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Finotonlimab with chemotherapy in recurrent or metastatic head and neck cancer: a randomized phase 3 trial

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Immunotherapy combined with chemotherapy regimen has been shown to be effective in recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). However, due to the small number of patients, its efficacy remains controversial in Asian populations, particularly in mainland China. Here a randomized, double-blind phase 3 trial evaluated the efficacy and safety of finotonlimab (SCT-I10A), a programmed cell death 1 (PD-1) monoclonal antibody, combined with cisplatin plus 5-fluorouracil (C5F) for the first-line treatment of R/M HNSCC. Eligible patients (n = 370) were randomly 2:1 assigned to receive finotonlimab plus C5F (n = 247) or placebo plus C5F (n = 123). The primary endpoint was overall survival (OS). In the finotonlimab plus C5F group, OS was 14.1 months (95% confidence interval (CI) 11.1–16.4), compared with 10.5 months (95% CI 8.1–11.8) in the placebo plus C5F group. The hazard ratio was 0.73 (95% CI 0.57–0.95, P = 0.0165), meeting the predefined superiority criteria for the primary endpoint. Finotonlimab plus C5F showed significant OS superiority compared with C5F alone and acceptable safety profile with R/M HNSCC, supporting its use as a first-line treatment option for R/M HNSCC. These results validate the efficacy and safety of the combination of finotonlimab and C5F in Asian patients with R/M HNSCC. ClinicalTrials.gov identifier: NCT04146402.

Head and neck tumors, primarily originating from the mucosal epithelium of the oral cavity, pharynx and larynx[1], rank as the sixth cause of global cancer incidence in 2022 (ref. 2), posing a serious threat to public health. Notably, approximately 90% of head and neck tumors are squamous cell carcinoma. In China, the incidence of head and neck squamous cell carcinoma (HNSCC) was approximately 140,000 cases in 2022 (ref. 3), ranking sixth in the incidence rate of male patients with cancer and seventh in the mortality rate of overall patients with cancer. The main risk factors are tobacco smoking and alcohol consumption, while human papillomavirus (HPV) was a critical factor in oropharyngeal cancer[2,4,5]. More than 65% of patients with locally advanced HNSCC will experience recurrence or metastasis (R/M), which cannot be treated with surgery or radiotherapy, leading to a poor prognosis with survival of 6–9 months without treatment[6].

Since the initial report by Kish et al. in 1982 (ref. 7), the combination of platinum and 5-fluorouracil (PF) has consistently been the most used first-line treatment for R/M HNSCC, including in mainland China[8]. The first targeted therapy for HNSCC is cetuximab plus PF, as demonstrated by the EXTREME study comparing this combination with standard PF treatment[9]. Recently, findings from the KEYNOTE-048 trial have suggested that combining pembrolizumab with chemotherapy is a promising option for the Caucasian population, showing favorable efficacy and safety compared with chemotherapy in combination with cetuximab[10]. However, the efficacy of pembrolizumab with chemotherapy is controversial in Asian patients, owing to the small size of the Asian patient subgroup, which accounts for only 20% of the study population[11], and, especially, the lack of patients from mainland China, because the KEYNOTE-048 trial did not recruit patients from mainland China.

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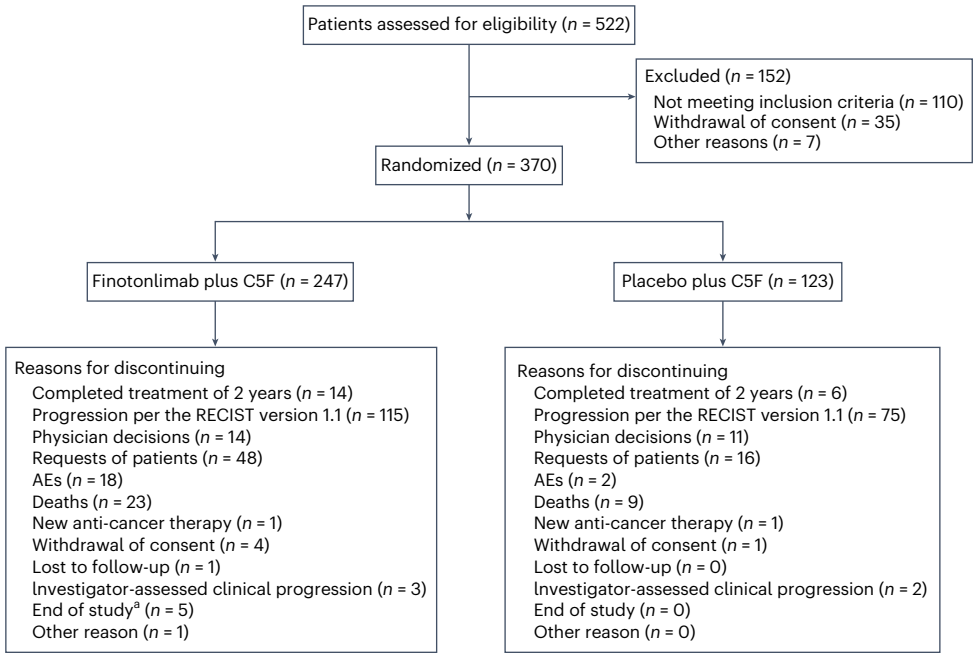

Fig. 1 | Trial profile. [a]Five patients in the finotonlimab plus C5F group discontinued due to the end of the study other than for the intended reason (such as PD or intolerable toxicity). Among these five patients, one patient was given continuous finotonlimab maintenance therapy on schedule until they reached 2 years of the treatment according the trial protocol, and other four patients refused to receive continuous finotonlimab maintenance therapy.

Finotonlimab (SCT-I10A), developed by Sinocelltech Ltd., is a humanized IgG4 monoclonal antibody engineered to target the programmed cell death 1 (PD-1), with a molecular weight of approximately 145 kD and comprising 1,326 amino acids. It has been shown to inhibit tumor growth in both mouse models and human patients[12,13].

Here, we present the results of the phase 3 trial evaluating finotonlimab plus cisplatin plus 5-fluorouracil (C5F) as the first-line treatment for patients with R/M HNSCC.

Results

Patients disposition

Between 31 December 2019 and 16 March 2022, 522 patients were screened (Fig. 1). Of these, 370 were eligible to be randomly enrolled in the finotonlimab plus C5F group ($n = 247$) or the placebo plus C5F group ($n = 123$) and received treatment. The data cutoff date was 31 July 2023. Five patients in the finotonlimab plus C5F group discontinued due to the end of the study other than for the intended reason (such as disease progression or intolerable toxicity). Among these five patients, one patient was given continuous finotonlimab maintenance therapy on schedule until they reached 2 years of the treatment according the trial protocol, and other four patients refused to receive continuous finotonlimab maintenance therapy.

Baseline demographic and disease distributions were generally similar in the two groups (Table 1). PD-1 tumor proportion score (TPS) of 50% or greater was observed in 23.5% (58/247) of patients in the finotonlimab plus C5F group and 24.4% (30/123) of patients in the placebo plus C5F group. The percentage of patients with a PD-1 combined positive score (CPS) of 1 or higher was 89.5% (221/247) in the finotonlimab plus C5F group and 94.3% (116/123) in the placebo plus C5F group. 86.5% (320/370) of the patients enrolled were male, which was consistent with the high incidence and high mortality of the male population in HNSCC[14].

All patients were required to be followed until withdrawal of informed consent form, death or loss to follow-up. The median follow-up time was 25.7 months (95% confidence interval (CI) 23.1–28.0) and 26.4 months (95% CI 22.6–34.2), respectively, in the finotonlimab plus C5F group and placebo plus C5F group. At the data cutoff date, 5.7% (14/247) of patients in the finotonlimab plus C5F group and 4.9% (6/123) of patients in the placebo plus C5F group completed 2 years of treatment.

Primary outcomes

In total, 65.6% (162/247) of patients in the finotonlimab plus C5F group and 77.2% (95/123) of patients in the placebo plus C5F group died. The median overall survival (OS) was 14.1 months (95% CI 11.1–16.4) and 10.5 months (95% CI 8.1–11.8) in the finotonlimab plus C5F group and placebo plus C5F group, respectively. The hazard ratio (HR) was 0.73 (95% CI 0.57–0.95, $P = 0.0165$) (Fig. 2a).

Secondary outcomes

The median progression-free survival (PFS) was 5.8 months (95% CI 5.5–7.1) in the finotonlimab plus C5F group and 5.6 months (95% CI 4.9–5.8) in the placebo plus C5F group. The HR was 0.77 (95% CI 0.59–1.00, $P = 0.0493$) (Fig. 3a). PFS rates calculated at 3, 6 and 9 months in the finotonlimab plus C5F group were significantly higher than those in the placebo plus C5F group (Extended Data Table 1). The objective response rate (ORR) in the finotonlimab plus C5F group was 39.9% (95% CI 33.71–46.37) and in the placebo plus C5F group was 29.4% (95% CI 21.42–38.46). The rate difference of ORR was 10.92% (95% CI 0.70–21.14, $P = 0.042$). In the finotonlimab plus C5F group, 26 patients had complete response (CR) and 71 patients had partial response (PR). In the placebo plus C5F group, 8 patients had CR and 27 patients had PR. Duration of response (DoR) was 19.3 months (95% CI 8.2 to non-evaluable (NE)) in the finotonlimab plus C5F group and 5.0 months (95% CI 4.2–7.1) in the placebo plus C5F group. HR was 0.52 (95% CI 0.30–0.90, $P = 0.0187$; Fig. 3b). The disease control rate (DCR) was 79.8% (95% CI 74.23–84.69) and 76.5% (95% CI 67.82–83.76) in the finotonlimab plus C5F group and the placebo plus C5F group, respectively (Extended Data Table 2).

