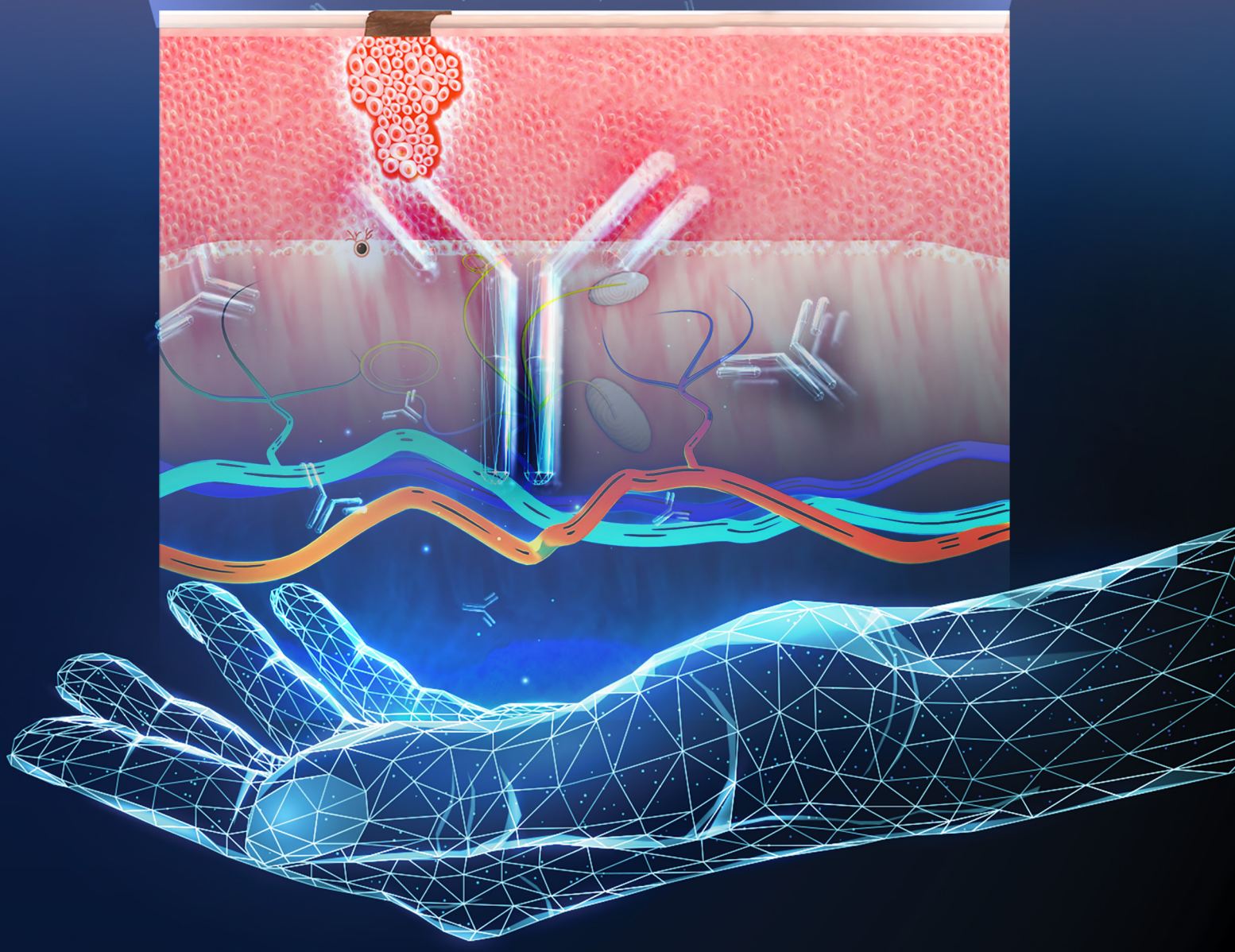
Navigating Clinical Challenges in cSCC:

Leveraging AI Tools for Improved Decision-Making Across the Continuum of Care



MED LEARNING GROUP

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This activity is supported by an independent educational grant from Regeneron Pharmaceuticals, Inc.

Navigating Clinical Challenges in cSCC: Leveraging AI Tools for Improved Decision-Making Across the Continuum of Care

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PROGRAM OVERVIEW

This activity immerses learners in interactive, case-based discussions led by multidisciplinary experts to address clinical challenges in the evolving continuum of high-risk cutaneous squamous cell carcinoma (cSCC). Experts will overview dynamic approaches to risk stratification, the role of adjuvant immunotherapy, and emerging strategies for neoadjuvant treatment, while highlighting the importance of multidisciplinary care and proactive management of immunotherapy-related adverse events. To enrich the learning experience, participants will also have access to an AI virtual assistant that provides on-demand resources and reflection points to facilitate learning and retention of key concepts.

TARGET AUDIENCE

This activity is designed to meet the educational needs of medical oncologists, radiation oncologists, surgeons (Mohs and surgical oncologists), dermatologists, advanced practice professionals (including nurse practitioners and physician assistants), and nurses who are involved in the treatment and care of patients with high-risk cSCC.

LEARNING OBJECTIVES

Upon completion of this enduring activity, attendees will have improved ability to:

1. Identify patients with high-risk cSCC, through risk stratification criteria and staging
2. Assess the clinical data for emerging neoadjuvant immunotherapies for the treatment of cSCC and how to utilize neoadjuvant approaches in clinical practice
3. Evaluate the clinical data for current and emerging adjuvant immunotherapies to inform their integration into clinical practice for cSCC treatment

4. Determine the importance of multidisciplinary care to improve disease and patient outcomes for individuals living with cSCC
5. Apply interprofessional strategies to manage AEs in patients undergoing immunotherapy for cSCC

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Nikhil Khushalani, MD	Consulting Fees: Bistol Myers Squibb, Merck, Novartis, Regeneron, Iovance Biotherapeutics, Nektar Therapeutics, Instil Bio, IO Biotech, Replimune, Mural Oncology, MyCareGorithm, Delcath Systems, Sun Pharma Contacted Research: BMS, BioNTech, Merck, Celgene, Novartis, GSK, HUYABIO, IDEAYA Biosciences, Regeneron, Replimune, Modulation Therapeutics Ownership Interest: Bellicum, Asensus Surgical Travel Support: Castle Biosciences, Regeneron Data and Safety Monitoring Boards: Incyte, AstraZeneca

Michael R. Migden, MD	Consulting Fees: Regeneron, Replimune, Philogen, Sun Pharma, Feldan Therapeutics, Stamford, StimLabs Contracted Research: Regeneron, Replimune, Sol-Gel Technologies
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Module 1 - Identifying High-Risk Cutaneous Squamous Cell Carcinoma (cSCC)

Nina A Ran, MD, MPH, MSTR

Moh’s Micrographic Surgery and Dermatologic Oncology
Brigham and Women’s Hospital
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The Purpose of Risk Stratification

Prior to surgery

- To identify patients who require radiologic staging
- To identify patients who require multidisciplinary care
- To inform decision-making regarding neoadjuvant therapy
- To inform primary treatment

Following surgery

- To identify patients who may benefit from adjuvant therapy
- To identify patients who may benefit from surveillance imaging

Throughout the treatment process:

To aid physicians in counseling patients about their tumor and prognosis

Resources Available to Risk Stratify cSCC

NCCN National Comprehensive Cancer Network®

riSCC riSCC Calculator

ACS AJCC
American Joint Committee on Cancer
American College of Surgeons

Erasmus MC Cancer Institute

Brigham and Women's Hospital
Founding Member, Mass General Brigham

Case Example

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

- Patient presents for surgical consultation for a biopsy-proven squamous cell carcinoma on the scalp

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

What information about **the patient** is useful for risk stratification and decision-making?

- Age
- Sex
- Immune status
- Overall health and comorbidities

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

Patient factors

- Male
- 75 years old
- Myasthenia gravis; on azathioprine for over a decade

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

What information about **the tumor history and presentation** is useful for risk stratification and decision-making?

- Preoperative size
- Whether tumor is rapidly growing
- History of previous tumor treated in this area (primary vs recurrent tumor)
- History of radiation or chronic inflammation at the site
- Whether the site is symptomatic
- Whether the lesion appears fixed on exam

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

Tumor history and presentation

- Preoperative size: 5 cm
- Rapidly growing
- Primary tumor
- No history of radiation or chronic inflammation at the site
- Lesion is tender
- Lesion appears fixed

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

What information about **the tumor pathology** is useful for risk stratification and decision-making?

- Histologic differentiation
- Depth of invasion
- Perineural invasion
- Lymphovascular invasion

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

Tumor pathology

- Moderate differentiation
- Invading at least dermis—biopsy captured only dermis
- No perineural invasion observed on biopsy
- No lymphovascular invasion observed on biopsy

Image courtesy of Nina Ran, MD, MPH, MSTR

NCCN Risk Stratification: Very High Risk

STRATIFICATION TO DETERMINE TREATMENT OPTIONS FOR LOCAL cSCC BASED ON RISK FACTORS FOR LOCAL RECURRENCE, METASTASES, OR DEATH

Risk group	Low risk	High risk	Very high risk
Treatment options	SCC-4	SCC-5	SCC-5 and SCC-6
H&P			
Location/diameter (cm)	Trunk, extremities <2 cm	Trunk, extremities 2 cm to ≤4 cm	>4 cm (any location)
		Head, neck, hands, feet, pretibia, and anogenital area (any size)	
Clinical borders	Wel -defined	Poorly defined	
Primary vs recurrent	Primary	Recurrent	
Immunosuppression	(–)	(+)	
Site of prior RT or chronic inflammation	(–)	(+)	
Rapid growth tumor	(–)	(+)	
Neurologic symptoms	(–)	(+)	
Pathology (SCC-A)			
Degree of differentiation	Well or moderately differentiated		Poorly differentiated
Histologic subtype	(–)	(+)	(+)
Depth: Thickness or level of invasion	<2 mm thick and no invasion beyond subcutaneous fat	2 to 6 mm depth and no invasion beyond subcutaneous fat	>6 mm or invasion beyond subcutaneous fat
Perineural involvement	(–)	(+)	Tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm
Lymphatic or vascular involvement	(–)	(–)	(+)

NCCN Recommendations for Very High Risk

VERY-HIGH-RISK cSCC

Very-high-risk cSCC with significant risk of extensive local recurrence, nodal, or in-transit metastasis

TREATMENT PLANNING

- Multidisciplinary consultation at center with specialized expertise to discuss options
- Radiologic staging
  - MRI with and without contrast or CT with contrast and/or ultrasound
  - Abnormal lymph nodes identified by imaging studies (SCC-8)

or

- Consider SLNB in cases that are recurrent or with multiple high-risk features

and

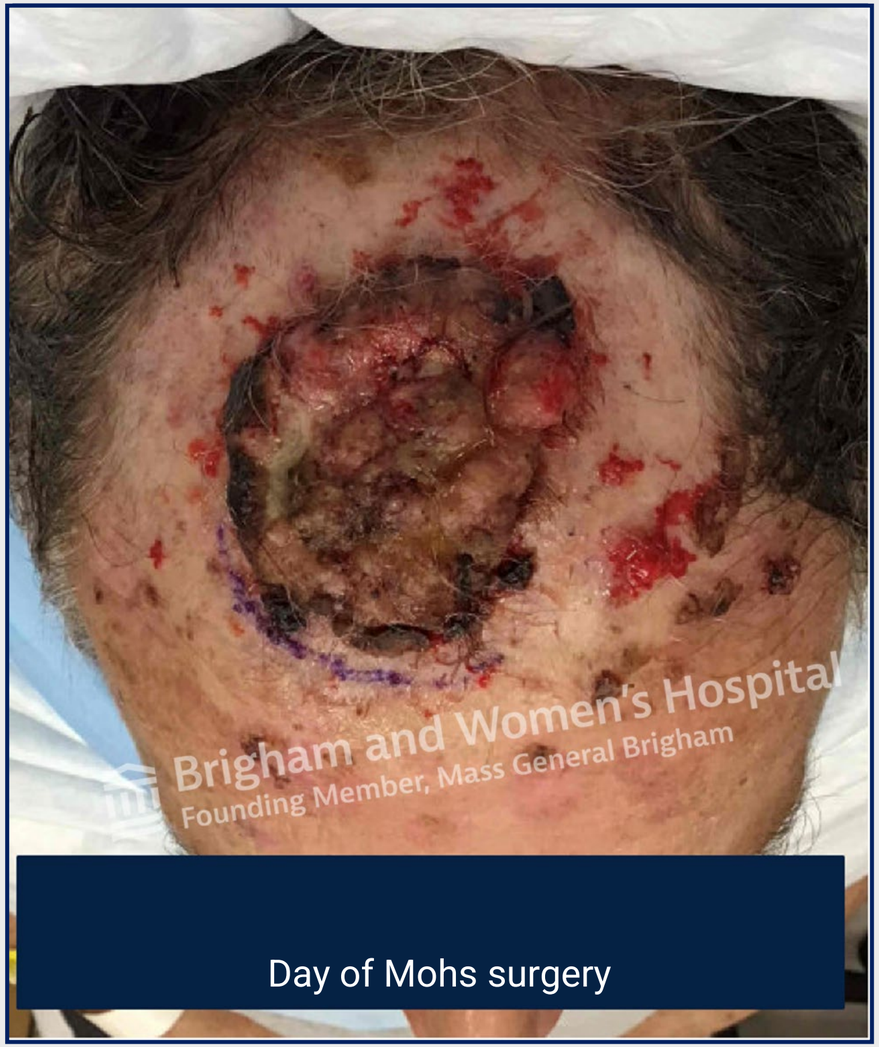
- Consider neoadjuvant therapy with cemiplimab-rwic if
  - Nonreactive nonkeratoacanthomatous rapid growth tumors
  - In-transit metastasis
  - Borderline resectable
  - Surgery alone may not be curative or may result in significant functional limitation

Pause for discussion on

Consideration of imaging
Consideration of MDC
Consideration of neoadjuvant cemiplimab

CT = computed tomography; MRI = magnetic resonance imaging; SLNB = sentinel lymph node biopsy.

Case 1 Continuation: Biopsy-Proven cSCC on the Right Parietal Scalp



Patient presents for surgical consultation for a biopsy-proven squamous cell carcinoma on the scalp

↓

Head CT negative for bone invasion

Neck CT negative for lymph node metastasis

↓

Multidisciplinary tumor board:

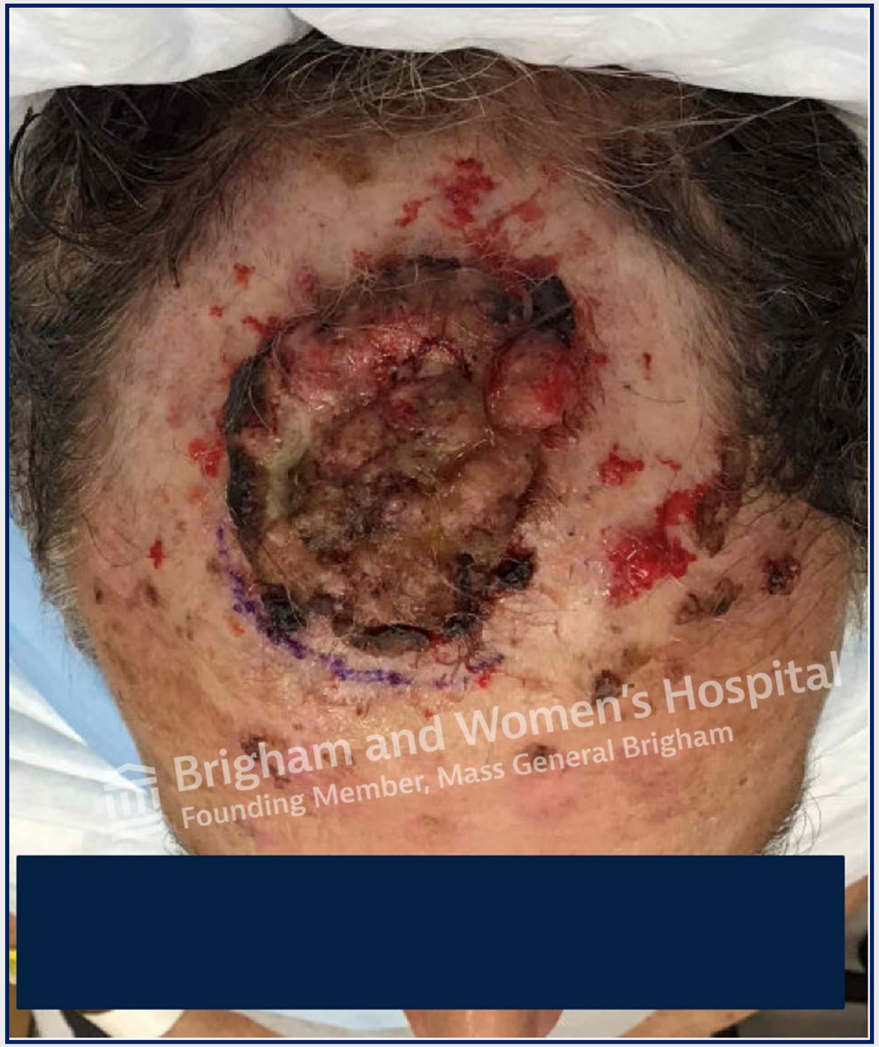
Not a good candidate for neoadjuvant cemiplimab and for general anesthesia; upfront surgery recommended

↓

Underwent Mohs surgery

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp



- Male
- 75 years old
- Myasthenia gravis; on azathioprine for over a decade

- Preoperative diameter: 5 cm
- Moderate differentiation
- Invasion to galea
- No perineural invasion on biopsy or Mohs debulk
- No lymphovascular invasion on biopsy or Mohs debulk

AJCC8 = 8th edition of the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual*; BWH = Brigham and Women's Hospital staging system.

Image courtesy of Nina Ran, MD, MPH, MSTR

AJCC 8th Edition T Staging: T3

4.1 Definition of Primary Tumor (T)

✓	*T Category*	*T Criteria*
	TX	Primary tumor cannot be assessed
	Tis	Carcinoma *in situ*
	T1	Tumor smaller than or equal to 2 cm in greatest dimension
	T2	Tumor larger than 2 cm, but smaller than or equal to 4 cm in greatest dimension
→	T3	Tumor larger than 4 cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion*
	T4	Tumor with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion
	T4a	Tumor with gross cortical bone/marrow invasion
	T4b	Tumor with skull base invasion and/or skull base foramen involvement

*Deep invasion is defined as invasion beyond the subcutaneous fat or > 6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

Brigham and Women's Hospital Staging: T2b

Table 3. Alternative T staging system

Alternative T staging system	Definition	Patients in study cohort, number (%)
T0	In situ SCC	Not included
T1	0 risk factors	134 (52)
T2a	1 risk factor	67 (26)
→ **T2b**	2–3 risk factors	49 (19)
T3	4 risk factors or bone invasion	6 (2)

Risk factors

- **Tumor diameter 2 cm or greater**
- Poorly differentiated histology
- Perineural invasion
- **Tumor invasion beyond subcutaneous fat**
  - Bone invasion automatically upstages to T3

Jambusaria-Pahlajani A, et al. *JAMA Dermatol*. 2013;149(4):402-410.

Staging Systems

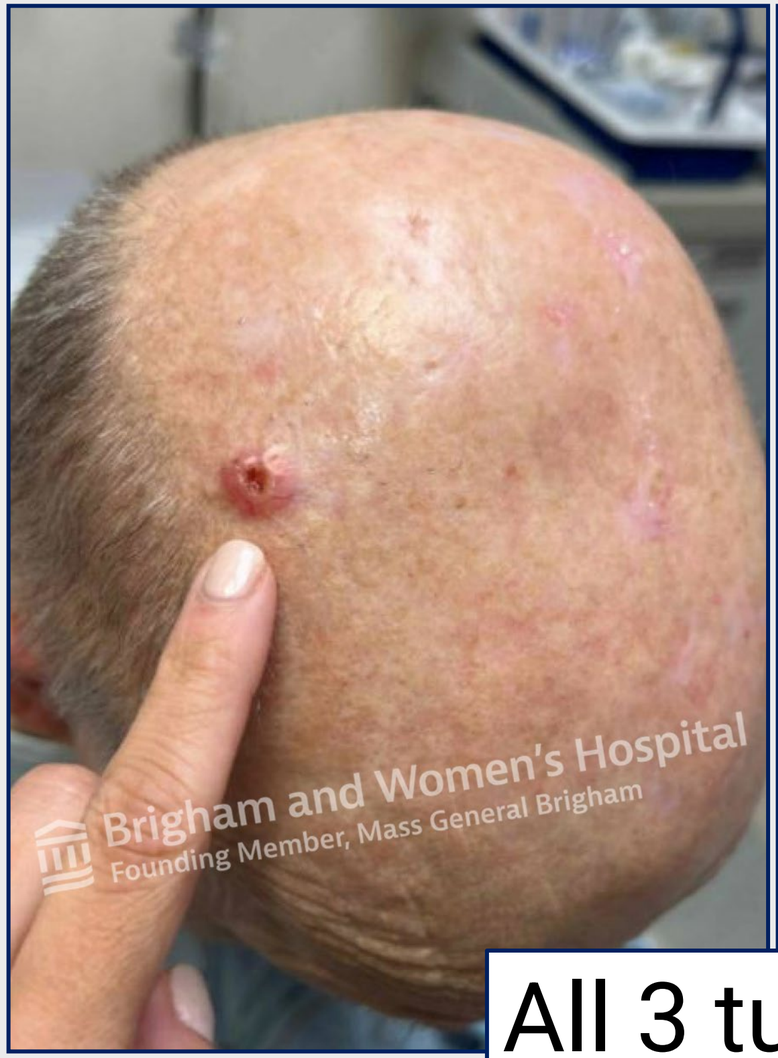
Discussion on the benefits/drawbacks of staging system

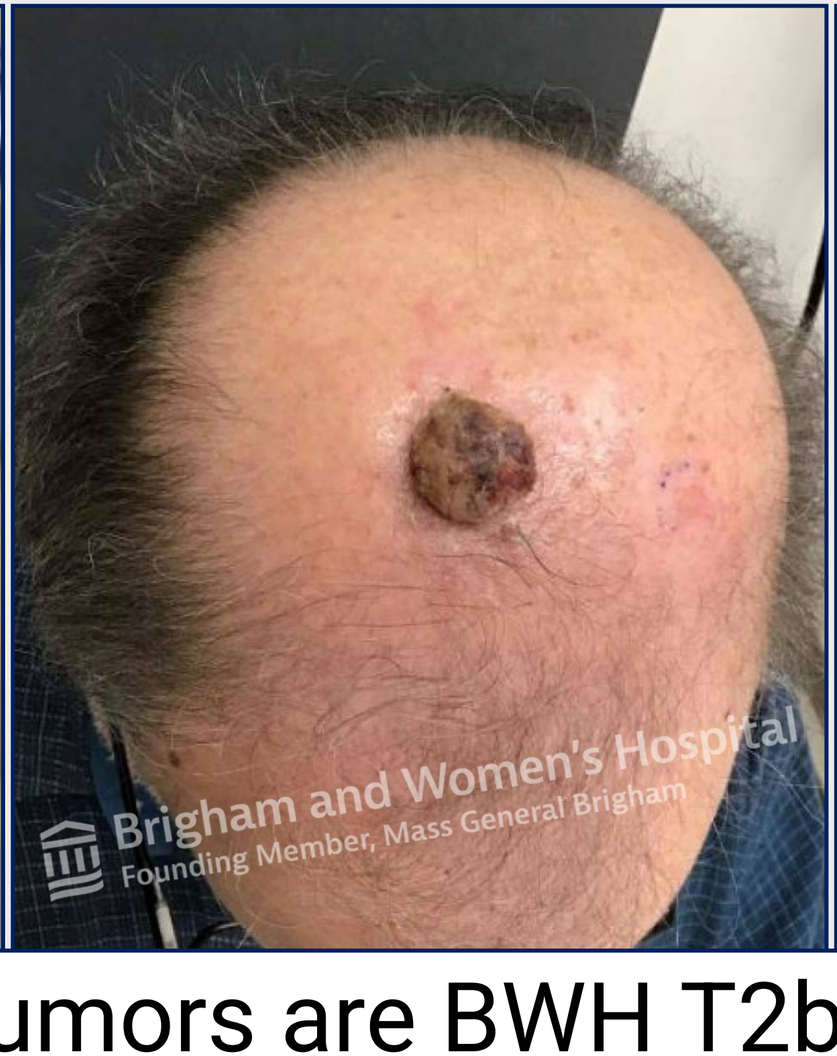
Benefits including

- Unified language to discuss risk
- Advantageous for study recruitment

Drawbacks including

- Tumors with the same stage can have different risks
- Predictions of risk are not precise
- AJCC8 for head/neck tumors only
- Do not include patient-associated factors (age, sex, immune status)





All 3 tumors are BWH T2b and are assigned the same risk.

