ASTRUM-005

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ASTRUM-005: Serplulimab, A Novel Anti-PD-1 Antibody, Plus Chemotherapy versus Chemotherapy as First-Line Treatment for Extensive-Stage Small-Cell Lung Cancer: An International Randomized Phase 3 Study

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Background

SCLC

- Accounts for ~15% of lung cancers[1], ES-SCLC accounts for about 2/3 of SCLC[2]
- 5-year OS <7%[2]
- For the past 30 years, etoposide-platinum (EP) has been the standard first-line therapy[2]

Immunotherapy for SCLC

- Atezolizumab or durvalumab (PD-L1) in combination with EP was approved by FDA as the first-line treatment of ES-SCLC[3]. However, PD-L1 antibodies can only prolong the OS by around 2 months[4–5].
- Moreover, the efficacy of PD-1 inhibitors in SCLC patients remains unclear.

OS, overall survival; *PD-1*, programmed death 1; *PD-L1*, programmed death ligand-1; *SCLC*, small-cell lung cancer;

1. Govindan R et al. *J Clin Oncol*. **2006**; 24 (28): 4539-44.
2. Paz-Ares L et al. *Lancet*. **2019**; 394 (10212): 1929-1939.
3. TECENTRIQ® FDA Label and IMFINZI® FDA Label
4. Horn L et al. *N Engl J Med*. **2018**; 379 (23): 2220-2229.
5. Paz-Ares L et al. *Lancet*. **2019**; 394 (10212): 1929-1939.

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Background

As there still exist huge unmet medical needs, more beneficial immunotherapies need to be explored to further support the applications of checkpoint inhibitors in SCLC.

Serplulimab (PD-1)

- Serplulimab showed excellent anti-tumor activity with a manageable safety profile in the pivotal study ASTRUM-010, and was approved for the treatment of MSI-H solid tumor patients by China NMPA in March 2022[1–2].

Here, we report the results from the interim analysis of the phase 3 ASTRUM-005 study evaluating the efficacy and safety of serplulimab plus chemotherapy versus placebo plus chemotherapy in first-line ES-SCLC patients.

NMPA, National Medical Products Administration; *PD-1*, programmed death 1; *SCLC*, small-cell lung cancer;

1. Qin SK et al. *JCO.* **2021** 39:15_suppl, 2566-2566
2. https://www.henlius.com/en/NewsDetails-3512-26.html

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Study Design

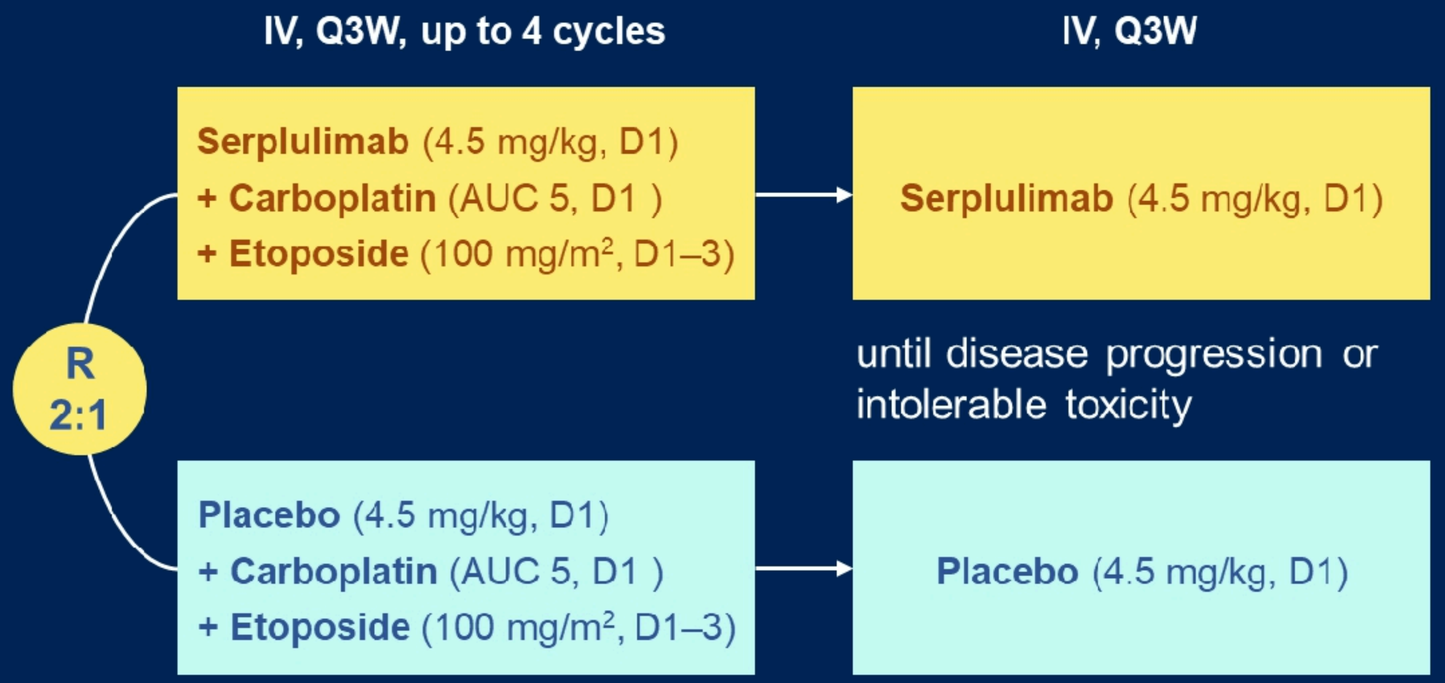
A randomized, double-blind, multicenter, placebo-controlled, phase 3 trial (NCT04063163)

