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MOORES CANCER CENTER

Managing Oropharynx Cancer: Opportunities for De-escalation

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NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

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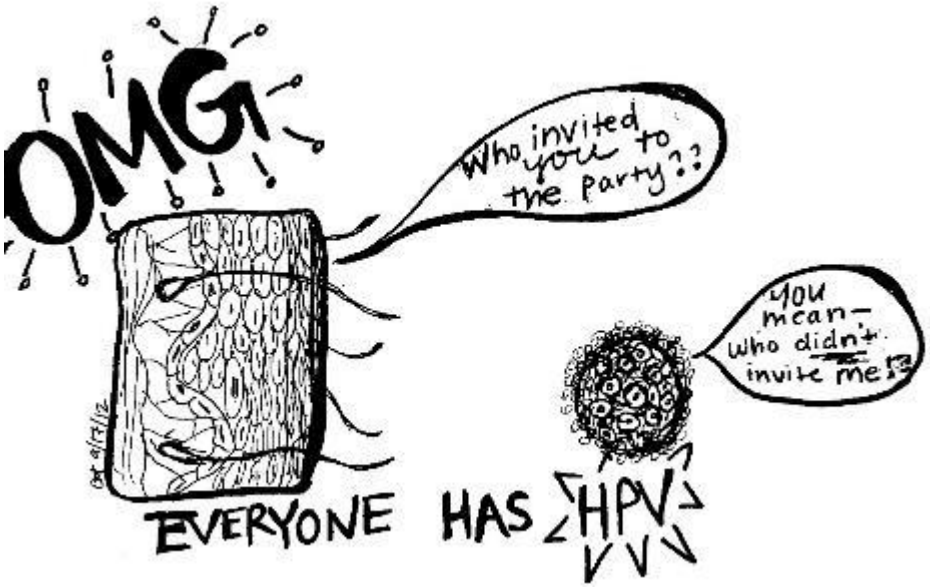
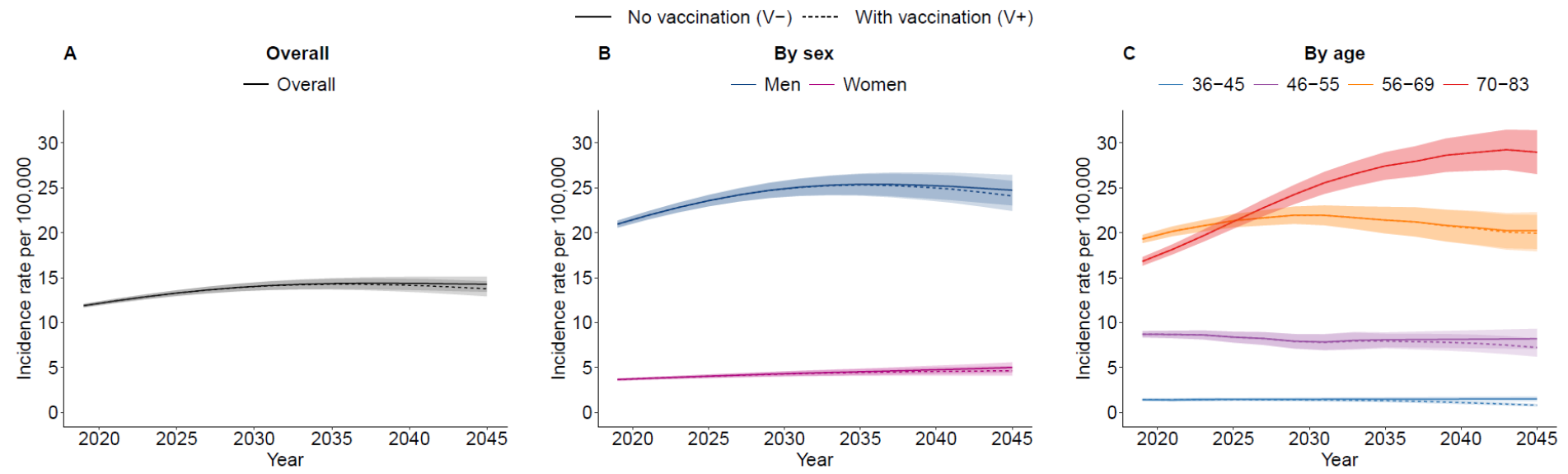
Oropharynx Cancer Causes

- Mainly squamous cell carcinoma due to two major factors
  - Smoking and alcohol related, long term exposure
  - HPV (Human papilloma virus) related in the throat, most people are exposed in their teens and 20s
  - Other rare or unknown causes



Projected Incidence Rate of Oropharynx Cancer in the US

Zhang et al, JAMA Oncology 2021



	2018–19	2024–25	2034–35	2044–45
Overall: V−	11.9	13.3	14.3	14.3
Overall: V+	11.9	13.3	14.3	13.8

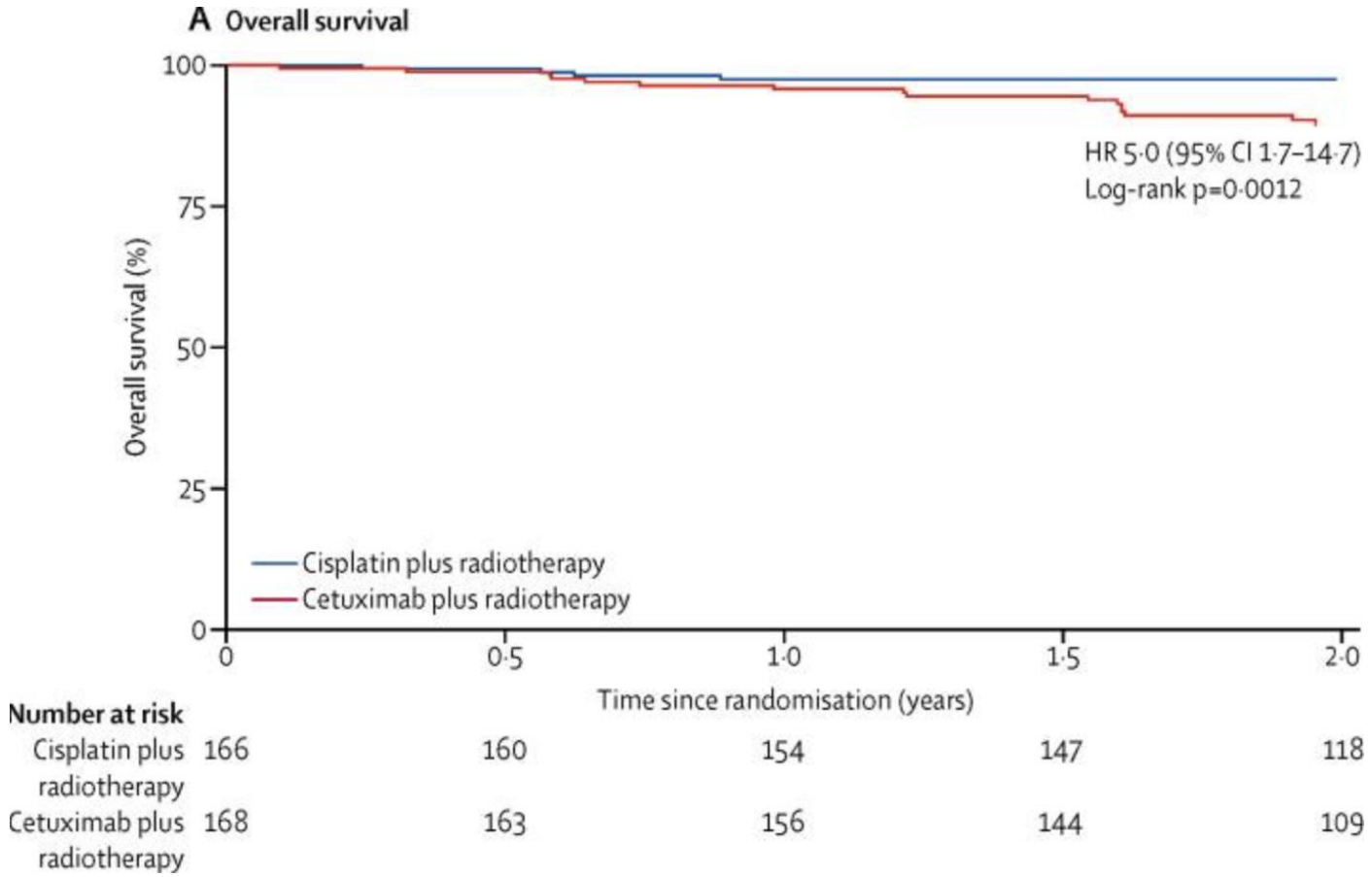
	2018–19	2024–25	2034–35	2044–45
Men: V−	21.0	23.6	25.4	24.7
Men: V+	21.0	23.6	25.3	24.1
Women: V−	3.7	4.0	4.5	5.0
Women: V+	3.7	4.0	4.4	4.6

