



Multidisciplinary Approaches to Cancer Symposium

Tumor Board: Management of Oral Cavity Cancers

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Panel & Disclosures

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- *No relevant financial relationships*
- *No relevant financial relationships*
- *Consultant for Fulgent and Merus*

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This presentation has been peer-reviewed and no conflicts were noted.



Oral Cancer: Background

- Background:
 - Most common mucosal head and neck cancer site
 - Oral tongue and floor of mouth are most common
 - SCC is dominant histology
 - HPV is not a major driver
 - Increasing incidence in young women without traditional risk factors



Oral Cancer: Treatment



Standard of Care:

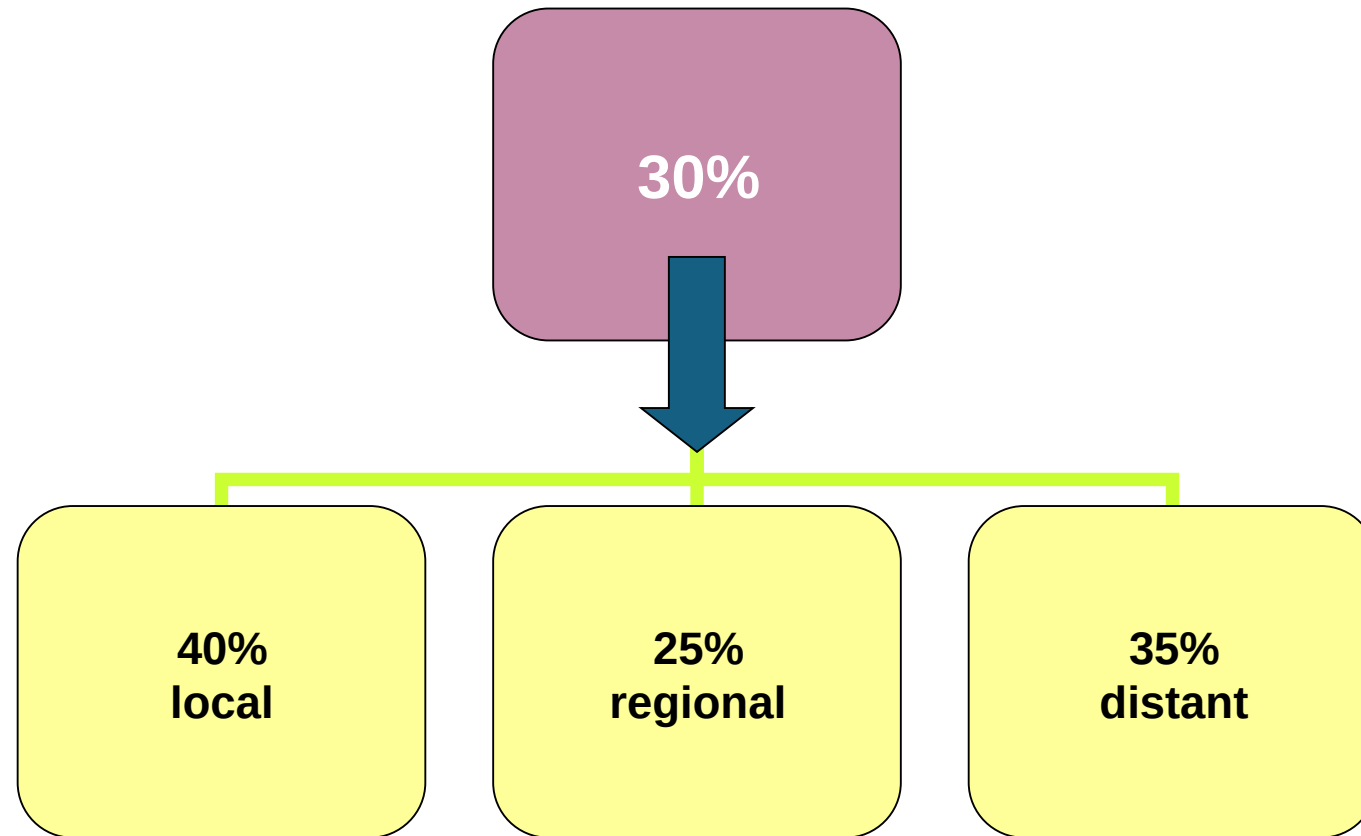
Surgery and appropriate neck management
Same stage reconstruction
Pathology-directed postoperative RT or
chemoRT
Rehabilitation



Dual Objective:

1-Cure Cancer,
2-Restore form and function

Oral Cancer: Failures After Treatment

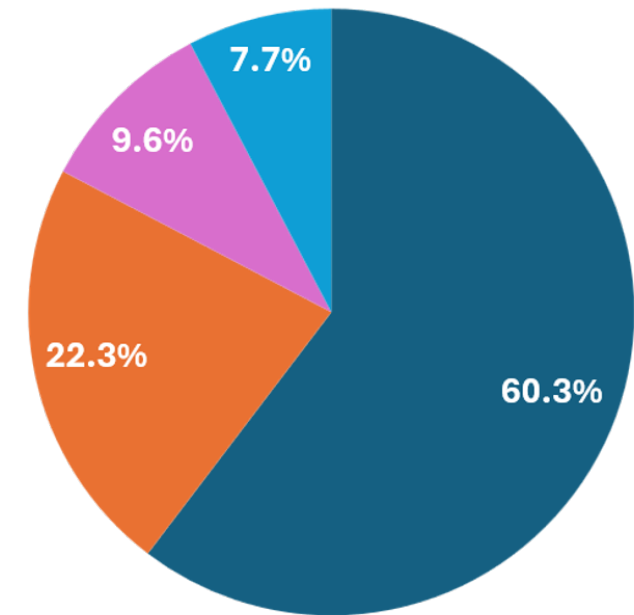


Keynote 689: New Perioperative Paradigm

- Randomized Phase 3 trial of perioperative ICI with Pembrolizumab vs SOC in resectable CPS positive LA-HNSCC
 - 2019-2022
 - 24 countries, 192 institutions
 - cT4B, cN3, cM1 excluded
 - Majority of cases were OC, 219/363
 - Median follow-up 38.3 months

Primary tumor subsite distribution

■ Oral cavity ■ Larynx ■ Oropharynx ■ Hypopharynx



KEYNOTE-689

ClinicalTrials.gov, NCT03765918

Pembrolizumab added in both neoadjuvant and adjuvant setting

- 2 cycles of neoadjuvant pembro before surgery
- Surgery
- 15 cycles of adjuvant pembro after surgery (3 + 12)
- Both neoadjuvant and adjuvant at a dose of 200 mg every 3 weeks

All patient received adjuvant RT + pembro after surgery

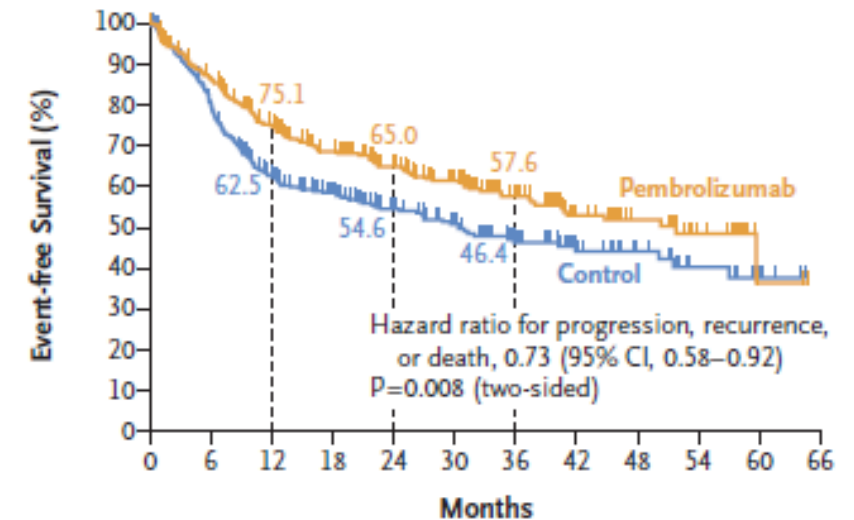
- Path high-risk patients also received adjuvant *high-dose* cisplatin

ORIGINAL ARTICLE

Neoadjuvant and Adjuvant Pembrolizumab in Locally Advanced Head and Neck Cancer

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C Total Population



No. at Risk

Pembrolizumab	363	287	232	191	157	129	88	55	34	21	2	0
Control	351	258	183	147	110	88	59	37	25	15	7	0

- Improved EFS; HR 0.73
 - Greater effect in tumors with higher PDL-1 expression
 - Benefit mainly in decreasing distant metastasis – “immune priming”
 - FDA approved periop Pembro in June 2025
- Impact on OS not yet reported but favorable trend noted.
- <https://doi.org/10.1056/nejmoa2415434>

KEYNOTE-689

[ClinicalTrials.gov, NCT03765918](https://clinicaltrials.gov/ct2/show/study/NCT03765918)

- Surgery completed in 88%
- MPR 9.3%; 13.7% in CPS ≥ 10
- Path CR 3.0%
- R0 resection 89.1% vs. 84.7%
- High risk path 38.9% vs. 50.5%
- Treatment de-escalation
 - Lower use of adjuvant Cisplatin
 - Lower median dose of RT
- 73.3% initiated adjuvant XRT
- Less than 50% completed the full experimental protocol
- Significant attrition due to:
 - Toxicity
 - Tumor progression on neoadjuvant therapy
 - Surgical complications
 - Delay to RT
 - Patient refusal



KEYNOTE-689

ClinicalTrials.gov, NCT03765918

- 360 patients treated
- 194 patients discontinued
- 54% dropout rate
- 30/8% discontinued during neoadjuvant phase
- 15/4% discontinued because of progressive disease while in neoadjuvant Pembro
- 322/360 patients (88.7%) went to surgery, 1 case found unresectable in OR

https://www.nejm.org/doi/suppl/10.1056/NEJMoa2415434/suppl_file/nejmoa2415434_appendix.pdf

194 Discontinued all study treatment

30 During neoadjuvant phase

- 4 Adverse event
- 1 Lost to follow-up
- 1 Nonstudy anticancer therapy
- 7 Participant withdrawal
- 2 Physician decision
- 15 Progressive disease

