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Exploratory Biomarker Analysis of the Phase 3 ASTRUM-004 Study: Serplulimab Plus Chemotherapy as First-line Treatment for Advanced Squamous Non-Small-Cell Lung Cancer

Caicun Zhou[1], Yanping Hu[2], Ekaterine Arkania[3], Saadettin Kilickap[4], Kejing Ying[5], Fei Xu[6], Lin Wu[7], Xiang Wang[8], Maksym Viguro[9], Tamta Makharadze[10], Lijuan Guo[11], Fang Yang[11], Yali Liu[11], Xinyi Yang[11], Chen Hu[11], Qingyu Wang[11], Jing Li[11], Chen Ling[11], Yongqiang Shan[11], Jun Zhu[11]

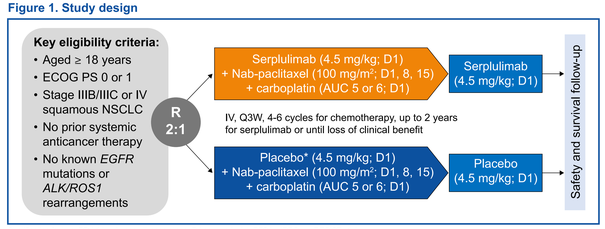
[1]Medical Oncology Department, Shanghai Pulmonary Hospital, Shanghai, China; [2]Department of Medical Oncology, Hubei Cancer Hospital, Wuhan, China; [3]Israeli-Georgian Multiprofile Medical Center Healthycore, Tbilisi, Georgia; [4]Medical Oncology Department, Hacettepe University – Faculty of Medicine, Ankara, Turkey; [5]Pneumology, Sir Run Run Shaw Hospital, Zhejiang University, School of Medicine, Hangzhou, China. [6]Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; [7]Medical Oncology Department, Hunan Cancer Hospital, Changsha, China; [8]Medical Oncology, Xuzhou Central Hospital/ The Fourth People's Hospital of Xuzhou, Xuzhou, China; [9]Clinical Research Department, Medical Center "Mriya Med-Service", Kryvyi Rih, Ukraine; [10]High Technology Hospital MedCenter Ltd, Tbilisi, Georgia; [11]Shanghai Henlius Biotech, Inc., Shanghai, China

Background

- Adding immunotherapy to chemotherapy has demonstrated improved efficacy over chemotherapy alone in patients with treatment-naïve, advanced, or metastatic squamous non-small-cell lung cancer (sqNSCLC).[1-3]
- However, biomarkers that can predict the efficacy of immunotherapy in patients with sqNSCLC remain to be determined.[1,3]
- The phase 3 ASTRUM-004 study demonstrated that serplulimab plus chemotherapy as a first-line treatment for advanced sqNSCLC significantly improved progression-free survival (PFS) and overall survival (OS) compared with placebo plus chemotherapy.[4]
- In this exploratory biomarker analysis of ASTRUM-004, we retrospectively evaluated the association of genetic mutations with patient outcomes.

Methods

Figure 1. Study design



Stratification factors: PD-L1 level, race, disease stage. Primary endpoint: PFS by IRRC per RECIST v1.1.
*Eligible patients were allowed to cross over to serplulimab monotherapy after progressive disease per protocol.
AUC, area under the concentration–time curve; D, day; ECOG PS, Eastern Cooperative Oncology Group performance score; IRRC, independent radiological review committee; IV, intravenous; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; Q3W, once every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

- Eligible patients were planned to be randomized (2:1) to receive serplulimab or placebo, both in combination with chemotherapy (**Figure 1**).
- Genetic mutations were assessed by the Med1CDx panel in the biomarker evaluable population (BEP).
- The objective response rate (ORR) was compared between treatment arms and the odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated using a stratified Cochran–Mantel–Haenszel method. Median PFS and OS were estimated using the Kaplan–Meier method. Comparisons between treatment arms, performed, and hazard ratios (HR) and their 95% CIs were estimated by a stratified Cox proportional hazards model.

