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JADE: phase 3 study of sequential dostarlimab post chemoradiotherapy in patients with locally advanced unresected HNSCC

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ABSTRACT

Introduction: Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 5% of cancer cases worldwide, with more than half of patients presenting with locally advanced (LA) disease. Treatment of LA HNSCC is multimodal and may include concomitant cisplatin-based chemoradiotherapy (CRT) or surgery; however, recurrence rates are high, and there is an unmet need for new treatments. Immune checkpoint inhibitors that target programmed death receptor-1 (PD-1) are standard of care for recurrent/metastatic HNSCC, but outcomes for anti-PD-1 and anti-PD-(ligand [L])1 therapies with CRT in LA HNSCC have been variable. Dostarlimab, an anti-PD-1 therapy approved in advanced endometrial cancer and mismatch repair-deficient solid tumors is being investigated across other tumor types, including HNSCC. JADE is a global, multicenter, double-blind, placebo-controlled, randomized phase 3 study evaluating the efficacy and safety of dostarlimab as post-cisplatin-based CRT sequential therapy in patients with LA unresected PD-L1-expressing HNSCC. JADE seeks to overcome the limitations of previous studies by incorporating both PD-L1 selection and solely sequential administration of dostarlimab soon after CRT.

Methods: The primary endpoint is event-free survival, with overall survival as a key secondary endpoint; safety and tolerability, pharmacokinetics, immunogenicity, biomarkers, and patient-reported outcomes will also be assessed.

Clinical trial registration: www.clinicaltrials.gov identifier is NCT06256588.

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1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the most common malignancies worldwide and accounted for 950,000 new cases and 480,000 cancer-related deaths globally in 2022 [1,2]. Although trends for specific subtypes of HNSCC vary, incidence of this cancer overall is expected to increase by 53% to reach 1.45 million new cases annually by 2045 [3]. Risk of developing HNSCC is multifactorial. The most common risk factors are tobacco and alcohol use, and men are at two- to fourfold higher risk compared with women [4]. Human papillomavirus (HPV) infection is also a major risk factor, accounting for roughly 30% of new oropharyngeal carcinomas worldwide in 2018 [5]. Over half of patients with HNSCC present with locally advanced (LA) disease (stages III – IVB) at diagnosis, representing approximately 50% of cases in the United States and Europe [6,7] and 60–75% in South America and Asia [7,8]. Estimated 5-year survival rates for patients with LA HNSCC range from 50% to 70% [6,9].

The current standard of care for LA HNSCC is a multimodal approach that may include surgery followed by adjuvant radiotherapy with or without concurrent chemotherapy, or definitive concurrent cisplatin-based chemoradiotherapy (CRT) alone in patients with unresected disease [10–12]. The choice between surgery and CRT is informed by technical resectability, predicted functional outcome or organ preservation concerns, presence of comorbidities, and patient preference [10]. For patients with resectable disease, the standard of care is likely to evolve to include the addition of perioperative programmed death-1 (PD-1) immune checkpoint inhibitors to standard adjuvant radiotherapy/chemoradiotherapy following the recent positive findings of the phase 3 studies NIVOPOSTOP and KEYNOTE-689 [11,12]. The findings of KEYNOTE-689 resulted in the first US Food and Drug Administration (FDA) approval for pembrolizumab in adults with resectable LA HNSCC whose tumors express PD-L1 with a combined positive score (CPS) ≥1 [13]. These findings are particularly notable given that up to 55% of patients