Images courtesy of Nina Ran, MD, MPH, MSTR

Tumor-Specific Risk Prediction Modeling: Erasmus

Prediction of metastatic risk in patients with cutaneous squamous cell carcinoma (cSCC)

Erasmus MC Cancer Institute

This web-based calculator has been developed by the Skin Cancer Research Group of the Department of Dermatology at the Erasmus MC Cancer Institute in Rotterdam, and validated in an external cohort of cSCC patients, as described in Rentroia-Pacheco et al (2023) .

This model has only been developed and validated in cSCC and not in mucosal or genital SCC.

Patient characteristics

Age, in years

75

Age, in years. Patients should be adults (18 years or older)

Sex

Male

Number of prior cSCCs

2

Tumor location

Scalp or neck

Tumor characteristics

Tumor diameter, in cm

5

Macroscopic tumor diameter, as measured by a pathologist, in centimeters. Decimals are allowed e.g. 2.2

Tissue involvement

Beyond subcutaneous fat

Deepest layer of tissue involvement

Differentiation Grade

Good/moderate

Differentiation grade according to the adjusted Broder classification system: good/moderate differentiation 0-75% undifferentiated cells, poor/undifferentiated >75% undifferentiated cells.

Perineural or lymphovascular invasion

Absent

Presence of perineural invasion (>=0.1mm) or lymphovascular invasion of any size

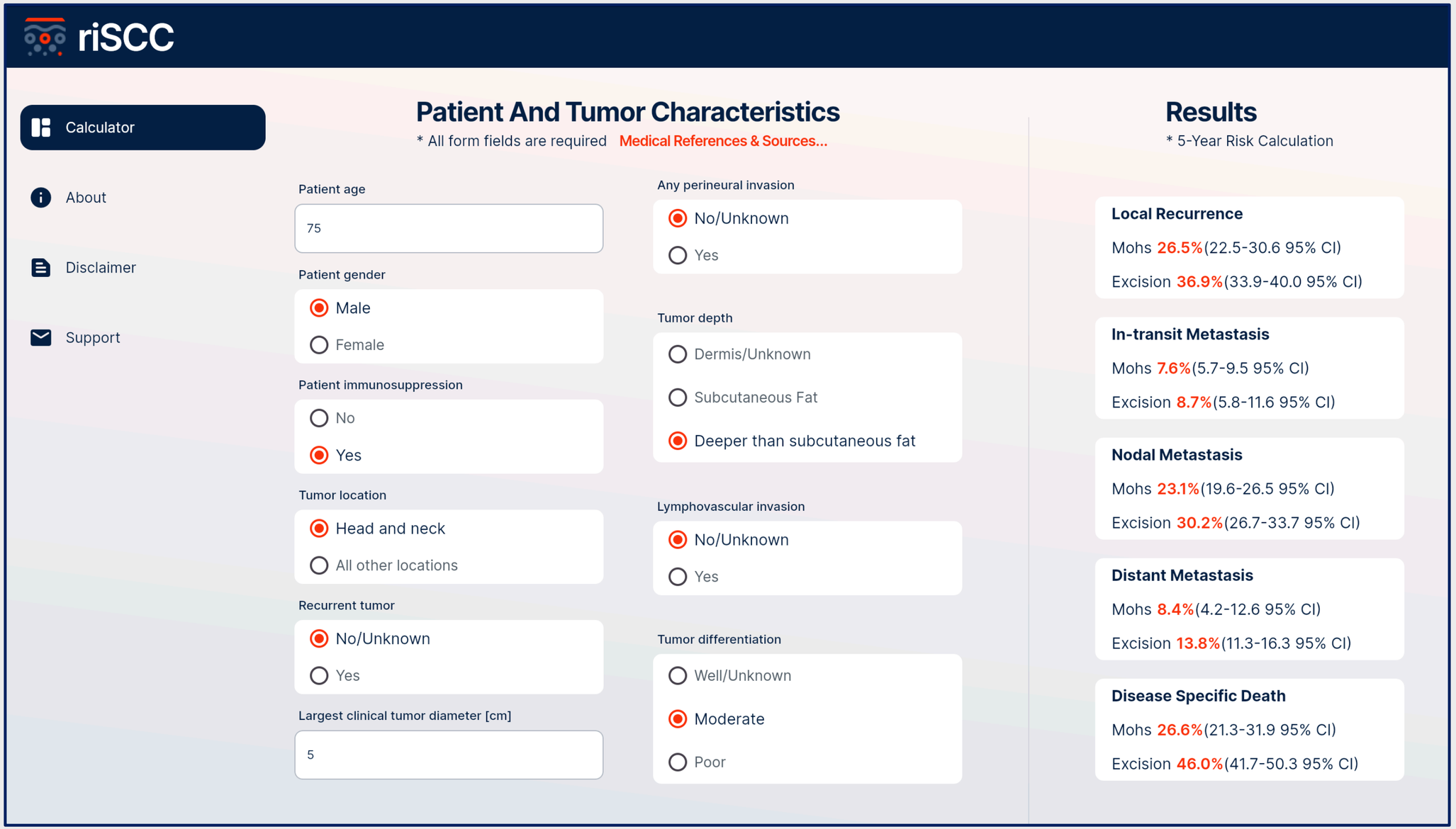
Predict

A patient with these characteristics has a probability of :

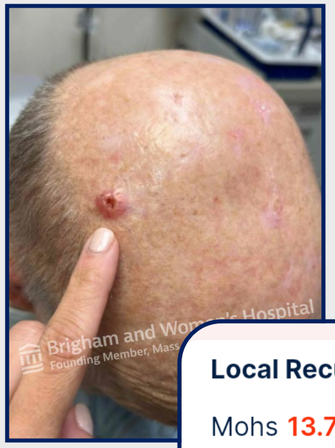
- **7.8** % of developing a metastasis within 1 year
- **14** % of developing a metastasis within 3 years
- **15.6** % of developing a metastasis within 5 years

DISCLAIMER: Currently, this calculator can only be used for research purposes. It cannot be used as a medical device. Erasmus MC has no liability for any medical decision taken based on the information provided by the calculator.

Tumor-Specific Risk Prediction Modeling: riSCC



Images courtesy of Nina Ran, MD, MPH, MSTR



Local Recurrence

Mohs **13.7%**(10.7-16.8 95% CI)

Excision **19.8%**(18.2-21.5 95% CI)

In-transit Metastasis

Mohs **3.1%**(2.3-3.8 95% CI)

Excision **3.6%**(2.4-4.7 95% CI)

Nodal Metastasis

Mohs **15.2%**(12.9-17.5 95% CI)

Excision **20.3%**(18.1-22.5 95% CI)

Distant Metastasis

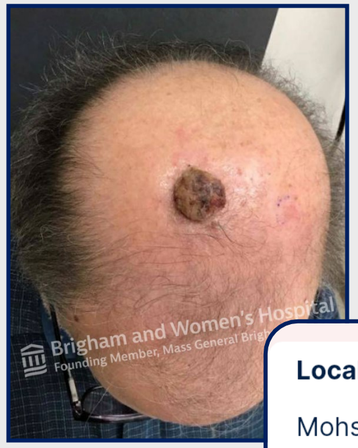
Mohs **5.0%**(2.8-7.1 95% CI)

Excision **8.3%**(7.0-9.6 95% CI)

Disease Specific Death

Mohs **8.6%**(5.0-12.1 95% CI)

Excision **16.3%**(14.8-17.9 95% CI)



Local Recurrence

Mohs **8.8%**(6.3-11.3 95% CI)

Excision **12.9%**(11.6-14.1 95% CI)

In-transit Metastasis

Mohs **0.8%**(0.5-1.0 95% CI)

Excision **0.9%**(0.5-1.2 95% CI)

Nodal Metastasis

Mohs **8.6%**(7.0-10.1 95% CI)

Excision **11.6%**(10.0-13.1 95% CI)

Distant Metastasis

Mohs **1.1%**(0.5-1.7 95% CI)

Excision **1.9%**(1.5-2.2 95% CI)

Disease Specific Death

Mohs **7.2%**(4.0-10.5 95% CI)

Excision **13.9%**(12.6-15.2 95% CI)

Local Recurrence

Mohs **26.5%**(22.5-30.6 95% CI)

Excision **36.9%**(33.9-40.0 95% CI)

In-transit Metastasis

Mohs **7.6%**(5.7-9.5 95% CI)

Excision **8.7%**(5.8-11.6 95% CI)

Nodal Metastasis

Mohs **23.1%**(19.6-26.5 95% CI)

Excision **30.2%**(26.7-33.7 95% CI)

Distant Metastasis

Mohs **8.4%**(4.2-12.6 95% CI)

Excision **13.8%**(11.3-16.3 95% CI)

Disease Specific Death

Mohs **26.6%**(21.3-31.9 95% CI)

Excision **46.0%**(41.7-50.3 95% CI)

Images courtesy of Nina Ran, MD, MPH, MSTR

Module 2 - Developing Treatment Plans for Patients With High-Risk cSCC: Neoadjuvant Therapy

Neil D. Gross, MD, FACS

Professor, Department of Head and Neck Surgery
MD Anderson Cancer Center
Houston, Texas

Case #2: History

History of present illness (HPI)

- A 71-year-old female with a history over several months of a painful right nasal skin lesion
- Biopsy: Squamous cell carcinoma
- Presented to Mohs for resection

Past medical history (PMHx)

- History of prior nonmelanoma skin cancers
- No immunosuppression
- No prior radiation

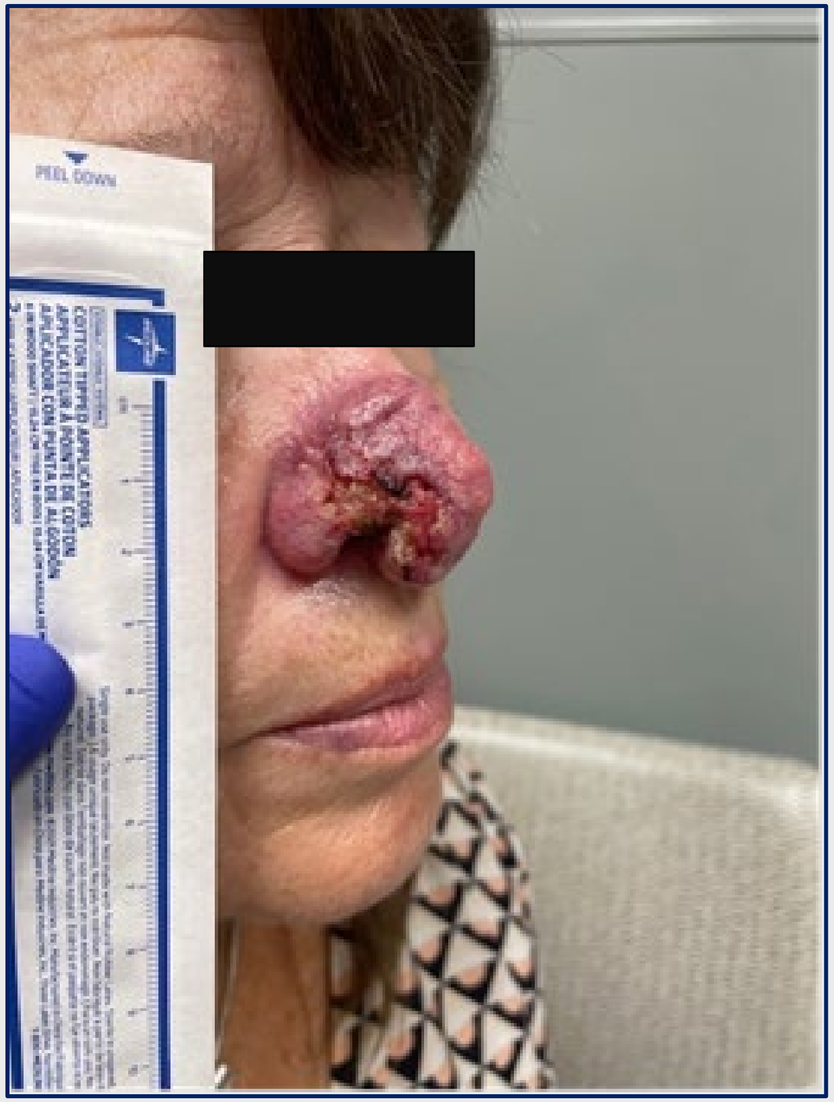


Image courtesy of Neil Gross, MD, FACS

Case #2: Exam

- **General:** No acute distress; normocephalic and atraumatic; tearful
- **Nose:** **Deeply ulcerative mass with full thickness involvement of right nasal ala and nasal tip**
- **Neck:** No adenopathy
- **Neurologic assessment:** Cranial nerves are intact

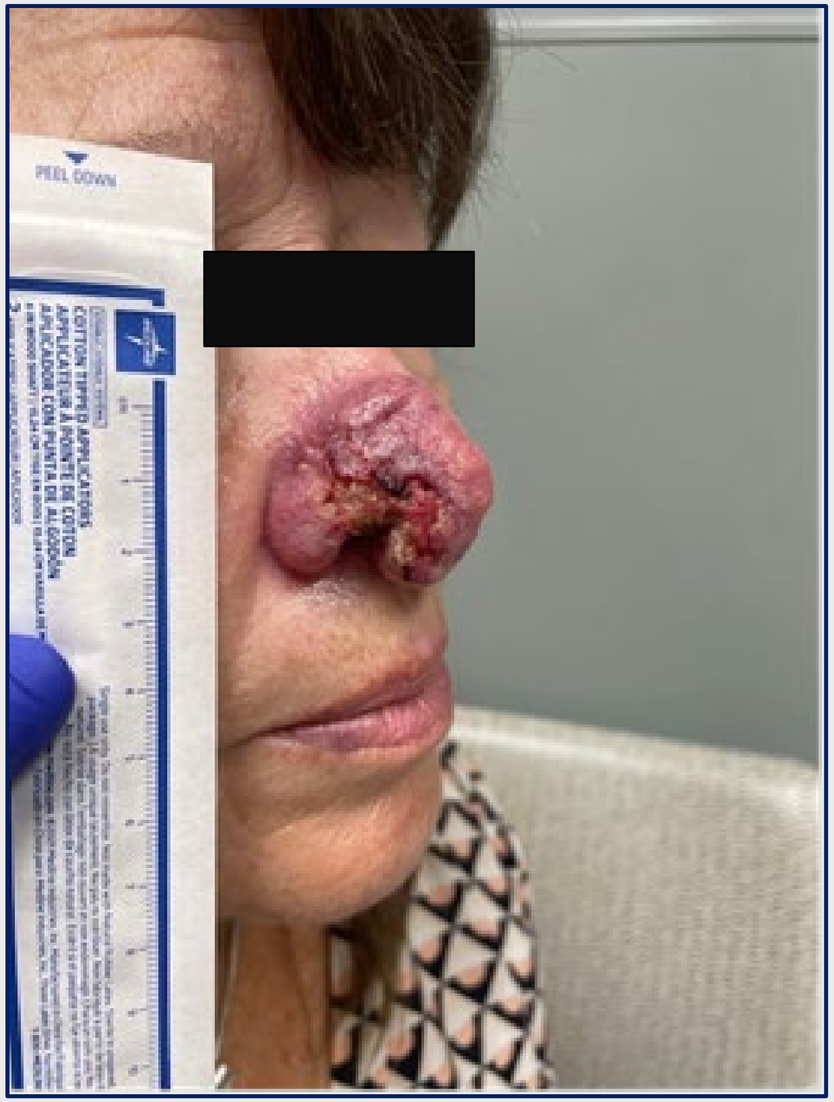


Image courtesy of Neil Gross, MD, FACS

Case #2: Baseline Imaging

- 1.7 x 2.7 x 1.5 cm enhancing lesion of the right nasal ala
- No bone involvement
- No cranial nerve involvement
- No adenopathy

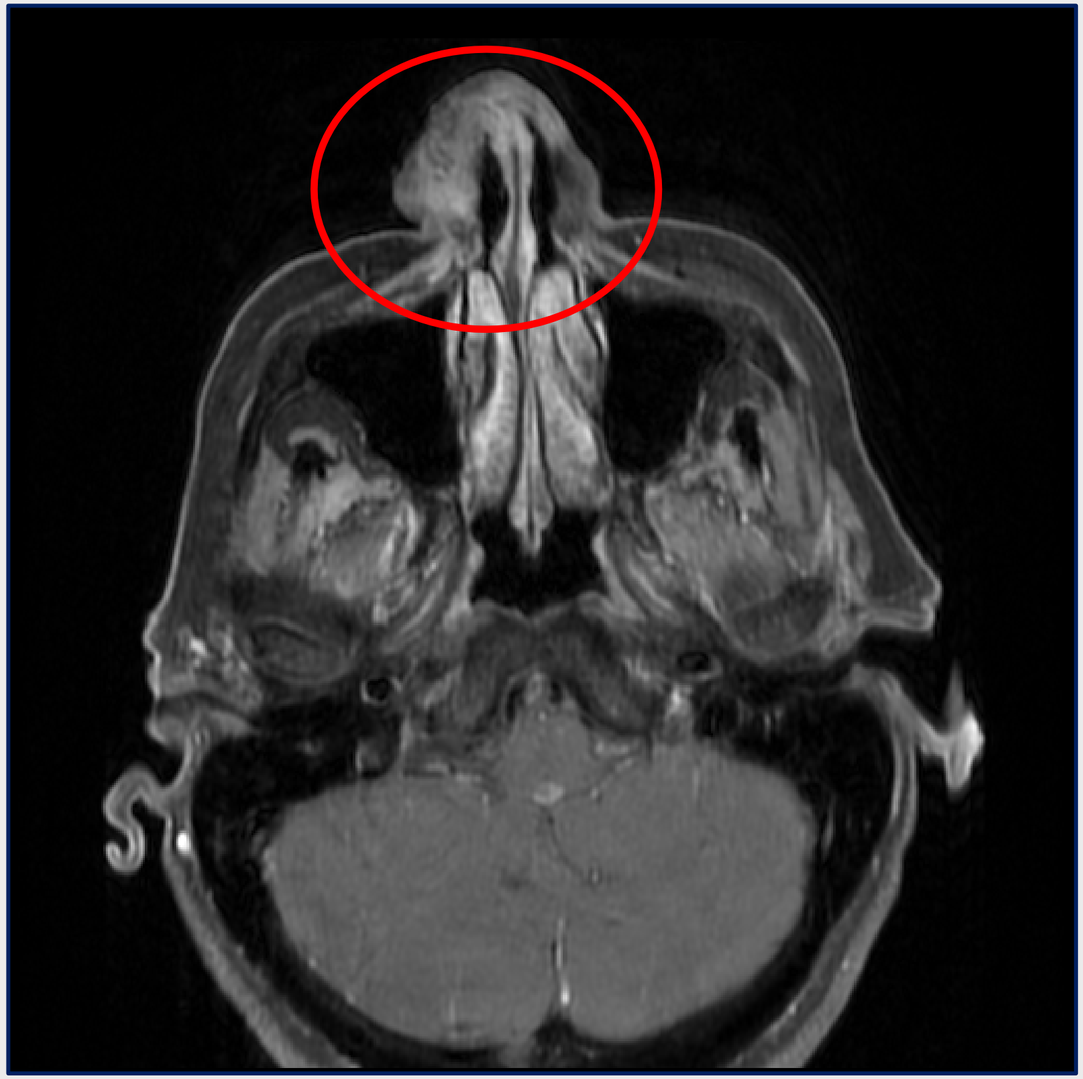


Image courtesy of Neil Gross, MD, FACS

Case #2: Classification

American Joint Committee on Cancer (AJCC) 8: Stage III

- cT3: Tumor larger than 4 cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion*
- cN0: No regional lymph node metastasis
- cM0: No distant metastasis

*Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor).

What About Adjuvant Therapy?

KEYNOTE-630
NCT03833167

NEWS RELEASE

Company Provides Update on Phase 3 KEYNOTE-867 and KEYNOTE-630 Trials

2024-08-29

C-POST
NCT03969004

Adjuvant (cemiplimab) Significantly Improves Disease-Free Survival (DFS) After Surgery in High-Risk Cutaneous Squamous Cell Carcinoma (CSCC) in Phase 3 Trial

January 13, 2025 at 6:15 AM EST

PDF Version

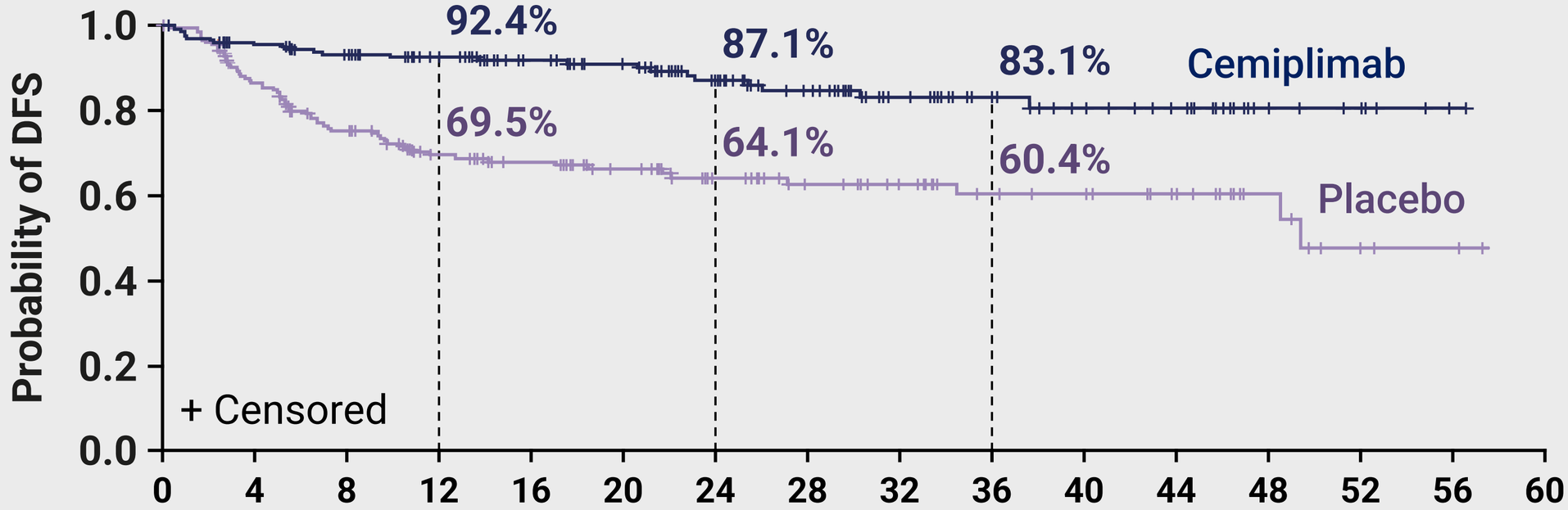
Primary endpoint of DFS met at first prespecified interim analysis, showing a 68% reduction in the risk of disease recurrence or death in patients with high-risk CSCC after surgery compared to placebo

Koyfman SA, et al. American Society of Clinical Oncology (ASCO) 2025; Abstract 6000. Rischin D, et al. ASCO 2025: Abstract 6001.

