Clinical Study Protocol

Study Title: An Exploratory Study of Neoadjuvant Vibecortamab Combined with Putilimab in Locally Advanced Laryngeal Cancer – A Single-Arm, Phase II Study

Applicant Institution: Department of Otorhinolaryngology Head and Neck Surgery, Tangdu Hospital, Air Force Medical University

Version: V1.0

Date: March 12, 2026

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Compliance Statement

This study is conducted in compliance with **Good Clinical Practice (GCP)**, the Measures for the Administration of Clinician-Initiated Clinical Research in Medical and Health Institutions (for Trial Implementation), and the Declaration of Helsinki. The study will be performed strictly in accordance with this protocol. All researchers must complete relevant training. The study will be initiated only after written approval from the Ethics Committee and written informed consent from participants. Any protocol amendment requires re-review and approval by the Ethics Committee.

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1. Study Summary

Title： An Exploratory Study of Neoadjuvant Vibecortamab Combined with Putilimab in Locally Advanced Laryngeal Cancer

Study Background： Laryngeal carcinoma is one of the most common malignancies of head and neck squamous cell carcinoma (HNSCC), with a high proportion of locally advanced cases. Approximately 189,000 new cases and 103,000 deaths occur worldwide each year. Laryngeal cancer severely impairs vocalization, swallowing and other physiological functions, and significantly reduces quality of life.

Current treatment for locally advanced laryngeal cancer is dominated by surgery-based comprehensive therapy. Platinum-based chemotherapy has improved laryngeal function preservation to a certain extent, but has not significantly improved overall survival, and 5-year survival rate remains low. Concurrent chemoradiotherapy often causes severe late toxicities, which negatively affect organ function and long-term survival.

The efficacy of neoadjuvant chemotherapy has reached a bottleneck. Immune checkpoint inhibitors (PD-1 inhibitors) and EGFR-targeted antibody-drug conjugates (ADCs) have shown promising prospects in HNSCC. Putilimab, a PD-1 inhibitor, can relieve the suppression of the immune system by cancer cells and enhance T-cell anti-tumor activity. Vibecortamab (MRG003), an EGFR-ADC, can specifically target EGFR-overexpressing tumor cells and exert potent cytotoxic effects. The combination can synergistically activate the tumor microenvironment through immunogenic cell death, achieving enhanced efficacy.

This combination regimen has shown significant efficacy in recurrent/metastatic nasopharyngeal carcinoma and treatment-naive HNSCC. This study aims to extend this strategy to neoadjuvant therapy for locally advanced laryngeal cancer, evaluate its efficacy and safety, and provide evidence for optimizing treatment strategies.

Study Design： This is a prospective, single-arm, single-center, phase II study. A total of 10 patients with pathologically confirmed stage III–IVA locally advanced laryngeal cancer (glottic, supraglottic, subglottic) will be enrolled.

All patients will receive 3 cycles of neoadjuvant therapy with vibecortamab combined with putilimab, q3w, administered on day 1 of each cycle. Imaging evaluation will be performed 3–4 weeks after neoadjuvant therapy. Surgery (radical resection of laryngeal cancer + neck dissection) will be performed within 4 weeks if judged resectable by the investigator. If initially unresectable, the MDT team may discuss adding 1–2 cycles of neoadjuvant therapy before re-evaluation.

Stratified adjuvant therapy will be given based on postoperative pathological results:

1. Patients with pathological complete response (pCR): maintenance therapy with the same regimen for 1 year starting 4–8 weeks after surgery;
2. Patients with major pathological response (MPR): standard postoperative adjuvant therapy;
3. Patients with T3/T4 or node-positive disease with high-risk factors (perineural invasion, lymphovascular tumor thrombus, etc.): radiotherapy or concurrent chemoradiotherapy within 6 weeks after surgery.

Primary Endpoint： Pathological complete response (pCR) rate.

