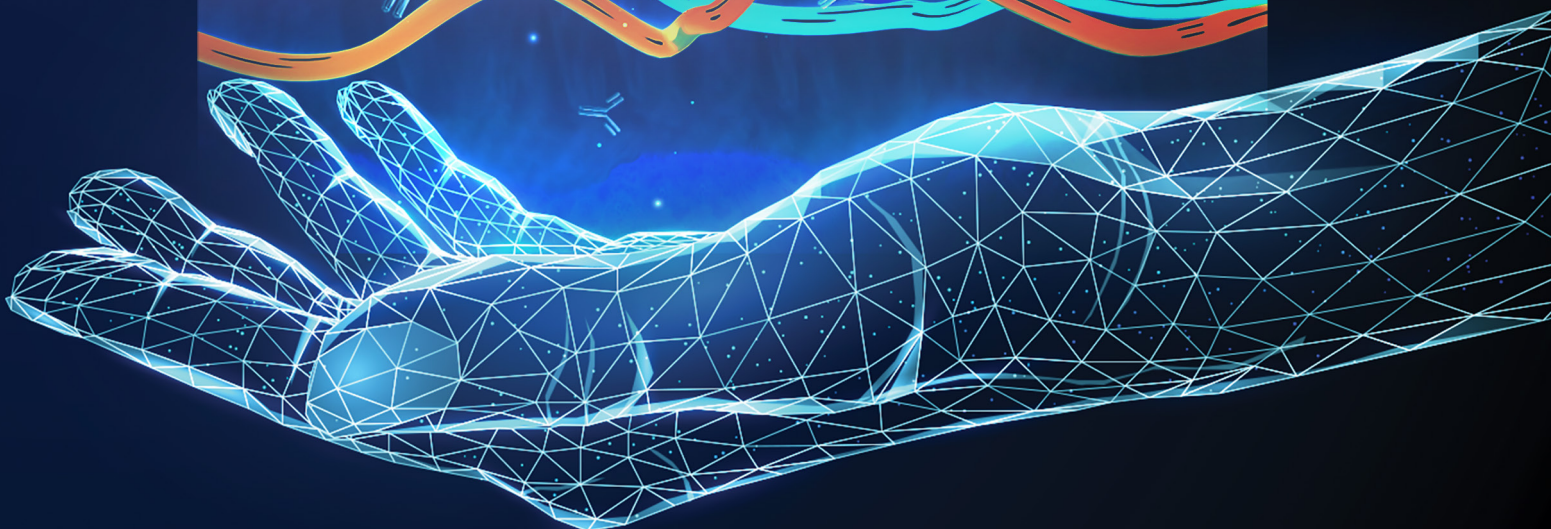
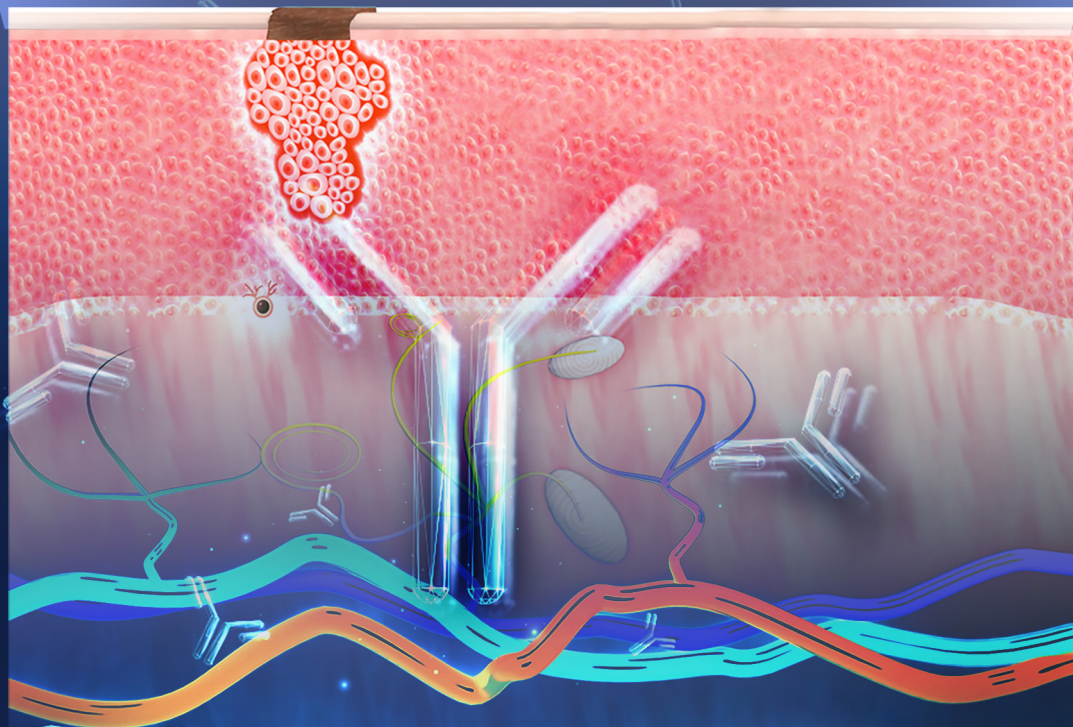


Navigating Clinical Challenges in cSCC:

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



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. Evaluate the clinical data for current and emerging adjuvant immunotherapies to inform their integration into clinical practice for cSCC treatment
3. Determine the importance of multidisciplinary care to improve disease and patient outcomes for individuals living with cSCC
4. Apply interprofessional strategies to manage AEs in patients undergoing immunotherapy for cSCC

JOINT ACCREDITATION STATEMENT



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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

Nina Ran, MD	Consulting fees: Received consulting fees from Chronicle Medical Software. Has a consulting contract with Regeneron Pharmaceuticals (no fees have been paid)
--------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------

All relevant financial relationships have been mitigated.

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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
Dana-Farber Cancer Institute
Boston, Massachusetts



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

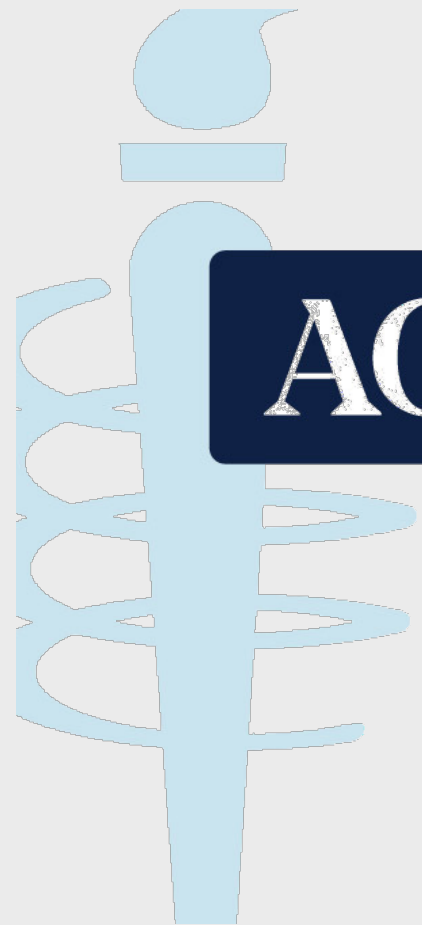
Resources Available to Risk Stratify cSCC



National Comprehensive
Cancer Network®



riSCC Calculator



American Joint Committee
on Cancer
American College of Surgeons



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

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

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



Patient factors

- Male
- 75 years old

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

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

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

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



Tumor pathology

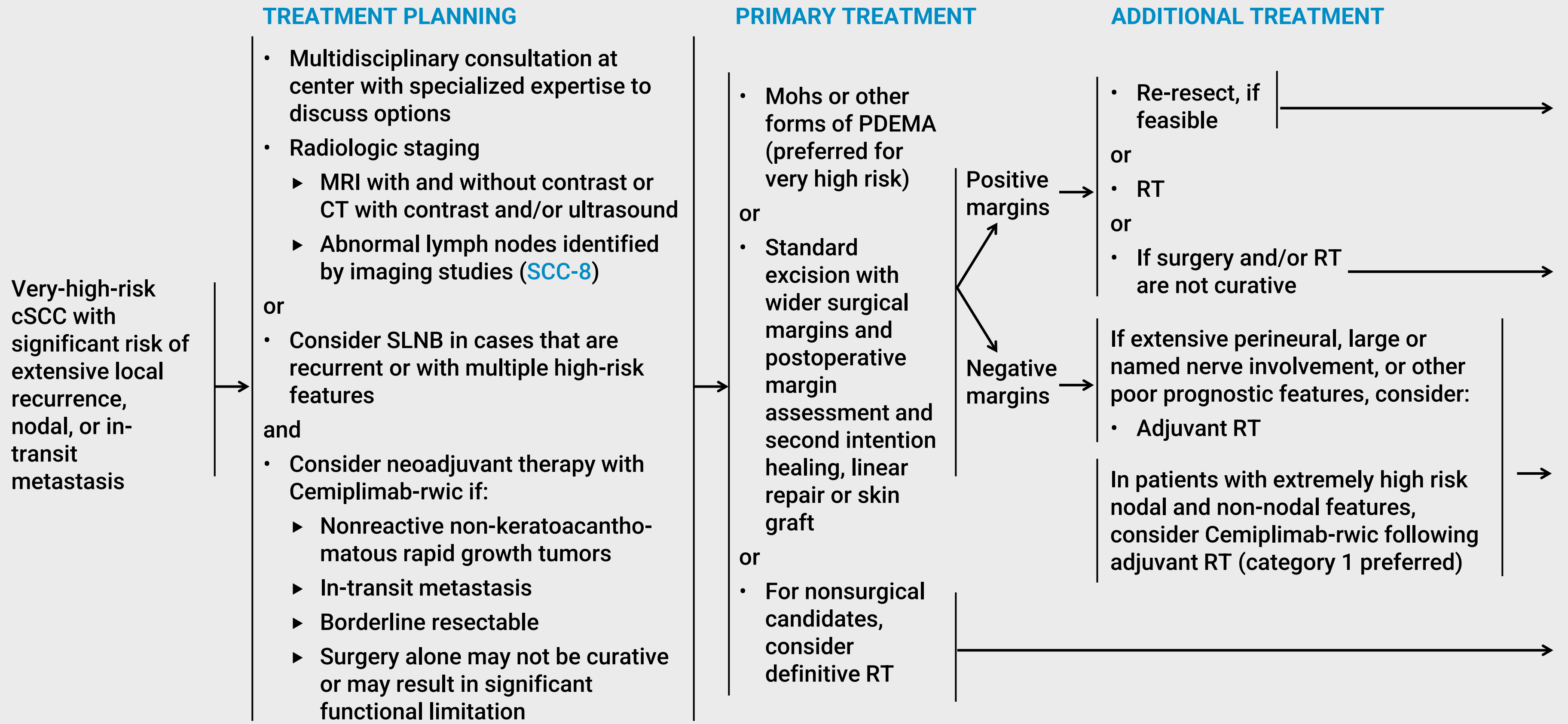
- Moderate differentiation
- Invading at least dermis—biopsy captured only dermis
- No perineural invasion observed on biopsy
- No lymphovascular invasion observed on biopsy

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 Head, neck, hands, feet, pretibia, and anogenital area (any size)	>4 cm (any location)
Clinical borders	Well-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 cSCC



CT = computed tomography; MRI = magnetic resonance imaging; RT = radiotherapy; PDEMA = peripheral and deep en face margin assessment; SLNB = sentinel lymph node biopsy.

