UC San Diego

Neoadjuvant treatment of Head & Neck Cancer

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Disclosures

Regeneron Advisory Board member

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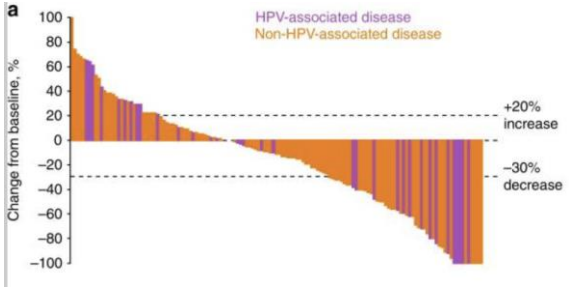
Neoadjuvant immunotherapy in Head & Neck Cancer

1. Rationale: Why give neoadjuvant?
2. Neoadjuvant-Adjuvant immunotherapy is approved! A critical look at the data
3. Case presentation: How do we integrate into clinical practice?

Immunotherapy for Recurrent/Metastatic HNSCC

KEYNOTE-012: ORR 18%



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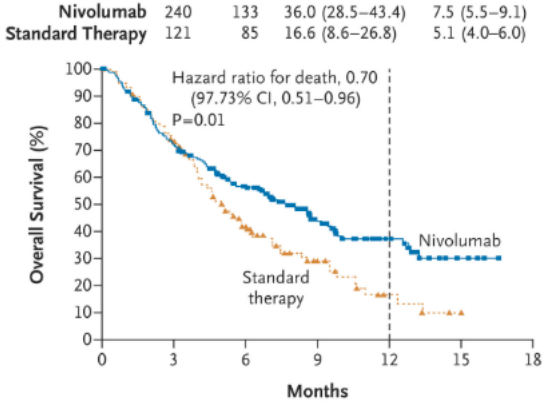
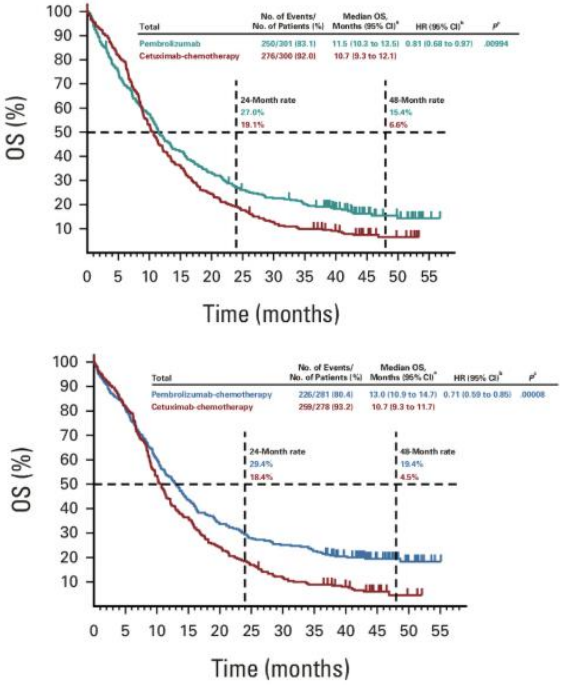
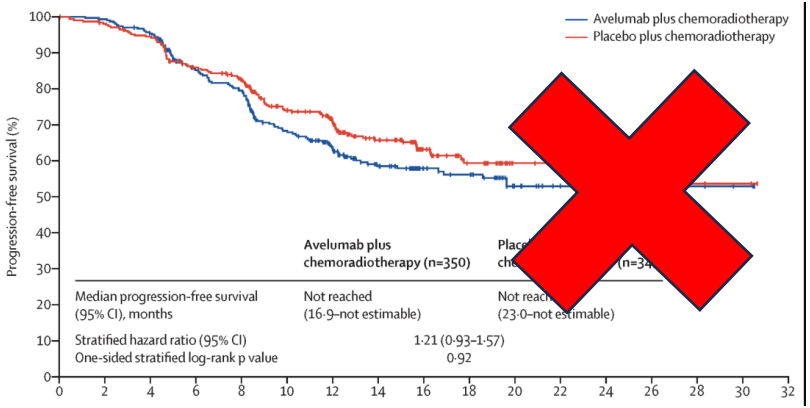


KEYNOTE-048: IO +/- chemotherapy

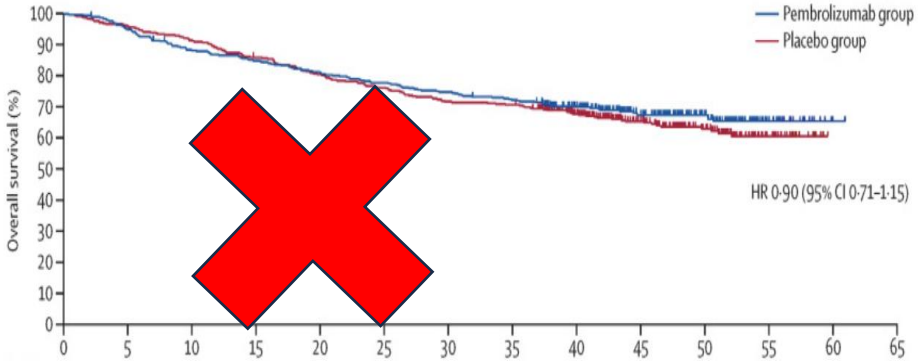


Multiple failed trials adding immunotherapy for Head & Neck in the curative setting

