IGCS 2024
Annual Global Meeting
DUBLIN

Cadonilimab plus Chemotherapy with or without Bevacizumab as First-line Treatment for Persistent, Recurrent, or Metastatic Cervical Cancer: A Randomized, Double-blind, Placebo-controlled Phase 3 Study (COMPASSION-16)

X. Wu[1], Y. Sun[2], H. Yang[3], J. Wang[4], H. Lou[5], D. Li[6], K. Wang[7], Z. Hui[8], T. Wu[9], Y. Li[10], C. Wang[11], G.Li[12], Y. Wang[13], D. Li[14], Y. Tang[15], M. Pan[16], H. Cai[17], T. Liu[18], Y. Xia[18]

1.Fudan University Shanghai Cancer Center, Shanghai, China; 2.Clinical oncology school of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China; 3.Yunnan Cancer Hospital, Kunming, China; 4.Hunan Cancer Hospital,Changsha, China; 5.Zhejiang Cancer Hospital, Hangzhou, China; 6.The Affiliated Hospital of Southwest Medical University, Luzhou, China; 7.Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; 8.The Fourth Hospital of Hebei Medical University, Shijiazhuang, China; 9.Changde First People's Hospital, Changde, China; 10.The First Affiliated Hospital of Bengbu Medical College, Bengbu, China; 11.Liaoning Cancer Hospital, Shenyang, China; 12.Union Hospital affiliated to Tongji Medical College, Wuhan, China; 13.Zhujiang Hospital of Southern Medical University, Guangzhou, China; 14.Cancer Hospital of Shandong First Medical University, Jinan, China;15.Affiliated Cancer Hospital of Chongqing University, Chongqing,China; 16.Jiangxi Maternal and Child Health Hospital, Nanchang,China; 17.Radiotherapy Department, Gansu Provincial Hospital, Lanzhou, China, 18. Akeso Biopharma Inc., Zhongshan, China

IGCS INTERNATIONAL GYNECOLOGIC CANCER SOCIETY

In Collaboration With

Fáilte Ireland

Disclosure

No conflicts of interests to disclose

Introduction

- **Cadonilimab is a first-in-class bi-specific antibody targeting PD-1 and CTLA-4. Cadonilimab monotherapy has been approved by China's NMPA, for use in advanced cervical cancer at second or later lines, regardless of PD-L1 status.**
- **Pembrolizumab combined with platinum-based chemotherapy ± bevacizumab is currently the first-line standard of care for persistent, recurrent, or metastatic cervical cancer patients with PD-L1 expression positive (CPS≥1)[1][2].**
- **A phase II study (COMPASSION-13) showed impressive efficacy of cadonilimab combined with chemotherapy ± bevacizumab in the first-line treatment of cervical cancer[3][4] :**
  - ✓ The ORR was around 80%, and was 75% even in PD-L1 negative patients.
  - ✓ The 1-year OS rate was over 80%.
- **This Phase III study (COMPASSION-16) evaluate the efficacy and safety of cadonilimab in 1L treatment for cervical cancer.**

[1]Tewari KS, Sill MW, et al. N Engl J Med. 2014;370(8):734-743.
[2]Bradley J. Monk et al. JCO 41, 5505-5511(2023).
[3]Jing Wang et al., JCO 40, 106-106(2022).
[4]Lou H, Cai H, et al. Clin Cancer Res. 2024;30(8):1501-1508.
NMPA:National Medical Products Administration; CPS: Combined Positive Score

Study Design

- **Randomized, placebo-controlled, multicenter, double-blind, phase III trial**

Key eligibility Criteria

- Persistent, recurrent, or metastatic cervical cancer
- Histologically types include squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma.
- No prior systemic therapy.
- ECOG PS 0-1.

R 1:1

Cadonilimab Group(n=222)

Cadonilimab 10mg/kg+Paclitaxel 175mg/m^2+Cisplatin 50mg/m^2 or Carboplatin AUC4-5±Bevacizumab 15mg/kg，q3w×6

Maintenance therapy

Cadonilimab 10mg/kg ±Bevacizumab 15mg/kg，q3w

Placebo Group(n=223)

Placebo+Paclitaxel 175mg/m^2+Cisplatin 50mg/m^2 or Carboplatin AUC4-5 ±Bevacizumab 15mg/kg，q3w×6

Maintenance therapy

Placebo±Bevacizumab 15mg/kg，q3w

✓ **Treatment continued until**

- disease progression
- unacceptable toxicity
- cadonilimab/placebo treatment for 2 years.

✓ Safety and survival follow-up are performed after the end of treatment.

Stratification factors:

- Use of Bevacizumab (Yes vs No)
- Prior CCRT(Yes vs No)

Primary Endpoints:

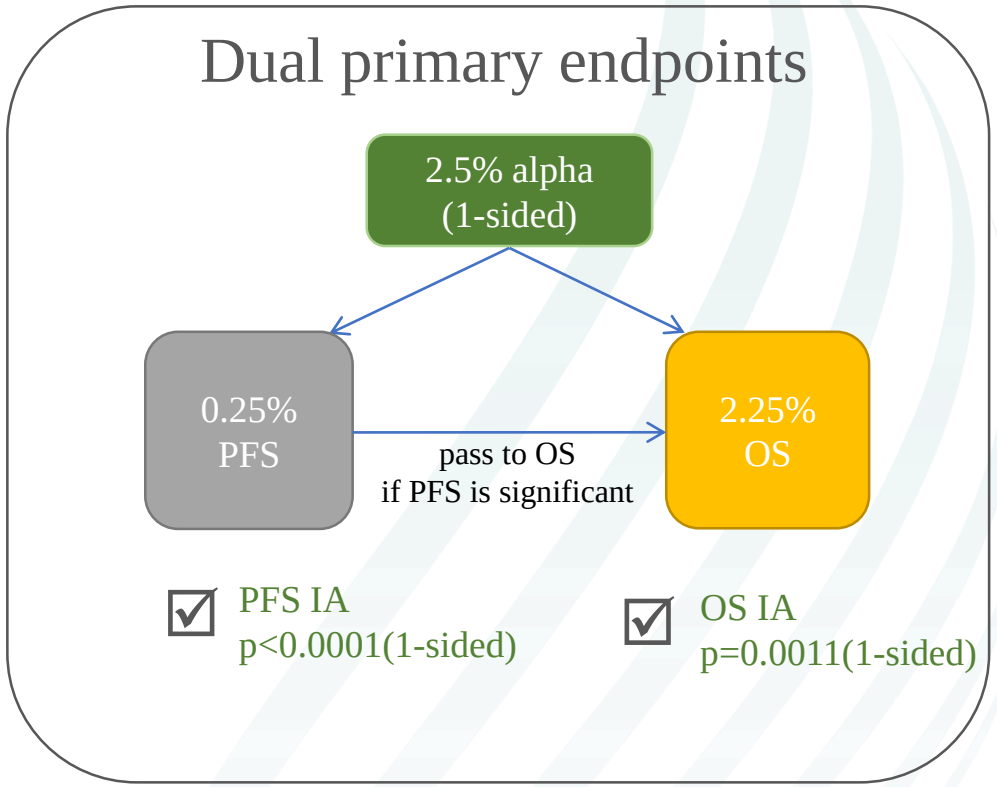
- PFS assessed by BICR according to RECIST v1.1
- OS