	2018–19	2024–25	2034–35	2044–45
36–45: V−	1.4	1.5	1.5	1.5
36–45: V+	1.4	1.4	1.3	0.8
46–55: V−	8.7	8.4	8.1	8.2
46–55: V+	8.7	8.4	7.9	7.2

What is the current standard of care for treating previously untreated locally advanced oropharynx cancer?

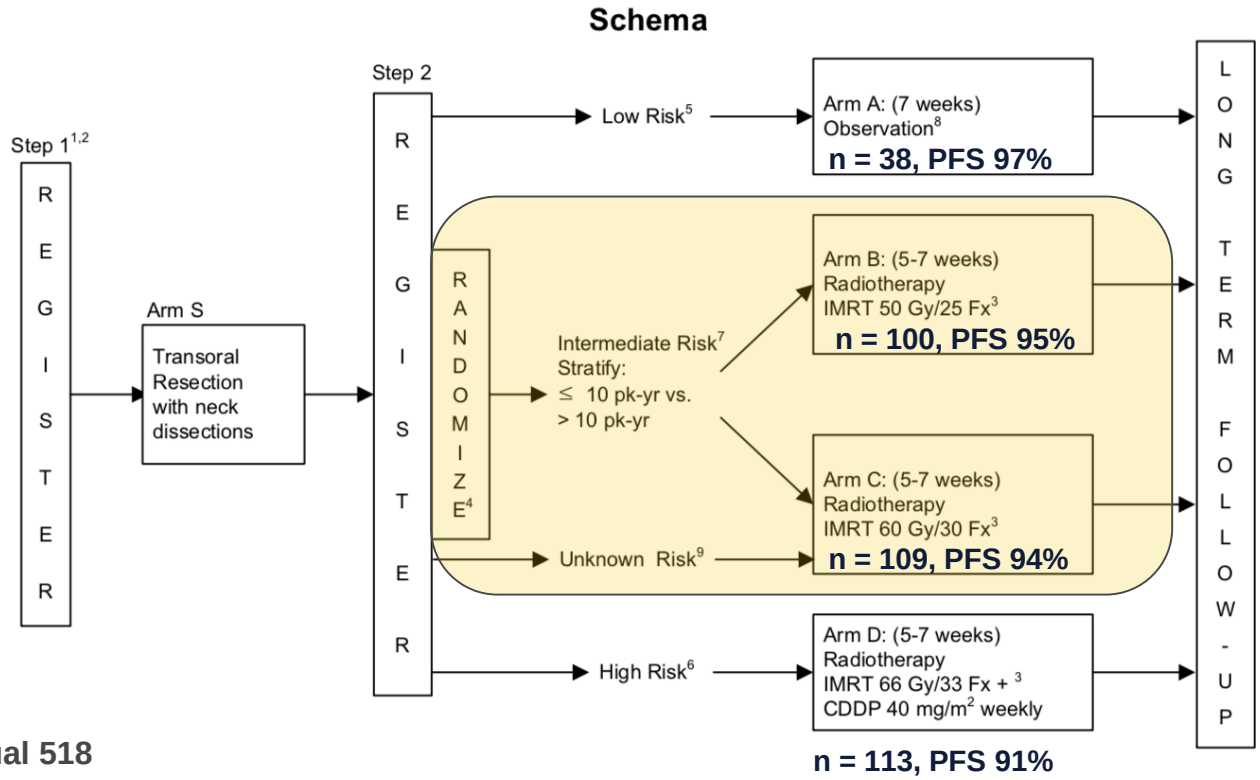
Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial

Mehanna et al., Lancet 2019



ECOG-3311 – Transoral Surgery Followed by Low-Dose or Standard Dose RT for HPV OPSCC Has Excellent Oncologic Outcomes

➢**ECOG-3311 – Transoral Surgery Followed by Low-Dose or Standard Dose RT for HPV OPSCC**



Intermediate Risk:
- "close" (< 3mm) margin(s)
- "**Minimal" (≤ 1mm) ECE**
- 2-4 metastatic lymph nodes
- perineural invasion
- lymphovascular invasion

≤ 1mm ENE: no chemo and randomized to 50 vs 60 Gy

Accrual 518

Eligible patients had AJCC VII Stage III-IVa T1-2 p16+ squamous cell carcinoma of the oropharynx amenable to transoral resection, with no matted nodes, and were candidates for radiation and cisplatin

Ferris et al. JCO 2022

Treatment for Oropharynx Early Stage Cancers (T1-2N0-1M0) (single metastatic node –ENE)

Single Modality Therapy

- Primary excision with staging neck dissection (single node with no extranodal extension/ENE)

  OR

- Radiotherapy

- Contralateral staging neck dissection/RT based on laterality of primary tumor

Intermediate Risk HPV+ Oropharynx disease

Multimodality Therapy with Potential De-escalation

- **Concurrent chemotherapy (cisplatin) and radiation**
- Primary excision + neck dissection/postop RT
  - RT dose reduction (50 Gy) and avoidance of systemic therapyt for intermediate risk (ECOG 3311) potential de-escalation

