis regarding race, the sponsor conducted a new sensitivity analysis to determine the efficacy of serplulimab in combination with chemotherapy in non-Asian patients with ES-SCLC. In this new analysis, the sponsor excluded the Asian population from the ASTRUM-005 study and compared the results with those of the IMpower133 study. The results can be found in Table 14 (sensitivity analysis 1). In comparison to atezolizumab, the risk of death was reduced by 50% (HR 0.50, 95% CI: 0.29 to 0.85) with serplulimab in the non-Asian patients of the ASTRUM-005 study.

Table 14 Results of new sensitivity MAIC analyses for OS (ASTRUM-005 vs IMpower133)

Type	Matching Baseline Characteristics Variables	HR (95% CI)
New sensitivity analysis 1	Based on the list of variables used in the primary analysis, only including non-Asians from the ASTRUM-005	0.50 (0.29, 0.85)
New sensitivity analysis 2	Based on the list of variables used in the primary analysis, excluding all never-smokers from the ASTRUM-005	0.71 (0.5, 1.01)
New sensitivity analysis 3	Based on the list of variables used in the primary analysis, including Baseline Tumour Burden [1]	0.73 (0.51, 1.04)

Note: HR-Hazard Ratio, CI-Confidence Interval
1. The mean and standard deviation (SD) of the sum of the longest diameters of target lesions at baseline in the ASTRUM-005 study were calculated using actual values. In the IMpower133 study, the mean value was replaced with the median, and the SD referred to the ASTRUM-005 study.

b) Smoking status considerations

The proportion of never-smokers in the ASTRUM-005 study (19.8%) was higher than that in the IMpower133 study (3.0%) and CASPIAN study (6.9%). However, the proportion of never-smokers in the non-Asian population (8.7%) was similar to those previously reported. It has been shown that the proportion of lung cancer in never smokers is higher in east Asia with one third of all lung cancer patients are never-smokers: 39.7%, 38%, 32.8% in China, South Korea, and Japan, respectively (Zhou 2018, Cho 2017, Yano 2008).

Furthermore, genomic mutation analysis was performed to explore the genomic profiles of smokers and never-smokers in ASTRUM-005. Interestingly, SCLC patients showed similar smoking-related genomic mutation patterns regardless of their smoking histories, SCLC patients who have never smoked may develop transversion mutations from other sources unrelated to direct tobacco exposure (Cheng 2024).

The sponsor applied the MAIC approach to balance the smoking status distribution and conducted also a new sensitivity analysis excluding all never-smokers from the ASTRUM-005 study based on the key confounder combination in the primary analysis. The results can be found in Table 14 (sensitivity analysis 2), comparing to atezolizumab, the risk of death was reduced by 29% (HR 0.71, 95% CI: 0.5 to 1.01) with serplulimab upon excluding never-smokers.

c) Baseline tumour burden considerations

Regarding the baseline tumour burden, the sponsor used the median of the sum of the maximum diameters of target lesions as a substitute for the mean and referenced the standard deviation of this variable from the ASTRUM-005 study. Based on the key confounding factors in the primary analysis, tumour burden was included as a matching variable in the new sensitivity analysis. The risk of death was reduced by 25% when comparing serplulimab with atezolizumab (HR 0.73, 95% CI: 0.51 to 1.04, see Table 14, sensitivity analysis 3). The sum of the longest diameter of target lesions at baseline was essentially comparable between the ASTRUM-005 and IMpower133 studies (Table 15).

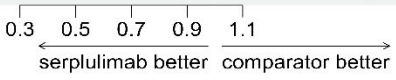
Table 15 Baseline tumour burden of the ASTRUM-005 and IMpower133 studies

	ASTRUM-005		IMpower133	
	serplulimab	Control	atezolizumab	Control
Sum of longest diameter of target lesions at baseline, median (range), mm	117.7 (13.8-323.7)	120.5 (14.5-269.6)	113.0 (12.0-325.0)	105.5 (15.0-353.0)

The sponsor claimed that even in unfavourable conditions for serplulimab, the new sensitivity analysis results were consistent with the previously submitted analysis. According to the results of the primary analysis and all sensitivity analyses (including the previously submitted and new analyses), after balancing important baseline characteristics of patients using the MAIC approach, the HRs of serplulimab compared to atezolizumab consistently ranged from 0.7 to 0.8 with the upper bounds of the 95% CIs being very close to 1 (mostly slightly above 1 but some just below 1) (Figure 7).

