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ASTRUM-007: First-line serplulimab versus placebo in combination with chemotherapy in PD-L1–positive oesophageal squamous cell carcinoma

A randomised, double-blind, multicentre phase 3 trial

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DECLARATION OF INTERESTS

Professor Jing Huang has served a consulting or advisory role for Merck Sharpe & Dohme (MSD) Oncology and Roche.

Background

- Oesophageal cancer is one of the most common cancers worldwide, ranking tenth in terms of incidence and sixth for mortality among all cancers in 2020.[1]
- Asia accounts for about 80% of all oesophageal cancer cases in the world, and 54% of all cases occur in China.[2]

Serplulimab *HLX10*, anti–PD-1 monoclonal antibody

Several clinical trials have demonstrated that serplulimab has promising antitumour efficacy and a manageable safety profile in a variety of cancers. Serplulimab has been approved by the China National Medical Products Administration (NMPA) in March 2022 for the treatment of advanced unresectable or metastatic MSI-H solid tumours.

1. Sung H, *et al*. Global Cancer Statistics 2020. *CA Cancer J Clin.* **2021**;71(3):209-249. DOI: 10.3322/caac.21660.
2. Global Cancer Observatory. International Agency for Research on Cancer. https://gco.iarc.fr/. Accessed 24 Oct 2022.

MSI-H, microsatellite instability-high; **PD-1**, programmed cell death protein 1.

Study Design

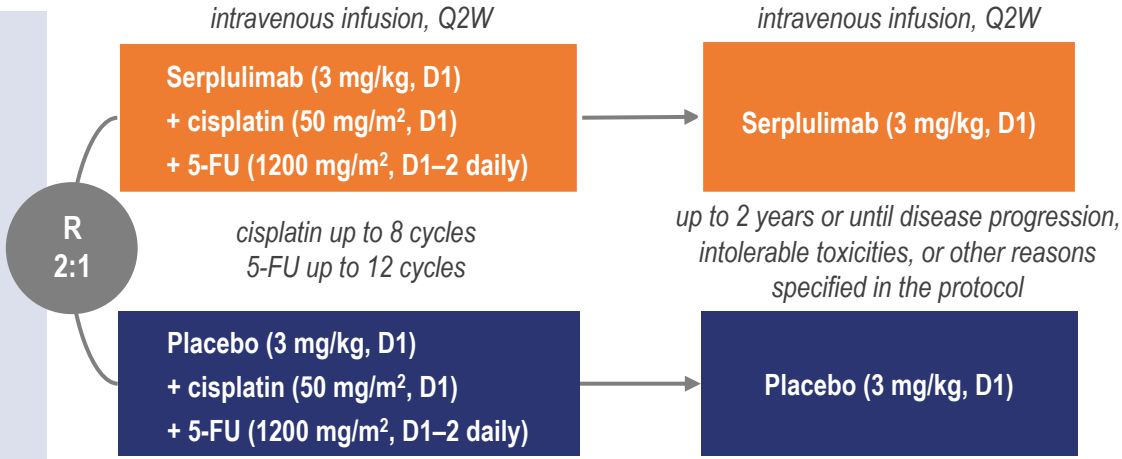
A randomised, double-blind, multicentre, placebo-controlled phase 3 trial (NCT03958890)

Main inclusion criteria

- Age 18–75 years
- Histologically confirmed locally advanced or distantly metastatic ESCC which cannot be cured by surgery or chemoradiotherapy
- No prior systemic therapy for current ESCC
- At least 1 measurable lesion
- PD-L1–positive (CPS ≥1)
- ECOG PS 0–1

Stratification factor

- PD-L1 expression level (1≤ CPS <10 vs. CPS ≥10)
- Age (<65 years vs. ≥65 years)
- Disease status (locally advanced vs distantly metastatic)