Main inclusion criteria

- Histologically/cytologically diagnosed with ES-SCLC
- No prior systemic therapy for ES-SCLC
- At least one measurable lesion
- ECOG PS 0/1

Stratification factors

- PD-L1 expression levels (negative: TPS <1%, positive: TPS ≥1%, or NA)
- Brain metastases (Yes vs No)
- Age (<65 vs ≥65)



Primary endpoint: OS

Secondary endpoints: PFS, ORR, DOR, Safety and immunogenicity

AUC, area under curve; *DOR*, duration of response; *ECOG PS*, Eastern Cooperative Oncology Group performance status; *ES-SCLC*, extensive-stage small-cell lung cancer; *IV*, intravenous infusion; *NA*, not available; *ORR*, objective response rate; *OS*, overall survival; *PFS*, progression-free survival; *PD-L1*, programmed death ligand-1; Q3W, every 3 weeks; *TPS*, tumor proportion score;

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Statistical Consideration

Sample size calculation

- 567 patients were planned to be enrolled
  - Assume median OS in placebo group of 10 months
  - Assume a drop-off rate of 20%
- 342 OS events will provide 85% power to assess a HR of 0.7 at α=0.05 (two-sided)

Data analyses

- One interim analysis and final analysis were planned (O'Brien-Fleming-type alpha spending function)
  - Interim analysis will be conducted when 226 deaths accrued, at α=0.012 (two-sided)
  - Final analysis will be conducted when 342 deaths accrued, at α=0.046 (two-sided)

HR, hazard ratio; *OS*, overall survival;

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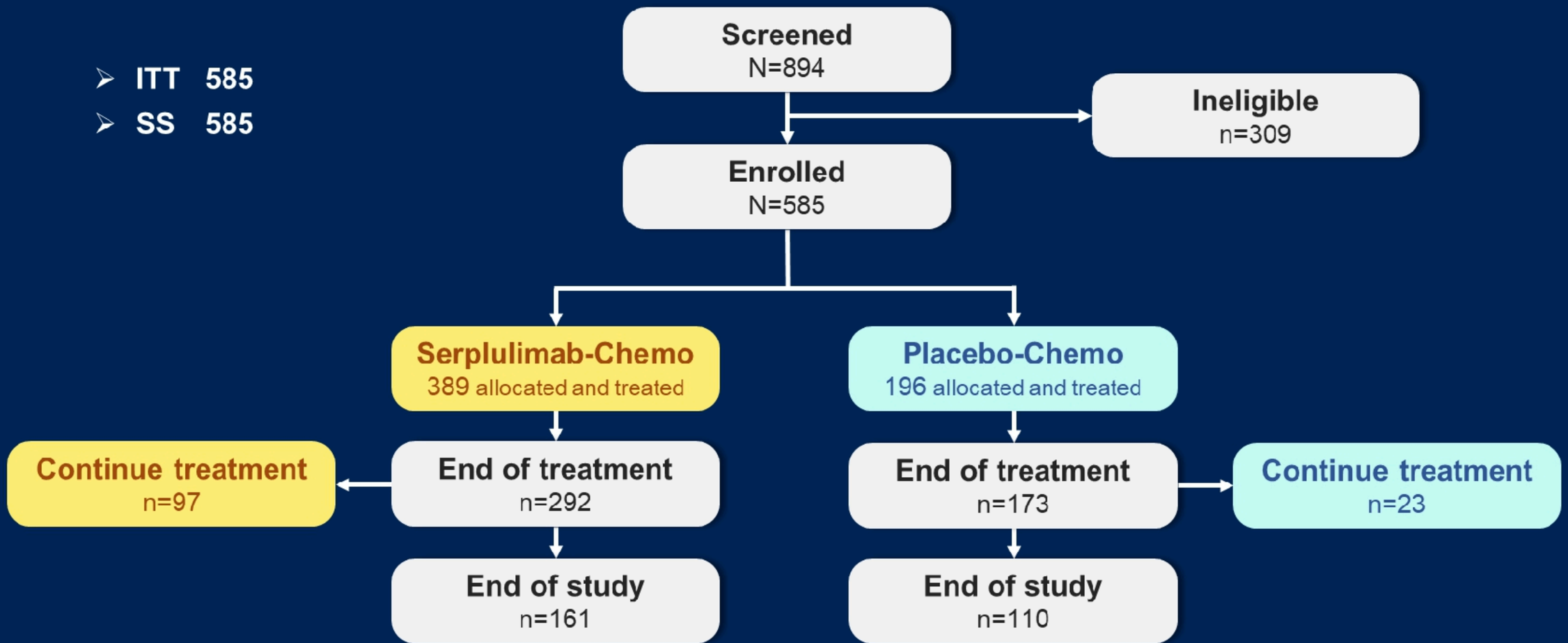
Treatment Disposition