Adapted from NCCN guidelines. Squamous cell skin cancer V1.2026 (www.nccn.org/professionals/physician_gls/pdf/squamous.pdf). Accessed 1/26/2026.

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



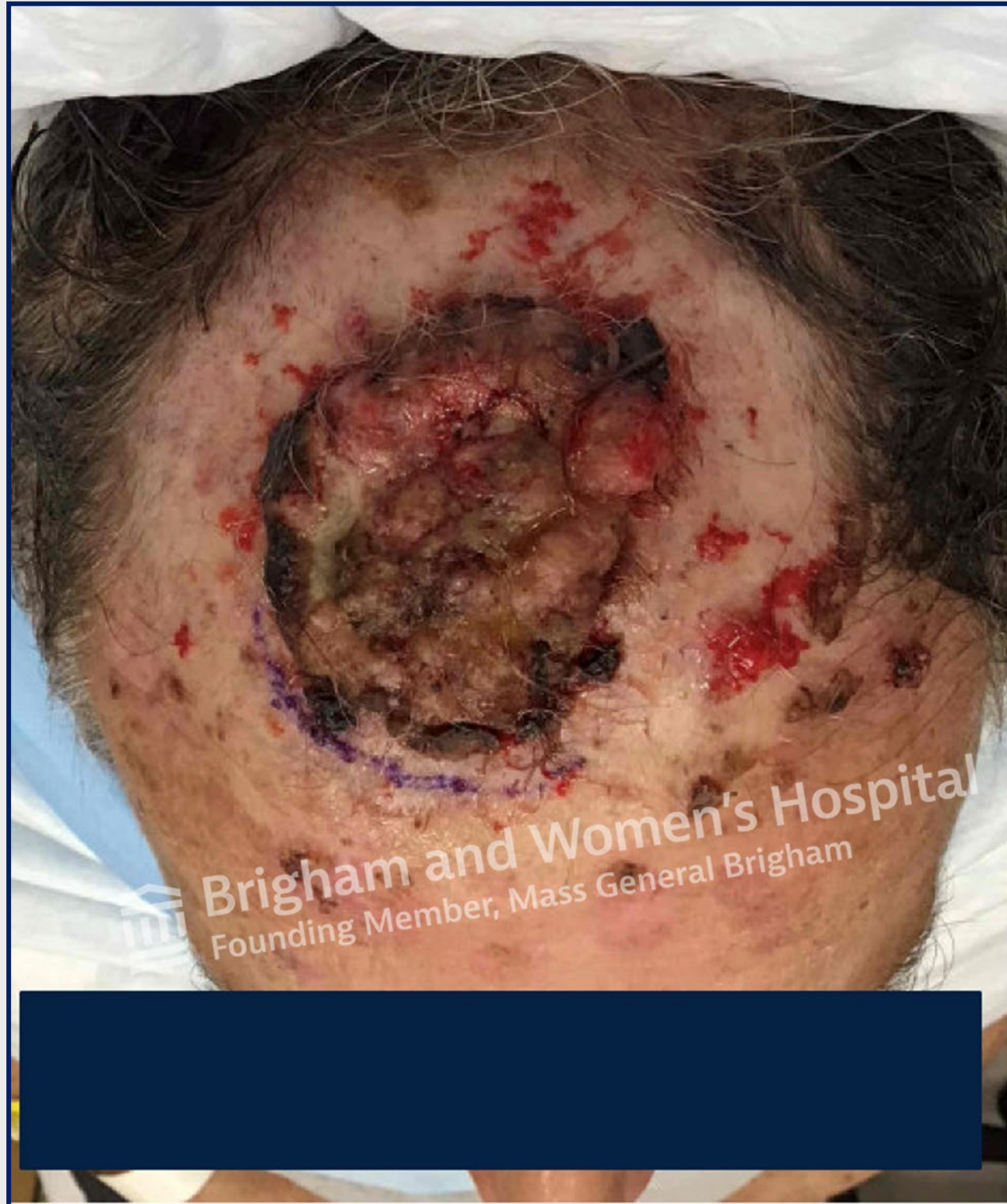
Patient presents for surgical consultation for a biopsy-proven squamous cell carcinoma on the scalp

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

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



- Male
- 75 years old

- 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

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 <i>in situ</i>
	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 <u>larger than 4 cm</u> in maximum dimension or minor bone erosion or perineural invasion or <u>deep invasion</u> *
	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



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.

Tumor-Specific Risk Prediction Modeling: Erasmus



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



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

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

Sex

Number of prior cSCCs

Tumor location

Tumor characteristics

Tumor diameter, in cm

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

Tissue involvement

Deepest layer of tissue involvement

Differentiation Grade

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

Presence of perineural invasion (≥ 0.1 mm) 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



Calculator

- About
- Disclaimer
- Support

Patient And Tumor Characteristics

* All form fields are required [Medical References & Sources...](#)

Patient age: 75

Patient gender: Male Female

Patient immunosuppression: No Yes

Tumor location: Head and neck All other locations

Recurrent tumor: No/Unknown Yes

Largest clinical tumor diameter [cm]: 5

Any perineural invasion: No/Unknown Yes

Tumor depth: Dermis/Unknown Subcutaneous Fat Deeper than subcutaneous fat

Lymphovascular invasion: No/Unknown Yes

Tumor differentiation: Well/Unknown Moderate Poor

Results

* 5-Year Risk Calculation

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)





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)

Module 2 - Developing Treatment Plans for High-Risk cSCC: Adjuvant Therapy

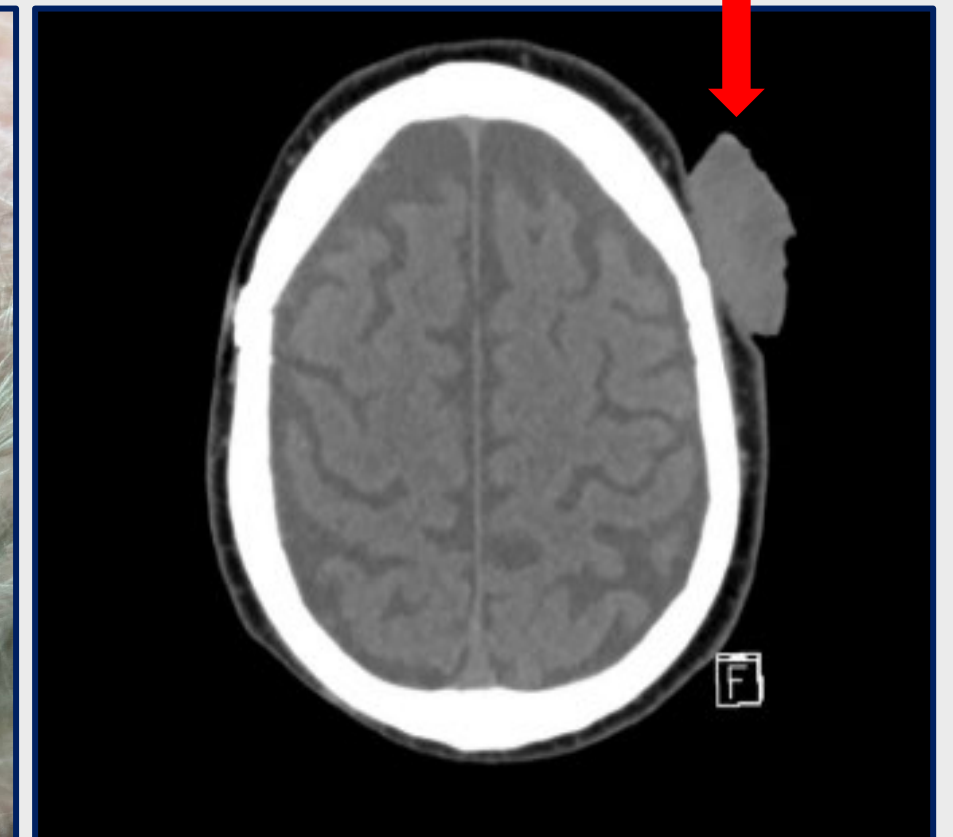


Nikhil I. Khushalani, MD

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

Case #2: 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: 5.1 cm extracranial mass
 - Approximating but not invading outer table
 - CT of neck/thorax
 - No evidence of metastases



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/csc-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