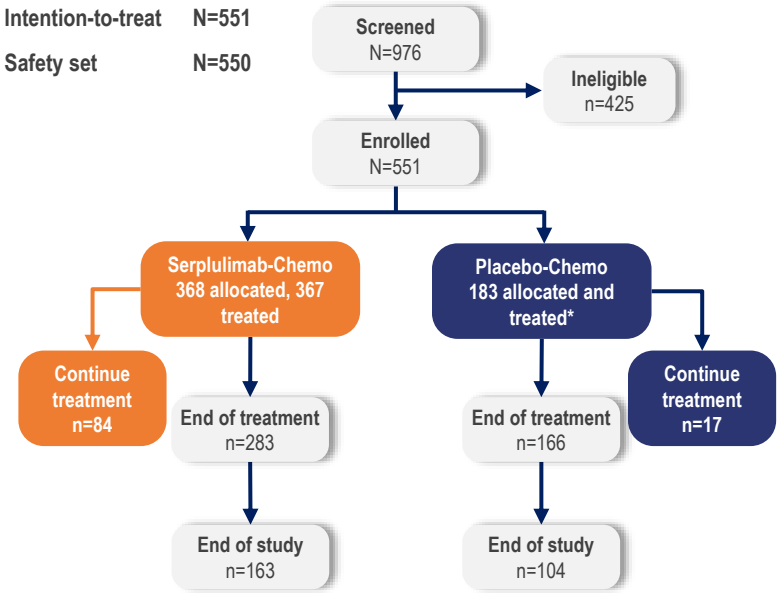


- **Primary endpoints:** PFS by IRRC per RECIST v1.1, OS
- **Secondary endpoints:** PFS by IRRC per iRECIST, PFS by investigators per RECIST v1.1 and iRECIST, ORR, DOR, safety, etc.

Statistical considerations: 540 patients, with 339 PFS events and 388 OS events needed respectively to achieve a power of 80% to show a HR of 0.68 for PFS at a one-sided α level of 0.005 and 0.73 for OS at a one-sided α level of 0.02 for comparison between the serplulimab-chemo group and the placebo-chemo group. The interim analysis of OS was planned to be performed during the final analysis of PFS, when approximately 339 IRRC-assessed PFS events had been observed in the Intention-to-treat population. The threshold for statistical significance was 0.01 (two-sided) for the final log-rank analysis of PFS and 0.01 (two-sided) for the interim log-rank analysis of OS (adjusted according to the actual 266 OS events and O'Brien-Fleming-like α-spending function).

CPS, combined positive score; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ESCC**, oesophageal squamous cell carcinoma; **iRECIST**, immune-RECIST; **IRRC**, independent radiological review committee; **ORR**, objective response rate; **OS**, overall survival; **PD-L1**, programmed cell death protein ligand 1; **PFS**, progression-free survival; **R**, randomisation; **RECIST**, Response Evaluation Criteria in Solid Tumors.

Patient Disposition and Baseline Characteristics



*Includes 15 patients who were randomised to receive placebo-chemo but received serplulimab-chemo due to an error in drug distribution.