The 12-month OS rate was significantly higher in the finotonlimab plus C5F group (53.5%, 95% CI 47.1–59.6) compared with the placebo plus C5F group (39.4%, 95% CI 30.7–47.9, $P < 0.0001$). Similar differences were observed in 18-month and 24-month OS rates, indicating that finotonlimab plus C5F extended OS in patients with R/M HNSCC.

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Table 1 | Baseline demographic and disease characteristics in the FAS

	Finotonlimab plus C5F (*N*=247, %)	Placebo plus C5F (*N*=123, %)	*P* value[b]
Sex, *n* (%)			0.2424
Male	210 (85.0)	110 (89.4)	
Female	37 (15.0)	13 (10.6)	
Age (years), *n* (%)			0.3457
Median (min, max)	60.0 (30, 90)	60.0 (32, 77)	
Age (years), *n* (%)			0.2454
<65 years	164 (66.4)	89 (72.4)	
≥65 years	83 (33.6)	34 (27.6)	
Nationality, *n* (%)			0.2803
Han	230 (93.1)	118 (95.9)	
Others	17 (6.9)	5 (4.1)	
Height (cm) (mean±s.d.)	165.8±7.2	165.7±7.2	0.9349
Weight (kg) (mean±s.d.)	58.3±10.3	59.4±11.3	0.3408
BMI (kg m^{-2}), median (min, max)	21.0 (13.1, 30.1)	21.3 (14.3, 31.2)	0.2595
HPV[a], *n* (%)			0.9024
Negative	22 (8.9)	12 (9.8)	
Positive	8 (3.2)	4 (3.3)	
TPS, *n* (%)			0.8467
<50%	189 (76.5)	93 (75.6)	
≥50%	58 (23.5)	30 (24.4)	
CPS, *n* (%)			
<1	26 (10.5)	7 (5.7)	0.1242
≥1	221 (89.5)	116 (94.3)	
≥20	114 (46.2)	68 (55.3)	0.0979
ECOG PS score, *n* (%)			0.6309
0	47 (19.0)	26 (21.1)	
1	200 (81.0)	97 (78.9)	
Disease stage, *n* (%)			0.1422
Relapse only	96 (38.9)	36 (29.3)	
Metastasis	150 (60.7)	87 (70.7)	
No relapse/metastasis	1 (0.4)	0	
Primary site, *n* (%)			0.9885
Oral cavity	96 (38.9)	47 (38.2)	
Oropharynx	30 (12.1)	16 (13.0)	
Hypopharynx	56 (22.7)	29 (23.6)	
Larynx	65 (26.3)	31 (25.2)	
Previous treatment			
Surgery	203 (82.2)	102 (82.9)	0.8600
Radiotherapy	139 (56.3)	69 (56.1)	0.9741
Platinum-based compounds[c]	82 (33.2)	40 (32.5)	0.8960
EGFR inhibitors[c]	14 (5.7)	7 (5.7)	0.9928

[a]HPV detected only in oropharyngeal cancer [b]The two-sided *P* value of categorical data was calculated by chi-square test. The *P* value of continuous data was calculated by ANOVA. [c]Systemic therapy in a multi-modality treatment with disease progression more than six months after the end of treatment. Platinum compounds included cisplatin, carboplatin, oxaliplatin, nedaplatin, and lobaplatin. EGFR inhibitors include cetuximab and nimotuzumab. BMI, body mass index.

Quality-of-life assessments using the EORTC QLQ-C30 (V3) scale have indicated that the finotonlimab plus C5F group showed superior improvements in overall health status, physical functioning and the alleviation of symptoms such as pain, nausea and vomiting, insomnia, appetite loss and diarrhea, compared with the placebo plus C5F group. Furthermore, evaluations with the EORTC QLQ-H&N35 scale revealed that the finotonlimab plus C5F group was more effective in alleviating perceived problems, discomfort, the use of painkillers, the use of nutritional supplements and issues with weight loss. However, in terms of improving pain issues, social difficulties and saliva viscosity, the placebo plus C5F group showed superiority over the finotonlimab plus C5F group.

Analysis of exome sequencing suggest that mutations in seven genes (*KMT2D*, *RYR3*, *UNC80*, *MUC3A*, *CCDC141*, *APOB* and *TNC*) might lead to longer OS in patients treated with finotonlimab plus C5F. Conversely, mutations in three genes (*NOTCH2*, *UTRN* and *WNK1*) could result in shorter OS for patients receiving the finotonlimab plus C5F treatment. Additionally, in the finotonlimab plus C5F group, the detection of ct825 in the blood indicated that patients with *TET2* mutations might have longer OS compared with those without such mutations. However, in the finotonlimab plus C5F group, mutations in 11 genes (*EPHA5*, *IRS1*, *HNF1A*, *NOTCH2*, *KIT*, *PALB2*, *APC*, *FLT3*, *AJUBA*, *ERBB2* and *ARID1A*) could potentially lead to shorter OS. However, there were no statistically significant differences in these analyses. The analysis also showed no statistical difference in the inflammatory T cell gene expression between the two treatment groups, and there was no significant correlation between peripheral blood tumor mutational burden and OS in either group.

Additional planned secondary endpoints not reported in this manuscript are pharmacokinetic endpoints.

Subgroup analyses

Subgroup analysis of OS conducted on the basis of gender, age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), TPS, CPS, HPV status, primary tumor site, and tumor recurrence and metastasis are shown in Fig. 2b. Among patients with TPS ≥50%, 23.5% (58/247) of patients in the finotonlimab plus C5F group showed a median OS of 18.2 months (95% CI 11.1–NE), and 24.4% (30/123) of patients in the placebo plus C5F group showed a median OS of 10.4 months (95% CI 5.3–15.7). The HR was 0.56 (95% CI 0.33–0.96, $P = 0.0333$). In patients with CPS ≥1, 64.3% (142/221) of patients in the finotonlimab plus C5F group and 75.9% (88/116) of patients in the placebo plus C5F group reached the endpoint of death. Median OS in the patients with CPS ≥1 was 14.3 months (95% CI 11.2–17.5) in the finotonlimab plus C5F group and 10.6 months (95% CI 8.1–11.9) in the placebo plus C5F group. HR was 0.73 (95% CI 0.56–0.96, $P = 0.0219$). Among patients with CPS ≥20, 53.5% (61/114) of patients in the finotonlimab plus C5F group and 80.9% (55/68) in the placebo plus C5F group reached the endpoint of death. The median OS in the finotonlimab plus C5F group was twice as long as that in the placebo plus C5F group, with 20.1 months (95% CI 13.8–NE) and 10.1 months (95% CI 7.6–11.8), respectively. The HR was 0.50 (95% CI 0.35–0.72, $P = 0.0002$).

Safety

As shown in Table 2, 98.9% (366/370) patients experienced treatment-emergent adverse events (TEAEs). Treatment-related adverse events (TRAEs) were observed in 67.2% (166/247) of patients in the finotonlimab plus C5F group and 54.5% (67/123) of patients in the placebo plus C5F group. Adverse events (AEs) that occurred at a rate greater than 5% and were more than 2% higher in the finotonlimab group than in the control group were as follows: decreased appetite (10.9% versus 7.3%), nausea (13.8% versus 11.4%), hypothyroidism (19.8% versus 11.4%), dermatitis (13.0% versus 4.1%), hypokalemia (8.5% versus 2.4%) and hyperthyroidism (7.3% versus 2.4%). Grade 3–5 TRAEs were noted in 25.1% (62/247) of patients in the finotonlimab plus C5F group