- ITT 585
- SS 585



- As of data cut-off date Oct 22, 2021, the median follow-up duration was 12.3 months

AE, adverse event; *ITT*, intention-to-treat set; *PD*, progressive disease; *SS*, safety set;

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Baseline Characteristics

	Serplulimab-Chemo (n=389)	Placebo-Chemo (n=196)
Age, median (range), years	63 (28–76)	62 (31–83)
≥65, n (%)	154 (39.6)	77 (39.3)
Male, n (%)	317 (81.5)	164 (83.7)
Asian, n (%)	262 (67.4)	139 (70.9)
Smoker status, n (%)		
Current	102 (26.2)	48 (24.5)
Former	206 (53.0)	113 (57.7)
Never	81 (20.8)	35 (17.9)
SOD of target lesion, median (range), mm	117.7 (13.8–323.7)	120.5 (14.5–269.6)
ECOG PS 1, n (%)	318 (81.7)	164 (83.7)
Prior systemic therapy [a], n (%)		
Chemotherapy	9 (2.3)	3 (1.5)
Other	1 (0.3)	2 (1.0)
PD-L1 expression levels, n (%)		
Positive, TPS ≥1%	62 (15.9)	34 (17.3)
Negative, TPS <1%	317 (81.5)	152 (77.6)
Not available [b]	10 (2.6)	10 (5.1)
Brain metastases, n (%)	50 (12.9)	28 (14.3)
Liver metastases, n (%)	99 (25.4)	51 (26.0)

[a] 11 patients had prior therapies for limited-stage SCLC (treatment-free interval ≥6 months). 1 patient had prior therapy for gastric cancer (>5 years ago).
[b] PD-L1 TPS was not evaluable or had no data mostly due to inappropriate sectioning by participating sites or poor sample quality (i.e., not enough evaluable cells).

ECOG PS, Eastern Cooperative Oncology Group performance status; *PD-L1*, programmed death ligand-1; *SCLC*, small-cell lung cancer; *SOD*, sum of diameters; *TPS*, tumor proportion score;

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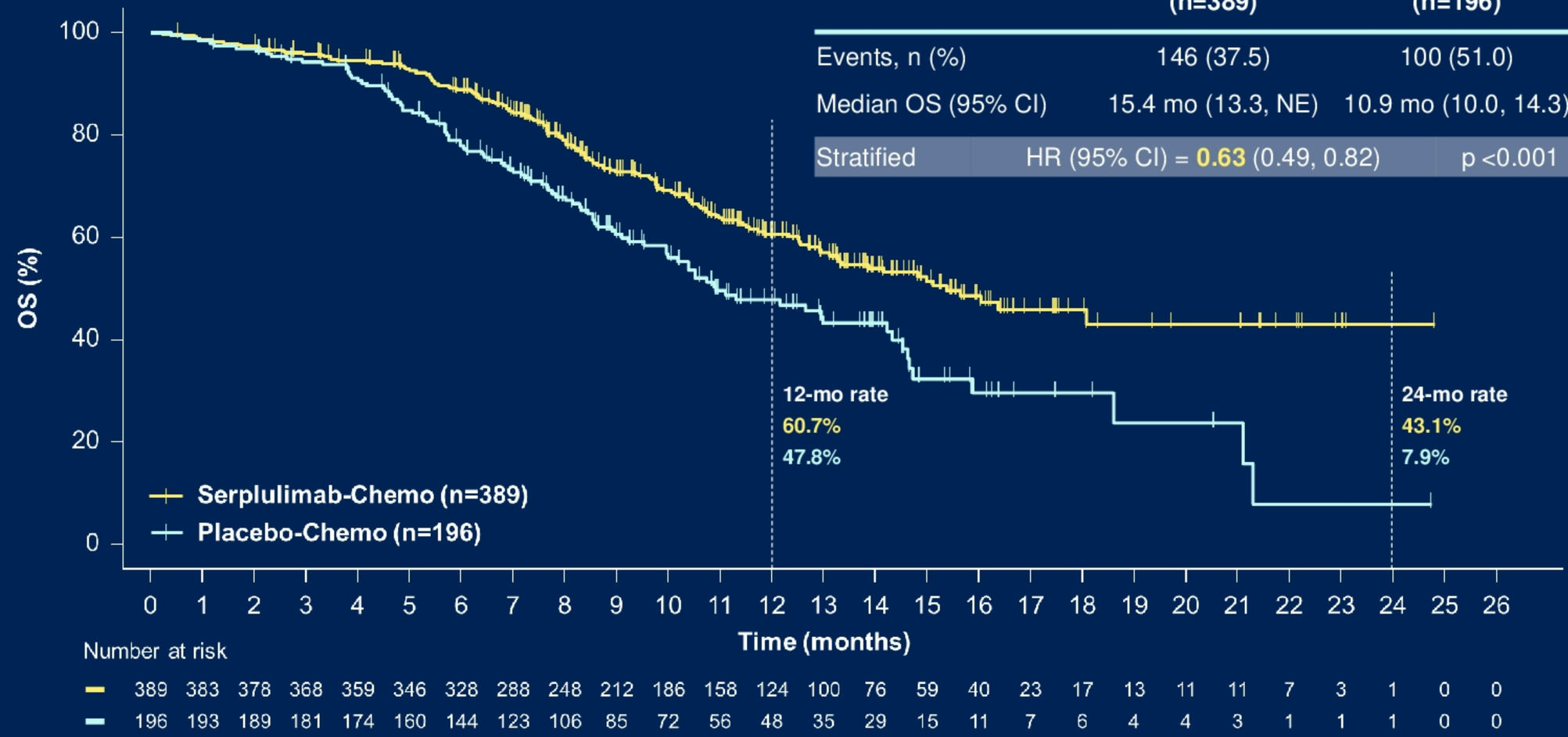
Overall Survival