Adjuvant Cemiplimab in High Risk cSCC

C-POST Trial

	# of events	Median disease-free survival (months)
Cemiplimab	24	NR (NE–NE)
Placebo	65	49.4 (48.5–NE)
HR for disease recurrence or death	0.32 (95% CI, 0.20–0.51) $p < .001$	



Patients at risk

Cemiplimab	209	172	157	132	116	104	83	66	47	33	27	22	9	6	1	0
Placebo	206	161	130	94	82	69	53	42	36	26	24	18	10	4	2	0

CI = confidence interval; cSCC = cutaneous squamous cell carcinoma; DFS = disease-free survival; HR = hazard ratio; NE = not evaluable; NR = not reached.

Rischin D, et al. *New Engl J Med.* 2025;393:774-785.

What About Neoadjuvant Therapy?

Neoadjuvant Cemiplimab

Phase 2 nonrandomized, multicentre study (Australia, Germany, United States)

Primary endpoint

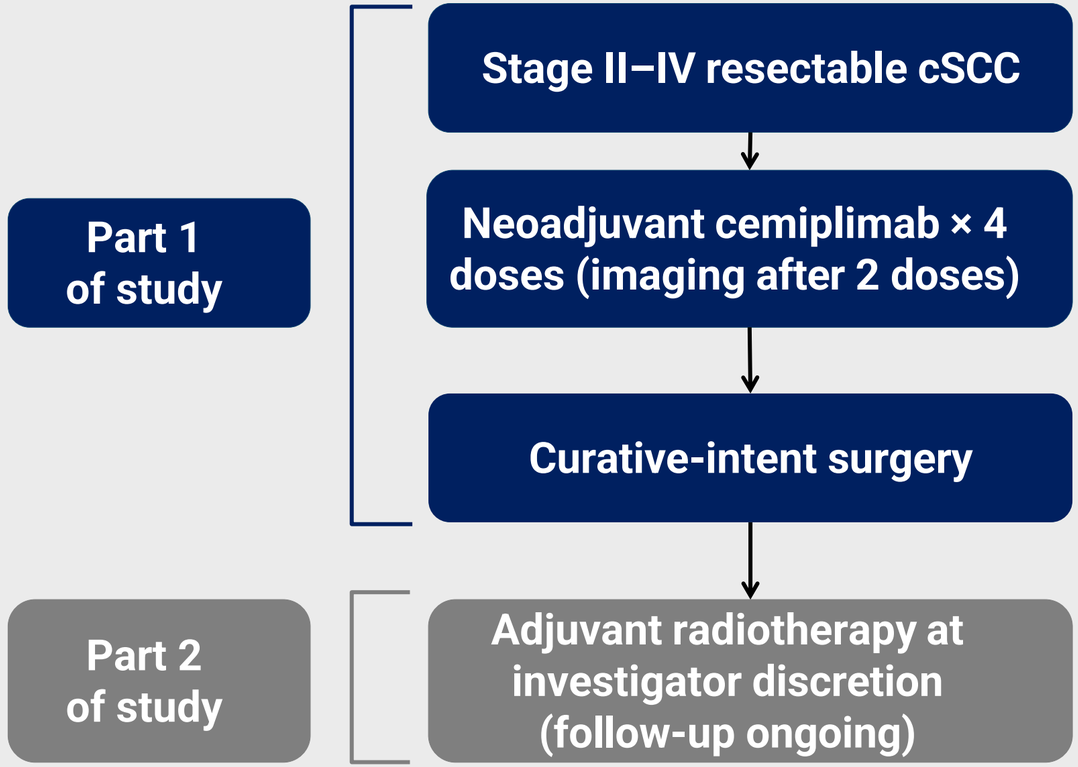
- pCR (0% viable tumor) rate per ICPR
  - Null hypothesis: pCR rate = 25%

Secondary endpoints

- MPR (>0% but ≤10% viable tumor) rate per ICPR
- pCR and MPR rates per local pathology review
- Radiological ORR per RECIST 1.1
- Safety and tolerability

Correlative analyses

- Exploration of TMB and PD-L1 expression with treatment response

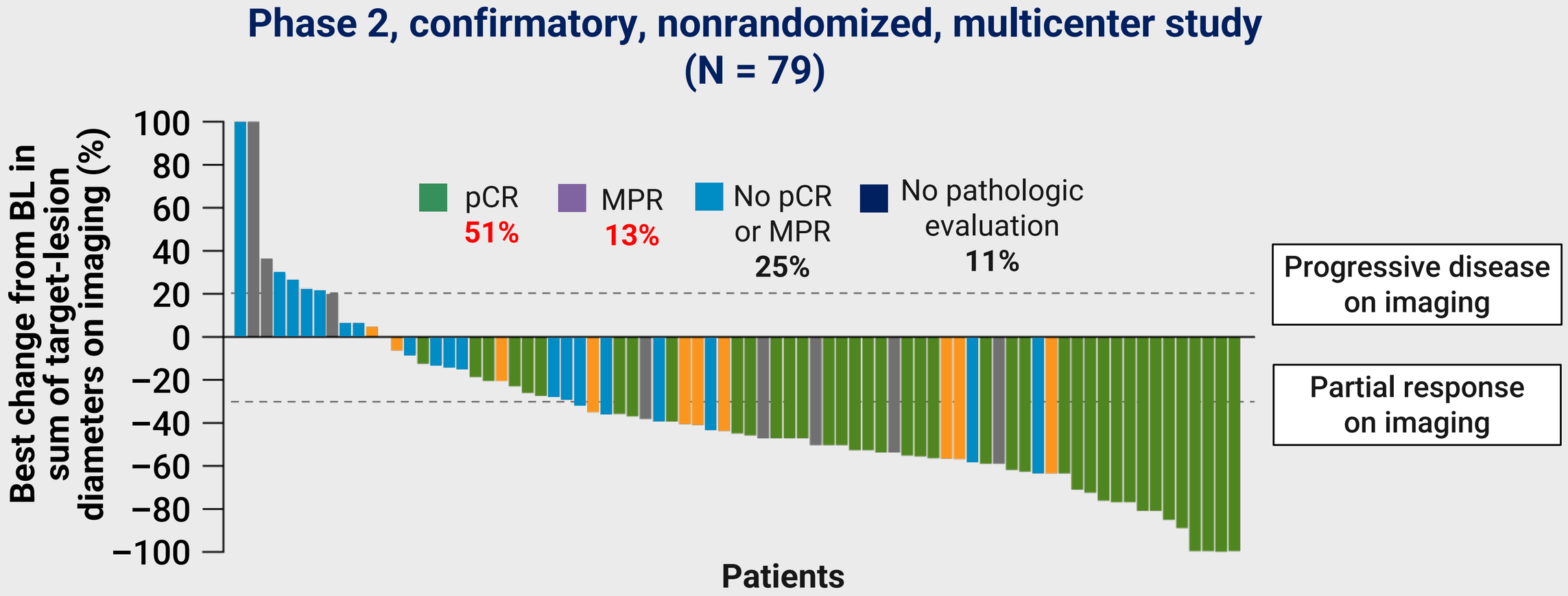


ICPR = independent central pathologic review; MPR = major pathological response; ORR = objective response rate; pCR = pathologic complete response; PD-L1 = programmed cell death-ligand 1; RECIST = Response Evaluation Criteria in Solid Tumours; TMB = tumor mutational burden.

Gross ND, et al. *Lancet Oncol*. 2023;24:1196-1205.

Phase 2 Neoadjuvant Cemiplimab for Stage II to IV cSCC

Results

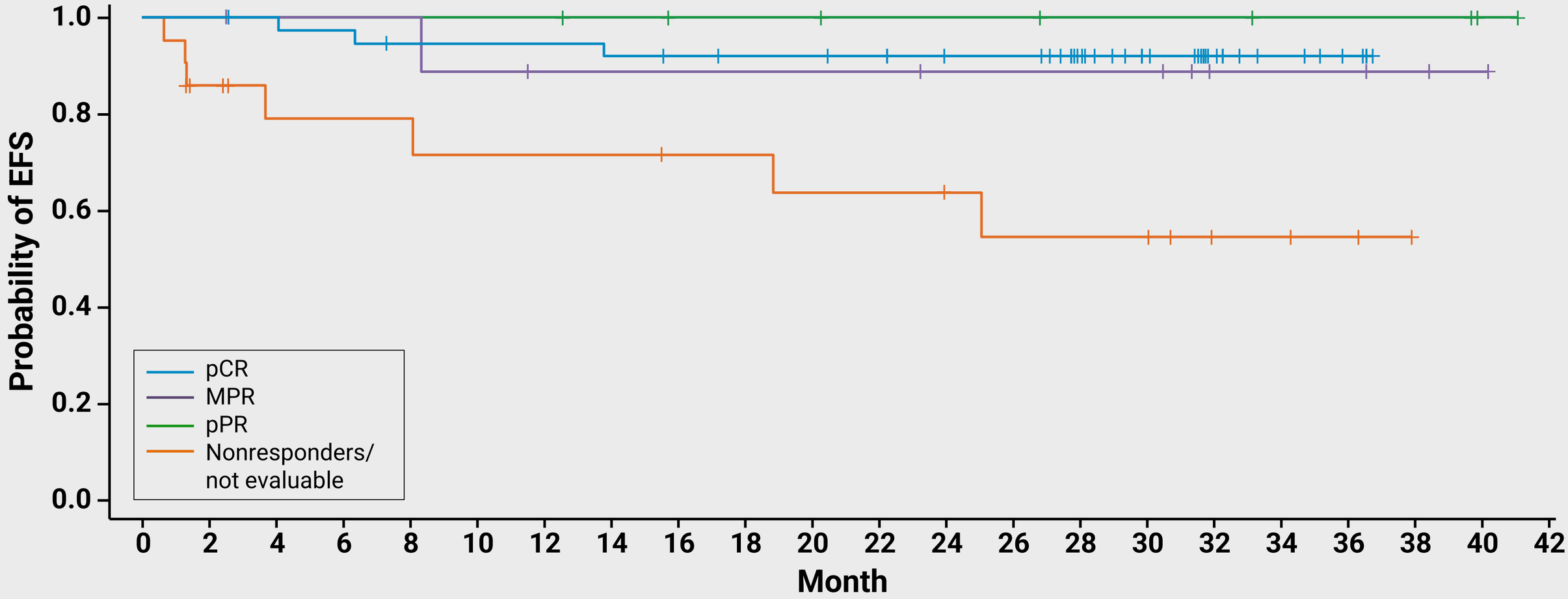


BL = baseline; pCR = pathologic complete response (absence of viable tumor cells in surgical specimen); MPR = major pathological response (presence of viable tumor cells that constitute ≤10% of surgical specimen).

Gross ND, et al. *N Engl J Med*. 2022;387:1557-1568.

Phase 2 Neoadjuvant Cemiplimab for Stage II to IV cSCC

Results



Median follow-up = 29.4 months (range: 1.3–41.3)

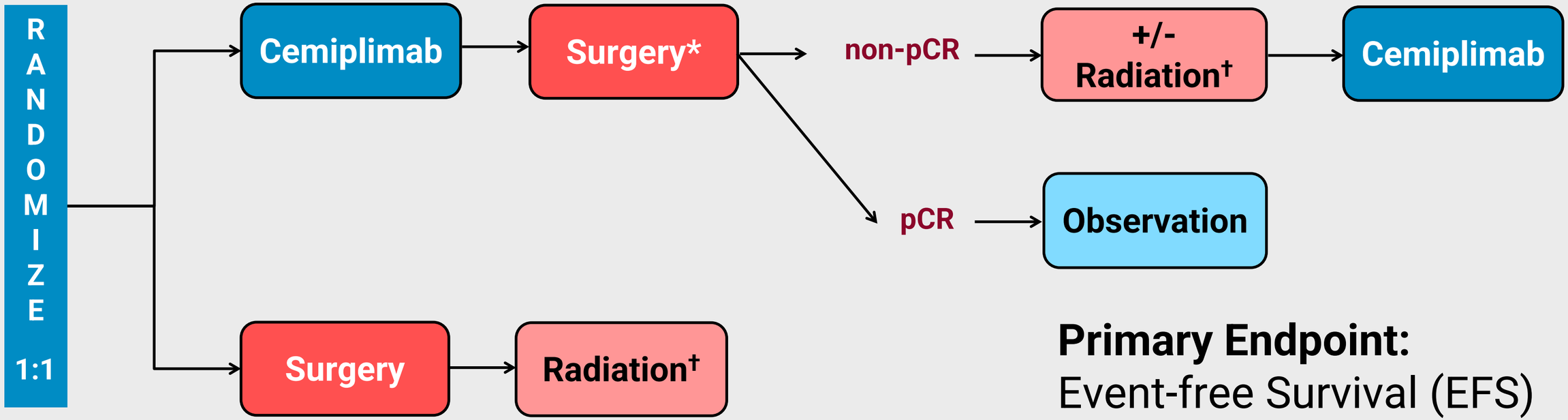
EFS = event-free survival.

Gross ND, et al. *Lancet Oncol.* 2023;24:1196-1205. Rischin D, et al. European Society for Medical Oncology (ESMO) 2024.

NRG-HN014 Schema

Randomized Phase 3 Trial

N = 420



Primary Endpoint:
Event-free Survival (EFS)

* Response-adapted oncologic surgery
†As indicated per protocol
pCR = pathologic complete response.

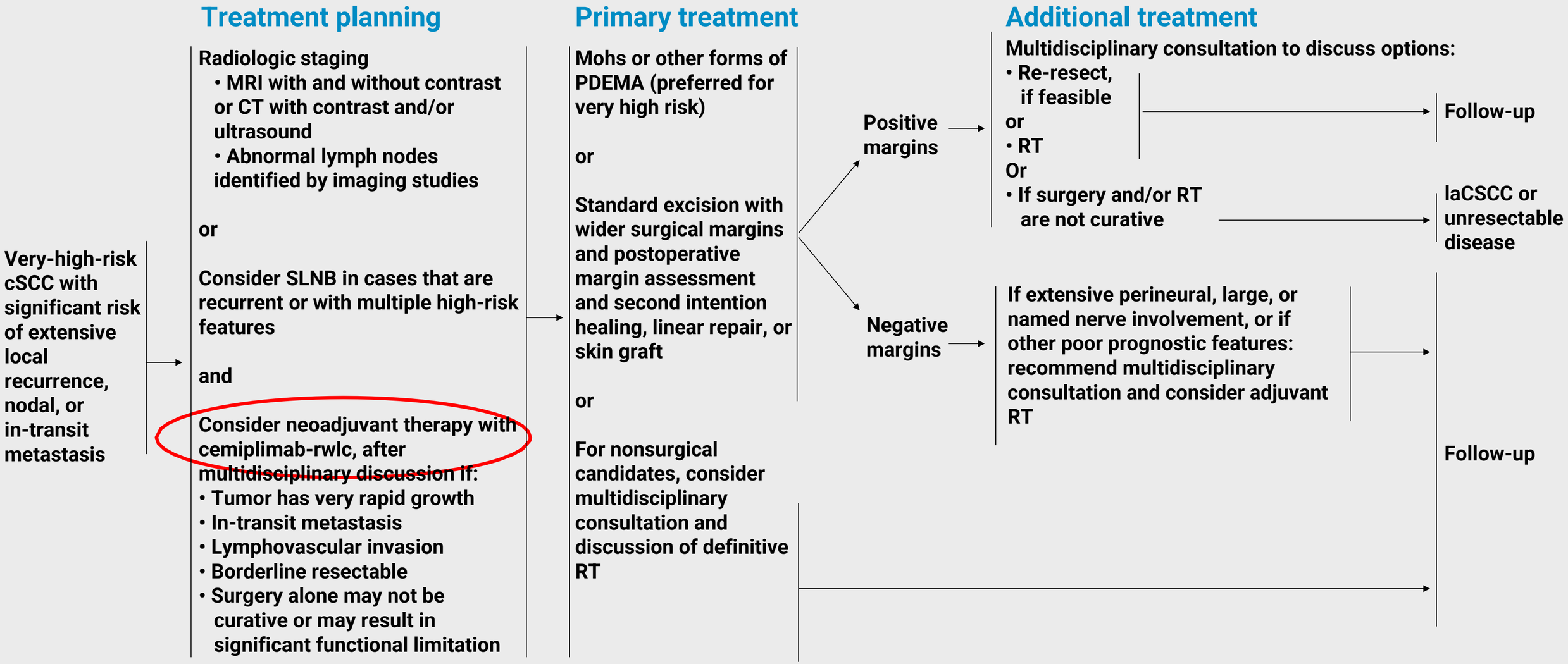
ClincalTrials.gov: NCT06568172

CCTG TROG CANCER RESEARCH NRG ONCOLOGY
Advancing Research. Improving Lives.

When to Consider Neoadjuvant Therapy?

NCCN guidelines version 1.2026 squamous cell skin cancer

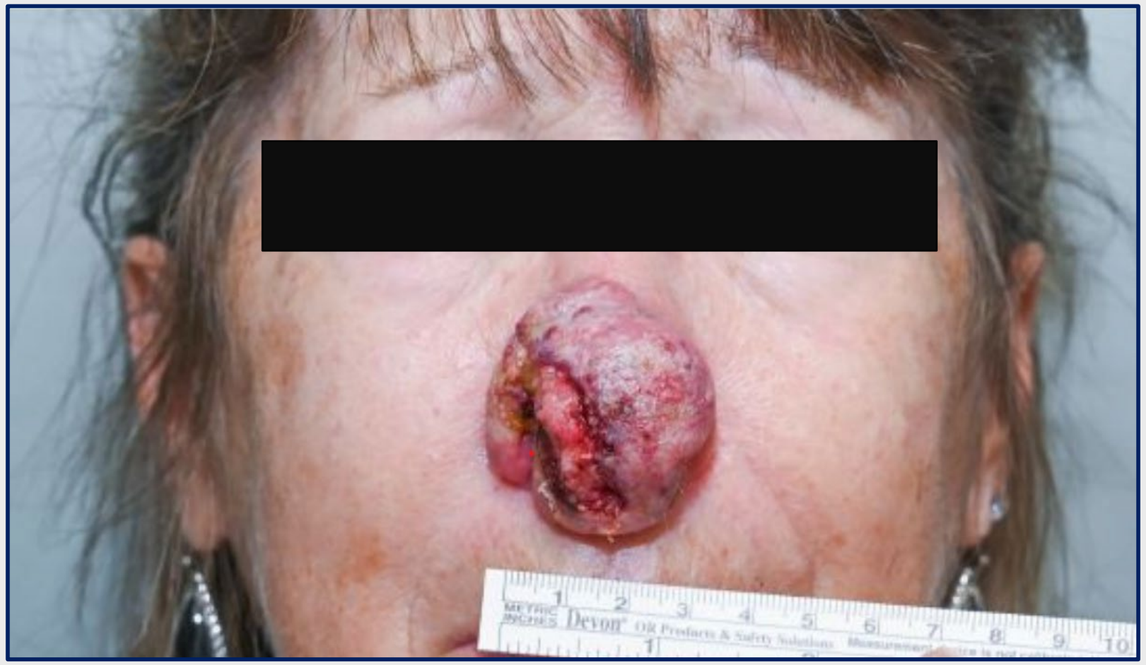
Very-high-risk cSCC

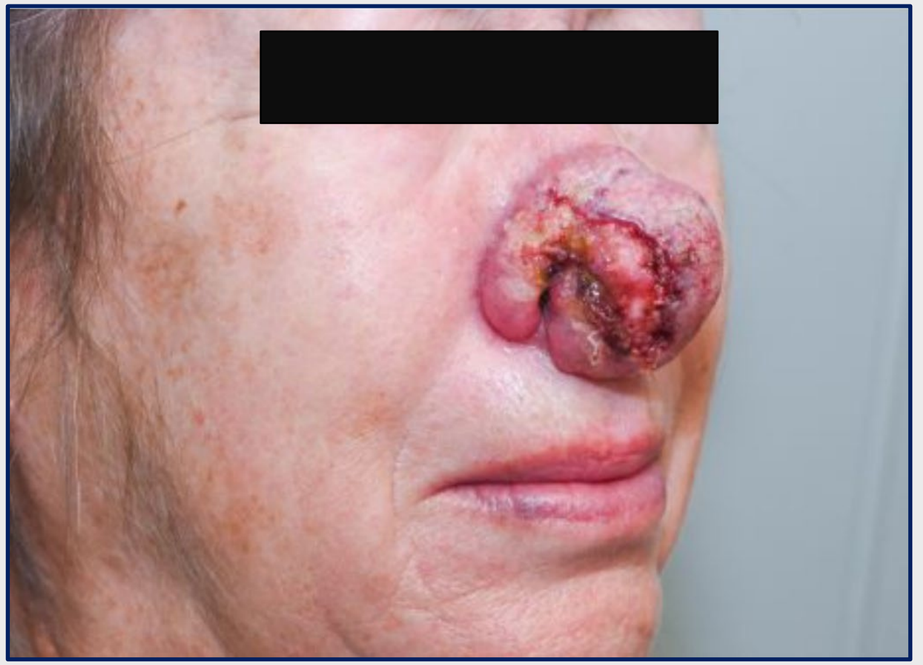


National Comprehensive Cancer Network (NCCN). Guidelines for squamous cell skin cancer, V1.2026 (www.nccn.org/professionals/physician_gls/pdf/squamous.pdf). Accessed 12/5/2025.