55 During surgery phase

- 9 Adverse event
- 2 Clinical progression
- 1 Noncompliance with study drug
- 1 Nonstudy anticancer therapy
- 8 Participant withdrawal
- 6 Physician decision
- 28 Progressive disease

109 During adjuvant phase

- 52 Adverse event
- 1 Clinical progression
- 1 Noncompliance with study drug
- 2 Nonstudy anticancer therapy
- 12 Participant withdrawal
- 5 Physician decision
- 36 Progressive disease



Tough to safely implement outside of clinical trial environment:

Multimodality
complex
treatment
algorithm

Careful and
nuanced patient
selection

Tight
multidisciplinary
coordination

Time sensitive
handoffs

Resource
intensive

Prolonged
treatment,
51 weeks



Surgeon shoulders major responsibility

- Patient selection is the most important first step!
- Assess technical and functional resectability
- Detailed clinical exam and radiographic assessments at baseline
- What is the appropriate surgical program?
- Obtain necessary biomarker testing
- Finalize clinical stage for patient
- Multi-D Review
- Is patient Pembro eligible?
- Can treatment begin without delaying surgery?
- Establish a firm surgical date within 4-6 weeks of first Pembro dose

Surgeon shoulders major responsibility

- Weekly active monitoring of patient and tumor
- Surgeon to reassess patient after C1 with exam +/- imaging
- Escalate quickly to immediate surgery if evidence of disease progression, inability for function sparing surgery with further delay, or inoperability.
- Update presurgical assessments and imaging after C2 and before surgery
- Plan for any necessary expansion of original surgical plan
- Multi-D review of final path
- Adjuvant RT/Pembro +/- high dose cisplatin



NCCN

- Updating practice guidelines to incorporate Keynote 689 and Nivo postop paradigms in a safe and effective manner.
- Significant concerns regarding real-life implementation
- Significant caution advised
- Significant vigilance needed
- Tight care coordination mandatory
- Resource intense paradigm
- Yet to be seen if ultimately worth it; improved OS?
- JNCCN manuscript in process

Patients not Suitable for Perioperative IO:

- Patients with larynx, hypopharynx, oropharynx cancers suitable for organ preservation strategy rather than upfront surgery
- P16 positive OPC
- T4B, N3, M1 patients
- Patients with CPS 0
- Patients at risk for inoperability if early tumor progression
- Patients w/ prior history of XRT
- Patients w/ contraindication for immunotherapy
- Patients who refuse IO



Postoperative Radiation

- How does your radiation plan change based on treatment response?

No response to perioperative pembrolizumab

Standard risk-adapted PORT: 60–66 Gy to the operative bed, 60 Gy to high risk neck, 66 if ENE, 54–57 Gy elective neck, concurrent cisplatin for positive margin or ENE

RTOG 9501 / EORTC 22931: chemoradiation improved locoregional control in margin+ or ENE disease

Complete pCR at the primary and nodes

Still cover the preoperative disease volume; de-escalation of dose or volume is not yet supported outside a trial (typically 60 Gy)

KEYNOTE-689: pCR only 3.0%, mPR 9.3% (13.7% if CPS ≥10) — a rare scenario

Complete pCR at the primary, PR at the nodes

primary bed to ??? Gy, 60 Gy to high risk neck, 66 if ENE, 54–57 Gy elective neck

KEYNOTE-689: high-risk pathology in 38.9% of the pembrolizumab arm vs 50.5% with standard care

Partial response at the primary, pCR at the nodes

60–66 Gy to the operative bed, ??? Gy to neck

Only 73.3% started adjuvant radiation on trial — protect package time of 11–13 weeks

Response-adapted de-escalation remains investigational: plan to the preoperative extent of disease in all four scenarios. KEYNOTE-689 EFS HR 0.73; benefit driven mainly by fewer distant events.



Nivopostop: New postoperative High-Risk Paradigm

- 40-45% of postoperative high-risk cases experience recurrent disease after SOC adjuvant CRT
- Nivopostop is a randomized Phase III study adding adjuvant Nivolumab to postop management of high-risk patients
 - High-risk: Margin +, ENE +, ≥ 4 nodes, multiple PNI
 - Adjuvant high-dose cisplatin also given for Margin +, and/or ENE+



Nivopostop Trial

- 680 patients, 332 got Nivopostop
- 6 European countries, 82 sites
- 2018-2024
- HR 0.76 DFS; Improved LR control
- Patient $\leq$ 75 years old
- ECOG 0-1
- Majority OC: 192 (58%)

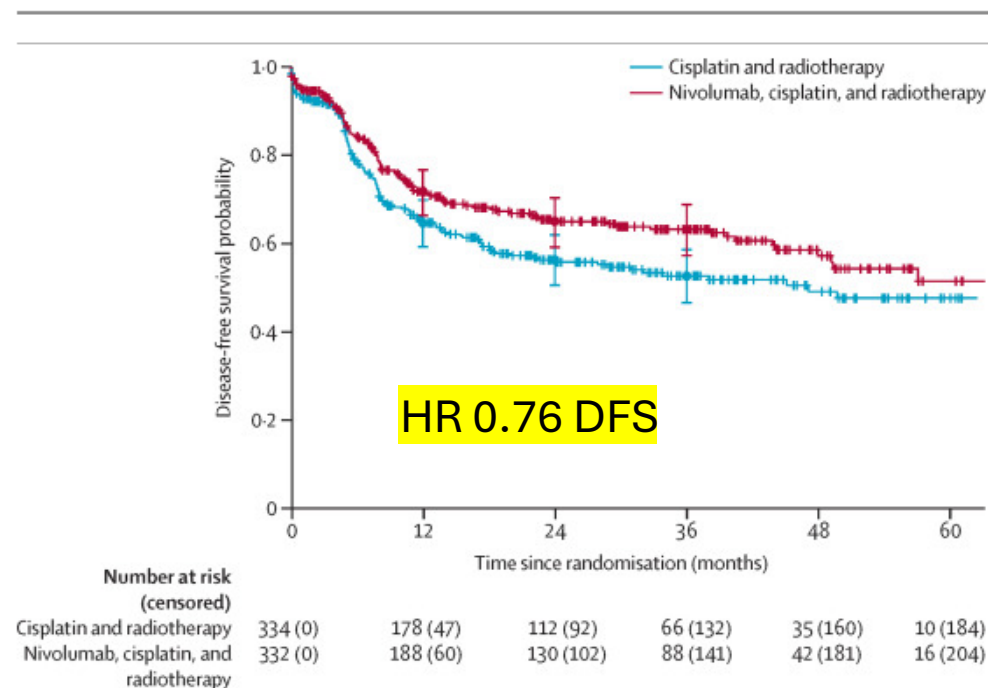
Nivopostop: New Postop High-Risk Paradigm

Clinical Trial > Lancet. 2026 Jan 24;407(10526):363-374. doi: 10.1016/S0140-6736(25)01850-1.

Epub 2025 Dec 22.

Nivolumab added to cisplatin and radiotherapy versus cisplatin and radiotherapy alone after surgery for people with squamous cell carcinoma of the head and neck at a high risk of relapse (GORTEC 2018-01 NIVOPOST-OP): a randomised, open-label, phase 3 trial

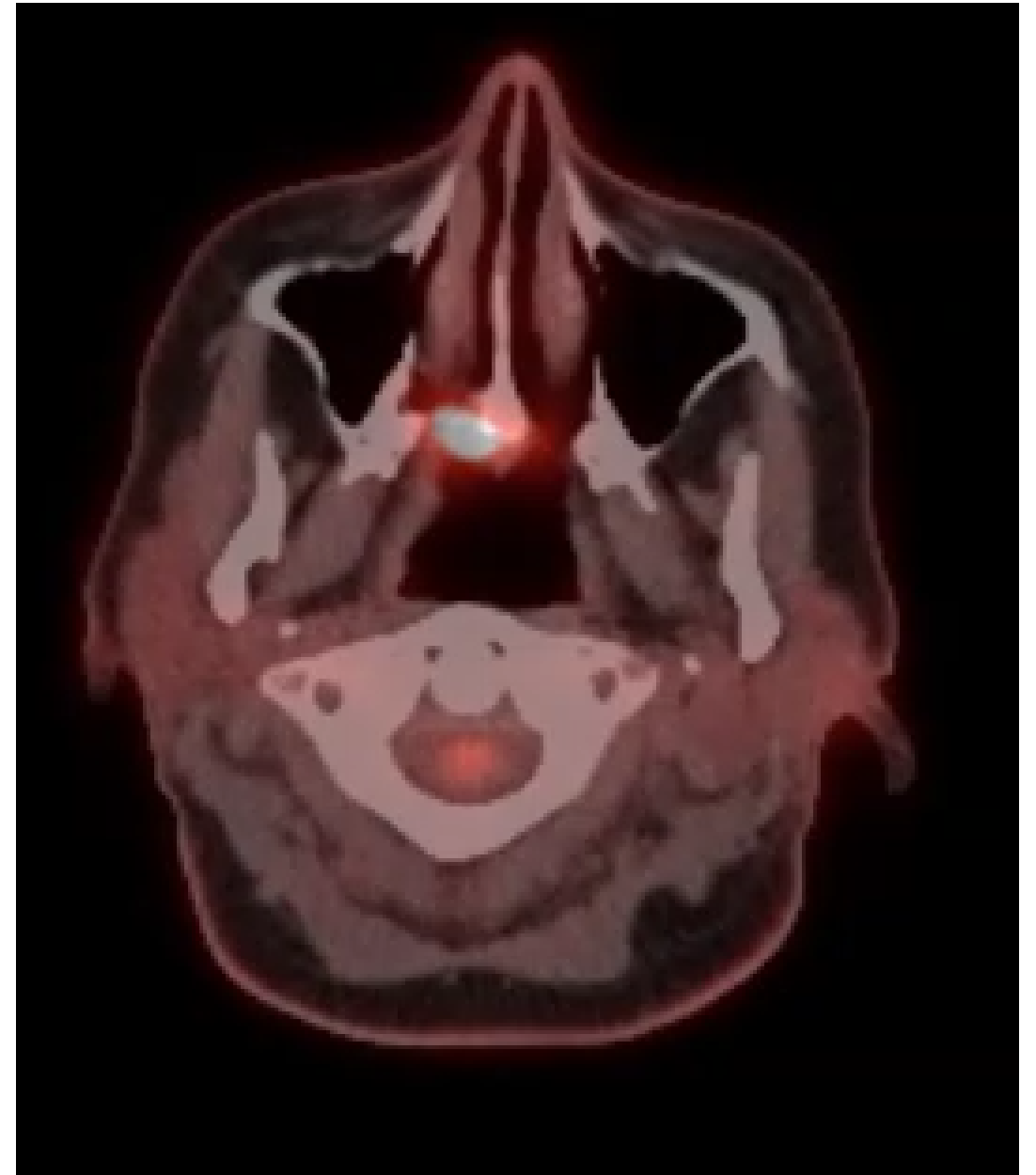
Jean Bourhis¹, Anne Aupérin², Christian Borel³, Gautier Lefebvre⁴, Severine Racadot⁵, Lionel Geoffrois⁶, Xu Shan Sun⁷, Esma Saada⁸, Beatriz Cirauqui⁹, Tomasz Rutkowski¹⁰, Stephanie Henry¹¹, Anouchka Modesto¹², Alison Johnson¹³, Sophie Chapet¹⁴, Benoit Calderon¹⁵, Christian Sire¹⁶, Olivier Malard¹⁷, Matthieu Binaud¹⁸, Antonio Da Silva Motta¹⁹, Sebastien Thureau²⁰, Yoann Pointreau²¹, Pierre Blanchard²², Guillaume Buiret²³, Laurence Bozec²⁴, Stephane Lopez²⁵, Julie Vanbockstael²⁶, Matthieu Bosset²⁷, Charlotte Greilsamer²⁸, Amaury Daste²⁹, Antoine Bruna³⁰, France N'Guyen²², Maria Plana³¹, Eluska Iruarizaga³², Stephane Temam²², Caroline Even²², Elisabeth Perez Ruiz³³, Mahasti Bert³⁴, Eleni Karamouza², Juliette Thariat¹³, Joanna Kazmierska³⁵, Amanda Psyrris³⁶, Ricard Mesia³⁷, Yungan Tao³⁸