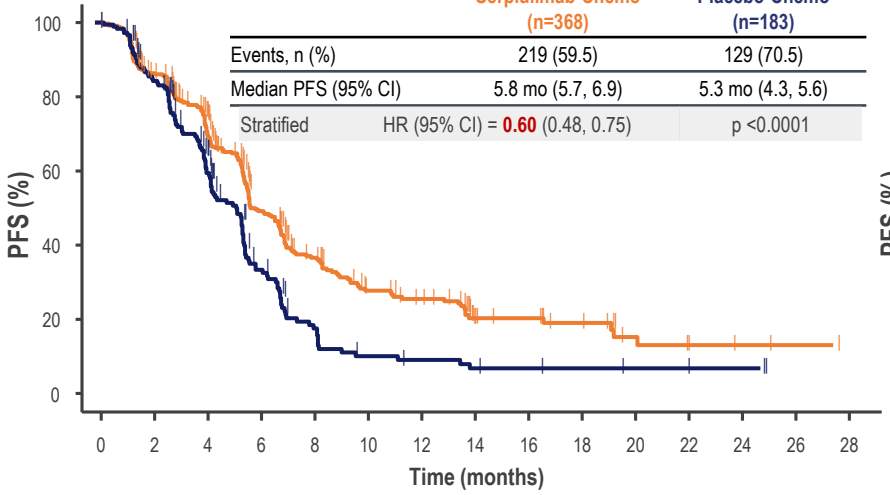
	Serplulimab-Chemo (n=368)	Placebo-Chemo (n=183)
Age, median (interquartile range), years	64 (57–68)	64 (57–68)
≥65, n (%)	169 (45.9)	85 (46.4)
Sex, n (%)		
Male	317 (86.1)	153 (83.6)
Female	51 (13.9)	30 (16.4)
ECOG PS of 1, n (%)	275 (74.7)	130 (71.0)
Disease status, n (%)		
Locally advanced	46 (12.5)	29 (15.8)
Distantly metastatic	322 (87.5)	154 (84.2)
Number of organs with metastases, n (%)		
1	184 (50.0)	104 (56.8)
≥2	184 (50.0)	79 (43.2)
Sites of metastases, n (%)		
Lymph node	365 (99.2)	182 (99.5)
Lung	96 (26.1)	42 (23.0)
Liver	71 (19.3)	32 (17.5)
Bone	48 (13.0)	15 (8.2)
PD-L1 expression, n (%)		
1≤ CPS <10	206 (56.0)	104 (56.8)
CPS ≥10	162 (44.0)	79 (43.2)
Smoking status, n (%)		
Current or former smoker	232 (63.0)	115 (62.8)
Never smoked	136 (37.0)	68 (37.2)

- As of 15 April 2022 (data cutoff), the median follow-up duration was 14.9 months.

CPS, combined positive score; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **PD-L1**, programmed cell death protein ligand 1.

Progression-free Survival by IRRC per RECIST 1.1

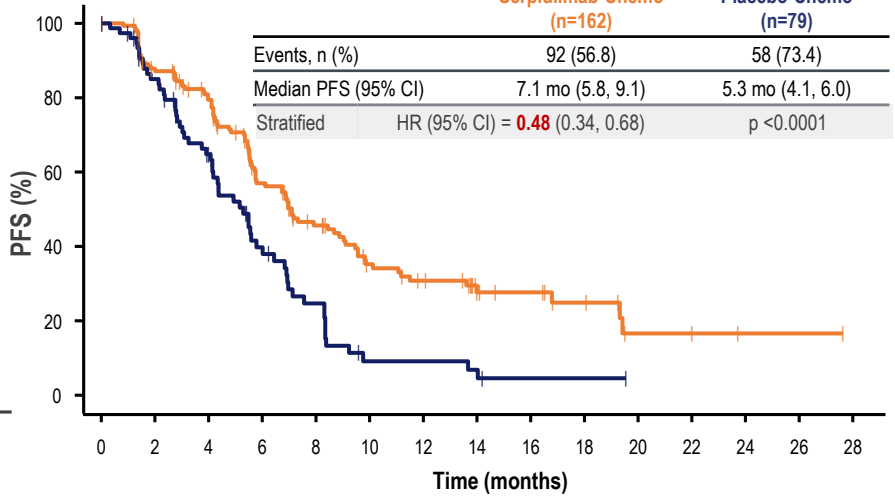
ITT population



Number at risk

Serplulimab-Chemo	368	295	236	129	82	53	44	22	19	14	7	4	2	1	0
Placebo-Chemo	183	144	102	43	21	10	8	7	5	4	3	3	2	0	0

PD-L1 CPS ≥10



Number at risk

Serplulimab-Chemo	162	133	111	69	48	32	26	14	12	8	3	3	1	1	0
Placebo-Chemo	79	61	43	22	13	4	4	3	1	1	0	0	0	0	0

CI, confidence interval; **CPS**, combined positive score; **HR**, hazard ratio; **IRRC**, independent radiological review committee; **ITT**, intention-to-treat; **PD-L1**, programmed cell death protein ligand 1; **PFS**, progression-free survival; **RECIST**, Response Evaluation Criteria in Solid Tumors.