Second Endpoints:

PFS assessed by INV, ORR, DoR, DCR, TTR, Safety

Statistical Analyses

- Estimated sample size:
  - **440 patients**
  - Assuming HR=0.68,overall α=0.25%(one-sided), power=80% for PFS
  - Assuming HR=0.70,overall α=2.25%(one-sided), power=84.9% for OS



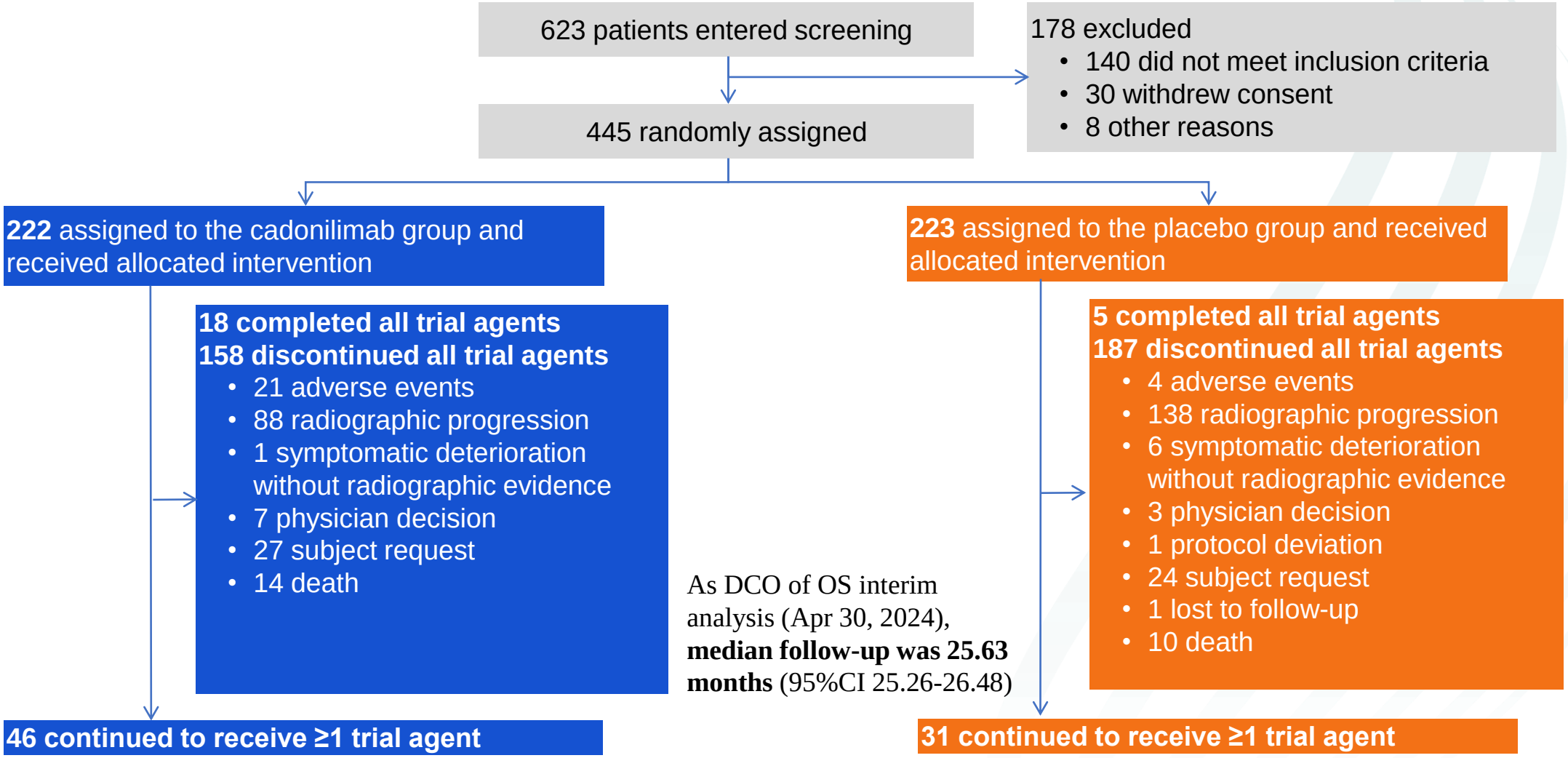
- Interim analysis:

IA*	Events	DCO# Date	P-value boundary(1-sided)
PFS IA	261	September 04,2023	0.0005
OS IA	193	April 30,2024	0.0060

- Analysis methods:
  - A stratified log-rank test was used to compare PFS/OS between treatment groups
  - PFS/OS were estimated using the Kaplan-Meier method and HRs were through a stratified regression model