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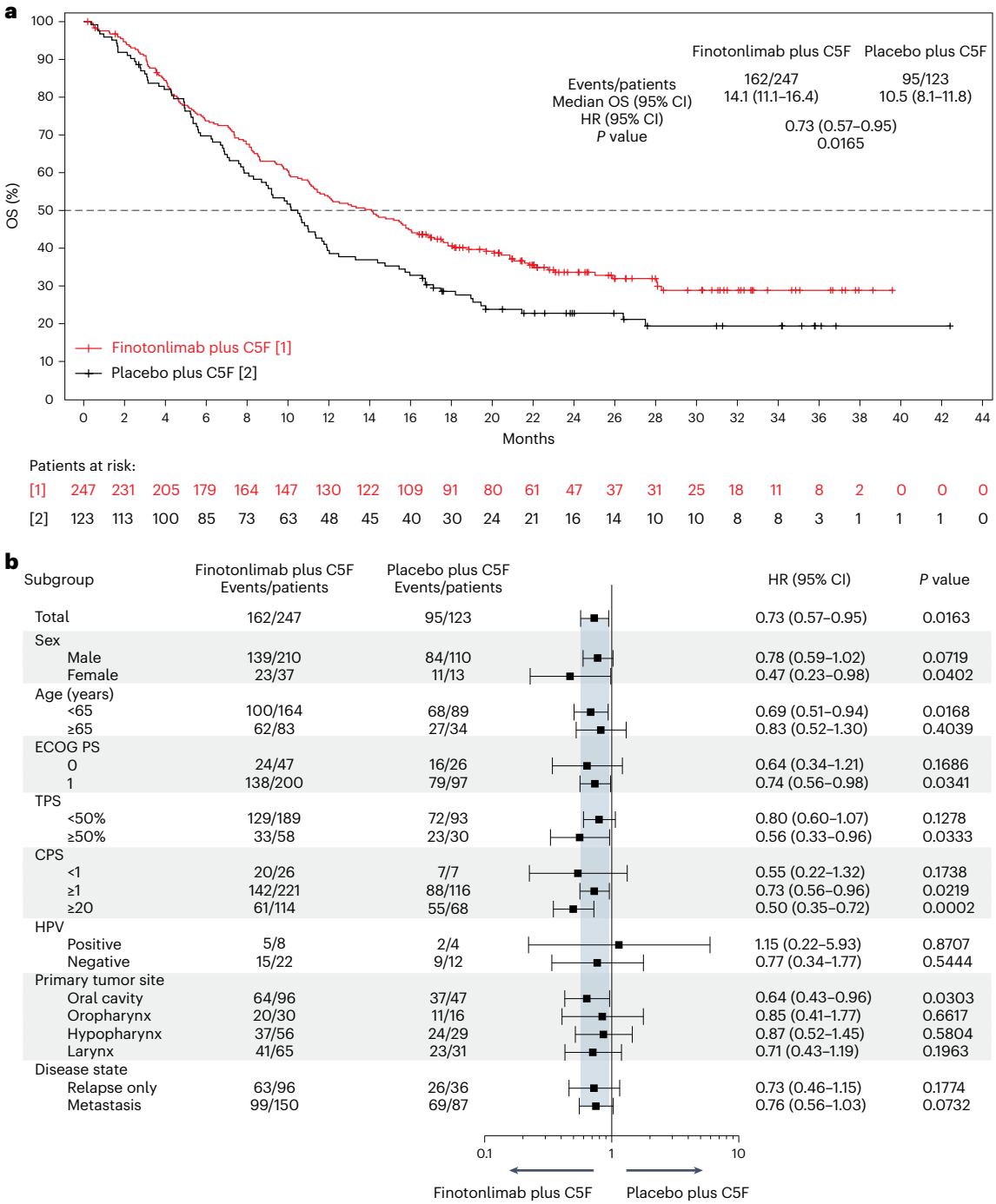

Fig. 2 | Kaplan–Meier curves of OS and subgroup analysis. a, OS survival curves evaluated by the Kaplan–Meier method reflecting data from surviving and censored patients in the finotonlimab plus C5F group and placebo plus C5F group. The short vertical lines represent censored data. The horizontal dashed line show median survival, which defined the time when 50% of patients survived. **b**, Subgroup analysis of OS. The gray shadow represents the OS (95% CI) of all patients in the FAS. The data are presented as point estimates and 95% CI of the HR. The 95% CI of OS was calculated on the basis of the Brookmeyer–Crowley method. The HR and two-sided 95% CI were estimated using the stratification-based COX proportional risk model. The *P* value was calculated using a stratified log-rank based method. OS, overall survival.

and 17.1% (21/123) of patients in the placebo plus C5F group. Within the finotonlimab plus C5F group, 3.6% (9/247) of patients had TRAEs leading to treatment discontinuation, with none occurring in the placebo plus C5F group.

In this study, the incidence of immune-related adverse events (irAEs) in the finotonlimab plus C5F group and in the placebo plus C5F group was 38.9% (96/247) and 22.0% (27/123), respectively. As shown in Extended Data Table 3, the most common irAEs were hypothyroidism (17.8%, 44/247) and dermatitis (10.9%, 27/247). Serious adverse events (SAEs) related to finotonlimab or placebo emerged in 13.0% (32/247) of patients in the finotonlimab plus C5F group and 6.5% (8/123) of patients in the placebo plus C5F group. The most common SAEs in the finotonlimab plus C5F group were anemia (3.2%, 8/247), in the placebo plus C5F group were leukopenia (1.6%, 2/123). Five patients died due to TRAEs, with 1.2% (3/247) of patients in the finotonlimab plus C5F group and 1.6% (2/123) of patients in the placebo plus C5F group.

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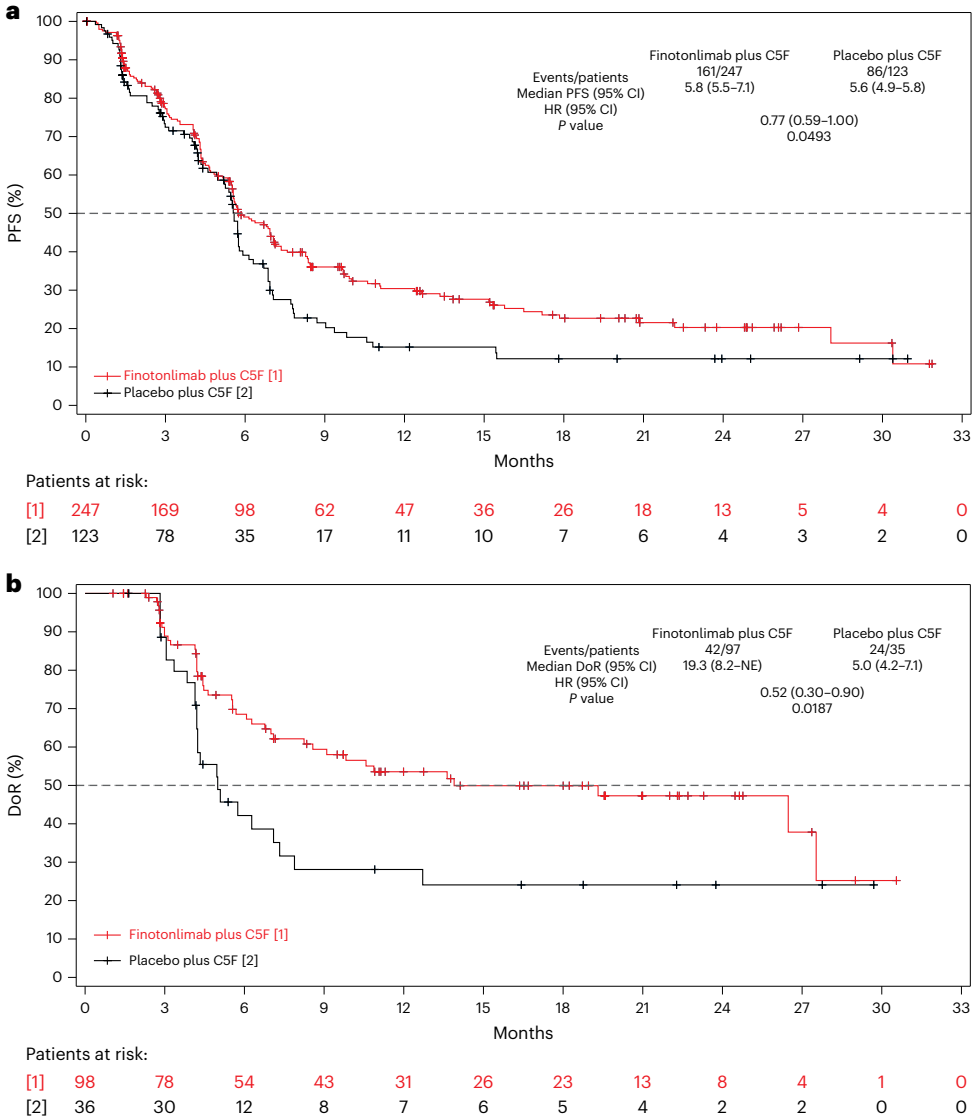

Fig. 3 | Kaplan–Meier curves of PFS and DoR. a,**b**, Survival curves of PFS (**a**) and DoR (**b**) over time evaluated by the Kaplan–Meier method. The horizontal dashed line shows the median PFS or DoR. The 95% CI of PFS was calculated on the basis of the Brookmeyer–Crowley method. HR and two-sided 95% CI were estimated using the stratification-based COX proportional risk model. The *P* value was calculated using a stratified log-rank based method.

In the finotonlimab plus C5F group, the causes of death were hyperprogressive tumors, bone marrow suppression and unknown death. In the placebo plus C5F group, unknown death and bleeding were the causes. There were no deaths attributed to irAEs. Infusion reactions occurred at a low rate for both groups, with 1.2% (3/247) of patients in the finotonlimab plus C5F group and 0.8% (1/123) of patients in the placebo plus C5F group. There were no grade 3 or higher infusion reactions, no infusion reactions leading to death and no infusion reactions necessitating treatment discontinuation.

Serum samples were collected before study drug administration in cycles 1, 3 and 6 and every four cycles. In this study, a total of 247 patients who were treated with finotonlimab plus C5F were included in the immunogenicity analysis. Of these, 3.2% (8/247) of patients were tested positive for anti-drug antibody (ADA). Neutralizing antibodies were detected in one patient.