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Article highlights

Introduction

- Immune checkpoint inhibitors (ICIs) targeting programmed death receptor-1 (PD-1) are standards of care for recurrent/metastatic head and neck squamous cell carcinoma (HNSCC); however, outcomes have been variable for ICIs in locally advanced (LA) HNSCC when combined with standard chemoradiotherapy (CRT), possibly due to concurrent versus sequential (post-CRT) administration and inclusion of study populations unselected for PD-ligand 1 (PD-L1) expression.
- Recent phase 3 data in the LA resected HNSCC setting have demonstrated the benefit of perioperative neoadjuvant and adjuvant anti-PD-1 therapies with post-operative CRT, ultimately leading to a US Food and Drug Administration (FDA) approval in this setting.
- Dostarlimab is an anti-PD-1 monoclonal antibody approved for use in advanced endometrial cancer and mismatch repair-deficient recurrent or advanced solid tumors and is under investigation across other tumor types, including HNSCC.
- JADE is a randomized phase 3 study assessing the efficacy and safety of dostarlimab versus placebo as sequential therapy following cisplatin-based CRT in patients with PD-L1-positive LA unresected HNSCC.
- The JADE study seeks to overcome the limitations of previous studies by incorporating PD-L1 selection of patients and sequential administration of dostarlimab soon after CRT.

Methods

- The primary endpoint is event-free survival and the key secondary endpoint is overall survival.
- Other study endpoints include safety and tolerability, pharmacokinetics, immunogenicity, biomarkers, and patient-reported outcomes.

Conclusions

- The findings from JADE aim to improve outcomes of patients with LA unresected HNSCC and could potentially change the current standard of care.

with LA HNSCC develop disease recurrence [14,15]. Approximately 60–80% of patients with LA HNSCC, however, have unresected tumors [16,17], which have a higher risk of recurrence versus resectable tumors [18]. As such, there is a need for novel first-line systemic therapies in LA unresected HNSCC to improve disease control, organ preservation, and survival.

The development of immune checkpoint inhibitors in LA HNSCC is supported by studies in the recurrent or metastatic setting, which demonstrated improved overall survival (OS) with PD-1 inhibitors; pembrolizumab and nivolumab currently represent the standard of care [19,20]. There is growing interest in understanding how these existing therapies might be leveraged or enhanced through immunologic mechanisms, including for LA unresected disease. Notably, radiotherapy-induced DNA double-strand breaks caused by CRT are associated with upregulation of programmed death-ligand 1 (PD-L1) expression on tumor cells, and radiotherapy-induced inflammatory cell death releases tumor antigens into the tumor microenvironment [21–25]. These observed immunostimulatory effects of CRT result in a tumor microenvironment that is conducive for immune checkpoint inhibitor therapy, such as anti-PD-(L)1 immunotherapies. Anti-PD-(L)1 treatments administered before, concurrently, or after CRT have been investigated, and correlations have been found between deregulated DNA damage response signals, lower DNA repair capacities, and treatment response [26].

Randomized trials have investigated the potential of anti-PD-(L)1 therapies in LA unresected HNSCC. To date, results among patients with LA HNSCC managed non-surgically have been variable [9,27,28]. For example, in KEYNOTE-412, concurrent administration of CRT with pembrolizumab failed to meet the primary endpoint of event-free survival (EFS) compared with placebo plus CRT in patients with LA unresected HNSCC unselected for PD-L1 status in the primary analysis. Results from a subgroup analysis of KEYNOTE-412, however, suggested a potential benefit with pembrolizumab in patients with high PD-L1 expression levels [9]. In an updated analysis after longer follow-up, a statistically significant improvement in EFS was reported with pembrolizumab in the overall population, with a trend of greater benefit by PD-L1 expression level [29]. In the JAVELIN Head and Neck 100 Study, concurrent administration of the anti-PD-L1 treatment avelumab with CRT in patients with LA unresected HNSCC failed to meet the primary endpoint of improved progression-free survival (PFS) compared with placebo plus CRT; however, an exploratory analysis indicated a potential PFS benefit among patients whose tumors expressed high levels of PD-L1 [27].