	Serplulimab-Chemo (n=389)	Placebo-Chemo (n=196)
Events, n (%)	146 (37.5)	100 (51.0)
Median OS (95% CI)	15.4 mo (13.3, NE)	10.9 mo (10.0, 14.3)
Stratified	HR (95% CI) = **0.63** (0.49, 0.82)	p <0.001



CI, confidence interval; *HR*, hazard ratio; *mo*, month; *NE*, not evaluable; *OS*, overall survival;

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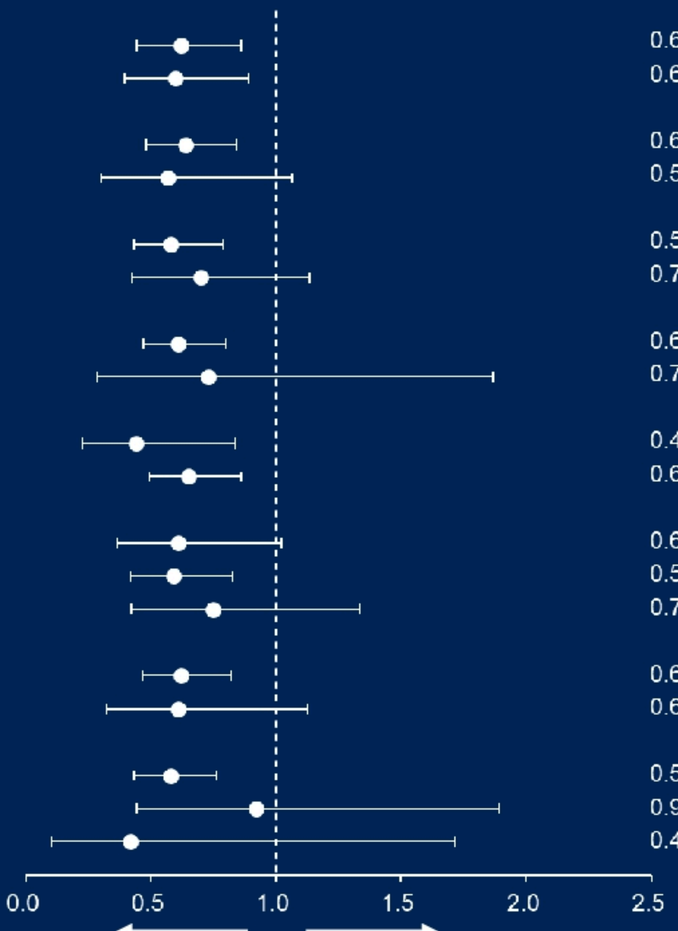
Overall Survival in Subgroups