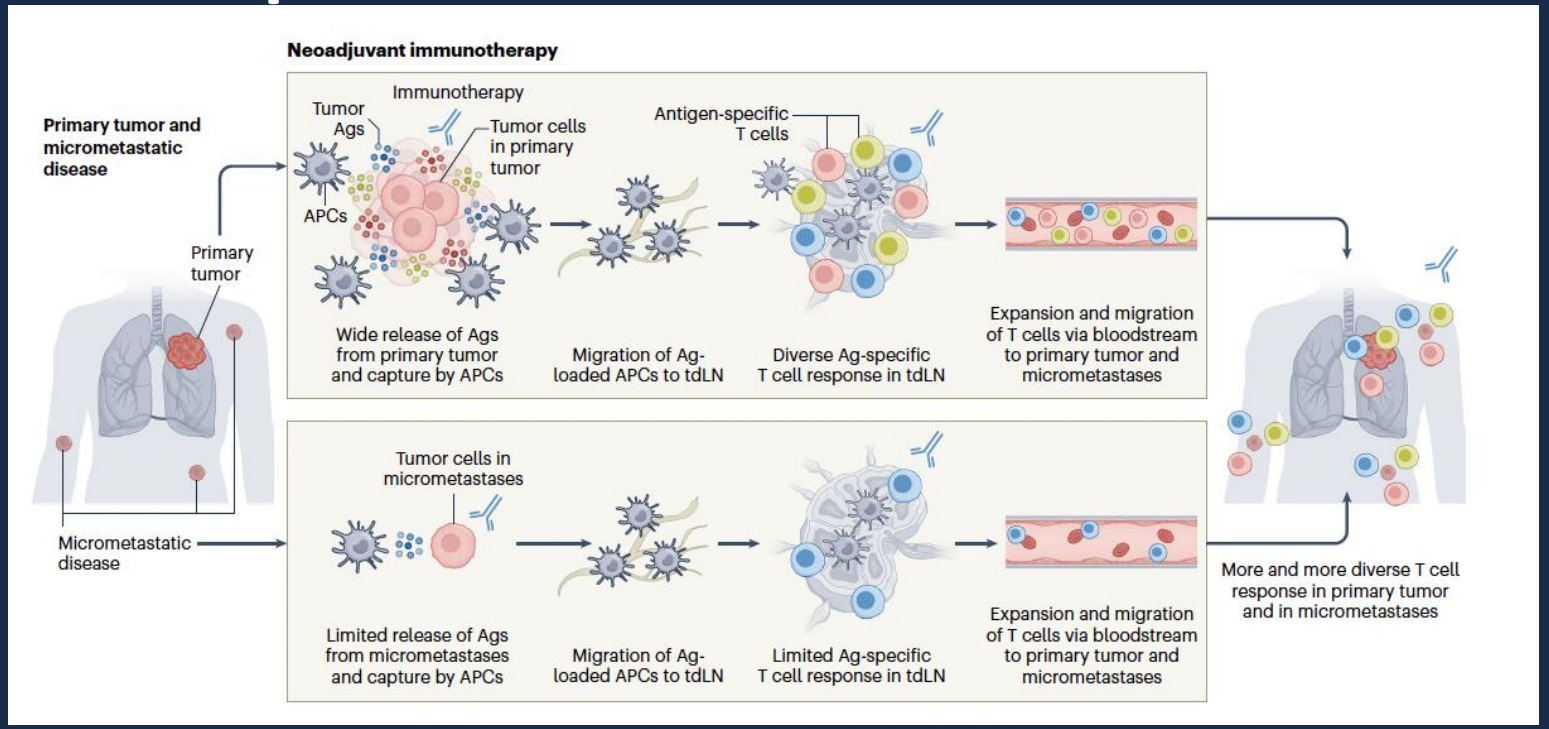
Javelin: CRT +/- Avelumab



Keynote-412:CRT +/- Pembrolizumab



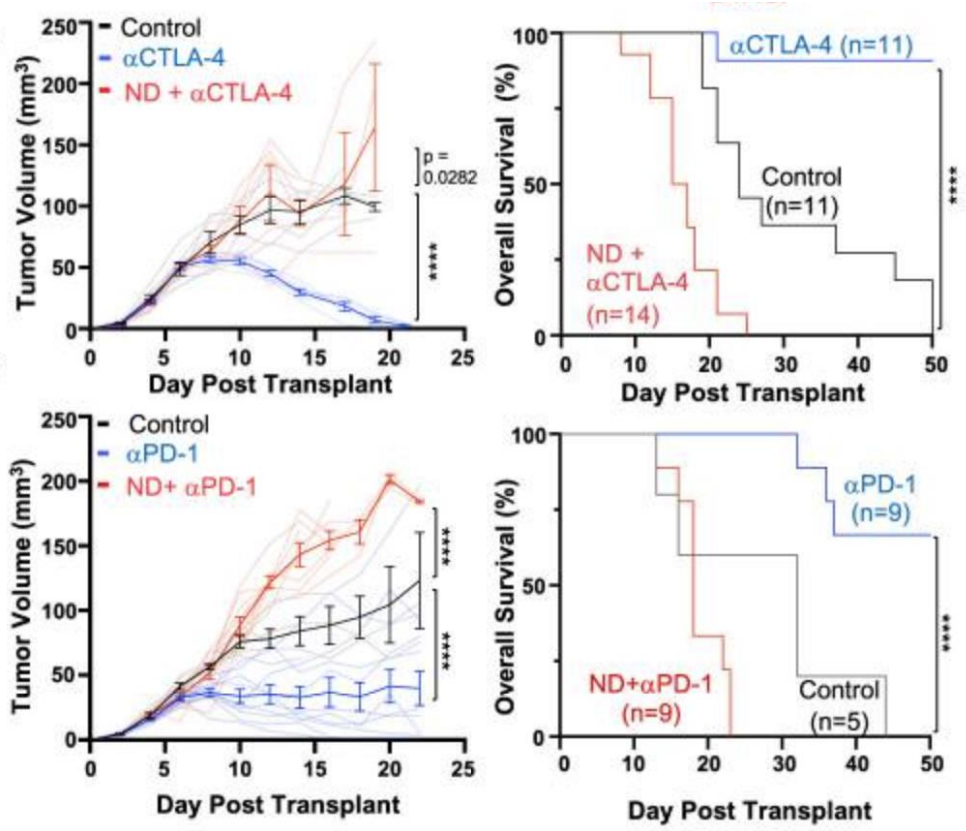
Neoadjuvant immunotherapy primes a diverse T-cell response