Case #2: Neoadjuvant Immunotherapy

- Clinical progression after 1 cycle of cemiplimab

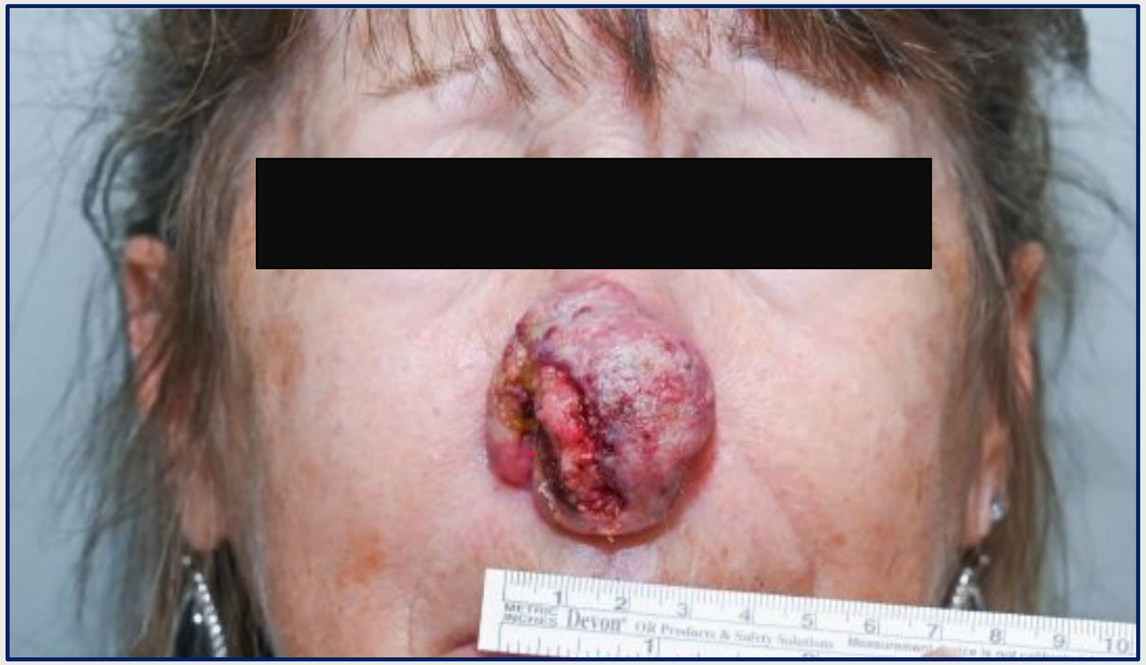




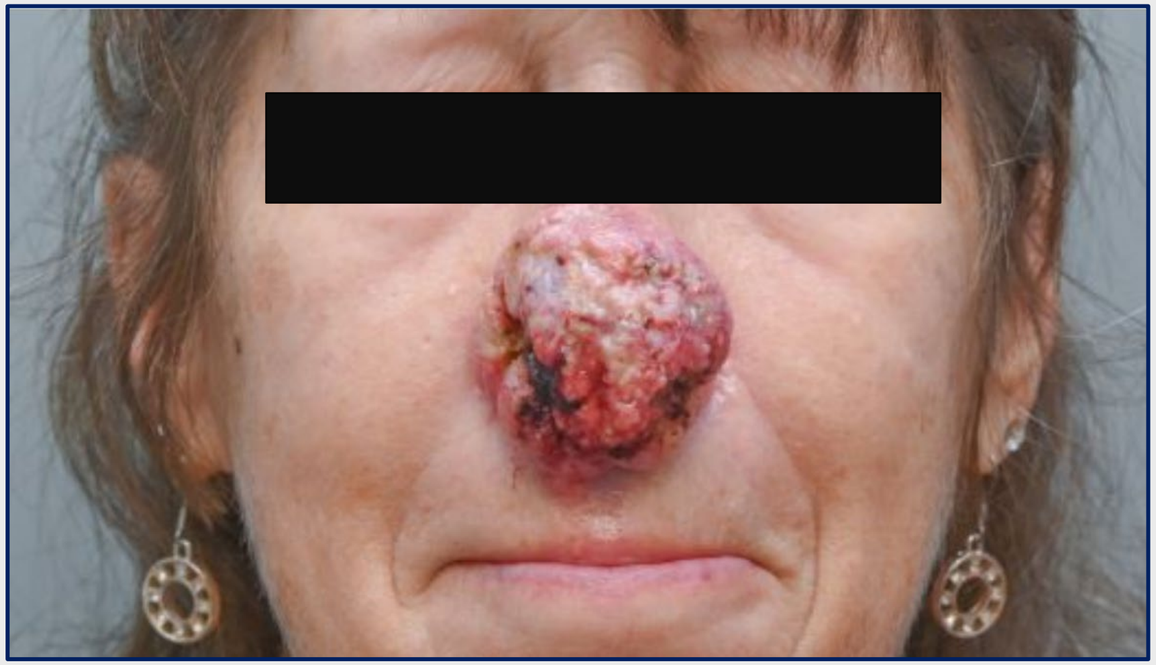
Images courtesy of Neil Gross, MD, FACS

Case #2: Neoadjuvant Immunotherapy

- Clinical progression after 2 cycles of cemiplimab



POST Cycle 1

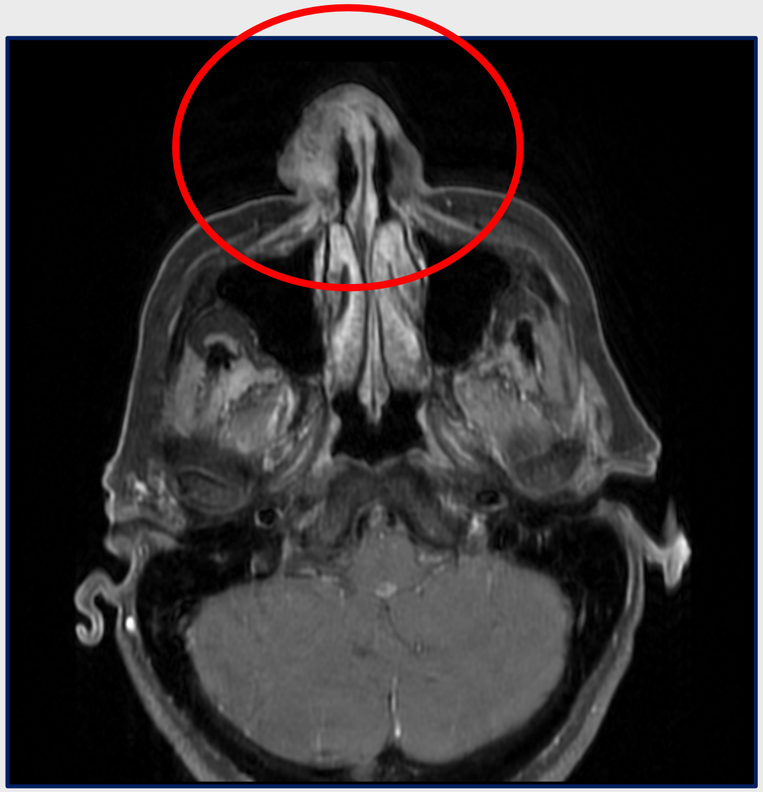


POST Cycle 2

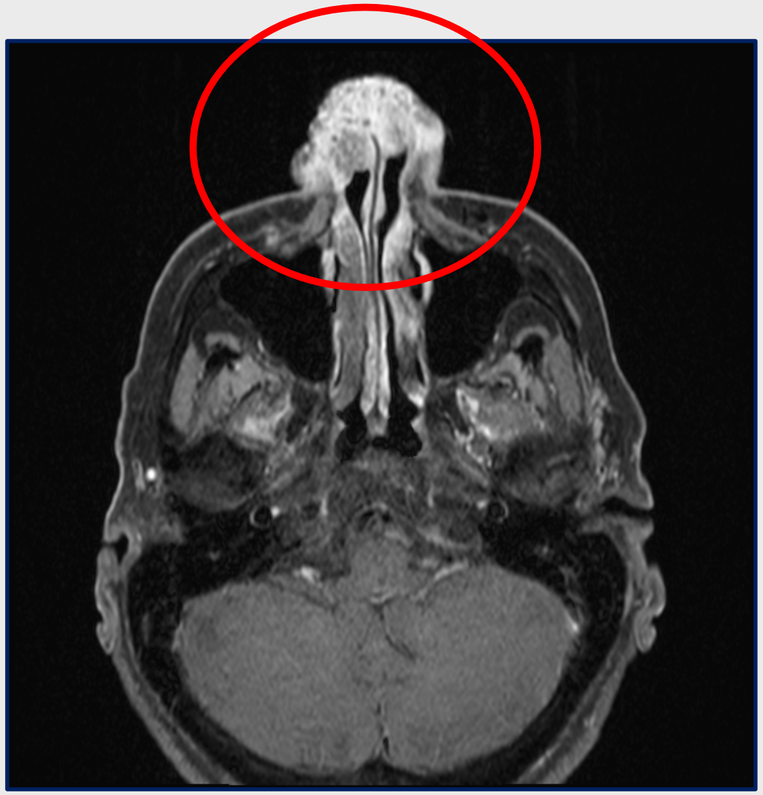
Images courtesy of Neil Gross, MD, FACS

Case #2: Neoadjuvant Immunotherapy

- Radiographic progression after 2 cycles of cemiplimab



Baseline

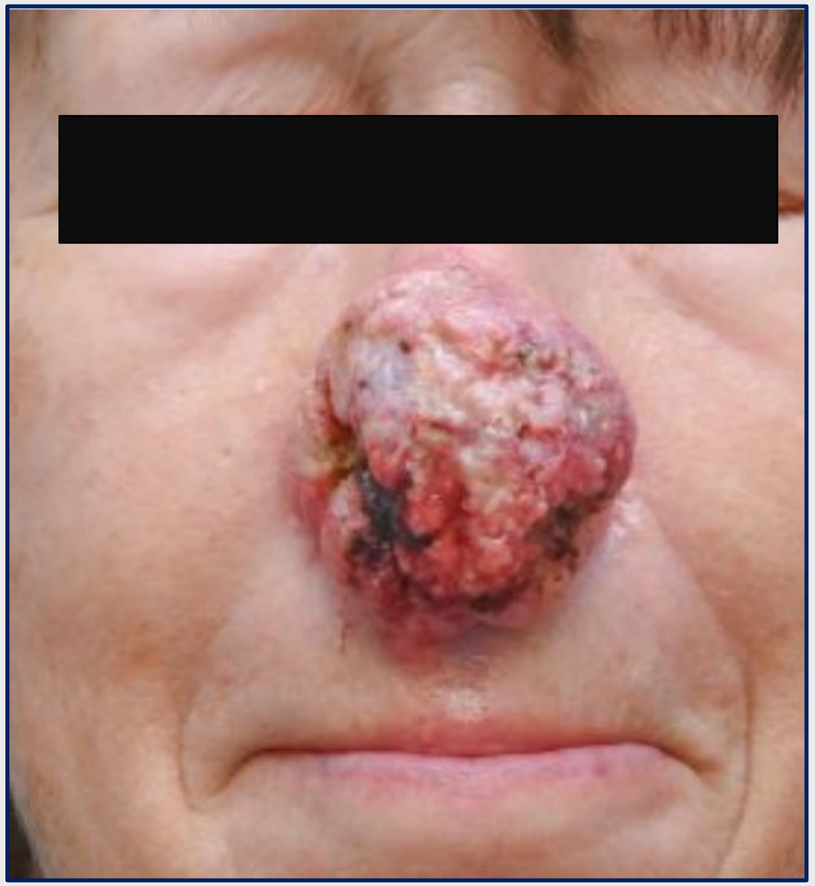


POST Cycle 2

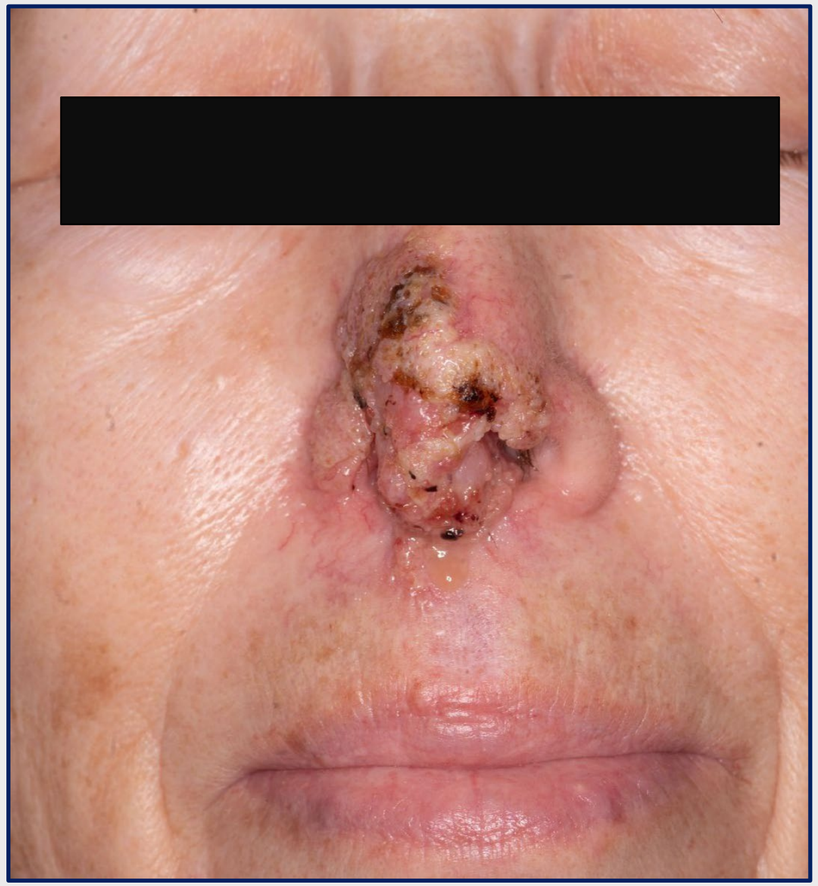
Images courtesy of Neil Gross, MD, FACS

Case #2: Neoadjuvant Chemotherapy

- Switched to carboplatin/paclitaxel



Post immunotherapy



Post chemotherapy

Images courtesy of Neil Gross, MD, FACS

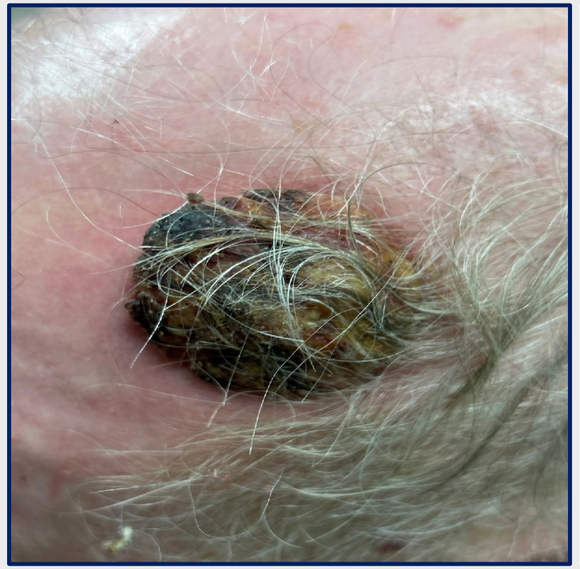
Module 3 - Developing Treatment Plans for High-Risk cSCC: Adjuvant Therapy

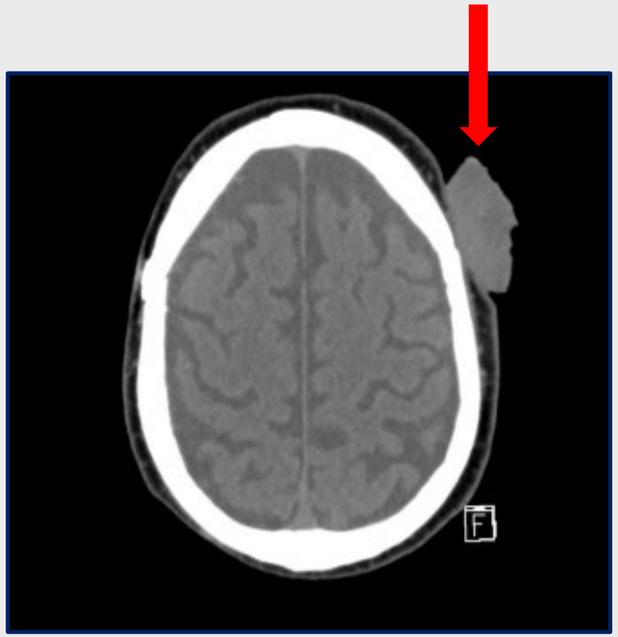
Nikhil I. Khushalani, MD

Vice-Chair and Senior Member
Department of Cutaneous Oncology
Moffitt Cancer Center
Tampa, Florida

Case #3: Introduction

- A 72-year-old male, farmer, with evident sun-damaged skin and multiple actinic keratoses; 3 prior cutaneous squamous cell carcinomas (SCCs) surgically treated on scalp and shoulder
- Developed a new rapidly growing mass on the left frontal scalp with intermittent bleeding
  - Examination with 5 cm exophytic left scalp mass with foul-smelling discharge
  - Biopsy: Moderately differentiated SCC; no perineural/lymphovascular (LV) invasion
  - Computed tomography (CT) of head: 5.1cm extracranial mass
    - Approximating but not invading outer table
  - CT of neck/thorax
    - No evidence of metastases





Images courtesy of Nikhil I. Khushalani, MD.

Defining High-Risk Disease

Personalised decision making to predict absolute metastatic risk in cutaneous squamous cell carcinoma: development and validation of a clinico-pathological model

Barbara Rentroia-Pacheco,[a] Selin Tokez,[a] Edo M. Bramer,[a] Zoe C. Venables,[b,c,d] Harmen J. G. van de Werken,[e] Domenico Bellomo,[f] David van Klaveren,[g] Antien L. Mooyaart,[h] Loes M. Hollestein,[a,i] and Marlies Wakkee[a,*]

https://emc-dermatology.shinyapps.io/cscc-abs-met-risk/

riSCC: A personalized risk model for the development of poor outcomes in cutaneous squamous cell carcinoma

Anokhi Jambusaria-Pahlajani, MD, MSCE,[a] Vincent Jeanselme, PhD,[b] David M. Wang, MD,[c] Nina A. Ran, MD, MS,[c] Emily E. Granger, MD,[d] Javier Cañueto, MD,[e] David G. Brodland, MD,[f] David R. Carr, MD, MPH,[g] Joi B. Carter, MD,[h] John A. Carucci, MD, PhD,[i] Kelsey E. Hirotsu, MD,[j] Emily E. Karn, MS,[c] Shlomo A. Koyfman, MD,[k] Aaron R. Mangold, MD,[l] Fabio Muradás Girardi, MD, MSc,[m] Kathryn T. Shahwan, MD,[g] Divya Srivastava, MD,[n] Allison T. Vidimos, RPh, MD,[o] Tyler J. Willenbrink, MD,[f] Ashley Wysong, MD, MS,[p] William Lotter, PhD,[q] and Emily S. Ruiz, MD, MPH[c]

https://riscc.scoutconsortium.org/

Systematic Review

The Prognostic Value and Clinical Utility of the 40-Gene Expression Profile (40-GEP) Test in Cutaneous Squamous Cell Carcinoma: Systematic Review and Meta-Analysis

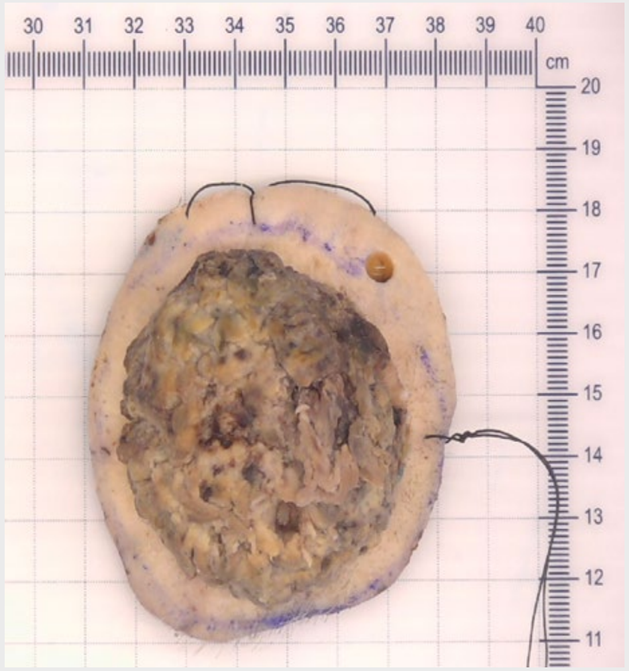
Razan Masarwy [1,2], Shahaf Shilo [1,2], Narin Nard Carmel Neiderman [1,2], Liyona Kampel [1,2], Gilad Horowitz [1,2], Nidal Muhanna [1,2] and Jobran Mansour [1,2,*]

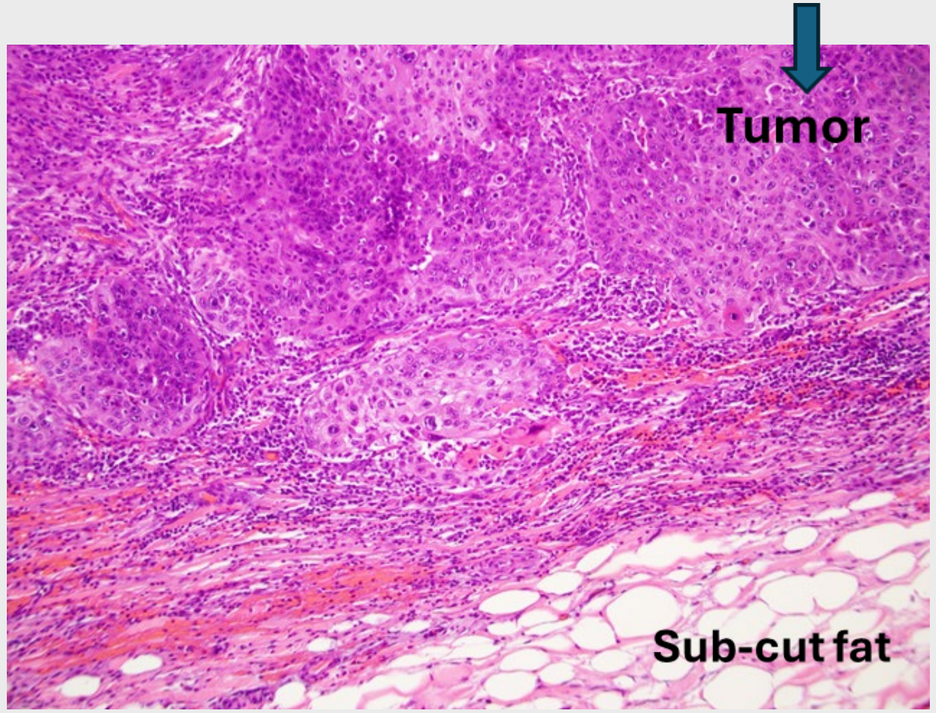
Case Presentation

Undergoes radical excision of scalp SCC

Pathology

- 5.8 cm, residual invasive moderately differentiated SCC
- Cytokeratin 5/6 and p63 positive
- Negative margins
- Diffuse actinic keratosis





Images courtesy of Nikhil I. Khushalani, MD.