Case 1: 48 yo nonsmoking woman

- *Healthy until noticing tongue pain 1/2026. Works as a data analyst. Married with 2 kids*
- *Lesion on right tongue biopsied 2/2026*
- *3/10/26 exam showed 3-4 cm tongue ulcer with >1.0 cm deep induration. No palpable nodes.*
- *Preoperative imaging showed 3.4 cm right oral tongue mass with no obvious LAN. No distant mets.*
- *4/1/26: Right hemiglossectomy with bilateral neck dissection given involvement of deep tongue tissue near midline raphe w/ radial forearm free flap for reconstruction*





Next steps? Surgery? Induction IO?



4/1/2026 Definitive Surgery

Synoptic Checklist

ORAL CAVITY 8th Edition - Protocol posted: 6/21/2023

ORAL CAVITY - All Specimens

SPECIMEN

Procedure	Glossectomy: Hemiglossectomy
TUMOR	
Tumor Focality	Unifocal
Tumor Site	Oral cavity
Tumor Subsite	Ventral surface of tongue
Tumor Laterality	Right
Tumor Size	Greatest Dimension (Centimeters): 3.5 cm
Histologic Type	Squamous cell carcinoma, conventional (keratinizing)
Histologic Grade	G3, poorly differentiated
Tumor Depth of Invasion (DOI)	18 mm
Lymphatic and / or Vascular Invasion	Not identified
Perineural Invasion	Present
Extent / Type of Perineural Invasion	Intratumoral
Worst Pattern of Invasion (WPOI)	WPOI 1-4

MARGINS

Specimen Margin Status for Invasive Tumor	All specimen margins negative for invasive tumor
Distance from Invasive Tumor to Closest Specimen Margin	4 mm
Closest Specimen Margin(s) to Invasive Tumor	deep

REGIONAL LYMPH NODES

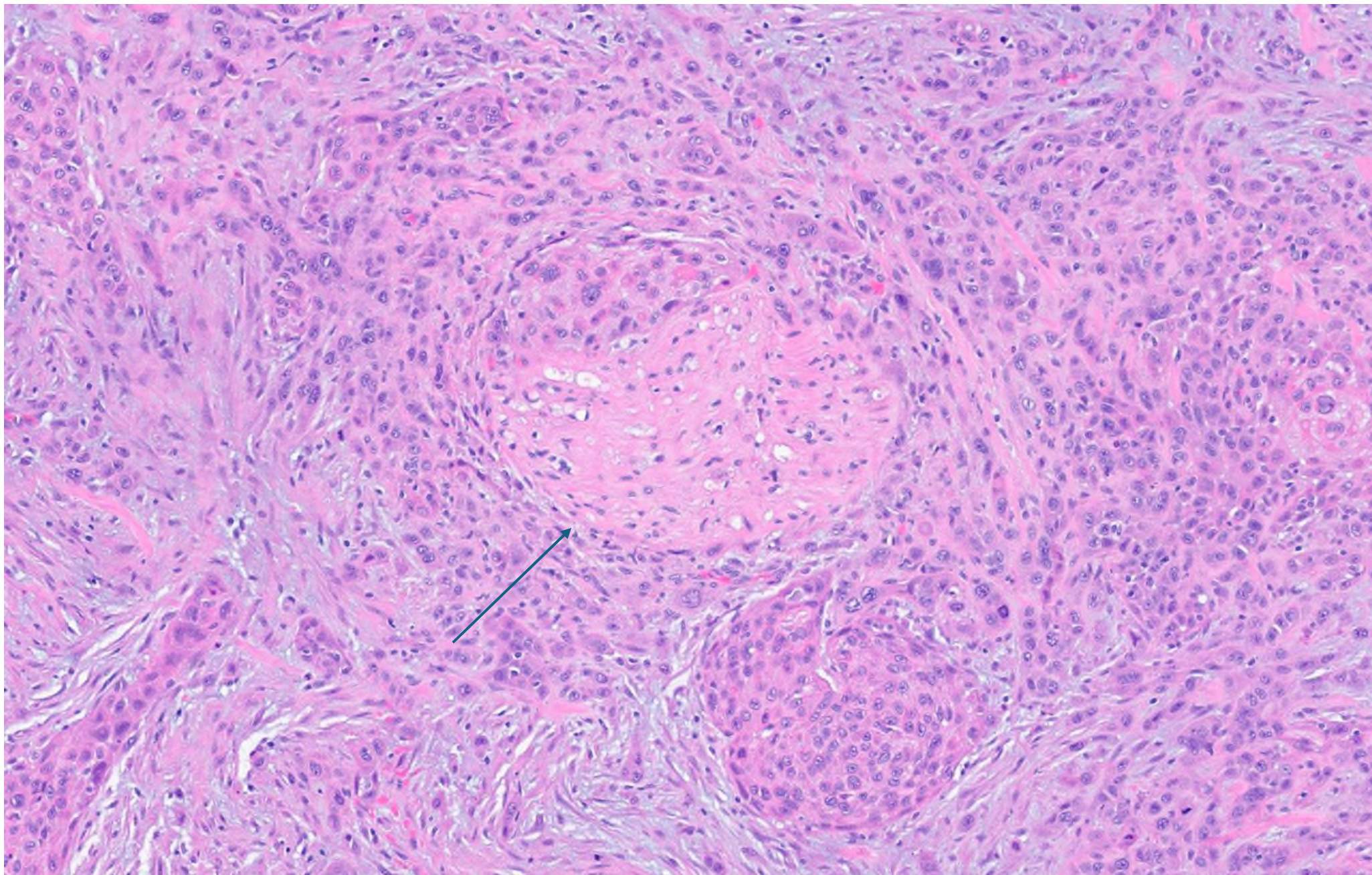
Regional Lymph Node Status	Tumor present in regional lymph node(s)
Number of Lymph Nodes with Tumor	2
Laterality of Lymph Node(s) with Tumor	Ipsilateral (including midline)
Size of Largest Nodal Metastatic Deposit	0.9 cm
Extranodal Extension (ENE)	Present
Distance of ENE from Lymph Node Capsule	Greater than 2 mm (macroscopic ENE)
Number of Lymph Nodes Examined	52