*IA: Interim Analysis
#DCO: Data cut-off

Patient disposition

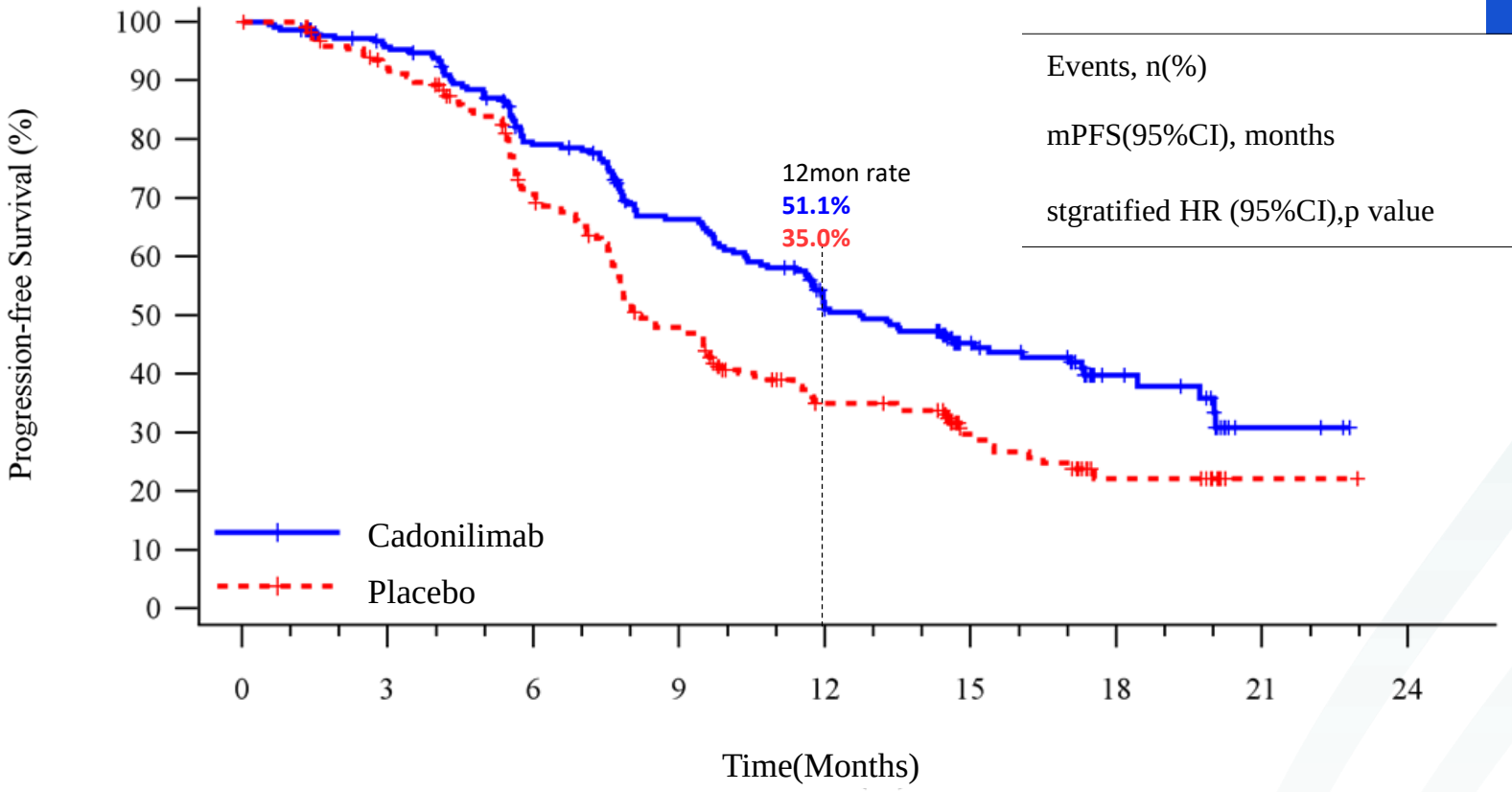


Baseline characteristics

	Cadonilimab (N = 222)	Placebo (N = 223)
Age, median (range)	55.9(23,75)	55.6(23,75)
ECOG PS 1, n(%)	151 (68.0)	136 (61.0)
Squamous Cell Carcinoma, n(%)	182 (82.0)	188 (84.3)
FIGO Stage at initial diagnosis, n (%)		
I	47 (21.2)	40 (17.9)
II	43 (19.4)	54 (24.2)
IIIA	3 (1.4)	3 (1.3)
IIIB	17 (7.7)	17 (7.6)
IIIC	60 (27.0)	62 (27.8)
IVA	2 (0.9)	3 (1.3)
IVB	50 (22.5)	42 (18.8)
Unknown	0	2 (0.9)
Prior CCRT, n(%)	107 (48.2)	108 (48.4)
Cisplatin, n(%)	92 (41.4)	100 (44.8)
Bevacizumab Administration, n (%)	133 (59.9)	132 (59.2)
Tumor Burden,Median(range) (mm)	47(10,284)	42.5(11,213)

	Cadonilimab (N = 222)	Placebo (N = 223)
Metastasis Status, n (%)		
Yes	168 (75.7)	155 (69.5)
No	54 (24.3)	68 (30.5)
Common Sites of Metastasis, n (%)		
Lymph Nodes	87 (39.2)	83 (37.2)
Lung	72 (32.4)	71 (31.8)
Bone	28 (12.6)	28 (12.6)
Liver	21 (9.5)	20 (9.0)
Other	32 (14.4)	30 (13.5)
PD-L1 Expression, n (%)		
CPS<1	62 (27.9)	54 (24.2)
CPS 1 - <10	64 (28.8)	68 (30.5)
CPS>=10	91 (41.0)	89 (39.9)
Unknown	5 (2.3)	12 (5.4)