Case Presentation

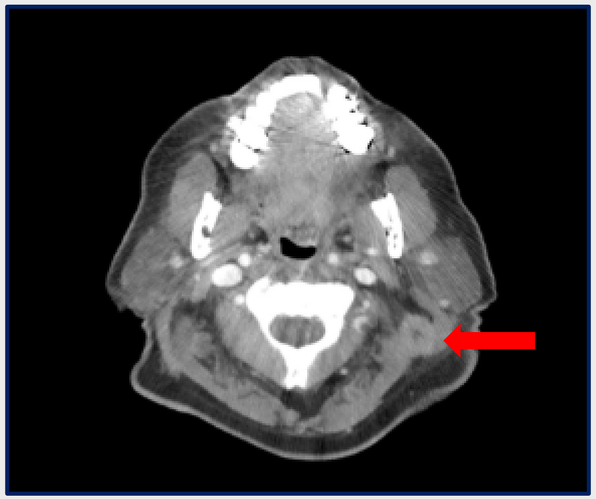
Received adjuvant radiotherapy: 66 Gy

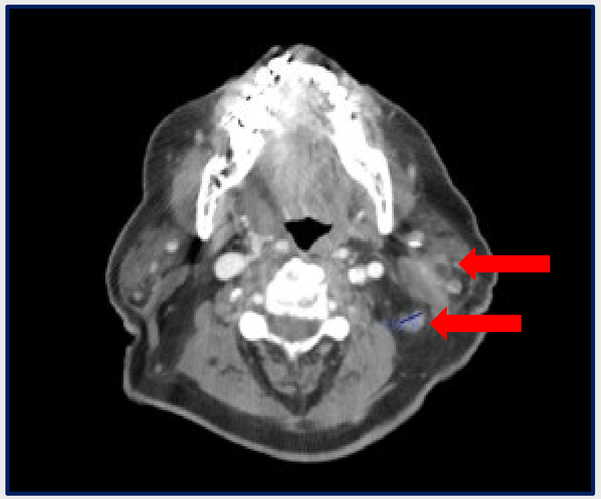
- Is there a role for radiation to the nodal basin(s) when there is no nodal metastasis identified?

Should this patient also receive adjuvant systemic therapy?

Case Presentation

- Developed left neck swelling 8 months following completion of radiation therapy
- Palpable left level 2 adenopathy plus fullness in the left parotid region
- CT of neck shown below; 2 cm and 0.9 cm (lymph [L]) level 2 nodes; 1.6 cm (L) parotid node
- Fine-needle aspiration, level 2 node: SCC with surrounding lymphoid tissue





Images courtesy of Nikhil I. Khushalani, MD.

Case Presentation

Patient undergoes left parotidectomy plus left modified radical neck dissection

- 1/2 intra-parotid nodes involved with SCC; 1.7 cm with extra-capsular extension (ECE)
- 3/33 left neck nodes with metastatic SCC; largest 2.4 cm with ECE

No distant metastases; excellent functional status

What should the next option(s) for treatment include?

a) Adjuvant radiotherapy (RT) to left neck

b) Adjuvant cemiplimab for 1 year

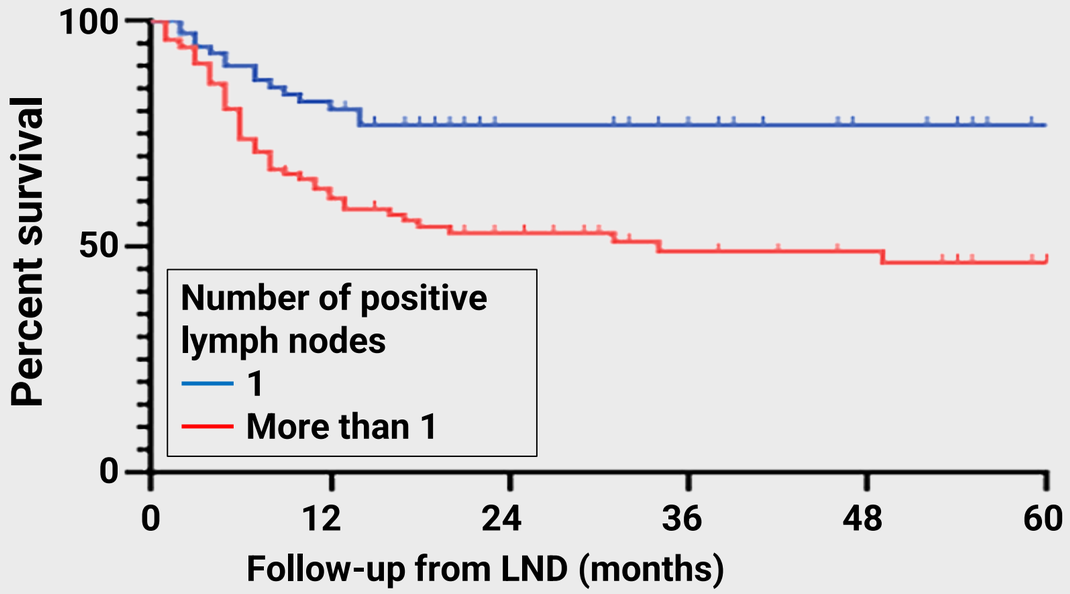
c) Adjuvant RT to left neck followed by adjuvant cemiplimab for 1 year

d) Adjuvant cetuximab for 1 year

e) Observation

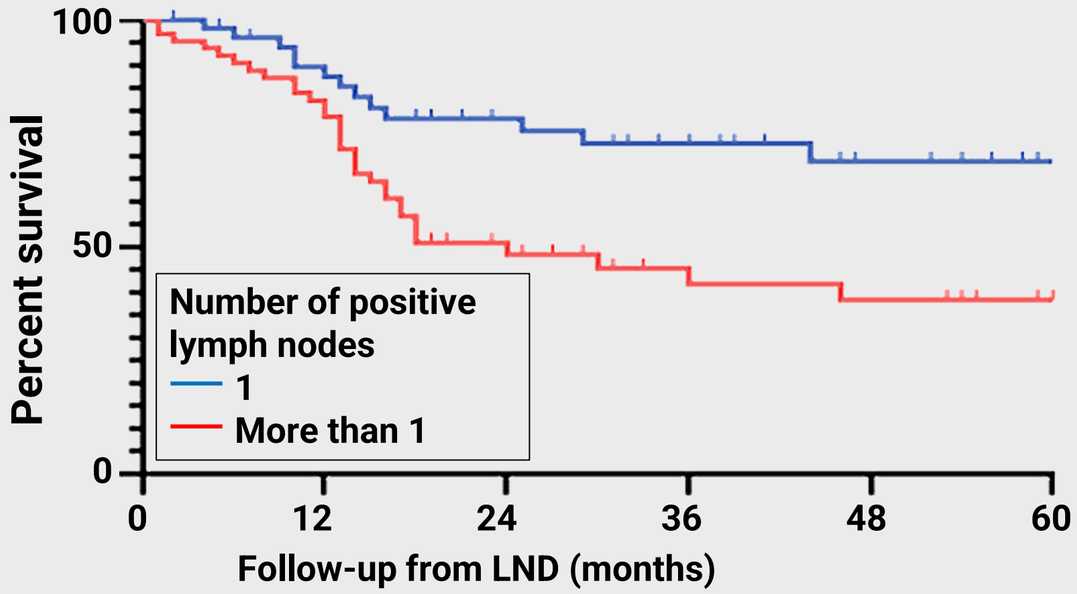
Outcomes After Lymphadenectomy in Cutaneous SCC (cSCC)

Recurrence-free survival after LND



Number at risk						
PL = 1	71	48	32	26	20	12
PL > 1	118	52	33	23	20	14

Disease-specific survival after LND



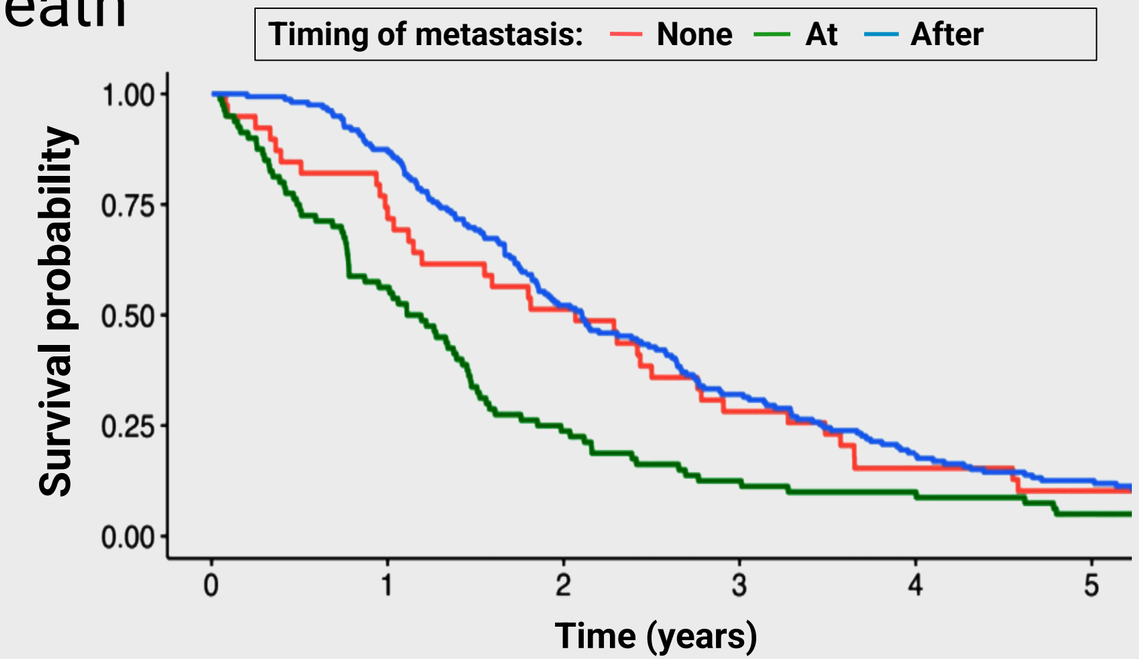
Number at risk						
PL = 1	51	40	28	22	16	9
PL > 1	63	44	19	12	10	5

LND = lymph node dissection; PL = positive lymph node.

Huis In't Veld, et al. *Ann Surg Oncol.* 2023;30(8):5017-5026.

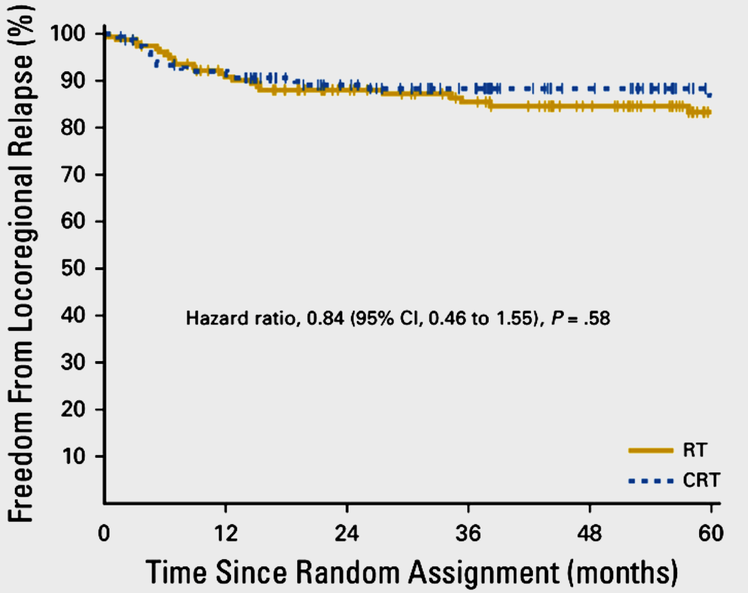
Patterns of Disease-Specific Death (DSD) in cSCC

- Retrospective cohort of cSCC from 12 centers from October 1991 to July 2023
- N = 14,824 patients (23,165 tumors)
- 304 (2.1%) patients with disease-specific death
  - Full data on 278 patients
- 124 (45%) with local recurrence
- 239 (86%) with metastases
  - In-transit (18%), nodal (66%), distant (35%)
- **65% died from loco-regional disease, and 35% died from distant disease**



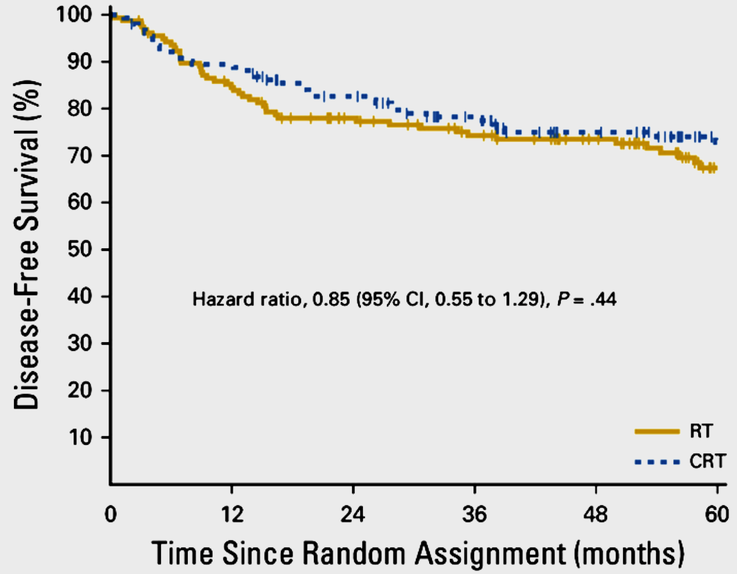
Gibson FT, et al. *J Am Acad Dermatol.* 2025 (https://www.jaad.org/article/S0190-9622(25)02985-8/abstract). Accessed 12/3/2025.

Adjuvant Radiotherapy +/– Chemotherapy
TROG 05:01



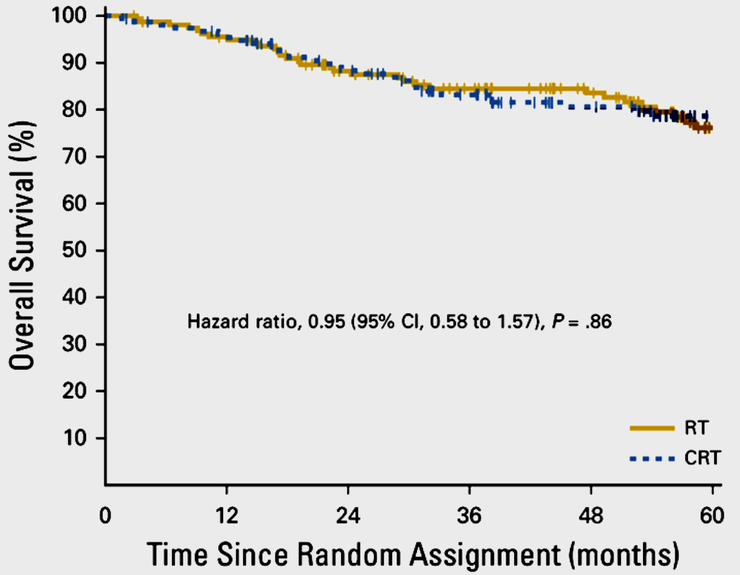
No. at risk (No. of events):

RT	157 (0)	133 (14)	112 (18)	99 (21)	83 (22)	57 (23)
CRT	153 (0)	136 (12)	115 (16)	101 (17)	83 (17)	59 (18)



No. at risk (No. of events):

RT	157 (0)	130 (24)	110 (34)	97 (39)	82 (40)	56 (46)
CRT	153 (0)	135 (16)	117 (26)	101 (32)	82 (36)	59 (38)



No. at risk (No. of events):

RT	157 (0)	147 (7)	124 (18)	108 (23)	89 (24)	60 (31)
CRT	153 (0)	143 (7)	124 (17)	107 (24)	87 (27)	61 (29)

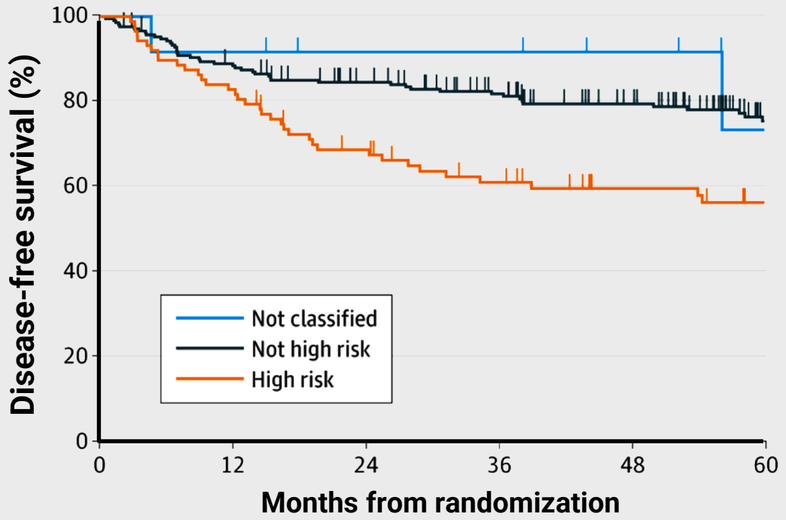
SUMMARY:

<u>No benefit</u> was found with the addition of weekly carboplatin to standard post-operative radiotherapy (60-66 Gy) after resection of high-risk cutaneous squamous cell carcinoma.

Porceddu SV, et al. *J Clin Oncol.* 2018;36(13):1275-1283.

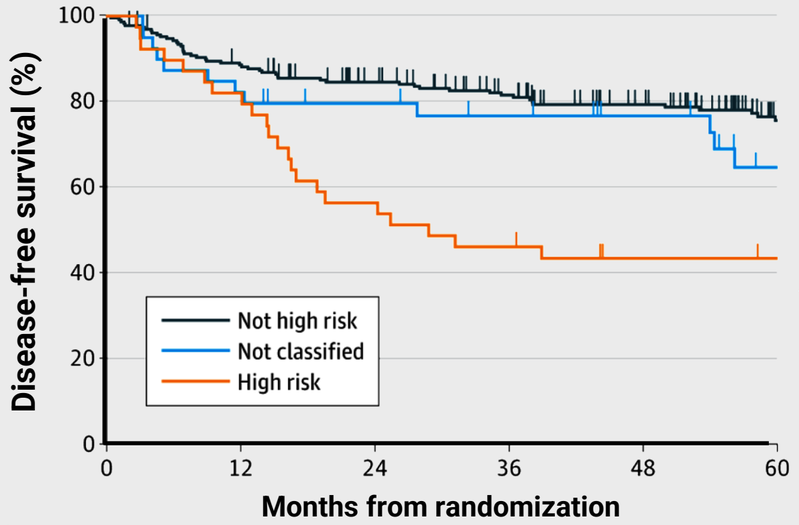
Can We Further Stratify to Define “High-Risk”?

Post-hoc analysis of TROG 05:01



No. at risk						
High risk	88	72	56	46	36	31
Not high risk	210	182	162	143	121	80
Not classified	12	11	9	9	7	4

High-risk subgroup defined as
“extranodal extension (ECE)
AND nodal size ≥22 mm”
5-year DFS: 56%
5-year OS: 59%



No. at risk						
High risk	39	32	22	18	14	13
Not high risk	231	201	177	155	129	88
Not classified	40	32	28	25	21	14

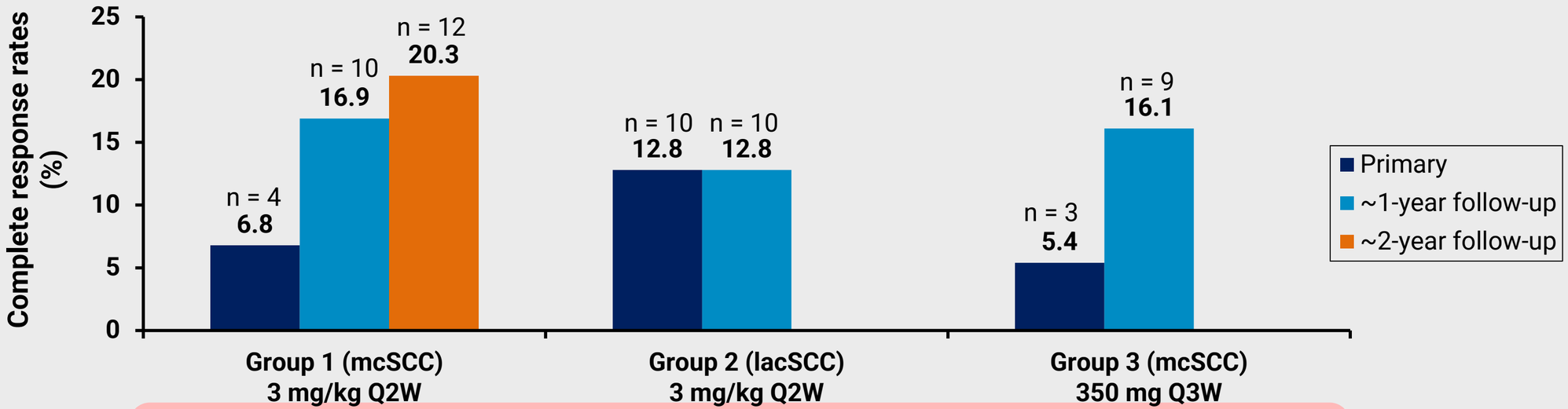
High-risk subgroup restricting analysis to T1 to T4 primary tumors plus nodal ECE and node size ≥22 mm
5-year DFS: 43%

DFS = disease-free survival; OS = overall survival.

Porceddu SV, et al. *JAMA Otolaryngol Head Neck Surg.* 2025;151(10):938-945.

EMPOWER: Cemiplimab in cSCC

N = 193	Cohort 1	Cohort 2	Cohort 3
Dose	3 mg/kg q2w	3 mg/kg q2w	350 mg q3w
ORR (%)	**50.8**	**44.9**	**42.9**
CR (%)	20.3	12.8	16.1
mPFS	18.1 months (95% CI, 10.3–24.3)		



Cemiplimab, pembrolizumab, and cosibelimab are currently approved for advanced, unresectable cSCC.

CI = confidence interval; CR = complete response: lacSCC = locally advanced cutaneous squamous cell carcinoma; mcSCC = metastatic cutaneous squamous cell carcinoma; mPFS = medican progression-free survival; ORR = objective response rate; q2w = every 2 weeks; q3w = every 3 weeks.

Rischin D, et al. *J Immunother Cancer.* 2021;9(8):e002757.

Cemiplimab-Post Operative Skin Trial (C-POST) – Key Inclusion & Exclusion Criteria

Key inclusion criteria
High-risk cSCC, defined by ≥1 high-risk category
Macroscopic gross resection of all disease
Completion of postoperative radiation therapy (≥50 Gy BED) within 2–10 weeks of randomization
ECOG performance status of 0 or 1
Adequate hepatic, renal, and bone marrow function

Key exclusion criteria
SCC arising from noncutaneous sites
Concurrent malignancy other than localized cSCC and certain low-risk diagnoses permitted per protocol
Hematologic malignancies except for patients with CLL who have not required treatment within 6 months of randomization
History of solid organ transplant except corneal transplants

BED = biologically effective dose; CLL = chronic lymphocytic leukemia; ECOG = Eastern Cooperative Oncology Group.

