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ASTRUM-004: A Phase 3 Study of Serplulimab Plus Chemotherapy as First-line Treatment for Advanced Squamous Non-small-cell Lung Cancer

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Background

- Squamous NSCLC accounts for 25–30% of NSCLC cases,[1] with low frequency of targetable gene alterations.[2,3]
- Adding PD-1/PD-L1 inhibitor to chemotherapy has demonstrated improved outcomes in the first-line setting.[4–9]
- However, preferred treatment options with a favorable risk-benefit ratio are still limited in the global setting.

Serplulimab, a novel anti-PD-1 monoclonal antibody, improved survival in patients with various tumor types, and has been approved by China NMPA for MSI-H solid tumors, extensive-stage SCLC, and squamous NSCLC.

Here we report results from the final analysis of the phase 3 ASTRUM-004 study evaluating the efficacy and safety of serplulimab versus placebo, combined with carboplatin/nab-paclitaxel, as a first-line treatment for locally advanced or metastatic squamous NSCLC.

MSI-H, microsatellite instability-high; NMPA, National Medical Products Administration; NSCLC, non-small-cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; SCLC, small-cell lung cancer;

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Study Design

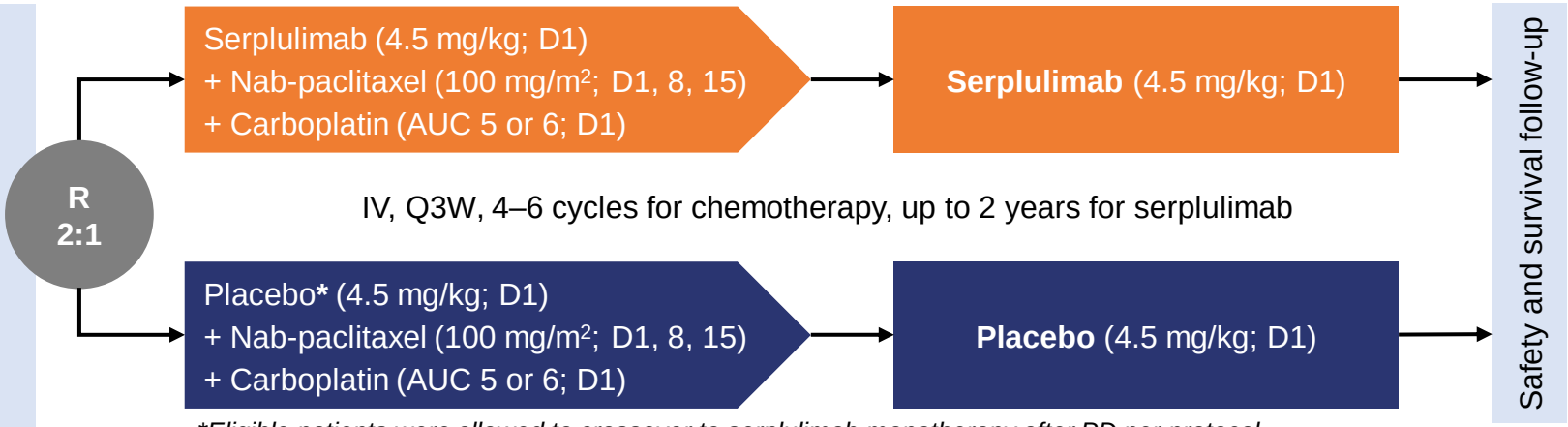
Randomized, double-blind, multicenter, international phase 3 trial

Main eligibility criteria

- ≥18 years
- ECOG PS 0 or 1
- Stage IIIB/IIIC or IV squamous NSCLC
- No prior systemic anticancer therapy
- No known *EGFR* mutations or *ALK*/*ROS1* rearrangements

Stratification factors

- PD-L1 level (TPS <1% *vs* 1%≤ TPS <50% *vs* TPS ≥50%)
- Race (Asian *vs* non-Asian)
- Disease stage (stage IIIB/IIIC *vs* IV)