Secondary Endpoints： Surgical margin status (first and second margins), major pathological response (MPR) rate, imaging response rate (RECIST 1.1), swallowing and vocal function, treatment-related complications.

Exploratory Endpoints

Disease-free survival (DFS), 5-year overall survival (OS) rate.

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2. Introduction

2.1 Rationale and Background

Head and neck tumors refer to tumors originating from multiple anatomical regions of the head and neck, more than 90% of which are squamous cell carcinoma[1]. Head and neck squamous cell carcinoma (HNSCC) arises from mucosal epithelial tissues of the oral cavity, oropharynx, nasal cavity, paranasal sinuses, middle ear, hypopharynx, and larynx.Squamous cell carcinoma of the head and neck (SCCHN) impairs patients' appearance, basic physiological functions, sensory functions, and speech functions, thereby compromising quality of life, with high rates of morbidity and mortality.According to GLOBOCAN 2018 data released by the International Agency for Research on Cancer (IARC):globally, head and neck cancer (excluding nasopharyngeal carcinoma) ranks **8th** in incidence and **9th** in mortality.There were 705,781 new cases and 358,144 deaths annually worldwide[2].In China, there are approximately 68,000 new cases and 35,316 deaths from head and neck cancer (excluding nasopharyngeal carcinoma) each year[3].

Laryngeal carcinoma belongs to head and neck squamous cell carcinoma (HNSCC) and is a highly prevalent malignant tumor worldwide. As one of the most common malignant tumors in the head and neck region, laryngeal carcinoma has a global annual incidence of approximately 2.4 per 100,000 population, accounting for 2%–5% of all systemic malignant tumors, with substantial regional variations in incidence [4]. The incidence is relatively high in Eastern Europe, South America, and Southeast Asia, while it is lower in North America and Western Europe.In China, the incidence of laryngeal carcinoma is approximately 1.5–3.4 per 100,000 population. The incidence is significantly higher in males than in females, with a male-to-female ratio of about 7–10:1 [5]. The disease predominantly affects individuals aged 50–70 years [6], and a slight upward trend in incidence has been observed among young patients in recent years.The pathogenesis of laryngeal carcinoma is closely associated with long-term tobacco smoking, excessive alcohol consumption, air pollution, occupational exposure (e.g., prolonged contact with dust and chemical toxins), and human papillomavirus (HPV) infection. Among these, the synergistic effect of smoking and alcohol consumption significantly increases the risk of developing laryngeal carcinoma and represents the most important risk factor.

At diagnosis, approximately 30–40% of patients with head and neck squamous cell carcinoma (HNSCC) present with early-stage disease (clinical stage I–II). Favorable disease control and long-term survival can be achieved through radical surgery or radiotherapy alone [7]. In contrast, more than 60% of patients are diagnosed at stage III–IV (i.e., locally

advanced or distant metastatic disease, such as large tumors with local invasion, regional lymph node metastasis, or distant metastasis) [8].Based on whether patients are eligible for or tolerate surgical resection, the primary treatment modalities for locally advanced HNSCC include surgery or concurrent chemoradiotherapy (cCRT) [9]. However, these patients carry a high risk of local recurrence and distant metastasis, resulting in poor prognosis, with a 5-year overall survival rate of less than 50% [10]. Furthermore, no significant breakthroughs in therapeutic strategies have been made in the past two decades.

For patients with locally advanced HNSCC, resectability largely depends on tumor location and size. In addition, organ function preservation, quality of life, risk of postoperative recurrence or distant metastasis are also critical factors to be considered when choosing between surgery and concurrent chemoradiotherapy [7, 11].Among patients receiving concurrent chemoradiotherapy, 43% develop severe late toxicities [12], which severely impair organ function preservation, quality of life, and long-term survival, including xerostomia, dental and oral mucosal injury, fibrosis, trismus, and esophageal stricture [13].Currently, neoadjuvant therapy followed by surgery or radiotherapy has become a commonly used treatment strategy [14]. However, the efficacy of conventional neoadjuvant chemotherapy regimens such as TPF has reached a plateau in HNSCC. Exploring more effective neoadjuvant strategies to improve resectability and prolong overall survival remains a highly important research direction.

