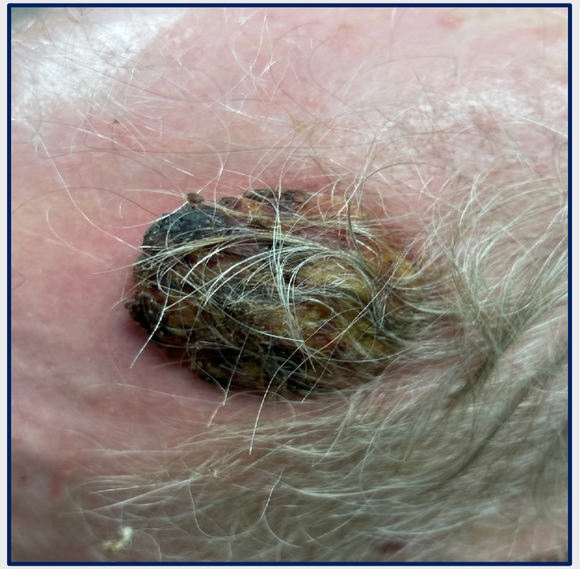
Module 3 - Developing Treatment Plans for High-Risk cSCC: Adjuvant Therapy

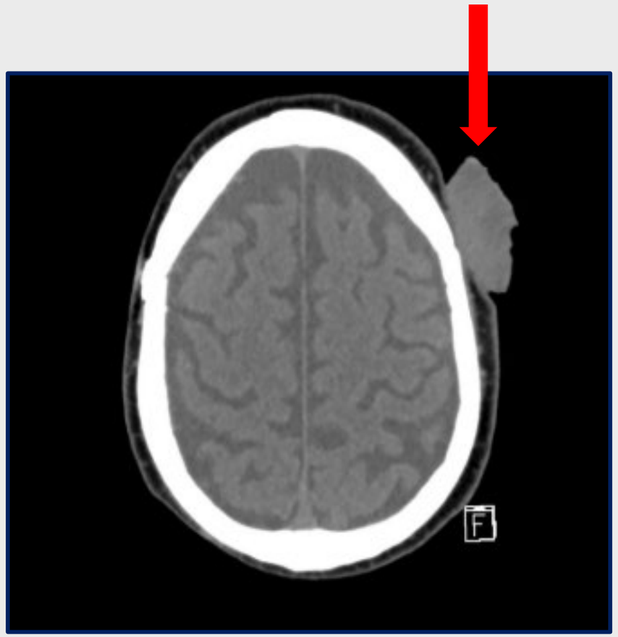
Nikhil I. Khushalani, MD

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

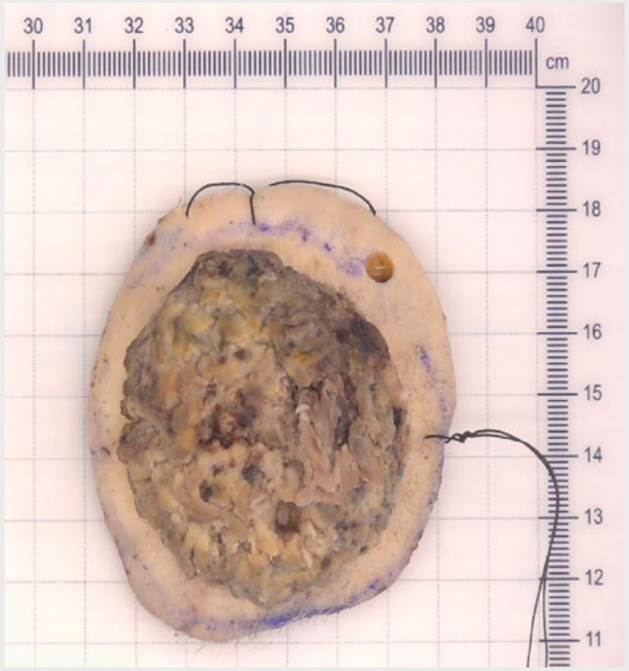
Razan Masarwy [1,2], Shahaf Shilo [1,2], Narin Nard Carmel Neiderman [1,2], Liyona Kampel [1,2], Gilad Horowitz [1,2], Nidal Muhanna [1,2] and Jobran Mansour [1,2,*]