Figure 7 Forest plot for all MAIC analysis results of OS (ASTRUM-005 vs IMpower133)

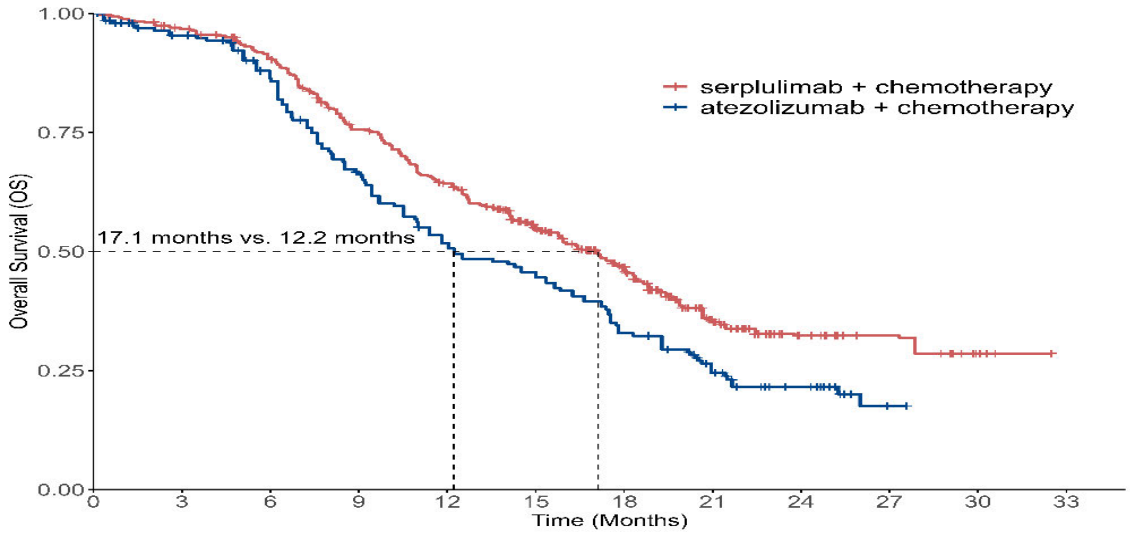
MAIC Analysis	Effective Sample Size (ESS) Active Arm	Control Arm	HR (95% CI)
Primary analysis	240	126	0.72 (0.51, 1.01)
Submitted sensitivity analysis 1	301	151	0.78 (0.56, 1.08)
Submitted sensitivity analysis 2	117	58	0.70 (0.48, 1.02)
Submitted sensitivity analysis 3	210	100	0.77 (0.53, 1.10)
Submitted sensitivity analysis 4	219	105	0.74 (0.52, 1.07)
Submitted sensitivity analysis 5	215	102	0.78 (0.54, 1.12)
Submitted sensitivity analysis 6	225	108	0.76 (0.53, 1.09)
Submitted sensitivity analysis 7	236	116	0.74 (0.53, 1.05)
Submitted sensitivity analysis 8	244	120	0.73 (0.52, 1.03)
Submitted sensitivity analysis 9	248	119	0.75 (0.53, 1.06)
Submitted sensitivity analysis 10	257	124	0.74 (0.53, 1.04)
Submitted sensitivity analysis 11	26	9	0.38 (<0.1, >10)
Submitted sensitivity analysis 12	2	1	Inf (NA, NA)
Submitted sensitivity analysis 13	127	58	0.57 (0.38, 0.86)
New sensitivity analysis 1	92	37	0.50 (0.29, 0.85)
New sensitivity analysis 2	219	122	0.71 (0.50, 1.01)
New sensitivity analysis 3	226	94	0.73 (0.51, 1.04)



Note:
1. The new sensitivity analysis was based on the existing data already submitted.
2. The IPD-pseudo dataset was reconstructed from Kaplan-Meier curve published in the IMpower133 study.

Based on the IPD-pseudo dataset reconstructed from literature for the IMpower133 study, it was observed that the Kaplan-Meier curve for serplulimab compared to atezolizumab consistently favoured serplulimab. The Kaplan-Meier curve showed a continued and stable separation after the 5th month (Figure 8).

Figure 8 Kaplan-Meier curve for OS (serplulimab vs atezolizumab)



- *Significant benefit vs durvalumab*

In addition to the previously submitted sensitivity analysis, the sponsor supplemented new sensitivity analyses. The results from the three new sensitivity analyses are listed in Table 16. It could be seen that even in unfavourable conditions for serplulimab, the new sensitivity analysis results were consistent with the previously submitted analysis and supported the conclusion that serplulimab could demonstrate a significant survival benefit for ES-SCLC patients compared to durvalumab.

Table 16 Results of new sensitivity MAIC analyses for OS (ASTRUM-005 vs CASPIAN)

Type	Matching Baseline Characteristics Variables	HR (95% CI)
New sensitivity analysis 1	Based on the list of variables used in the primary analysis, only including non-Asians from the ASTRUM-005	0.59 (0.36, 0.96)
New sensitivity analysis 2	Based on the list of variables used in the primary analysis, excluding all never-smokers from the ASTRUM-005	0.76 (0.55, 1.04)

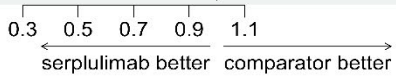
Note: HR-Hazard Ratio, CI-Confidence Interval

Based on the results of the primary analysis and all sensitivity analyses (including the previously submitted and new analyses), the HRs for serplulimab relative to durvalumab consistently ranged between 0.7 and 0.85, with the upper limit of the 95% CIs being very close to 1 (mostly slightly above 1, but some just below 1) (Figure 9). This indicated that although the matching process might have led to a reduction in ESS, which could have potentially lowered the power for achieving statistical significance, the improvement in survival benefit was indeed clinically meaningful and close to statistical significance. Such consistent results were unlikely to occur by chance or that the true value for each comparison lay at the extreme upper end of the 95% CI for the HR. The most likely explanation for these results was

that serplulimab indeed offers a significant survival benefit over and above that achievable by durvalumab.

Figure 9 Forest plot for all MAIC analysis results of OS (ASTRUM-005 vs CASPIAN)

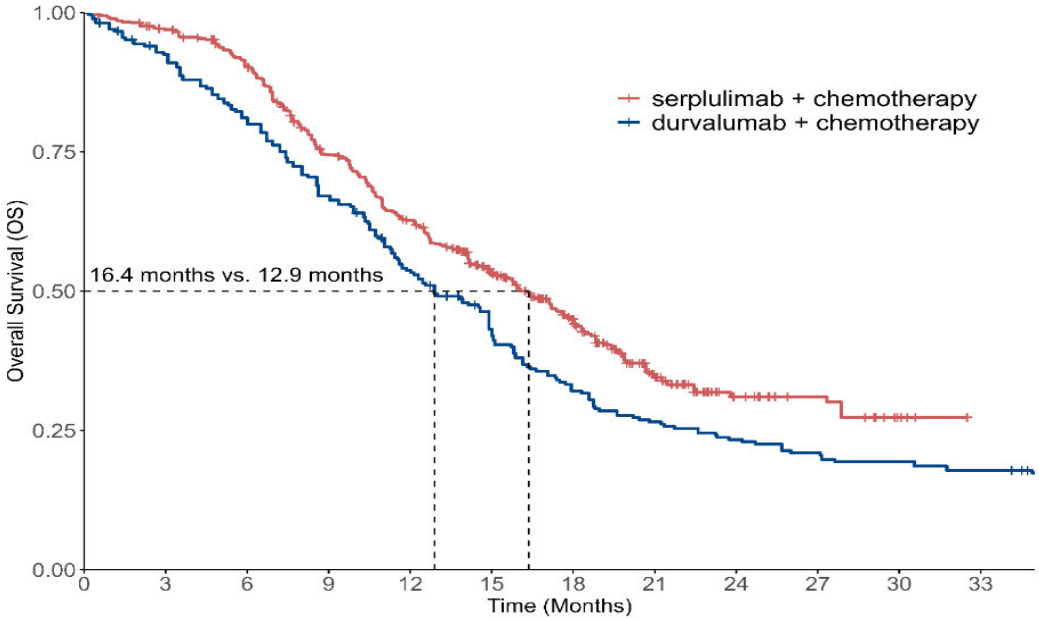
MAIC Analysis	Effective Sample Size (ESS) Active Arm	Control Arm	HR (95% CI)
Primary analysis	256	134	0.78 (0.57, 1.05)
Submitted sensitivity analysis 1	316	163	0.84 (0.63, 1.12)
Submitted sensitivity analysis 2	174	77	0.77 (0.56, 1.07)
Submitted sensitivity analysis 3	256	134	0.77 (0.57, 1.05)
Submitted sensitivity analysis 4	253	125	0.80 (0.59, 1.09)
Submitted sensitivity analysis 5	258	128	0.80 (0.59, 1.08)
Submitted sensitivity analysis 6	272	132	0.82 (0.60, 1.11)
Submitted sensitivity analysis 7	278	137	0.81 (0.60, 1.09)
Submitted sensitivity analysis 8	28	26	0.50 (<0.1, >10.0)
Submitted sensitivity analysis 9	1	1	Inf (NA, NA)
Submitted sensitivity analysis 10	133	60	0.64 (0.43, 0.93)
New sensitivity analysis 1	105	42	0.59 (0.36, 0.96)
New sensitivity analysis 2	221	122	0.76 (0.55, 1.04)



Note:
1. The new sensitivity analysis was based on the existing data already submitted.
2. The IPD-pseudo dataset was reconstructed from Kaplan-Meier curve published in the CASPIAN study.

Based on the reconstructed IPD pseudo dataset from the literature for the CASPIAN study, it was observed that the Kaplan-Meier curves for serplulimab consistently favoured serplulimab over durvalumab, demonstrating sustained and stable separation throughout the treatment period (Figure 10).

Figure 10. Kaplan-Meier curve for OS (serplulimab vs durvalumab)



The sponsor claimed that based on the aforementioned results, serplulimab demonstrated a remarkably consistent and close to statistically significant benefit compared to atezolizumab and durvalumab in

patients with ES-SCLC, and these consistent results were unlikely to occur by chance. Serplulimab indeed provides a significant and clinically meaningful survival benefit over and above that achievable by atezolizumab and durvalumab. Moreover, according to Systematic Literature Reviews (SLR) using Network Meta-Analyses (NMA) published over the past two years (Wang et al., 2023; Zhang et al., 2023; Zhu et al., 2023; Y. Liu et al., 2024), serplulimab consistently showed favourable outcomes in OS and had a comparable incidence of grade 3 or higher adverse events to other immune checkpoint inhibitors.

COMP discussion

- *Comparison against* atezolizumab

Lacking a direct comparison between serplulimab and atezolizumab, the applicant has conducted MAICs to compare the effects on overall survival of serplulimab to atezolizumab. Since the study populations of the clinical trials ASTRUM-005 and IMpower133 for serplulimab and atezolizumab respectively were not fully comparable, the anchored MAICs (with the respective placebo arm as an anchor) aim to adjust for differences in predictive variables between the two studies. The set of variables used for the adjustment in the primary MAIC reweighted the ASTRUM-005 population to match the distribution of these variables in the IMpower133 trial and hence ensured comparability of these variables in the resulting comparison.

The anchored MAIC relies on the assumption that all relevant predictive variables are included in the adjustment. The sponsor has provided a detailed methodological description of the selection of adjustment variables, including the clinically most relevant variables age, smoking status, ECOG performance status, and metastatic sites (brain and liver). Importantly, several analyses based in different sets of matching variables were presented as sensitivity analyses, and the distributions of baseline variables after the adjustment for the main analyses were presented.

However, since imbalances between the reweighted ASTRUM-005 and IMpower133 studies remained regarding other potentially predictive variables (e.g. sex, race, disease stage, baseline tumour burden) sensitivity analyses were conducted including these variables in the adjustment as well. The consistent result of all sensitivity analyses, and particularly the important sensitivity analyses 2, 3, 7 and 13 that include sex, disease stage and race, and new sensitivity analysis 3 that includes baseline tumour burden in addition to the variables in the primary indirect comparison method (ECOG; Smoking Status; Brain Metastases; Liver Metastases), support the robustness of the indirect comparisons presented by the applicant. All sensitivity analysis estimated a benefit of serplulimab compared to atezolizumab measured with the hazard ratio of at least 0.78.

Overall, Hetronifly showed a better overall survival outcome compared to atezolizumab based on the indirect comparisons and this was confirmed by the additional sensitivity analysis conducted by the sponsor.

- *Comparison against* durvalumab

Lacking a direct comparison between serplulimab and durvalumab, the applicant has conducted MAICs to compare the effects on overall survival of serplulimab to durvalumab. Since the study populations of the clinical trials ASTRUM-005 and CASPIAN for serplulimab and durvalumab respectively were not fully comparable, the anchored MAICs (with the respective placebo arm as an anchor) aim to adjust for differences in predictive variables between the two studies. The set of variables used for the adjustment in the primary MAIC reweighted the ASTRUM-005 population to match the distribution of these variables in the CASPIAN trial and hence ensured comparability of these variables in the resulting comparison.

The anchored MAIC relies on the assumption that all relevant predictive variables are included in the adjustment. The sponsor has provided a detailed methodological description of the selection of adjustment variables, including the clinically most relevant variables age, smoking status, ECOG performance status, and metastatic sites (brain and liver). Importantly, several analyses based in different sets of matching variables were presented as sensitivity analyses, and the distributions of baseline variables after the adjustment for the main analyses were presented.

However, since imbalances between the reweighted ASTRUM-005 and CASPIAN studies remained regarding other potentially predictive variables (e.g. sex, race, disease stage, baseline tumour burden) sensitivity analyses were conducted including these variables in the adjustment as well.

The consistent result of all sensitivity analyses, and particularly the important sensitivity analyses 2, 4, 10 that include sex, disease stage and race in addition to the variables in the primary indirect comparison method (ECOG; Smoking Status; Brain Metastases; Liver Metastases), support the robustness of the indirect comparisons presented by the applicant. All sensitivity analysis estimated a benefit of serplulimab compared to durvalumab measured with the Hazard Ratio of at least 0.84.

Overall, Hetronifly showed a better overall survival outcome compared to durvalumab based on the indirect comparisons and this was confirmed by the additional sensitivity analysis conducted by the sponsor.

COMP conclusion

Based on the above data the COMP considered that the indirect comparison between Hetronifly and the PD-L1 inhibitors showed a better overall survival outcome for Hetronifly in the ASTRUM-005 trial, with a median OS of 15.8 months compared to 12.3 months and 12.9 months for atezolizumab and durvalumab, respectively.

These results suggest that Hetronifly may offer a significant benefit in terms of efficacy, as demonstrated through the indirect comparisons. Overall, the indirect comparisons robustly showed that Hetronifly offers a meaningful survival advantage in comparison to the other two authorised checkpoint inhibitors.

6. COMP final position on review of criteria for orphan designation adopted on 05 December 2024

Based on the assessment of the detailed grounds for appeal and the argumentations presented by the sponsor during the oral explanation, the COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of small cell lung cancer (hereinafter referred to as "the condition") is estimated to remain below 5 in 10,000 and was concluded to be 1.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life threatening due to its rapid progression and the development of widespread metastases, with a poor 5-year overall survival;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Hetronifly may be of potential significant benefit to those affected by the orphan condition still holds. Hetronifly showed a better overall survival outcome compared to atezolizumab and durvalumab. These results suggest that Hetronifly may offer a significant benefit in terms of efficacy, as demonstrated through indirect comparisons.

The COMP, having considered the detailed grounds for appeal submitted by the sponsor and all the supporting data on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The COMP recommends that Hetronifly, serplulimab, for treatment of small cell lung cancer (EU/3/22/2731) is not removed from the Community Register of Orphan Medicinal Products.