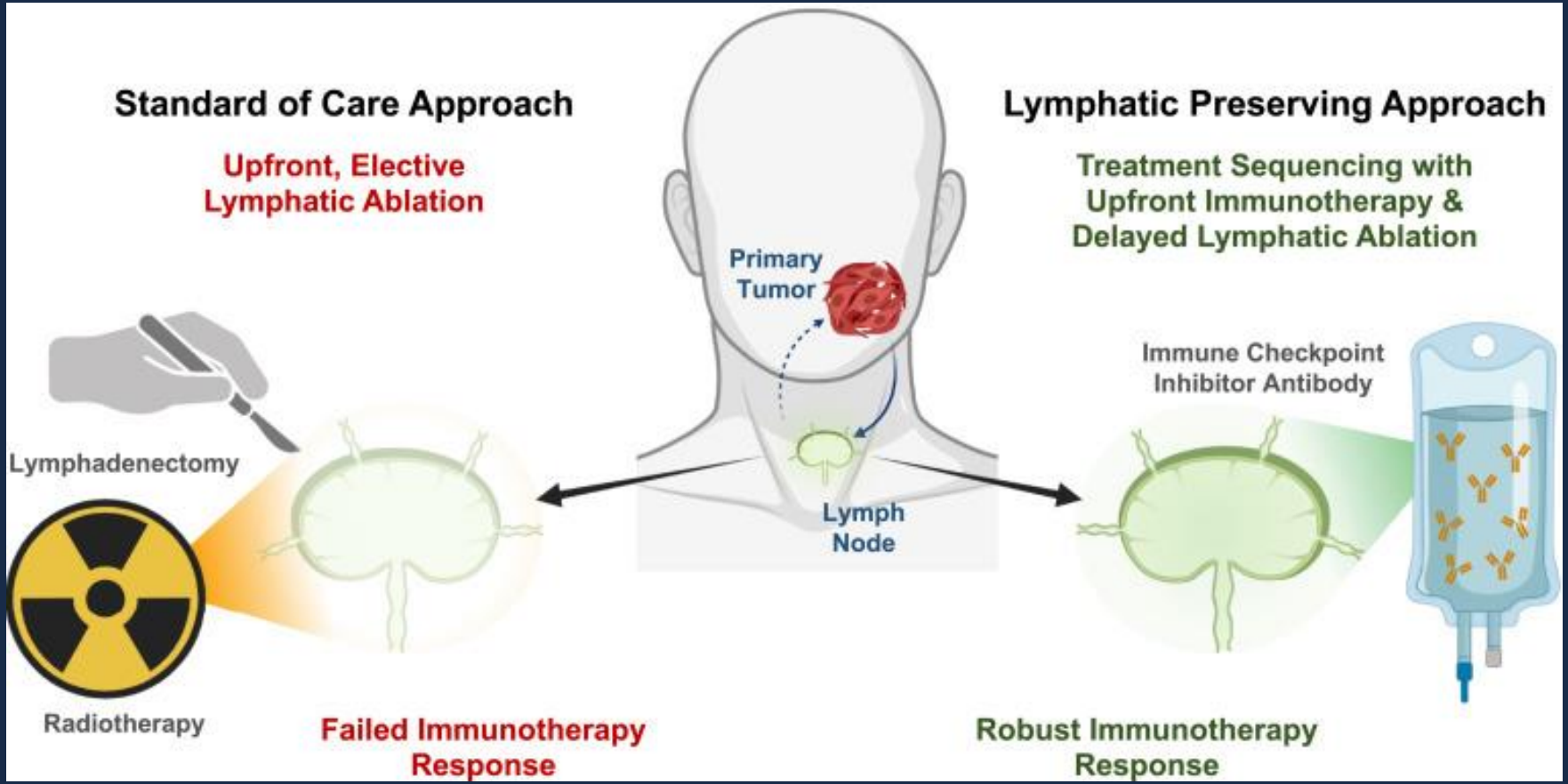
Awada, G., Cascone, T., van der Heijden, M.S. *et al.* The rapidly evolving paradigm of neoadjuvant immunotherapy across cancer types. *Nat Cancer* **6**, 967–987 (2025).

Treatment prior to lymphatic ablation

- Preclinical models of head & neck cancer
- Tumor models responsive to immune checkpoint inhibitors (anti-PD-1 and anti-CTLA4)
- Response was LOST if neck dissection as performed prior to ICI treatment
- Similar effect with radiation ablation of regional lymph nodes



Saddawi-Konefka et al. Nat Commun. 2022 Jul 25;13:4298.



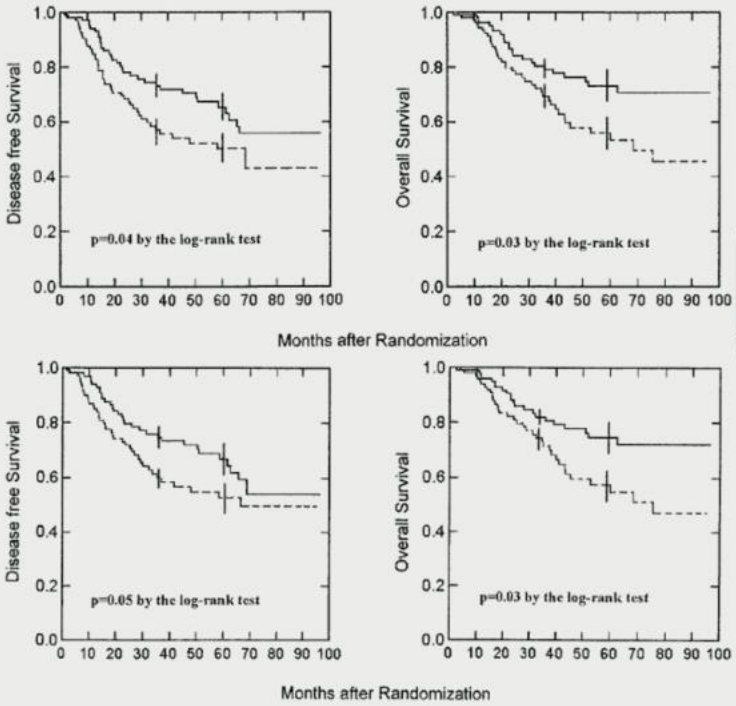
Saddawi-Konefka R, Schokrpur S, Gutkind J **Let it be: Preserving tumor-draining lymph nodes in the era of immuno-oncology**. Cancer Cell, 42, 930-933

FDA approves neoadjuvant and adjuvant pembrolizumab for resectable locally advanced head and neck squamous cell carcinoma

On June 12, 2025, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck) for adults with resectable locally advanced head and neck squamous cell carcinoma (HNSCC) whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin after surgery, and then as a single agent.