Results

- The clinical data cutoff date was January 31, 2023.
- A total of 537 eligible patients were enrolled (358 patients in the serplulimab group and 179 patients in the placebo group); 309 patients with detectable samples were included in the BEP.

Table 1. Baseline characteristics and efficacy results in the BEP and ITT

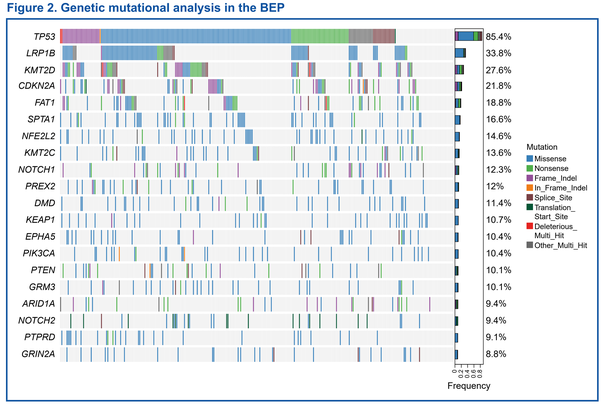
Baseline characteristics		BEP		ITT	
		Serplulimab (n = 212)	Placebo (n = 97)	Serplulimab (n = 358)	Placebo (n = 179)
Age	< 65 years	131 (62)	53 (55)	204 (57)	106 (59)
	≥ 65 years	81 (38)	44 (45)	154 (43)	73 (41)
Sex	Male	192 (91)	89 (92)	321 (90)	167 (93)
	Female	20 (9)	8 (8)	37 (10)	12 (7)
ECOG PS	0	34 (16)	13 (13)	65 (18)	26 (15)
	1	178 (84)	84 (87)	293 (82)	153 (85)
Race	Asian	157 (74)	65 (67)	240 (67)	119 (66)
	Non-Asian	55 (26)	32 (33)	118 (33)	60 (34)
Disease stage	IIIB/IIIC	63 (30)	24 (25)	103 (29)	40 (22)
	IV	149 (70)	73 (75)	255 (71)	139 (78)
PD-L1 expression, TPS	< 1%	77 (36)	33 (34)	135 (38)	68 (38)
	1% to < 50%	67 (32)	37 (38)	119 (33)	58 (32)
	≥ 50%	68 (32)	27 (28)	104 (29)	53 (30)
Smoking status	Never smoked	43 (20)	21 (22)	50 (14)	20 (11)
	Former smoker	146 (69)	65 (67)	229 (64)	122 (68)
	Current smoker	23 (11)	11 (11)	79 (22)	37 (21)
Metastasis	Brain	8 (4)	13 (13)	20 (6)	18 (10)
	Liver	22 (10)	10 (10)	40 (11)	17 (9)
Efficacy					
ORR, %		61.8	38.1	56.7	40.2
PFS, months, median (95% CI)		9.2 (7.2-12.2)	5.6 (4.3-6.8)	8.3 (7.0-9.8)	5.7 (5.1-6.8)
HR (95% CI)		0.57 (0.41-0.80)		0.53 (0.42-0.67)	
OS, months, median (95% CI)		24.7 (19.8-33.1)	18.5 (14.2-21.0)	22.7 (18.6-27.4)	18.2 (14.1-20.6)
HR (95% CI)		0.70 (0.51-0.97)		0.73 (0.58-0.93)	

ITT, intent-to-treat; TPS, tumor proportion score.

Baseline characteristics and gene mutation status

- Baseline characteristics and efficacy in the BEP were comparable with those in the ITT (**Table 1**).
- Mutation analysis demonstrated that the most frequently mutated genes were *TP53* (85%), *LRP1B* (34%), and *KMT2D* (28%) (**Figure 2**), consistent with published data.[5-7]