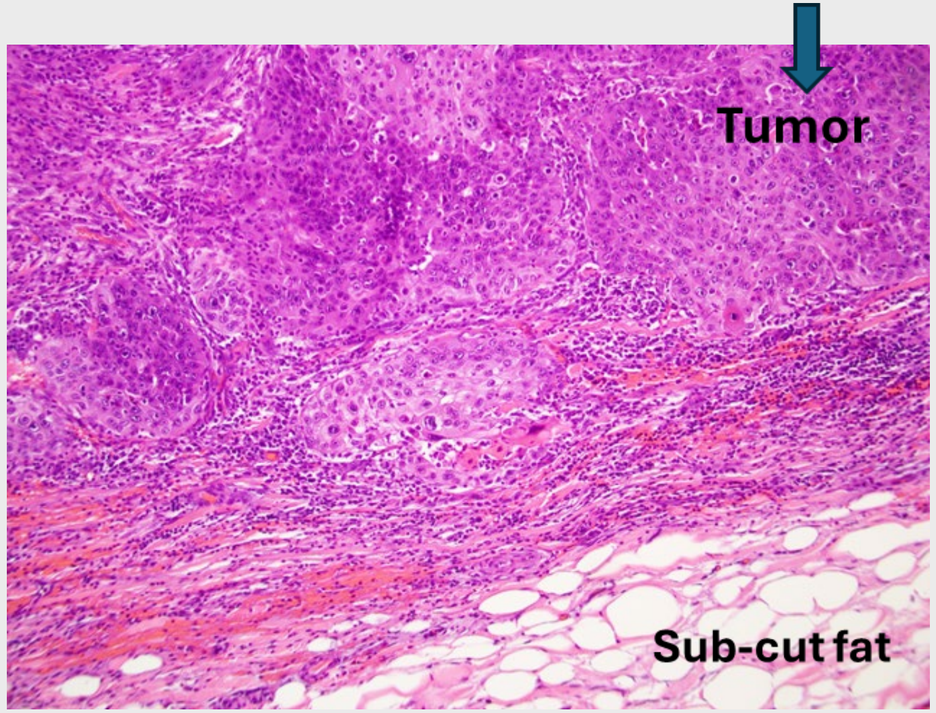
Case Presentation

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

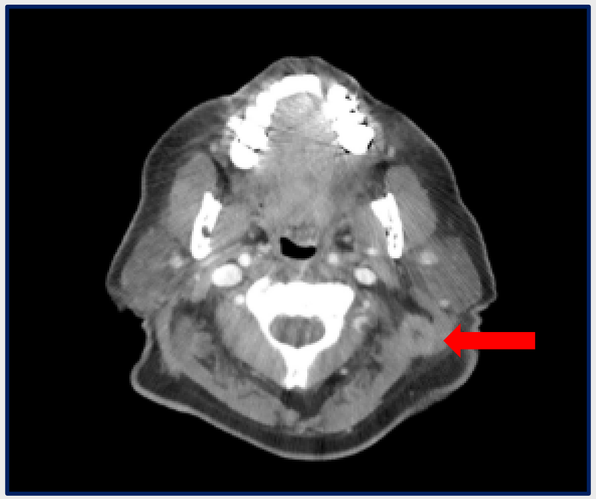
Received adjuvant radiotherapy: 66 Gy

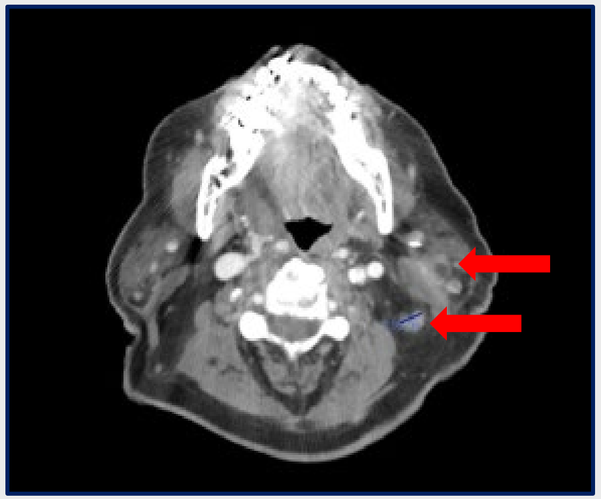
- Is there a role for radiation to the nodal basin(s) when there is no nodal metastasis identified?