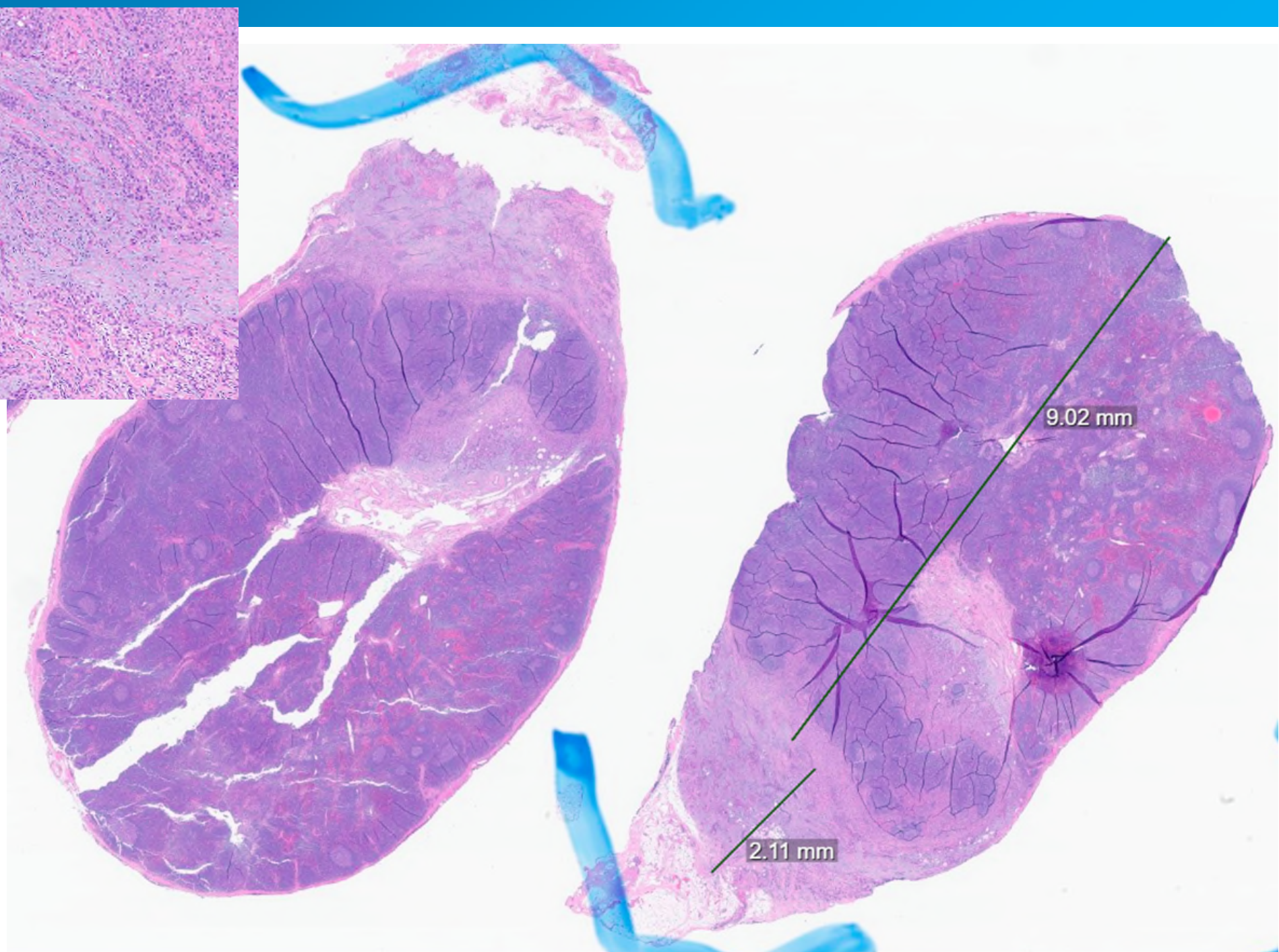
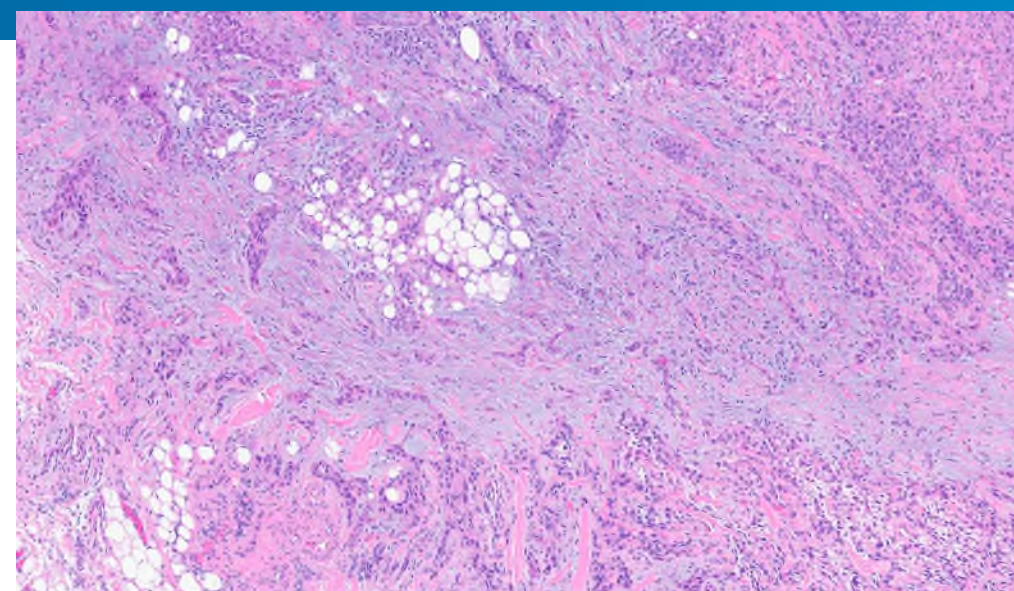
pTNM CLASSIFICATION (AJCC 8th Edition)

Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

pT Category	pT3
pN Category	pN3b







Patient received adjuvant CRT with nivolumab

- *Completed adjuvant CRT with Q3wk Nivolumab and continues on Nivolumab as per protocol*
- *PET/CT ordered late September*
- *Retrospectively this patient was staged cT3-4AN0 and could have qualified for Keynote 689*

HopeSeq Solid Tumors Comprehensive Final			4/13/2026
result			
Result			
HopeSeq Solid Tumors Comprehensive			
FORMALIN FIXED PARAFFIN EMBEDDED TISSUES - TONGUE, RIGHT HEMIGLOSSECTOMY AND FLOOR OF MOUTH RESECTION - (OM26-01045-A2/S26-04116-A7), COMPREHENSIVE GENOMIC ANALYSIS:			
Genomic Alterations Detected	Allele Frequency (%) or Copy Number Value	FDA-Approved Therapies in patient's tumor*	FDA-Approved Therapies in other tumor type*
CDKN2A (c.247C>T; p.H83Y)	28%	None	None
TP53 (c.374C>T; p.T125M)	15%	None	None
TUMOR MUTATIONAL BURDEN STATUS (TMB)			
Low (TMB Score: 0.53)			
MICROSATELLITE STATUS (MSI)			
Stable			
PD-L1 22C3 FDA (KEYTRUDA®) for HNSCC (Head & Neck Squamous Cell Carcinoma)			
PD-L1 EXPRESSION			
Combined Positive Score (CPS): 80			
Testing for PD-L1 was performed at City of Hope. Please see S26-04116.			



Treatment based on NIVOPOSTOP

Adjuvant nivolumab added to postoperative chemoradiation in high-risk resected HNSCC

Would this patient be a candidate for adjuvant nivolumab?

Yes if resected with high-risk pathology and fit for cisplatin-based chemoradiation. Trial population: patients 75 years or younger, majority oral cavity primaries, oropharynx under 5%.

What clinical situations do you consider adjuvant nivolumab?

High-risk pathology: positive margin, extranodal extension, 4 or more involved nodes, or multiple perineural invasion — 40–45% of these patients still recur after standard postoperative chemoradiation.

Timing and duration of treatment?

Nivolumab starts with postoperative chemoradiation (radiation still within 6 weeks of surgery) and continues after it, with high-dose cisplatin for margin-positive or ENE disease. Disease-free survival HR 0.76 with improved locoregional control.



Concurrent RT + Immunotherapy: are we helping or hurting?

Multiple trials have combined immunotherapy with conventionally fractionated radiation and produced negative results

Table. Clinical Trials of Concurrent Immune Checkpoint Inhibitors and Conventionally Fractionated CRT With Negative Outcomes

Clinical trial	Phase	Cancer type	Treatment arm	ICI target	Reference
PACIFIC 2	3	NSCLC	Concurrent durvalumab + CRT vs SOC CRT	PD-L1	NCT03519971
NRG-HN005	2/3	HNSCC	Concurrent reduced-dose RT + nivolumab vs reduced-dose RT + cisplatin vs SOC CRT	PD-1	NCT03952585
JAVELIN-HNSCC 100	3	HNSCC	Concurrent avelumab + CRT vs SOC CRT	PD-L1	NCT02952586
GORTEC-2017-01 (REACH)	3	HNSCC	Concurrent avelumab + cetuximab + RT vs SOC (cisplatin-cetuximab + RT)	PD-L1	NCT02999087
KEYNOTE 412	3	HNSCC	Concurrent pembro + CRT vs SOC CRT	PD-1	NCT03040999
CALLA	3	Cervical SCC	Concurrent durvalumab + CRT → adjuvant durvalumab vs SOC CRT	PD-L1	NCT03830866
NRG-GI002	2	Rectal cancer	FOLFOX → CRT + pembro preop vs FOLFOX → CRT preop	PD-1	NCT02921256

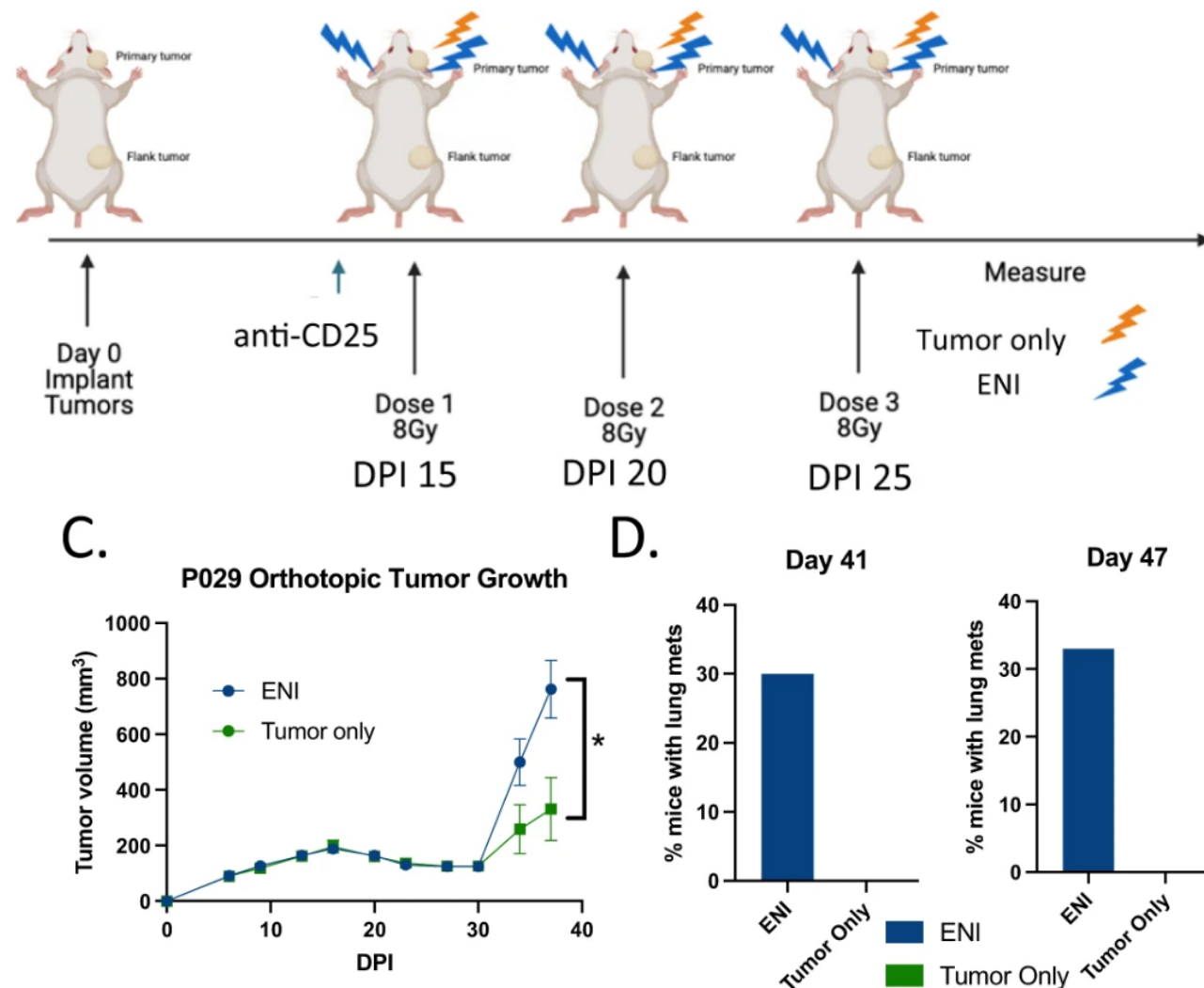
Abbreviations: CRT, chemoradiotherapy; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; pembro, pembrolizumab; preop, preoperatively; RT, radiotherapy; SCC, squamous cell carcinoma; SOC, standard of care; →, followed by.