Primary endpoint: PFS by BICR in ITT



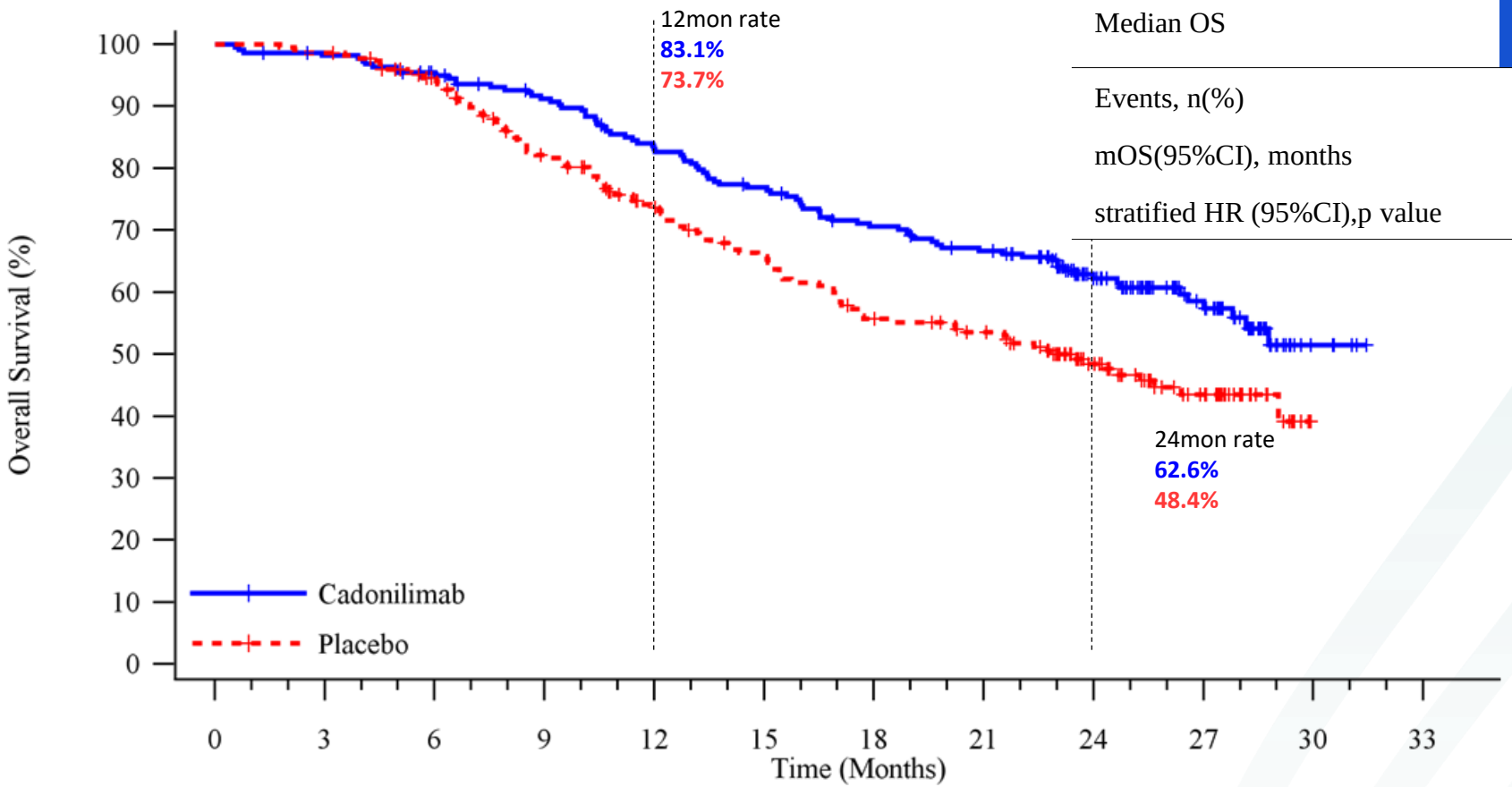
Median PFS	Cadonilimab (n=222)	Placebo (n=223)
Events, n(%)	117 (52.7)	144 (64.6)
mPFS(95%CI), months	12.7 (11.6, 16.1)	8.1 (7.7, 9.6)
stgratified HR (95%CI),p value	0.62(0.49,0.80), p < 0.0001	

DCO:2023-9-4
median follow up:17.87 months

No, at risk(Events)

Cadonilimab	222 (0)	199 (9)	159 (43)	128 (68)	93 (97)	57 (107)	22 (113)	3 (117)	0 (117)
Placebo	223 (0)	196 (17)	142 (61)	94 (106)	59 (130)	30 (137)	13 (144)	1 (144)	0 (144)

Primary endpoint: OS in ITT



Median OS	Cadonilimab (n=222)	Placebo (n=223)
Events, n(%)	86 (38.7)	107 (48.0)
mOS(95%CI), months	NR* (27.0, NR)	22.8 (17.6, 29.0)
stratified HR (95%CI),p value	0.64 (0.48, 0.86), p=0.0011	