This is the first approval for HNSCC in 6 years and the first overall perioperative approval for locally advanced HNSCC.

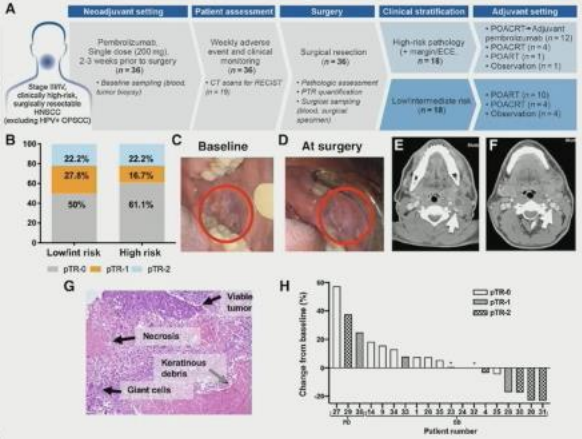
Neoadjuvant (Peri-operative) Immunotherapy Trials



Stefani et al. Cancer. 2002. 95 (1):90-7

AACR American Association for Cancer Research

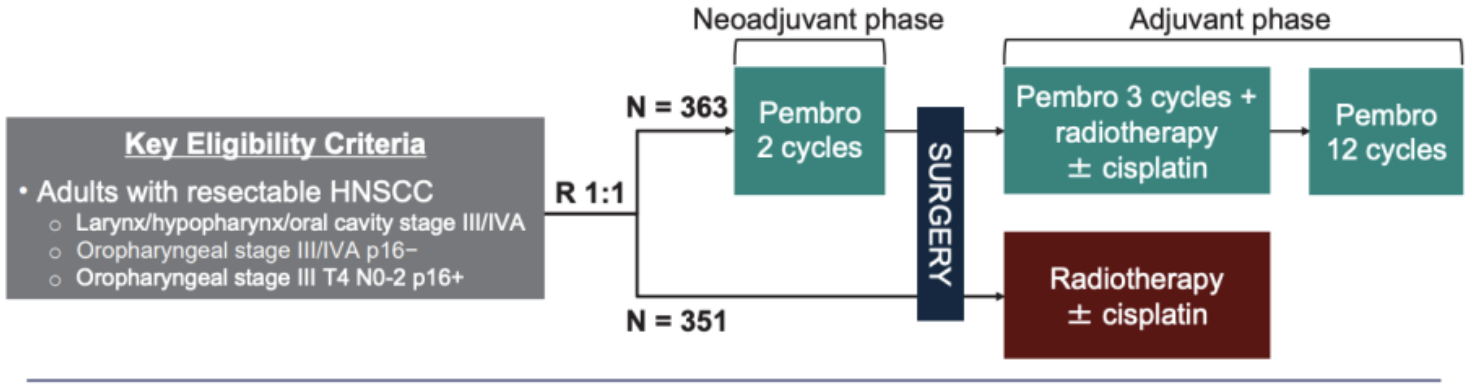
From: **Neoadjuvant and Adjuvant Pembrolizumab in Resectable Locally Advanced, Human Papillomavirus–Unrelated Head and Neck Cancer: A Multicenter, Phase II Trial**



Uppaluri R et al. 2020. CCR

Wise-Draper et al. 2022. CCR

KEYNOTE-689 Study Schema



Primary endpoint: Event Free Survival

Key secondary endpoints: Major pathological response and Overall Survival

Other secondary endpoints include: Safety

Figure 2

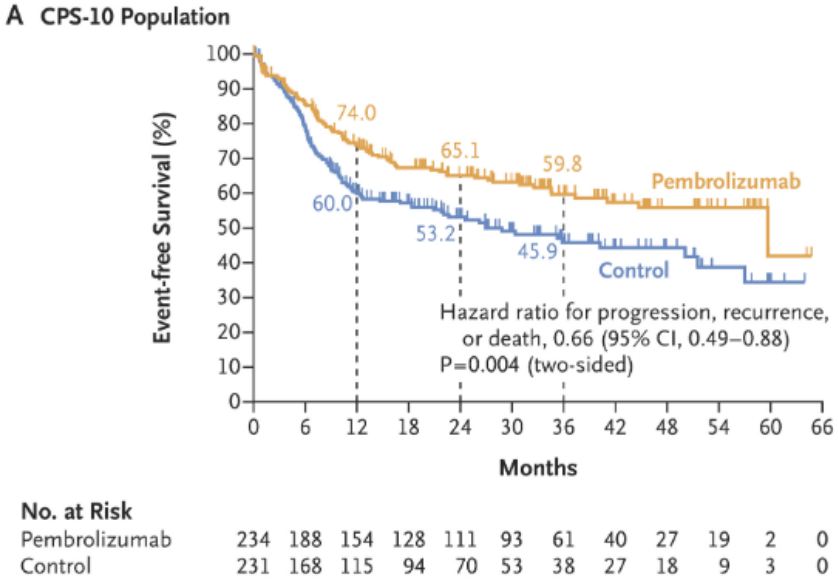
Who was included?