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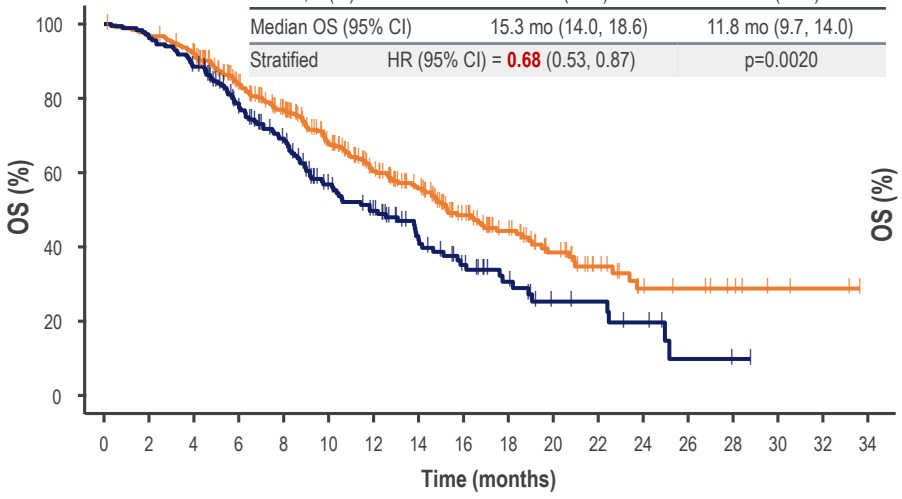
Overall Survival

ITT population

	Serplulimab-Chemo (n=368)	Placebo-Chemo (n=183)
Events, n (%)	163 (44.3)	104 (56.8)
Median OS (95% CI)	15.3 mo (14.0, 18.6)	11.8 mo (9.7, 14.0)
Stratified	HR (95% CI) = **0.68** (0.53, 0.87)	p=0.0020

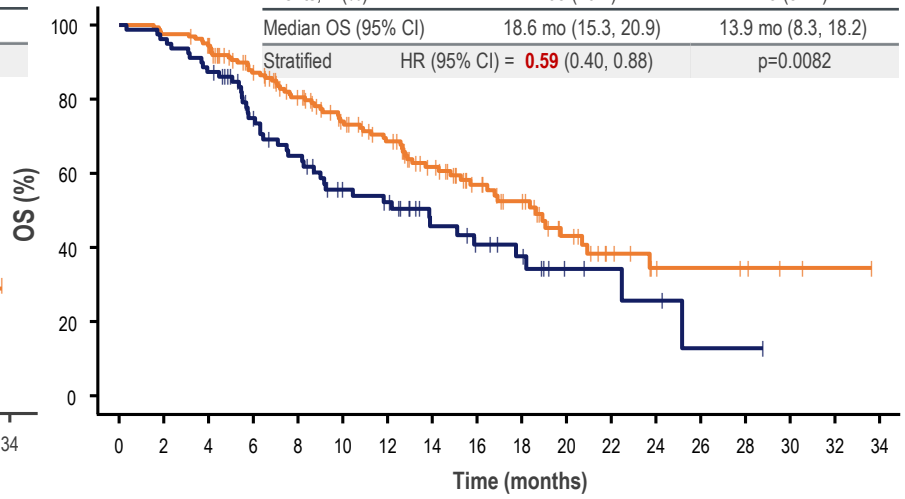


Number at risk

Serplulimab-Chemo	368	356	335	275	225	177	140	112	77	55	35	21	11	9	6	3	2	0
Placebo-Chemo	183	177	161	129	105	73	60	40	28	19	11	9	6	2	1	0	0	0