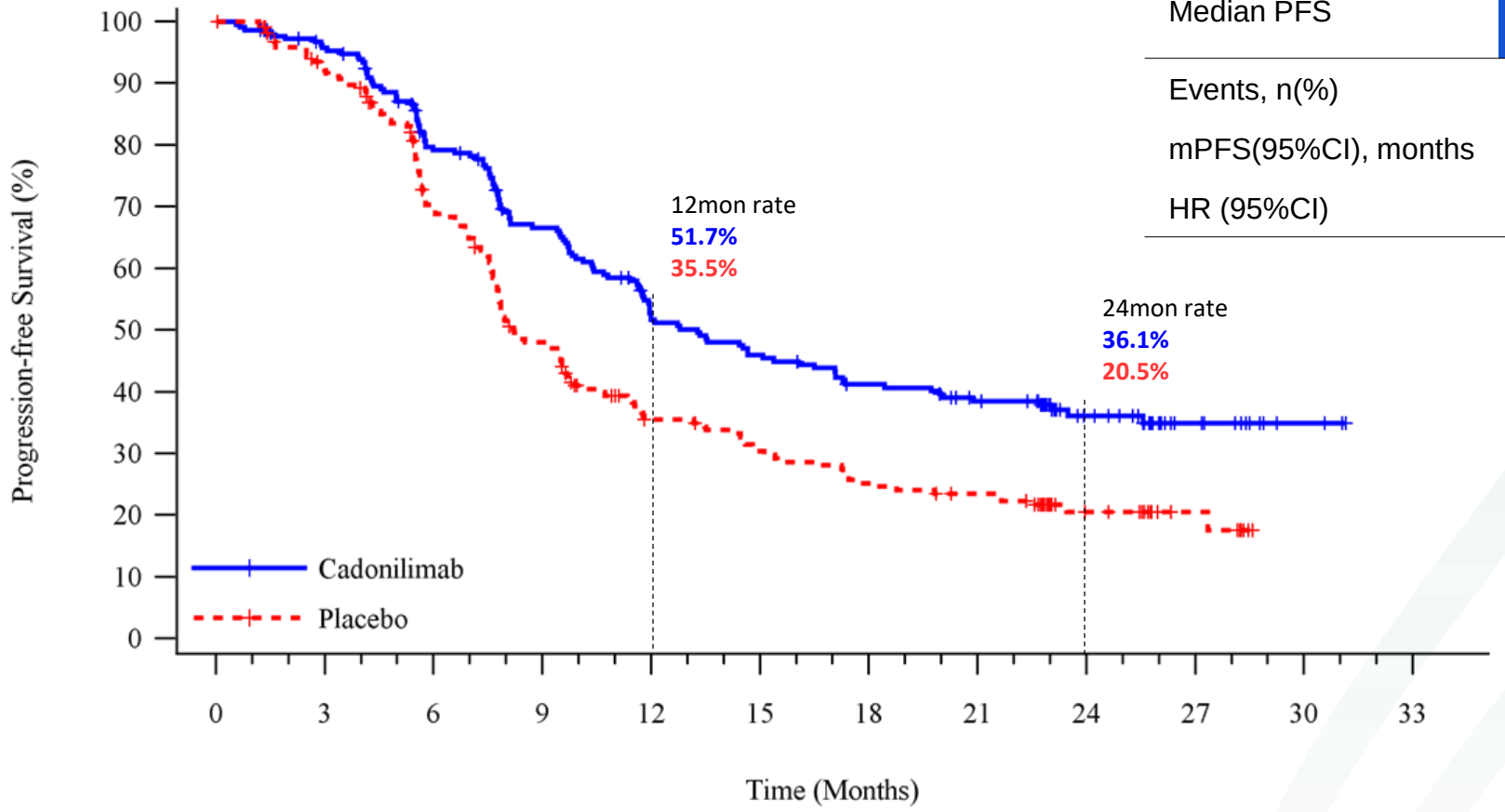
*NR: Not reached

DCO:2024-4-30
median follow up: 25.63 months

No. at risk (Events)

Cadonilimab	222 (0)	215 (4)	205 (10)	192 (19)	174 (36)	160 (49)	145 (62)	135 (70)	92 (78)	51 (82)	6 (86)	0 (86)
Placebo	223 (0)	220 (3)	202 (12)	169 (38)	143 (55)	124 (70)	104 (89)	95 (93)	60 (101)	32 (106)	0 (107)	

PFS by BICR in ITT update



Median PFS	Cadonilimab (n=222)	Placebo (n=223)
Events, n(%)	126 (56.8)	157 (70.4)
mPFS(95%CI), months	13.3 (11.6, 17.1)	8.2 (7.7, 9.6)
HR (95%CI)	0.62(0.49,0.79)	

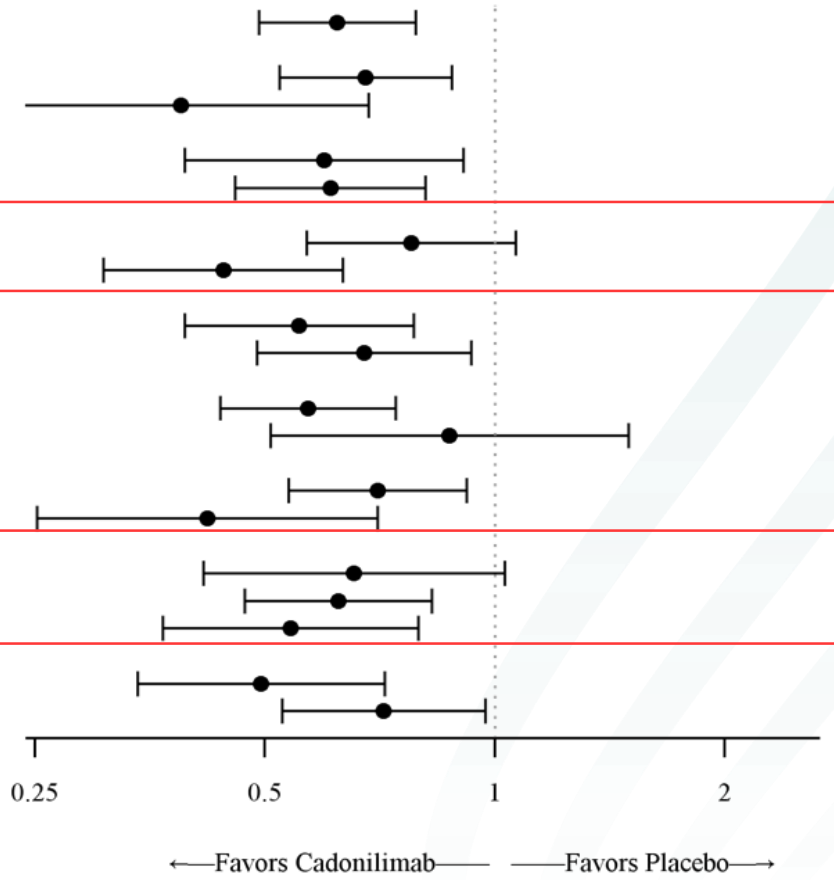
DCO:2024-4-30
median follow up: 25.63 months

No. at risk (Events)

Cadonilimab	222 (0)	200 (9)	160 (43)	131 (68)	99 (97)	88 (108)	77 (117)	68 (122)	35 (125)	14 (126)	3 (126)	0 (126)
Placebo	223 (0)	196 (17)	143 (62)	96 (107)	63 (131)	53 (140)	44 (149)	39 (152)	17 (156)	7 (156)	0 (157)	