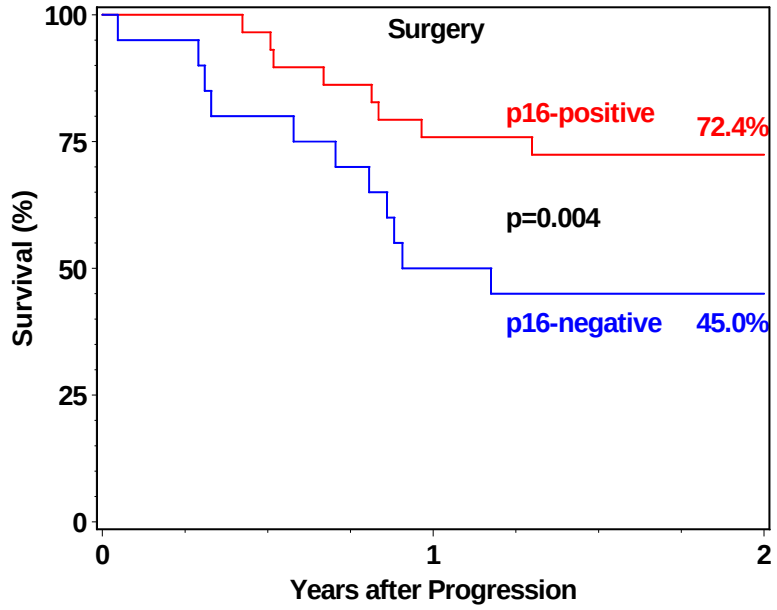
HPV negative Oropharynx Cancer (T1-2N1-2M0)
Multimodality Therapy with Potential Treatment **Intensification**

- Concurrent chemotherapy and radiation
- Consider primary excision +/- neck dissection with postop RT +/- chemotherapy for treatment intensification
  - de Almeida et al JAMA OtoHNS 2015, n=410, age, tobacco, and tumor stage and other adverse histopathologic features did not remain significant on multivariate analysis
  - Small cohorts showing 80-90% OS/DFS for HPV- TORS patients treated with multimodality therapy

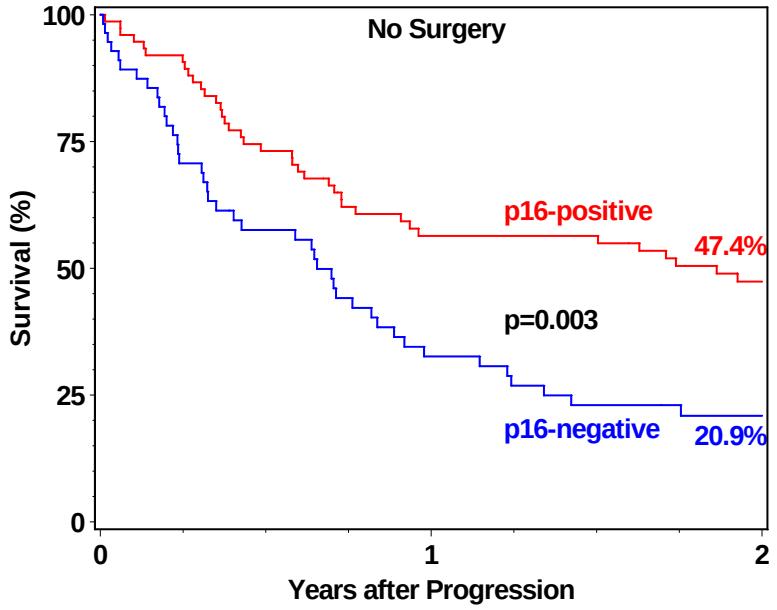
Late Stage (T3-4 or N2+) Oropharynx disease
Multimodality Therapy

- Concurrent chemotherapy and radiation
- Primary excision +/- neck dissection/postop RT for selected (T1-2) HPV negative
  - Concurrent cisplatinum for Extranodal Extension (ENE), positive margins (Bernier et al., Cooper et al. NEJM 2004)
- Induction chemotherapy and radiation (Vermorken NEJM 2007)+/- concurrent chemotherapy
- **Clinical trial enrollment**

Surgical salvage improves survival after recurrence of OPSCC



No. at Risk			
p16-positive	29	22	21
p16-negative	20	10	9



No. at Risk			
p16-positive	76	39	30
p16-negative	56	17	10

Fakhry et al. JCO 2014

Head and Neck Cancer Care is a Team Sport

- Team Approach associated with **improved survival**
  - Lewis et al., Head and Neck, MDACC
  - Liao et al., Head and Neck, 2016, Taiwan

- Head and Neck Surgery
- Radiation Oncology
- Medical Oncology
- Plastic/Reconstructive Surgery
- Speech Language Pathology
- Dental, OMF prosthodontics
- Nursing
- Patient Navigator

- Dietary/Nutrition
- Lymphedema therapy
- Physical Therapy
- Occupational Therapy
- Social Work
- Psychiatry
- Pain/Palliative Medicine

Why try to improve outcomes for oropharynx cancer if survival is so good with current standard therapy?

- In RTOG 0522, grade 3-4 late toxicity rates were 57.4% in RT cisplatin arm
  - Caudell et al Int J Rad Onc Biophys 2022

Immunotherapy: a Long History in the Making

1890s
1st CA vaccine developed (Coley)

1973
Discovery dendritic c
(Steinman)

William Coley and the birth of cancer immunotherapy

New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York. It came out yester-

CE PHASE
IOW

ine)

2011
1st checkpoint inhibitor approved for CA

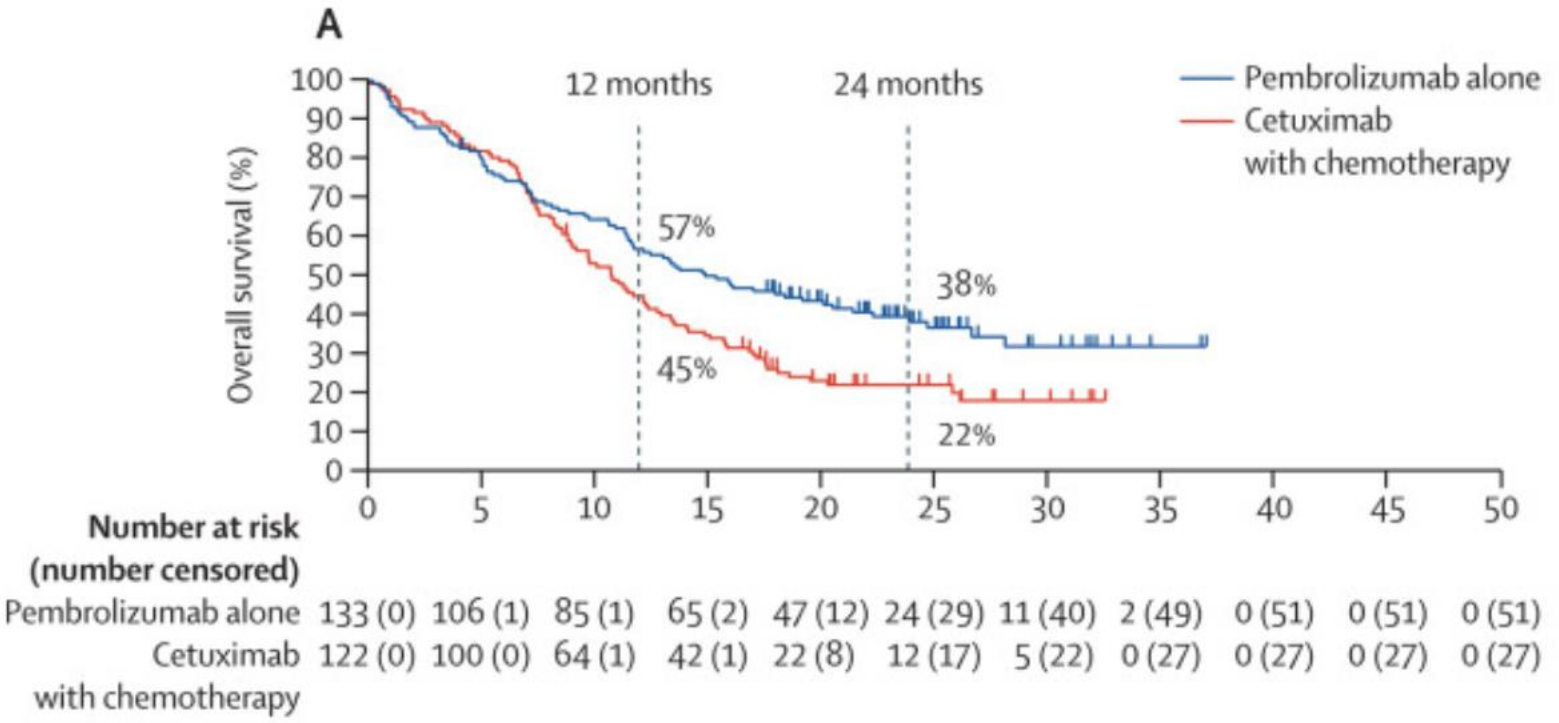
2010
1st cellular immunotherapy approved for CA