PD-L1 CPS ≥10

	Serplulimab-Chemo (n=162)	Placebo-Chemo (n=79)
Events, n (%)	65 (40.1)	43 (54.4)
Median OS (95% CI)	18.6 mo (15.3, 20.9)	13.9 mo (8.3, 18.2)
Stratified	HR (95% CI) = **0.59** (0.40, 0.88)	p=0.0082

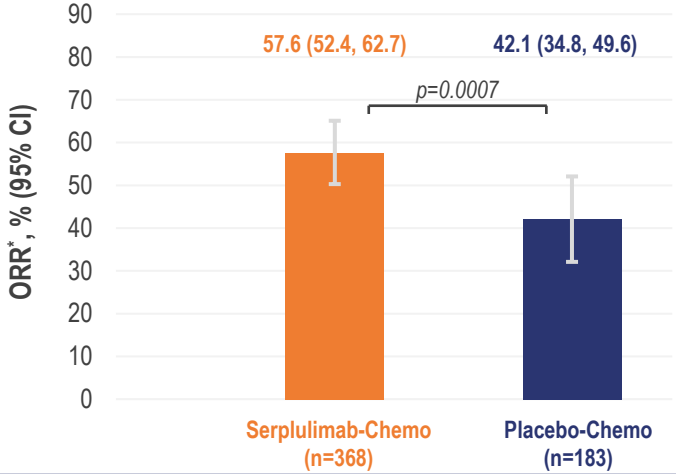


Number at risk

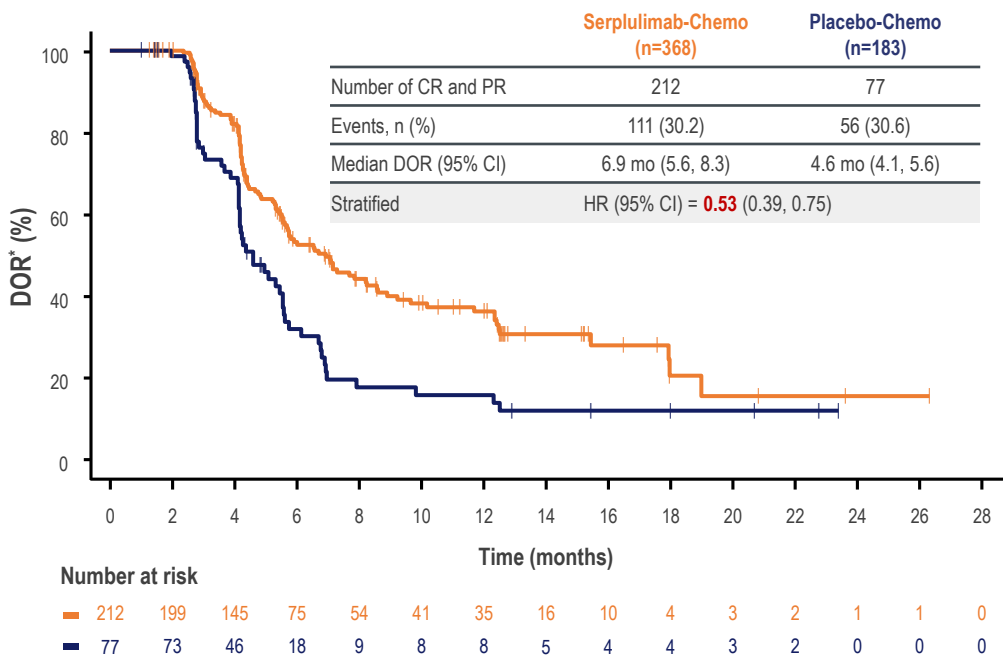
Serplulimab-Chemo	162	158	151	127	105	87	75	57	41	33	20	12	6	5	4	2	1	0
Placebo-Chemo	79	76	69	53	44	33	30	19	15	12	6	4	3	1	1	0	0	0

CI, confidence interval; **CPS**, combined positive score; **HR**, hazard ratio; **ITT**, intention-to-treat; **OS**, overall survival; **PD-L1**, programmed cell death protein ligand 1.