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

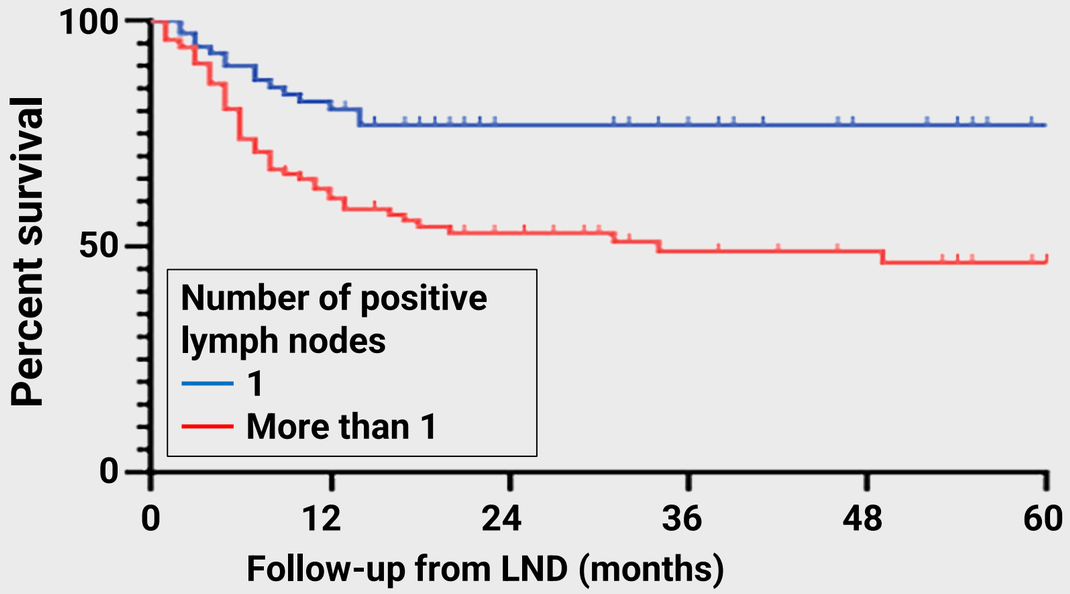
c) Adjuvant RT to left neck followed by adjuvant cemiplimab for 1 year

d) Adjuvant cetuximab for 1 year

e) Observation

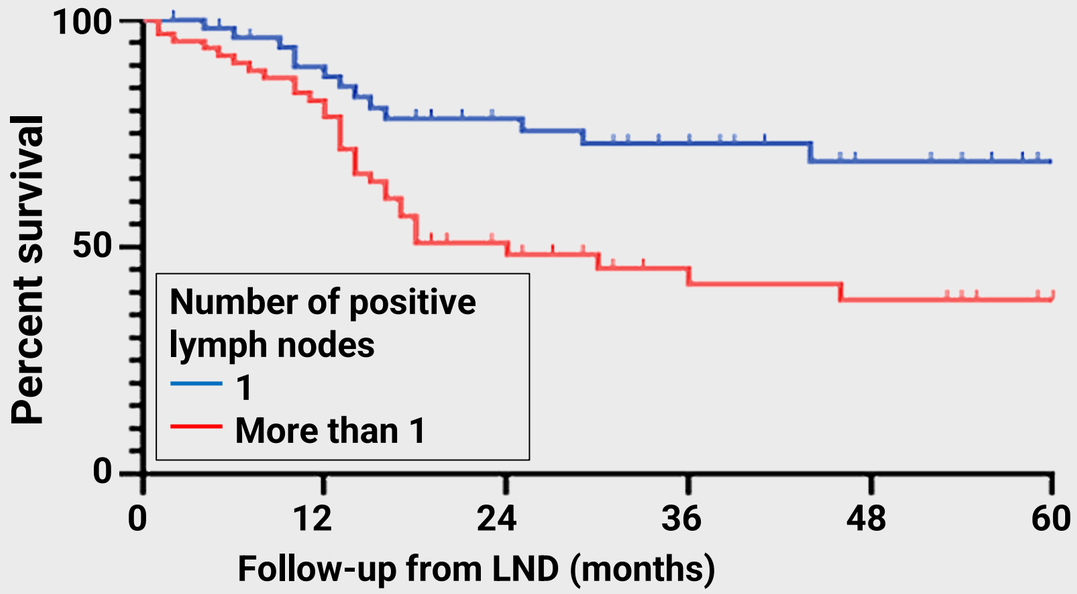
Outcomes After Lymphadenectomy in Cutaneous SCC (cSCC)