Lesterhuls WJ. *J Clin Oncol*. 2008

Elie Metchnikoff & Paul Ehrlich won the Nobel Prize 3 months later

Pembrolizumab as first line therapy for recurrent metastatic HNSCC

Burtness et al. Lancet 2019



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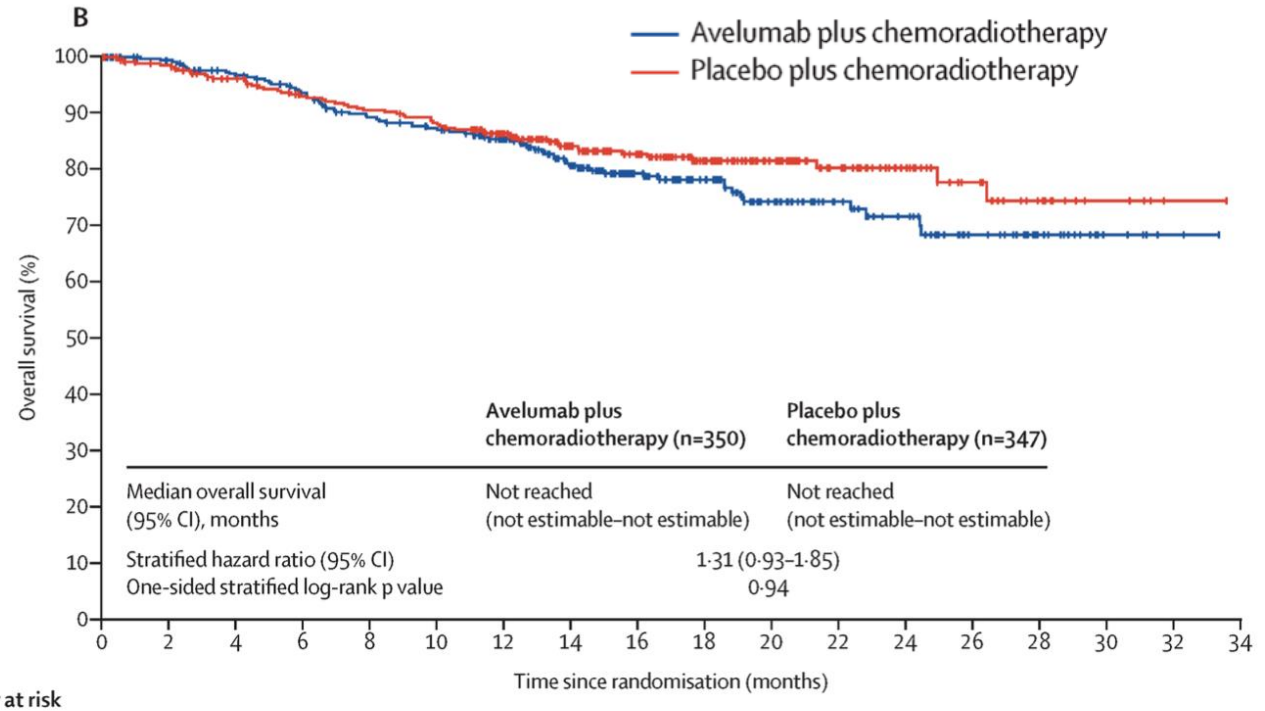
JAVELIN: PD-1 inhibition does not work concurrently with chemoradiation

Lee et al. Lancet Oncology 2021



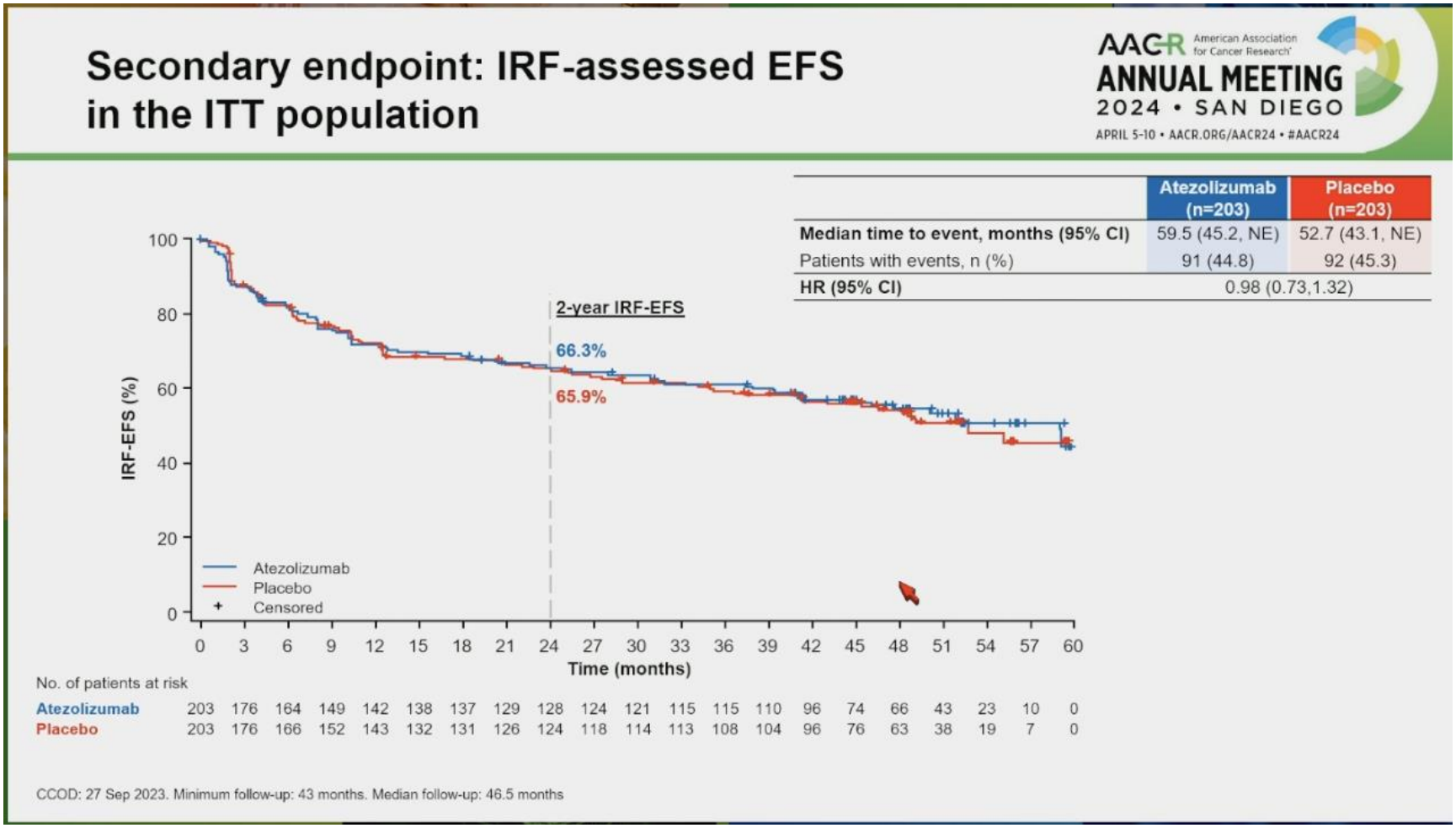
Number at risk (number censored)