All patients initially received cisplatin, with the exception of one patient who was directly administered carboplatin due to the low creatinine clearance and the grade 1 creatinine elevation observed during the screening period. Due to toxicity, 6.5% (16/246) of patients in the finotonlimab plus C5F group and 6.5% (8/123) of patients in the placebo plus C5F group switched from cisplatin to carboplatin. The chemotherapy dose reductions due to toxicity were as follows: 11.9% (44/369) of patients for cisplatin, 28.0% (7/25) of patients for carboplatin and 20.0% (74/370) of patients for 5-fluorouracil. Specifically, among those experiencing dose reductions twice, there were 1.4% (5/369) of patients for cisplatin and 1.1% (14/370) of patients for 5-fluorouracil.

In summary, the profile of AEs observed in the finotonlimab plus C5F group, encompassing all types and grades, was similar to that seen in the placebo plus C5F group with no new AEs reported. The most frequent AEs experienced by the finotonlimab plus C5F group during the study period were hypothyroidism (19.8%, 49/247) and anemia (19.4%, 48/247). The most common irAEs were hypothyroidism (17.8%, 44/247) and dermatitis (10.9%, 27/247).

Sensitivity analyses

Three sensitivity analyses were conducted on the median OS (Extended Data Table 4), and the results were consistent with those of the primary analysis. The consistency showed robustness and generalizability to different clinical scenarios. The sensitivity analysis of PFS was performed by defining different censoring criteria, and the results showed

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Table 2 | AEs in the SS

	Finotonlimab plus C5F (*N*=247, %)		Placebo plus C5F (*N*=123, %)	
	Any grade	Grade 3–5	Any grade	Grade 3–5
Treatment-emergent events	243 (98.4)	173 (70.0)	123 (100.0)	77 (62.6)
Treatment-related events	166 (67.2)	62 (25.1)	67 (54.5)	21 (17.1)
Immune-related events	96 (38.9)	11 (4.5)	27 (22.0)	2 (1.6)
Infusion-related events	3 (1.2)	0	1 (0.8)	0
TEAEs occurring in 5% or more of patients in either group				
Hypothyroidism	49 (19.8)	0	14 (11.4)	0
Anemia	48 (19.4)	20 (8.1)	29 (23.6)	9 (7.3)
Leukopenia	38 (15.4)	9 (3.6)	21 (17.1)	8 (6.5)
Nausea	34 (13.8)	0	14 (11.4)	0
Dermatitis	32 (13.0)	0	5 (4.1)	0
Neutropenia	30 (12.1)	9 (3.6)	15 (12.2)	5 (4.1)
Thrombocytopenia	28 (11.3)	5 (2.0)	13 (10.6)	3 (2.4)
Decreased appetite	27 (10.9)	2 (0.8)	9 (7.3)	0
Vomiting	26 (10.5)	0	12 (9.8)	0
Renal function test abnormal	21 (8.5)	6 (2.4)	8 (6.5)	1 (0.8)
Hypokalemia	21 (8.5)	0	3 (2.4)	0
Hepatic enzyme increased	19 (7.7)	3 (1.2)	8 (6.5)	1 (0.8)
Hyponatremia	19 (7.7)	2 (0.8)	11 (8.9)	2 (1.6)
Constipation	18 (7.3)	0	8 (6.5)	0
Hyperthyroidism	18 (7.3)	0	3 (2.4)	0
Asthenia	16 (6.5)	2 (0.8)	9 (7.3)	1 (0.8)
Weight decreased	15 (6.1)	1 (0.4)	10 (8.1)	0
Stomatitis	14 (5.7)	0	6 (4.9)	0
Lymphocyte count decreased	13 (5.3)	0	3 (2.4)	0
Pyrexia	13 (5.3)	6 (2.4)	8 (6.5)	2 (1.6)

The data are presented as *n* (%). The classification was based on system organ classification and preferred terminology. Cases were counted only once per patient according to greatest severity, even if the patient reported one or more events under each subcategory.

that PFS was not significantly different between the finotonlimab plus C5F group and the placebo plus C5F group (Extended Data Table 5).

Post-hoc analyses

As shown in Extended Data Table 1, the analysis of 36-month restricted mean survival time (RMST) demonstrated a longer OS in the finotonlimab plus C5F group than in the placebo plus C5F group (17.9 months (95% CI 16.2–19.6) and 14.5 months (95% CI 12.4–16.7), RMST ratio 1.23 (95% CI 1.03–1.47), $P = 0.0169$). In 24-month RMST for PFS analysis, the finotonlimab plus C5F group showed a longer PFS than did the placebo plus C5F group (9.8 months (95% CI 8.7–11.0) and 7.4 months (95% CI 6.0–8.8), RMST ratio 1.32 (95% CI 1.06–1.65), $P = 0.0104$).

Discussion

The results of this randomized, double-blind phase 3 trial demonstrated that finotonlimab plus C5F improved OS and reduced the risk of death in patients with R/M HNSCC compared with placebo plus C5F. Additionally, the OS and PFS rates estimated in 12 months, 18 months, 24 months and 36 months were increased significantly in the finotonlimab plus C5F group compared with the placebo plus C5F group.

Compared with similar studies[8–10], the patients in this study had worse baseline characteristics, as shown by the presence of more older patients (≥65 years), poorer physical fitness (ECOG PS score 1) and fewer HPV-positive patients, which may led to worse results. OS could be influenced by patient-related factors, for example, in the subsequent anti-cancer therapy, the use of PD-1/PD-L1 monoclonal antibodies was higher in the placebo plus C5F group (finotonlimab plus C5F group versus placebo plus C5F group: 17.4% versus 23.6%), which prolonged OS of the placebo plus C5F group. Finotonlimab plus C5F group had a 3.6-month longer median OS (14.1 months versus 10.5 months) and a 27% reduction in the risk of death compared with the placebo plus C5F group. In total, 39.9% of patients in the finotonlimab plus C5F group had objective responses and 10.7% of them had CR. The mDoR of finotonlimab plus C5F group was significantly longer than that of placebo plus C5F group (19.3 months versus 5.0 months). In the Keynote-048 trial, pembrolizumab combined with chemotherapy demonstrated an improvement in OS compared with cetuximab plus chemotherapy in the overall patient population, with median OS of 13.0 months versus 10.7 months, respectively (HR 0.77; 95% CI 0.63–0.93; $P = 0.0034$)[10]. However, in the Asian subgroup, pembrolizumab with chemotherapy failed to show a OS benefit over cetuximab with chemotherapy group, with a respective median OS of 10.4 months and 10.8 months (HR 1.03; 95% CI 0.68–1.58). Additionally, the mDoR was notably shorter for pembrolizumab with chemotherapy treatment at 5.7 months in the Asian subgroup[15]. The ambiguous results among the Asian subgroup could be attributed to the limited patient numbers, representing just 20% of the total study patients[11], and, especially, the lack of patients from mainland China, because the KEYNOTE-048 trial did not recruit patients from mainland China, which consequently led to the un-endorsement of the pembrolizumab combined chemotherapy for treating Chinese patients with R/M HNSCC. Conversely, the result of this study yields robust evidence pointing to the superior effectiveness of pairing the PD-1 monoclonal antibody finotonlimab with C5F, especially

in Chinese patients. These results provide more effective treatment regimens compared with C5F alone as the first-line treatment for R/M HNSCC within this ethnic patient population.

The sensitivity analyses of OS with different variables showed outcomes similar to those from the main analysis, reinforcing the reliability of the primary findings. Finotonlimab plus C5F exhibited a therapeutic advantage in the first-line treatment of patients with PD-L1-positive R/M HNSCC, with a median OS of 20.1 months in the CPS ≥20 subgroup, which was notably longer than the overall population's median OS of 14.1 months. This trend mirrors that of the KEYNOTE-048 trial, where pembrolizumab, when combined with chemotherapy, showed a median OS of 14.7 months in the CPS ≥20 patient population, compared with the overall patient population's median OS of 13 months[10].

The safety profile of finotonlimab plus C5F was favorable, with no unexpected safety signals observed[10]. Most infusion-related and irAEs were grade 1–2. This is in keeping with the reported safety data for pembrolizumab[16]. TRAEs with an incidence of ≥10% and a 2% higher incidence in the finotonlimab plus C5F group than in the placebo plus C5F group included decreased appetite (10.9% versus 7.3%), nausea (13.8% versus 11.4%), hypothyroidism (19.8% versus 11.4%) and dermatitis (13.0% versus 4.1%). Compared with pembrolizumab, finotonlimab plus C5F had a similar or lower incidence of decreased appetite, nausea, dermatitis and a higher incidence of hypothyroidism. Hypothyroidism was also observed in the placebo plus C5F group with a high incidence (11.4%), which may be attributed to the fact that some patients in this study had previously undergone radiotherapy and surgery. Finotonlimab-related skin disorders were 13%, much lower than that caused by cetuximab (77.3% and 82%)[8,10]. Incidence of immunogenicity after finotonlimab plus C5F treatment was low[17].