Evidence indicates that preoperative chemotherapy (neoadjuvant therapy) can improve the prognosis of locally advanced HNSCC. A retrospective study demonstrated that neoadjuvant chemotherapy achieved pathological complete response (pCR, defined as no residual viable tumor cells) in 18.8% of HNSCC patients and major pathological response (MPR, defined as viable tumor cells ≤10%) in another 18.8%. Moreover, MPR was positively correlated with better overall survival (OS) [15]. Therefore, improving the pathological response rate of neoadjuvant therapy can prolong survival in patients with resectable locally advanced HNSCC.

In recent years, immune checkpoint inhibitors, such as anti-PD-1 monoclonal antibodies, have developed rapidly in the treatment of advanced head and neck squamous cell carcinoma and have been recommended by multiple international guidelines.KEYNOTE-048 [16], a global, multicenter, prospective, randomized controlled phase III trial, compared the efficacy of pembrolizumab monotherapy / pembrolizumab plus chemotherapy versus the standard EXTREME regimen (cetuximab plus platinum plus fluorouracil) as first-line treatment in patients with recurrent or metastatic HNSCC (R/M HNSCC).In the overall population, pembrolizumab monotherapy was non-inferior to cetuximab plus chemotherapy, whereas pembrolizumab combined with chemotherapy showed a significant advantage.For pembrolizumab monotherapy versus cetuximab plus chemotherapy:median overall survival

(OS) was 11.5 months versus 10.7 months, HR = 0.83 (95% CI 0.70–0.99), P = 0.0199.For pembrolizumab plus chemotherapy versus cetuximab plus chemotherapy: median OS was 13.0 months versus 10.7 months, HR = 0.72 (95% CI 0.60–0.87), P = 0.0034,representing a 2.3-month improvement in median OS and a 28% reduction in the risk of death. Pembrolizumab monotherapy provided long-term survival benefit in patients with PD-L1 combined positive score (CPS) ≥1 (4-year OS rate: 16.7% vs 5.9%) or CPS ≥20 (4-year OS rate: 21.6% vs 8.0%).Pembrolizumab plus chemotherapy conferred OS benefit in the overall population (4-year OS rate: 19.4% vs 4.5%), with a favorable safety profile. CheckMate 141 [17] and KEYNOTE-040 [18] were also global, multicenter, prospective, randomized controlled phase III trials. Both anti-PD-1 agents (nivolumab and pembrolizumab) significantly prolonged overall survival and improved quality of life compared with investigator's choice standard therapy in patients with disease progression within 6 months after prior platinum-based treatment.

A study investigated neoadjuvant therapy with nivolumab combined with weekly carboplatin/paclitaxel in patients with resectable locally advanced head and neck squamous cell carcinoma. All 27 patients underwent surgical resection. Of these, 11/26 patients (42%) (excluding those with unknown primary site) achieved pathological complete response (pCR) in the primary tumor;18/26 patients (69%) achieved major pathological response (MPR) or pCR. These findings indicate that nivolumab combined with the TP regimen represents a promising neoadjuvant strategy for resectable locally advanced HNSCC.

The IMCISION study [20] was a phase I/II trial of neoadjuvant immunotherapy in resectable HNSCC. Thirty-two patients received preoperative dual immunotherapy (PD-1 inhibitor at weeks 1 and 3 plus CTLA-4 inhibitor at week 1) or PD-1 inhibitor monotherapy (at weeks 1 and 3). CT evaluation was performed at week 4, and surgery was conducted at week 5. Among the 29 evaluable patients, 9 achieved pathological complete response (pCR). These preliminary results demonstrate that immunotherapy as a neoadjuvant strategy exhibits potential favorable antitumor activity in the preoperative setting for patients with resectable locally advanced HNSCC.