Subgroups	Serplulimab-Chemo (n=389)	Placebo-Chemo (n=196)	HR (95% CI)
Age			
< 65 years	89/235 (37.9)	60/119 (50.4)	0.62 (0.45, 0.86)
≥ 65 years	57/154 (37.0)	40/77 (51.9)	0.60 (0.40, 0.89)
Sex			
Male	121/317 (38.2)	84/164 (51.2)	0.64 (0.48, 0.84)
Female	25/72 (34.7)	16/32 (50.0)	0.57 (0.30, 1.06)
Race			
Asian	103/262 (39.3)	74/139 (53.2)	0.58 (0.43, 0.79)
Non-Asian	43/127 (33.9)	26/57 (45.6)	0.70 (0.43, 1.13)
Ethnicity			
Non-Hispanic or Latino	134/366 (36.6)	92/184 (50.0)	0.61 (0.47, 0.80)
Other	12/23 (52.2)	8/12 (66.7)	0.73 (0.29, 1.87)
ECOG PS			
0	21/71 (29.6)	16/32 (50.0)	0.44 (0.23, 0.84)
1	125/318 (39.3)	84/164 (51.2)	0.65 (0.49, 0.86)
Smoker status			
Current	37/102 (36.3)	24/48 (50.0)	0.61 (0.36, 1.02)
Former	75/206 (36.4)	58/113 (51.3)	0.59 (0.42, 0.83)
Never	34/81 (42.0)	18/35 (51.4)	0.75 (0.42, 1.33)
Brain metastases			
No	123/339 (36.3)	82/168 (48.8)	0.62 (0.47, 0.82)
Yes	23/50 (46.0)	18/28 (64.3)	0.61 (0.33, 1.13)
PD-L1 expression levels			
TPS < 1%	121/317 (38.2)	83/152 (54.6)	0.58 (0.44, 0.76)
TPS ≥ 1%	22/62 (35.5)	11/34 (32.4)	0.92 (0.44, 1.89)
Not available	3/10 (30.0)	6/10 (60.0)	0.42 (0.10, 1.72)



CI, confidence interval; *HR*, hazard ratio; *PD-L1*, programmed death ligand-1; *TPS*, tumor proportion score;

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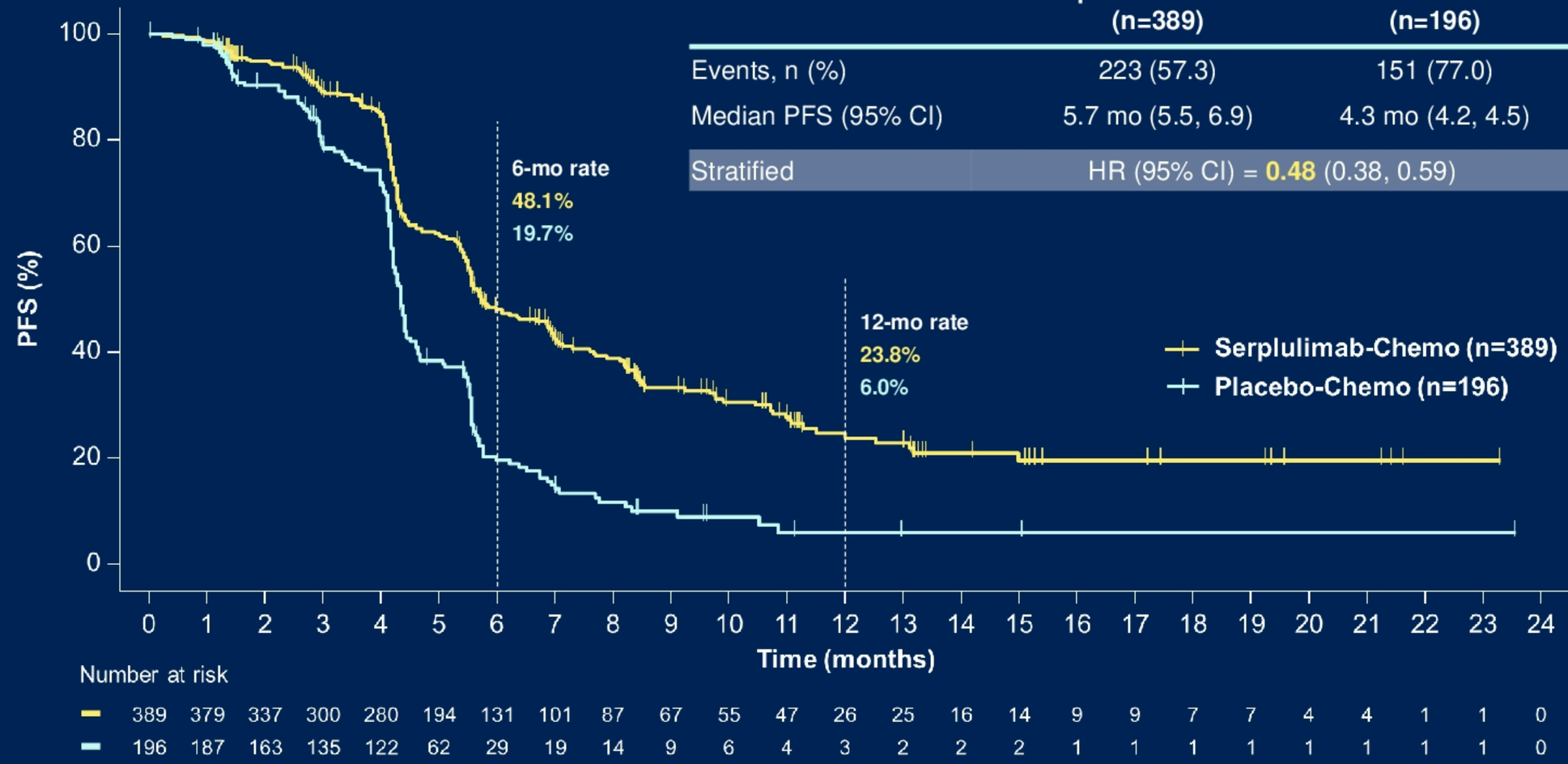
Progression-free survival by IRRC per RECIST 1.1