Hypothesis: Large treatment volumes, long duration of treatment exposes lymphocytes to cytotoxic radiation



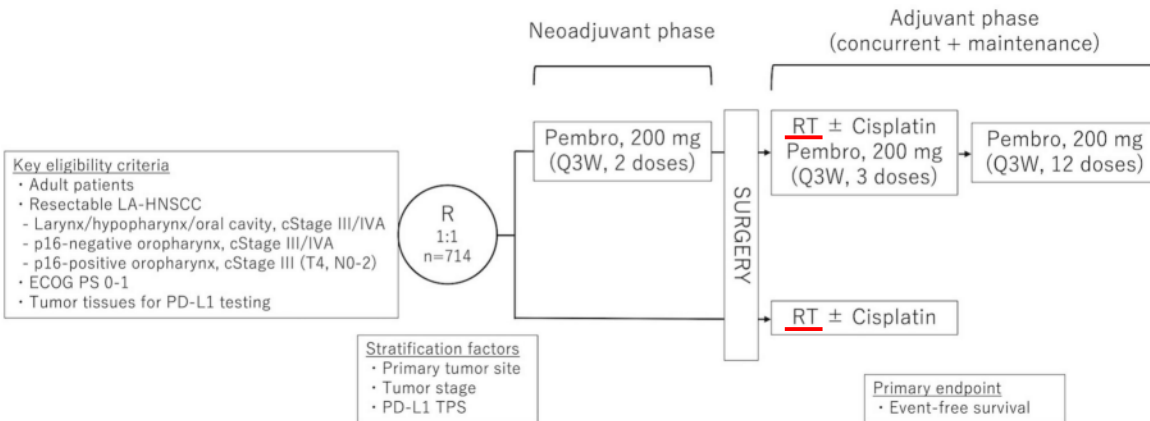
RT + Immunotherapy: helping or hurting?

- Orthotopic mouse model
- SBRT to primary or primary + ENI
- Mice receiving ENI had more lung metastases and primary tumor growth
- Neck dissection also associated with increased primary tumor size
- ENI leads to reduction in circulating activated CD4 and CD8 T cells
- ENI or neck dissection reduces regional recurrences

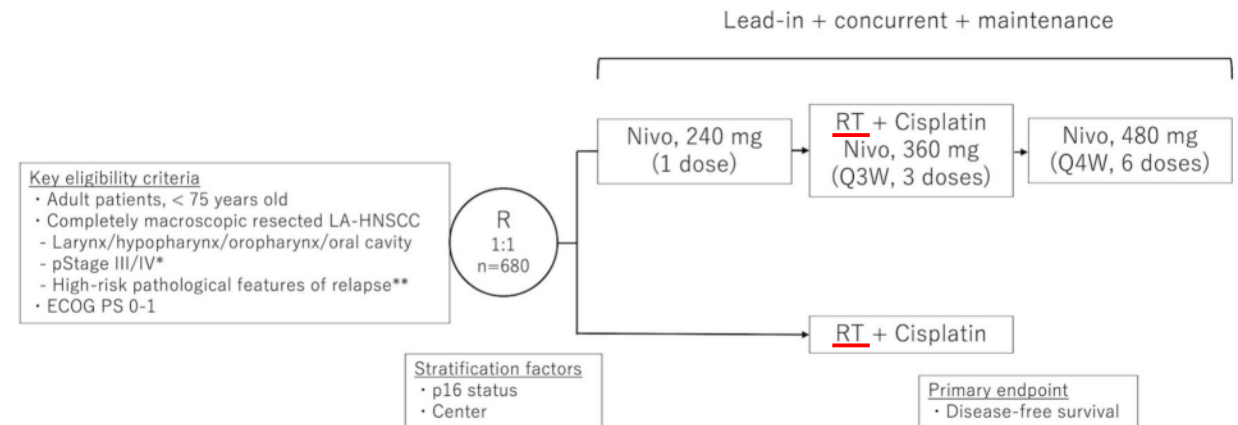


Radiation in the IO era: *mostly* unchanged

KEYNOTE 689



NIVOPOSTOP



- Concurrent and adjuvant (+/- neoadjuvant) immunotherapy were **added** to adjuvant RT
- No de-escalation of radiation doses or volumes were formally tested or proven
- Mild de-intensification: radiation dose and cisplatin based on post-induction pathology on KEYNOTE-689. **44.4% vs 32.5%** met high-risk criteria.



Postoperative Radiation: General Principles

- Timing:
 - start within 6 weeks of surgery and complete treatment by 11–13 weeks post-op; longer package time worsens local control
- Technique:
 - IMRT/VMAT with daily image guidance, 2 Gy per fraction, 5 fractions per week
- Doses:
 - high risk: 66 Gy in 33 fractions to regions of positive margin or extranodal extension
 - intermediate risk: 60 Gy in 30 fractions to the operative bed and involved nodal levels
 - elective: 54–57 Gy to uninvolved at-risk nodal levels
- Target:
 - primary: preoperative tumor volume plus the surgical bed, flap and scar, expanded for microscopic spread
 - neck: nodal levels at risk depending on location of gross disease and published drainage patterns



Radiation considerations in the IO era: Timing

- Timing of RT was moderately delayed relative to SoC
 - NIVOPOSTOP:
 - Median time to chemoRT 7.7 weeks (IQR 6.6–8.6)
 - Median time to chemoRT+ Nivo: 8.0 weeks (IQR 6.9–9.0)
 - KEYNOTE-689:

Table S2A. Cumulative Number of Participants Who Started Adjuvant Therapy After Surgery by Week, All Randomized Participants Who Underwent Surgery and Received Adjuvant Therapy.*

Weeks Post-Surgery	Pembrolizumab N = 267	Control N = 267
≤6	124 (46.4)	93 (34.8)
≤7	199 (74.5)	172 (64.4)
≤8	219 (82.0)	205 (76.8)
≤9	242 (90.6)	233 (87.3)
≤10	253 (94.8)	242 (90.6)

Data are n (%).

*In the pembrolizumab group, adjuvant pembrolizumab was planned to start concomitantly with postoperative radiotherapy or chemoradiotherapy.



Radiation considerations in the IO era: Toxicity

- Median age on both studies was ~60 years old
- KEYNOTE-689
 - Serious treatment related AEs 19.1% (pembrolizumab) vs 10.5% (control)
 - No clear difference in radiation-related AEs
- NIVOPOSTOP
 - More serious adverse events (33% vs 19%)
 - More RT-related serious AEs (13% vs 6%)
 - G3–4 dysphagia: 24% vs 18%

	Cisplatin and radiotherapy (n=306)					Nivolumab, cisplatin, and radiotherapy (n=312)				
	Any grade	Grade 3-5	Grade 3	Grade 4	Grade 5	Any grade	Grade 3-5	Grade 3	Grade 4	Grade 5
Treatment-related adverse events										
Any	304 (99%)	211 (69%)	209 (68%)	16 (5%)	2 (1%)	301 (96%)	230 (74%)	227 (73%)	30 (10%)	2 (1%)
Serious	59 (19%)	48 (16%)	45 (15%)	4 (1%)	2 (1%)	104 (33%)	91 (29%)	84 (27%)	14 (4%)	2 (1%)
Nivolumab-related adverse events										
Any	NA	NA	NA	NA	NA	213 (68%)	64 (21%)	58 (19%)	6 (2%)	2 (1%)
Leading to nivolumab discontinuation	NA	NA	NA	NA	NA	25 (8%)	14 (4%)	12 (4%)	2 (1%)	0
Serious	NA	NA	NA	NA	NA	32 (10%)	25 (8%)	21 (7%)	3 (1%)	2 (1%)
Cisplatin-related adverse events										
Any	291 (95%)	157 (51%)	154 (50%)	16 (5%)	2 (1%)	286 (92%)	176 (56%)	168 (54%)	27 (9%)	1 (<1%)
Leading to cisplatin discontinuation	54 (18%)	37 (12%)	34 (11%)	4 (1%)	0	65 (21%)	49 (16%)	41 (13%)	10 (3%)	0
Serious	54 (18%)	44 (14%)	41 (13%)	4 (1%)	2 (1%)	75 (24%)	68 (22%)	58 (19%)	13 (4%)	1 (<1%)
Radiotherapy-related adverse events										
Any	297 (97%)	156 (51%)	156 (51%)	2 (1%)	0	294 (94%)	161 (52%)	159 (51%)	9 (3%)	0
Serious	18 (6%)	12 (4%)	12 (4%)	1 (<1%)	0	39 (13%)	30 (10%)	28 (9%)	4 (1%)	0

Since the same adverse events can be related to several treatments (nivolumab, cisplatin, and radiotherapy), the number of participants with treatment-related adverse events is not the sum of participants with adverse events related to nivolumab, cisplatin, and radiotherapy. N/A=not applicable.

