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

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Background

two-thirds of patients with small cell lung cancer (SCLC) were diagnosed at the stage with a 5-year survival rate of <2% [1,2].

Adding a programmed -ligand 1–(PD-L1)/programmed 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].

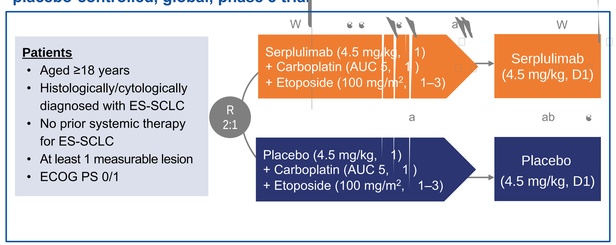
- the updated of the ASTRUM-005 study (data date of June 3, 2022"# the median OS was 15.8 in the serplulimab group versus 11.1 in the placebo group (hazard ratio, 0.62 *P* <0.) [7].
- Serplulimab is a fully humanized G4 monoclonal antibody against the PD-1 receptor [ ]. the ASTRUM-005 study, a PD-L1 tumor proportion score ≥1% did not appear to be associated with better response to serplulimab plus chemotherapy.
- Here we a retrospective biomarker analysis of ASTRUM-005 trial (NCT04063163 to evaluate between genetic mutations, and hematological parameters and efficacy

Methods

Biomarker Analysis of the ASTRUM-005 Study

Figure 1

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



Statistical Analysis

Results

Serum Proteomics

Table 1

Table 2 Figure 2

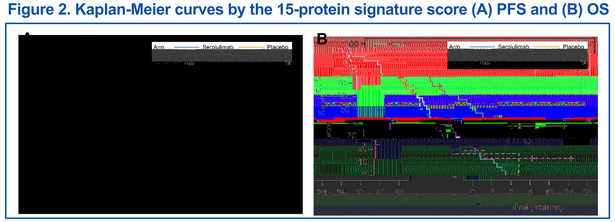
Table 1. The 15-protein signature

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)	
	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

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



Genomic Mutations

RB1

Table 3

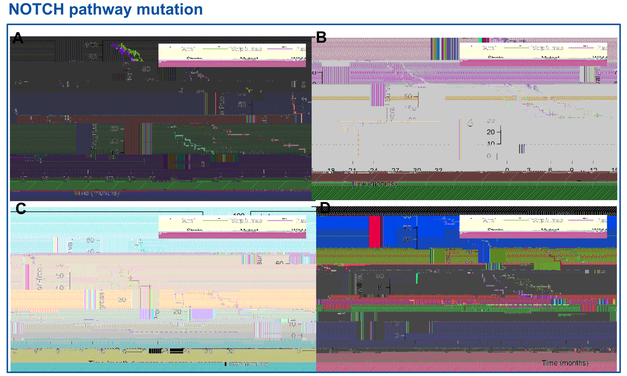
RB1

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

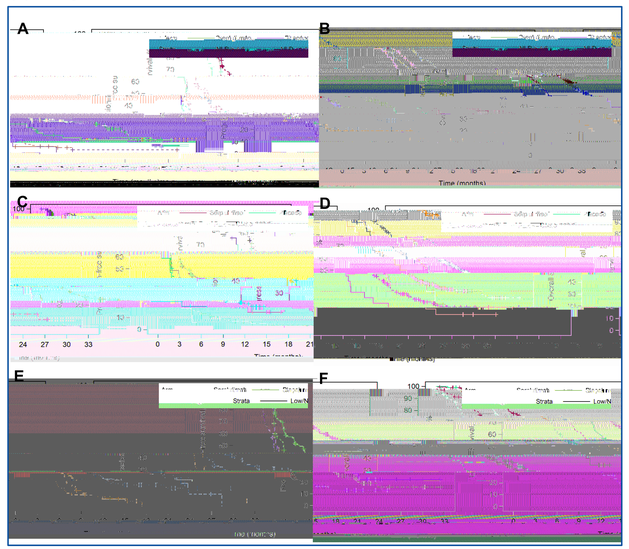
Figure 4

Table 4

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

Covariant	Univariant			Multivariant (N = 581)		Interaction
	N	Hazard ratio (95% CI)		Hazard ratio (95% CI)		
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

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

References

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