The sequence of treatment modalities may also play an important role in the response to immune checkpoint inhibitors in LA unresected HNSCC. It is possible that depletion of T cells and changes within the tumor microenvironment induced by radiotherapy may diminish responses to PD-(L)1 therapy [30]. As such, preclinical evidence suggests that allowing for sparing and infiltration of activated immune cells within the tumor microenvironment following irradiation may be preferable [21], and thus, sequential administration of immune checkpoint inhibitors to radiotherapy may be advantageous to concurrent administration. Indeed, in a randomized, phase 2 study in patients with LA unresected HNSCC, administration of pembrolizumab with CRT numerically improved PFS when initiated 2 weeks after CRT, compared with concurrent administration [31]. Other studies in unresected solid tumors have demonstrated clinical benefit with adjuvant anti-PD(L)1 therapy sequenced soon after CRT completion [32–34]. Conversely, the IMvoke010 study, which assessed maintenance therapy with the anti-PD-L1 treatment atezolizumab up to 16 weeks following definitive multimodal treatment (resection and/or CRT), failed to meet the primary endpoint of EFS among a heterogeneous population of patients with LA HNSCC who were unselected for PD-L1 status; however, subgroup analysis of EFS among those with high PD-L1 expression potentially favored atezolizumab [28].

Taken together, the evidence base supports the notion that, in patients with LA unresected HNSCC who have PD-L1-positive tumors, administration of anti-PD-1 immunotherapy sequentially soon after CRT may provide a clinical benefit. JADE (NCT06256588) is a randomized phase 3 study evaluating the anti-PD-1 monoclonal antibody dostarlimab in patients with PD-L1-positive LA unresected HNSCC. Dostarlimab is approved for use in advanced endometrial cancer and mismatch repair-deficient (dMMR) recurrent or advanced solid tumors [35–37]. The design of JADE combines aspects of previous trials in the LA

unresected HNSCC setting whilst overcoming their limiting factors to address the unmet need for novel therapeutic strategies that improve outcomes and survival in this patient population.

2. Methods

2.1. Study design

JADE is an ongoing global, multicenter, double-blind, randomized phase 3 study designed to evaluate the efficacy and safety of dostarlimab versus placebo as post-cisplatin-based CRT sequential therapy in patients with LA unresected, PD-L1-positive HNSCC (Figure 1).

2.2. Participants

Study eligibility criteria have been disclosed previously [38] and are summarized in Table 1. Eligible patients are aged 18 years or over with newly diagnosed histologically confirmed LA unresected HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx; with only one primary HNSCC tumor, no evidence of distant metastatic disease and a tumor PD-L1 expression of CPS ≥1 determined centrally using the Agilent 22C3 assay. A CPS ≥1 was selected based on observed responses for patients with a CPS ≥1 in the KEYNOTE-412 study [9]. Patients with oropharyngeal primary tumors must have known p16 status. Tumor-specific eligibility is defined

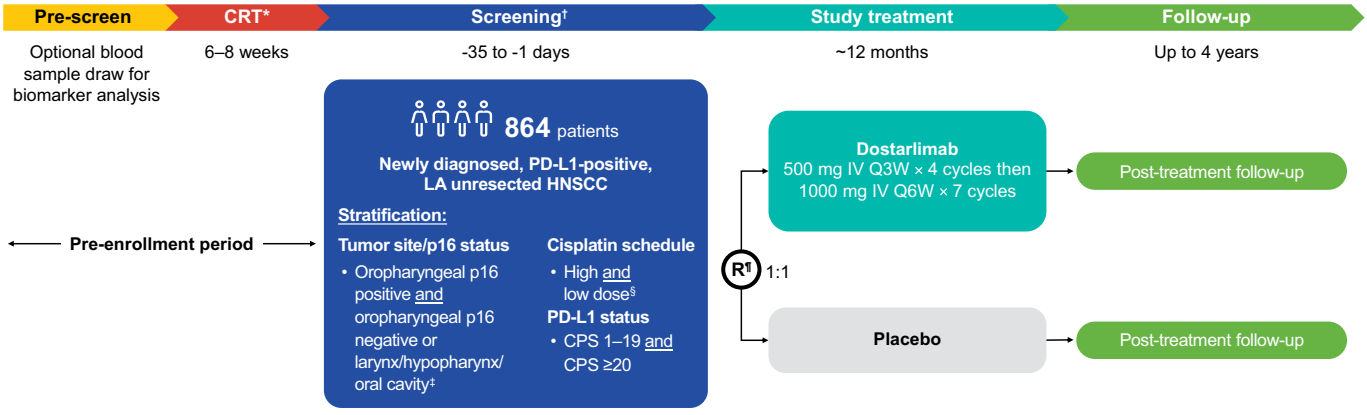

Figure 1. Study schema.