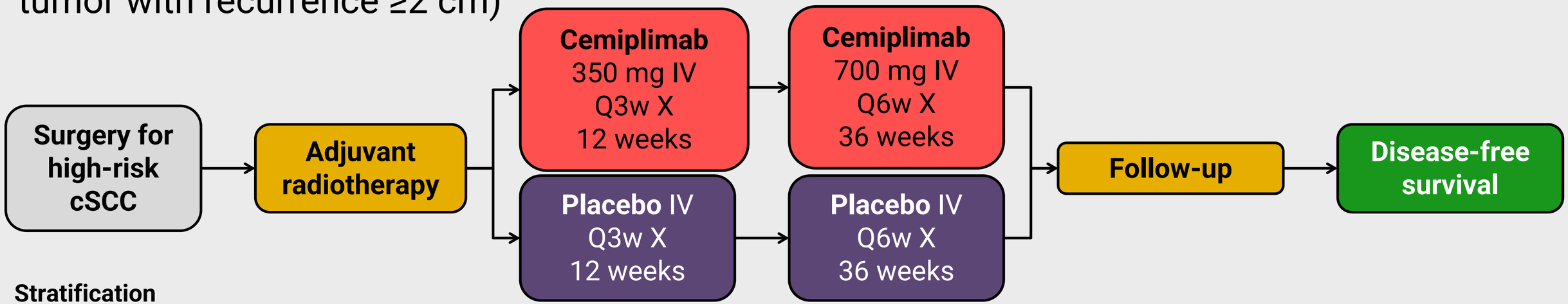
Rischin D, et al. *N Engl J Med.* 2025;393:774-785.

C-POST Schema

HIGH-RISK DEFINITIONS:

NODAL: ECE + 1 node ≥20 mm, or ≥3 involved nodes

NON-NODAL: In-transit disease; perineural invasion (clinical or radiographic of named nerve); T4 disease; local recurrence + 1 additional feature (nodal ≥N2b, ≥T3, poorly differentiated tumor with recurrence ≥2 cm)



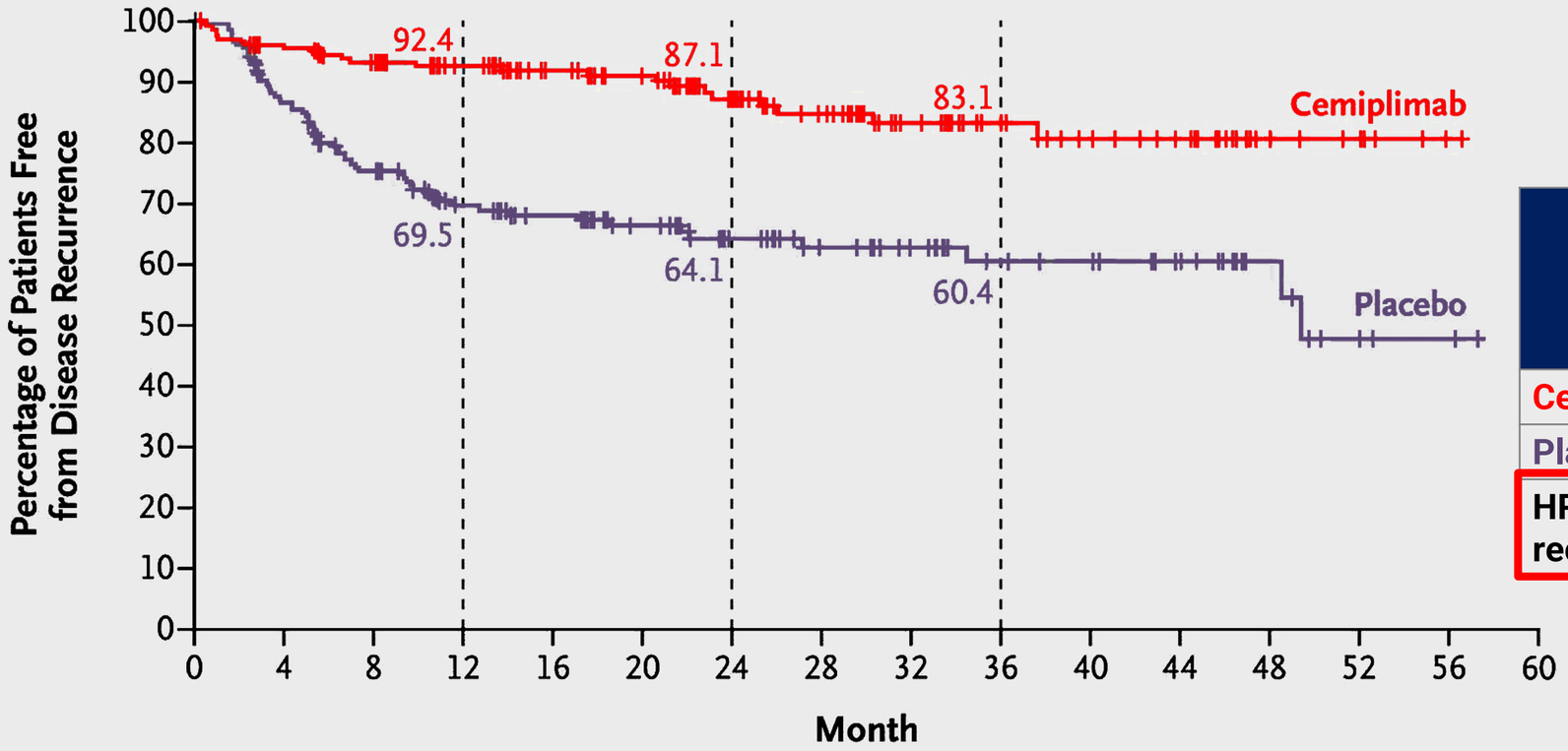
Stratification

- Head/neck or Non-head/neck
- Geography: North America vs Australia/New Zealand vs Rest of World
- ECOG 0 vs 1
- Nodal vs Nonnodal
- CLL – Yes or No

IV = intravenous.

Rischin D, et al. *N Engl J Med.* 2025;393:774-785 (and supplemental material).

C-POST: Disease-Free Survival



	# of events	Median disease-free survival (months)
Cemiplimab	24	NR (NE–NE)
Placebo	65	49.4 (48.5–NE)
HR for disease recurrence or death	0.32 (95% CI, 0.20–0.51) *P* < .001	

No. at Risk

Cemiplimab	209	172	157	132	116	104	83	66	47	33	27	22	9	6	1	0
Placebo	206	161	130	94	82	69	53	42	36	26	24	18	10	4	2	0

HR = hazard ratio; NE = not evaluable; NR = not reached.

Rischin D, et al. *N Engl J Med.* 2025;393:774-785.

Adverse Events With Adjuvant Cemiplimab

Adverse events during treatment period, according to grade*

Event	Cemiplimab (N = 205)		Placebo (N = 204)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
	number of patients with event (percent)			
Any adverse event	187 (91.2)	49 (23.9)	182 (89.2)	29 (14.2)
Serious adverse event	36 (17.6)	31 (15.5)	19 (9.3)	14 (6.9)
Adverse event leading to discontinuation of cemiplimab or placebo	20 (9.8)	16 (7.8)	3 (1.5)	2 (1.0)
Adverse event leading to death†	2 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)
Adverse events in ≥10% of the patients in either group‡				
Fatigue	45 (22.0)	1 (0.5)	44 (21.6)	0
Pruritus	33 (16.1)	1 (0.5)	25 (12.3)	0
Rash	33 (16.1)	1 (0.5)	18 (8.8)	0
Diarrhea	32 (15.6)	3 (1.5)	38 (18.6)	0
Arthralgia	26 (12.7)	0	25 (12.3)	0
Hypothyroidism	24 (11.7)	1 (0.5)	6 (2.9)	0
Maculopapular rash	23 (11.2)	0	12 (5.9)	0
Bowen's disease	16 (7.8)	1 (0.5)	21 (10.3)	2 (1.0)

No new safety signals were found with adjuvant cemiplimab compared to its use in the advanced setting.

* Shown are adverse events that developed or worsened during the treatment period and any adverse events that were considered by the investigator to be related to cemiplimab or placebo that occurred during the posttreatment period but before part 2 of the trial (subsequent cemiplimab treatment). † 1 death due to pneumonia was considered by the investigator to be unrelated to cemiplimab, and 1 death due to myositis was considered by the investigator to be related to cemiplimab. 1 death due to pneumonia and 1 death due to new primary malignant lung neoplasm were both considered by the investigator to be unrelated to placebo. ‡ Patients were counted only once according to the worst grade for multiple occurrences within a preferred term.

Rischin D, *N Engl J Med.* 2025;393:774-785.

KEYNOTE-630: Adjuvant Pembrolizumab

Key eligibility criteria

- High-risk locally advanced (LA) cSCC
- Underwent surgery with curative intent
- Completed adjuvant radiotherapy (last dose ≥4 weeks and ≤16 weeks from randomization)

Stratification factors (yes vs no)

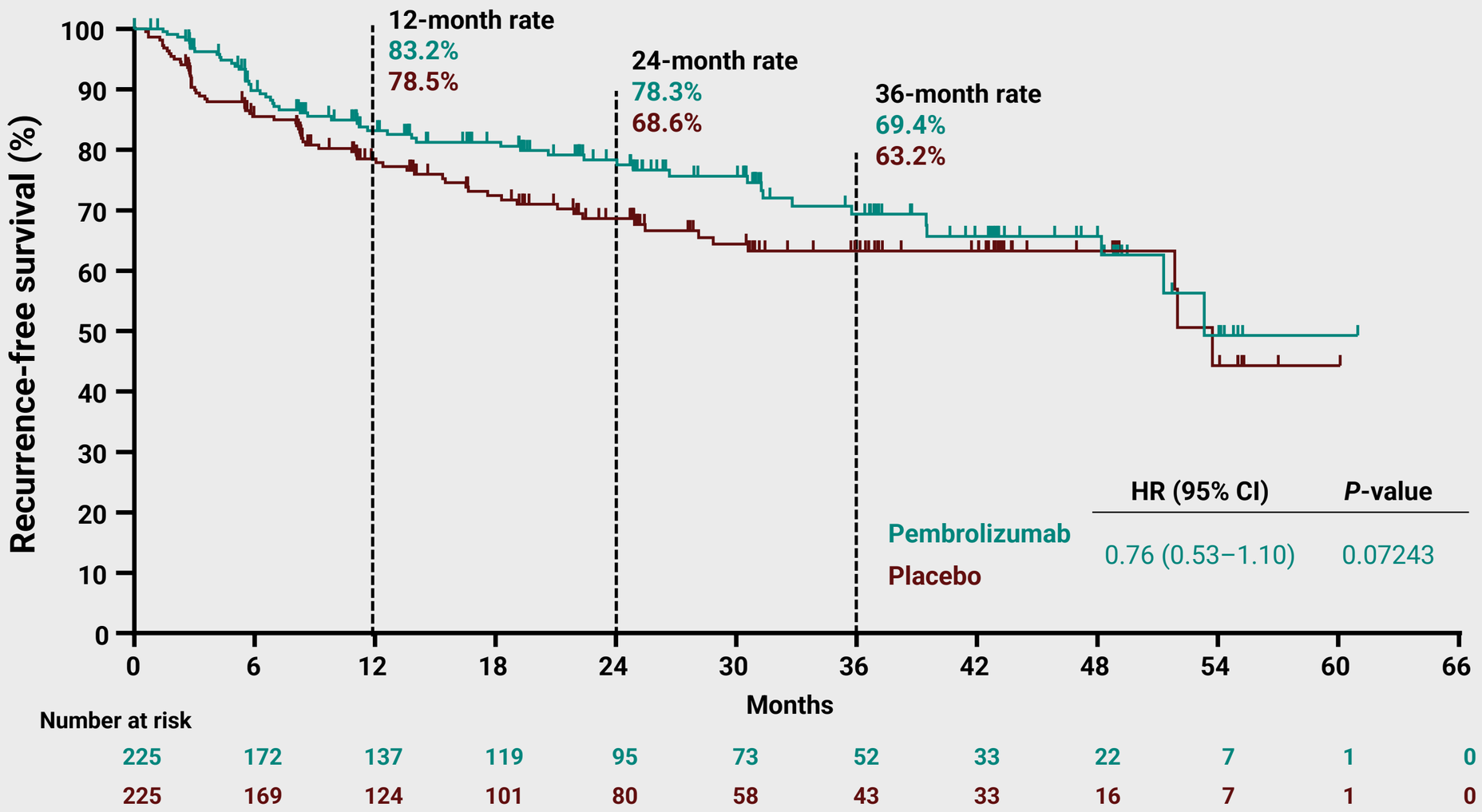
- Extracapsular extension
- Cortical bone invasion
- Prior systemic therapy

N = 450
Adjuvant pembrolizumab or placebo

Primary endpoint: Investigator-assessed recurrence-free survival

Koyfman SA, et al. American Society of Clinical Oncology (ASCO) 2025; Abstract 6000.

KN-630: DFS



Koyfman SA, et al. ASCO 2025; Abstract 6000.

So Why Did Two Trials With Similar Design Have Contradicting Results?

- Definitions of high-risk disease?
- Definitions of “events” that counted toward relapse-free survival (RFS)/disease-free survival (DFS)?
- Timing of adjuvant radiotherapy?
- Other?

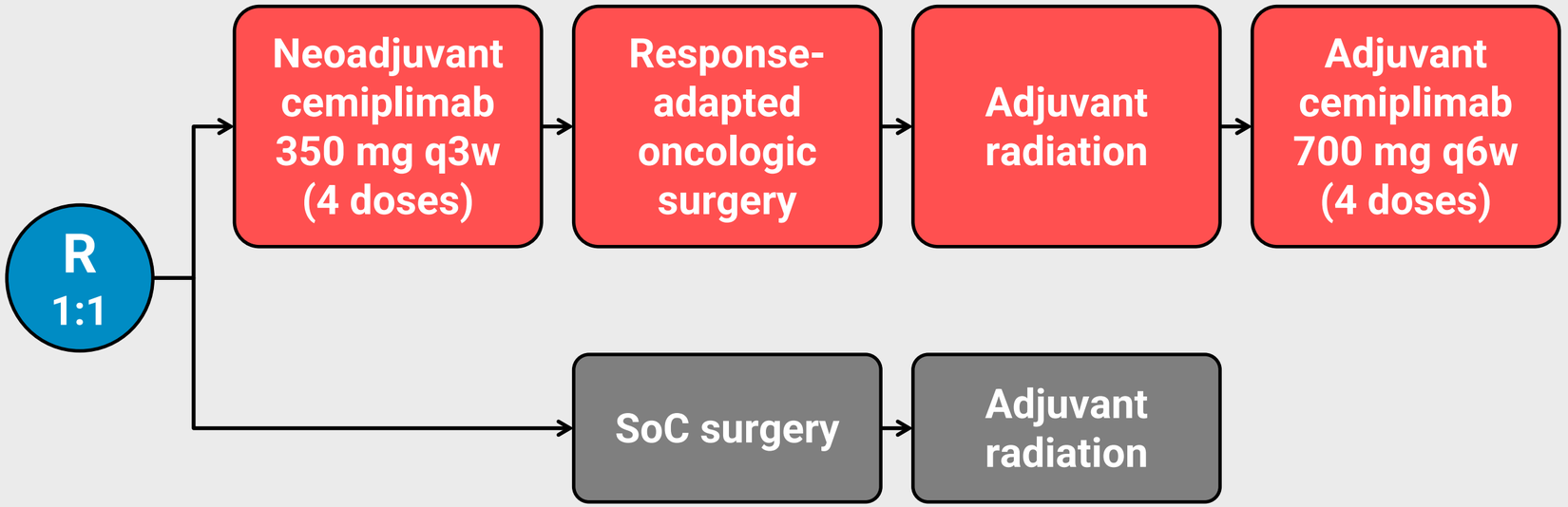
Event	Pembrolizumab n = 225	Placebo n = 225
Any recurrence	31 (13.8)	57 (25.3)
Distant metastasis	10 (4.4)	26 (11.6)
Death	35 (15.6)	24 (10.7)

Next Steps: NRG-HN014 Trial Schema

Neoadjuvant Cemiplimab, Followed by Surgery and Adjuvant Radiation, and Potentially by Adjuvant Cemiplimab

Inclusion criteria

- cSCC
- Stage III–IV
- Resectable with curative intent
- ECOG PS 0–2



- **Primary endpoint:** EFS
- **Key secondary endpoints:** Toxicity, DFS, DSS, OS, pathologic response, RT utilization, QoL

DSS = disease-specific survival; PS = performance status; R = randomization; QoL = quality of life; SoC = standard of care.

NCT06568172 (https://clinicaltrials.gov/study/NCT06568172). Accessed 12/2/2025.

Conclusions:

- Adjuvant cemiplimab is now an approved option for patients with cSCC at high risk for recurrence after surgery and radiation

- Decision to offer adjuvant therapy should be carefully balanced using defined criteria for *high-risk* disease and medical comorbidity

Module 4 - Multidisciplinary Care of cSCC

Michael R. Migden, MD

Professor, Department of Dermatology
University of Texas MD Anderson Cancer Center
Houston, Texas

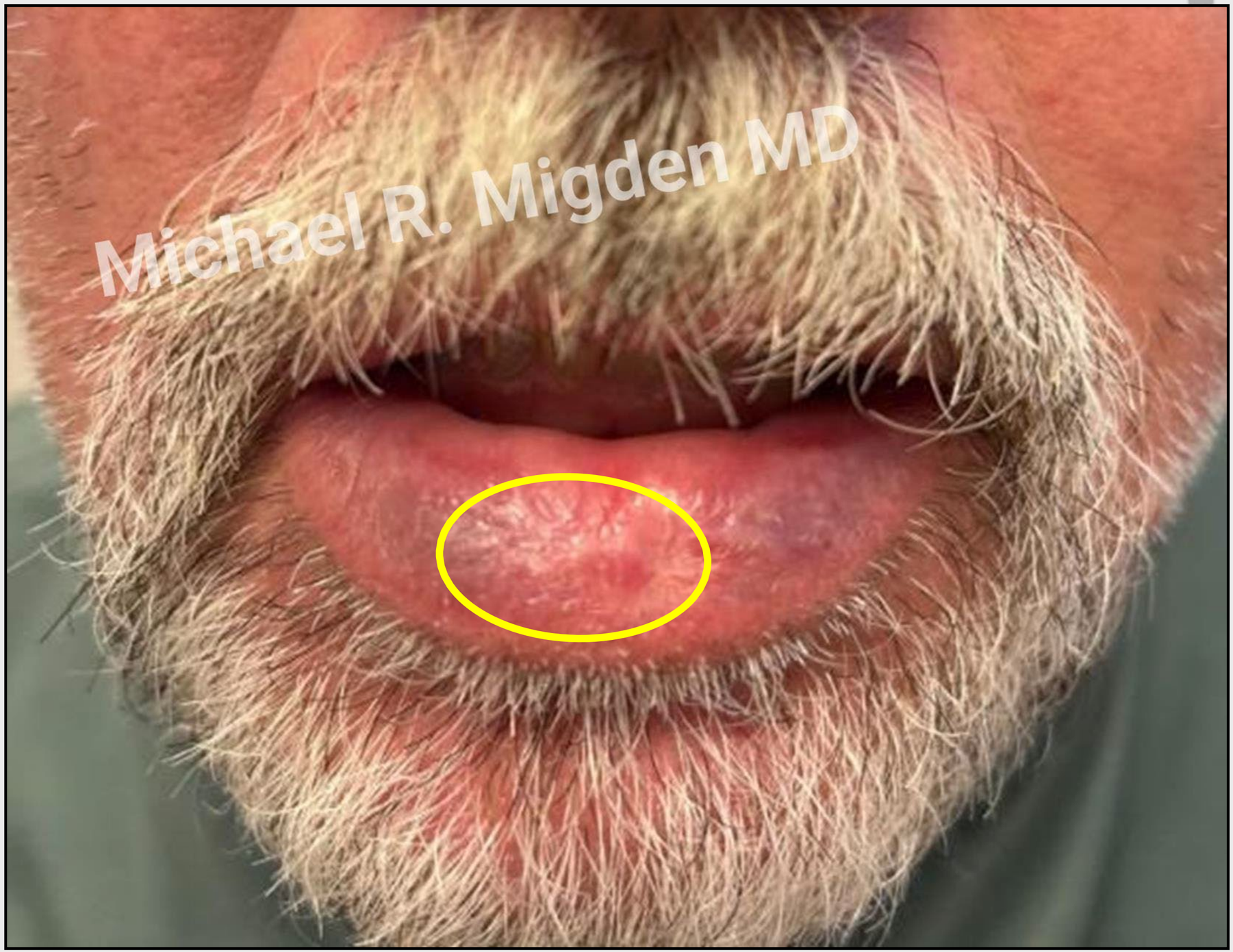
Multidisciplinary Specialists in the Care of Patients With High-Risk cSCC

- Dermatologist
- Head and neck surgeon
- Medical oncologist
- Dermatopathologist
- +/- other specialists as needed regarding toxicities
- Mohs surgeon
- Surgical oncologist
- Radiation oncologist
- Radiologist

When Is Extensive Mohs Appropriate for Aggressive, Larger SCC?

- Patient medically stable and not experiencing “surgical fatigue”
  - Symptom control oral analgesia/anxiolysis adequate: No moderate or deep sedation
- Imaging: Tumor depth achievable (eg, not parotid); resectable in Mohs setting
- Adequate confidence: Precise tumor mapping/probability of obtaining clear margins
- **“Moat” resection** in very large cases; may combine with HNS central en bloc excision
- **With** approved, **effective, systemic treatment (single agent) and NCCN supportive neoadjuvant, the consequences of immediate large surgery** should be weighed against the risks associated with immunotherapy; surgery **at what cost?**

HNS = head and neck surgery. NCCN = National Comprehensive Cancer Network.