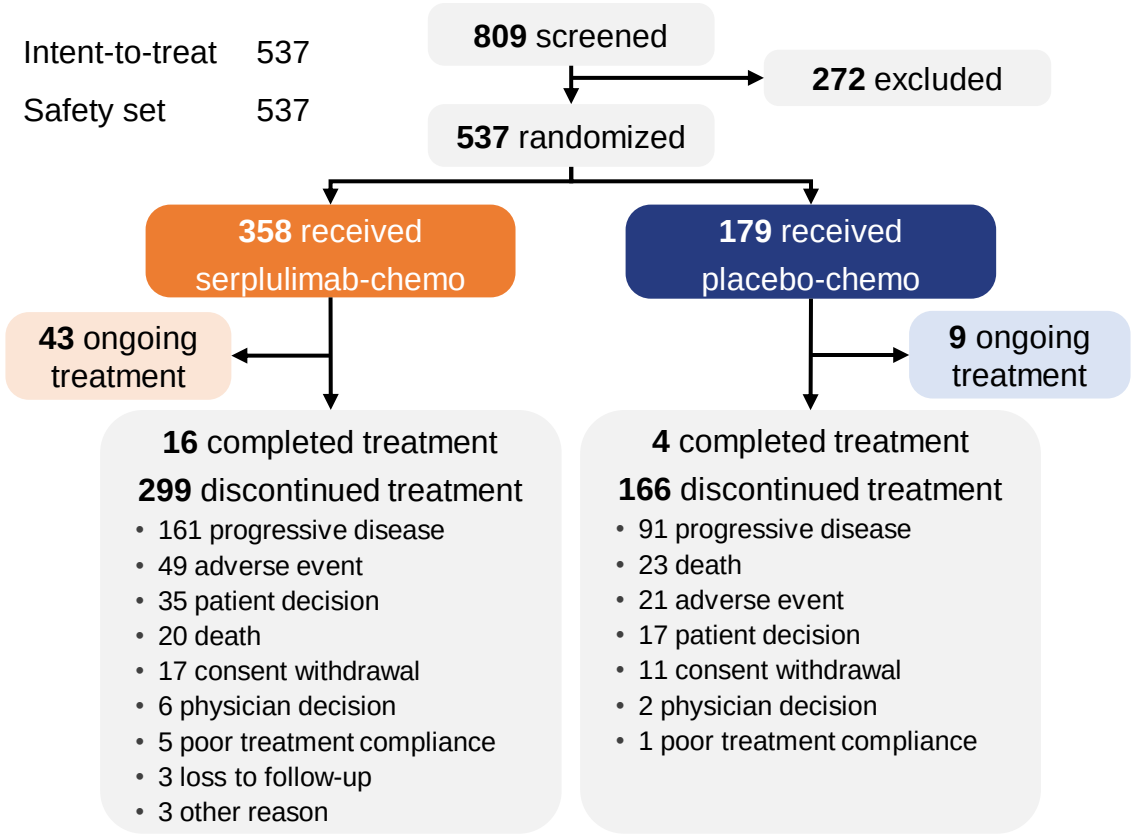
**Eligible patients were allowed to crossover to serplulimab monotherapy after PD per protocol.*

- **Primary endpoint:** PFS by IRRC per RECIST v1.1
- **Secondary endpoints:** OS, PFS, ORR, DOR, safety, exploration of biomarkers

Statistical analysis: The 1st interim analysis of OS was performed at the time of PFS final analysis, when approximately 99 deaths had occurred. The 2nd interim analysis of OS was performed when 198 deaths were observed. **The final OS analysis** were performed when **299 deaths** had occurred. PFS and OS were tested sequentially at an overall 2-sided α level of 0.05. The multiplicity-adjusted 2-sided α level was 0.0002, 0.012, and **0.046** for OS at the 1st and the 2nd interim analysis, and the final analysis, respectively.

AUC, area under the concentration-time curve; D, day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group perform status; IRRC, independent radiological review committee; IV, intravenous infusion; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TPS, tumor proportion score