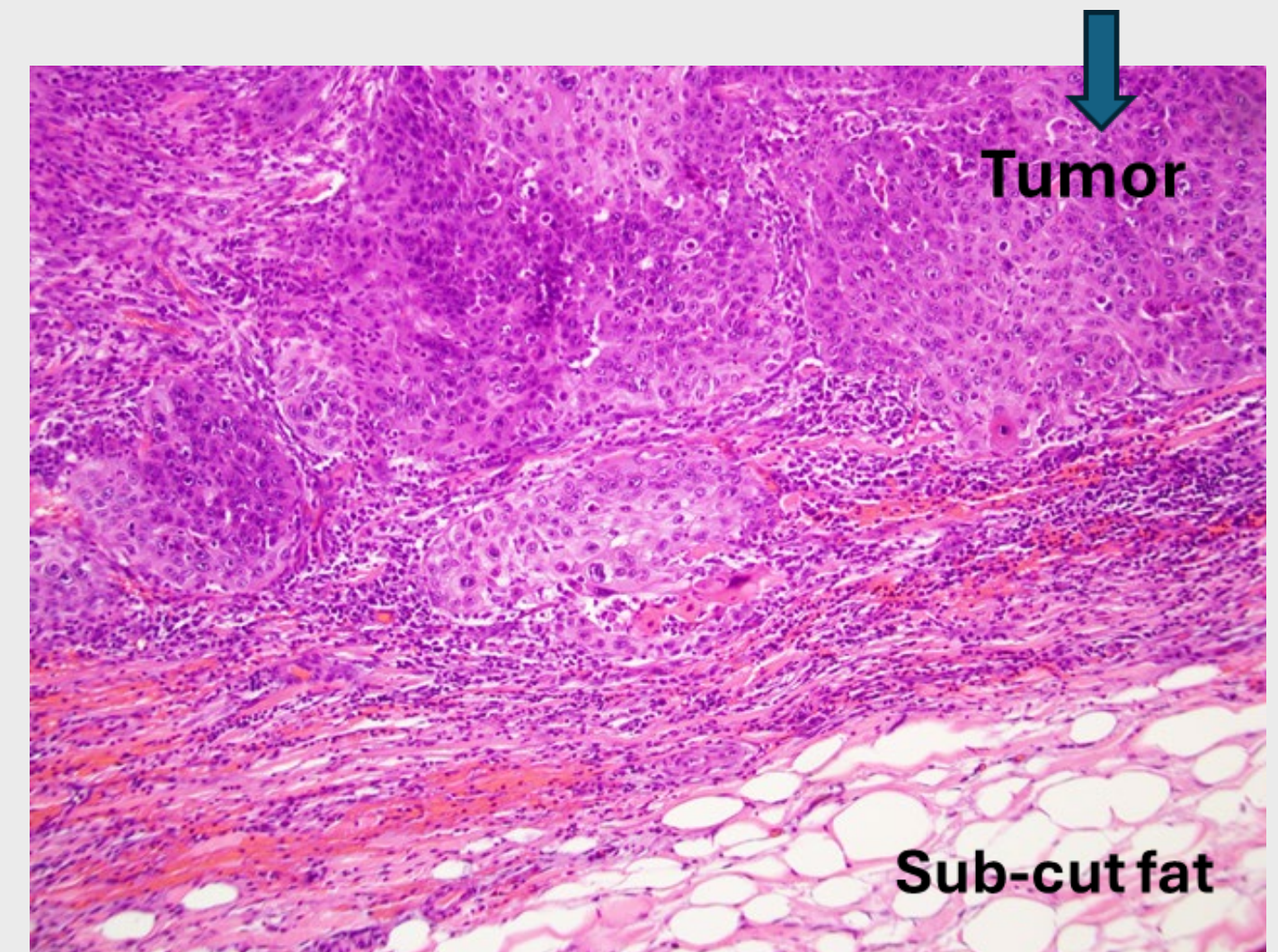
Razan Masarwy^{1,2} , Shahaf Shilo^{1,2} , Narin Nard Carmel Neiderman^{1,2}, Liyona Kampel^{1,2}, Gilad Horowitz^{1,2}, Nidal Muhanna^{1,2} and Jobran Mansour^{1,2,*}

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





Case Presentation

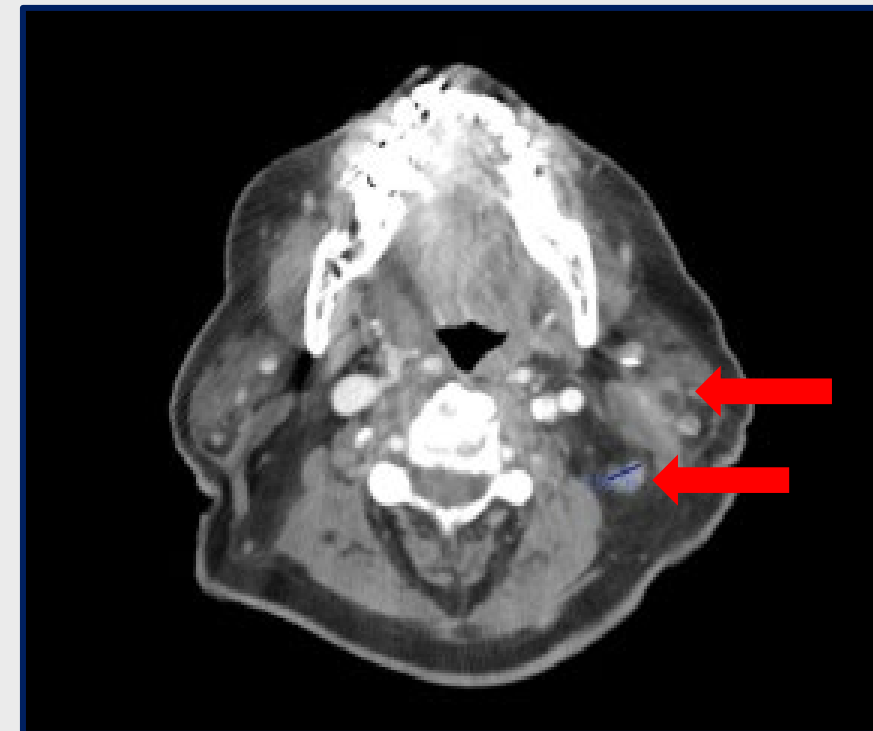
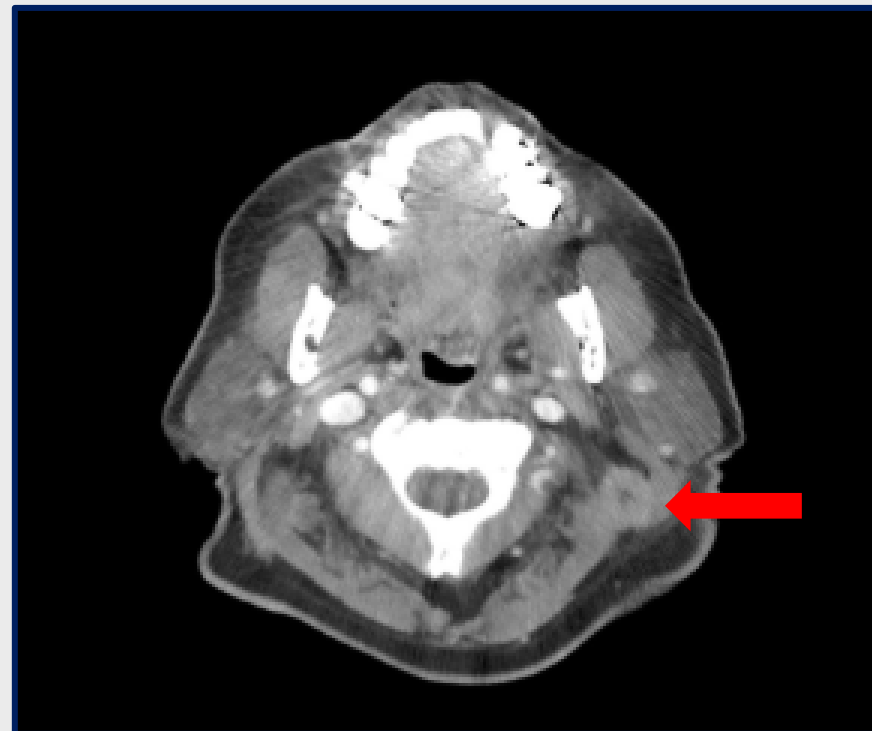
Received adjuvant radiotherapy: 66 Gy

- 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



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

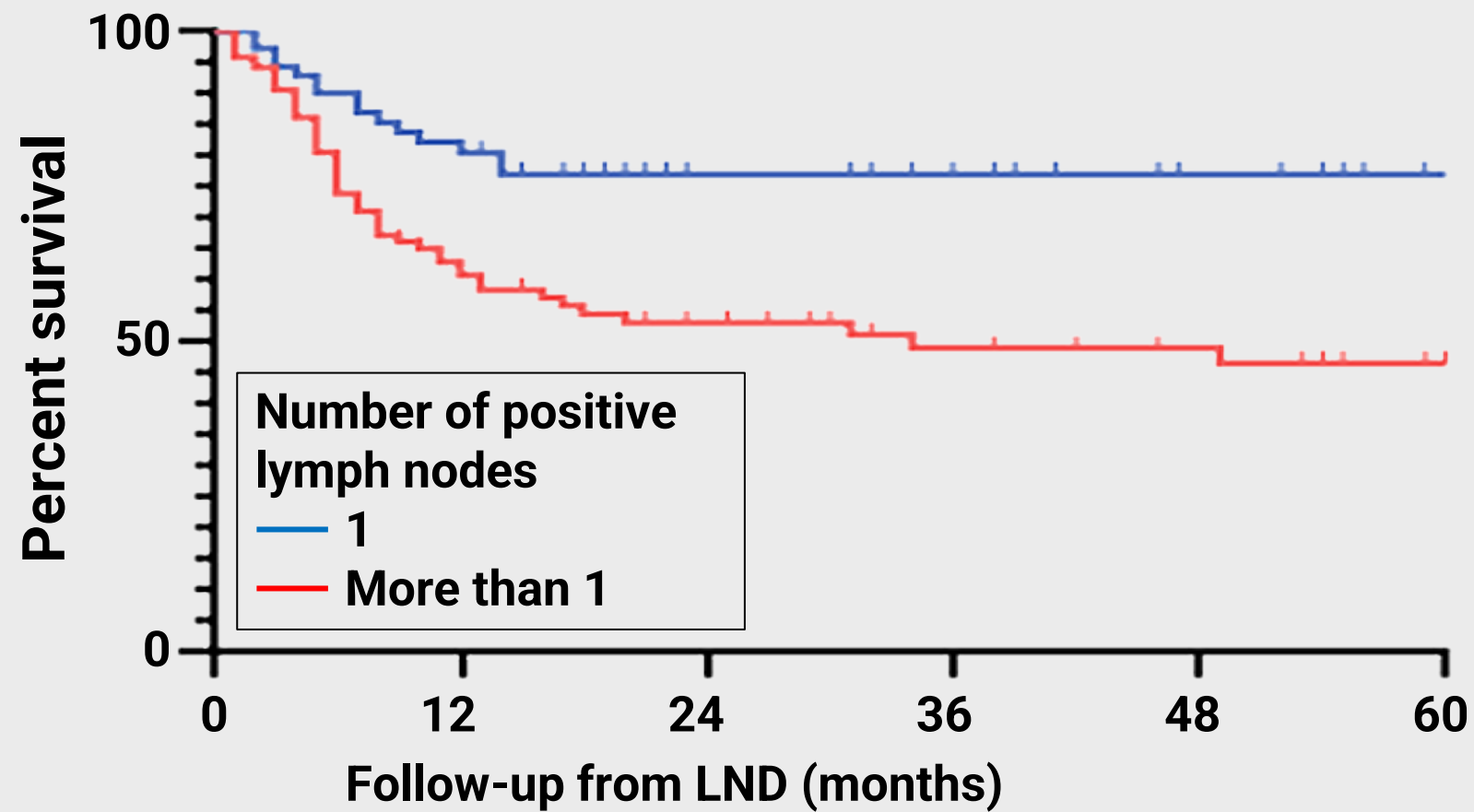
No distant metastases; excellent functional status