*Consent can be taken prior to or during CRT; †standard screening period is 28–35 days; however, up to 42 days is permitted to allow for CRT-related toxicity resolution (Grade ≤2 per CTCAE v5.0); ‡independent of p16 status; §high-dose Q3W and low-dose Q1W; ¶participants will be randomized between 28 and 35 days inclusive after completion of CRT as standard but not earlier, or per the permitted extension (42 days post-CRT).

Abbreviations: CPS, combined positive score; CRT, chemoradiation; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; LA HNSCC, locally advanced head and neck squamous cell carcinoma; PD-L1, programmed death-ligand 1; QXW, every X weeks.

Table 1. Key eligibility criteria.

Inclusion criteria	Exclusion criteria

• Age ≥18 years old.
• Newly diagnosed unresected histologically confirmed LA HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx, with only one primary HNSCC tumor and no evidence of distant metastatic disease.
• PD-L1-positive tumor status defined as CPS ≥1 determined centrally using the Agilent 22C3 assay.
• For oropharyngeal tumors, patients must have p16 IHC testing using CINtec p16 histology assay (local or central laboratory); p16 IHC-positive defined as ≥70% of carcinoma tumor cells with nuclear and cytoplasmic moderate to strong staining.
• TNM staging per AJCC (8th edition) [39].
  ◦ p16-positive oropharyngeal tumors: T4 (N0–N3), M0 or N3 (T1–T4), M0.
  ◦ p16-negative oropharyngeal tumors or tumors of the larynx, hypopharynx, or oral cavity independent of p16 status: any T3–T4 (N0–N3), M0 or any N2a-N3 (T1–T4), M0.
• Completed concurrent cisplatin CRT with curative intent.
  ◦ Minimum cumulative cisplatin exposure of 200 mg/m^2 delivered as high-dose Q3W (e.g., 100 mg/m^2 for 2 cycles) or as low-dose Q1W (e.g., 40 mg/m^2 for 5 cycles) and total radiation dose of 65–72 Gy over 6–7 weeks (up to +7 days if required) to high-risk disease sites.
  ◦ Dose delays and dose modification permitted per local standard practice, provided all other requirements are met.
• ECOG performance status of 0 or 1.
• Adequate organ function.
	• Prior RT, systemic therapy, targeted therapy, surgery, or induction therapy for HNSCC not considered part of CRT.
	  ◦ CRT combinations with components other than cisplatin and RT.
	• Prior immune checkpoint inhibitor therapy, including antibodies or drugs targeting PD-1, PD-L1, or PD-L2, or any agent targeting other stimulatory or coinhibitory T-cell receptors.
	• Patients with toxicity of CTCAE Grade >2 from CRT; patients with Grade 3 CRT toxicities 28–35 days post-CRT may be eligible for randomization delay to Day 42 post-CRT to allow resolution to Grade ≤2.
	  ◦ Patients with irreversible or slowly resolving Grade >2 CRT toxicities that are not reasonably expected to be exacerbated by study intervention (e.g., hearing loss, neuropathy, audiometric abnormalities without Grade ≥2 hearing loss) may be eligible.
	  ◦ Feeding tubes alone are not exclusionary unless associated with a persistent Grade >2 CRT toxicity likely exacerbated by dostarlimab.
	• Patients with additional malignancy that progressed or required active treatment within the past 2 years;
	  ◦ Patients with curatively treated superficial esophageal cancer (tumor *in situ* or T1a) fully resected by endoscopy, localized HNSCC treated by curative surgery alone, basal cell carcinoma of the skin, superficial bladder cancer, or *in situ* cancers (e.g., cervical or breast cancer) are eligible if they are not expected to affect evaluation of the study intervention.