Table 3: Number of participants with adverse events and serious adverse events (all periods together)

How to bring this all together?

- **Post-operative IO** — ADRISK vs NIVOPOSTOP — why one failed and one succeeded
- **Peri-operative chemo-IO** — KEYNOTE-689, CAMORAL and AK112: an evolving paradigm and recent updates
- **A recipe for success** — Population, risk, agent, dosing, duration — the winning formula
- **Choosing a path** — Pembrolizumab up front or nivolumab after pathology
- **What we still don't know** — Key unanswered questions and next steps



Updates from ASCO 2026 and ESMO 2025

Parameter	KN-689 (Success) Practice changing	CAMORAL (Success) more data needed	AK112 +AP
Design (resectable)	Neo: Pembro 2 cycles → Surgery → Adj: aRCH + Pembro 12mo	Neo: Camrelizumab+Chemo 2 cycles → Surgery → Adj: aRCH + Camreli 15mo	Neo: Ivonescimab+Chemo 3 cycles → . surgery → Adj RT + AK112
IO Agent	Pembrolizumab (PD-1)	Camrelizumab (PD-1)	Ivonescimab
N (patients)	714 (363 vs 351)	125 (63 vs 62)	36 single arm
Population	60% OC, <4% HPV+ Stage III-IVA	82% OC, 2.5% HPV+ Stage III-IVB	19% OC, Hypopharynx 47%
Neoadjuvant Chemo	NO - IO monotherapy	YES - nab-paclitaxel/carbo	Yes- cisplatin nabpaclitaxel
Neoadjuvant Cycles	2 cycles (6 weeks)	2 cycles (6 weeks)	3
Primary Endpoint	EFS: HR 0.73 (p=0.008)	EFS: HR 0.25 (p=0.004)	NR
pCR Rate	0% (by design)	25.4%	53%
MPR Rate	9.4%	47.6%	78 %
Key Success Factor	2 neo doses + 1 year adj IO HPV- enrichment	Neo IO+chemo synergy Very high response rates	Neo bispecific +chemo synergy Very high larynx preservation rate 92%, 100% R0 resection



Post-Operative Immunotherapy: Tale of Two Trials

Parameter	ADRISK (Failed)	NIVOPOSTOP (Succeeded)
Design	aRCH + Pembrolizumab vs aRCH	aRCH + Nivolumab vs aRCH
IO Agent	Pembrolizumab (anti-PD-1)	Nivolumab (anti-PD-1)
IO Timing	During & after aRCH (12 mo)	1 dose before + 6 mo after aRCH
N (patients)	204 (102 vs 102)	666 (332 vs 334)
Primary Endpoint	EFS: HR 0.81 (NS, p=0.42)(underpowered)	DFS: HR 0.76 (p=0.034)
HPV+ OPC in IO arm	45% (46/102)	5% (16/332)
Oral Cavity in IO arm	23% (24/102)	58% (192/332)
High Risk Only	No - 36% intermediate risk(dilution)	Yes - 100% high risk*
Key Finding	No benefit in HPV+ population	Benefit in HPV- high-risk disease

Is there a Recipe for Successful IO use in LA-HNSCC?

Population Selection

HPV- Disease

- ✓ <4% HPV+ (all successful trials)
- ✗ >69% HPV+ (ADRISK failed)
- 💡 HPV- tumors have immunosuppressed TME with room for benefit

Risk Stratification

True High-Risk Only

- ✓ 100% high-risk features
- ✗ Mixed risk features may dilute the benefit
- 💡 High baseline failure (40-50%) needed to show benefit

IO Agent Selection

PD-1 > PD-L1

- ✓ All successes used anti-PD-1
- ✗ COMPARE and IMVOKE 10 used anti-PD-L1
- 💡 PD-1 blockade more effective in adjuvant setting

Neoadjuvant Dosing

≥2 Cycles Optimal

- ✓ KN-689, CAMORAL: 2 cycles
- ✗ COMPARE: Only 1 dose for definite CRT no surgery
- 💡 Adequate time for immune priming essential

Chemotherapy Synergy

IO + Chemo = Best

- ✓ CAMORAL: 47.6% MPR!
- ✗ IO monotherapy: 9.4% MPR
- 💡 Chemo enhances immunogenicity via DAMP release

Adjuvant Duration

12+ Months Ideal

- ✓ KN-689, CAMORAL: 12-15 mo
- ✗ Too short: <6 months (NIVOPOS used 6 months)
- 💡 Extended therapy maintains immune surveillance

Timing Strategy

Neo + Adjuvant Best

- ✓ Prime → Surgery → Consolidate
 - 💡 Neoadjuvant primes immune system before surgery
- NIVO POST approach preferred when surgery can't be delayed.

Statistical Power

Well-Powered Design

- ✗ ADRISK: Underpowered
- 💡 Adequate events needed to detect benefit

Biomarker Selection

HPV status and PD-L1 CPS

- ✓ HPV status may be a better predictor in some settings
- 💡 Both Biology and biomarkers matter

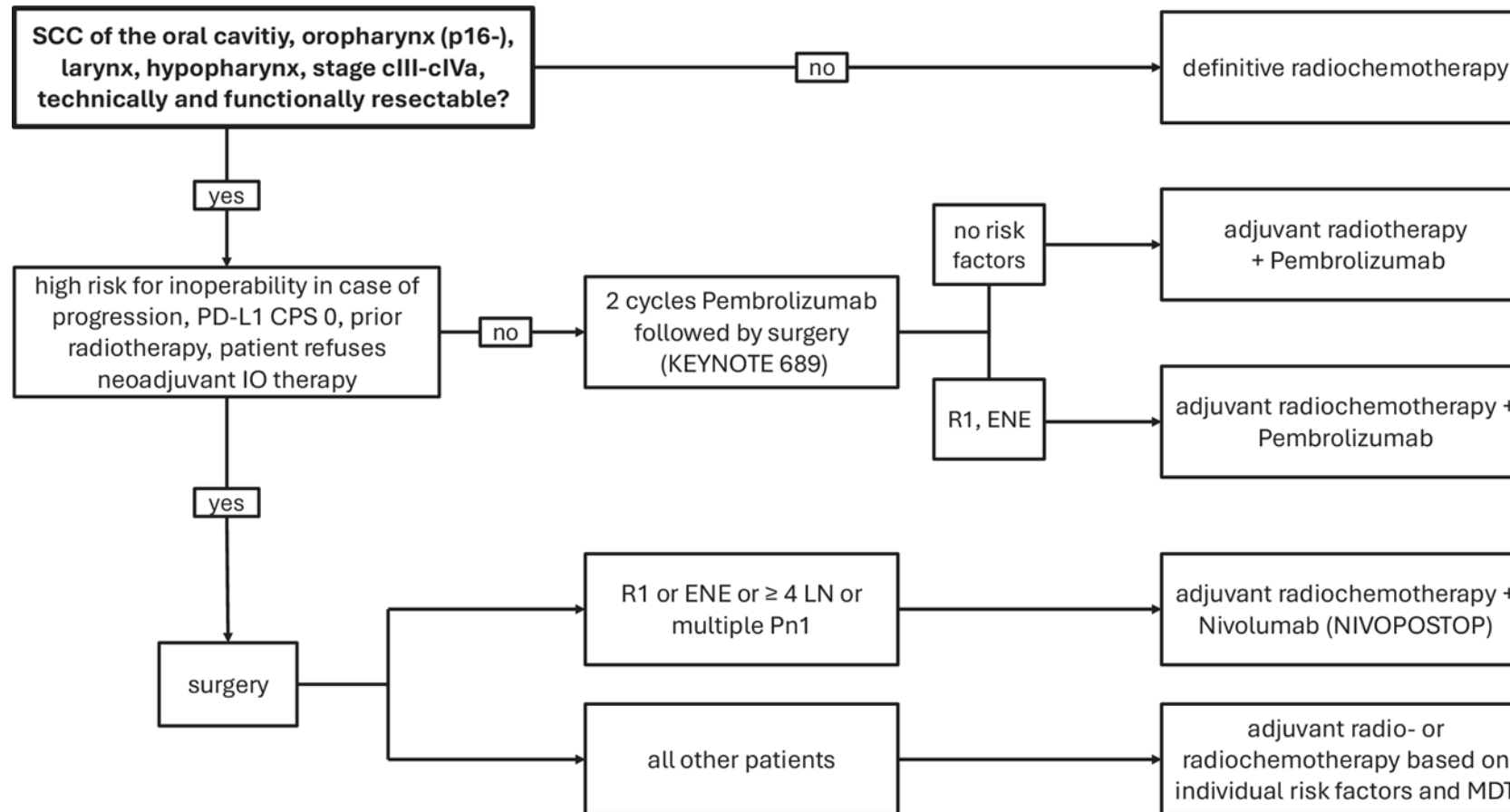
WINNING FORMULA? : HPV negative High-Risk + PD-1 inhibitor + 2-cycle Neo-priming (± Chemo for max response) + 12-month Adjuvant

**Perioperative immunotherapy in locally advanced head and neck squamous cell carcinoma: an Austrian consensus-based treatment algorithm**

Teresa Magnes · Martin Burian · Dietmar Thurnher · Florian Kocher · Wolfgang Eisterer · Birgit Gruenberger · Josef Singer · Petra Georg · Markus Brunner · Falk Roeder · Frank Wolf · Uta Ganswindt · Benjamin Walch · Anton Kugler · Thomas Winder · Fabian Sommer · Lukas Poyntner · Benedikt Hofauer · Thomas Melchardt · Alexander Egle · Thorsten Fuereeder

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[10.1007/s12254-026-01123-1](https://doi.org/10.1007/s12254-026-01123-1)



Which Path: Pembrolizumab or Nivolumab?