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)

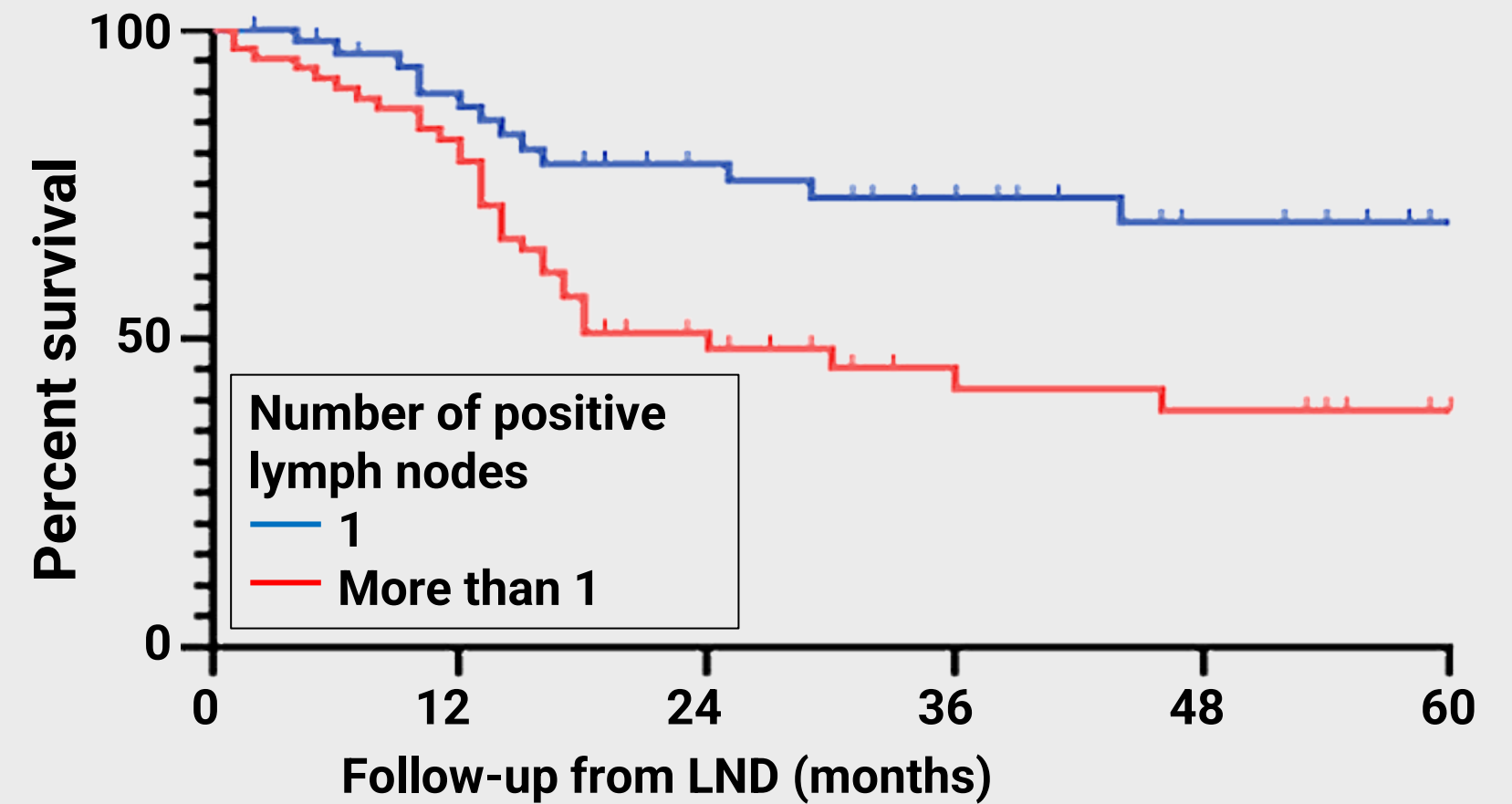
Recurrence-free survival after LND



Number at risk

	0	12	24	36	48	60
PL = 1	71	48	32	26	20	12
PL > 1	118	52	33	23	20	14

Disease-specific survival after LND



Number at risk

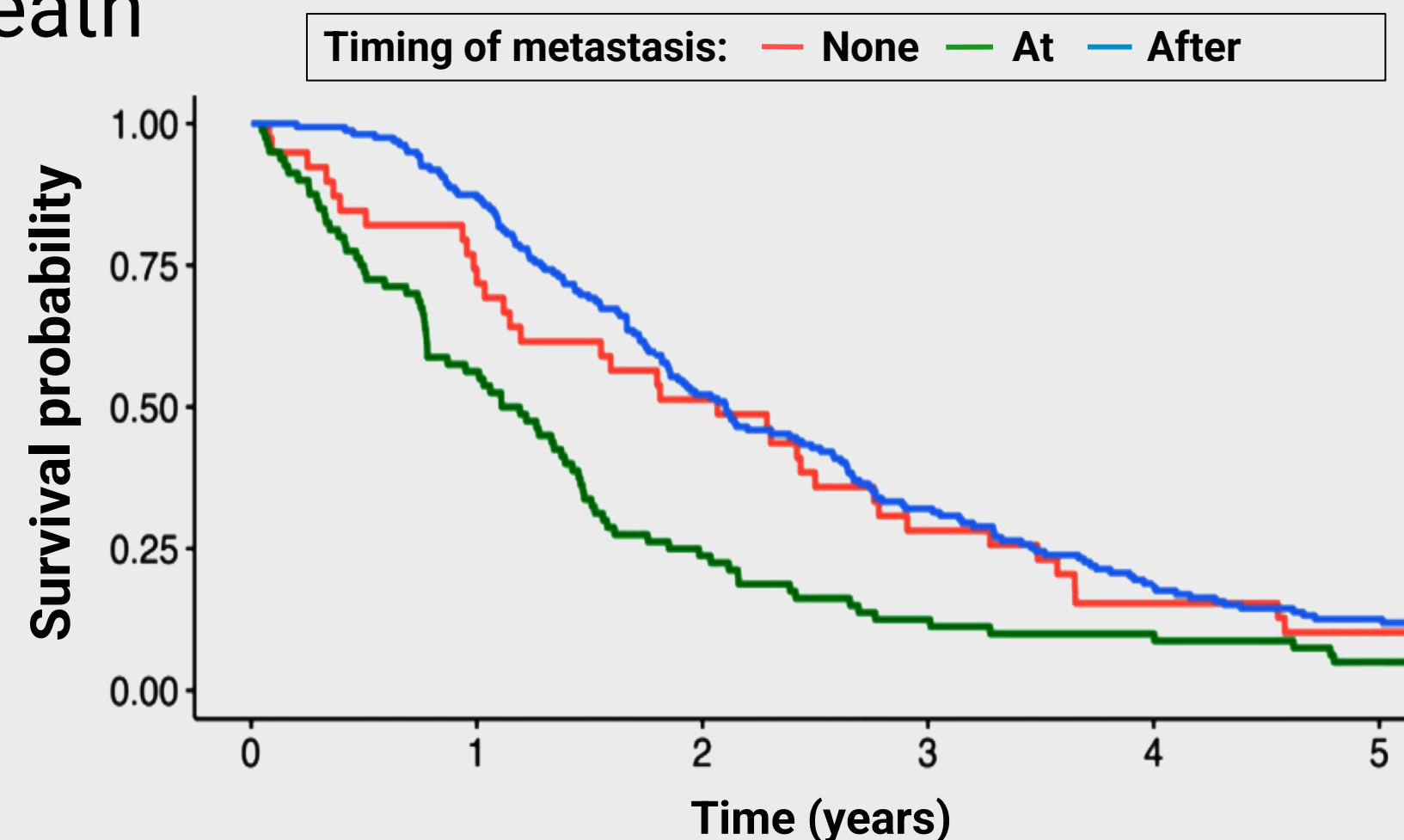
	0	12	24	36	48	60
PL = 1	51	40	28	22	16	9
PL > 1	63	44	19	12	10	5