Abbreviations: AJCC, American Joint Committee on Cancer; CPS, combined positive score; CRT, chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events Grade; ECOG, Eastern Cooperative Oncology Group; HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemistry; LA, locally advanced; PD-1, programmed death receptor-1; PD-LX, programmed death ligand X; QXW, every X weeks; RT, radiotherapy; TNM, tumor, node, metastasis.

per tumor, node, metastasis (TNM) staging according to the 8th edition of the American Joint Committee on Cancer manual [39] and dependent on the primary tumor site: for p16-positive oropharyngeal tumors, T4 (N0–N3), M0 or N3 (T1–T4), M0; and for p16-negative oropharyngeal tumors or tumors of the larynx, hypopharynx, or oral cavity independent of p16 status, any T3–T4 (N0–N3), M0 or any N2a-N3 (T1–T4), M0. All patients must have completed concurrent cisplatin-based CRT with curative intent. Additional eligibility criteria include an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, with adequate organ function.

Ineligible patients include those with prior surgery for HNSCC, radiation, systemic, targeted, or induction therapy for management of HNSCC that is not considered part of CRT. Additionally, patients who have received prior immune checkpoint inhibitor therapy, including antibodies or drugs targeting PD-1, PD-L1, or PD-L2, or any agent targeting other stimulatory or coinhibitory T-cell receptors, are not eligible. Patients with toxicity of Common Terminology Criteria for Adverse Events Grade (CTCAE) >2 from CRT at time of randomization will be excluded. Patients with Grade >2 CRT toxicities 28–35 days post-CRT may be eligible for randomization delay to Day 42 post-CRT to allow resolution to Grade ≤2, although patients with irreversible or slowly resolving Grade >2 CRT toxicities that are not reasonably expected to be exacerbated by study intervention may be eligible. Patients with additional malignancy that has progressed or required active treatment within the past 2 years are not eligible; however, exceptions may be applicable for patients with certain cancers that have been curatively treated, as noted in Table 1. Randomization delay to 42 days-post CRT may be permitted to complete full evaluation and, where necessary, completion of curative treatment and investigation of eligible concurrent malignancies.

2.3. Assignment of interventions

Eligible patients enrolled in the study are randomized 1:1 to receive either dostarlimab 500 mg intravenous (IV) every 3 weeks (Q3W) for 4 cycles followed by dostarlimab 1000 mg IV Q6W for 7 cycles, or IV placebo following the same schedule (totaling 11 cycles of study intervention over approximately 12 months). Participants are randomized within 28–35 days post-CRT and preferably dosed within 24 hours (although within 3 days is acceptable). For patients who experience Grade >2 CRT-related toxicities, randomization and dosing may be delayed up to 42 days post-CRT to allow resolution to Grade ≤2. Dosing is not permitted after 42 days post-CRT. Participants are stratified by: tumor site or p16 status (oropharyngeal p16-positive and oropharyngeal p16-negative or laryngeal/hypopharyngeal/oral cavity tumor independent of p16 status); cisplatin schedule (high-dose Q3W and low-dose Q1W); and PD-L1 status (CPS 1–19 and CPS ≥20).

2.4. Endpoints

Table 2 summarizes study endpoints. The primary endpoint is EFS, as assessed by Blinded Independent Central Review (BICR), with the objective to evaluate the efficacy of dostarlimab as sequential therapy following CRT compared with placebo. EFS was selected as the primary endpoint given that it incorporates radiologic, surgical, and mortality components that reflect the continuum of care and is a recognized endpoint for LA HNSCC in clinical trials, including by the FDA, following an industry workshop held in 2021 [9,12,28,40,41]. In addition, EFS has previously demonstrated a strong correlation with OS in LA HNSCC [42].

The key secondary endpoint is OS. Additional secondary endpoints include EFS per investigator assessment; safety and

Table 2. Study endpoints.