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



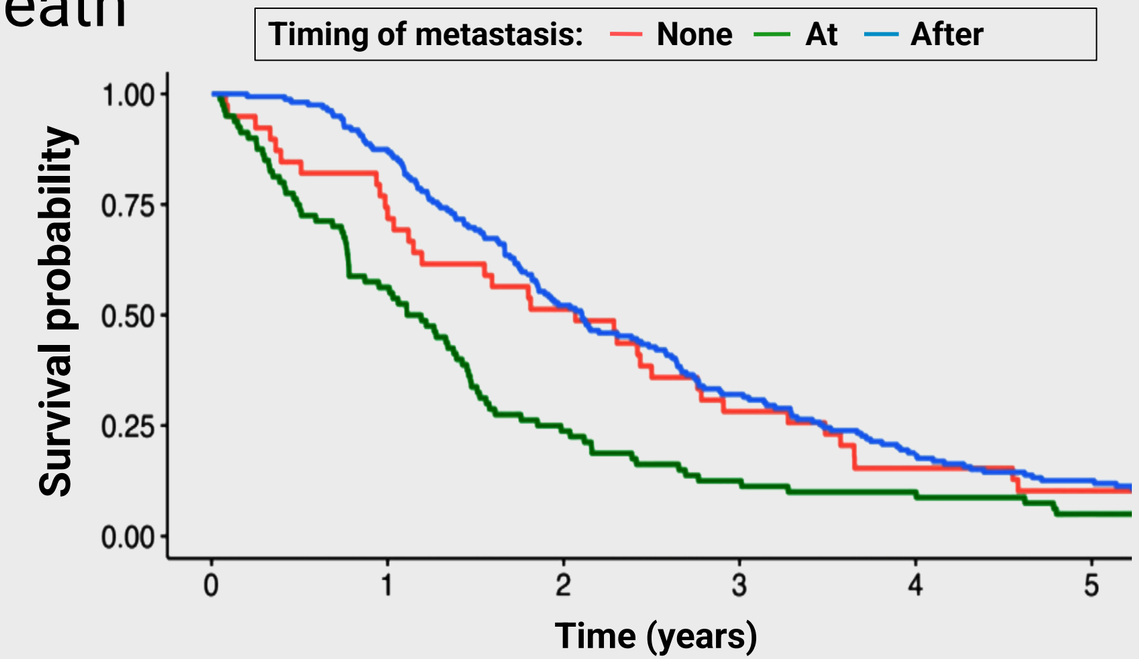
Number at risk						
PL = 1	51	40	28	22	16	9
PL > 1	63	44	19	12	10	5

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

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

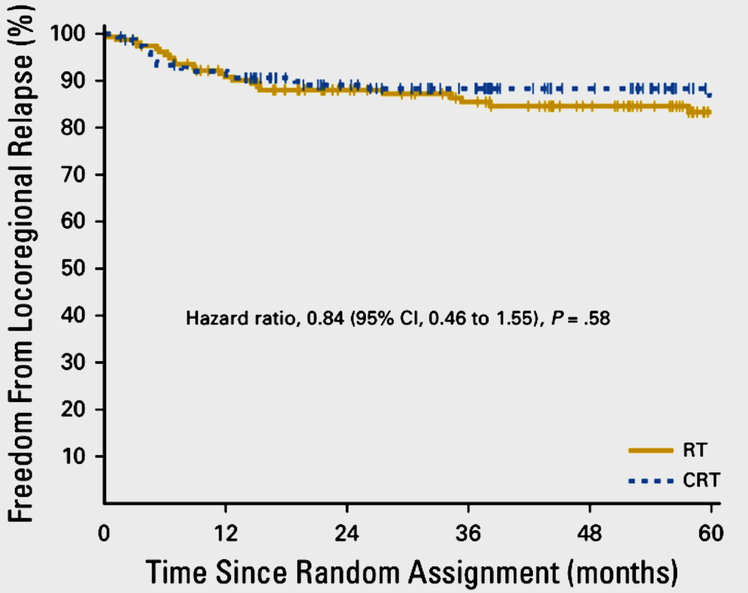
Patterns of Disease-Specific Death (DSD) in cSCC

- 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**



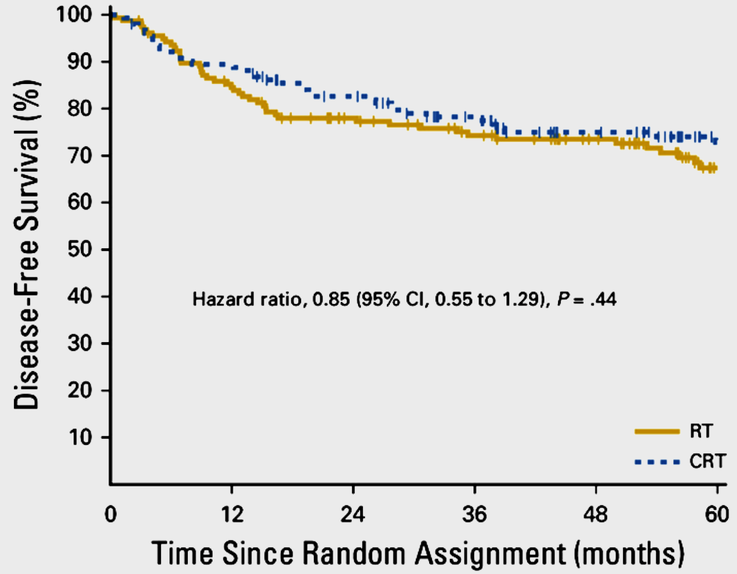
Gibson FT, et al. *J Am Acad Dermatol.* 2025 (https://www.jaad.org/article/S0190-9622(25)02985-8/abstract). Accessed 12/3/2025.