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

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

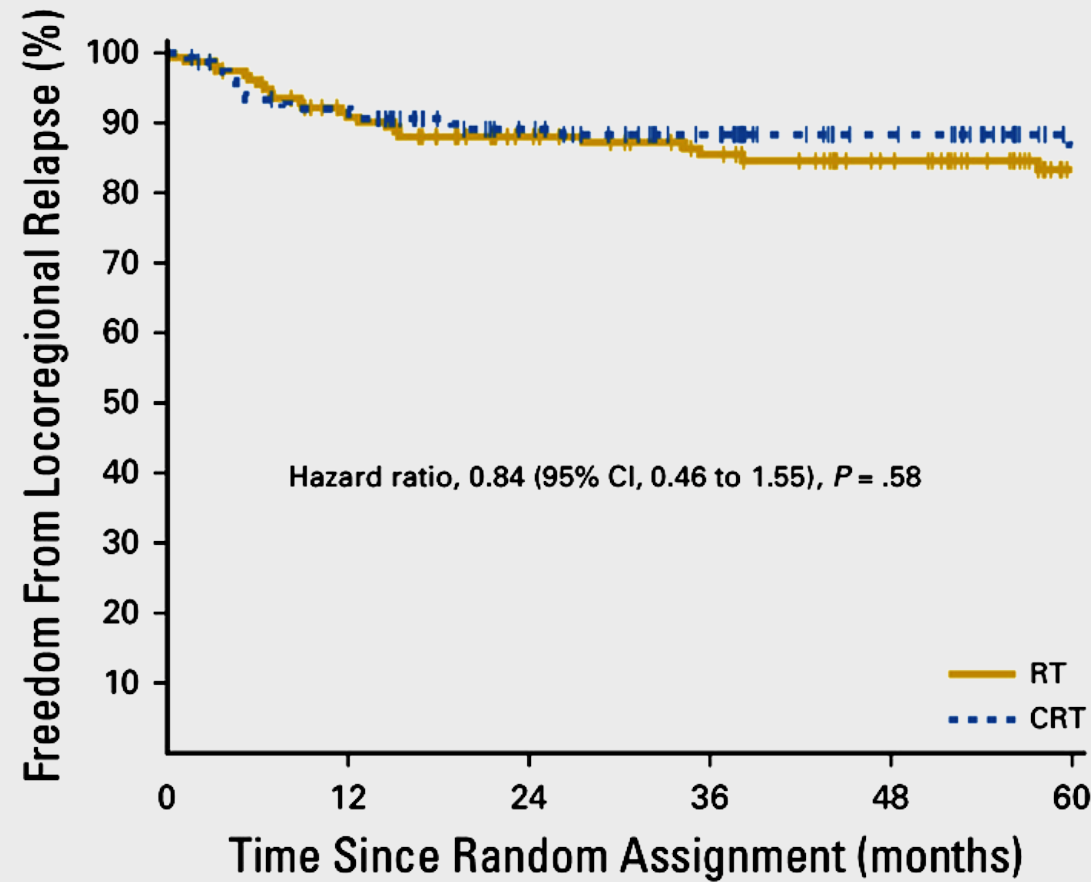
Patterns of Disease-Specific Death (DSD) in cSCC

- 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**



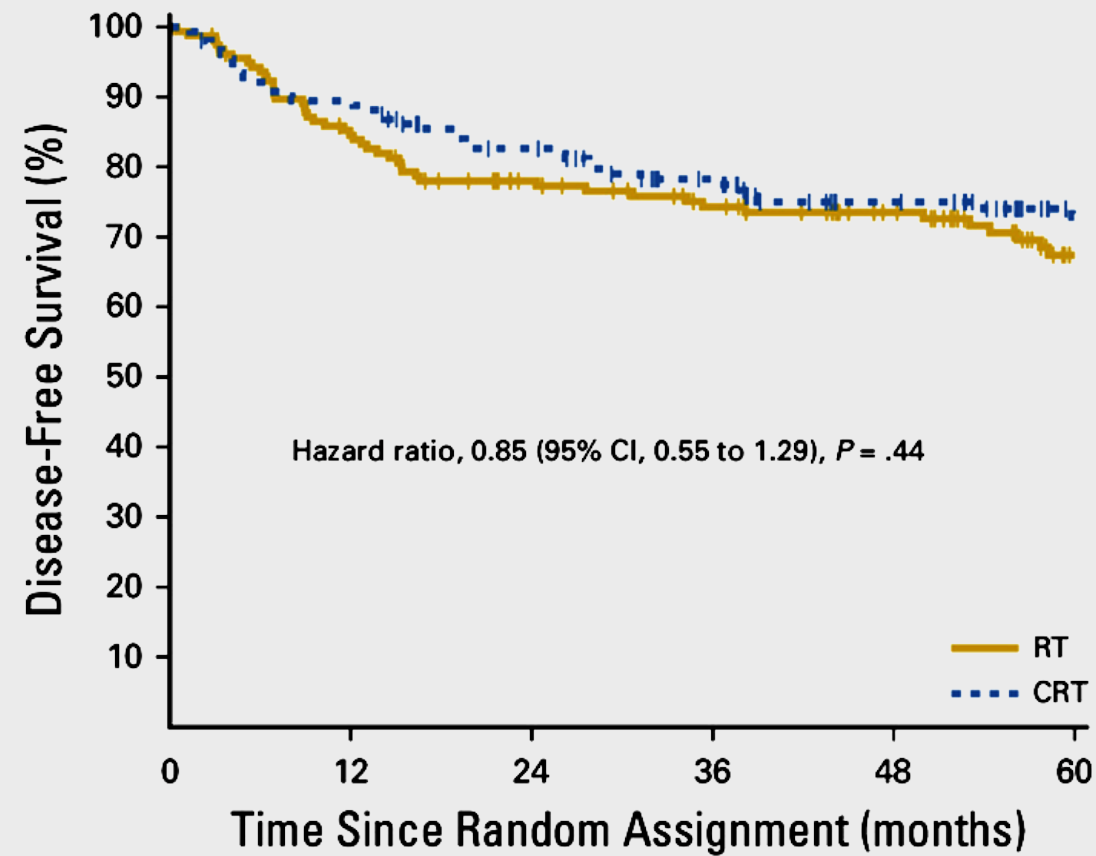
Adjuvant Radiotherapy +/- Chemotherapy

TROG 05:01



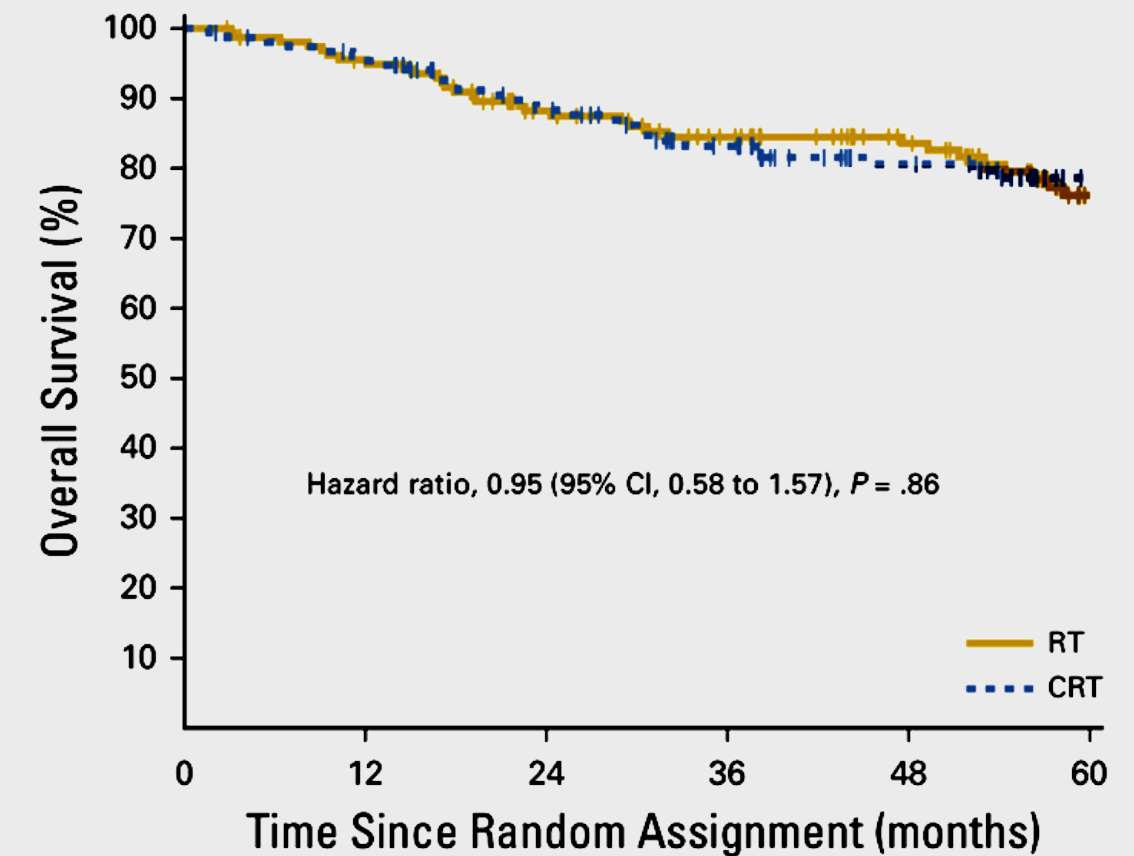
No. at risk (No. of events):

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):

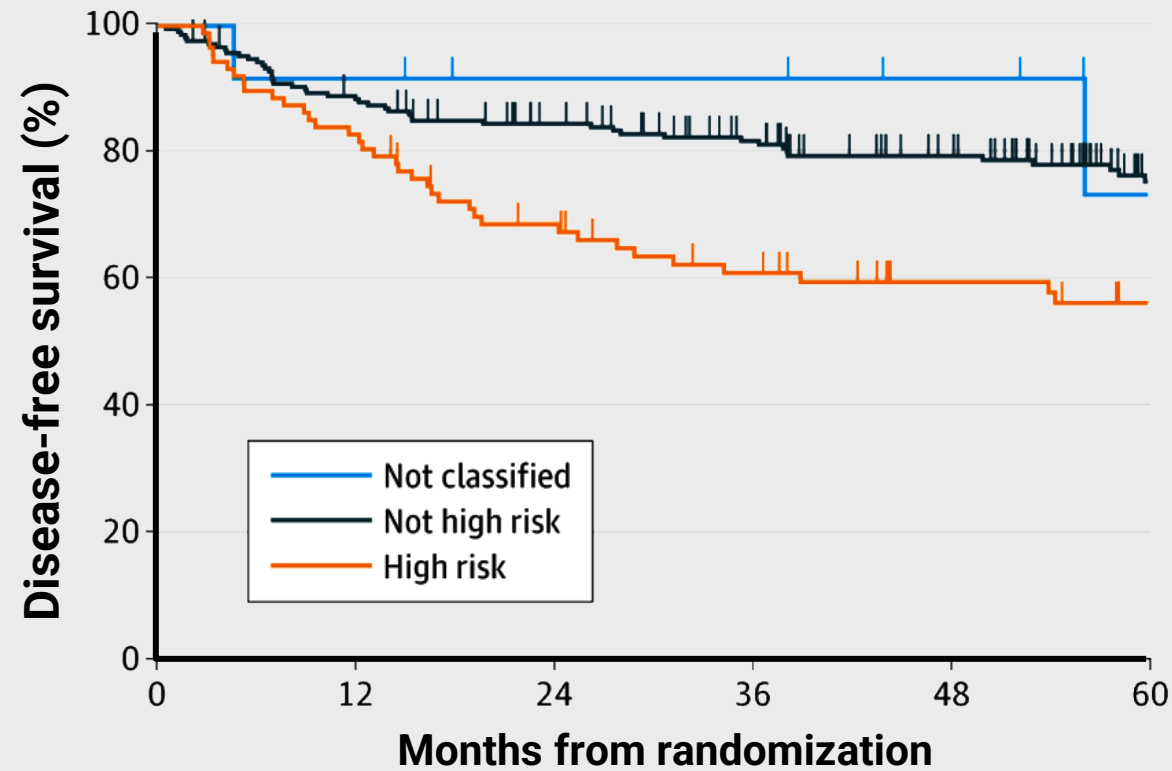
RT	157 (0)	147 (7)	124 (18)	108 (23)	89 (24)	60 (31)
CRT	153 (0)	143 (7)	124 (17)	107 (24)	87 (27)	61 (29)

SUMMARY:

No benefit 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.