Endpoint(s)	
Primary	EFS where an event is defined as the earliest date of: • First record of locoregional progression or recurrence, or distant metastasis per RECIST 1.1 as per BICR. • Salvage surgery* at the primary tumor site at any time if invasive cancer is present. • Neck dissection or surgery* performed >20 weeks after completion of CRT if invasive cancer is present. • Death from any cause.
Secondary	**Key:** OS, defined as time from randomization to death from any cause EFS with radiographic assessment per RECIST 1.1 as per investigator assessment • Number of participants with TEAEs, immune-mediated TEAEs, and SAEs by severity. • Number of participants with TEAE and SAEs leading to dose delays, withdrawal, or death. • Number of participants with clinically significant changes in laboratory, vital signs, and safety assessment parameters. Serum concentrations and relevant PK parameters (e.g., C-EoI and C trough) for dostarlimab Number of participants with ADA against dostarlimab
Tertiary/Exploratory/ Other	TSST, defined as the time from the date of randomization to the earliest date of second next-line therapy or death due to any cause Efficacy analysis (EFS/OS) by PD-L1 status using alternative CPS cutoffs – differential efficacy in participants with PD-L1 (CPS 1–19 or CPS ≥20) and p16-positive/-negative status (oropharyngeal) Biomarker assessments that evaluate PD-L1 and p16 expression, ctDNA, immunophenotyping, transcriptional and proteomic signatures, tumor analytics, and radiomic features Assessments that evaluate HRQoL

*Surgery performed according to protocol-defined criteria, which includes a mandatory ^{18}F-FDG-PET/CT scan to assess for residual disease at Week 8.

Abbreviations: ADA, anti-drug antibody; BICR, blinded independent central review; CPS, combined positive score; CRT, chemoradiotherapy; CT, computed tomography; ctDNA, circulating tumor deoxyribonucleic acid; EFS, event-free survival; FDG-PET, fluorodeoxyglucose positron emission tomography; HPV, human papillomavirus; HNSCC, head and neck squamous cell carcinoma; HRQoL, health-related quality of life; LA, locally advanced; OS, overall survival; PD-L1, programmed death-ligand 1; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; TSST, time to second subsequent therapy.

tolerability outcomes (including adverse events, immune-mediated adverse events, dose delays, withdrawals, and death related to adverse events); and clinically significant changes in laboratory, vital signs, and safety assessment parameters. Serum concentrations and pharmacokinetic (PK) parameters of dostarlimab will also be documented as a secondary endpoint, as will immunogenicity, determined by incidence of anti-drug antibodies against dostarlimab.

Exploratory endpoints include time to second subsequent treatment (TSST), and EFS and OS by PD-L1 status by CPS expression level. The study will also examine changes in health-related quality of life (HRQoL) to evaluate the impact of treatment on disease-related symptoms but also to assess patient experiences of adverse events. Biomarker analyses that evaluate PD-L1 and p16 expression, ctDNA, immunophenotyping, transcriptional and proteomic signatures, tumor analytics, and radiomic features will be conducted to identify potential predictors of treatment response.

2.5. Study assessments

Potential participants identified prior to undergoing definitive CRT with curative intent have the option for pre-screening assessments. These include optional archival tissue evaluation of PD-L1 and p16 (for which consent may occur prior to or during CRT). Additionally, optional pre-screening collection of a blood sample for biomarker analysis, which is required to be taken prior to CRT.

Mandatory screening assessments will be carried out once participants have undergone CRT and have been consented for the main study. In the screening period, demographic, medical history, and baseline characteristics, including evaluation of PD-L1 and p16 status (oropharynx only) of tumor tissues from immunohistochemistry, will be assessed (if not already tested during pre-screening). The screening period will begin after completion of CRT, defined as the last dose of cisplatin or radiation (whichever is administered last), and will last up to the day of randomization (28–35 days post-CRT or 42 days for randomization delay to allow improvement of CRT-related toxicities to Grade ≤2). All timepoints for assessments will be anchored to the day of randomization.

Efficacy assessments for EFS will include radiographic and local pathologic evaluation of residual and/or new disease as applicable. The first efficacy assessment will be conducted 12 weeks post-CRT completion (at Week 8 [±7 days] post-randomization), including a ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT) scan per standard of care [10], and a CT scan or magnetic resonance imaging for Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 evaluation. Subsequently, RECIST 1.1 disease assessments will be conducted Q12W up to Week 152, then Q24W thereafter until disease progression, withdrawal of consent, end of study, loss to follow-up, or death. Follow-up for OS will continue until the end of study, withdrawal of consent, loss to follow-up, or death.