With the increasingly widespread application of immunotherapy in HNSCC, neoadjuvant immunotherapy for head and neck squamous cell carcinoma has gradually become a research hotspot. At present, several phase II clinical trials are exploring the neoadjuvant regimen of immunotherapy combined with chemotherapy for HNSCC [19]. Preliminary results demonstrate that neoadjuvant immunotherapy plus chemotherapy achieves favorable efficacy in improving pathological response rates and tumor downstaging in locally advanced HNSCC. It creates favorable conditions for surgical resection and may even improve overall survival in patients.

Pucotelimab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody that

specifically binds to the PD-1 receptor. This binding inhibits the interaction of PD-1 with its ligands PD-L1 and PD-L2, thereby reversing the immunosuppressive effect of cancer cells on the immune system and enabling the immune system to recognize and attack cancer cells again. The development of pucotelimab is based on an in-depth understanding of the PD-1 signaling pathway, which plays a key role in the tumor microenvironment. By blocking PD-1 signaling, pucotelimab enhances T-cell activity and improves their ability to recognize and kill tumor cells, thereby inhibiting tumor growth and metastasis. Pucotelimab also employs antibody engineering technology with mutations introduced in the Fc region to enhance binding affinity to Fc receptors. Compared with other PD-1 inhibitors, it has a prolonged half-life, improved efficacy, and better patient compliance. The antitumor mechanism of pucotelimab lies in blocking the PD-1 signaling pathway, relieving immune suppression by cancer cells, and restoring and enhancing the ability of immune cells to recognize and eliminate cancer cells. In July 2022, pucotelimab was approved by the National Medical Products Administration (NMPA) for the treatment of unresectable or metastatic high microsatellite instability (MSI-H) or mismatch repair-deficient (dMMR) advanced solid tumors. In this trial, 100 subjects received pucotelimab 200 mg intravenously once every three weeks. With a median follow-up of 22.5 months, the overall objective response rate (ORR) was 49%. The ORR was 58.1% in second-line colorectal cancer (CRC) patients and 53.6% in ≥ third-line CRC patients. Even in patients with relapsed/refractory CRC who had failed treatment with three prior agents (fluoropyrimidines, irinotecan, oxaliplatin), the ORR remained as high as 50%. Median progression-free survival (mPFS) and median overall survival (mOS) had not been reached in the full analysis set (FAS) or the CRC subgroup [3]. In September of the same year, its second indication was approved for unresectable or metastatic melanoma following failure of prior systemic therapy. This study enrolled 119 patients who received pucotelimab 3 mg/kg intravenously once every three weeks, with a median follow-up of 19.32 months. The ORR in the overall population was 20.2%, the highest among similar approved agents. The ORR was 36.4% for cutaneous melanoma and 33.3% for melanoma of unknown primary. Pucotelimab significantly prolonged long-term survival, with an mOS of 17.2 months in the overall population and 20.1 months in acral melanoma; mOS had not been reached in cutaneous melanoma patients [7]. A randomized, open-label, multicenter phase III trial (HX008-III-MM-01) is currently underway evaluating pucotelimab combined with transcatheter arterial chemoembolization (TACE) as first-line therapy for stage IV M1c melanoma with liver metastasis. In addition, multiple studies of pucotelimab in solid tumors are ongoing: A single-arm, multicenter phase Ib trial of pucotelimab combined with capecitabine and oxaliplatin as first-line treatment for advanced gastric cancer enrolled 35 patients. As of May 2021, with a median follow-up of 22.0 months, the ORR was 60.0% (75.0% in CPS ≥1 patients), median PFS was 9.2 months, median duration of response (mDOR) was 12.3 months, and mOS was 15.3 months [8]. A single-arm,