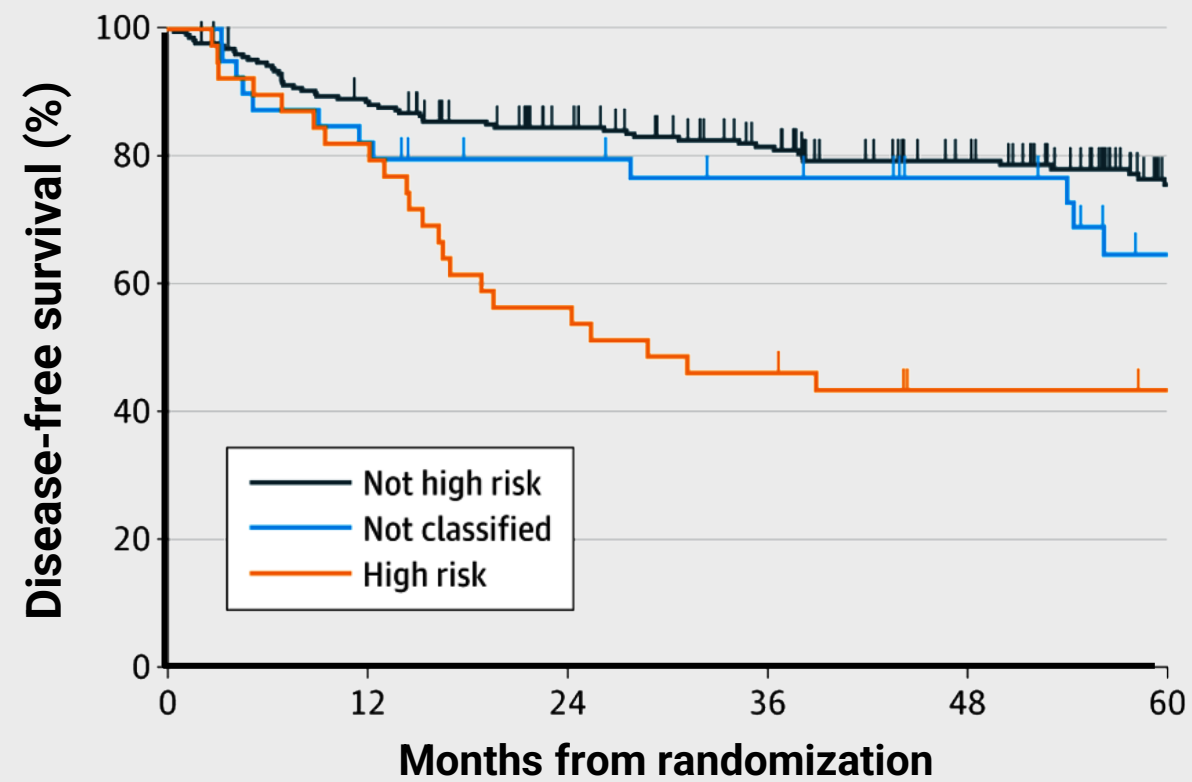
Can We Further Stratify to Define “High-Risk”?

Post-hoc analysis of TROG 05:01



No. at risk	0	12	24	36	48	60
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%



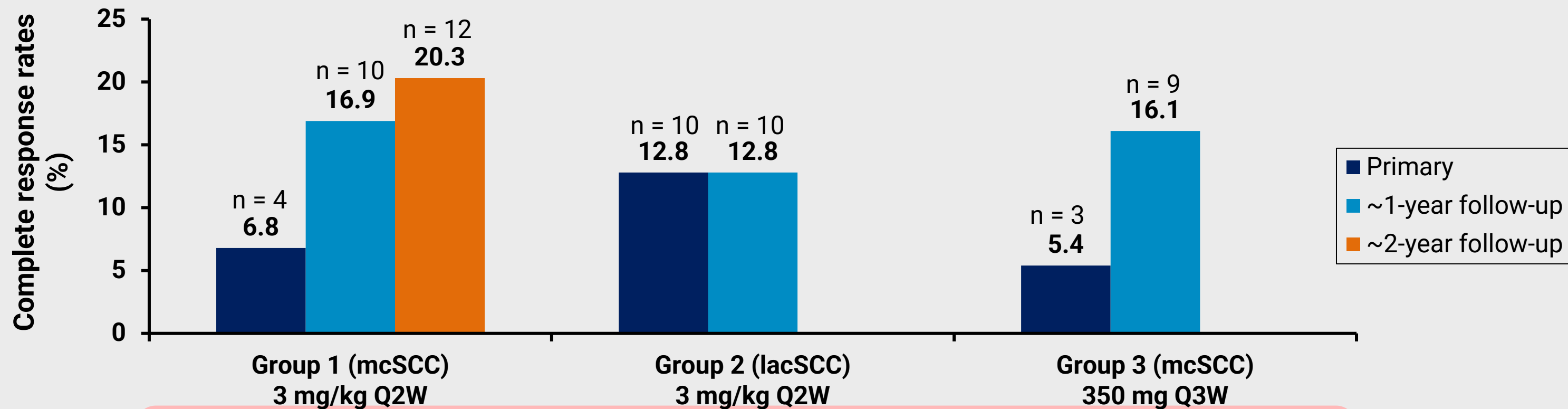
No. at risk	0	12	24	36	48	60
High risk	39	32	22	18	14	13
Not high risk	231	201	177	155	129	88
Not classified	40	32	28	25	21	14

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.

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 = median 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

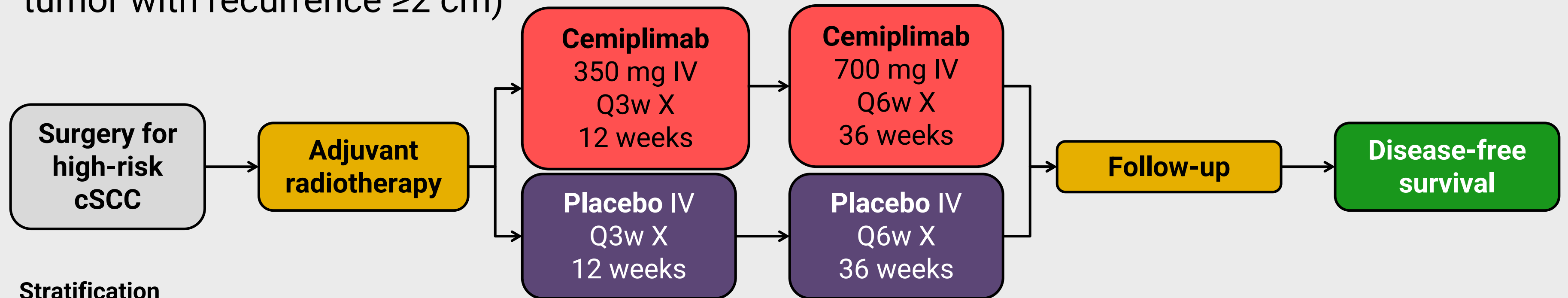
History of solid organ transplant except corneal transplants

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 $\geq N2b$, $\geq T3$, poorly differentiated tumor with recurrence ≥ 2 cm)



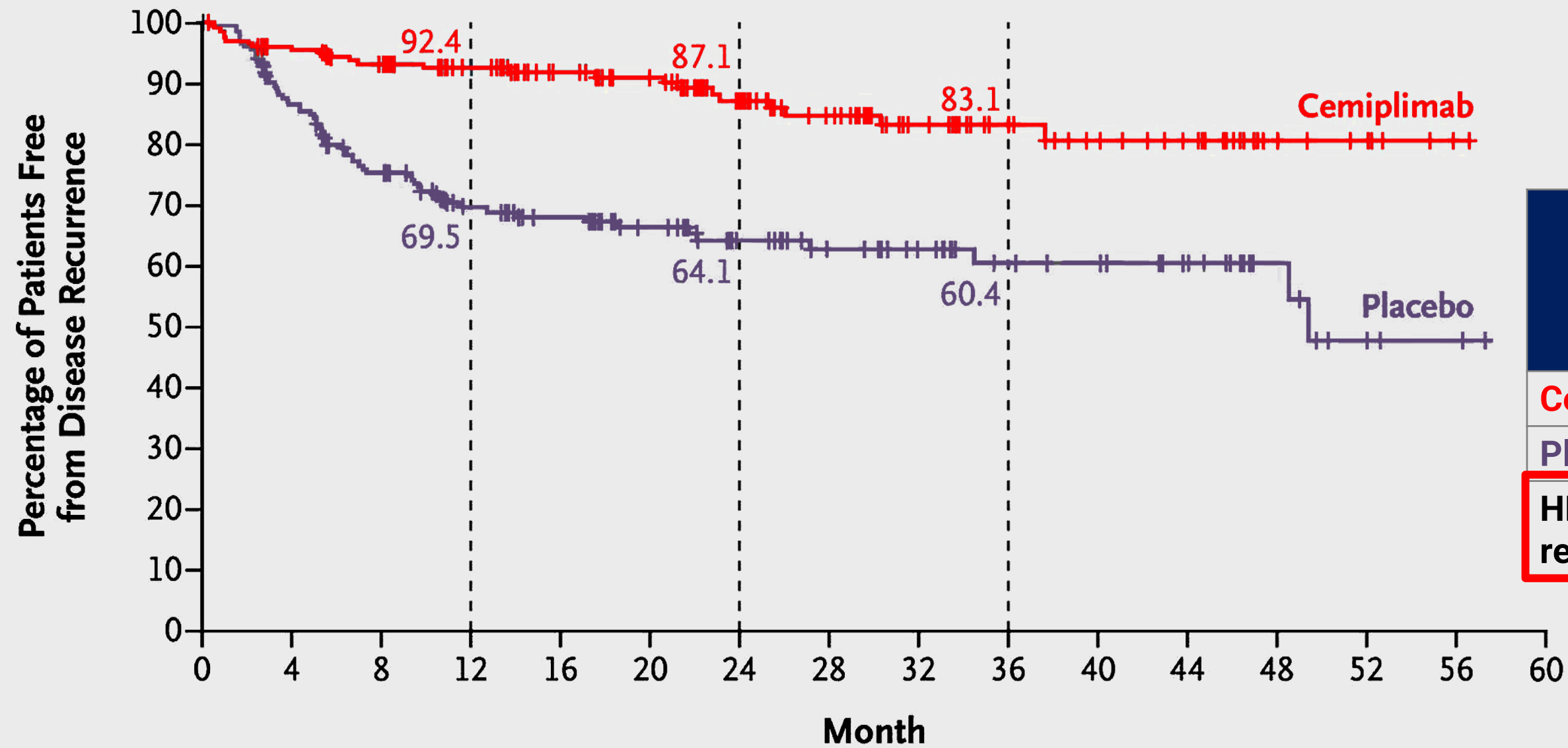
Stratification

- 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) <i>P</i> < .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
	<i>number of patients with event (percent)</i>			
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.