Adjuvant Radiotherapy +/– Chemotherapy
TROG 05:01



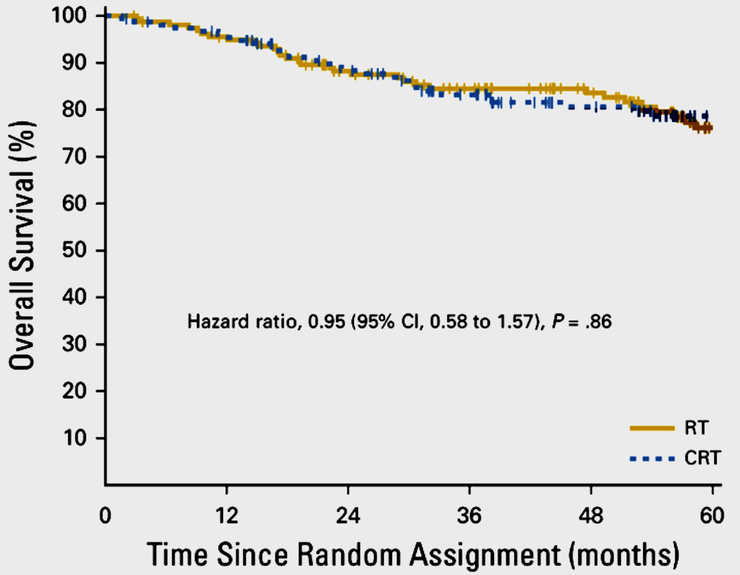
No. at risk (No. of events):

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)

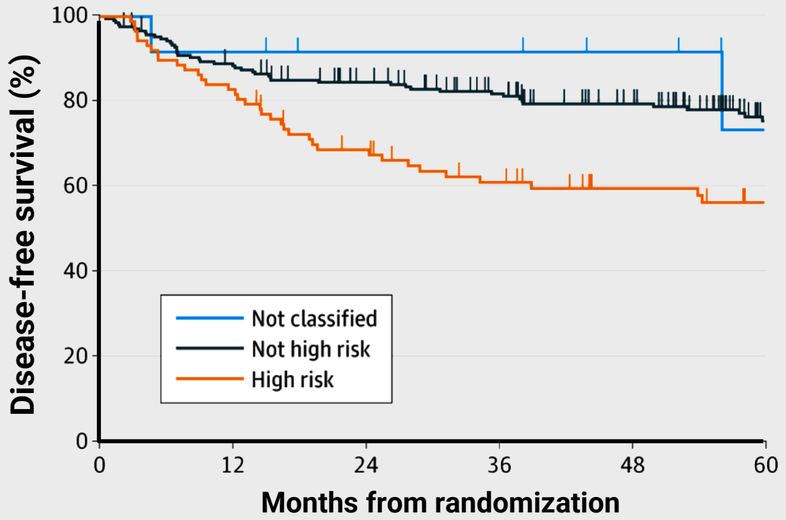
SUMMARY:

<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.

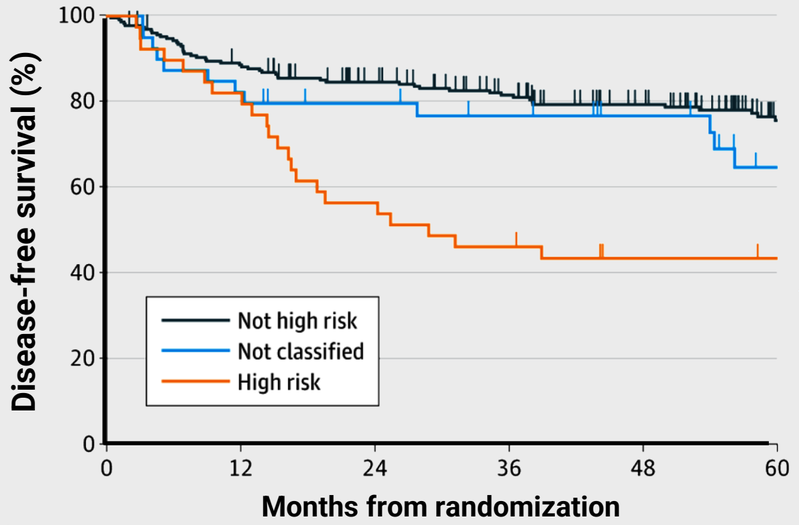
Can We Further Stratify to Define “High-Risk”?