The decision is made before surgery: commit to perioperative pembrolizumab upfront or resect first and let pathology direct adjuvant nivolumab.

KEYNOTE-689: perioperative pembrolizumab

Decision point: before any surgery, on clinical stage and biomarker

Choose when: resectable clinical stage 3–4A, CPS 1 or higher, HPV-negative, no risk of losing the surgical window, and surgery can occur within 4–6 weeks of the first dose

Regimen: 2 neoadjuvant plus 15 adjuvant cycles of 200 mg every 3 weeks, with adjuvant radiation and cisplatin for high-risk pathology

Evidence: EFS HR 0.73, driven by fewer distant events; cost is a 51-week course, 12.7% progression on neoadjuvant therapy, and only 42.7% completing the full protocol

NIVOPOSTOP: postoperative nivolumab

Decision point: after resection, on final pathology

Choose when: surgery is urgent or already done, CPS 0 or unknown, or the patient cannot commit to a prolonged perioperative course; age 75 or younger and cisplatin-eligible

Trigger: high-risk pathology — positive margin, extranodal extension, 4 or more nodes, multiple perineural invasion

Evidence: DFS HR 0.76 with improved locoregional control in a group where 40–45% still recur after standard postoperative chemoradiation

Common to both: never delay an operation that may become inoperable, start radiation within 6 weeks of surgery, and make the call at tumor board with CPS and p16 in hand. Neither applies to T4B or N3 disease, p16-positive oropharynx suited to organ preservation, prior radiation, or contraindications to immunotherapy.



Key unanswered questions:



Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Tumour Review

Comparative review of KEYNOTE-689 and NIVOPOSTOP trials and their impact on perioperative immunotherapy in locally advanced head and neck cancer

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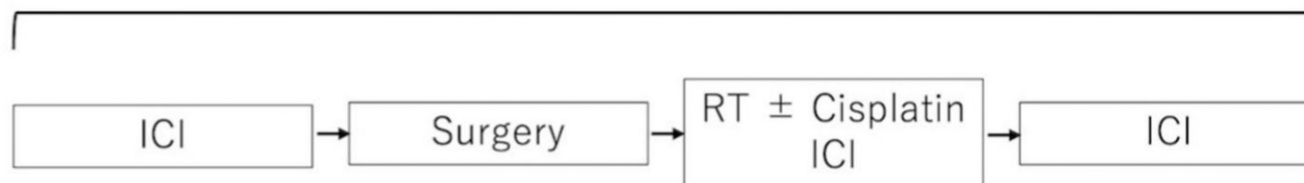
Uncertain patient subgroups

- PD-L1 CPS <1
- Non-squamous-cell histology
- Hypopharyngeal and p16-positive oropharyngeal tumors
- Poor ECOG PS
- Children and super-elderly patients

Unresolved endpoints

- Overall survival benefit
- Cost-effectiveness
- Real-world implementation

Which components are essential — and for how long?



Defining the optimal neoadjuvant regimen

- ICI-monotherapy
- Chemotherapy
- Immuno-chemotherapy

Response-adapted de-escalation

What to spare or reduce?

- Adjuvant RT, cisplatin, and/or ICI
- Organ-preserving approaches instead of radical surgery

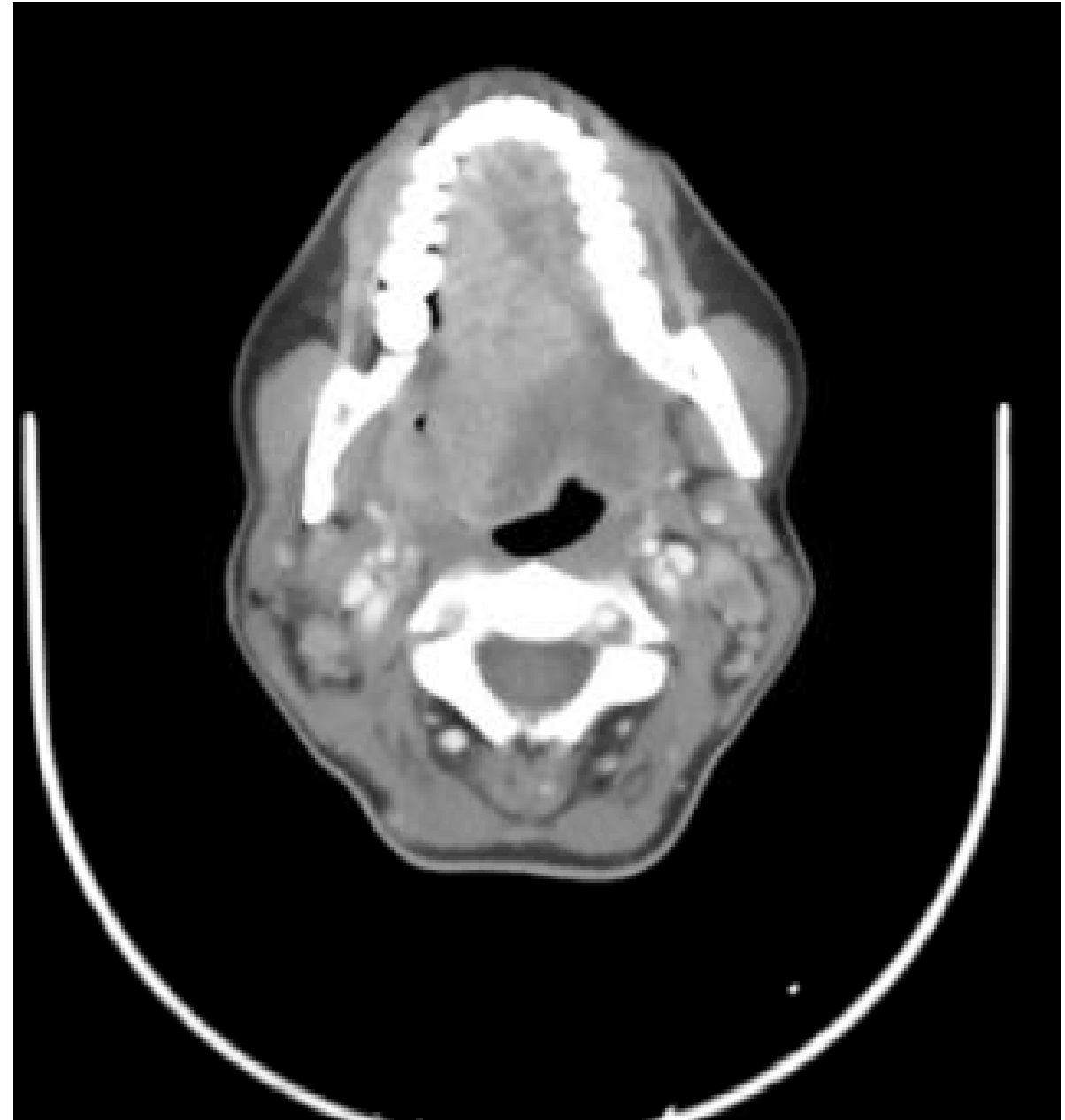
How to decide?

- Major pathologic response
- High-risk pathological features
- ctDNA-guided surveillance



Case 2:

- 45 yo nonsmoking female
 - CSW/ but now offers animal therapy at a ranch w/ therapy horses.
- 4/2026; P16 negative SCC right oral tongue cancer
- cT3N2bM0, CPS 80



Onc Hx

Stage: cT3N2b

ECOG PS = 0

Relevant Markers: P16 negative, PD-L1 80-90%

Prior Oncologic Treatment:

5/18/2026-7/30/2026: Nivolumab/Carbo/Taxol (Weekly Carbi AUC 2/Taxol 100mg/m² + Nivolumab 240mg q2 weeks x 6 cycles then received Carbo AUC5 /Taxol 175mg/m² /Nivo 240mg on 7/30)

Past relevant history:

4/16/2026: Biopsy of the right oral tongue ulceration revealed squamous cell carcinoma