Safety assessments will be conducted at screening, throughout treatment, and until 90 days following the last dose of dostarlimab or placebo. Additional safety, biomarker, patient-reported outcome, PK, and immunogenicity assessments will be conducted throughout the study period.

Study design features of JADE and other key prior phase 3 trials in LA unresected HNSCC are summarized in Table 3.

2.6. Statistical considerations, sample size, and recruitment

The planned sample size is for 864 participants to be enrolled and randomized to detect a statistical difference in the primary endpoint of EFS between dostarlimab versus placebo treatment arms. Detailed statistical methods are described in the Statistical Analysis Plan.

As of December 2025, JADE is recruiting in Argentina, Australia, Belgium, Brazil, Canada, China, Czechia, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Mexico, Norway, Poland, Portugal, Republic of Korea, Romania, Spain, Sweden, Switzerland, Taiwan, Türkiye, the United Kingdom, and the United States. Additional countries are planned.

Table 3. Key features of JADE versus key completed phase 3 studies assessing ICIs in patients with LA unresected HNSCC.

	JADE [38]	KEYNOTE-412 [9]	JAVELIN H&N 100 [27]	IMvoke010* [28]
ClinicalTrials.gov registry number	NCT06256588	NCT03040999	NCT02952586	NCT03452137
Biomarker selection	PD-L1 CPS ≥1 required	PD-L1 unselected	PD-L1 unselected	PD-L1 unselected
CRT backbone	Completed cisplatin-RT	Cisplatin + RT	Cisplatin + RT	NA†
ICI treatment	Dostarlimab (anti-PD-1)	Pembrolizumab (anti-PD-1)	Avelumab (anti-PD-L1)	Atezolizumab (anti-PD-L1) (anti-PD-L1)
ICI dosing/duration	11 cycles (~15 months) post-CRT	17 cycles (~12 months)	Q2W (up to 12 months maintenance)	Q3W (up to 12 months maintenance)
Timing versus CRT	Sequential adjuvant	Priming + concurrent + maintenance	Priming + concurrent + maintenance	Sequential adjuvant
Primary endpoint	EFS	EFS	PFS	EFS
Key secondary endpoints	OS, EFS (inv), safety, HRQoL, PK, ADA	OS, safety, HRQoL	OS, ORR, DoR, pCR	OS, safety
Status	Ongoing	Negative (EFS not met)	Negative (futility)	Negative (EFS not met)

*Approximately 40% of patients had resected disease; †multimodal definitive treatment.

Abbreviations: ADA, anti-drug antibodies; CPS, combined positive score; CRT, chemoradiotherapy; DoR, duration of response; EFS, event-free survival; HNSCC, head and neck squamous cell carcinoma; HRQoL, health-related quality of life; ICI, immune-checkpoint inhibitor; inv, individual assessment; LA, locally advanced; NA, not applicable; ORR, objective response rate; OS, overall survival; pCR, pathological complete response; PD-(L)1, programmed death-(ligand) 1; PFS, progression-free survival; PK, pharmacokinetics; QXW, every X weeks; RT, radiotherapy.

The study started in March 2024 and primary completion is expected in June 2028, with an estimated study completion in October 2029.

3. Ethics and dissemination

The study design and schedule of activities were shared with a patient advocacy group to gain their input into how the study could be designed to minimize the burden associated with study participation, and to identify the study outcomes considered most important to participants. Prior to the study being initiated, the protocol, protocol amendments, informed consent form, investigator's brochure, and other relevant documents (e.g., advertisements) were submitted to an institutional review board/independent ethics committee by the investigator and were reviewed and approved. This trial is being conducted in accordance with the protocol, the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines, and the International Council for Harmonisation Good Clinical Practice guidelines. Patients participating in this study must provide informed consent prior to screening for study eligibility. The data from the study will be submitted for publication once available.