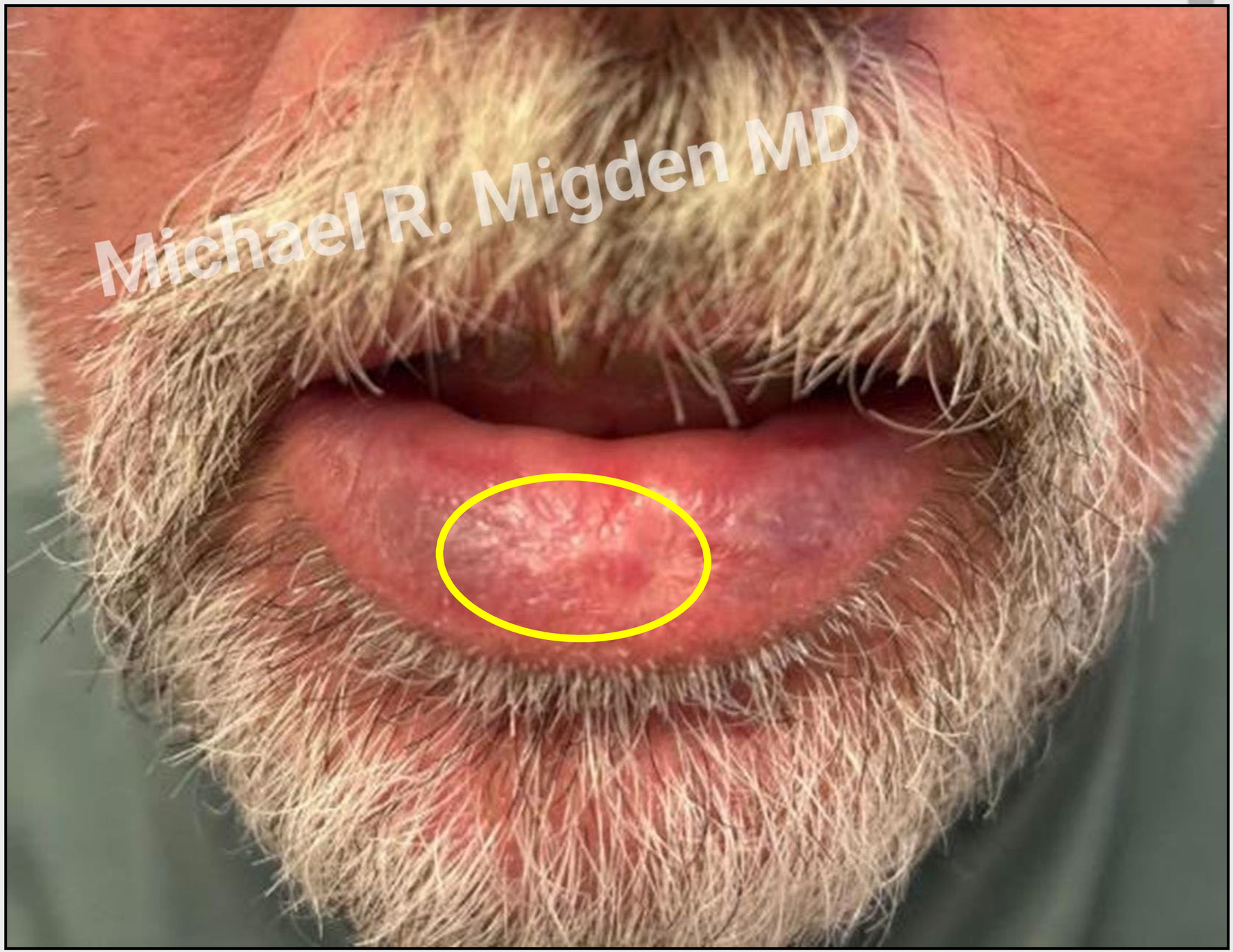


Case #4 - Introduction

- A 59-year-old male with 1.5 x 1.4 cSCC lower dry lip vermillion
- Ill-defined after biopsy
- Outside path: Well-differentiated cSCC

Image courtesy of Michael R. Migden, MD

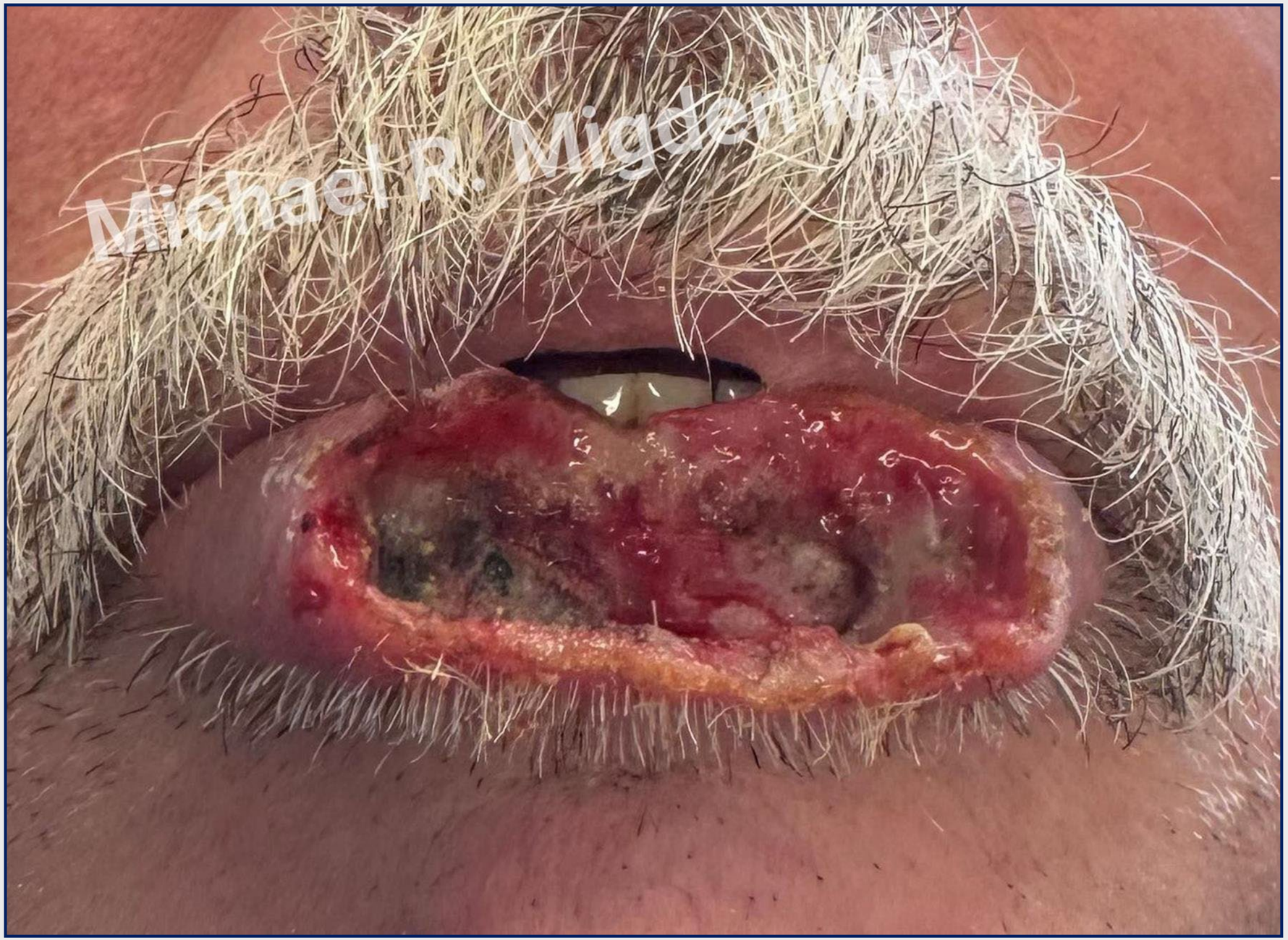
cSCC = cutaneous squamous cell carcinoma.



Case #4

- A 59-year-old male with 1.5 x 1.4 cSCC lower dry lip vermillion
- Ill-defined after biopsy
- Outside path: Well-differentiated cSCC
- **Path Re-read academic center: Moderate to poor differentiated cSCC**

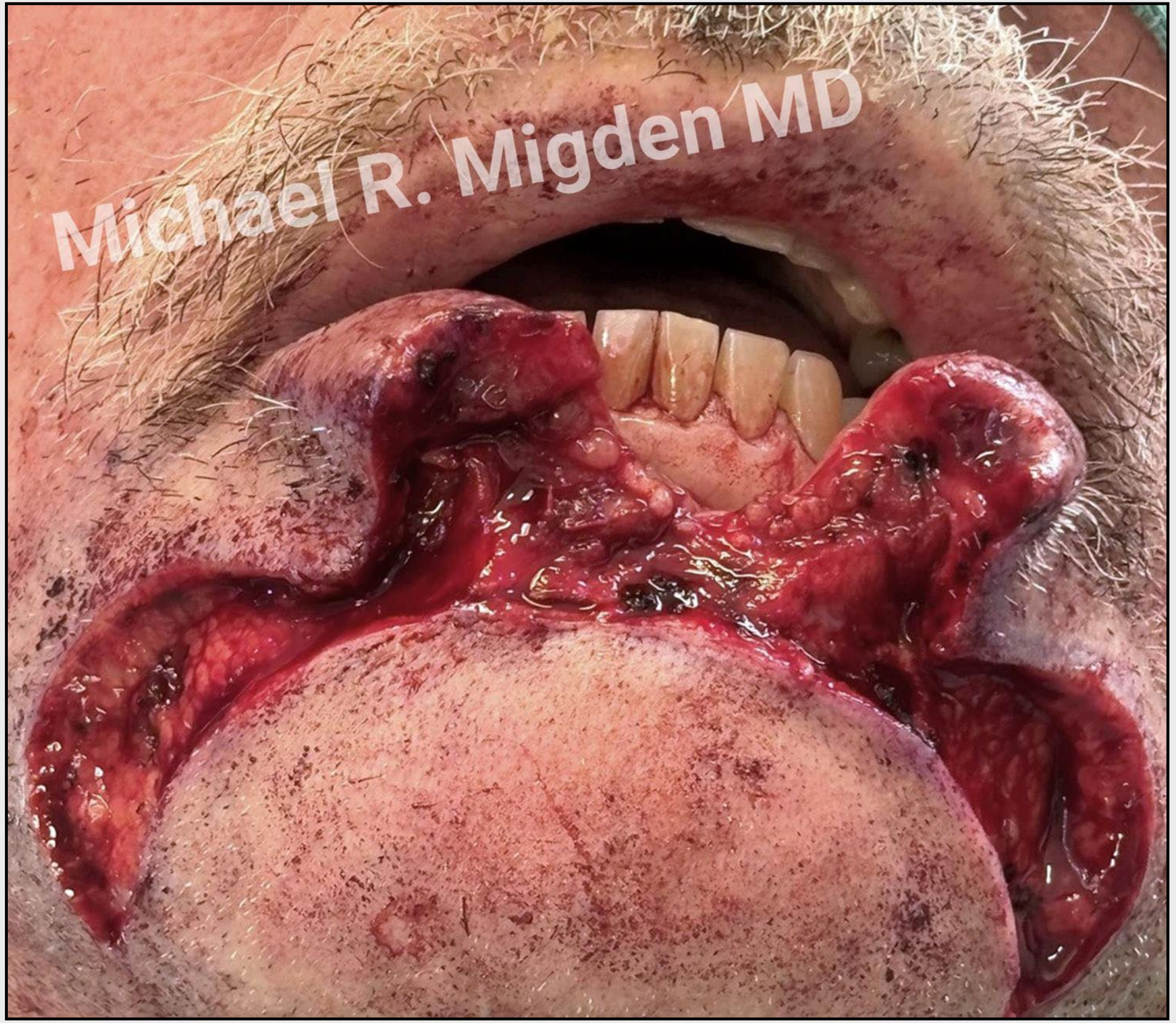
Image courtesy of Michael R. Migden, MD



Case #4

- Mohs clear in 2 stages
- En face stage IHC #1 beyond Mohs read: Minute foci poorly differentiated cSCC with perineural invasion 0.2 mm caliber
- En face stage IHC #2 read: **Positive single cells**, small clusters, **poorly differentiated cSCC**

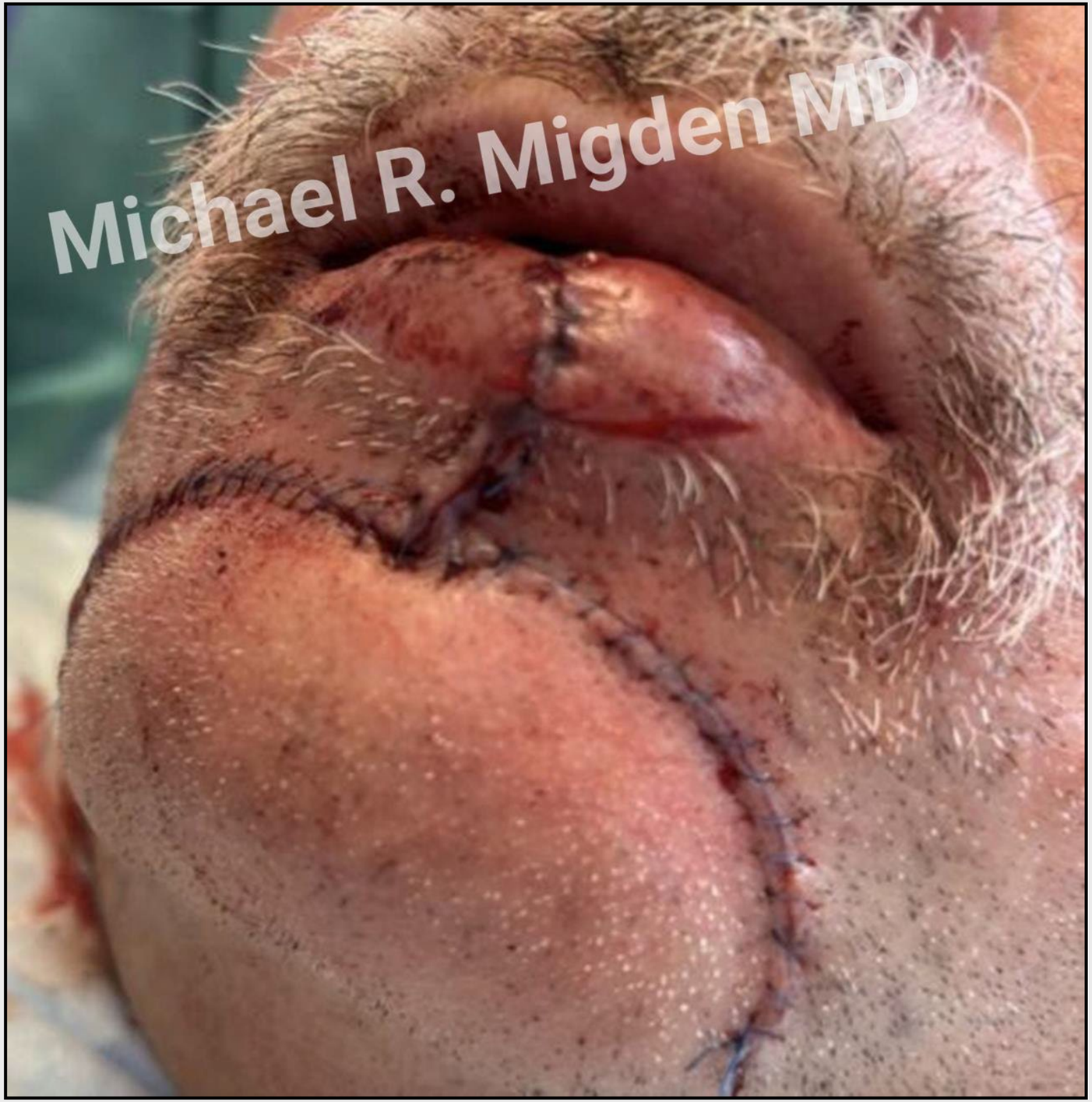
Image courtesy of Michael R. Migden, MD



Case #4

- Central en face biopsy IHC #3: Unequivocal carcinoma not identified
- Bilateral crescentic advancement flap local anesthesia + symptom control prescription

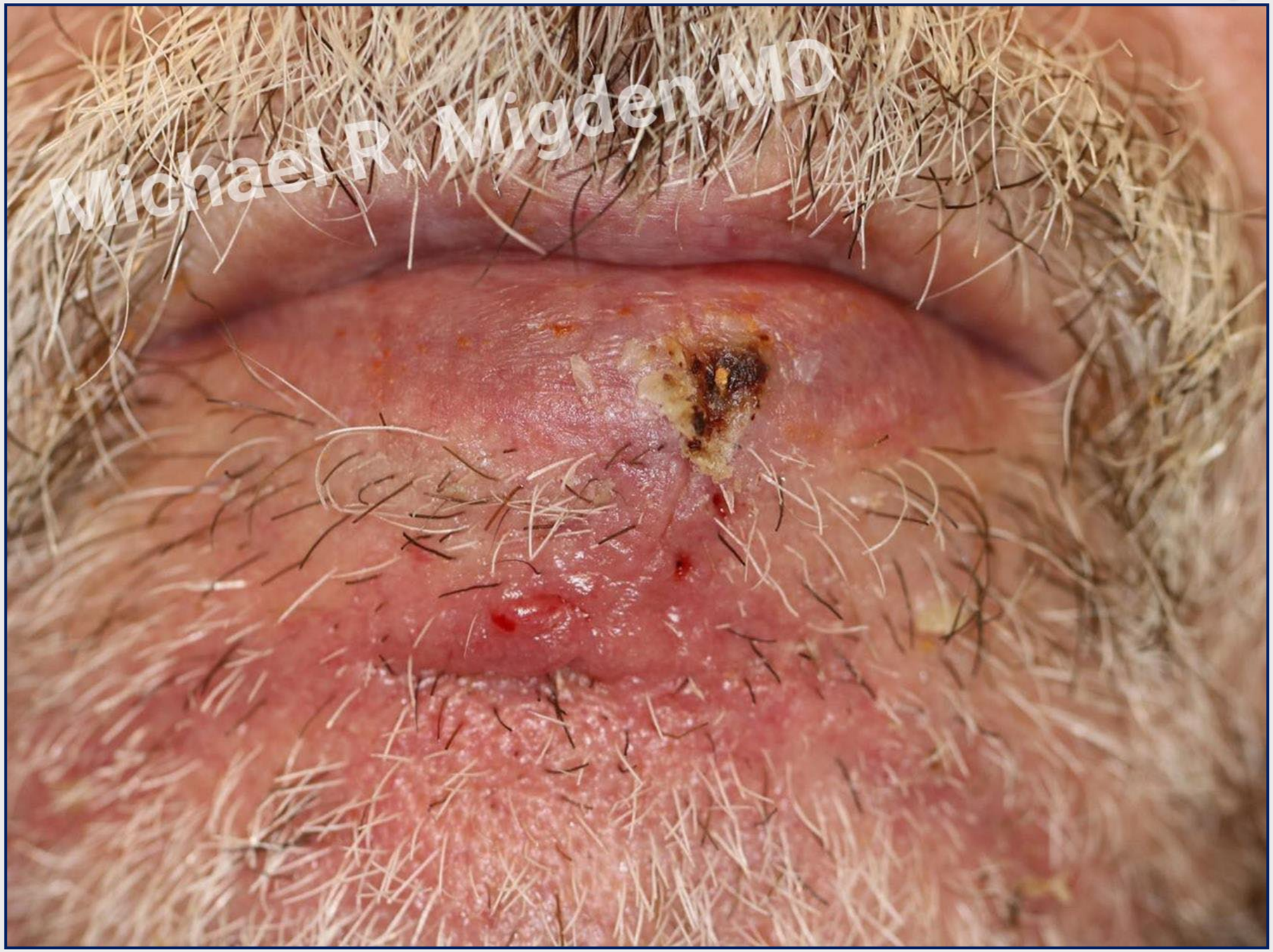
Image courtesy of Michael R. Migden, MD



Case #4

- Bilateral crescentic advancement flaps using local anesthesia

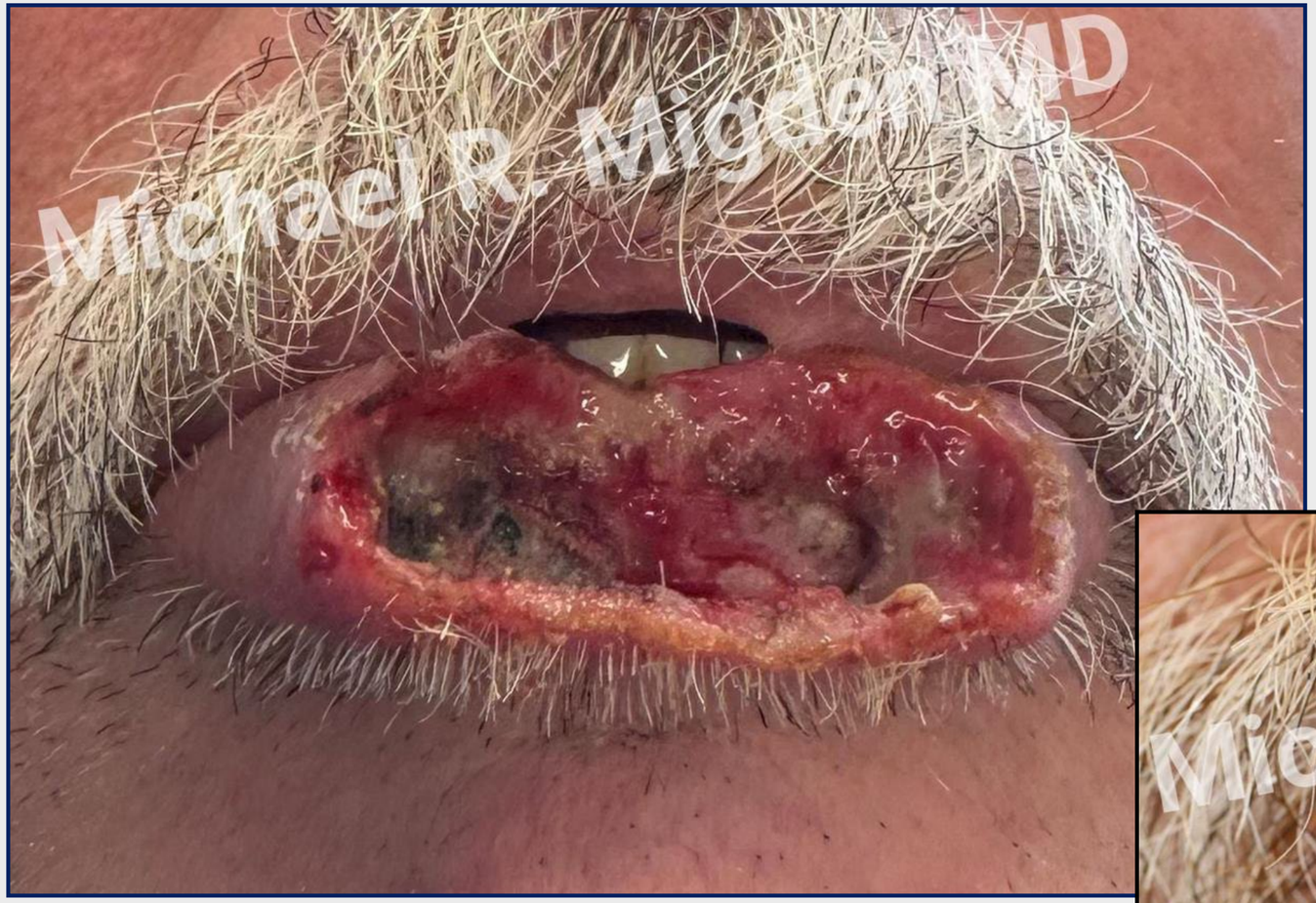
Image courtesy of Michael R. Migden, MD



Case #4

- Postoperative stereotactic radiosurgery (SR) 11 days out from reconstruction
- Patient undergoing RT