The main limitation of this study was that the trial used C5F as the control and did not compare finotonlimab with pembrolizumab or cetuximab. This was because these treatments had not yet been approved by the China National Medical Products Administration when the trial commenced. A small number of patients switched from cisplatin therapy to carboplatin due to toxicity concerns. However, the effect of varying platinum therapies on the overall treatment evaluation was considered unimportant given that 99.7% (369/370) patients started with cisplatin and just 6.5% (24/369) later received carboplatin.

Currently, several clinical trials have assessed or are ongoing to evaluate the efficacy and safety of finotonlimab for the treatment of advanced solid tumors and lymphomas, colorectal cancer (NCT04229537) and esophageal squamous cell carcinoma (NCT04229537), hepatocellular carcinoma (NCT04560894) and advanced squamous cell non-small cell lung cancer (NCT04171284). These trials collectively demonstrate a clinically acceptable tolerability profile of finotonlimab, along with promising efficacy across multiple cancer types.

In summary, this phase 3 trial demonstrated that finotonlimab plus C5F showed significant OS superiority compared with C5F alone and an acceptable safety profile in Asian patients with R/M HNSCC, supporting its use as a first-line treatment option for R/M HNSCC.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-024-03110-7.

References

1. Gormley, M., Creaney, G., Schache, A., Ingarfield, K. & Conway, D. I. Reviewing the epidemiology of head and neck cancer: definitions, trends and risk factors. *Br. Dent. J.* **233**, 780–786 (2022).
2. Bray, F. et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **74**, 229–263 (2024).
3. Xia, C. et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin. Med. J.* **135**, 584–590 (2022).
4. Leemans, C. R., Snijders, P. J. F. & Brakenhoff, R. H. The molecular landscape of head and neck cancer. *Nat. Rev. Cancer* **18**, 269–282 (2018).
5. Braakhuis, B. J., Brakenhoff, R. H. & Leemans, C. R. Treatment choice for locally advanced head and neck cancers on the basis of risk factors: biological risk factors. *Ann. Oncol.* **23**, x173–x177 (2012).
6. Chow, L. Q. M. Head and neck cancer. *N. Engl. J. Med.* **382**, 60–72 (2020).
7. Kish, J. et al. Clinical trial of cisplatin and 5-FU infusion as initial treatment for advanced squamous cell carcinoma of the head and neck. *Cancer Treat. Rep.* **66**, 471–474 (1982).
8. Guo, Y. et al. First-line treatment with chemotherapy plus cetuximab in Chinese patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: efficacy and safety results of the randomised, phase III CHANGE-2 trial. *Eur. J. Cancer* **156**, 35–45 (2021).
9. Vermorken, J. B. et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N. Engl. J. Med.* **359**, 1116–1127 (2008).
10. Burtness, B. et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet* **394**, 1915–1928 (2019).
11. First-line combination therapy in metastatic or unresectable, recurrent HNSCC. *Keytruda* https://www.keytrudahcp.com/efficacy/hnscc-first-line-combination-therapy/ (2019).
12. Wang, R. et al. Antitumor activity of pegylated human interferon β as monotherapy or in combination with immune checkpoint inhibitors via tumor growth inhibition and dendritic cell activation. *Cell. Immunol.* **393-394**, 104782 (2023).
13. Bai, M. et al. Phase Ib study of anti-EGFR antibody (SCT200) in combination with anti-PD-1 antibody (SCT-I10A) for patients with RAS/BRAF wild-type metastatic colorectal cancer. *Cancer Biol. Med.* https://doi.org/10.20892/j.issn.2095-3941.2023.0301 (2023).
14. Viens, L. J. et al. Human papillomavirus-associated cancers—United States, 2008–2012. *MMWR Morb. Mortal. Wkly. Rep.* **65**, 661–666 (2016).
15. Ngamphaiboon, N. K. et al. Phase III KEYNOTE-048 study of first-line pembrolizumab for recurrent/metastatic head and neck squamous cell carcinoma: Asia vs non-Asia subgroup analysis. *Ann. Oncol.* **30**, ix97–ix106 (2019). (suppl_9).
16. Sun, J. M. et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet* **398**, 759–771 (2021).
17. Pinato, D. J. J. et al. Anti-drug antibodies related to CTLA-4, PD-1, or PD-L1 inhibitors across tumour types: a systematic review. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.2023.41.16_suppl.e14600 (2023).

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Methods

Ethics statement

The study protocol, informed consent form and other relevant documents were approved by the Independent Ethics Committee (Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College) before the clinical study was conducted. The study implementation process strictly followed the international harmonized ethical principles. The study has been performed in accordance with the Declaration of Helsinki.

Trial oversight

This is a randomized, double-blind phase 3 trial that recruited patients from 64 hospitals in mainland China (Supplementary Table 1). All patients signed the informed consent form before screening. The registration number was NCT04146402 on ClinicalTrials.gov and CTR20191160 on Chinadrugtrials.org.cn. Key inclusion criteria included histologically or cytologically confirmed diagnosis of HNSCC with the primary site in the oropharynx, hypopharynx or larynx and no prior systemic chemotherapy.

Inclusion criteria.

1. Voluntarily signed the informed consent form before screening.
2. Male or female, age ≥18 years.
3. ECOG PS score of 0–1.
4. Histologically or cytologically confirmed squamous cell carcinoma of HNSCC, originating from the oral cavity, oropharynx, hypopharynx or larynx.
5. Recurrent and/or metastatic HNSCC without indications for local curative treatment.
6. At least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. For lesions previously treated with radiotherapy, only those showing clear disease progression at least 3 months after the end of radiotherapy can be selected as target lesions.
7. Able to provide tumor tissue samples for PD-L1 immunohistochemistry testing.
8. Expected survival of more than 3 months.
9. Normal organ function, meeting the following criteria:
   (1) Hematology (no blood transfusion, erythropoiesis-stimulating agents, recombinant human granulocyte colony-stimulating factor or recombinant human granulocyte-macrophage colony-stimulating factor treatment within 14 days before screening): neutrophils $\geq 1.5 \times 10^9\ l^{-1}$, platelets $\geq 100 \times 10^9\ l^{-1}$, hemoglobin $\geq 90\ g\ l^{-1}$.
   (2) Liver function: alanine aminotransferase and aspartate aminotransferase ≤3× upper limit of normal (ULN) for patients without liver metastasis, and ≤5× ULN for patients with liver metastasis; total bilirubin ≤1.5× ULN (≤3× ULN for patients with Gilbert's syndrome).
   (3) Renal function: serum creatinine ≤1.5× ULN or creatinine clearance $\leq 50\ ml\ min^{-1}$.
   (4) Coagulation function: activated partial thromboplastin time, international normalized ratio and prothrombin time ≤1.5× ULN.
   (5) Echocardiogram: left ventricular ejection fraction (LVEF) ≥50%.
10. Females must agree to use contraception during the study and for 6 months after study completion (such as intrauterine devices, contraceptive pills or condoms), have a negative pregnancy test within 7 days before study entry and not be lactating. Males must agree to use contraception during the study and for 6 months after study completion.

Exclusion criteria.

1. Patients suitable for local treatment and willing to undergo local treatment.
2. Received systemic chemotherapy, excluding chemotherapy for local advanced disease as part of multi-modality treatment (with a treatment end time at least 6 months before the first trial drug). Note: the mentioned chemotherapy includes induction chemotherapy, synchronous chemoradiotherapy and adjuvant chemotherapy.
3. Disease progression within 6 months after completion of chemotherapy in multi-modality treatment for locally advanced squamous cell carcinoma of the head and neck (induction chemotherapy, synchronous chemoradiotherapy and adjuvant chemotherapy).
4. Previously received anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-CTLA-4 antibodies or any other immunotherapies targeting T cell co-stimulation or immune checkpoint pathways.
5. History of or concurrent malignancies within 5 years, excluding cured in situ cervical cancer, nonmelanoma skin cancer or tumors/cancers treated radically with no signs of disease for at least 5 years.
6. Received cetuximab treatment within the past 6 months before the first dose.
7. Peripheral neuropathy ≥grade 2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
8. Known active central nervous system metastases and/or carcinomatous meningitis. Patients with treated brain metastases are eligible if clinically stable for at least 2 weeks with no evidence of new or enlarging brain metastases and discontinued use of steroids 14 days before the administration of the study drug. Asymptomatic patients with brain metastases (that is, no neurological symptoms, no need for corticosteroids, and lesions ≤1.5 cm) can participate but require regular brain imaging as part of disease site assessments.
9. Has not recovered from any acute effects of prior surgery, chemotherapy or radiotherapy to ≤grade 1 (CTCAE) version 5.0 except for alopecia. Chronic late toxicities from prior radiotherapy and/or surgery are allowed if the nutritional status is stable (for example, chronic late toxicity in pharynx/larynx, such as xerostomia, speech and swallowing abnormalities).
10. Any component of the investigational drug or formulation that has led to a severe allergic reaction, including severe allergic reactions (CTCAE version 5.0 ≥grade 3) to other monoclonal antibodies, fluorouracil, cisplatin or platinum compounds.
11. Received anti-cancer drug therapy (for example, chemotherapy, hormone therapy, immunotherapy, antibody therapy or radiotherapy) within 4 weeks before or during the study, except palliative radiotherapy for bone to alleviate pain.
12. Received traditional Chinese medicine or Chinese patent medicine for anti-cancer treatment within ≤1 week before the first dose of study drug.
13. Underwent major surgery within the past 4 weeks or is expected to undergo major surgery during this study.
14. Requires the use of immunosuppressive drugs within 2 weeks before or during the study, excluding: (1) intranasal, inhaled or topical corticosteroids (for example, joint injections).; (2) physiological doses of systemic corticosteroids (≤10 mg per day prednisone or equivalent); (3) short-term (≤7 days) use of steroids for prevention or treatment of nonautoimmune allergic diseases.
15. Known active or history of autoimmune diseases with a potential for relapse (for example, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, autoimmune thyroid disease, multiple sclerosis, vasculitis, glomerulonephritis

and so on) or high risk (for example, requiring immunotherapy due to organ transplant). However, the following patients are allowed to participate: patients with stable type I diabetes on fixed-dose insulin; patients with autoimmune hypothyroidism requiring only hormone replacement therapy; and patients with skin diseases (for example, eczema or psoriasis without ocular symptoms) that do not require systemic treatment and cover less than 10% of the body surface area.