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

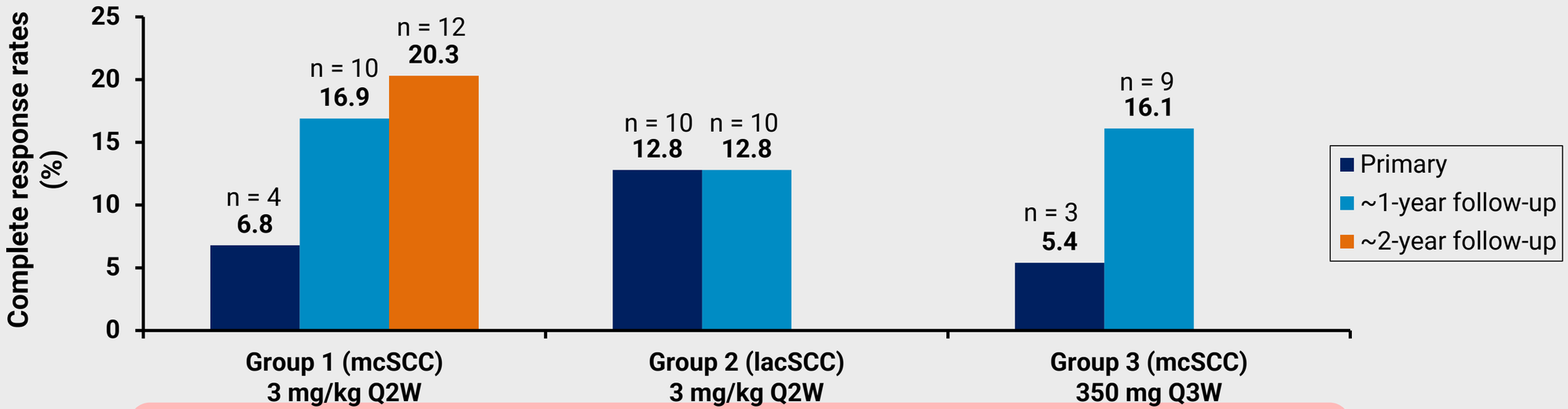
High-risk subgroup restricting analysis to T1 to T4 primary tumors plus nodal ECE and node size ≥22 mm
5-year DFS: 43%

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.

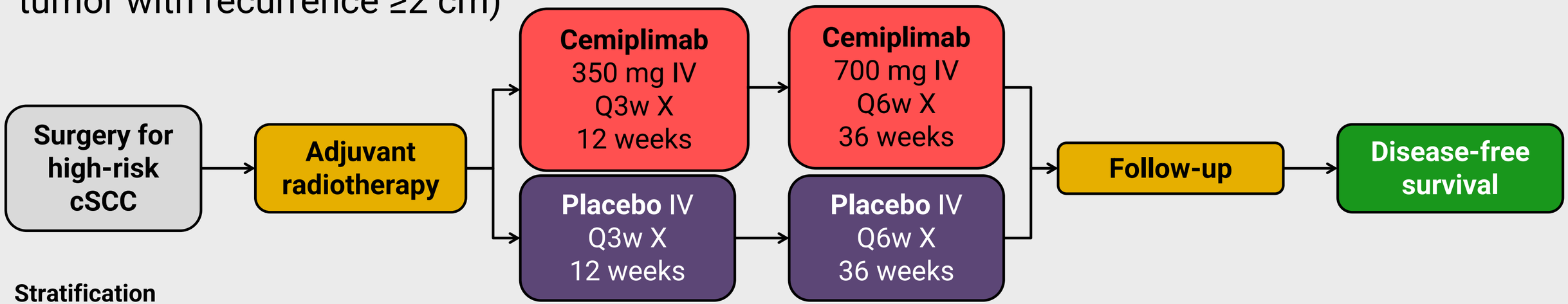
Rischin D, et al. *N Engl J Med.* 2025;393:774-785.

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)