Objective Response Rate and Duration of Response by IRRC per RECIST 1.1



	Serplulimab-Chemo (n=368)	Placebo-Chemo (n=183)
DCR, % (95% CI)	79.6 (75.1, 83.6)	76.0 (69.1, 82.0)
CR, n (%)	50 (13.6)	12 (6.6)
PR, n (%)	162 (44.0)	65 (35.5)
SD, n (%)	81 (22.0)	62 (33.9)
PD, n (%)	49 (13.3)	28 (15.3)
NE, n (%)	26 (7.1)	16 (8.7)



	Serplulimab-Chemo (n=368)	Placebo-Chemo (n=183)
Number of CR and PR	212	77
Events, n (%)	111 (30.2)	56 (30.6)
Median DOR (95% CI)	6.9 mo (5.6, 8.3)	4.6 mo (4.1, 5.6)
Stratified	HR (95% CI) = **0.53** (0.39, 0.75)	

* Confirmed ORR and confirmed DOR.

CI, confidence interval; **CR**, complete response; **DCR**, disease control rate; **DOR**, duration of response; **HR**, hazard ratio; **IRRC**, independent radiological review committee; **NE**, non-evaluable; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **RECIST**, Response Evaluation Criteria in Solid Tumors; **SD**, stable disease.

Safety Summary

	Serplulimab-Chemo (n=382*)	Placebo-Chemo (n=168*)
TEAEs, n (%)	379 (99.2)	167 (99.4)
Grade ≥3 TEAEs	243 (63.6)	99 (58.9)
SAEs	139 (36.4)	54 (32.1)
AESIs	132 (34.6)	31 (18.5)
IRRs	4 (1.0)	3 (1.8)
irAEs	132 (34.6)	30 (17.9)
TRAEs, n (%)	376 (98.4)	165 (98.2)
Grade ≥3 TRAEs	201 (52.6)	81 (48.2)
TRAEs leading to treatment discontinuation	130 (34.0)	39 (23.2)
TRAEs leading to death	11 (2.9)	3 (1.8)