Avelumab plus chemoradiotherapy	350 (0)	336 (12)	319 (20)	303 (26)	284 (31)	273 (36)	244 (59)	190 (101)	148 (140)	118 (168)	82 (199)	59 (222)	47 (232)	29 (248)	18 (259)	6 (271)	2 (275)	0 (277)
Placebo plus chemoradiotherapy	347 (0)	334 (8)	315 (19)	298 (26)	290 (26)	282 (27)	252 (51)	193 (104)	160 (134)	115 (177)	86 (206)	58 (233)	39 (252)	26 (264)	13 (276)	5 (284)	1 (288)	0 (289)

JAVELIN enrolled 697 patients with previously untreated locally advanced Stage III/IV SCC of the oropharynx, hypopharynx, larynx, or oral cavity who were eligible for definitive radiation and chemotherapy with curative intent. [7] 350 patients were assigned to receive avelumab at 10 mg/kg i.v. every two weeks plus cisplatin at 100 mg/m^2 every three weeks plus standard fractionation of 70 Gy in 35 fractions over 7 weeks and 347 patients were assigned to receive placebo plus the same radiation/cisplatin backbone.

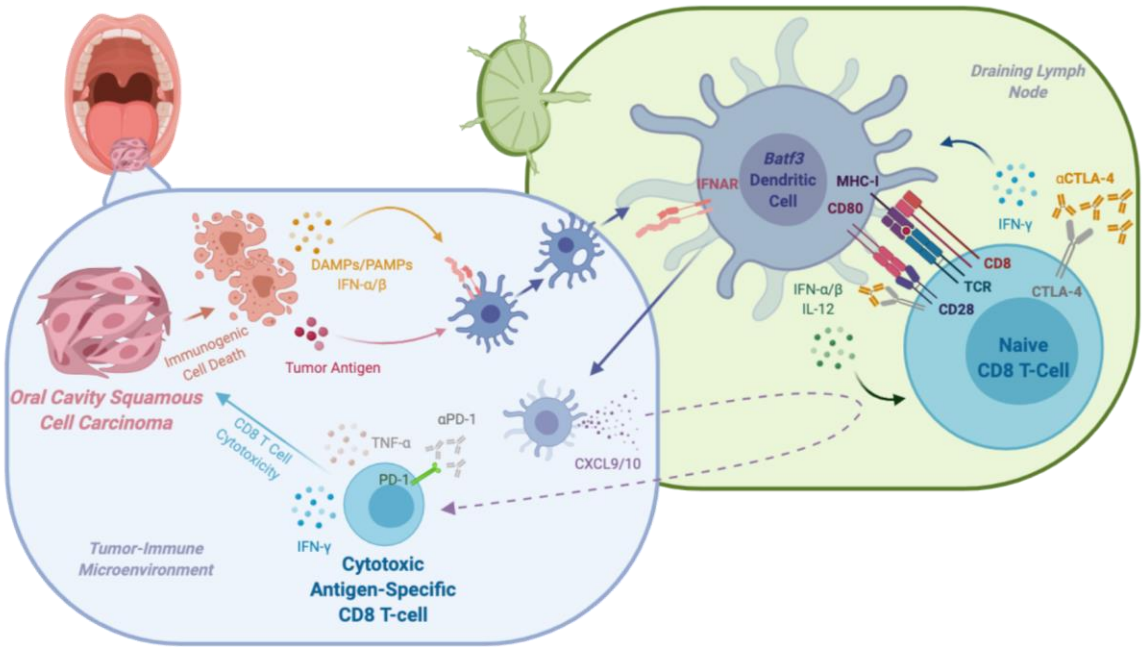
IMvoke010: PD-1 inhibition does not work concurrently with chemoradiation

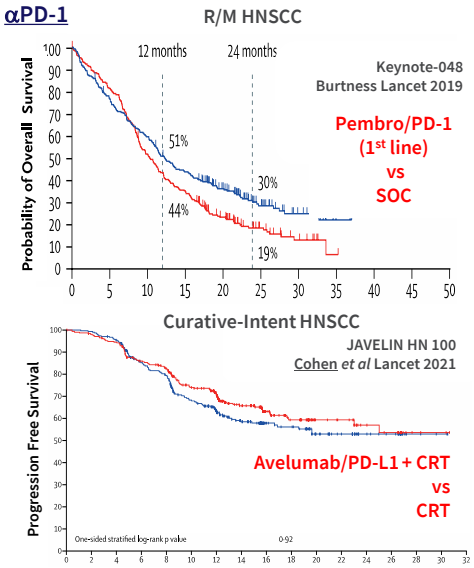
Lee et al. Lancet Oncology 2021



Immunologic View of Draining Lymphatics in HNSCC

Tumor Draining Lymphatics are Central to Coordinating Antitumor Immunity





What role do tumor draining lymphatics play in antitumor immunity?

