# Advanced Cutaneous Squamous Cell Carcinoma: Immuno-Oncology and the Evolving Landscape of Multidisciplinary Care

Presented by:

The Angeles Clinic & Research Institute & ACCC

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ACCC
Association of Community Cancer Centers

The Angeles Clinic
AND RESEARCH INSTITUTE
A CEDARS-SINAI AFFILIATE

# Speakers

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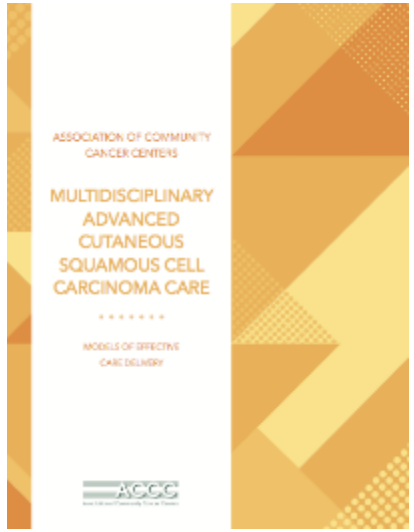
Santa Monica, CA

# Importance of Multidisciplinary Care

- Emerging multidisciplinary care models across the country.
- Association of Community Cancer Centers education program on *Multidisciplinary Advanced Cutaneous Squamous Cell Carcinoma Care*.

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Publication available in print and online!

# Disclosures

*Mark Faries Disclosures*

- Advisory Board:
  - Novartis, Array Biopharma, Pulse Bioscience, Castle Bioscience, Bristol Myers Squibb, Sanofi

# OBJECTIVES

To know:

1. Current data regarding the epidemiology of cutaneous squamous cell carcinoma (cSCC)
2. Potential preventative strategies for skin cancer, including cSCC
3. What modern, multidisciplinary options are available for local and regional treatment of cSCC
4. What systemic therapy options are available for treatment of advanced or metastatic cSCC
5. The precautions and potential toxicities of immuno-oncology therapies in cSCC

# Outline: Faries

Cutaneous Squamous Cell Carcinoma

- Epidemiology
- Diagnosis / Prognosis
- Primary Treatment
  - Surgery / Mohs'
- Staging
  - SLN
  - Imaging
- Follow up

# cSCC: Epidemiology

- Data are not great: Not captured in registries
- Second most common cancer
- Incidence approaching that of Basal Cell Carcinoma[1]
- Comparing incidence (1976-1984) vs (2000-2010)[2]
  - ➢ Increase of 263%
- Karia et al estimated (in USA, 2012)[3]
  - 5604 - 12,572 with cSCC developed nodal metastases
  - 3932 - 8791 deaths from cSCC (1.5-4% mortality rate?)