4. Conclusion

An unmet need exists for therapies to improve outcomes in patients with LA unresected HNSCC, given the high relapse rates following CRT with or without surgery [14]. Although anti-PD-1 therapies are approved for use in metastatic or recurrent HNSCC, and now in resected LA HNSCC, trials of anti-PD-(L)1 therapies have been unsuccessful when these treatments are administered concurrently with CRT in patients with LA unresected HNSCC who are unselected for PD-L1 expression.

The global, double-blind, randomized phase 3 JADE trial will investigate the anti-PD-1 monoclonal antibody, dostarlimab, as sequential therapy following CRT for patients with PD-L1-positive LA unresected HNSCC tumors. JADE aims to address the limitations of earlier studies of anti-PD-(L)1 agents in LA HNSCC, including through optimized sequential timing and PD-L1 selection. Its study design builds on evidence suggesting that initiating anti-PD-1 therapy soon after CRT, rather than concurrently, can exploit CRT-driven immune changes in the tumor microenvironment [21–24,31] and takes into account research suggesting improved treatment outcomes in patients with PD-L1-positive tumors [9,27].

The outcomes from JADE will enhance the understanding of the sequential use of anti-PD-1 therapies following CRT in patients with PD-L1-expressing LA unresected HNSCC, with the aim of improving the outcome of patients with LA HNSCC who are managed non-surgically, and could potentially change the current standard of care.

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Author contribution

- **All authors**: Conceptualization.
- **Lillian Siu, Barbara Burtness**, **Kevin Harrington**, **Amanda Psyrri, Makoto Tahara**, and **Jean-Pascal Machiels**: Data curation.
- **All authors**: Writing original draft, review, and editing.

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JP Machiels declares advisory board member or speaker roles with honoraria for Pfizer, Roche, Bayer, Merck Serono, Boehringer, Bristol Myers Squibb, Novartis, Incyte, Cue Biopharma, ALX Oncology, iTEOS, eTheRNA, NEKTAR, F-Star, Seagen, Genmab, Astellas, CureVac, MSD, GSK, Merus; travel expenses for Amgen, Bristol Myers Squibb, Pfizer, MSD, Gilead, Sanofi; data safety monitoring board role with honoraria for Psioxus; investigator and study coordinator role for the EORTC; and research funding to the institute for Pfizer, Roche, Bayer, Merck Serono, Boehringer-Ingelheim, Bristol Myers Squibb, Novartis, Incyte, Cue Biopharma, ALX Oncology, iTEOS, eTheRNA, NEKTAR, F-Star, Seagen, Genmab, Astellas, CureVac, MSD, GSK, Merus, EORTC, Amgen, MSD, Gilead, Sanofi, Psioxus.

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Ethical conduct of research

This trial is being conducted in accordance with the protocol, the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines, and the International Council for Harmonisation Good Clinical Practice guidelines. Patients participating in this study must provide informed consent prior to screening for study eligibility.

Data availability statement

Although data sharing is not applicable to this article as no new datasets were generated or analyzed, anonymized patient-level data will be available upon reasonable request after study completion.

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•• **This publication reported the primary analysis from a phase 3 study (NCT03040999) assessing pembrolizumab plus concurrent chemoradiotherapy in patients with locally advanced unresected head and neck squamous cell carcinoma. The addition of pembrolizumab to chemoradiotherapy did not significantly improve event-free survival compared with chemoradiotherapy alone.**

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•• **This presentation reported on the clinical data from a phase 3 study (NCT03576417) assessing adjuvant nivolumab plus chemoradiotherapy in patients with locally advanced head and neck squamous cell carcinoma. The addition of nivolumab to chemotherapy significantly improved disease-free survival, with a moderate increase in toxicity.**

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    - **This presentation reported updated data from a phase 3 study (NCT03040999) assessing pembrolizumab plus concurrent chemoradiotherapy in patients with locally advanced unresected head and neck squamous cell carcinoma. After longer follow-up, pembrolizumab plus chemoradiotherapy had a significant clinical benefit over placebo plus CRT, which was not achieved at the time of the primary analysis; no new safety signals were identified.**
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