	Serplulimab-Chemo (n=389)	Placebo-Chemo (n=196)
Events, n (%)	223 (57.3)	151 (77.0)
Median PFS (95% CI)	5.7 mo (5.5, 6.9)	4.3 mo (4.2, 4.5)
Stratified	HR (95% CI) = **0.48** (0.38, 0.59)	



CI, confidence interval; *HR*, hazard ratio; *IRRC*, independent radiological review committee; *mo*, month; *PD*, progressive disease; *PFS*, progression-free survival; *RECIST*, response evaluation criteria in solid tumors;

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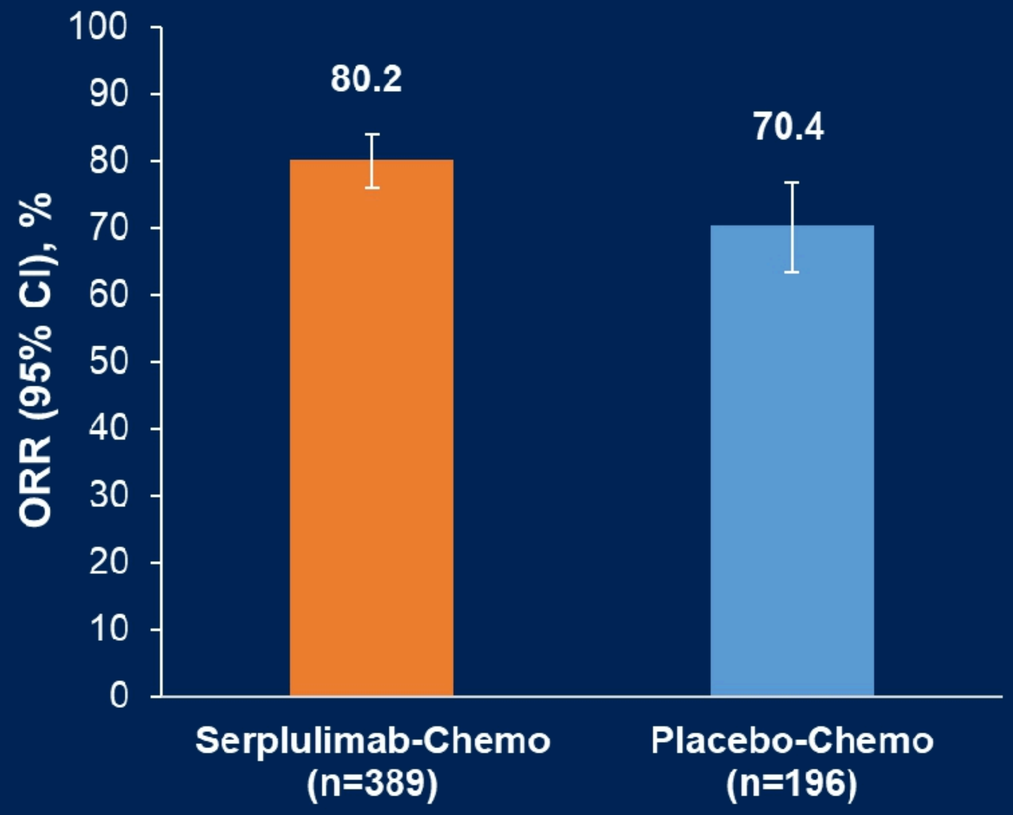
Summary of Response by IRRC per RECIST 1.1

	Serplulimab-Chemo (n=389)	Placebo-Chemo (n=196)
ORR, n (%) [95% CI]	**312 (80.2)** [75.9, 84.1]	**138 (70.4)** [63.5, 76.7]
Best overall response, n (%)		
CR	**3 (0.8)**	**0**
PR	309 (79.4)	138 (70.4)
SD	49 (12.6)	37 (18.9)
PD	9 (2.3)	11 (5.6)
NE or missing	19 (4.9)	10 (5.1)



CI, confidence interval; *CR*, complete response; *IRRC*, independent radiological review committee; *NE*, not evaluable; *ORR*, objective response rate; *PD*, progressive disease; *PR*, partial response; *RECIST*, response evaluation criteria in solid tumors; *SD*, stable disease;