Figure 2. Genetic mutational analysis in the BEP



Clinical outcomes by mutation status

- In order to identify predictive biomarkers for serplulimab treatment, we analyzed genes and signaling pathways with different mutation frequencies in responders (patients showing complete response or partial response) and non-responders (patients with stable disease or progressive disease) to serplulimab plus chemotherapy treatment. Mutations in the Notch signaling pathway and several other genes were identified.
- The ORR was consistently higher in patients treated with serplulimab versus placebo, regardless of gene mutation status. A trend of greater ORR was observed in patients treated with serplulimab who had these mutations (**Table 2**).
- Mutations in the Notch signaling pathway, especially for *NOTCH3*, were associated with longer median PFS in patients receiving serplulimab versus placebo, possibly due to their roles in the tumor microenvironment in sqNSCLC, which was consistent with previous findings (**Figure 3**).[8]

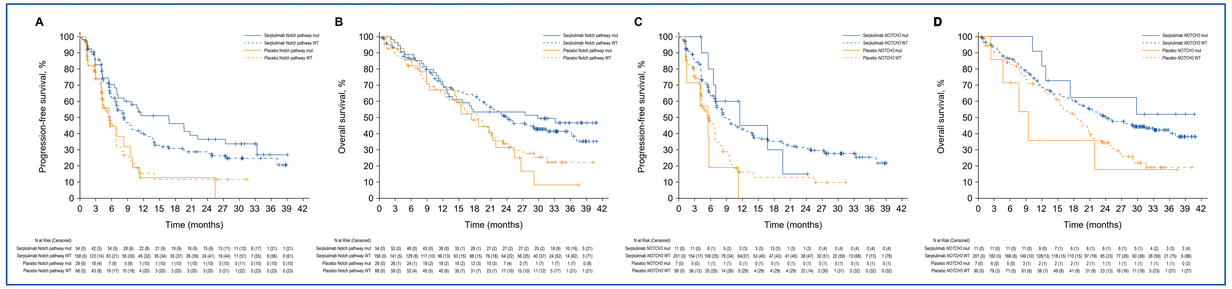
Table 2. ORR by mutation status

	Serplulimab (n = 212)		Placebo (n = 97)		OR (95% CI)
	No.	ORR (95% CI)	No.	ORR (95% CI)	
Notch signaling pathway					
Variant	40	74.1 (61.7-86.2)	10	34.5 (17.9-54.3)	5.85 (2.17-15.72)
Wild-type	100	63.3 (59.8-75.5)	27	39.7 (31.0-56.7)	2.76 (1.50-5.08)
NOTCH3					
Variant	11	100.0 (71.5-100.0)	3	42.9 (9.9-81.6)	NA
Wild-type	129	64.2 (61.1-74.8)	34	37.8 (29.9-51.7)	3.16 (1.86-5.39)
KMT2D					
Variant	42	73.7 (67.5-90.4)	10	35.7 (21.1-61.3)	6.30 (2.19-18.12)
Wild-type	98	63.2 (58.0-73.8)	27	39.1 (29.0-53.7)	2.83 (1.56-5.14)
PIK3C2G					
Variant	11	91.7 (71.5-100.0)	1	16.7 (0.4-64.1)	NA
Wild-type	129	64.5 (61.1-74.8)	36	39.6 (31.7-53.6)	2.93 (1.73-4.96)
EPHA3					
Variant	15	78.9 (58.6-96.4)	2	25.0 (3.2-65.1)	15.00 (1.98-113.56)
Wild-type	125	64.8 (61.4-75.3)	35	39.3 (31.4-53.5)	3.01 (1.76-5.14)
KEAP1					
Variant	15	62.5 (40.6-81.2)	2	22.2 (2.8-60.0)	5.83 (0.99-34.44)
Wild-type	125	66.5 (63.7-77.6)	35	39.8 (31.8-54.1)	3.29 (1.91-5.68)

NA, not applicable.

- Mutations in *KMT2D*, which is involved in the modulation of chromatin structure, and *PIK3C2G* and *EPHA3*, which regulate the tumor microenvironment, were associated with better clinical outcomes in the serplulimab arm compared with the placebo arm (**Figure 4**).
- Longer PFS and OS were observed in patients receiving serplulimab versus placebo regardless of mutation in *KEAP1*, whose mutation was reported unfavorable to the efficacy of immunotherapy in non-sqNSCLC (**Figure 5**).