FINAL PATHOLOGIC DIAGNOSIS

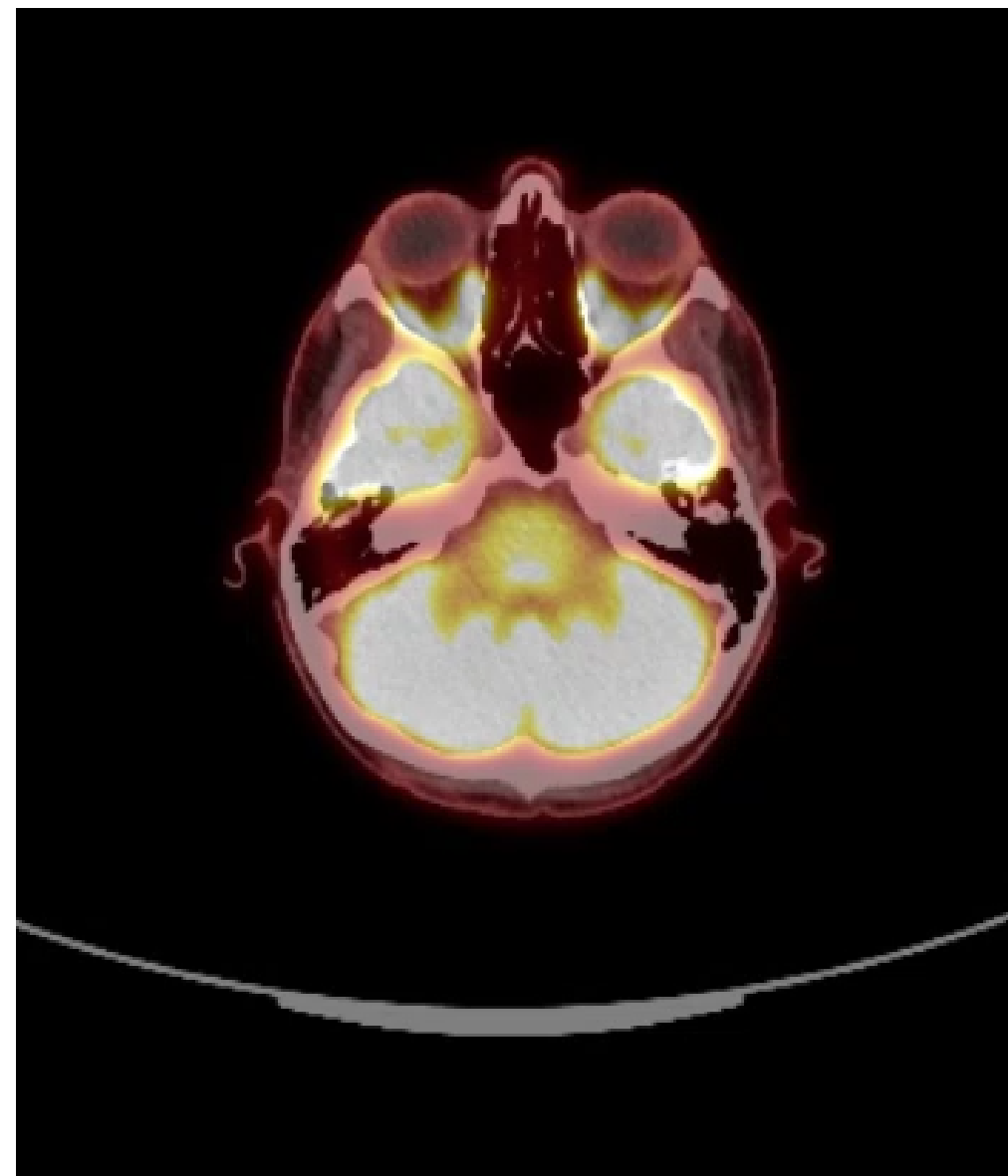
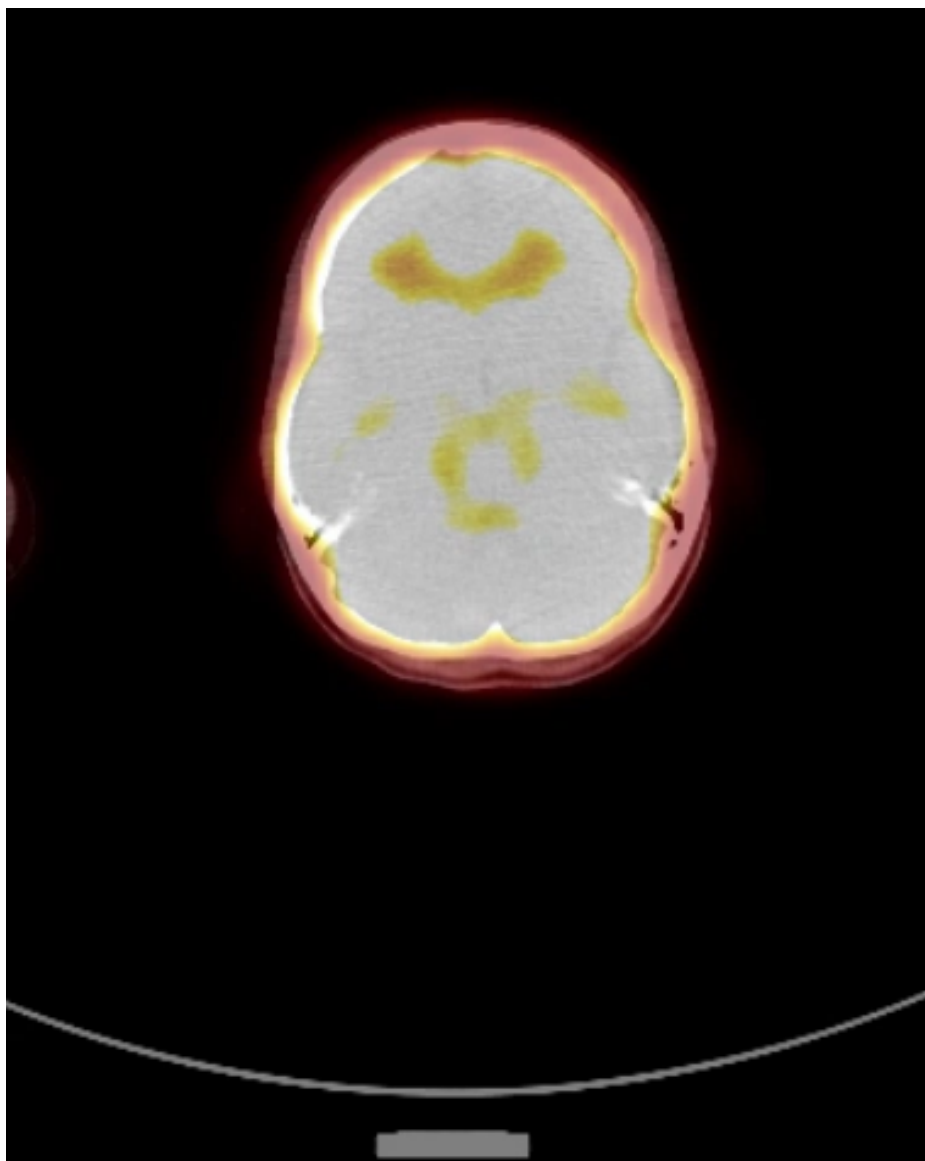
TONGUE, ("RIGHT TONGUE ULCER"), BIOPSY:

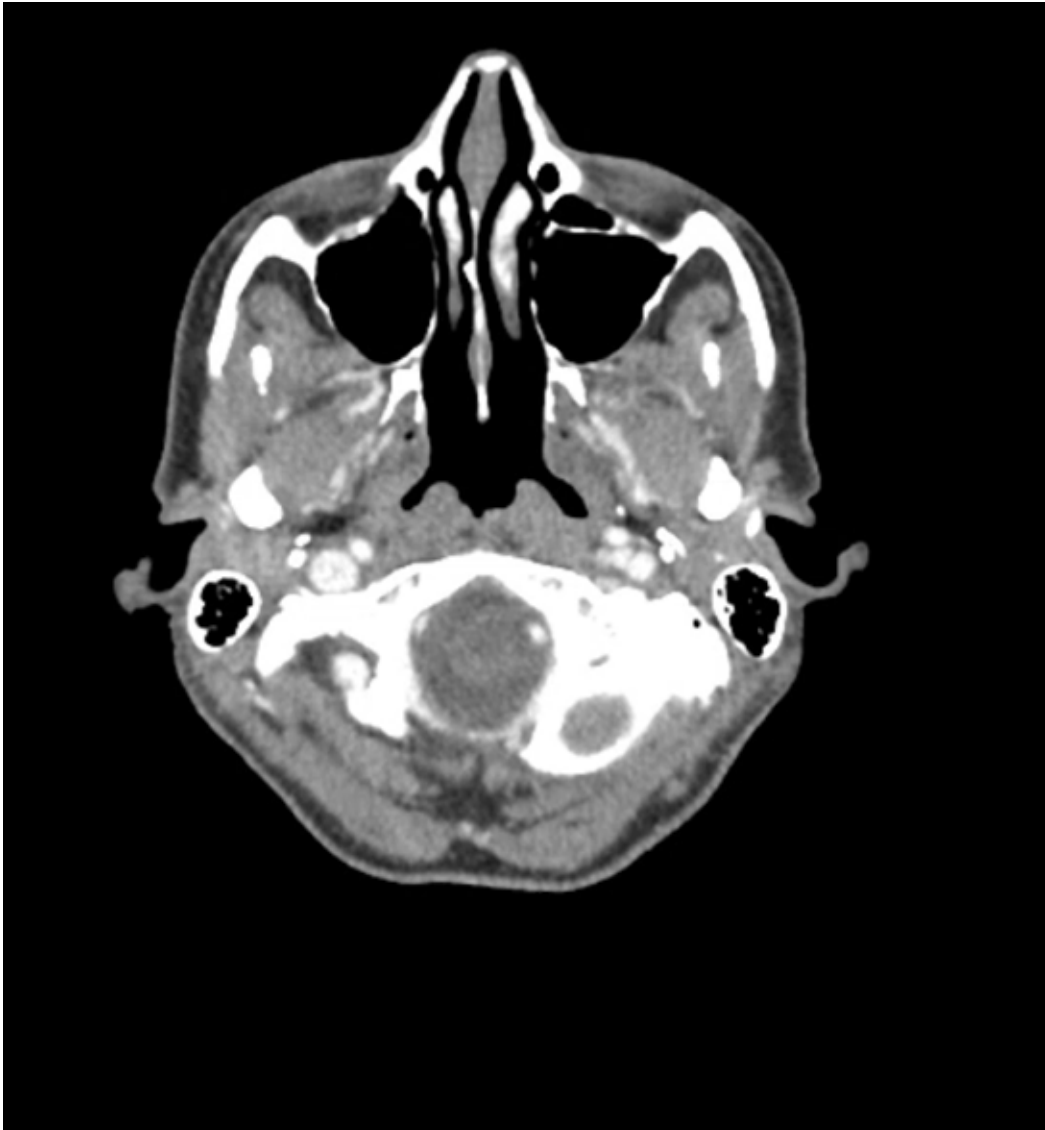
- KERATINIZING SQUAMOUS CELL CARCINOMA, MODERATELY DIFFERENTIATED; SEE COMMENT.
- P16 NEGATIVE BY IMMUNOHISTOCHEMISTRY.

5/18/2026-7/30/2026: Neoadjuvant chemoimmunotherapy with carboplatin, paclitaxel, and nivolumab at Kaiser.

6/26/2026: FNA of a thyroid nodule was benign.







- Neoadjuvant chemolO at Kaiser with complete response at primary site by imaging and exam. Persistent PET avid palpable right level 2 nodes.
- Went to NYC/MSKCC as she did not want glossectomy/ free flap
- Insurance didn't approve surgery in NYC so she came to COH.
- Exam showed marked response at primary site. No obvious residual just superficial mucosal markings/scar
- Refused any tongue surgery that would change appearance, and function of tongue. Refused any surgery that would require free flap at this stage.
- Open to small contour/function neutral excisions for path eval to guide subsequent therapy decisions. Open to bilateral neck dissection.