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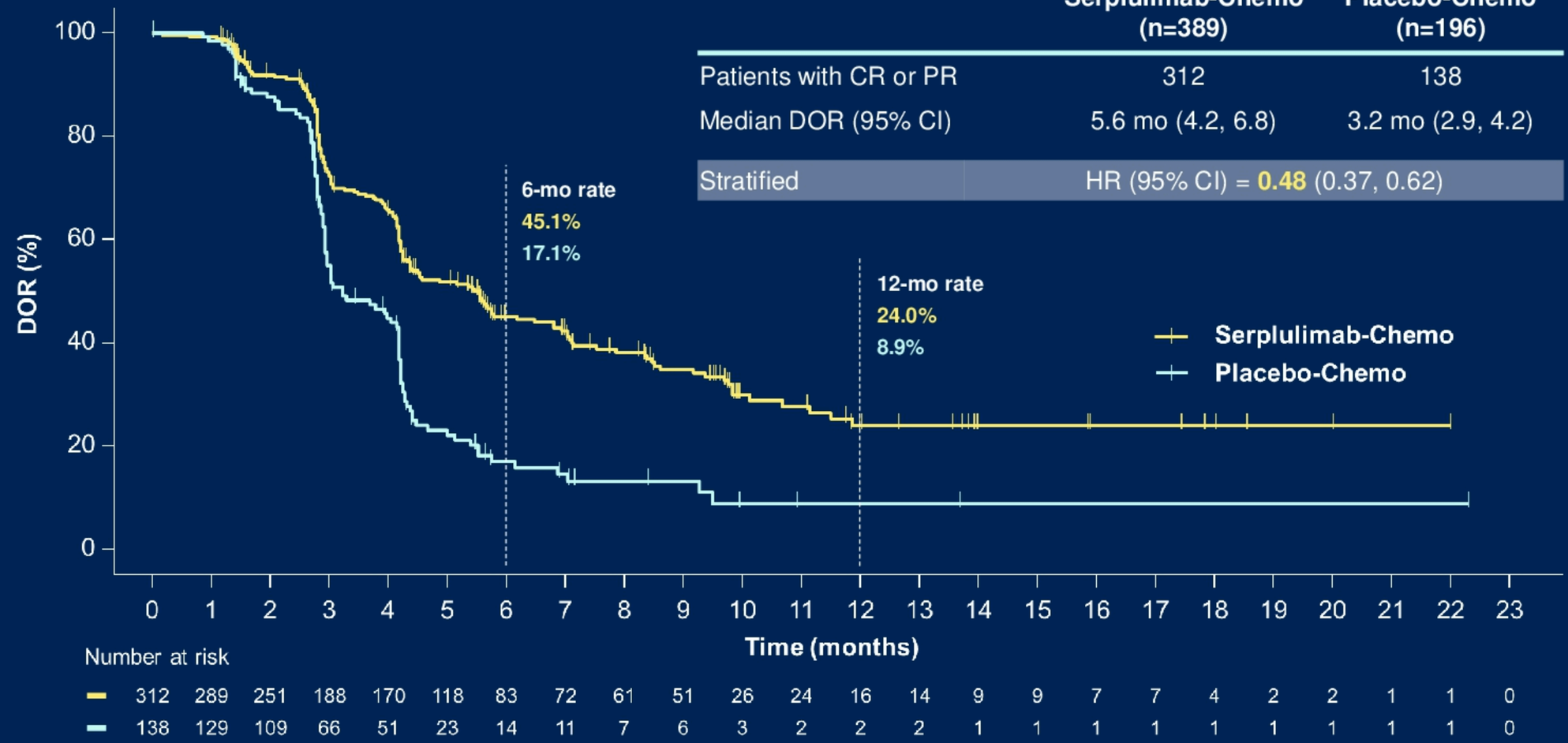
Duration of Response by IRRC per RECIST 1.1

	Serplulimab-Chemo (n=389)	Placebo-Chemo (n=196)
Patients with CR or PR	312	138
Median DOR (95% CI)	5.6 mo (4.2, 6.8)	3.2 mo (2.9, 4.2)
Stratified	HR (95% CI) = **0.48** (0.37, 0.62)	



CI, confidence interval; *CR*, complete response; *DOR*, duration of response; *HR*, hazard ratio; *IRRC*, independent radiological review committee; *mo*, month; *PR*, partial response; *RECIST*, response evaluation criteria in solid tumors;

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Safety Summary

	Serplulimab-Chemo (n=389)	Placebo-Chemo (n=196)
TEAEs, n (%)	372 (95.6)	191 (97.4)
CTCAE grade ≥3	321 (82.5)	157 (80.1)
SAEs	136 (35.0)	69 (35.2)
AESIs		
IRRs	7 (1.8)	1 (0.5)
irAEs	144 (37.0)	36 (18.4)
TRAEs related to serplulimab/placebo, n (%)	272 (69.9)	110 (56.1)
CTCAE grade ≥3	129 (33.2)	54 (27.6)
Leading to treatment discontinuation	19 (4.9)	8 (4.1)
Leading to death	3 (0.8)	1 (0.5)

- The most common irAEs in serplulimab group were: hypothyroidism (11.6%), hyperthyroidism (9.0%), and rash (3.1%)