multicenter phase II trial of pucotelimab combined with irinotecan as second-line treatment for advanced gastric cancer enrolled 58 patients. As of February 2021, with a median follow-up of 18.8 months, the ORR was 27.6% (38.5% in CPS ≥1 patients), mPFS was 4.2 months, mDOR was 12.8 months, and mOS was 12.1 months (17.7 months in CPS ≥1 patients) [9]. A single-arm, multicenter phase Ib trial of pucotelimab combined with cisplatin and gemcitabine as first-line treatment for triple-negative breast cancer (TNBC) enrolled 31 patients. As of August 4, 2021, with a median follow-up of 18.1 months, the ORR was 80.7% (1 complete response (CR), 24 partial responses (PR)), disease control rate (DCR) was 100%, and mPFS was 9.0 months, significantly superior to chemotherapy alone [10]. Promising results were observed in studies of pucotelimab combined with bevacizumab or lenvatinib as first-line treatment for advanced hepatocellular carcinoma (HCC): In the pucotelimab plus bevacizumab cohort (28 patients, pucotelimab 200 mg IV Q3W + bevacizumab 15 mg/kg IV Q3W), median follow-up was 15.2 months. ORR was 28.6%, DCR 75.0%, mPFS 7.5 months, and mOS not yet reached. In the pucotelimab plus lenvatinib cohort (47 patients, pucotelimab 200 mg IV Q3W + lenvatinib 12 mg/day [≥60 kg] or 8 mg/day [<60 kg]), median follow-up was 12.5 months. ORR was 36.2%, DCR 80.9%, mPFS 9.6 months [11].

Vebectotamab vedotin MRG003 is an antibody-drug conjugate (ADC) composed of the recombinant humanized anti-epidermal growth factor receptor (EGFR) monoclonal antibody JMT101 and the highly potent cytotoxic small molecule monomethyl auristatin E (MMAE) linked via a vc linker. Preclinical studies have demonstrated that MRG003 exhibits favorable safety profiles and significantly stronger antitumor activity than the EGFR-targeted monoclonal antibody Erbitux® (cetuximab). EGFR is overexpressed or aberrantly expressed in a variety of solid tumors, including nasopharyngeal carcinoma, head and neck squamous cell carcinoma, colorectal cancer, glioblastoma, renal cell carcinoma, lung cancer, prostate cancer, pancreatic cancer, and breast cancer (Martinelli et al., 2009). Based on preclinical pharmacodynamic findings, the initially proposed indications for MRG003 are EGFR-positive solid tumors, including colorectal cancer and head and neck cancer. Completed phase I clinical results of MRG003 have shown manageable safety and preliminary antitumor activity in patients with advanced solid tumors (HNSCC, nasopharyngeal carcinoma, colorectal cancer, etc.) who failed standard therapies. Phase II studies in HNSCC, nasopharyngeal carcinoma, non-small cell lung cancer, cholangiocarcinoma, gastric cancer, and a phase III study in HNSCC are currently ongoing. As of March 29, 2021, the phase I dose-escalation and dose-expansion clinical study (MRG003-001) was completed, with 61 patients enrolled and treated with MRG003. In the phase Ia dose-escalation stage, 22 patients received MRG003 at 7 dose levels: 0.1, 0.3, 0.6, 1.0, 1.5, 2.0, and 2.5 mg/kg. The recommended phase II dose was preliminarily determined as 2.5 mg/kg. In the phase Ib dose-expansion stage, 39 patients received at least one dose of MRG003 at 2.5 mg/kg, including 13 patients with squamous cell carcinoma of the head and neck (SCCHN), 14 with

nasopharyngeal carcinoma (NPC), and 12 with colorectal cancer (CRC), all showing favorable efficacy and safety. MRG003-005 is a phase II clinical trial in patients with recurrent or metastatic nasopharyngeal carcinoma. As of December 30, 2022, 61 subjects were enrolled in Part A, and 59 underwent at least one tumor assessment. Per independent review committee (IRC) assessment according to RECIST v1.1, the confirmed best overall response (BOR) was: CR in 2 patients, PR in 23, SD in 22, non-CR/non-PD in 1, and PD in 11. The confirmed objective response rate (ORR) was 42%, and the disease control rate (DCR) was 81%.