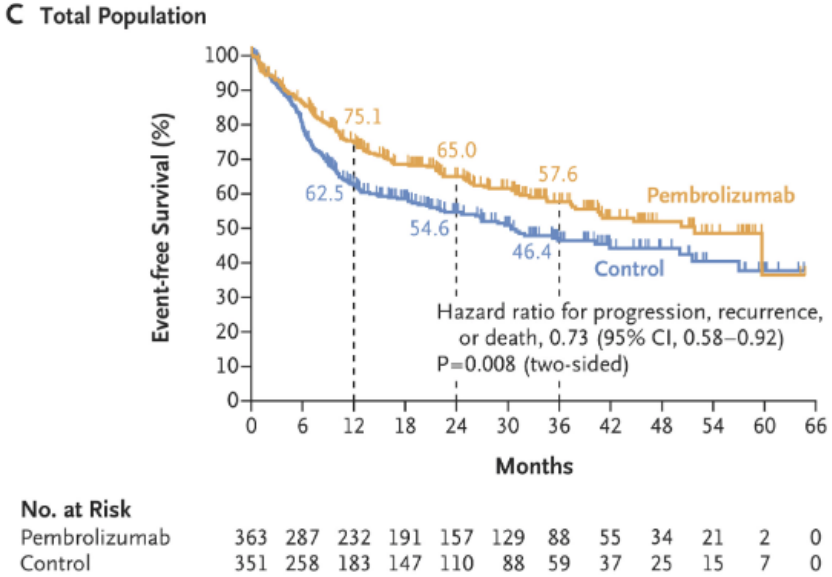
Characteristic	Pembrolizumab (N=363)	Control (N=351)
Median age (range) — yr	60.0 (29–82)	61.0 (22–87)
Male sex — no. (%)	286 (78.8)	277 (78.9)
ECOG performance-status score of 0 — no. (%)†	199 (54.8)	209 (59.5)
Primary tumor site — no. (%)		
Hypopharynx	28 (7.7)	26 (7.4)
Larynx	81 (22.3)	73 (20.8)
Oral cavity	219 (60.3)	213 (60.7)
Oropharynx	35 (9.6)	38 (10.8)
Missing	0	1 (0.3)
HPV status — no. (%)§		
Positive	12 (3.3)	15 (4.3)
Negative	351 (96.7)	335 (95.4)

Who was included?

Characteristic	Pembrolizumab (N=363)	Control (N=351)
PD-L1 status — no. (%)¶		
TPS ≥50%	103 (28.4)	107 (30.5)
CPS ≥10	234 (64.5)	231 (65.8)
CPS ≥1	347 (95.6)	335 (95.4)
CPS <1	13 (3.6)	14 (4.0)
Missing CPS	3 (0.8)	2 (0.6)
Current or former smoker — no. (%)		
Yes	293 (80.7)	267 (76.1)
No	64 (17.6)	81 (23.1)

Event free survival

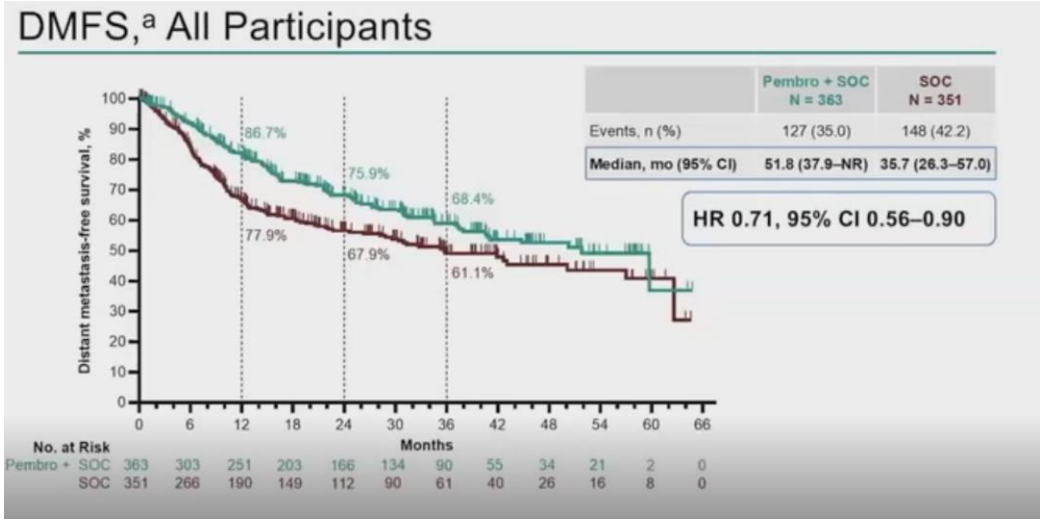




Mainly reduction in distant mets

	Pembro + SOC (N = 234)	SOC (N = 231)
Events, n (%)	85 (36.3)	107 (46.3)
Death	43 (18.4)	37 (16.0)
Distant PD	15 (6.4)	39 (16.9)
Local + distant PD	2 (0.9)	2 (0.9)
Local PD/recurrence	25 (10.7)	29 (12.6)
Median, mo (95% CI)	**59.7 (41.1–NR)**	**26.9 (18.3–51.5)**

HR 0.66, 95% CI 0.49–0.88, *P*=.0022*



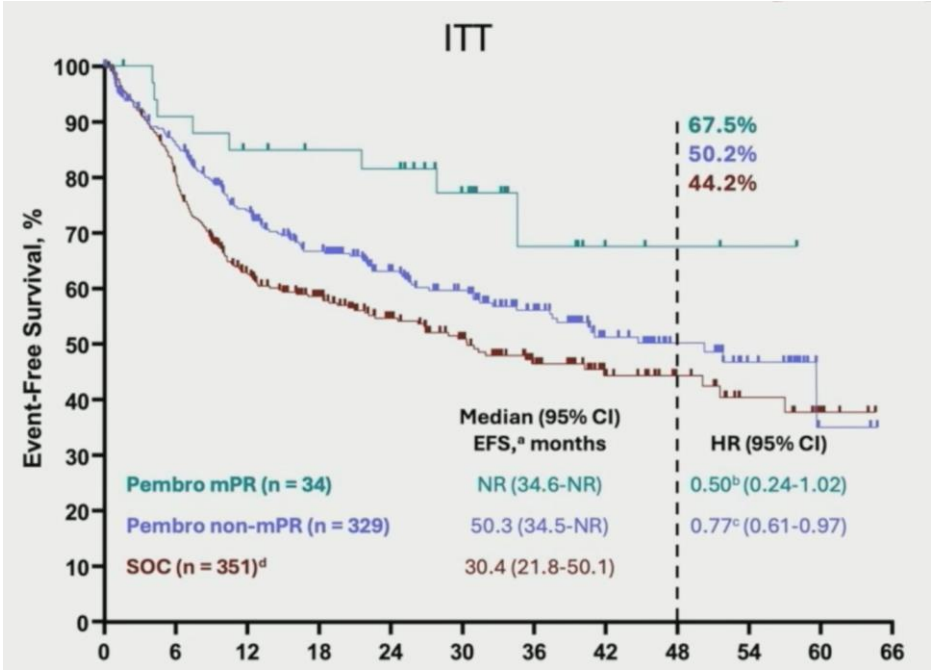
Limited pathologic responses

Pathological Response

	CPS ≥10 Population		CPS ≥1 Population		All Participants	
	Pembro + SOC n = 234	SOC n = 231	Pembro + SOC n = 347	SOC n = 335	Pembro + SOC N = 363	SOC N = 351
mPR, n (%)	32 (13.7)	0	34 (9.8)	0	34 (9.4)	0
Estimated difference (95% CI)	13.7 (9.7–18.7)		9.8 (7.0–13.3)		9.3 (6.7–12.8)	
P value	<0.00001*		<0.00001*		<0.00001*	
pCR, n (%)	10 (4.3)	0	11 (3.2)	0	11 (3.0)	0
Estimated difference (95% CI)	4.2 (2.1–7.6)		3.1 (1.6–5.6)		3.0 (1.5–5.3)	

mPR (≤10% residual invasive SCC) and pCR evaluated by **blinded** independent pathologist review.