PFS subgroup analysis

Subgroup	Cadonilimab No. of Events/ No. of Patients	Placebo No. of Events/ No. of Patients	Hazard Ratio (95% CI)
Overall	126/222	157/223	0.62 (0.49, 0.79)
Age			
<65 years	105/185	126/186	0.68 (0.52, 0.88)
≥65 years	21/37	31/37	0.39 (0.22, 0.68)
ECOG performance-status score			
0	36/71	57/87	0.60 (0.39, 0.91)
1	90/151	100/136	0.61 (0.46, 0.81)
Concomitant bevacizumab			
Yes	74/133	82/132	0.78 (0.57, 1.06)
No	52/89	75/91	0.44 (0.31, 0.63)
Prior CCRT			
Yes	58/107	76/108	0.55 (0.39, 0.78)
No	68/115	81/115	0.67 (0.49, 0.93)
Pathological Diagnosis			
Squamous cell carcinoma	96/182	133/188	0.57 (0.44, 0.74)
Non-Squamous cell carcinoma	30/40	24/35	0.87 (0.51, 1.50)
Metastatic			
Yes	104/168	110/155	0.70 (0.54, 0.92)
No	22/54	47/68	0.42 (0.25, 0.70)
PD-L1 combined positive score			
<1	37/62	39/54	0.65 (0.42, 1.03)
≥1	87/155	110/157	0.62 (0.47, 0.83)
≥10	46/91	60/89	0.54 (0.37, 0.79)
Cisplatin/Carboplatin			
Cisplatin	46/92	72/100	0.49 (0.34, 0.72)
Carboplatin	80/130	85/123	0.72 (0.53, 0.97)

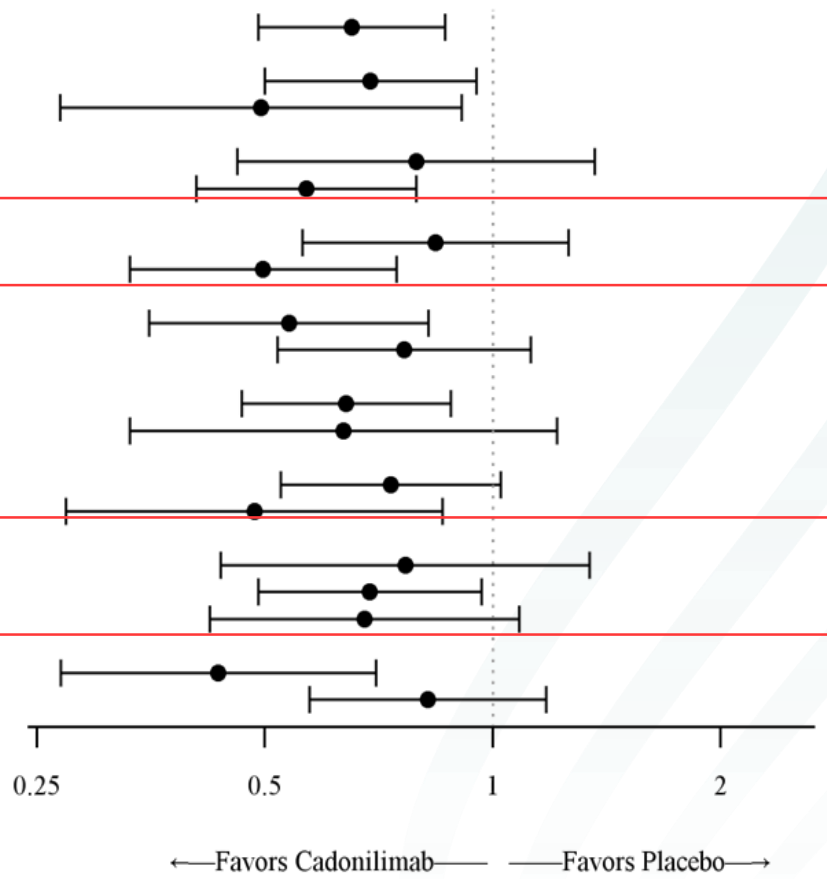


DCO: 2024-4-30

The hazard ratio and 95% CI are derived from unstratified Cox regression model.

OS subgroup analysis

Subgroup	Cadonilimab No. of Events/ No. of Patients	Placebo No. of Events/ No. of Patients	Hazard Ratio (95% CI)
Overall	86/222	107/223	0.65 (0.49, 0.87)
Age			
<65 years	68/185	82/186	0.69 (0.50, 0.95)
≥65 years	18/37	25/37	0.49 (0.27, 0.91)
ECOG performance-status score			
0	23/71	30/87	0.79 (0.46, 1.36)
1	63/151	77/136	0.57 (0.41, 0.79)
Concomitant bevacizumab			
Yes	47/133	47/132	0.84 (0.56, 1.26)
No	39/89	60/91	0.50 (0.33, 0.75)
Prior CCRT			
Yes	37/107	52/108	0.54 (0.35, 0.82)
No	49/115	55/115	0.76 (0.52, 1.12)
Pathological Diagnosis			
Squamous cell carcinoma	67/182	88/188	0.64 (0.47, 0.88)
Non-Squamous cell carcinoma	19/40	19/35	0.63 (0.33, 1.22)
Metastatic			
Yes	68/168	70/155	0.73 (0.52, 1.02)
No	18/54	37/68	0.48 (0.27, 0.86)
PD-L1 combined positive score			
<1	25/62	24/54	0.77 (0.44, 1.34)
≥1	61/155	74/157	0.69 (0.49, 0.97)
≥10	33/91	37/89	0.68 (0.42, 1.08)
Cisplatin/Carboplatin			
Cisplatin	26/92	48/100	0.43 (0.27, 0.70)
Carboplatin	60/130	59/123	0.82 (0.57, 1.18)