Patient Disposition and Baseline Characteristics



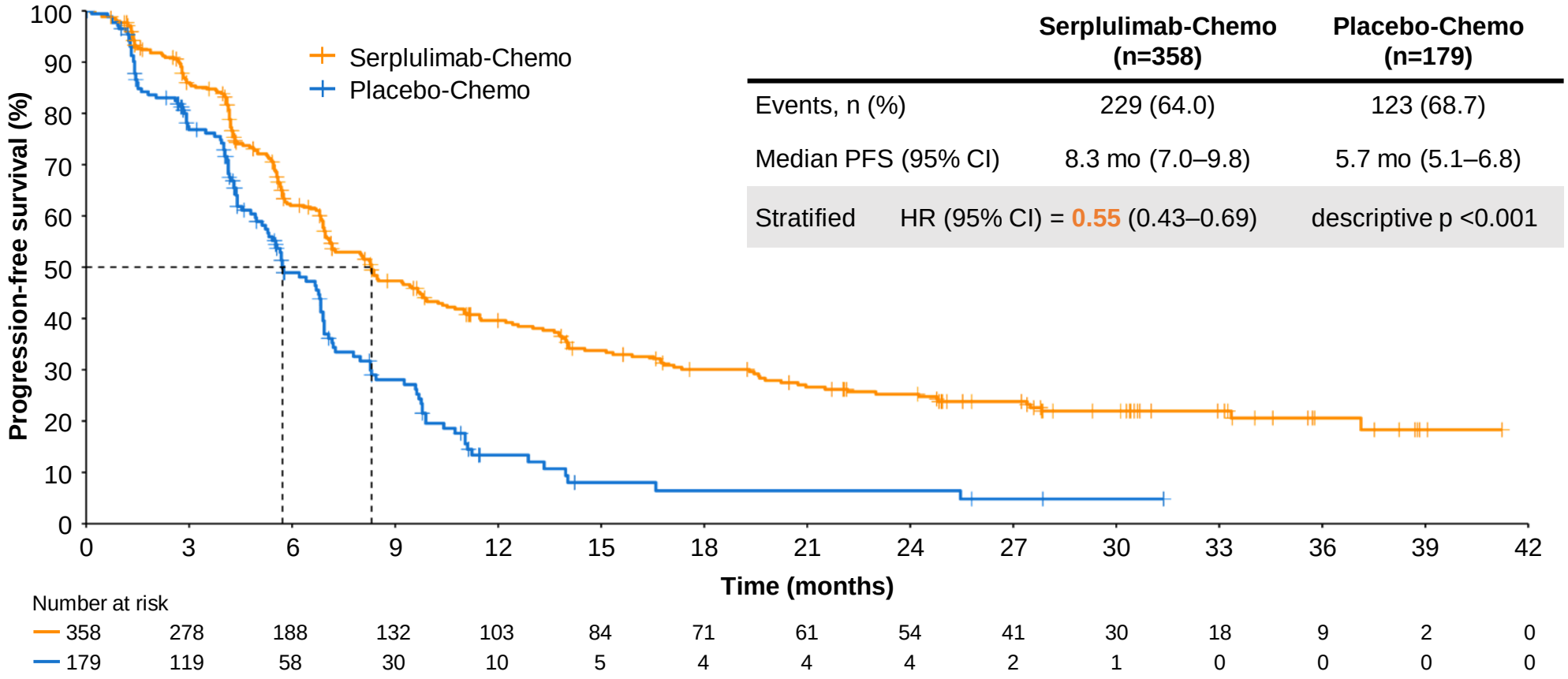
Data cutoff: January 31, 2023

Median follow-up duration: 31.1 months

	Serplulimab-Chemo (n=358)	Placebo-Chemo (n=179)
Median age (range), years	63.0 (41–81)	63.0 (35–86)
Sex, n (%)		
Male	321 (89.7)	167 (93.3)
Female	37 (10.3)	12 (6.7)
ECOG PS of 1, n (%)	293 (81.8)	153 (85.5)
Race, n (%)		
Asian	240 (67.0)	119 (66.5)
White	118 (33.0)	60 (33.5)
Disease stage, n (%)		
IIIB/IIIC	103 (28.8)	49 (27.4)
IV	255 (71.2)	130 (72.6)
PD-L1 expression, n (%)		
TPS <1%	135 (37.7)	68 (38.0)
1%≤ TPS <50%	119 (33.2)	58 (32.4)
TPS ≥50%	104 (29.1)	53 (29.6)
Smoking status, n (%)		
Current smoker	79 (22.1)	37 (20.7)
Former smoker	229 (64.0)	122 (68.2)
Never smoked	50 (14.0)	20 (11.2)
Liver metastasis, n (%)	40 (11.2)	17 (9.5)
Brain metastasis, n (%)	20 (5.6)	18 (10.1)

Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group perform status; PD-L1, programmed death-ligand 1; TPS, tumor proportion score

Updated PFS by IRRC per RECIST 1.1

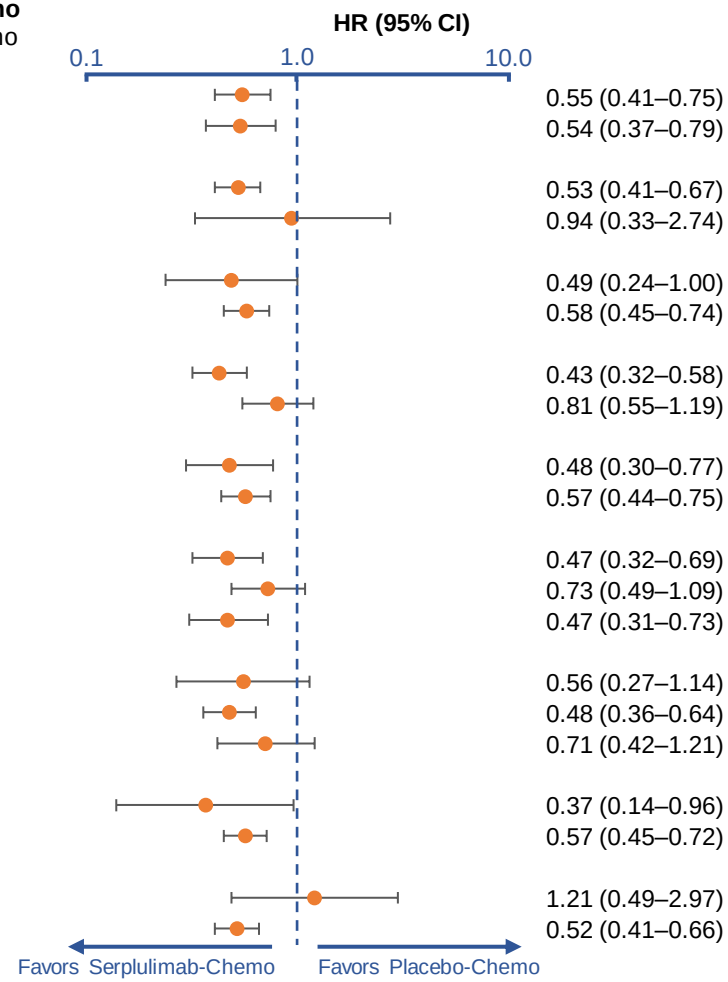


	Serplulimab-Chemo (n=358)	Placebo-Chemo (n=179)
Events, n (%)	229 (64.0)	123 (68.7)
Median PFS (95% CI)	8.3 mo (7.0–9.8)	5.7 mo (5.1–6.8)
Stratified	HR (95% CI) = **0.55** (0.43–0.69)	descriptive p <0.001

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IRRC, independent radiological review committee; mo, month; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors

Updated PFS in Subgroups

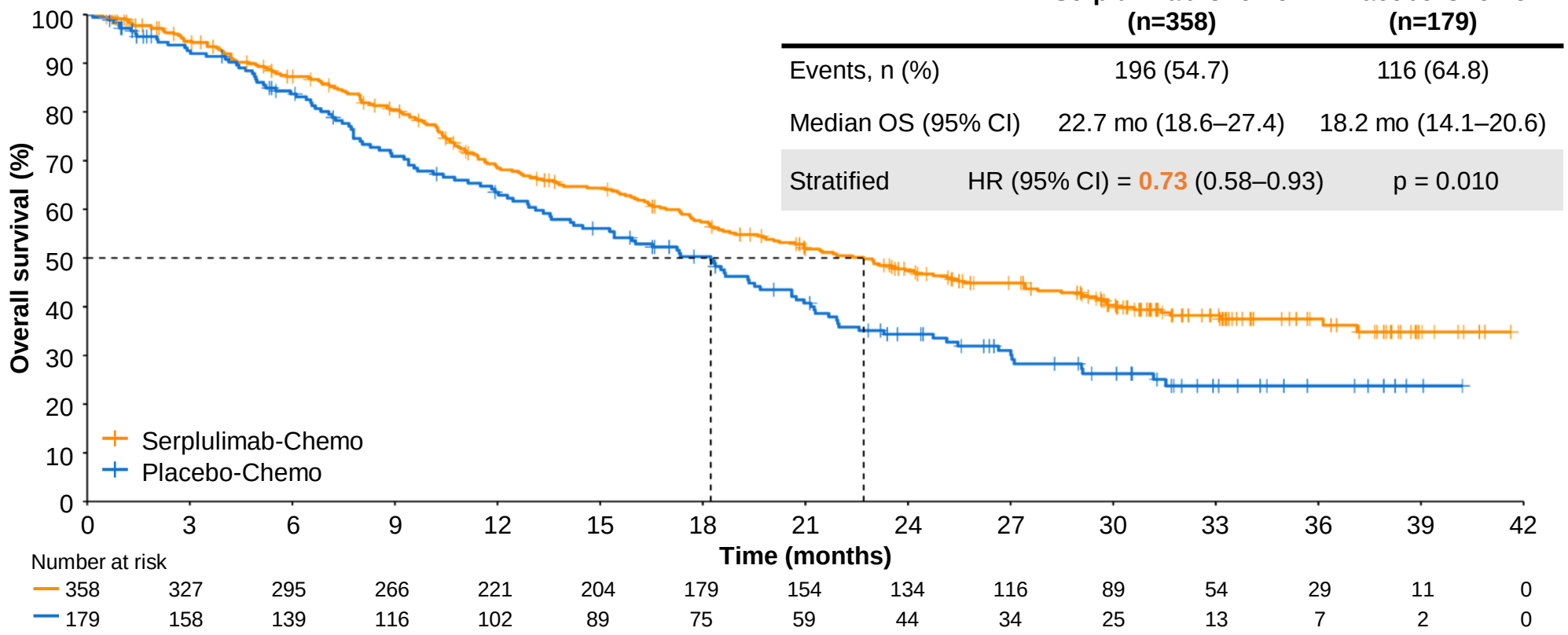
Subgroups	Serplulimab-Chemo events/patients	Placebo-Chemo events/patients	Serplulimab-Chemo median PFS, mo	Placebo-Chemo median PFS, mo	HR (95% CI)
Age					
<65 years	137/204	78/106	8.1	5.7	0.55 (0.41–0.75)
≥65 years	92/154	45/73	9.5	6.8	0.54 (0.37–0.79)
Sex					
Male	203/321	115/167	8.3	5.7	0.53 (0.41–0.67)
Female	26/37	8/12	9.2	6.7	0.94 (0.33–2.74)
ECOG PS					
0	43/65	15/26	12.6	5.7	0.49 (0.24–1.00)
1	186/293	108/153	8.0	5.7	0.58 (0.45–0.74)
Race					
Asian	143/240	79/119	9.9	5.8	0.43 (0.32–0.58)
Non-Asian	86/118	44/60	5.6	5.6	0.81 (0.55–1.19)
Disease stage					
Stage IIIB/IIIC	53/103	29/49	13.8	6.9	0.48 (0.30–0.77)
Stage IV	176/255	94/130	7.2	5.7	0.57 (0.44–0.75)
PD-L1 expression level					
TPS <1%	87/135	44/68	9.2	6.2	0.47 (0.32–0.69)
1%≤ TPS <50%	81/119	42/58	6.8	5.3	0.73 (0.49–1.09)
TPS ≥50%	61/104	37/53	11.5	6.9	0.47 (0.31–0.73)
Smoking status					
Never smoked	35/50	17/20	8.3	5.2	0.56 (0.27–1.14)
Former smoker	138/229	79/122	8.5	5.7	0.48 (0.36–0.64)
Current smoker	56/79	27/37	6.8	6.7	0.71 (0.42–1.21)
Brain metastasis					
Yes	14/20	12/18	6.9	4.9	0.37 (0.14–0.96)
No	215/338	111/161	8.4	6.4	0.57 (0.45–0.72)
Liver metastasis					
Yes	30/40	9/17	7.2	7.1	1.21 (0.49–2.97)
No	199/318	114/162	8.4	5.7	0.52 (0.41–0.66)



Prespecified subgroups: race, disease stage, and PD-L1 expression level; **post-hoc subgroups**: all others.