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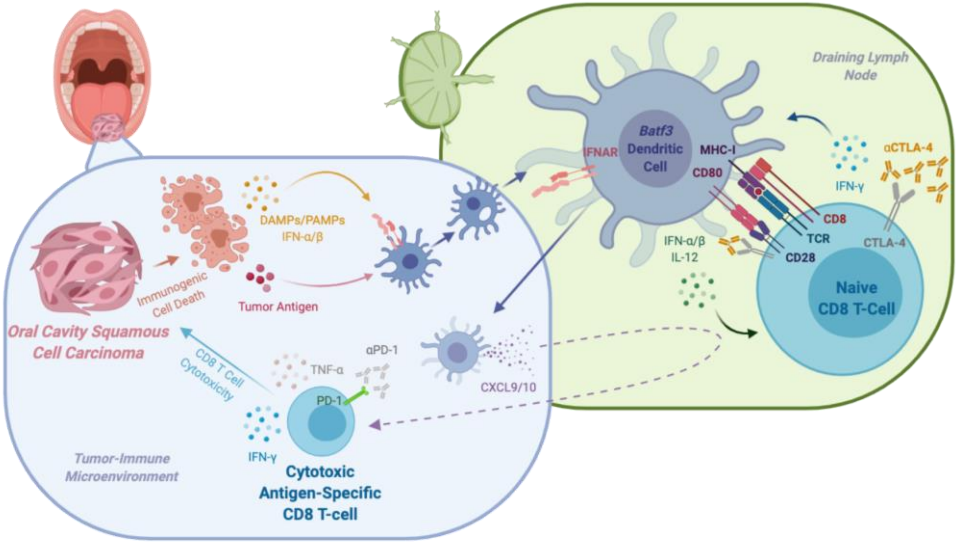
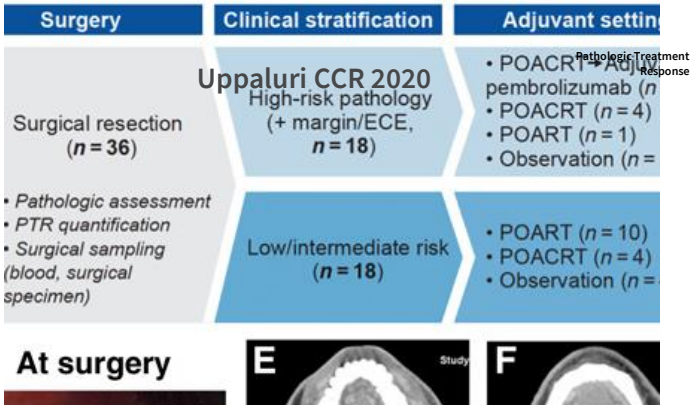
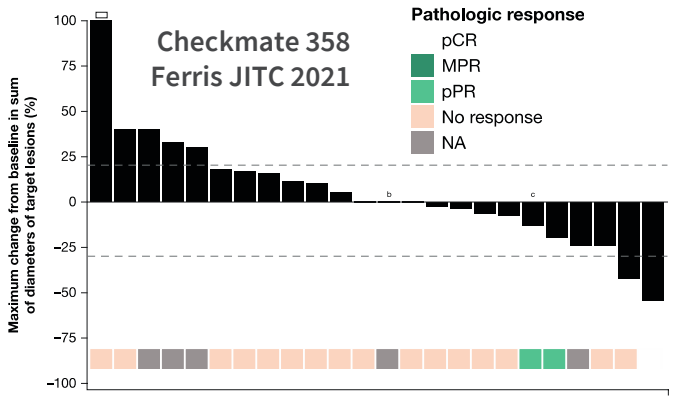
Immunologic Perspective of the Cancer Patient: Neoadjuvant anti-PD-1 immune therapy alone has modest effect in local disease



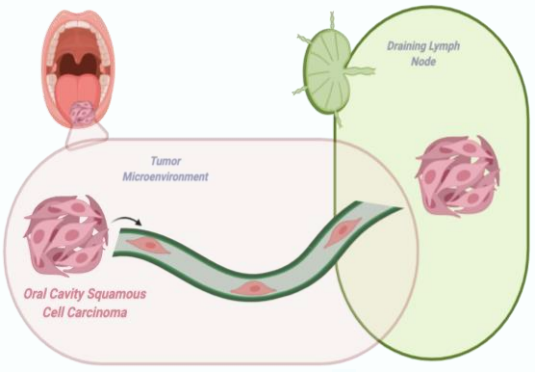




What role do tumor draining lymphatics play in antitumor immunity?

UC San Diego Health

Why is immune therapy more effective in the recurrent/metastatic setting?



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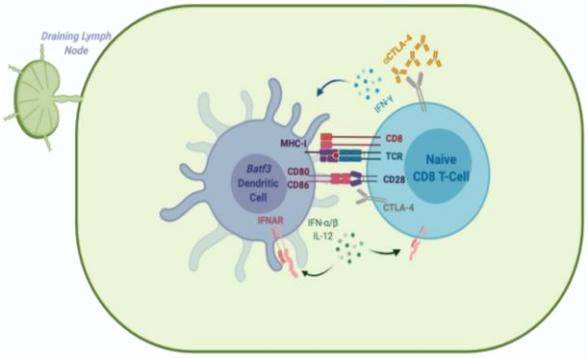


How can we explain the limited response of PD-1 monotherapy in the curative-intent setting?

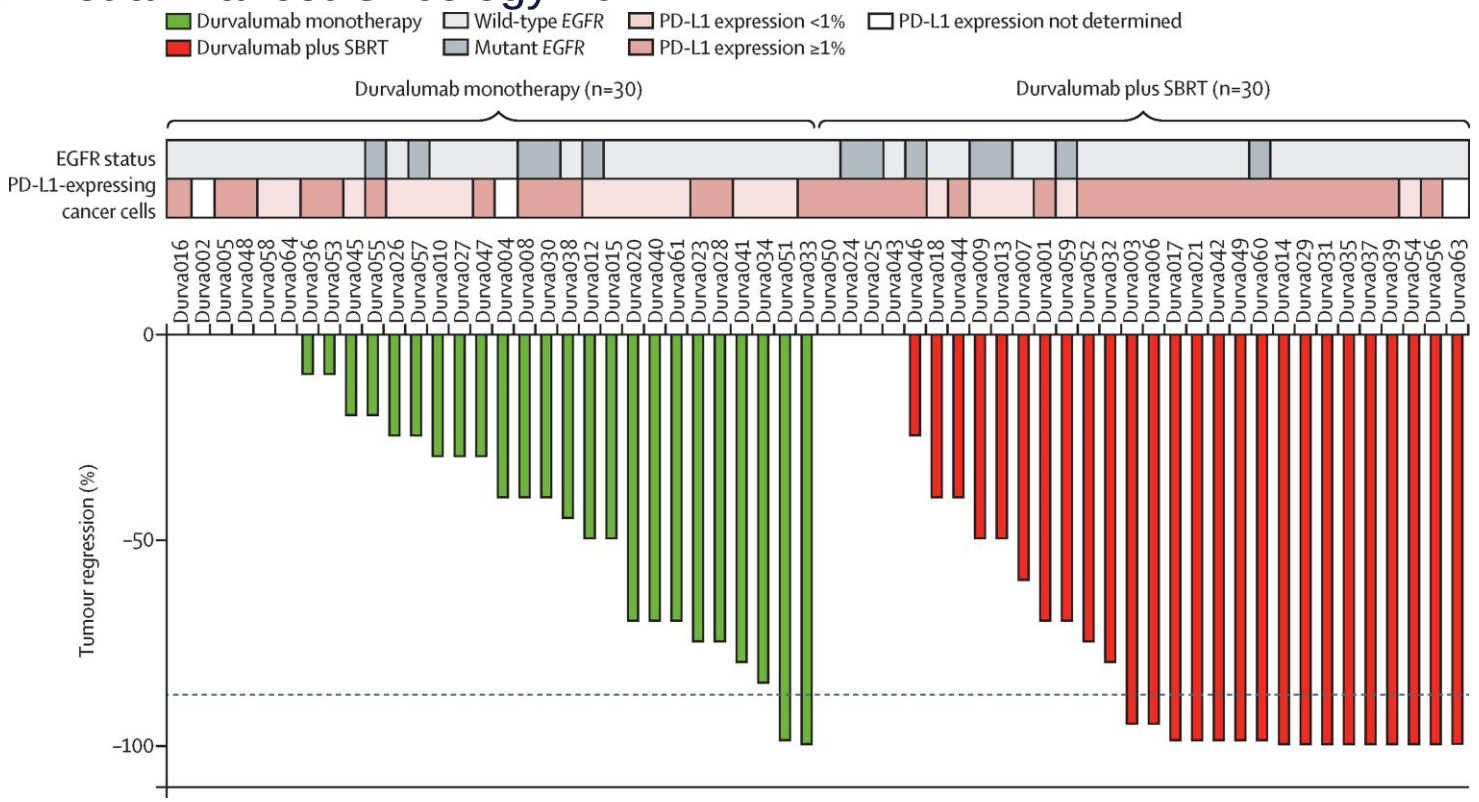
How can we reconcile the clinical benefit of lymphatic ablation with the destruction of an indispensable immune organ?