Cemiplimab: Expanded Adjuvant Indication in cSCC

Adjuvant Indication Approved in the United States and European Union

Indication: for the adjuvant treatment of adult patients with cutaneous squamous cell carcinoma at high risk of recurrence after surgery and radiation

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)

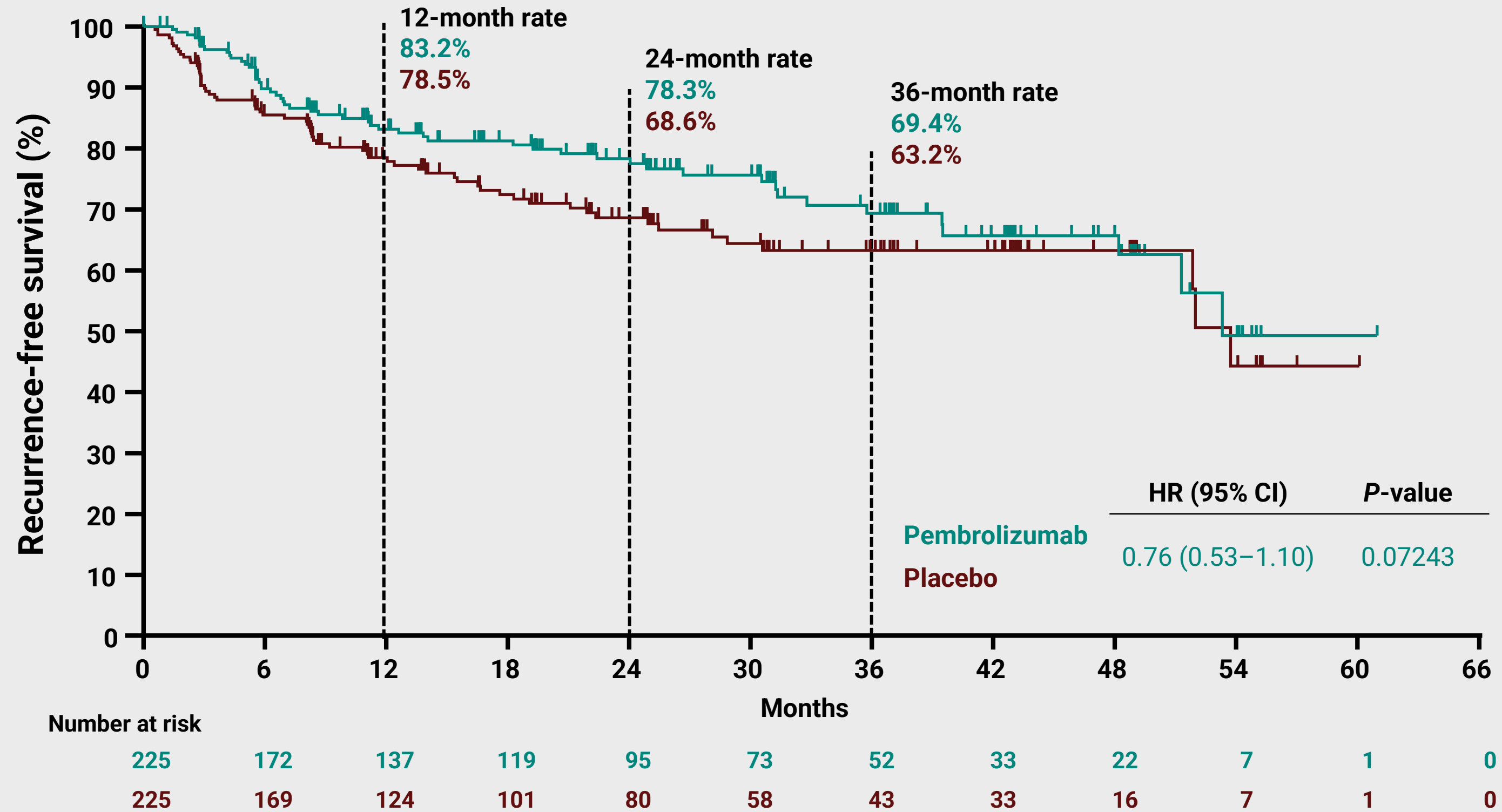
Stratification factors (yes vs no)

- Extracapsular extension
- Cortical bone invasion
- Prior systemic therapy

N = 450
Adjuvant pembrolizumab or placebo

Primary endpoint: Investigator-assessed recurrence-free survival

KN-630: DFS



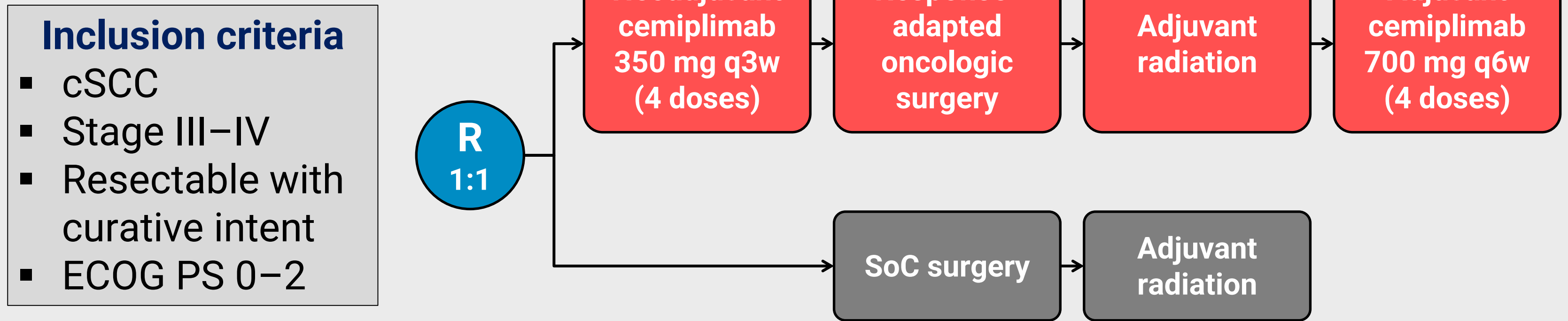
So Why Did Two Trials With Similar Design Have Contradicting Results?

- 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



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



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 3 - 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?**

A close-up photograph of a man's lower lip. The lip is surrounded by a thick, light brown beard. A yellow oval highlights a small, reddish, slightly raised lesion on the lower lip. The text "Michael R. Migden MD" is overlaid in white, semi-transparent font across the upper part of the image.

Michael R. Migden MD

Case #3 - 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.

Michael R. Migden MD



Case #3

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



Case #3

- 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**



Case #3

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



Case #3

- Bilateral crescentic advancement flaps using local anesthesia

Michael R. Migden MD

Case #3

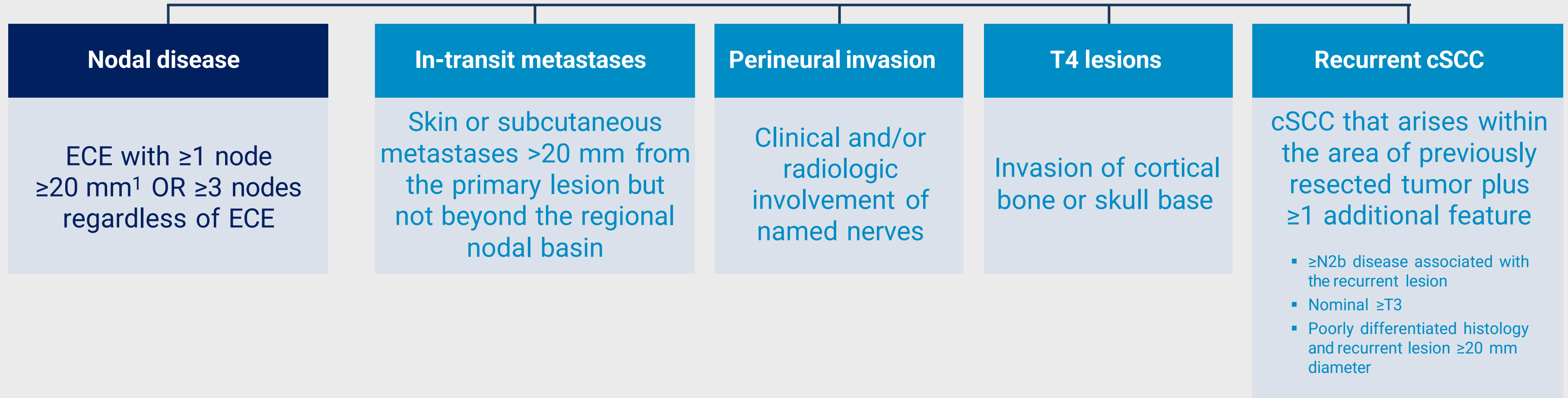
- Postoperative stereotactic radiosurgery (SR) 11 days out from reconstruction
- Patient undergoing RT



Image courtesy of Michael R. Migden, MD

C-POST Methods: High-Risk Criteria

Nodal and non-nodal high-risk criteria*



*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

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

Clinical/radiographic extent?

Is tumor well-defined?

Symptom control during procedure?

Opportunities for multidisciplinary collaboration?