Chemo, chemotherapy; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mo, month; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TPS, tumor proportion score

Overall Survival



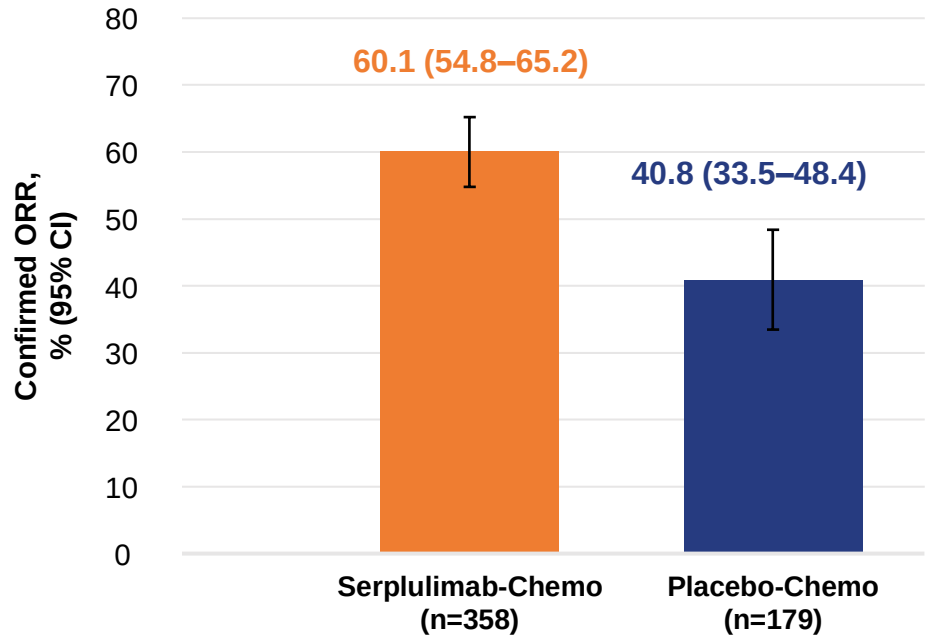
	Serplulimab-Chemo (n=358)	Placebo-Chemo (n=179)
Events, n (%)	196 (54.7)	116 (64.8)
Median OS (95% CI)	22.7 mo (18.6–27.4)	18.2 mo (14.1–20.6)
Stratified	HR (95% CI) = **0.73** (0.58–0.93)	p = 0.010