Hypothesis: Intact lymph nodes are key to promoting antitumor immunity by enhancing immunosurveillance along the tumor-immune-lymphatic axis and reversing the suppressive tumor immune microenvironment.

Does destroying the draining lymphatics impair locoregional immune response?

Why doesn't the addition of immunotherapy during chemoradiation help? SBRT before immunotherapy in early stage lung cancer enhances response

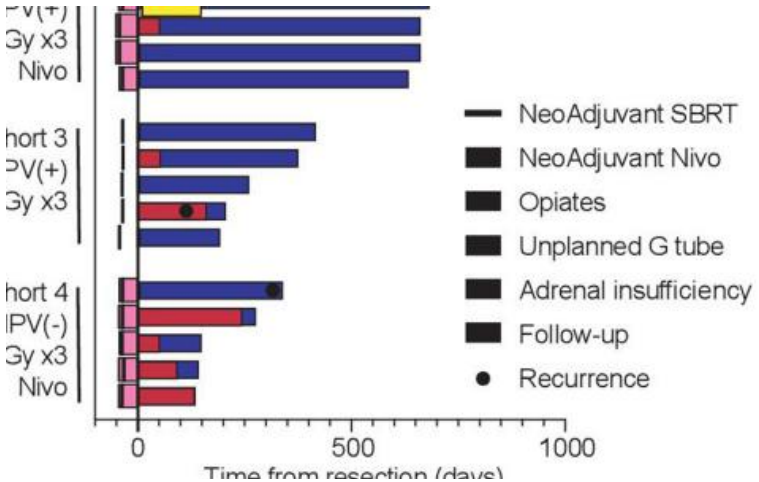
Altorki et al. Lancet Oncology 2021

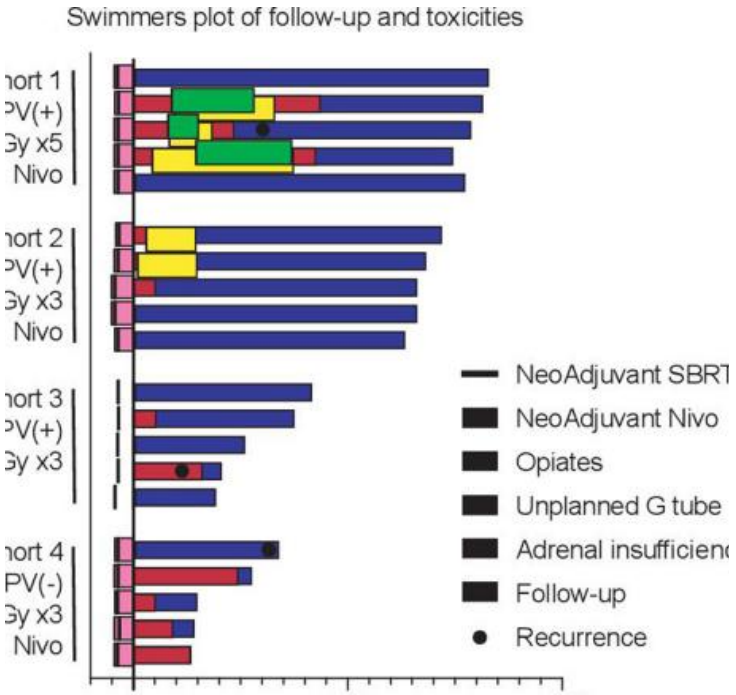


Neoadjuvant immunoradiotherapy has shown significant response in early-stage lung cancer, in which neoadjuvant PD-1 inhibition combined with SBRT resulted in a 53% MPR vs 6% for PD-1 inhibition alone. Quite notably, **this trial administered 8 Gy SBRT prior to immunotherapy**,

Neoadjuvant immunoradiotherapy results in high rate of complete pathological response and clinical to pathological downstaging in locally advanced head and neck squamous cell carcinoma

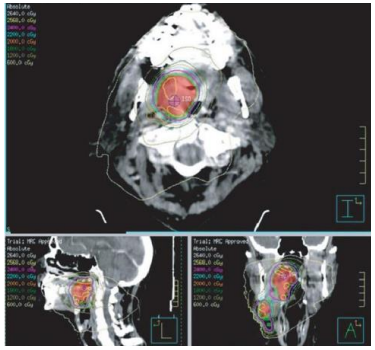
Leidner et al. JITC 2021 Providence





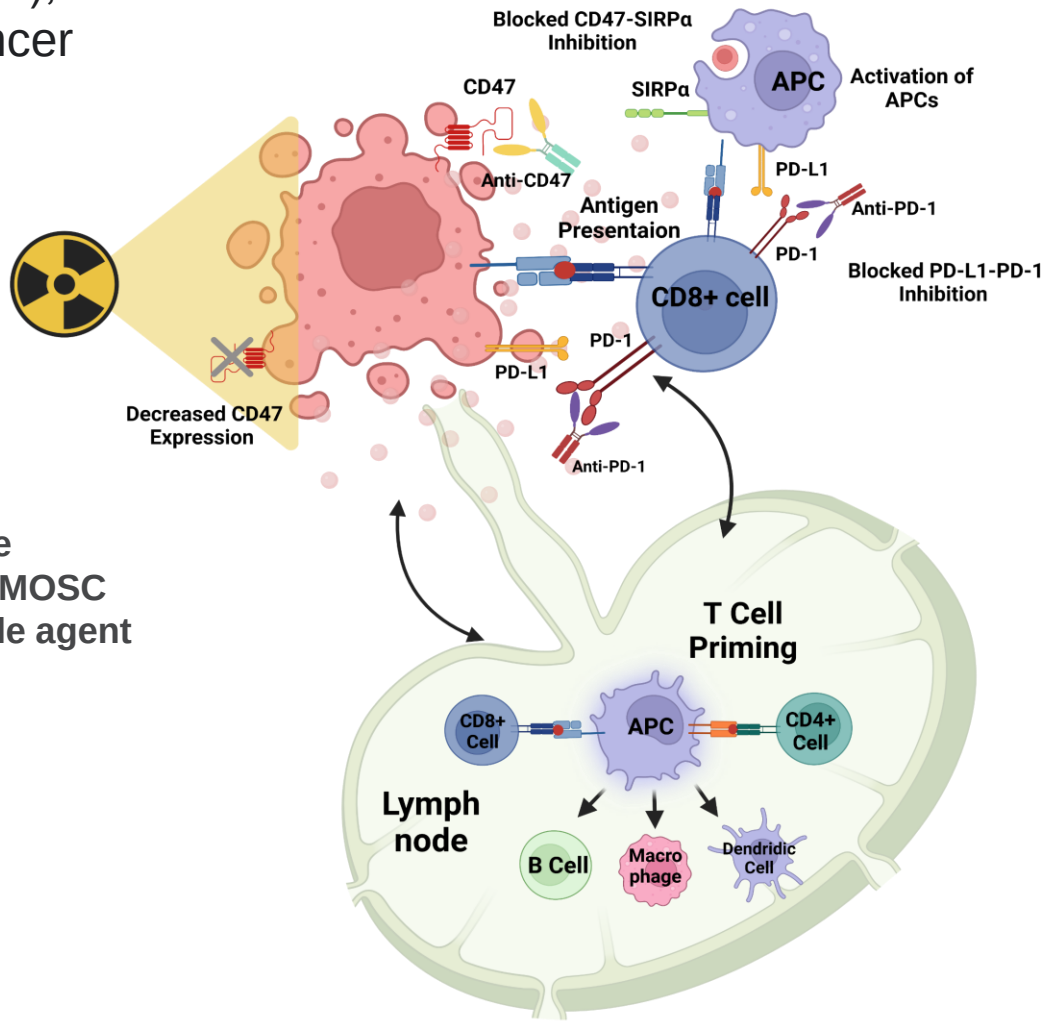
Neoadjuvant immunoradiotherapy (NIRT) – 8Gy x3 or 5 to gross tumor volume (GTV) in the middle of a PD1i sandwich followed by surgery – for untreated, resectable HNSCC:

- **Major pathologic response 86%**
- **Complete pathologic response 67%**
- **Clinical to pathological downstaging 90% of the patients**



Combination Neoadjuvant Immunoradiotherapy using anti-CD47 and PD1i

CD47 forms a signaling complex with signal-regulatory protein α (SIRPα), enabling the escape of these cancer cells from macrophage-mediated phagocytosis



Current Observation:

Evorpacept enhances antitumor immune response in combination with PD-1i in 4MOSC syngeneic HNSCC models and has single agent activity in HPV HNSCC models

Neoadjuvant Immunoradiotherapy with Evorpacept and Pembrolizumab for HPV Mediated Oropharynx Cancer

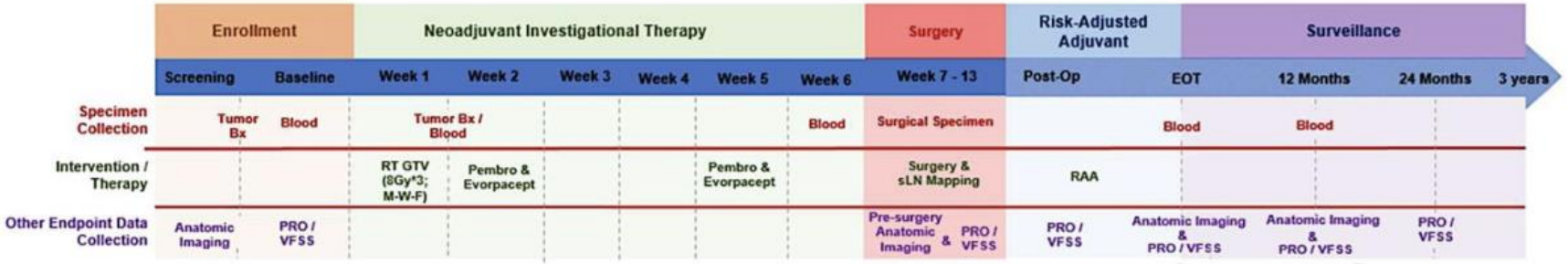
IRB: 806684 | NIRT HPV+ **PI: DR. JOSEPH CALIFANO |CRC: SOLENE POULHAZAN, X21562, PGR: 5470**

KEY INCLUSION	KEY EXCLUSION
• Stage I, T1-2 N1 M0 HPV+ OPSCC amenable to surgical resection (excluding patients with solitary lymph nodes less than 3 cm) • ECOG of 0 or 1	• Prior anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy or with an agent directed to another stimulatory or co-inhibitory T-cell receptor or has received any prior therapy with an anti-CD47 agent or anti-SIRPα agent. • Prior RT to the head and neck region • Patients in whom adjuvant CRT would be recommended regardless of response. • Other malignancy that is progressing or required tx within the past 2 years

STUDY TREATMENT

- **Week 1:** SBRT M-W-F (8 Gy x 3)
- **Week 2:** Pembro + Evorpacept (ALX)
- **Week 5:** Pembro + Evorpacept (ALX)
- **Week 7-13:** Surgery
- **Post-op:** Risk adjusted SOC Adjuvant (if indicated)

STUDY SCHEMA AND CALENDAR:



PI: Califano

Co-I: Sharabi, Cohen, Bell (Providence), Li (OHSU)

UC San Diego Providence OHSU

Phase II trial of Neoadjuvant Immunoradiotherapy for HPV negative HNSCC

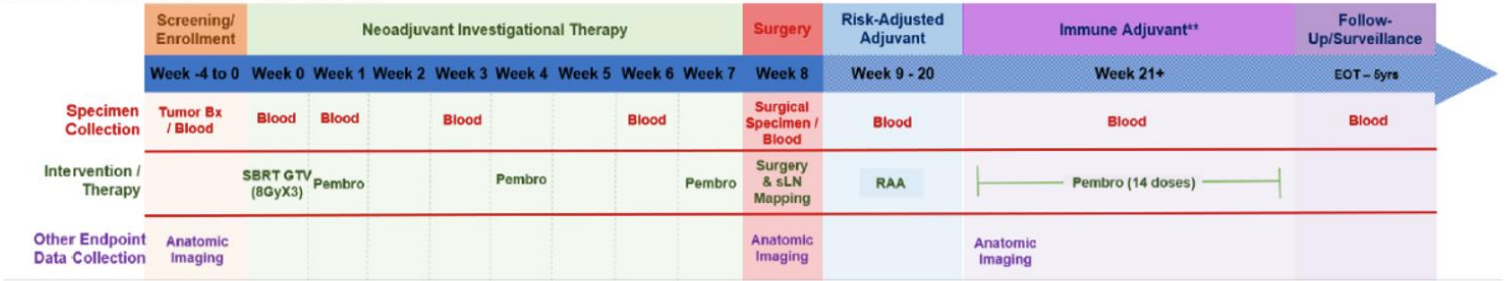
IRB: 805233 | NIRT HPV NEGATIVE **PI: DR. JOSEPH CALIFANO |CRC: SOLENE POULHAZAN, X21562, PGR: 5470**

KEY INCLUSION	KEY EXCLUSION
• Stage III-IVA HPV-negative HNSCC who are planned for surgical resection • Oral cavity, hypopharynx, and larynx cancer do not need HPV • ECOG of 0 or 1	• Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2 agent or stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137). • Prior RT to the head and neck region • Prior systemic anti-cancer therapy within 4 weeks • Other malignancy that is progressing or required tx within the past 2 years

STUDY TREATMENT

- **Week 0: SBRT M-W-F (8 Gy x 3)**
- **Week 1: Pembro**
- **Week 4: Pembro**
- **Week 7: Pembro**
- **Week 8 (must be week 8): Surgery**
- **Week 9-20: Risk Adjusted Adjuvant**
- **Week 21+: Immune Adjuvant 14 doses (if not RAA, immune adjuvant to start Week 12)**

STUDY SCHEMA AND CALENDAR:



Bryan Bell

Providence

UC San Diego

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  - Moores Cancer Center


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