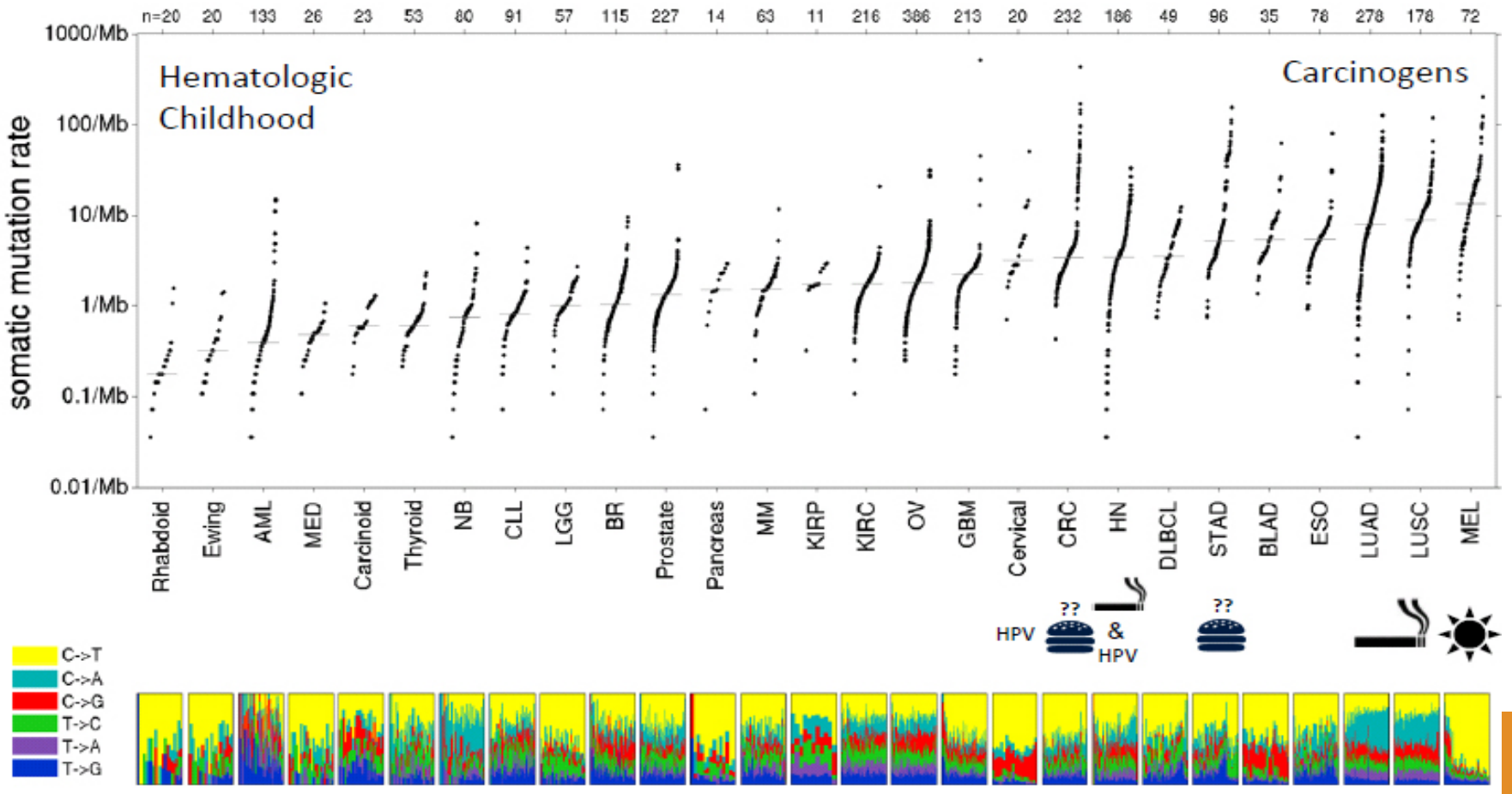

1. Rogers HW et al: Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas)in the U.S. population, 2012. *JAMA Dermatol*. 2015;151:1081-1086.
2. Muzic JG, Schmitt AR, Baum CL, et al. Incidence and trends of basal cell carcinoma and cutaneous squamous cell carcinoma: a population-based study in Olmsted County, Minnesota, 2000 to 2010. *Mayo Clin Proc*. 2017;92:890-898.
3. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. *J Am Acad Dermatol*. 2013;68:957-966.

# cSCC: Risk Factors

- Male > Female (3:1), Hx of sun exposure, Actinic Keratoses, Immunosuppression, Fitzpatrick Type 1, CLL
- Arsenic, tar, +/- HPV (periungual, anogenital), Smoking?
- Genetic:
  - xeroderma pigmentosum, Ferguson-Smith Syndrome, oculocutaneous albinism, epidermodysplasia verruciformis.
  - MC1R
- Drugs: BRAF monotherapy, Vismodegib
- Older age: Australia <40 yo: 7/100K, >70 yo: 2972/100K
- Prior SCC - 40% new cSCC at 5-years after first
  - 82% new cSCC at 5 years after >1 cSCC

1. Waldman cutaneous Squamous Cell Carcinoima. Hem Oncol Clin 2017

# cSCC: Risk Factors




TP53, RAS, CDKN2A

cSCC: 4x mutations of melanoma

TCGA

# cSCC: Risk Factors: Transplant

- Keratinocyte carcinomas are the most common cancers among white solid organ transplant patients.