AESI, adverse event of special interest; *CTCAE*, Common Terminology Criteria for Adverse Events; *irAE*, immune-related adverse event; *IRR*, infusion-related reaction; *SAE*, serious adverse event; *TEAE*, treatment-emergent adverse event; *TRAE*, treatment related adverse event;

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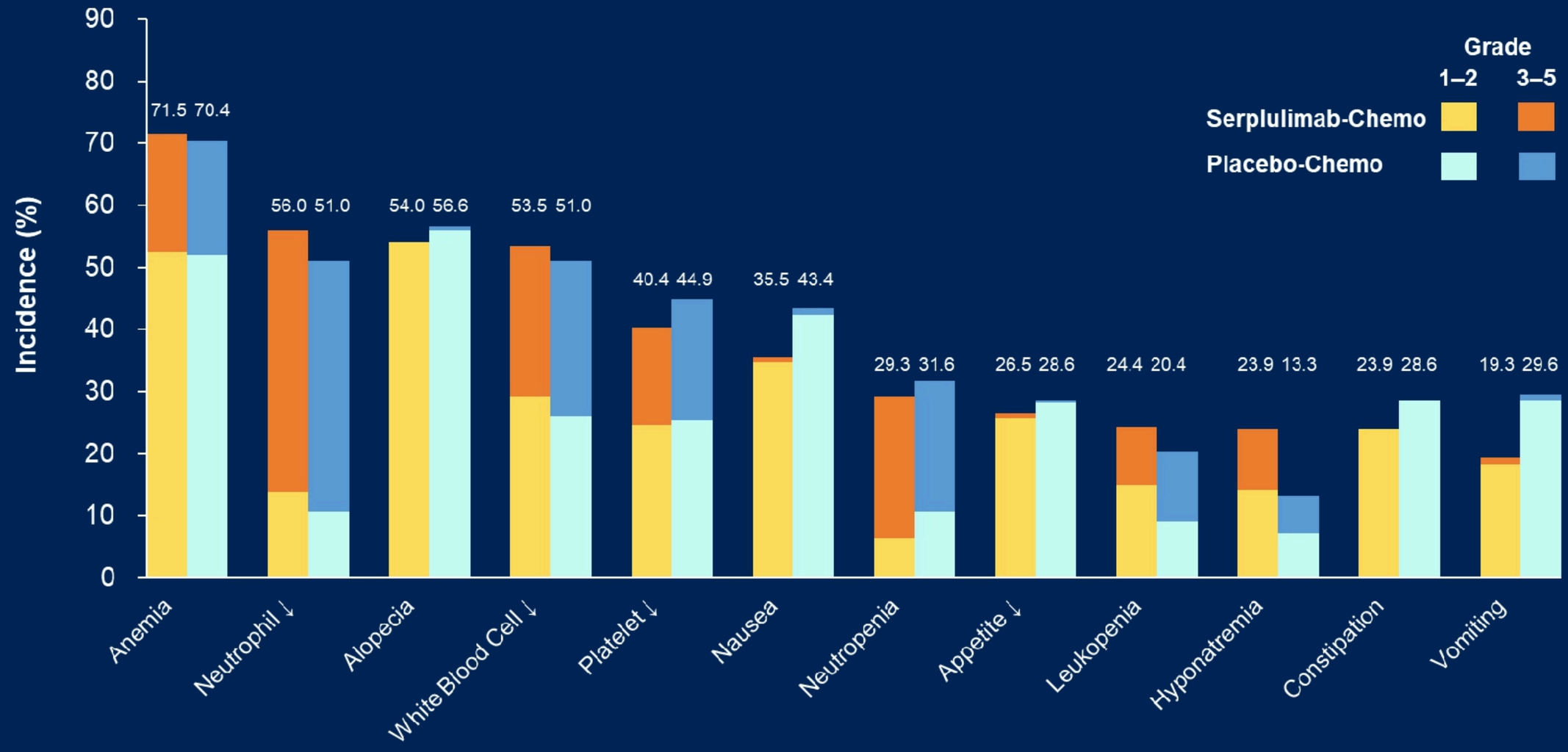
Most Common TEAEs



TEAE, treatment-emergent adverse event;

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Conclusions

- Serplulimab plus chemotherapy showed **consistent benefits in OS, PFS, ORR and DOR**.

  Long-term efficacy benefits were also observed;

  - ✓ mOS: 15.4 vs 10.9 months, HR=0.63, p <0.001
  - ✓ mPFS: 5.7 vs 4.3 months, HR=0.48

- Serplulimab plus chemotherapy showed a **manageable safety profile**;

  - ✓ No new safety signals were observed during the study

- The Orphan-Drug Designation (ODD) of serplulimab in SCLC has been granted by FDA.

  And the NDA of serplulimab in ES-SCLC is under review by NMPA.

DOR, duration of response; *ES-SCLC*, extensive-stage small-cell lung cancer; *FDA*, the United States Food and Drug Administration; *NDA*, new drug application; *NMPA*, National Medical Products Administration; *ORR*, objective response rate; *OS*, overall survival; *PFS*, progression-free survival;

Thank you