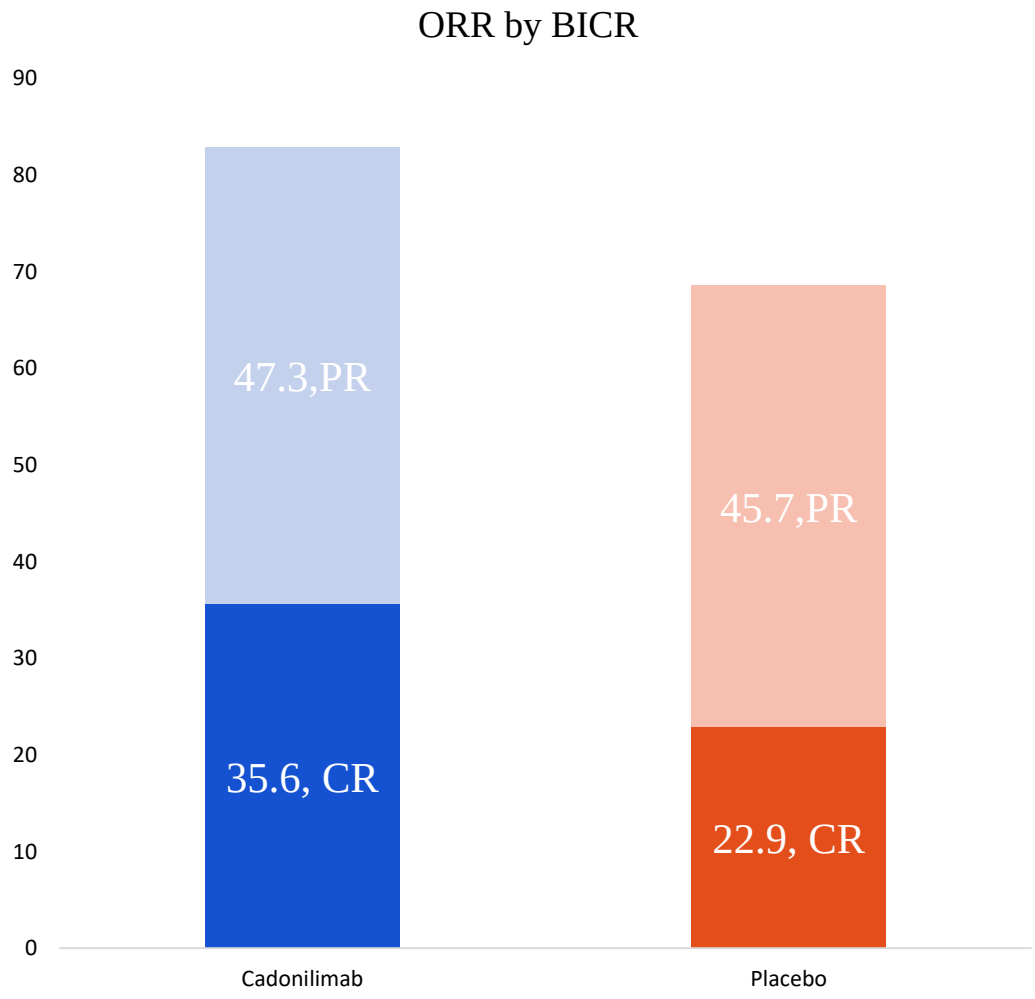
DCO: 2024-4-30

The hazard ratio and 95% CI are derived from unstratified Cox regression model.

Tumor response assessed by BICR

	Cadonilimab (N = 222)	Placebo (N = 223)
ORR (CR+PR)，%（95%CI）	**82.9** (77.3, 87.6)	**68.6** (62.1, 74.6)
DCR(CR+PR+SD), % (95% CI)	93.7 (89.6, 96.5)	91.9 (87.5, 95.1)
Best Overall Response, n (%)		
Complete Response (CR)	79 (35.6)	51 (22.9)
Partial Response (PR)	105 (47.3)	102 (45.7)
Stable Disease (SD)	24 (10.8)	52 (23.3)
Progressive Disease (PD)	4 (1.8)	11 (4.9)
DoR，median month (95% CI)	13.2 (10.5,18.7)	8.2 (6.6,11.7)

*16 patients did not have any post-baseline imaging assessment. 1 patient did not have any evaluable lesion per BICR.



Summary of safety

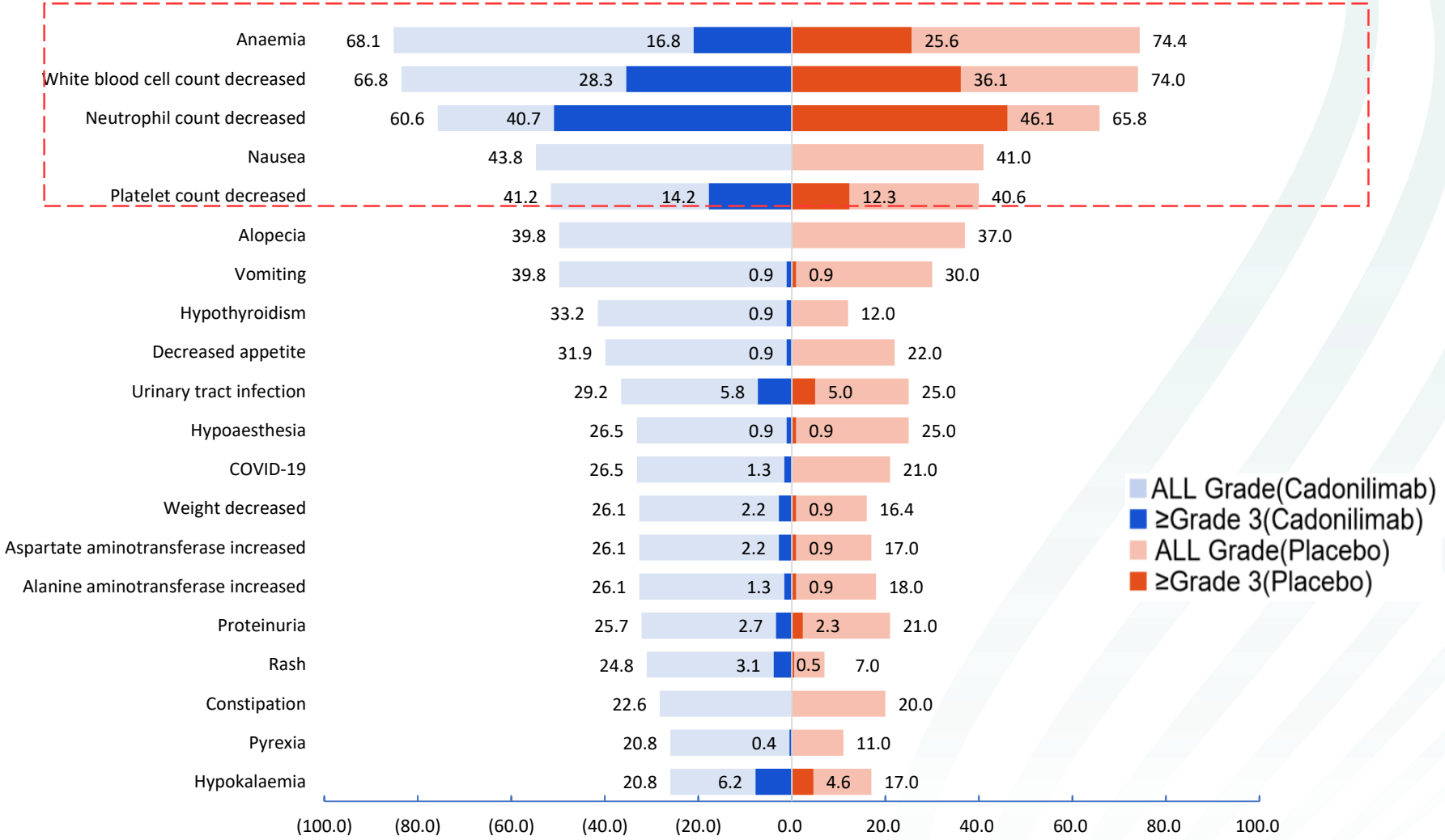
TEAE	Cadonilimab (N = 226)*	Placebo (N = 219)
Any Grade, n(%)	225 (99.6)	219 (100)
≥Grade 3, n (%)	193 (85.4)	176 (80.4)
SAE, n (%)	126 (55.8)	74 (33.8)
Led to discontinuation of any trial agent, n (%)	63 (27.9)	23 (10.5)
Led to Death, n (%)	12 (5.3)	7 (3.2)
irAE	103 (45.6)	15 (6.8)
≥Grade 3 irAE, n (%)	22 (9.7)	2 (0.9)