But major pathologic response was associated with improved outcomes



Reasons for Surgery Not Performed

ITT Population

	Pembro + SOC (N = 363)	SOC (N = 351)
Surgery status, n (%)		
Participants who underwent surgery	322 (88.7)	308 (87.7)
Participants who did not undergo surgery	41 (11.3)	43 (12.3)
Reasons for surgery not performed, n (%)		
Randomized not treated[a]	3 (0.8)	35 (10.0)
Discontinued treatment prior to surgery	30 (8.3)	0
Progressive disease	15 (4.1)	0
Withdrawal by participant	7 (1.9)	0
Adverse event	4 (1.1)	0
Physician decision	2 (0.6)	0
Lost to follow-up	1 (0.3)	0
Non-study anticancer therapy	1 (0.3)	0
Definitive (chemo)radiotherapy without surgery	8 (2.2)	8 (2.3)
Withdrawal by participant	3 (0.8)	5 (1.4)
Physician decision	2 (0.6)	2 (0.6)
Tumor found to be surgically unresectable	2 (0.6)	0
Adverse event	1 (0.3)	1 (0.3)

Progression in clinical trial

- If surgery was able to be performed, an “event” was not reported
- There was progression in many patients, but they were still able to proceed to surgery

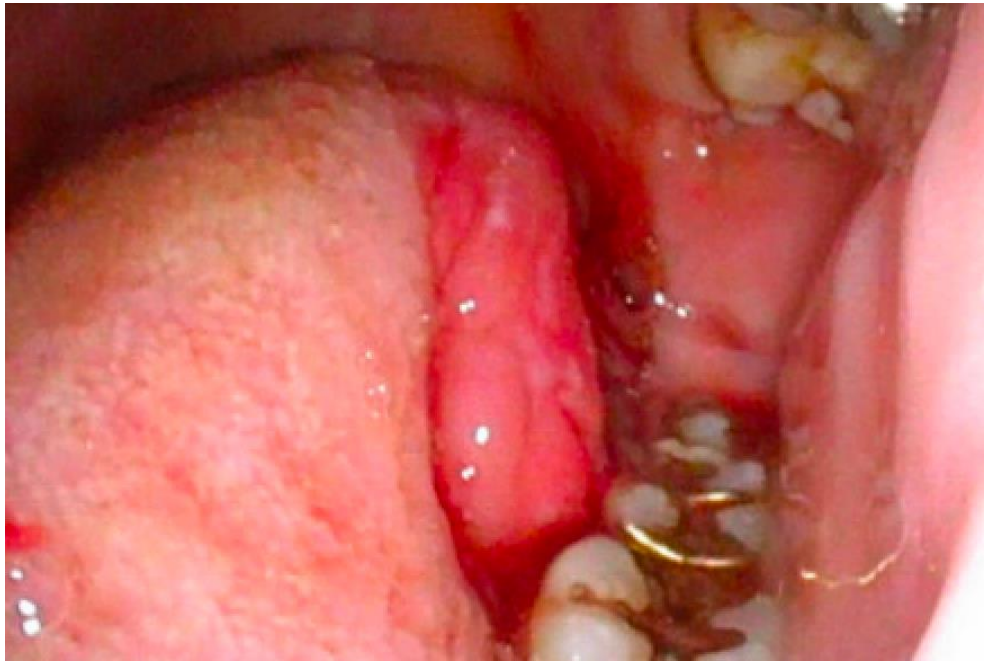
Table S2B. Reasons for Study Treatment Discontinuation Prior to the Adjuvant Phase, All Randomized Participants Who Did Not Receive Adjuvant Therapy.

Reason	Pembrolizumab N = 88	Control N = 76
Randomized, not treated	3 (3.4)	35 (46.1)
Adverse event	13 (14.8)	11 (14.5)
Associated with COVID-19	1 (1.1)	0
Clinical progression	2 (2.3)	1 (1.3)
Lost to follow-up	1 (1.1)	0
Noncompliance with study drug	1 (1.1)	2 (2.6)
Nonstudy anticancer therapy	2 (2.3)	1 (1.3)
Physician decision	8 (9.1)	9 (11.8)
Associated with COVID-19	1 (1.1)	0
Progressive disease	43 (48.9)	7 (9.2)
Withdrawal by participant	15 (17.0)	10 (13.2)

Data are n (%).