| Study | Outcome | Location | Kidney | Liver | Heart | Lung |
|---|---|---|---|---|---|---|
| Chapman 2013[62] | KC | Finland | 39·2 (29·3–51·4) | | | |
| | | Sweden | 57·7 (51·0–65·1) | 34·0 (17·0–60·6) | | |
| | | U.K. | 16·6 (15·9–17·3) | 6·6 (5·8–7·5) | 18·5 (16·9–20·3) | 16·1 (13·1–19·6) |
| Jensen 2010[6] | cSCC | Denmark | 81 (68–96) | 60 (27–113) | 113 (74–166) | 65 (28–128) |
| Jensen 2010[6] | BCC | Denmark | 6·9 (5·8–8·1) | 4·6 (2·1–8·7) | 5·6 (3·1–9·5) | 4·1 (1·7–8·5) |
| Krynitz 2013[3] | | | | | | |
| < 5 years | cSCC | Sweden | 53 (46–61) | 15 (7·2–28) | 67 (46–94)[a] | |
| 5–9 years | | | 92 (83–102) | 40 (25–61) | 218 (174–269)[a] | |
| 10–19 years | | | 165 (154–177) | 51 (31–80) | 357 (297–425)[a] | |
| ≥ 20 years | | | 206 (187–226) | | | |
| Krynitz 2013[3] | cSCC | Sweden | 121 (116–127) | 32 (24–42) | 198 (174–224)[a] | |

KTR, kidney transplant recipient; LiTR, liver transplant recipient; HTR, heart transplant recipient; LuTR, lung transplant recipient. [a]Heart and lung transplant recipients.

1. Madeleine Epidemiology of keratinocyte carcinomas after organ transplantation. BJD 2017

# cSCC: Geography / UV Exposure


1. Green and Olsen. Cutaneous squamous carcinoma: an epidemiological review. Brit J Dermatol. 2017

# cSCC: Prevention

Chemoprevention:
Vitamin B3: nicotinamide

May enhance DNA repair by preventing UVR-induced adenosine triphosphate depletion

*The* New England Journal *of* Medicine

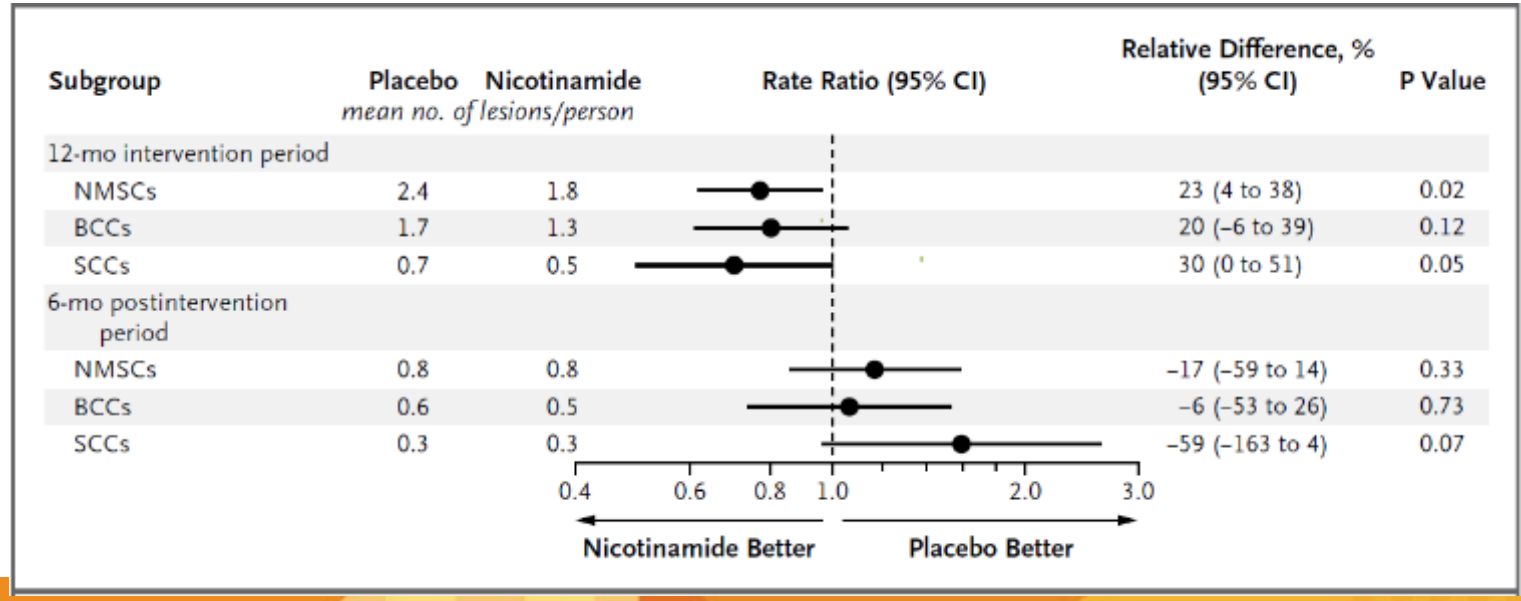
A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention

AC Chen, AJ Martin, B Choy, P Fernández-Peñas, RA Dalziell, CA McKenzie, RA Scolyer, HM Dhillon, JL Vardy, A Kricker, G St. George, N Chinniah, GM Halliday, DL Damian. 2015

Difluormethylornithine: decreases polyamine synthesis

NSAIDS

Field Therapy: 5-fluoruracil, diclofenac, PDT



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Field Therapy: 5-fluoruracil, diclofenac, PDT

SUN PROTECTION

Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial

A Green, G Williams, R Neale, V Hart, D Leslie, P Parsons, GC Marks, P Gaffney, D Battistutta, C Frost, C Lang, A Russell

*The Lancet 1999*

| Skin cancer | Participants | | Tumours | |
|---|---|---|---|---|
| | Daily sunscreen | No daily sunscreen | Daily sunscreen | No daily sunscreen |
| **Basal-cell carcinoma** | | | | |
| Number | 65 | 63 | 153 | 146 |
| Incidence per 100 000 | 2588 | 2509 | 6092 | 5814 |
| Rate ratio (95% CI) | 1·03 (0·73–1·46) | 1·00 | 1·05 (0·82–1·34) | 1·00 |
| **Squamous-cell carcinoma** | | | | |
| Number | 22 | 25 | 28 | 46 |
| Incidence per 100 000 | 876 | 996 | 1115 | 1832 |
| Rate ratio (95% CI) | 0·88 (0·50–1·56) | 1·00 | 0·61 (0·46–1·81) | 1·00 |

# cSCC Staging: AJCC 8 vs. BWH

**Table I.** American Joint Committee on Cancer (AJCC) cutaneous SCC staging system for tumors of the head and neck skin 8th edition

| T category | T criteria | N category | N criteria for pathologic N | M category | M criteria |
|---|---|---|---|---|---|
| TX | Primary tumor cannot be identified | NX | Regional lymph nodes cannot be assessed | M0 | No distant metastasis |
| Tis | Carcinoma in situ | N0 | No regional lymph node metastasis | M1 | Distant metastasis |
| T1 | Tumor <2 cm in greatest dimension | N1 | Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE * | | |
| T2 | Tumor ≥2 cm but <4 cm in greatest dimension | N2 | Metastasis in a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE+; or >3 cm but not >6 cm in greatest dimension and ENE−; or metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE−; or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE− | | |
| T3 | Tumor ≥4 cm in clinical diameter OR minor bone erosion OR perineural invasion OR deep invasion† | N2a | Metastasis in single ipsilateral or contralateral node ≤3 cm in greatest dimension and ENE+; or in a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE− | | |
| T4 | Tumor with gross cortical bone/marrow, skull base invasion, and/or skull base foramen invasion | N2b | Metastasis in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE− | | |
| T4a | Tumor with gross cortical bone/marrow invasion | N2c | Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE− | | |
| T4b | Tumor with skull base invasion and/or skull base foramen involvement | N3 | Metastasis in a lymph node >6 cm in greatest dimension and ENE−; or in a single ipsilateral node >3 cm in greatest dimension and ENE+; or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE+ | | |
| | | N3a | Metastasis in a lymph node >6 cm in greatest dimension and ENE− | | |
| | | N3b | Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE+; or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE+ | | |

High-risk features:

- Diameter ≥2 cm
- Poorly differentiated
- