6390

Exploratory Biomarker Analysis of the Phase 3 ASTRUM-005 Study: Serplulimab Versus Placebo Plus Chemotherapy for Extensive-stage Small Cell Lung Cancer

Ying Cheng[1], Liang Han[2], Lin Wu[3], Jun Chen[4], Hongmei Sun[5], Guilan Wen[6], Yinghua Ji[7], Anastasia Zimina[8], Jianhua Shi[9], Zhijie Pan[10], Jinsheng Shi[11], Xicheng Wang[12], Fang Yang[13], Xinyi Yang[13], Mengkai Chen[13], Shiqi Zhong[13], Qingyu Wang[13], Jing Li[13], Jiancheng Cheng[13], Chen Ling[13], Yongqiang Shan[13], Jun Zhu[13], the ASTRUM-005 Study Group

[1]Jilin Cancer Hospital, Changchun, China; [2]Xuzhou Central Hospital, Xuzhou, China; [3]Hunan Cancer Hospital/the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China; [4]Tianjin Medical University General Hospital, Tianjin, China; [5]Jiamusi Cancer Hospital, Jiamusi, China; [6]The First Affiliated Hospital of Nanchang University, Nanchang, China; [7]The First Affiliated Hospital of Xinxiang Medical University, Xinxiang, China; [8]Budgetary Healthcare Institution of Omsk Region "Clinical Oncology Dispensary", Omsk, Russian Federation; [9]Linyi Cancer Hospital, Linyi, China; [10]The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China; [11]Cangzhou People's Hospital, Cangzhou, China; [12]The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, China; [13]Shanghai Henlius Biotech, Inc., Shanghai, China

Background

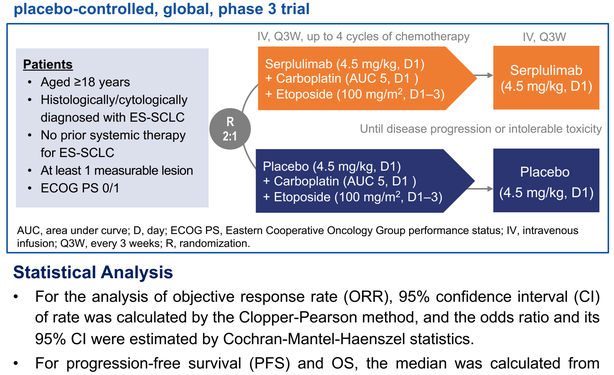
- About two-thirds of patients with small cell lung cancer (SCLC) were diagnosed at the extensive stage with a 5-year survival rate of <2% [1,2].
- Adding a programmed death-ligand 1 (PD-L1)/programmed death 1 (PD-1) inhibitor to chemotherapy for first-line therapy significantly improved overall survival (OS) in patients with extensive-stage SCLC (ES-SCLC) [3-6].
- In the updated analysis of the ASTRUM-005 study (data cutoff date of June 13, 2022), the median OS was 15.8 months in the serplulimab group versus 11.1 months in the placebo group (hazard ratio, 0.62; descriptive *P* <0.001) [7].
- Serplulimab is a fully humanized immunoglobulin G4 monoclonal antibody against the PD-1 receptor [8]. In the ASTRUM-005 study, a PD-L1 tumor proportion score ≥1% did not appear to be associated with better response to serplulimab plus chemotherapy.
- Here we report a retrospective biomarker analysis of the ASTRUM-005 trial (NCT04063163) to evaluate the association between proteome signature, genetic mutations, and hematological parameters and efficacy.

Methods

Biomarker Analysis of the ASTRUM-005 Study

- Study design of ASTRUM-005 is presented in **Figure 1**.
- Serum proteomics data were generated via the Olink® Explore 3072 platform, which consists of 8 panels including inflammation, neurology, cardiometabolic, and oncology.
- Genomic mutations were assessed by a Med1CDx™ panel.
- Hematologic parameters included neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lactate dehydrogenase (LDH) levels.
- Biomarker discovery and validation process: Biomarker candidates were first selected from the different expressed parameters between responders (patients showing complete response or partial response) and nonresponders (patients with stable disease or progressive disease). For serum proteomics, selected predictive/prognostic biomarkers were then validated in an independent dataset.

Figure 1. Study design of ASTRUM-005: A randomized, double-blind, placebo-controlled, global, phase 3 trial



AUC, area under curve; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous infusion; Q3W, every 3 weeks; R, randomization.

Statistical Analysis

- For the analysis of objective response rate (ORR), 95% confidence interval (CI) of rate was calculated by the Clopper-Pearson method, and the odds ratio and its 95% CI were estimated by Cochran-Mantel-Haenszel statistics.
- For progression-free survival (PFS) and OS, the median was calculated from product-limit (Kaplan-Meier) estimates, while n was the number of patients in each subgroup category. The hazard ratio and its 95% CI were estimated using an unstratified Cox proportional hazards model; Efron's method was used to handle ties.
- For serum proteomics, differentially expressed proteins (DEP) were identified using a t-test between responders and nonresponders in the treatment group. Predictive/prognostic biomarkers are identified through generalized linear model selection with 5-fold validation.
- The optimal cutoffs for hematological parameters to predict efficacy were determined using X-tile [9].
- Multivariate Cox regression was conducted to identify independent biomarkers.
- The clinical data cutoff date was June 13, 2022.

Results

Serum Proteomics

- Proteomic profiling results were obtained from 168 patients; 128 in the serplulimab group and 40 in the placebo group.
- The proteomic profiles were compared between responders and nonresponders in the serplulimab group, and 181 DEP were identified. The 15-protein signature was selected from the DEP using a generalized linear model selection with 5-fold validation (**Table 1**).
- The predictive model based on the 15-protein signature showed an AUC of 0.982 in the training set, and 0.918 and 0.545 in the validation sets for the serplulimab and the placebo groups, respectively.
- Patients with high signature scores, which were generated from the protein set analysis of the 15-protein signature, derived benefits from adding serplulimab to chemotherapy in terms of PFS and OS (**Table 2** and **Figure 2**), while those with low signature scores did not appear to derive benefits.

Table 1. The 15-protein signature

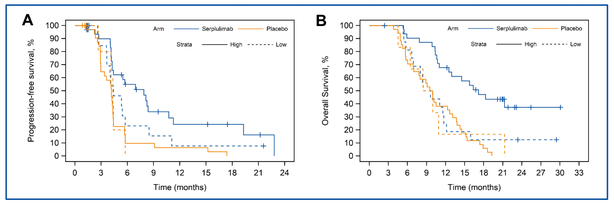
ENPP2	GAL	CCDC50	WASF3	PLCB1
SMC3	PRKAG3	PAPPA	SH3BGRL2	TSPAN1
VCAN	PRC1	CEACAM20	ACTN2	MMP7

Table 2. Response to treatment by the 15-protein signature score

	Serplulimab (n=48)		Placebo (n=40)		Hazard ratio (95% CI)	*P*
	n	Median, month (95% CI)	n	Median, month (95% CI)		
Progression-free survival						
High signature score	31	7.9 (4.3, 10.7)	34	4.2 (3.0, 4.3)	0.36 (0.21, 0.65)	<0.001
Low signature score	17	4.4 (3.6, 5.8)	6	4.3 (2.7, NA)	0.65 (0.22, 1.94)	0.488
Overall survival						
High signature score	31	17.2 (11.0, NA)	34	9.7 (6.9, 12.7)	0.27 (0.15, 0.49)	<0.001
Low signature score	17	9.1 (6.7, 11.7)	6	9.2 (4.5, NA)	0.76 (0.29, 1.98)	0.570

NA, not available.

Figure 2. Kaplan-Meier curves by the 15-protein signature score (A) PFS and (B) OS



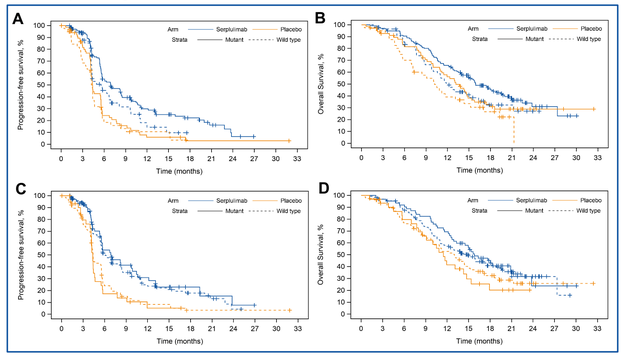
Genomic Mutations

- Genetic mutation data were available for 305 patients; after excluding 3 outliers, 302 patients were included in the analysis.
- Patients with mutations in the *RB1* gene or the NOTCH pathway had higher response rates to serplulimab-chemotherapy compared with those without mutations (**Table 3**).
- Patients with *RB1* mutations and treated with serplulimab-chemotherapy had a tendency towards longer PFS and OS (**Figure 3**).

Table 3. Objective response rate by mutation status

	Serplulimab (n=193)		Placebo (n=109)		Odds ratio (95% CI)
	n	ORR, % (95% CI)	n	ORR, % (95% CI)	
RB1					
Wild type	55	58.2 (44.1, 71.4)	41	51.2 (35.1, 67.1)	1.42 (0.61, 3.29)
Mutant	138	80.4 (72.8, 86.7)	68	69.1 (56.7, 79.8)	1.79 (0.88, 3.62)
NOTCH					
Wild type	130	68.5 (59.7, 76.3)	78	62.8 (51.1, 73.5)	1.26 (0.68, 2.34)
Mutant	63	85.7 (74.6, 93.3)	31	61.3 (42.2, 78.2)	2.77 (0.94, 8.15)

Figure 3. Kaplan-Meier curves by mutation status (A) PFS by *RB1* mutation, (B) OS by *RB1* mutation, (C) PFS by NOTCH pathway mutation, and (D) OS by NOTCH pathway mutation



Hematological Parameters

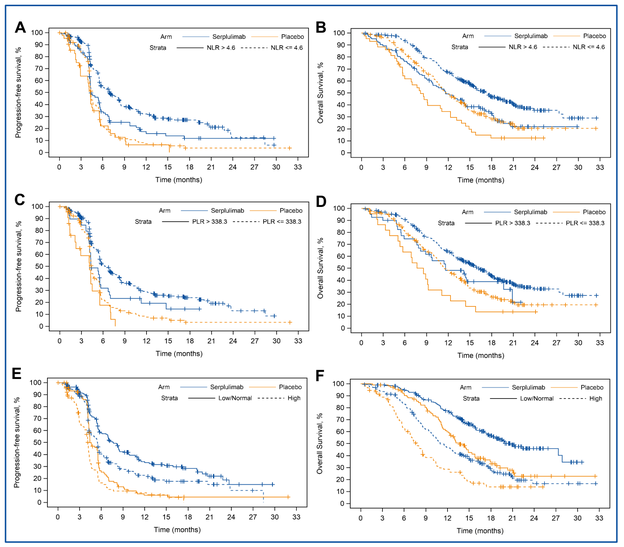
- Among all 585 patients, 583 had available test results for NLR and PLR, while 582 had available test results for LDH.
- High levels of baseline NLR, PLR, and LDH level were correlated with shorter PFS and OS in both treatment groups (**Figure 4**).
- The multivariate Cox regression model showed that baseline NLR and LDH level were independent prognostic biomarkers (**Table 4**).

Table 4. Prediction of patient outcomes by using the Cox regression model

Covariant	Univariant			Multivariant (N = 581)		Interaction *P*
	N	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	*P*
Arm (ref: Placebo)	585	0.61 (0.50-0.76)	<0.001	0.57 (0.46-0.71)	<0.001	-
Age (ref: ≥65 years)	585	0.92 (0.74-1.13)	0.407	-	-	-
Sex (ref: Male)	585	0.81 (0.61-1.07)	0.138	-	-	-
Race (ref: White)	585	0.91 (0.72-1.14)	0.392	-	-	-
TPS (ref: TPS <1%)	566	0.77 (0.57-1.04)	0.109	-	-	-
BrMe (ref: No)	585	1.29 (0.97-1.72)	0.077	-	-	-
MSI (ref: MSS/MSI-L)	305	0.93 (0.54-1.61)	0.807	-	-	-
Stage (ref: IV)	585	0.77 (0.58-1.04)	0.086	-	-	-
ECOG (ref: 1)	585	0.68 (0.50-0.91)	0.011	0.77 (0.57-1.04)	0.092	0.87
NLR (ref: NLR ≤4.6)	583	1.63 (1.30-2.05)	<0.001	1.45 (1.15-1.83)	0.002	0.97
PLR (ref: PLR ≤338.3)	583	1.51 (1.10-2.07)	0.011	-	-	-
LDH (ref: Normal/low)	582	2.18 (1.77-2.68)	<0.001	2.12 (1.71-2.62)	<0.001	0.83

BrMe, brain metastases; MSI, microsatellite instability; MSI-L, microsatellite instability low; MSS, microsatellite stable; TPS, tumor proportion score; ref, reference.

Figure 4. Kaplan-Meier curves by hematological parameters (A) PFS by NLR, (B) OS by NLR, (C) PFS by PLR, (D) OS by PLR, (E) PFS by LDH level, and (F) OS by LDH level



Conclusions

- There is an urgent need to identify reliable biomarkers that can predict response to immunotherapy plus chemotherapy in patients with ES-SCLC.
- Our results showed that a 15-protein signature score exhibited potential as a predictive biomarker for the efficacy of serplulimab plus chemotherapy.
- Additionally, mutations in the *RB1* gene and the NOTCH pathway were associated with a more favorable treatment response to serplulimab plus chemotherapy.
- Furthermore, baseline NLR and LDH were independent prognostic biomarkers for ES-SCLC.
- These findings shed light on the potential of new biomarkers for immunotherapy plus chemotherapy in patients with ES-SCLC, which warrant further investigation.

Acknowledgment and Disclosures

- We would like to express our gratitude to the patients who participated in the trial, their families, the principal investigators, clinicians, study coordinators, and nurses.
- This study was funded by Shanghai Henlius Biotech, Inc. Editorial support was provided by Chen Hu and Feng Qin of Shanghai Henlius Biotech, Inc. and Parexel (funded by Shanghai Henlius Biotech, Inc).
- Fang Yang, Xinyi Yang, Mengkai Chen, Shiqi Zhong, Qingyu Wang, Jing Li, Jiancheng Cheng, Chen Ling, Yongqiang Shan, and Jun Zhu are employees of Shanghai Henlius Biotech, Inc. No other disclosures were reported.

References

1. Rudin CM, et al. Nat Rev Dis Primers. 2021;7:3.
2. Gong J, et al. J Oncol Pract. 2018;14:359–366.
3. Liu SV, et al. J Clin Oncol. 2021;39:619–630.
4. Paz-Ares L, et al. ESMO Open. 2022;7:100408.
5. Wang J, et al. Lancet Oncol. 2022;23:739–747.
6. Cheng Y, et al. JAMA. 2022;328:1223–1232.
7. Cheng Y, et al. Ann Oncol. 2022;33:S1562.
8. Issafras H, et al. PLoS One. 2021;16:e0257972.
9. Camp R L, et al. Clin Cancer Res. 2004;10:7252–7259.

Presenter: Ying Cheng, MD. E-mail: jl.cheng@163.com