16. Known history of interstitial lung disease, noninfectious pneumonia or suspected interstitial lung disease. Patients with past drug-induced or radiation-induced noninfectious pneumonia without symptoms may be included.
17. History of human immunodeficiency virus infection (positive human immunodeficiency virus test), acquired or congenital immunodeficiency diseases, organ transplantation or hematopoietic stem cell transplantation.
18. Hepatitis B or C virology test meeting any of the following: (1) positive hepatitis B surface antigen with peripheral blood hepatitis B virus deoxyribonucleic acid titer ≥104 copies ml^{-1} or ≥2,000 IU ml^{-1}; (2) positive hepatitis C virus antibody with a hepatitis C virus RNA level above the detection limit of the analysis method.
19. Active or uncontrollable infection requiring systemic treatment or active infection within the past 2 weeks or 2 weeks before the first dose of the study drug.
20. Vaccination with live virus vaccines within the past 4 weeks. Vaccination with nonlive seasonal influenza vaccines is allowed.
21. Clinical symptoms, requiring clinical intervention or effusion cavity (such as pleural effusion and ascites) with a stable time of less than 4 weeks.
22. Known severe internal medical conditions, such as grade 3 or above heart dysfunction (New York Heart Association [NYHA]), ischemic heart disease (for example, myocardial infarction or angina), poorly controlled diabetes (fasting blood glucose ≥10 mmol l^{-1}) or poorly controlled hypertension (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg) within 3 months before the first dose of the study drug.
23. Medical or psychiatric history or laboratory abnormality that may interfere with result interpretation.
24. Currently enrolled in another investigational device or drug study, or less than or equal to 4 weeks since discontinuation of another investigational drug or device.
25. Known alcohol or drug addiction.
26. Conditions identified by the investigator that may affect the patient's compliance with the protocol and assessment of study endpoints, making the patient inappropriate for study participation.

Study procedures

This study comprised two phases: combination chemotherapy phase and maintenance phase. The treatment duration was 2 years (35 cycles, 3 weeks as a cycle). For the combination chemotherapy phase (cycles 1–6), finotonlimab or placebo was administered at 200 mg on day 1 of each cycle. Cisplatin (75 mg m^{-2}) was given at day 1, and 5-fluorouracil (750 mg m^{-2}) was given at days 1–5. For patients who had discontinued due to nonhematological toxicity caused by cisplatin, carboplatin was considered as a substitute for cisplatin in subsequent cycles as a treatment drug, with a dosage target of an area under the curve (AUC) of 5. Chemotherapy was administered 1 h after finotonlimab or placebo infusion. All drugs were delivered intravenously. Chemotherapy should be stopped early if the patient experienced progressive disease (PD), intolerable toxicity, initiation of a new anti-cancer therapy or withdrawal of informed consent. In the maintenance phase (cycle 7 to the end of treatment), patients received finotonlimab or placebo alone (200 mg every three weeks (Q3W), intravenously) until PD, intolerable toxicity, initiation of new anti-cancer therapy, or the investigator's considered decision to discontinue treatment, withdrawal of informed consent, death or loss to follow-up. If none of these circumstances occurred, the maximum duration of treatment was 2 years. Dose reductions of finotonlimab or placebo were not permitted, and treatment could be interrupted or discontinued due to toxicity when necessary.

A centered stratified randomization approach was used. Patients eligible for enrollment after screening examination were randomized 2:1 into the finotonlimab plus C5F group and the placebo plus C5F group. Randomization was stratified on the basis of HPV status (negative versus positive, oropharyngeal cancer only), TPS (<50% versus ≥50%) and ECOG PS score (0 versus 1). The finotonlimab plus C5F group received finotonlimab plus C5F (cisplatin ((or carboplatin if not tolerated)/5-fluorouracil), and the placebo plus C5F group received placebo plus C5F (cisplatin (or carboplatin if not tolerated)/5-fluorouracil). Blinding was maintained using Interactive Network Response System, and the sponsor, investigators, clinical staff and patients remained blinded to treatment throughout the study.

Outcomes

The primary endpoint was OS, defined as the time from the initial study drug administration to the date of death from any cause. Secondary endpoints as assessed by the Blinded Independent Review Committee assessment included the following: (1) ORR, defined as the proportion of patients in confirmed CR and confirmed PR assessed by the RECIST version 1.1; (2) PFS, defined as the time from the date of the first study drug administration to the date of the first recorded PD or death from any cause; (3) DCR, defined as the proportion of patients achieving CR, PR or stable disease; (4) DoR, defined as the time between the first confirmed objective response (CR or PR) and the first PD or death from any cause. Additionally, 1-year survival rate and 2-year survival rate were defined as the probability of surviving for at least 1 year and 2 years after administration of study drug. Other secondary endpoints included safety endpoints, pharmacokinetic endpoints, the proportion of patients who survived in 12 months, 18 months and 24 months, quality of life evaluated by the EORTC QLQ-C30 (V3) and the EORTC QLQ-H&N35 scales, the correlation between efficacy and tumor tissue biomarkers (PD-L1, whole-exome sequencing results and inflammatory T cell gene expression profile) and the correlation between efficacy and baseline peripheral blood tumor mutational burden.

The evaluation of PD-L1 expression involved the determination of both the TPS and the CPS. TPS was defined as the percentage of tumor cells displaying PD-L1 membrane staining among all tumor cells. CPS was defined as the summation of PD-L1-stained tumor cells and tumor-associated immune cells, calculated within a set of 100 tumor cells.

Safety was assessed according to the CTCAE version 5.0 during the first dose of study drug and subsequent 28 + 7 days following the last dose of study drugs. Immunogenicity was evaluated by the presence of ADA and neutralizing antibodies. ADA levels were qualitatively measured using an electrochemiluminescence immunoassay on the MesoScale Discovery platform.

Statistical analysis

Assuming the median OS for the finotonlimab plus C5F group and placebo plus C5F group was 12.5 months and 8.5 months, respectively. The estimated HR between the two groups was 0.68, with a one-sided α of 0.025. According to the protocol, a 2:1 ratio was enrolled over an anticipated 24-month recruitment period, considering an annual dropout rate of no less than 12%. The planned sample size was 244 for the finotonlimab plus C5F group and 122 for the placebo plus C5F group, totaling 366 patients with a follow-up stage of at least 16 months after the last patient was randomized. To ensure that the OS at the last analysis cutoff reaches at least 70% maturity, a minimum of 266 events was required, achieving a power of 85%.

This trial incorporated two interim analyses. An independent data monitoring committee conducted data reviews and advised the

trial's continuation. The first interim analysis focused on the safety and tolerability, reviewed by the independent data monitoring committee. A total of 21 patients were enrolled: 15 received the finotonlimab plus C5F, and 6 received placebo plus C5F. Incidences of TRAEs, and ≥grade 3 TRAEs were similar between the finotonlimab plus C5F and placebo plus C5F groups. Most TRAEs were grade 1–2, with one patient each of ≥grade 3 anemia and rash. In the finotonlimab plus C5F group, one patient had a drug-related SAE of rash, and two experienced irAEs: rash and hypothyroidism. No infusion-related AEs were reported at the time of data analysis. The second interim analysis focused on the safety and assessed the ORR of the treatment. A total of 75 patients were randomized: 50 in the finotonlimab plus C5F group and 25 in the placebo plus C5F group. The ORR in the finotonlimab plus C5F group was 20.8% (n = 48), with PRs, while the ORR in the placebo plus C5F group was 29.2% (n = 24). The incidence rates of TEAEs, ≥grade 3 TEAEs and ≥grade 3 TRAEs were comparable between the finotonlimab plus C5F and placebo plus C5F groups. The incidence of TRAEs in the finotonlimab plus C5F group and placebo plus C5F group were 66% (n = 50) and 56% (n = 25), respectively. Most TRAEs were grade 1–2. The most common ≥grade 3 TRAE was anemia (both 8% in the two groups).