By leveraging immunogenic cell death (ICD) induced by ADCs to synergistically activate the tumor microenvironment, a 1+1 > 2 therapeutic enhancement can be achieved. Combination therapy with vebectotamab vedotin (MRG003) and immunotherapy has demonstrated breakthrough therapeutic potential across solid tumors, with its application rapidly expanding from the later-line to the first-line setting. The combination of vebectotamab vedotin and pucotelimab (a PD-1 inhibitor) has been granted Breakthrough Therapy Designation. This regimen achieved an objective response rate (ORR) of 66.7% and a disease control rate (DCR) of 93.3% in recurrent/metastatic nasopharyngeal carcinoma (NPC), and an ORR of 60% in treatment-naive head and neck squamous cell carcinoma (HNSCC), with efficacy significantly superior to current standard therapies.

Although patients with locally advanced HNSCC can currently be treated with surgery, concurrent chemoradiotherapy, or even immunotherapy combinations, they still face challenges including limited disease control rates, as well as the pressing clinical needs for organ function preservation, improved quality of life, and long-term survival. Therefore, based on the above promising clinical data, this study extends the combination strategy to the locally advanced disease setting by investigating neoadjuvant/adjuvant therapy. We designed an investigator-initiated phase II clinical trial evaluating neoadjuvant therapy with pucotelimab with or without MRG003 in locally advanced laryngeal carcinoma. This regimen is expected to enhance the response rate to immunotherapy and improve the efficacy of neoadjuvant treatment in laryngeal cancer.

2.2 Risk–Benefit Assessment

Potential risks: immune-related adverse events (irAEs, such as pneumonitis, thyroid dysfunction), hypersensitivity, myelosuppression, surgical complications, etc.

Potential benefits: improved pCR rate, better swallowing and vocal function, reduced surgical trauma and complications, improved quality of life, prolonged survival.

Risk control: regular laboratory and imaging monitoring, laryngoscopy; adverse events

monitored according to NCI CTCAE 5.0; MDT dynamic evaluation of resectability.

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3. Study Objectives and Endpoints

3.1 Objectives

Primary objective: To evaluate the pathological complete response (pCR) rate of neoadjuvant vibecortamab combined with putilimab in locally advanced laryngeal cancer.

Secondary objectives:

1. Surgical margin status (first and second margins);
2. Quality of life (swallowing and vocal function);
3. Major pathological response (MPR) rate;
4. Imaging response (RECIST 1.1);
5. Safety (surgical and chemoradiotherapy complications).

Exploratory objectives:

1. Disease-free survival (DFS);
2. 5-year overall survival (OS) rate.

3.2 Study Measures

Category	**Endpoint**	**Definition/Assessment**
Primary	pCR rate	No residual viable tumor cells in primary tumor and lymph nodes
Secondary	Surgical margins (first and second)	First margin: pre-neoadjuvant; second margin: post-neoadjuvant. Clear margin: ≥5 mm from invasive tumor to edge (NCCN 2025)
	MPR rate	Residual viable tumor <10% in primary site
	Imaging response rate	Enhanced CT/MRI, RECIST 1.1 (CR/PR/SD/PD)
	Function preservation	Swallowing (EAT-10) and vocal function (VHI-13)

Category	Endpoint	Definition/Assessment
		at multiple time points
Safety	Grade ≥3 AE rate	NCI CTCAE 5.0
	Surgical complications	Wound infection, pharyngocutaneous fistula, bleeding, tracheostomy, etc.
	Chemoradiotherapy complications	irAEs, myelosuppression, fatigue, nausea, skin reaction, mucositis, etc.