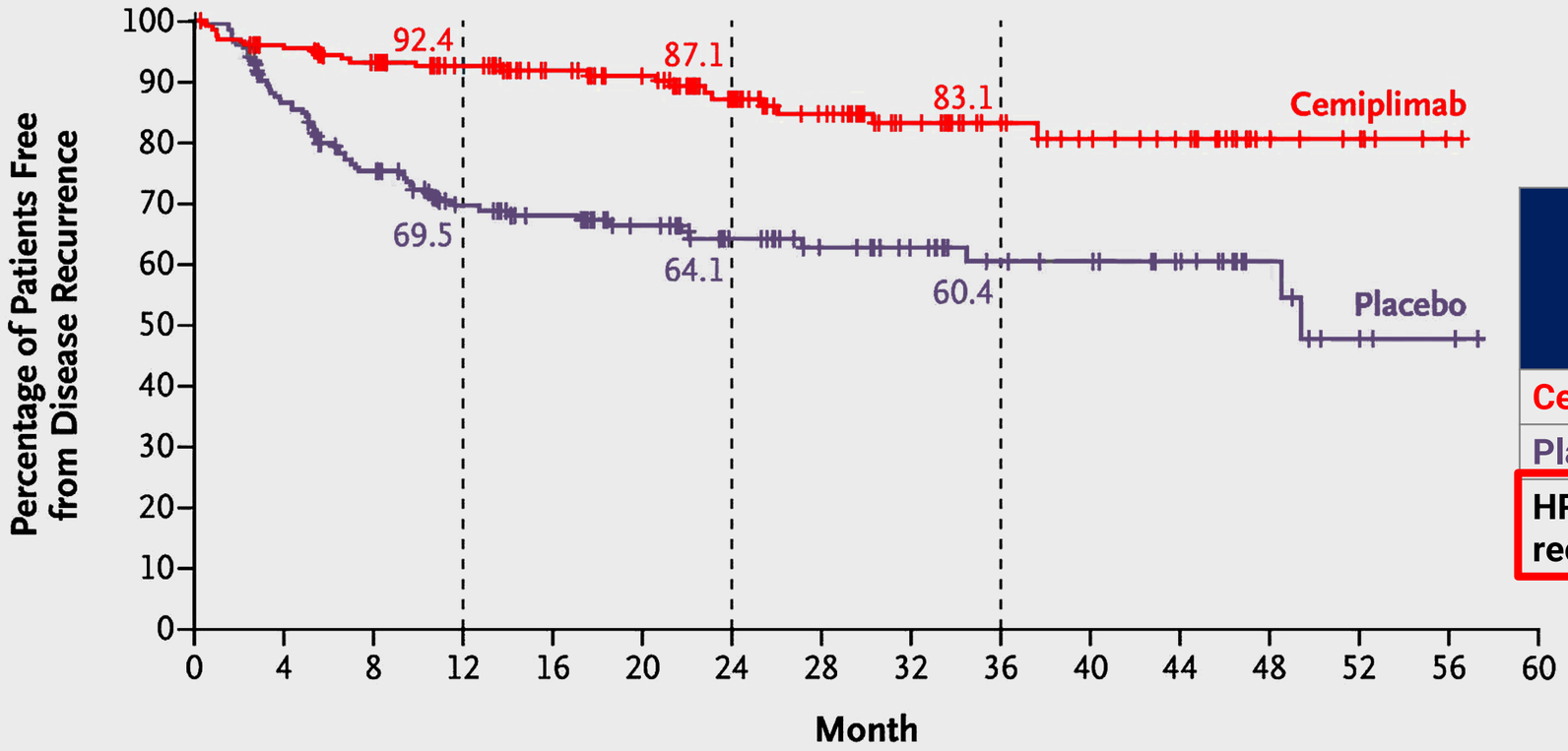
Stratification

- 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)

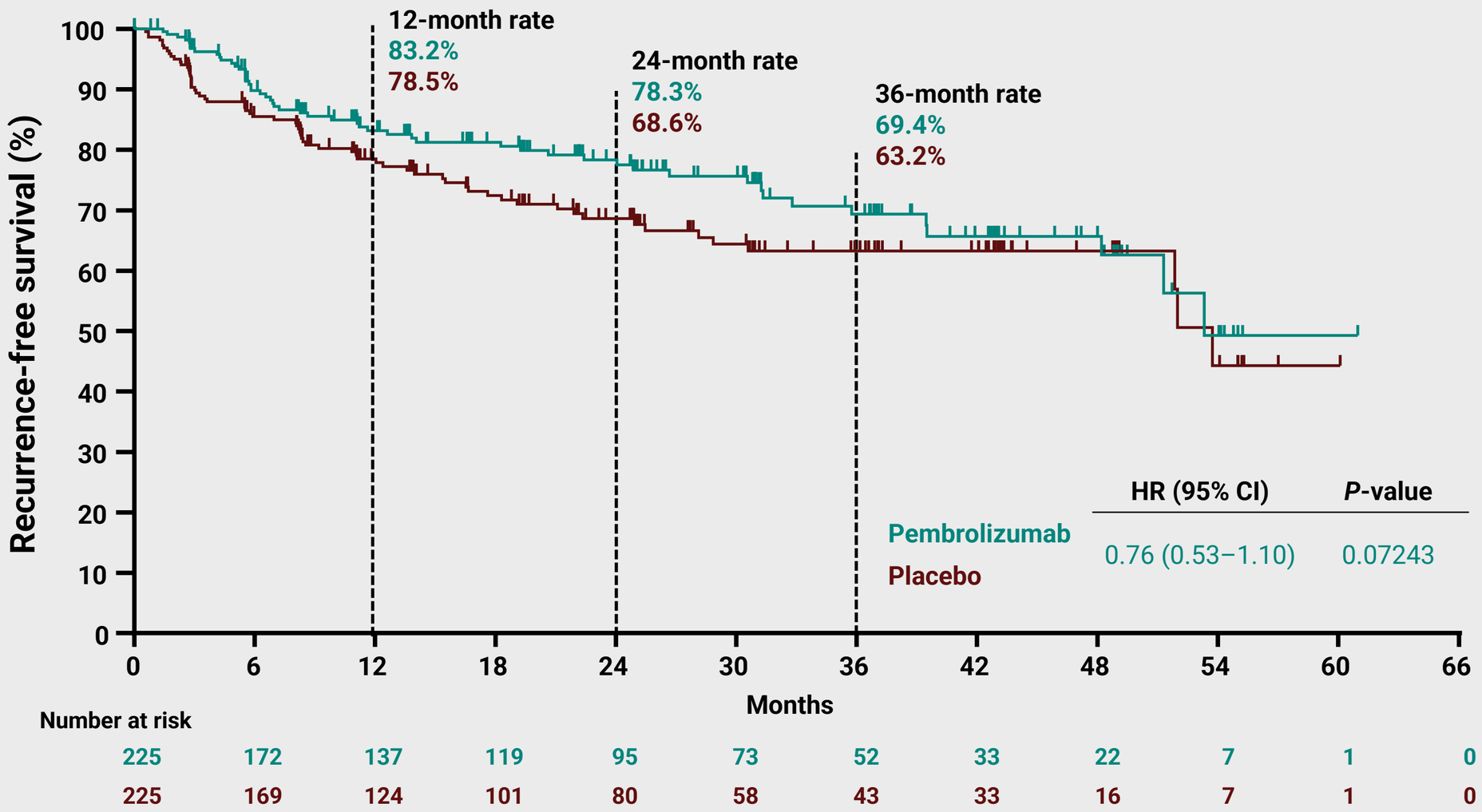
- Extracapsular extension
- Cortical bone invasion
- Prior systemic therapy