2-stage model adjusted OS for trial crossover

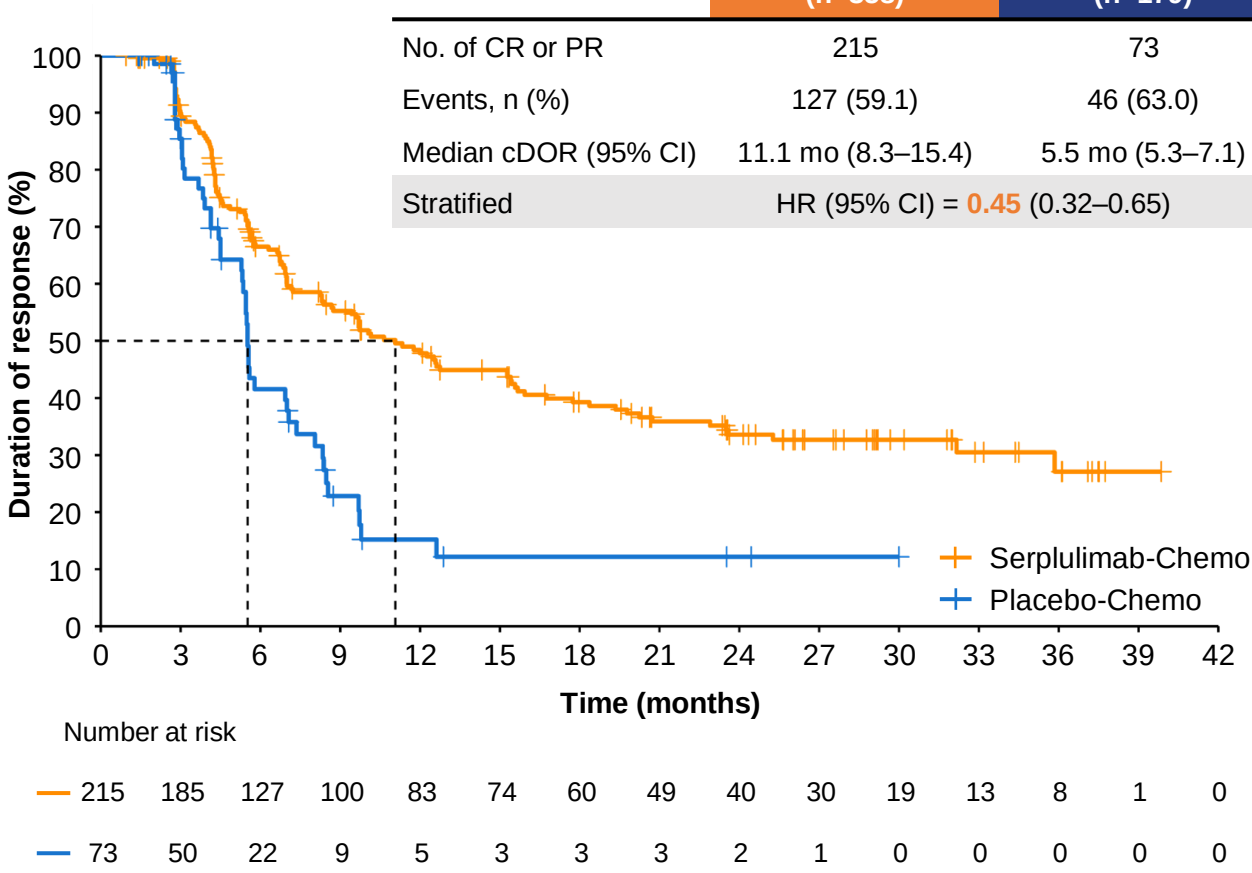
97 patients crossed over to serplulimab arm; adjusted median OS in placebo-chemo arm: 11.5 mo (95% CI 9.6–13.5); adjusted HR **0.49** (95% CI 0.37–0.64)

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; mo, month; OS, overall survival

Tumor Response by IRRC per RECIST v1.1



Confirmed BOR, n (%)		
Complete response	12 (3.4)	1 (0.6)
Partial response	203 (56.7)	72 (40.2)
Stable disease	85 (23.7)	62 (34.6)
Progressive disease	26 (7.3)	23 (12.8)
NE or NA	32 (8.9)	21 (11.7)