Figure 3. Kaplan–Meier analysis of PFS and OS by Notch signaling pathway (A and B) and *NOTCH3* mutations (C and D)



mut, mutant; WT, wild-type.

Figure 4. Kaplan–Meier analysis of PFS and OS by *KMT2D* (A and B), *PIK3C2G* (C and D), and *EPHA3* mutations (E and F)

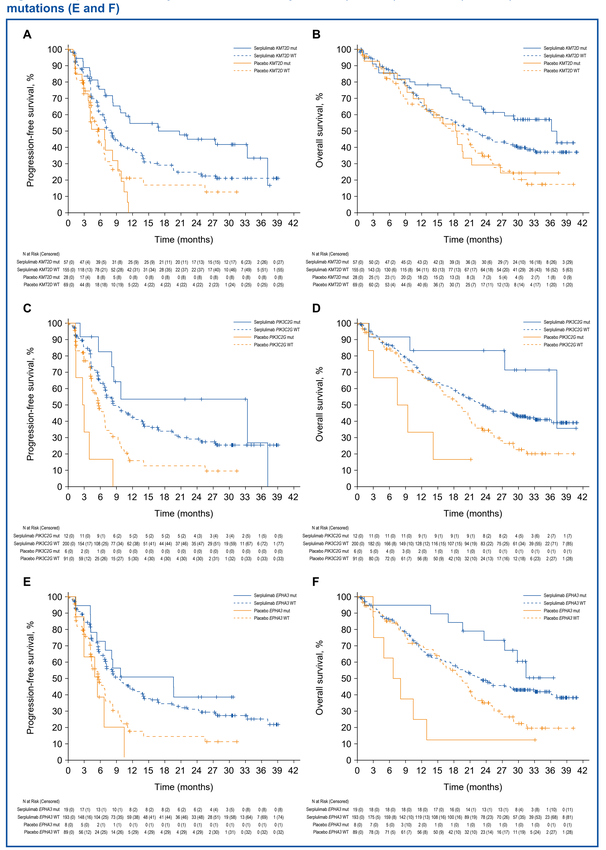
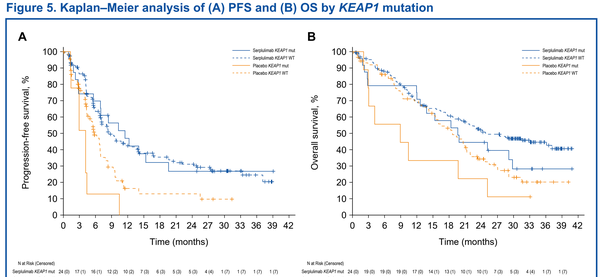


Figure 5. Kaplan–Meier analysis of (A) PFS and (B) OS by *KEAP1* mutation



Conclusions

- The exploratory biomarker analysis suggests improved clinical benefit with the addition of serplulimab to chemotherapy regardless of genetic mutation status.
- Compared to those without mutations, patients with mutations in the Notch signaling pathway, *KMT2D*, *PIK3C2G*, or *EPHA3* may derive more clinical benefit when serplulimab was added.
- These findings further support serplulimab plus chemotherapy as a standard of care for patients with first-line sqNSCLC.

References

1. Paz-Ares L, et al. *N Engl J Med*. 2018;379:2040-2051.
2. Paz-Ares L, et al. *Lancet Oncol*. 2021;22:198-211.
3. Jotte R, et al. *Thorac Oncol*. 2020;15:1351-1360.
4. Zhou C, et al. *Cancer Cell*. 2024;12;42:198-208.E3.
5. Xu F, et al. *Oncoimmunology*. 2020;9:1731943.
6. Yu J, et al. *Cancers*. 2022;14:3382.
7. Pan Y, et al. *Cancer Cell*. 2023;41:88-105.
8. Zhou C, et al. *J Thorac Oncol*. 2023;18:93-105.

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Corresponding author: Caicun Zhou, MD. E-mail: caicunzhoudr@163.com