The full analysis set (FAS) encompassed patients who had received at least one dose of study drug was used to analyze OS and PFS. The safety set (SS) encompassed patients who had received at least one dose of study drug was used to analyze safety. For baseline demographic and disease distributions analyses, the P value of categorical data was calculated by chi-square test and the P value of continuous data was calculated by analysis of variance (ANOVA). OS data include patients who survived at the end of the study or for follow-up patients who were censored at the end contact date. In the PFS and DoR analyses, data from patients who were not suffering from PD or dead at the date of the final tumor assessment were deleted. The Kaplan–Meier method was used to estimate the median time to OS, PFS and DoR, as well as to plot survival curves. The Brookmeyer–Crowley method was used to calculate the 95% CIs for these estimates. This was a superior design to demonstrate that finotonlimab plus C5F group was superior to the placebo plus C5F group in terms of OS. OS and PFS were compared between the two groups of patients using a stratified log-rank-based method, and the difference between the groups was considered statistically significant if the bilateral P value was less than 0.05. HR and two-sided 95% CI were estimated using the stratification-based COX proportional risk model. The model employed survival time as the dependent variable and treatment group as the independent variable, with the same stratification factors as the log-rank test, that is, HPV status (negative versus positive, oropharyngeal cancer only), TPS (<50% versus ≥50%) and ECOG PS score (0 versus 1). Event ties was handled using the Efron method. For ORR and DCR, their 95% CIs were calculated by the Clopper–Pearson method. Comparisons between the two groups were made by calculating the ORR rate difference and the DCR rate difference, 95% CI and P values based on the stratified Cochran–Mantel–Haenszel method. All P values were two-sided and calculated using stratified methods, with strata based on actual HPV status, TPS score and ECOG PS score. The calculation of the P value has been added to the figure and table legends.

Three sensitivity analyses were performed on the primary endpoints. These analyses included adjusting the placebo plus C5F group's survival data using the Rank Preserving Structural Failure Time model for patients receiving new anti-PD-1 treatment, centering observations for the death censored at the date when new anti-cancer therapy was used, and using stratification factors recorded in the randomization system when they were not consistent with the true values. All statistical analyses were carried out using SAS software version 9.4 (SAS Institute).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The supporting data for most figures and tables can be found directly within them, while the subgroup analysis data are available in Supplementary Information. Patient-related information cannot be disclosed due to confidentiality agreements. The trial protocol and statistical analysis plan (SAP) will be made available in Supplementary Information. For inquiries regarding access to clinical study documents, please direct your email to the corresponding author with detailed proposals. Requests will be promptly reviewed by the primary investigator and the sponsor to ascertain whether they are subject to any confidentiality obligations. We aim to respond to all requests within 8 weeks. Source data are provided with this paper.

Code availability

Analyses were carried out using commercially available software (SAS version 9.4, SAS Institute Inc.) in accordance with SAP guidelines.

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Author contributions

Y. Shi was the principal investigator, contributing to trial design, supervision, coordination, patient enrollment, patient management, manuscript writing and revising. W. Guo, W.W., Yunteng Wu, M.F., X.H., P.H., Q.Z., P.D., X.Z., H.P., C.H., X.C., Shurong Zhang, Z.C., X.L., Y.D., S.Q., S.J., Songnan Zhang, L.G., Y. Sun, L.W., Y.L., H.W., G.L., Z.F., J.S., H.J., Y.B., J. Cui., Y.Z., W.C., X.J., L.Z., Q.C., D.X., Yunong Wu, J. Cao., R.W., G.H. and L.P. were investigators in this clinical trial, and contributed to patient enrollment and patient management. L.X. contributed to the experimental design, overall management and communication. W. Gai, Y. Wang and Y. Su contributed to the trial design, medical monitoring and supervision of the trial. All authors had access to all data in the trial and were ultimately responsible for the decision to submit the manuscript for publication. The authors were responsible for the accuracy and completeness of the data and the fidelity of the trial to the protocol. All authors read and approved the final version of the manuscript for publication.

Competing interests

L.X., W. Gai, Y. Wang and Y. Su are employees of Sinocelltech Ltd., Beijing, China. L.X. and W.G. hold potential stock option interests in the company. The other authors, who are investigators involved in this study, declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-024-03110-7.

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Extended Data Table 1 | OS and PFS rates

	Finotonlimab plus C5F (N=247)	Placebo plus C5F (N=123)		*P* value[a]
OS (95% CI)				
12-month (%)	53.5 (47.1-59.6)	39.4 (30.7-47.9)		<0.0001
18-month (%)	40.6 (34.4-46.7)	28.6 (20.8-36.8)		0.0023
24-month (%)	33.6 (27.5-39.8)	22.8 (15.6-30.7)		0.0017
36-month RMST (month)	17.9 (16.2-19.6)	14.5 (12.4-16.7)	RMST Ratio 1.23 (1.03-1.47)	0.0169
PFS (95% CI)				
3-month (%)	77.3 (71.3-82.1)	72.4 (63.3-79.7)		0.0260
6-month (%)	49.1 (42.2-55.5)	39.1 (29.5-48.6)		<0.0001
9-month (%)	36.0 (29.5-42.6)	21.5 (13.7-30.5)		0.0030
12-month (%)	30.4 (24.1-37.0)	15.2 (8.6-23.6)		0.0020
24-month RMST (month)	9.8 (8.7-11.0)	7.4 (6.0-8.8)	RMST Ratio 1.32 (1.06-1.65)	0.0104

[a]The two-sided *P* value was calculated using a stratified log-rank test based on group effects, HPV status, TPS score, and ECOG PS score.

C5F, cisplatin plus 5-fluorouracil; OS, overall survival; PFS, progression free survival; CI, confidence interval; TPS, tumor proportion score; ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; HPV, human papillomavirus; RMST, Restricted mean survival time.

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Extended Data Table 2 | Summary of responses in the FAS

	Finotonlimab plus C5F (N=243)	Placebo plus C5F (N=119)
CR[a], n (%)	26 (10.7)	8 (6.7)
PR[a], n (%)	71 (29.2)	27 (22.7)
SD, n (%)	97 (39.9)	56 (47.1)
PD, n (%)	26 (10.7)	17 (14.3)
NE[b], n (%)	23 (9.5)	11 (9.2)
ORR (CR + PR), n (%)	97 (39.9)	35 (29.4)
95% CI	(33.71-46.37)	(21.42-38.46)
Rate difference (%, 95% CI)	10.92 (0.70-21.14)	
P value	0.0416	
DCR (CR + PR + SD), n (%)	194 (79.8)	91 (76.5)
95% CI	(74.23-84.69)	(67.82-83.76)
Rate difference (%, 95% CI)	3.30 (-5.69-12.29)	
P value[c]	0.4655	

[a]CR and PR were confirmed overall best responses.

[b]NE included the absence of tumor evaluation after the first dose.

[c]The two-sided *P* value was computed using the Cochran-Mantel-Haenszel (CMH) method stratified by actual strata of HPV status, TPS score, and ECOG PS score..

FAS, full analysis set; C5F, cisplatin plus 5-fluorouracil; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, objective response rate; DCR, disease control rate; CI, confidence interval.

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Extended Data Table 3 | TRAEs (incidence ≥ 5%) and irAEs

	TRAE		irAE	
	Finotonlimab plus C5F (N=247, %)	Placebo plus C5F (N=123, %)	Finotonlimab plus C5F (N=247, %)	Placebo plus C5F (N=123, %)
Any grade	166 (67.2)	67 (54.5)	96 (38.9)	27 (22.0)
Hypothyroidism	49 (19.8)	14 (11.4)	44 (17.8)	11 (8.9)
Anemia	48 (19.4)	29 (23.6)	2 (0.8)	0
Leukopenia	38 (15.4)	21 (17.1)	0	0
Nausea	34 (13.8)	14 (11.4)	0	0
Dermatitis	32 (13.0)	5 (4.1)	27 (10.9)	4 (3.3)
Neutropenia	30 (12.1)	15 (12.2)	0	0
Thrombocytopenia	28 (11.3)	13 (10.6)	0	1 (0.8)
Anorexia	27 (10.9)	9 (7.3)	0	0
Vomiting	26 (10.5)	12 (9.8)	0	0
Renal function abnormal	21 (8.5)	3 (2.4)	7 (2.8)	2 (1.6)
Hypokalemia	21 (8.5)	8 (6.5)	0	0
Elevated liver enzymes	19 (7.7)	11 (8.9)	8 (3.2)	5 (4.1)
Hyponatremia	19 (7.7)	8 (6.5)	0	0
Constipation	18 (7.3)	8 (6.5)	0	0
Hyperthyroidism	18 (7.3)	3 (2.4)	18 (7.3)	3 (2.4)
Fatigue	16 (6.5)	9 (7.3)	0	0
Weight loss	15 (6.1)	10 (8.1)	0	0
Mucositis	14 (5.7)	6 (4.9)	0	0
Lymphocytopenia	13 (5.3)	8 (6.5)	0	0
Fever	13 (5.3)	3 (2.4)	0	0

C5F, cisplatin plus 5-fluorouracil; TRAE, treatment-related adverse events; irAE, immune-related adverse events.