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?

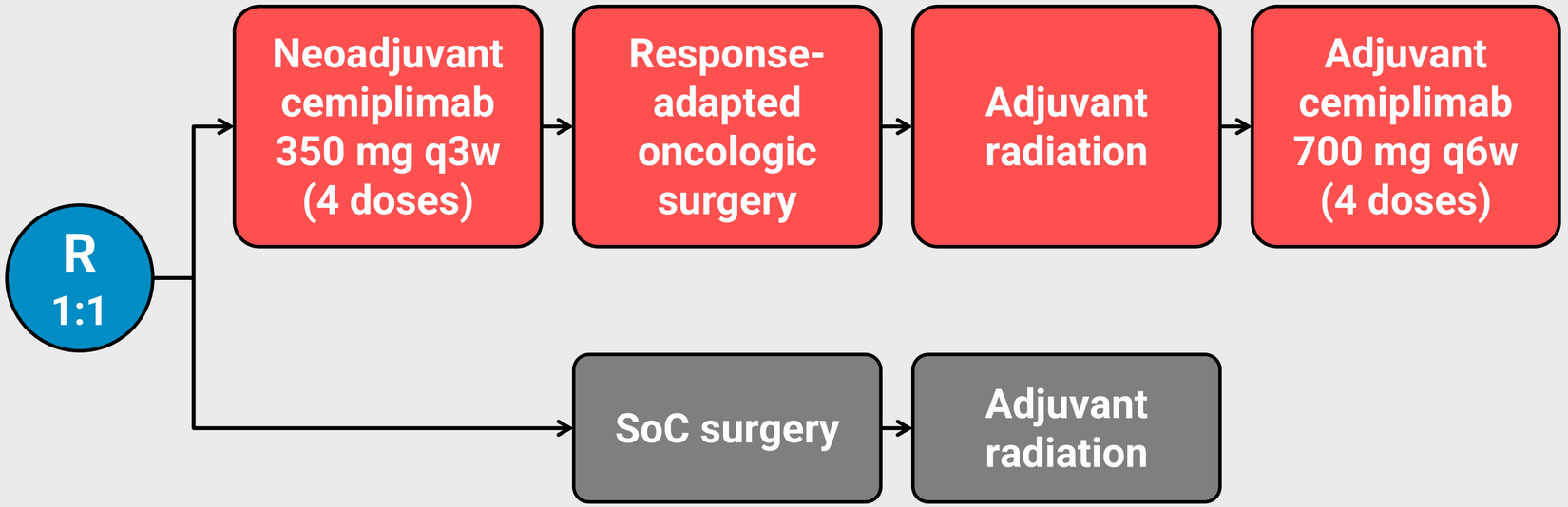
Event	Pembrolizumab n = 225	Placebo n = 225
Any recurrence	31 (13.8)	57 (25.3)
Distant metastasis	10 (4.4)	26 (11.6)
Death	35 (15.6)	24 (10.7)

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