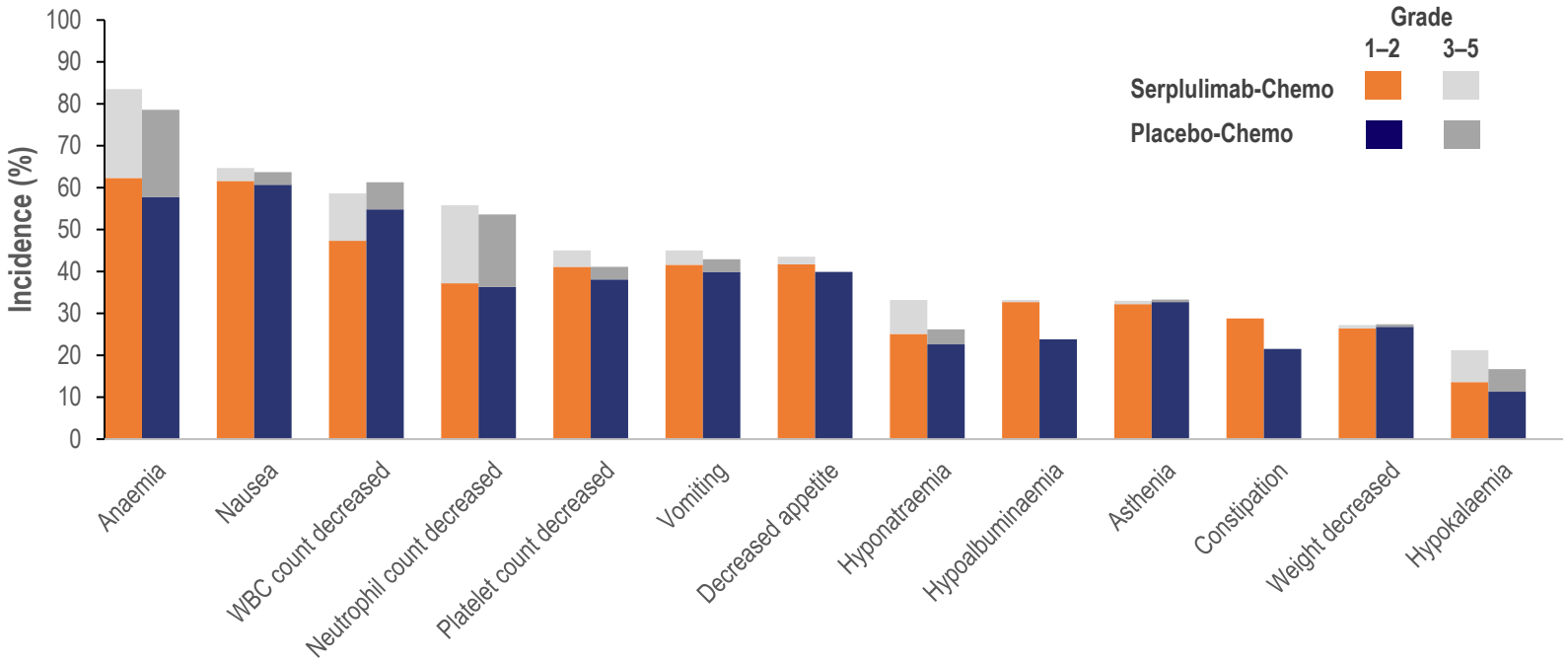
- Most common irAEs included immune-mediated hypothyroidism (10.7% vs. 2.4%), immune-mediated dermatitis (6.3% vs. 3.0%), and immune-mediated hyperthyroidism (4.5% vs. 2.4%).

* Including all patients who received at least one dose of study treatment; 15 patients who were randomised to receive placebo-chemo received serplulimab-chemo due to an error in drug distribution.

AESI, adverse event of special interest; **irAE**, immune-related adverse event; **IRR**, infusion-related reactions; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event; **TRAE**, treatment-related adverse event.

数据截止日期：2022-4-15

Most Common TEAEs



TEAEs with an incidence of >20% in either treatment group are shown.
TEAE, treatment-emergent adverse event; **WBC**, white blood cell.

数据截止日期：2022-4-15

Conclusions

- Serplulimab plus chemotherapy demonstrated **consistent clinical benefits** in OS, PFS, ORR, and DOR, and showed **significantly better antitumour activity** compared to chemotherapy alone;
  - ✓ Median PFS: 5.8 vs. 5.3 months, HR=0.60, p<0.0001
  - ✓ Median OS: 15.3 vs. 11.8 months, HR=0.68, p=0.0020
- Serplulimab plus chemotherapy showed **manageable safety**;
  - ✓ No new safety signal was identified during the trial.
- In conclusion, serplulimab combined with chemotherapy (cisplatin + 5-FU) showed significant efficacy and manageable safety in patients with previously untreated, locally advanced or distantly metastatic, PD-L1–positive ESCC. Based on the trial results, the New Drug Application for serplulimab in combination with chemotherapy for the treatment of ESCC has been accepted by China NMPA; this therapeutic regimen may provide a new treatment option for these patients.

DOR, duration of response; **ESCC**, oesophageal squamous cell carcinoma; **HR**, hazard ratio; **NMPA**, National Medical Products Administration; **ORR**, objective response rate; **OS**, overall survival; **PD-L1**, programmed cell death protein ligand 1; **PFS**, progression-free survival.

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