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Extended Data Table 4 | Sensitivity analysis of OS

	Finotonlimab plus C5F (N=247)	Placebo plus C5F (N=123)
Sensitivity Analysis 1[a]		
Total events (N, %)	162 (65.6)	95 (77.2)
Median OS (months,95% CI)	14.1 (11.1-16.4)	10.2 (7.8-11.7)
HR (95% CI)	0.69 (0.53-0.89)	
P value	0.0040	
Sensitivity Analysis 2[b]		
Total events (N, %)	140(56.7)	77(62.6)
Median OS (months,95% CI)	14.2 (11.2-17.5)	10.5 (8.3-11.7)
HR (95% CI)	0.72 (0.54-0.96)	
P value	0.0239	
Sensitivity Analysis 3[c]		
Total events (N, %)	162(65.6)	95(77.2)
Median OS (months,95% CI)	14.1 (11.1-16.4)	10.5 (8.1-11.8)
HR (95% CI)	0.73 (0.57-0.95)	
P value[d]	0.0165	

[a]Sensitivity analysis 1: adjustment of the placebo plus C5F group's survival data using the Rank Preserving Structural Failure Time (RPSFT) model for patients receiving new anti-PD-1 treatment;

[b]Sensitivity analysis 2: exclusion of death events observed on the date of using new anti-cancer drugs;

[c]Sensitivity analysis 3: stratification based on randomization with systematic entry of stratification factors.

[d]The two-sided p-value was calculated using a stratified log-rank test based on group effects, HPV status, TPS score, and ECOG PS score.

C5F, cisplatin plus 5-fluorouracil; OS, overall survival; HR, hazard ratio; CI, confidence interval; PD-1, programmed death 1; HPV, human papillomavirus; TPS, tumor proportion score; ECOG, Eastern Cooperative Oncology Group; PS, Performance Status.

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Extended Data Table 5 | Sensitivity analysis of PFS

	Finotonlimab plus C5F (N=247)	Placebo plus C5F (N=123)
Sensitivity Analysis 1[a]		
Total events (N, %)	143 (57.9)	78 (63.4)
Median PFS (months,95% CI)	5.7 (5.5-7.1)	5.6 (4.6-5.7)
HR (95% CI)	0.77 (0.58-1.03)	
P value	0.0715	
Sensitivity Analysis 2[b]		
Total events (N, %)	240 (97.2)	118 (95.9)
Median PFS (months,95% CI)	4.4 (4.2-5.5)	4.2 (3.3-4.5)
HR (95% CI)	0.84 (0.67-1.05)	
P value[c]	0.1222	

[a]Sensitivity analysis 1: Modification from primary analysis: The first disease progression or death more than two cycles after the last assessment was recorded as censored. The complete PFS censoring rules can be found in the statistical analysis plan.

[b]Sensitivity analysis 2: Modification from primary analysis:

a) Discontinuation of therapy for reasons other than completion of therapy was recorded as event.

b) Initiation of new anti-cancer therapy without PD was recorded as an event.

[c]The two-sided *P* value was calculated using a stratified log-rank test based on group effects, HPV status, TPS score, and ECOG PS score.

C5F, cisplatin plus 5-fluorouracil; PFS, progression free survival; HR, hazard ratio; CI, confidence interval; PD, progressive disease; HPV, human papillomavirus; TPS, tumor proportion score; ECOG, Eastern Cooperative Oncology Group; PS, Performance Status.

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	In this study, an electronic data capture system (EDC) was used for data collection and management.
Data analysis	Analyses were carried out using commercially available software (SAS version 9.4, SAS Institute Inc., Cary, NC, USA) in accordance with SAP guidelines.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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The supporting data for most figures and tables can be found directly in them, while the subgroup analysis data is available in the supplementary materials. Patient-related information cannot be disclosed due to confidentiality agreements. The trial protocol and Statistical Analysis Plan (SAP) will be made available in the supplementary materials. For inquiries regarding access to clinical study documents, please direct your email to the corresponding author with detailed proposals.

Requests will be promptly reviewed by the primary investigator and the sponsor to ascertain whether they are subject to any confidentiality obligations. We aim to respond to all requests within 8 weeks.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	86.5% (320/370) of the patients enrolled were male, which was consistent with the high incidence and high mortality of the male population in HNSCC. The study accounted for participant sex in its design, using a self-reporting system that offered binary gender choices "male" and "female".
Reporting on race, ethnicity, or other socially relevant groupings	Most are Han Chinese (93.1% (230/247) in the finotonlimab plus CF group and 95.9% (118/123) in the placebo plus CF group.
Population characteristics	Baseline demographic and disease distributions were generally similar in the two groups (Table 1). The mean age of the two groups was both 60.0 years. PD-1 tumor proportion score (TPS) of 50% or greater was observed in 23.5% (58/247) of patients in the finotonlimab plus CF group and 24.4% (30/123) of patients in the placebo plus CF group. The percentage of patients with a PD-1 combined positive score (CPS) of 1 or higher was 89.5% (221/247) in the finotonlimab plus CF group and 94.3% (116/123) in the placebo plus CF group. 86.5% (320/370) of the patients enrolled were male, which was consistent with the high incidence and high mortality of the male population in HNSCC.
Recruitment	Potential patients were identified on the basis of their diagnosis by the investigators or staff of the 64 hospitals in the mainland China participating in the study. Following the determination of eligibility for enrolment, the sponsor's medical monitor will conduct a secondary review of the patient's enrolment information.
Ethics oversight	The study protocol, informed consent form, and other relevant documents were approved by the Independent Ethics Committee (Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College) before the clinical study was conducted. The study implementation process strictly followed the international harmonized ethical principles. The study has been performed in accordance with the Declaration of Helsinki.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Assuming the median OS for the finotonlimab plus C5F group and placebo plus C5F group was 12.5 months and 8.5 months, respectively. The estimated HR between the two groups was 0.68, with a one-sided α of 0.025. According to the protocol, a 2:1 ratio was enrolled over an anticipated 24-month recruitment period, considering an annual dropout rate of no less than 12%. The planned sample size was 244 for the finotonlimab plus C5F group and 122 for the placebo plus C5F group, totaling 366 patients with a follow-up stage of at least 16 months after the last patient was randomized. To ensure that the OS at the last analysis cutoff reaches at least 70% maturity, a minimum of 266 events was required, achieving a power of 85%.
Data exclusions	There were no data exclusions up to the cut-off date for the data.
Replication	The immunogenicity assays were performed once and each sample were tested duplicated.
Randomization	A centered stratified randomization approach was used. Patients eligible for enrollment after screening examination were randomized 2:1 into the finotonlimab group and the control group. Randomization was stratified based on HPV status (negative vs. positive, oropharyngeal cancer only), Tumor Proportion Score (TPS, <50% vs. ≥50%), and ECOG PS score (0 vs. 1). The finotonlimab group received finotonlimab plus chemotherapy (cisplatin [or carboplatin if not tolerated]/5-fluorouracil), and the control group received placebo plus chemotherapy (cisplatin [or carboplatin if not tolerated]/5-fluorouracil).
Blinding	Blinding was maintained using Interactive Network Response System and the sponsor, investigators, clinical staff and patients remained blinded to treatment throughout the study.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

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☒	☐ ChIP-seq
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Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	The registration number was NCT04146402 on ClinicalTrials.gov and CTR20191160 on Chinadrugtrials.org.cn.
Study protocol	The protocol was in the supplementary material.
Data collection	Data from patients were collected and managed by an electronic data capture system (EDC). Between December 31, 2019, and Mar 16, 2022, 522 patients were screened from 64 hospitals in China. 370 were eligible to be randomly enrolled in the finotonlimab group (n = 247) or the control group (n = 123) and received treatment. The data cutoff was on July 31, 2023.
Outcomes	The primary endpoint was OS, defined as the time from the initial study drug administration to the date of death from any cause. Secondary endpoints as assessed by the Blinded Independent Review Committee (BIRC) assessment included the following: (1) ORR, defined as the proportion of patients in confirmed CR or confirmed PR assessed by the RECIST version 1.1. (2) PFS, defined as the time from the date of the first study drug administration to the date of the first recorded PD or death from any cause. (3) DCR, defined as the proportion of patients achieving CR, PR, or stable disease (SD). (4) DoR, defined as the time between the first confirmed objective response (CR or PR) and the first PD or death from any cause. Additionally, 1-year survival rate and 2-year survival rate were defined as the probability of surviving for at least 1 year and 2 years after administration of study drug. Other secondary endpoints included safety endpoints, pharmacokinetic endpoints, the proportion of patients who survived in 12 months, 18 months and 24 months, quality of life evaluated by the EORTC QLQ-C30 (V3) and the EORTC QLQ–H&N35 scales, the correlation between efficacy and tumor tissue biomarkers (PD-L1, whole exome sequencing results, inflammatory T-cell gene expression profile) and the correlation between efficacy and baseline peripheral bTMB. The evaluation of PD-L1 expression involved the determination of both the TPS and the CPS. TPS was defined as the percentage of tumor cells displaying PD-L1 membrane staining among all tumor cells. CPS was defined as the summation of PD-L1-stained tumor cells and tumor-associated immune cells, calculated within a set of 100 tumor cells. Safety was assessed according to the CTCAE version 5.0 during the first dose of study drug and subsequent 28+7 days following the last dose of study drugs. Immunogenicity was evaluated by the presence of ADA and NAb. ADA levels were qualitatively measured using an electrochemiluminescence immunoassay on the MesoScale Discovery platform.

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