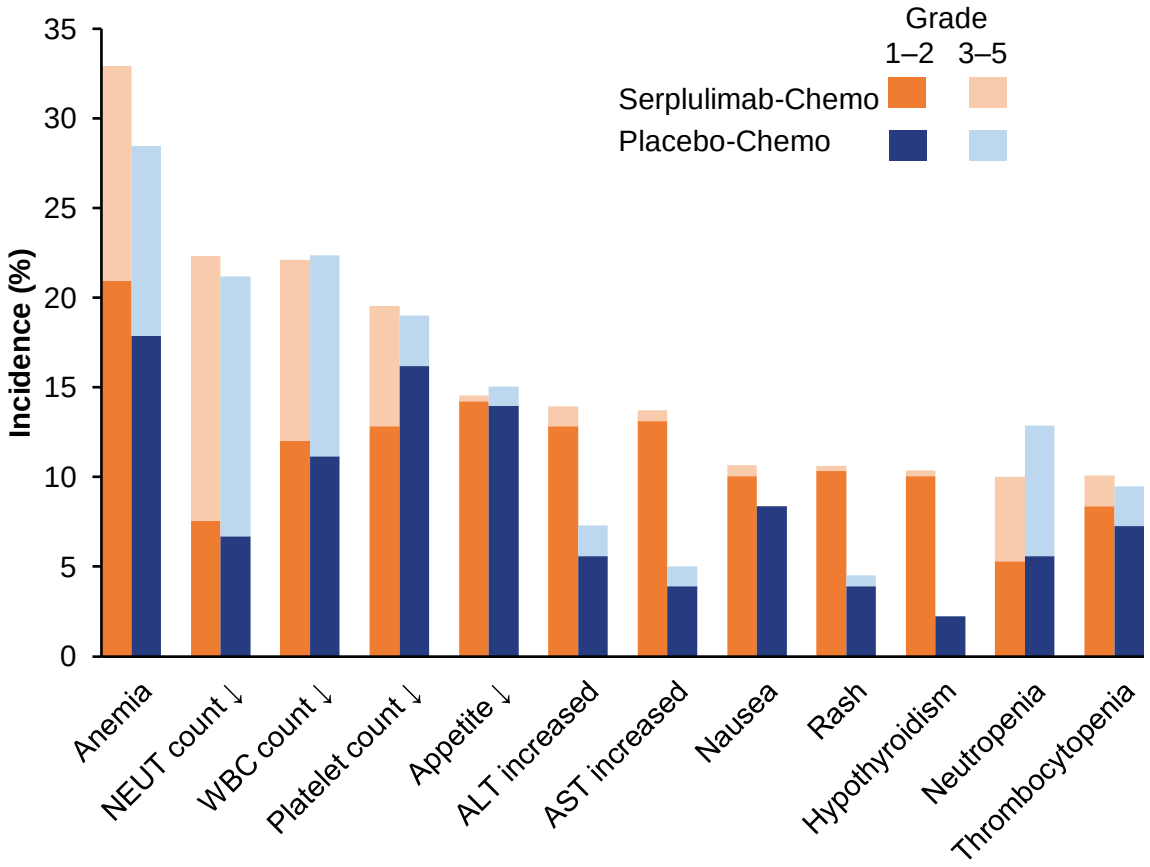


	Serplulimab-Chemo (n=358)	Placebo-Chemo (n=179)
No. of CR or PR	215	73
Events, n (%)	127 (59.1)	46 (63.0)
Median cDOR (95% CI)	11.1 mo (8.3–15.4)	5.5 mo (5.3–7.1)
Stratified	HR (95% CI) = 0.45 (0.32–0.65)	

BOR, best overall response; cDOR, confirmed duration of response; Chemo, chemotherapy; CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; IRRC, independent radiological review committee; mo, month; NA, not applicable; NE, not evaluable; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors

Safety Profile

	Serplulimab-Chemo (n=358)	Placebo-Chemo (n=179)
TEAE, n (%)	354 (98.9)	176 (98.3)
Grade ≥3	305 (85.2)	142 (79.3)
Serious	186 (52.0)	76 (42.5)
Leading to Tx discontinuation	80 (22.3)	27 (15.1)
Leading to death	49 (13.7)	19 (10.6)
AESI	109 (30.4)	31 (17.3)
irAE	106 (29.6)	31 (17.3)
IRR	4 (1.1)	0
TRAE, n (%)	345 (96.4)	170 (95.0)
Serious	119 (33.2)	49 (27.4)
Leading to death	4 (1.1)	5 (2.8)
Related to serplulimab/placebo	262 (73.2)	112 (62.6)
Grade ≥3	127 (35.5)	57 (31.8)
Leading to Tx discontinuation	37 (10.3)	9 (5.0)
Leading to death	4 (1.1)	2 (1.1)



[a] AEs related to serplulimab or placebo in ≥10% of patients in either group were shown.
[b] AEs occurred after trial crossover were not included.

AE, adverse event; AESI, adverse event of special interest; ALT, alanine transaminase; AST, aspartate aminotransferase; Chemo, chemotherapy; irAE, immune-related adverse event; IRR, infusion-related reaction; NEUT, neutrophil; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; Tx, treatment; WBC, white blood cell

Conclusions

- With 31.1 months of follow-up, serplulimab plus carboplatin/nab-paclitaxel showed consistent benefits in PFS, OS, ORR, and DOR.
  - Median OS at final analysis: 22.7 *vs* 18.2 months, HR = 0.73, p = 0.010
  - Updated median PFS at OS final analysis: 8.3 *vs* 5.7 months, HR = 0.55, descriptive p <0.001
- Serplulimab plus carboplatin/nab-paclitaxel showed a manageable safety profile, with no new safety signals being observed during the study.

In conclusion, adding serplulimab to carboplatin/nab-paclitaxel significantly improved survival in previously untreated patients with locally advanced or metastatic squamous NSCLC. The aforementioned combination regimen represents a new treatment option for this patient population in the global setting.

DOR, duration of response; HR, hazard ratio; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Acknowledgements

- Participants and their family members
- Investigators and research personnel at 85 study sites from 6 countries