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4. Study Population

4.1 Inclusion Criteria

1. Age 18–80 years, male or female;
2. Pathologically (histologically or cytologically) confirmed stage III–IVA locally advanced laryngeal cancer (UICC/AJCC 8th edition);
3. At least one measurable lesion per RECIST 1.1;
4. Male subjects agree to effective contraception for at least 180 days after last study treatment;
5. Female subjects are non-pregnant, non-lactating, with negative pregnancy test, and agree to effective contraception for at least 210 days after last study treatment;
6. ECOG performance status 0–2 within 3 days before first treatment;
7. Evidence of extranodal extension by imaging or pathology;
8. Voluntarily signed written informed consent;
9. Life expectancy ≥6 months;
10. Adequate organ function:
    - Hematology: WBC ≥4×10⁹/L; ANC ≥1.5×10⁹/L; platelets ≥100×10⁹/L; Hb ≥90 g/L;

- Renal: Cr ≤1.5×ULN or CrCl >60 mL/min;
- Hepatic: TBIL ≤1.5×ULN; AST/ALT ≤2.5×ULN;
- Coagulation: INR ≤1.5, PT/APTT ≤1.5×ULN;

11. Good compliance.

4.2 Exclusion Criteria

1. Pregnant or breastfeeding women;
2. Other malignancy within 5 years (except cured basal cell carcinoma, squamous cell carcinoma of skin, superficial bladder cancer, in situ carcinoma);
3. Anti-tumor therapy or participation in other clinical trials within 4 weeks before first study treatment;
4. Systemic corticosteroids (>10 mg prednisone equivalent daily) or immunosuppressants within 14 days before first dose;
5. Grade ≥3 bleeding event within 4 weeks before screening, high bleeding risk, coagulopathy, anticoagulant use;
6. Uncontrolled cardiac disease (NYHA ≥2 heart failure, unstable angina, myocardial infarction within 1 year, significant arrhythmia, QTc >450 ms (male)/>470 ms (female));
7. Severe comorbidities: active gastrointestinal bleeding, perforation, obstruction, severe infection;
8. Severe uncontrolled cardiovascular disease;
9. Active tuberculosis under treatment;
10. Prior anti-PD-1/PD-L1/PD-L2/CD137/CTLA-4 antibody therapy;
11. ECOG PS >2, hearing impairment, CrCl <50 mL/min, grade >1 neuropathy;
12. Positive HCV RNA;
13. Any condition that may increase risk or interfere with study evaluation.

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5. Study Design

5.1 Overall Design

Prospective, single-arm, single-center study.

Sample size: 10 patients.

Planned enrollment period: 12 months.

Follow-up period: 5 years.

5.2 Intervention

Phase	**Intervention**
Neoadjuvant combination	Vibecortamab 2.0 mg/kg IV infusion 60±10 min q3w; Putilimab 200 mg IV infusion 40±10 min q3w; 3 cycles total
Imaging assessment	Enhanced neck CT/MRI 3–4 weeks after cycle 3; RECIST 1.1
Surgery	Radical resection + neck dissection within 4 weeks; laryngeal function preservation as much as possible
Postoperative adjuvant	pCR: maintenance for 1 year; MPR: standard adjuvant; high-risk: radiotherapy/chemoradiotherapy

5.3 Data Collection

- Baseline: demographics, clinical features, pathology, imaging, laboratory tests;
- Treatment-related data: dosage, cycles, AEs (CTCAE 5.0), imaging response (ORR = CR+PR);
- Efficacy: residual tumor percentage, margin status, pCR/MPR;
- Follow-up: swallowing (EAT-10), vocal function (VHI-13), quality of life (UW-QOL, VAS), survival (DFS, OS).

5.4 Statistical Analysis

- pCR rate, MPR rate: descriptive percentage;
- DFS/OS: Kaplan–Meier method;
- Safety: frequency and proportion.

6. Ethical Requirements

This study complies with GCP, relevant national regulations and the Declaration of Helsinki. It will be initiated only after Ethics Committee approval. All patients must sign informed consent. Personal and clinical data will be strictly protected and kept confidential.

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