Image courtesy of Michael R. Migden, MD



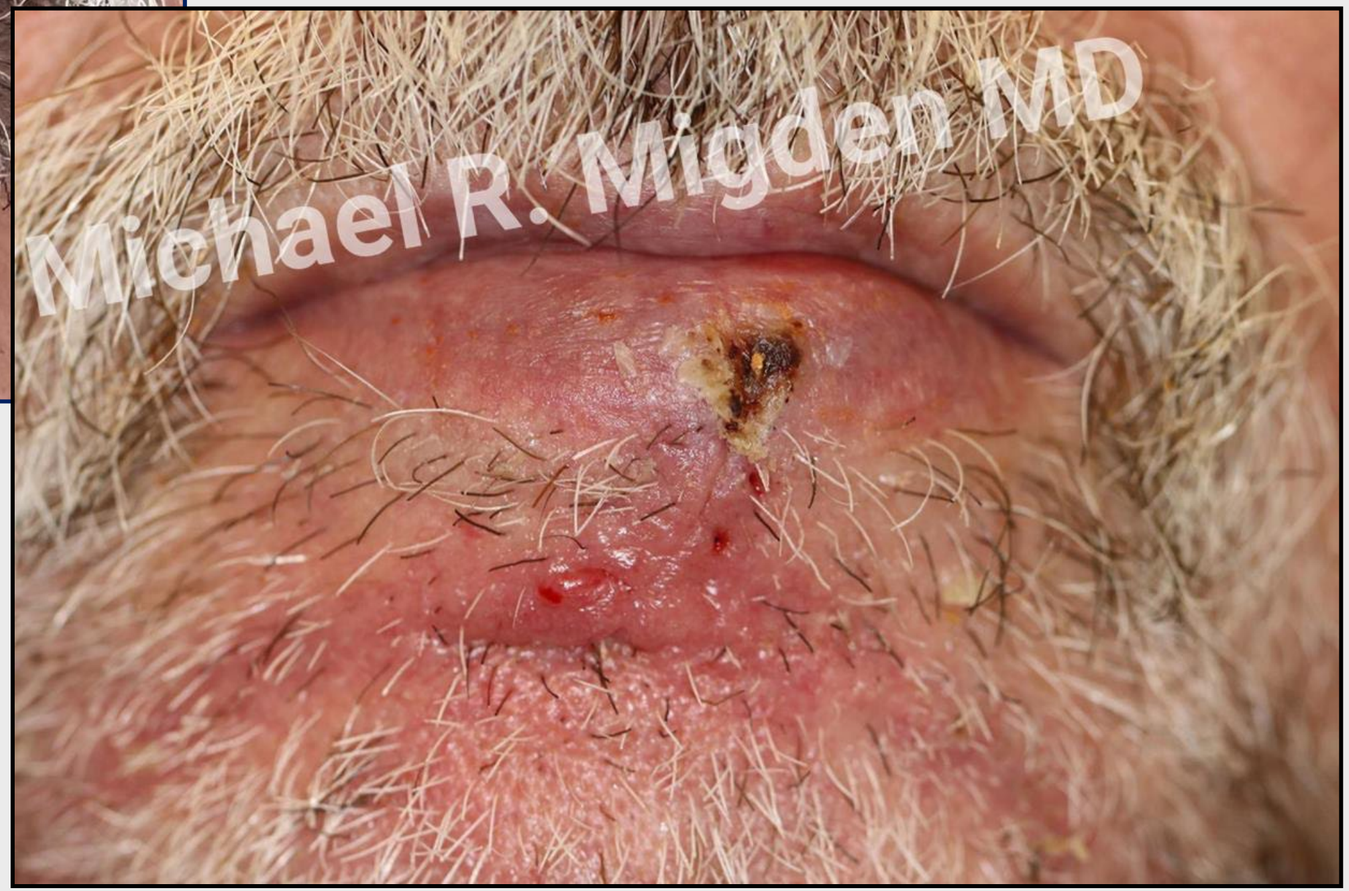


Image courtesy of Michael R. Migden, MD

C-POST Methods: High-Risk Criteria

Nodal and **non-nodal** high-risk criteria*

Nodal disease	In-transit metastases	Perineural invasion	T4 lesions	Recurrent cSCC
ECE with ≥1 node ≥20 mm[1] OR ≥3 nodes regardless of ECE	Skin or subcutaneous metastases >20 mm from the primary lesion but not beyond the regional nodal basin	Clinical and/or radiologic involvement of named nerves	Invasion of cortical bone or skull base	cSCC that arises within the area of previously resected tumor plus ≥1 additional feature ▪ ≥N2b disease associated with the recurrent lesion ▪ Nominal ≥T3 ▪ Poorly differentiated histology and recurrent lesion ≥20 mm diameter

*High-risk cSCC with both nodal and nonnodal features was categorized as high-risk nodal disease.

ECE = extracapsular extension.

Connolly E, et al. European SocieTy for Radiotherapy and Oncology (ESTRO) 2025; Abstract E25-1045.

Adjuvant Treatment of cSCC at High Risk of Recurrence

C-POST study

The safety of cemiplimab-rwlc was evaluated in patients with cSCC at high risk of recurrence after surgery and radiation in the C-POST study (see Clinical Studies [14.1]).

Patients were assigned to receive

- Cemiplimab-rwlc 350 mg (n = 140) or placebo (n = 140) intravenously every 3 weeks for 12 weeks, followed by 700 mg cemiplimab-rwlc or placebo intravenously every 6 weeks for an additional 36 weeks, or
- Cemiplimab-rwlc 350 mg every 3 weeks (n= 65) or placebo (n = 64) for up to 48 weeks

Treatment continued until disease recurrence, unacceptable toxicity, or up to 48 weeks.

The median duration of exposure was 48 weeks (range: 3 weeks to 52 weeks) in cemiplimab-rwlc-treated patients.

- Serious adverse reactions occurred in 18% of patients who received cemiplimab-rwlc; serious adverse reactions that occurred in >1% of patients in the cemiplimab-rwlc arm were pneumonia (1.5%), rash (1.5%), diarrhea (1.5%), adrenal insufficiency (1%), and arrhythmia (1%)
- Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received cemiplimab-rwlc; adverse reactions resulting in permanent discontinuation in >1% of patients were alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, and adrenal insufficiency
- Dosage interruptions due to an adverse reaction occurred in 22% of patients who received cemiplimab-rwlc; adverse reactions leading to interruptions in >1% of patients included COVID-19, diarrhea, alanine aminotransferase increased, urinary tract infection, upper respiratory tract infection, aspartate aminotransferase increased, edema, dyspnea, pneumonitis. pneumonia. and rash

Cemiplimab-rwlc (Libtayo®) prescribing information (PI) 2025 (https://www.libtayohcp.com/). Accessed 12/8/2025.

High/Very-High-Risk cSCC Sent for Mohs Surgery

Clinical/radiographic extent?

Is tumor well-defined?

Symptom control during procedure?

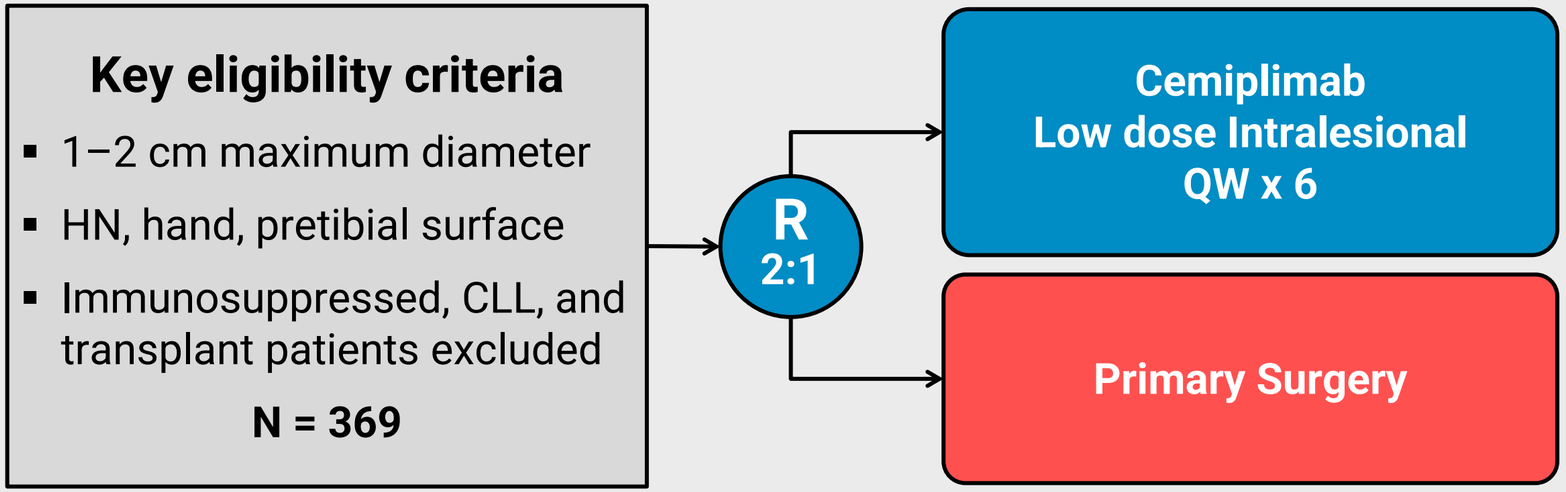
Opportunities for multidisciplinary collaboration?

“Intervene earlier and, where possible, locally”

Society for Immunotherapy of Cancer (SITC) 2023 plenary session panel consensus

Phase 3 Trial of Intralesional Cemiplimab in Patients with Early-Stage CSCC (NCT06585410): Study Design

Randomized, Open-label Study



Primary Endpoints

- EFS (both arms): 1 year and 3 year from randomization, per investigator assessment

Secondary Endpoints

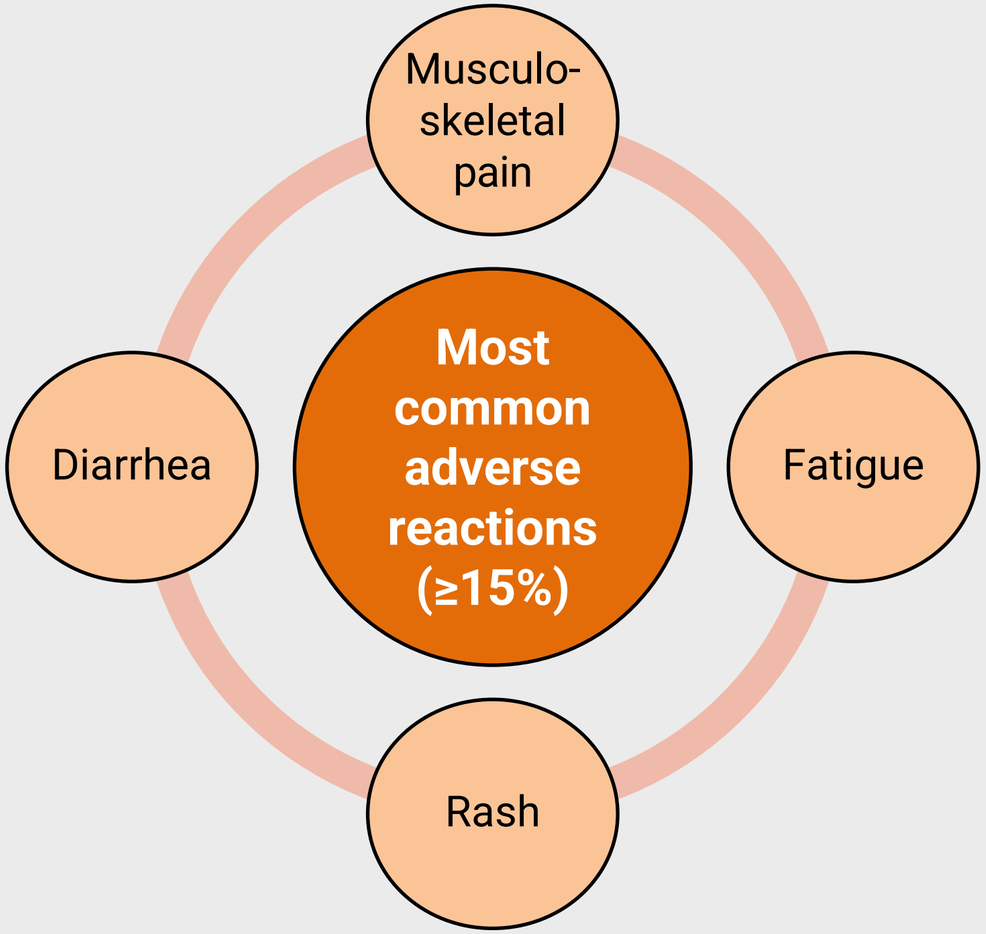
- CCR (experimental arm)
- Non-target lesions in region of TLs (experimental arm)
- Size of surgical defect
- Size of biopsy defect
- Safety and tolerability

CCR = composite complete response; CLL = chronic lymphocytic leukemia; CSCC = cutaneous squamous cell carcinoma; EFS = evainee survival; HN = head and neck; R = randomized; TL = target lesion.

ClinicalTrials.gov identifier: NCT06585410. Accessed December 10, 2025.

AEs Associated With Immunotherapy

Management requires a coordinated multidisciplinary approach



irAEs Can Occur In Any Organ System or Tissue

- Pneumonitis
- Colitis
- Hepatitis
- Endocrinopathies
- Dermatologic reactions
- Nephritis and kidney dysfunction
- Solid organ transplant rejection

AEs = adverse events; irAE = immune-related adverse event.

Cemiplimab-rwlc (Libtayo®) PI 2025 (https://www.libtayohcp.com/). Pembrolizumab (Kaytruda®) PI 2025 (https://www.keytruda.com/). URLs accessed 12/8/2025.

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immune Checkpoint Inhibitor-Related Toxicities

Version 1.2026 — October 23, 2025

NCCN Guidelines for Patients®

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

ASCO special articles

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

Bryan J. Schneider, MD[1]; Jarushka Naidoo, MD[2,3]; Bianca D. Santomasso, MD, PhD[4]; Christina Lacchetti, MHSc[5]; Sherry Adkins, MS[6]; Milan Anadkat, MD[7]; Michael B. Atkins, MD[8]; Kelly J. Brassil, PhD[6]; Jeffrey M. Caterino, MD, MPH[9]; Ian Chau, MD[10]; Marianne J. Davies, DNP[11]; Marc S. Ernstoff, MD[12]; Leslie Fecher, MD[1]; Monalisa Ghosh, MD[13]; Ishmael Jaiyesimi, DO, MS[14]; Jennifer S. Mammen, MD, PhD[15]; Aung Naing, MD[6], Loretta J. Nastoupil, MD[6]; Tanyanika Phillips, MD[16]; Laura D. Porter, MD[17]; Cristina A. Reichner, MD[18]; Carole Seigel, MBA[19], Jung-Min Song, MSN, RN, CNS[20]; Alexander Spira, MD, PhD[21]; Maria Suarez-Almazor, MD[6]; Umang Swami, MD[22]; John A. Thompson, MD[23]; Praveen Vikas, MD[24]; Yinghong Wang, MD[6]; Jeffrey S. Weber, MD, PhD[25]; Pauline Funchain, MD[20]; and Kathryn Bollin, MD[26]

abstract

PURPOSE To increase awareness, outline strategies, and offer guidance on the recommended management of immune-related adverse events (irAEs) in patients treated with immune checkpoint inhibitor (ICPi) therapy.

METHODS A multidisciplinary panel of medical oncology, dermatology, gastroenterology, rheumatology, pulmonology, endocrinology, neurology, hematology, emergency medicine, nursing, trialists, and advocacy experts was convened to update the guideline. Guideline development involved a systematic literature review and an informal consensus process. The systematic review focused on evidence published from 2017 through 2021.

RESULTS A total of 175 studies met the eligibility criteria of the systematic review and were pertinent to the development of the recommendations. Because of the paucity of high-quality evidence, recommendations are based on expert consensus.

RECOMMENDATIONS Recommendations for specific organ system–based toxicity diagnosis and management are presented. While management varies according to the organ system affected, in general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, except for some neurologic, hematologic, and cardiac toxicities. ICPi therapy may be suspended for most grade 2 toxicities, with consideration of resuming when symptoms revert ≤ grade 1. Corticosteroids may be administered. Grade 3 toxicities generally warrant suspension of ICPis and the initiation of high-dose corticosteroids. Corticosteroids should be tapered over the course of at least 4-6 weeks. Some refractory cases may require other immunosuppressive therapy. In general, permanent discontinuation of ICPis is recommended with grade 4 toxicities, except for endocrinopathies that have been controlled by hormone replacement. Additional information is available at www.asco.org/supportive-care-guidelines.

J Clin Oncol 39:4073-4126.

Table 3: Lung Toxicities

Management of immune-related adverse events for ICP: Update

3.1 Pneumonitis	
Workup and evaluation Should include the following: Pulse oximetry and CT chest!? Preferably with contrast if concerned for other etiologies such as pulmonary embolus. For grade 2 or higher, may include the following infectious workup: Nasal swab, sputum culture, and sensitivity, blood culture and sensitivity, urine culture, and sensitivity. COVID-19 evaluation—per institutional guidelines where relevant.	
Grading	**Management**
Grade 1: Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only	Hold ICP inhibitor or proceed with close monitoring. Monitor patients weekly with history and physical examination, pulse oximetry; may also offer chest imaging (CXR, CT) if uncertain diagnosis and/or to follow progress. Repeat chest imaging in 3-4 weeks or sooner if patient becomes symptomatic. In patients who have had baseline testing, may offer a repeat spirometry or DLCO in 3-4 weeks. May resume ICP inhibitor with radiographic evidence of improvement or resolution if held. If no improvement, should treat as grade 2.
Grade 2: Symptomatic; Involves more than one lobe of the lung or 25% to 50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL	Hold ICP inhibitor until clinical improvement to = Grade 1. Prednisone 1-2 mg/kg/d and taper over 4 to 6 weeks. Consider bronchoscopy with BAL = transbronchial biopsy. Consider empiric antibiotics if infection remains in the differential diagnosis after workup. Monitor at least once per week with history and physical examination, pulse oximetry, consider radiologic imaging; if no clinical improvement after 48 to 72 hours of prednisone, treat as grade 3. Pulmonary and infectious disease consults if necessary.
Grade 3: Severe symptoms; Hospitalization required: Involves all lung lobes or >50% of lung parenchyma; limiting self-care ADL; oxygen indicated.	Permanently discontinue ICP. Empiric antibiotics may be considered. Methylprednisolone IV 1 to 2 mg/kg/d. If no improvement after 48 hours, may add immunosuppressive agent. Options include infliximab or mycophenolate mofetil IV or IVIG or cyclophosphamide (See Table A2 for dosing). Taper corticosteroids over 4 to 6 weeks? Pulmonary and infectious disease consults if necessary. May consider bronchoscopy with BAL + transbronchial biopsy if patient can tolerate.
Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (intubation)	

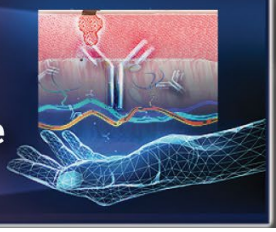
ADL = activity of daily living; BAL = bronchoalveolar lavage; CT = computed tomography; CXR = chest x-ray; DLCO = diffusing capacity of lung for carbon monoxide; ICP = immune checkpoint; IV = intravenous; IVIG = intravenous immune globulin.

[a]Subset of patients may develop chronic pneumonitis and may require longer taper. Chronic pneumonitis is a described phenomenon where the incidence is not known but <2%.

Schneider BJ, et al. *J Clin Oncol.* 2021;39(36):4073-4126.

Navigating Clinical Challenges in cSCC:

Leveraging AI Tools for Improved Decision-Making Across the Continuum of Care



Recent and key publications on high-risk cSCC

Resources on cSCC Risk Stratification

Resource	Address
Erasmus MC Cancer Institute. Prediction of metastatic risk in patients with cutaneous squamous cell carcinoma (cSCC). cSCC Risk Calculator.	https://emc-dermatology.shinyapps.io/cscc-abs-met-risk/
Gibson FT, Ran NA, Karn EE, et al. Patterns of disease-specific death from cutaneous squamous cell carcinoma: A multicenter retrospective cohort. *J Am Acad Dermatol*. 2026;2:658-660.	https://pubmed.ncbi.nlm.nih.gov/41076132/
Granger EE, Ran NA, Groover MK, et al. Most cutaneous squamous cell carcinoma recurrences occur in the first 3 years after diagnosis: A multicenter retrospective cohort study. *J Am Acad Dermatol*. 2024;91:957-960.	https://pubmed.ncbi.nlm.nih.gov/38971189/
Gupta N, Weitzman RE, Murad F, et al. Identifying Brigham and Women's Hospital stage T2a cutaneous squamous cell carcinomas at risk of poor outcomes. *J Am Acad Dermatol*. 2022;86:1301-1308.	https://pubmed.ncbi.nlm.nih.gov/34864111/
Huis In 't Veld EA, Boere T, Zuur CL, et al. Oncological outcome after lymph node dissection for cutaneous squamous cell carcinoma. *Ann Surg Oncol*. 202330:5017-5026.	https://pubmed.ncbi.nlm.nih.gov/36991168/
Jambusaria-Pahlajani A, et al. riSCC: A personalized risk model for the development of poor outcomes in cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 2025;93:73-81.	https://pubmed.ncbi.nlm.nih.gov/40024391/
Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, et al. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. *JAMA Dermatol*. 2013;149:402-410.	https://pubmed.ncbi.nlm.nih.gov/23325457/
Karia PS, Jambusaria-Pahlajani A, Harrington DP, Murphy GF, Qureshi AA, Schmults CD. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. *J Clin Oncol*. 2014;32:327-334.	https://pubmed.ncbi.nlm.nih.gov/24366933/
Masarwy R, Shilo S, Carmel Neiderman NN, et al. The prognostic value and clinical utility of the 40-gene expression profile (40-GEP) test in cutaneous squamous cell carcinoma: systematic review and meta-analysis. *Cancers (Basel)*. 2023;15:2456.	https://pubmed.ncbi.nlm.nih.gov/37173922/
National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology. Squamous Cell Skin Cancer. Version 1.2026.	https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1465
Porceddu SV, Connolly E, Bressel M, Wratten C, Liu HY, Rischin D. Prognostic subgroups for disease-free survival with cutaneous squamous cell carcinoma of the head and neck: A secondary analysis of a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. 2025;151:938-945.	https://pubmed.ncbi.nlm.nih.gov/40875250/

Ran NA, Granger EE, Brodland DG, et al. Risk factor number and recurrence, metastasis, and disease-related death in cutaneous squamous cell carcinoma. *JAMA Dermatol*. 2025;161:597-604.	https://pubmed.ncbi.nlm.nih.gov/40105853/
Rentroia-Pacheco B, Tokez S, Bramer EM, et al. Personalised decision making to predict absolute metastatic risk in cutaneous squamous cell carcinoma: Development and validation of a clinico-pathological model. *EClinicalMedicine*. 2023;63:102150.	https://pubmed.ncbi.nlm.nih.gov/37662519/
Ruiz ES, Karia PS, Besaw R, Schmults CD. Performance of the American Joint Committee on Cancer Staging Manual, 8th Edition vs the Brigham and Women's Hospital Tumor Classification System for Cutaneous Squamous Cell Carcinoma. *JAMA Dermatol*. 2019;155:819-825.	https://pubmed.ncbi.nlm.nih.gov/30969315/
Ruiz ES, Karia PS, Morgan FC, Schmults CD. The positive impact of radiologic imaging on high-stage cutaneous squamous cell carcinoma management. *J Am Acad Dermatol*. 2017;76:217-225.	https://pubmed.ncbi.nlm.nih.gov/27707594/
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