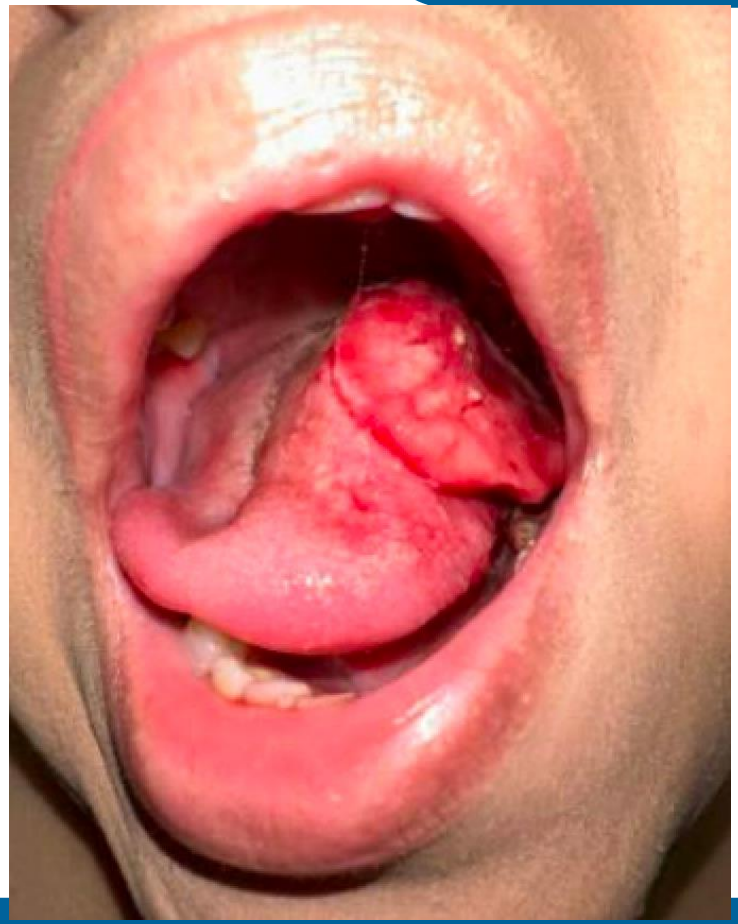
37 year old female

- Presents with oral tongue tumor
- Biopsy shows Squamous Cell Carcinoma
- Clinically positive nodes in level IB
- Imaging confirms no distant mets
- Stage T3N2bM0, Stage IV
- Next step in management?



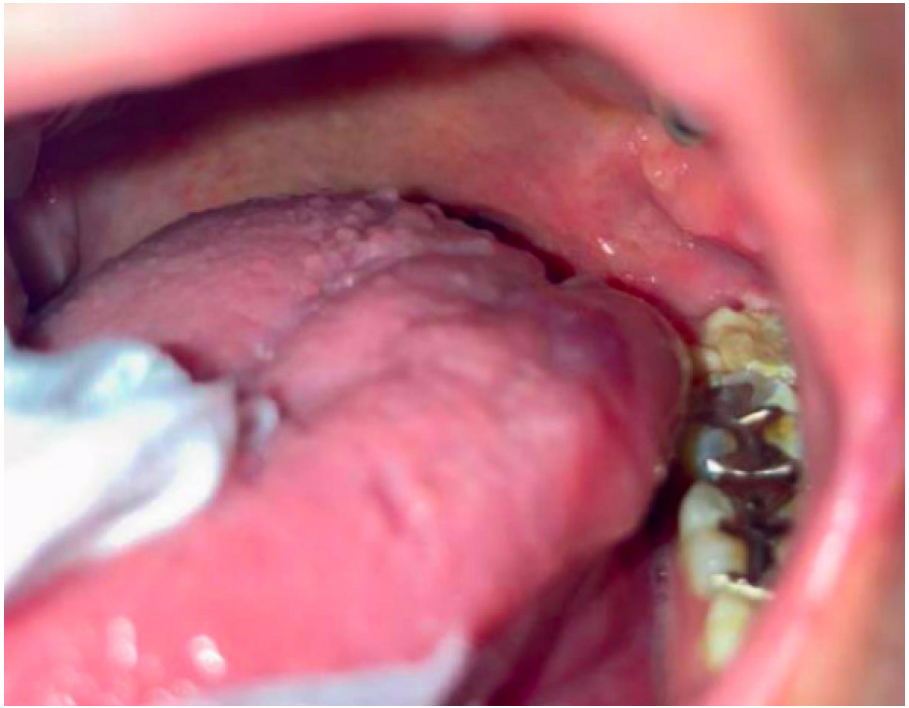
Neoadjuvant immunotherapy?

- Need CPS score
- Repeat biopsy was performed to obtain
- Insurance approved with outside medical oncologist
- After one cycle…



Added chemo

- Chemotherapy was added to immunotherapy for additional cyto reduction
- Had an excellent response
- Proceeded to surgery: Hemiglossectomy, neck dissection, ALT free flap reconstruction
- Path still showed deep invasion (DOI 24 mm, +PNI, +LVI, WPOI 5)



Neoadjuvant work-flow

RAD ONC

MED ONC

SURG ONC

Meet with radiation oncology before surgery

Stat consult to medical oncology

Once infusions are arranged, surgery date is identified

Add chemotherapy to second cycle if progression

Radiation simulation scheduled to start adjuvant within 6 weeks

Repeat biopsy on presentation for CPS

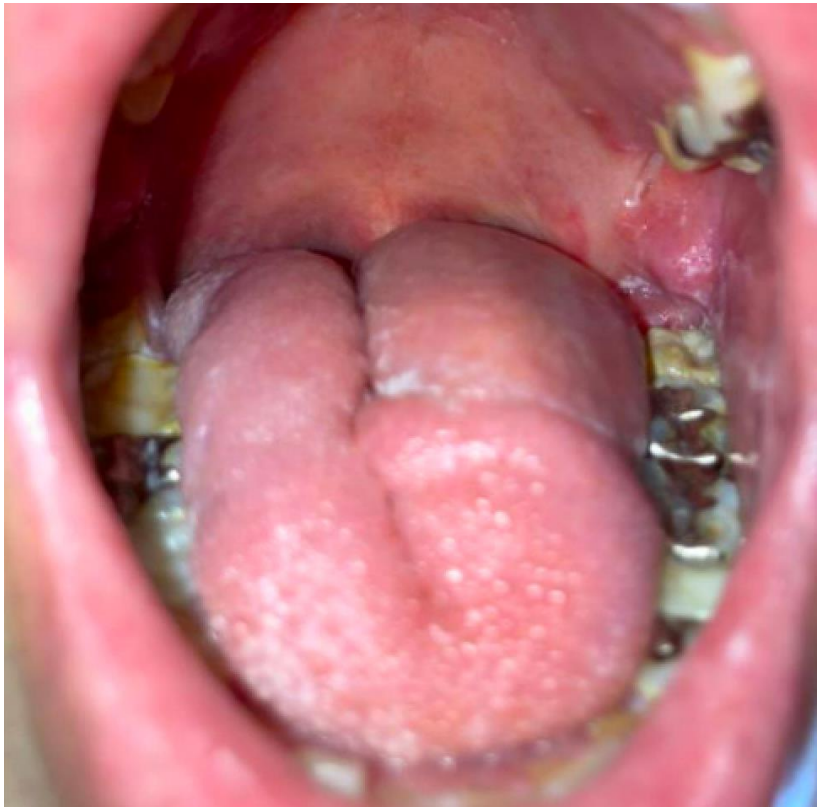
If CPS neg, straight to surgery

Planned interval imaging + Re-examination by surgeon before second cycle

Pathology reviewed to confirm adjuvant treatment plan

Communication!