Drug Exposure Cycle(median): Cadonilimab vs Placebo

- Cadonilimab/Placebo: 15.02 vs 12.33
- Carboplatin: 6.26 vs 6.14
- Cisplatin: 6.14 vs 6.10
- Paclitaxel: 6.19 vs 6.10
- Bevacizumab: 17.29 vs 14.38

*Due to protocol deviations, 4 patients in the control group were administered cadonilimab and were classified into the cadonilimab group during the safety analysis.

Most common (≥20% of patients) TEAEs



irAE in Cadonilimab group

	Cadonilimab Group(N=226)		Placebo Group(N=219)	
	Any grade	Grade 3-5	Any grade	Grade 3-5
All events	103 (45.6)	22 (9.7)	15 (6.8)	2 (0.9)
Hypothyroidism	61 (27.0)	1 (0.4)	5 (2.3)	0
Hyperthyroidism	33 (14.6)	1 (0.4)	0	0
Thyroiditis	8 (3.5)	0	2 (0.9)	0
Rash	6 (2.7)	1 (0.4)	1 (0.5)	0
Immune-mediated thyroiditis	5 (2.2)	1 (0.4)	0	0
Adrenal insufficiency	5 (2.2)	0	0	0
Hypopituitarism	3 (1.3)	2 (0.9)	1 (0.5)	0
Hyperglycemia	3 (1.3)	1 (0.4)	0	0
Drug eruption	3 (1.3)	1 (0.4)	0	0
Blood thyroid stimulating hormone increased	3 (1.3)	0	2 (0.9)	0
Secondary hyperthyroidism	3 (1.3)	0	1 (0.5)	0

irAE: Immune-related Adverse Event

* All irAEs have undergone a secondary adjudication process by the sponsor.

Conclusions

- Cadonilimab significantly prolonged both PFS and OS in the first-line cervical cancer population.
  - ✓ Median PFS was 12.7 vs 8.1 months, HR 0.62 (95% CI 0.49-0.80, p<0.0001).
  - ✓ Median OS was not reached vs 22.8 months, HR 0.64 (95% CI 0.48-0.86, p=0.0011).
- Benefit of cadonilimab was consistent across all prespecified subgroups, regardless of the use of bevacizumab or PD-L1 status.
  - ✓ In the population without bevacizumab, cadonilimab reduced the risk of death by 50% (HR 0.50).
  - ✓ In the CPS < 1 population, cadonilimab reduced the risk of death by 23% (HR 0.77).
- The safety of cadonilimab in combination with chemotherapy ± bevacizumab was manageable. No new signals were identified.
- **Cadonilimab in combination with chemotherapy ± bevacizumab may be a new standard treatment option for the ITT population in first-line cervical cancer.**

COMPASSION-16 study is published in Lancet

THE LANCET

Cadonilimab plus platinum-based chemotherapy with or without bevacizumab as first-line treatment for persistent, recurrent, or metastatic cervical cancer (COMPASSION-16): a randomised, double-blind, placebo-controlled phase 3 trial in China

Xiaohua Wu, Yang Sun, Hongying Yang, Jing Wang, Hanmei Lou, Dan Li, Ke Wang, Hui Zhang, Tao Wu, Yuzhi Li, Chunyan Wang, Guiling Li, Yifeng Wang, Dapeng Li, Ying Tang, Mei Pan, Hongyi Cai, Weihu Wang, Bing Yang, Hua Qian, Qiuhong Tian, Desheng Yao, Ying Cheng, Bing Wei, Xiumin Li, Tao Wang, Min Hao, Xiaohong Wang, Tiejun Wang, Juntao Ran, Hong Zhu, Lijing Zhu, Xianling Liu, Yunxia Li, Lihong Chen, Qingshan Li, Xiaojian Yan, Fei Wang, Hongbing Cai, Yunyan Zhang, Zhiqing Liang, Funan Liu, Yi Huang, Bairong Xia, Pengpeng Qu, Genhai Zhu, Youguo Chen, Kun Song, Meili Sun, Zhengzheng Chen, Qiang Zhou, Lina Hu, Guzhalinuer Abulizi, Hongyan Guo, Sihai Liao, Yijing Ye, Ping Yan, Qiu Tang, Guoping Sun, Ting Liu, Dongmei Lu, Mingxiu Hu, Zhongmin M Wang, Baiyong Li, Michelle Xia

Access to the article:

https://doi.org/10.1016/S0140-6736(24)02135-4

Acknowledgements

- All patients and their families participating in the study
- All investigators and research personnel who conducted this trial
- Sponsor: Akeso, Inc.
- 2024 International Gynecologic Cancer Society