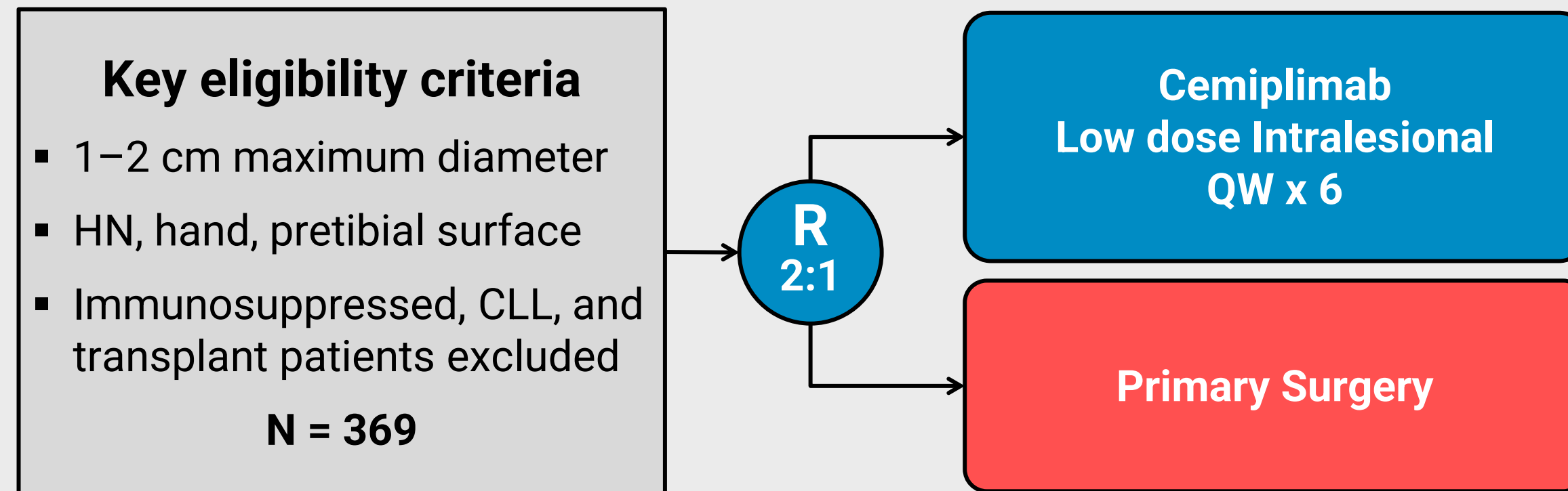
“Intervene earlier and, where possible, locally”



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

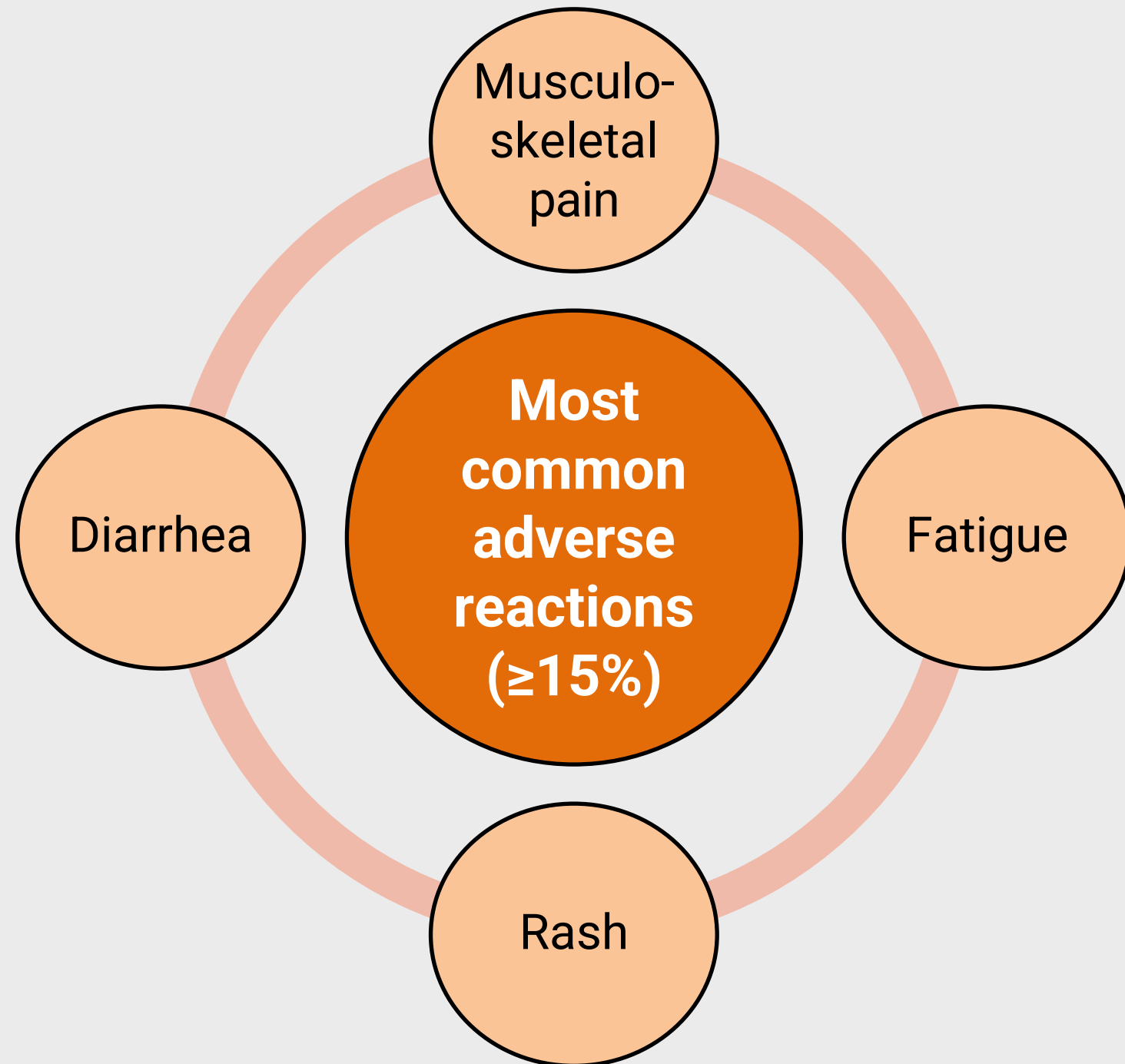
CCR = composite complete response; CLL = chronic lymphocytic leukemia; CSCC = cutaneous squamous cell carcinoma; EFS = event-free survival; HN = head and neck; R = randomized; TL = target lesion.



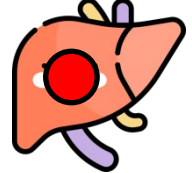

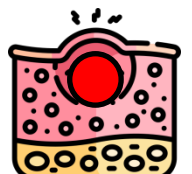
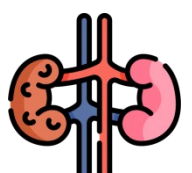
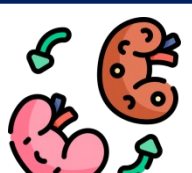
ClinicalTrials.gov identifier: NCT06585410. Accessed December 10, 2025.

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 (Keytruda®) PI 2025 (<https://www.keytruda.com/>). URLs accessed 12/8/2025.

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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.

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

Bryan J. Schneider, MD¹; Jarushka Naidoo, MD^{2,3}; Bianca D. Santomaso, MD, PhD⁴; Christina Lacchetti, MHSc⁵; Sherry Adkins, MS⁶; Milan Anadkat, MD⁷; Michael B. Atkins, MD⁸; Kelly J. Brassil, PhD⁶; Jeffrey M. Caterino, MD, MPH⁹; Ian Chau, MD¹⁰; Marianne J. Davies, DNP¹¹; Marc S. Ernstoff, MD¹²; Leslie Fecher, MD¹; Monalisa Ghosh, MD¹³; Ishmael Jaiyesimi, DO, MS¹⁴; Jennifer S. Mammen, MD, PhD¹⁵; Aung Naing, MD⁶; Loretta J. Nastoupil, MD⁶; Tanyanika Phillips, MD¹⁶; Laura D. Porter, MD¹⁷; Cristina A. Reichner, MD¹⁸; Carole Seigel, MBA¹⁹; Jung-Min Song, MSN, RN, CNS²⁰; Alexander Spira, MD, PhD²¹; Maria Suarez-Almazor, MD⁶; Umang Swami, MD²²; John A. Thompson, MD²³; Praveen Vikas, MD²⁴; Yinghong Wang, MD⁶; Jeffrey S. Weber, MD, PhD²⁵; Pauline Funchain, MD²⁰; and Kathryn Bollin, MD²⁶

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 \leq 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.

Table 3: Lung Toxicities

Management of immune-related adverse events for ICP: Update

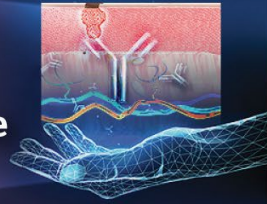
3.1 Pneumonitis	
<p>Workup and evaluation Should include the following: Pulse oximetry and CT chest! Preferably with contrast if concerned for other etiologies such as pulmonary embolus. For grade 2 or higher, may include the following infectious workup: Nasal swab, sputum culture, and sensitivity, blood culture and sensitivity, urine culture, and sensitivity. COVID-19 evaluation—per institutional guidelines where relevant.</p>	
Grading	Management
<p>Grade 1: Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only</p>	<p>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.</p>
<p>Grade 2: Symptomatic; Involves more than one lobe of the lung or 25% to 50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL</p>	<p>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.</p>
<p>Grade 3: Severe symptoms; Hospitalization required: Involves all lung lobes or >50% of lung parenchyma; limiting self-care ADL; oxygen indicated.</p>	<p>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.</p>
<p>Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (intubation)</p>	<p>May consider bronchoscopy with BAL + transbronchial biopsy if patient can tolerate.</p>

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.

^aSubset 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%.

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/csc-cc-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. <i>J Am Acad Dermatol</i> . 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. <i>J Am Acad Dermatol</i> . 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. <i>J Am Acad Dermatol</i> . 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. <i>Ann Surg Oncol</i> . 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. <i>J Am Acad Dermatol</i> . 2025;93:73-81.	https://pubmed.ncbi.nlm.nih.gov/40024391/
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Neoadjuvant Therapy For High-Risk cSCC

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Adjuvant Therapy for High-Risk cSCC

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Management of Immunotherapy-Related Adverse Events

Resource	Address
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