- Between med oncology and surgical oncology
  - Immediate identification of candidates
  - Infusion and surgical dates
- Biopsy tissue analysis
- CLOSE FOLLOW UP!
- Radiation ready for adjuvant therapy



Anti-PD1 + chemo

- Adding chemotherapy can result in deep pathologic responses

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Neoadjuvant Nivolumab plus Carboplatin and Paclitaxel in Patients with Locally Advanced Resectable Squamous Cell Carcinoma of the Head and Neck: A Phase II, Single-Arm Trial

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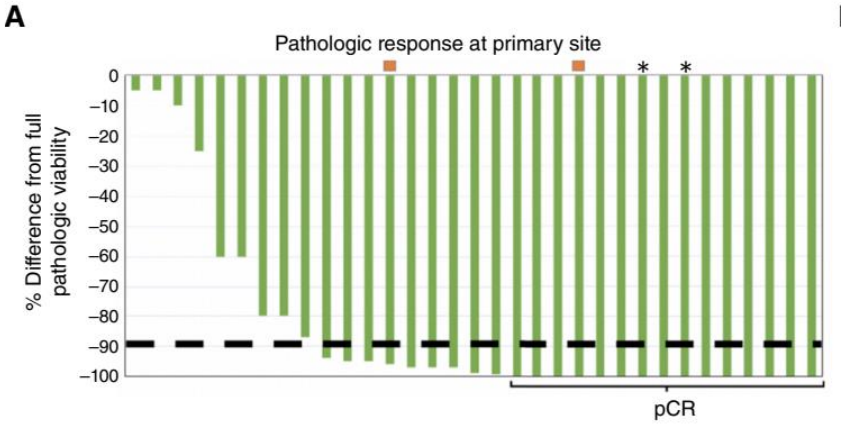

Anti-PD1 + chemo

- Adding chemotherapy can result in deep pathologic responses
- But those with pCR should still receive adjuvant treatment

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

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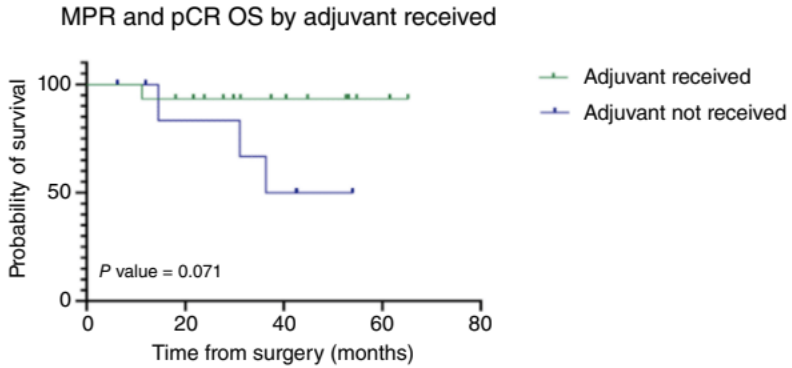
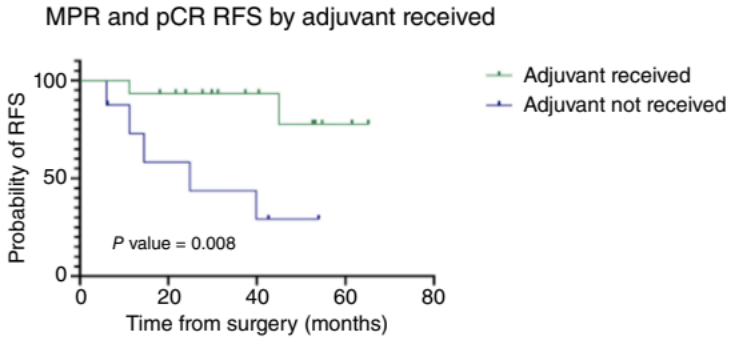




What's coming in the future?

- Anti-PD-1 + X for neoadjuvant treatment
  - Anti-PD-1 + focused radiation
  - Anti-PD-1 + chemotherapy
  - ICI combinations
  - Anti-PD-1 + bispecific antibody (Amivantanab)

SBRT + anti-PD-1 combination mediates tumor regression when either therapy alone is ineffective

Cancer Cell *43*, 757–775, April 14, 2025

Neoadjuvant and adjuvant amivantamab plus pembrolizumab in resectable, locally advanced HPV-unrelated head and neck squamous cell cancer: *Cohort 6 of the phase 1b/2 OrigAMI-4 study*

Skin cancer

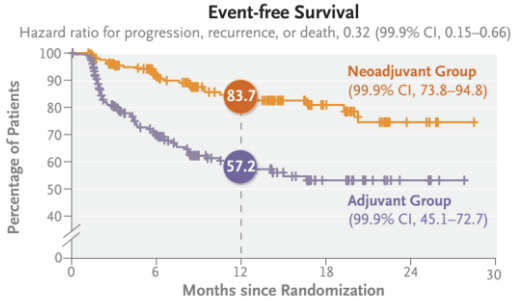
- **NRG-014** –neoadjuvant cemiplimab with Response adapted surgery and Response adapted adjuvant therapy
  - For cutaneous SCC
- **Melanoma**
  - Neoadjuvant/adjuvant pembro
  - Neoadjuvant IPI/NIVO

NRG-HN014

Open to Accrual

ARM 1
Standard of care surgery
↓
Adjuvant radiation (as indicated)

ARM 2
Neoadjuvant cemiplimab (REGN2810) q3 wks x 4 doses
↓
Response-adapted oncologic surgery
↓
Adjuvant radiation (as indicated)
↓
Adjuvant cemiplimab (REGN2810) q6 wks x 4 doses



Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma

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Thank you!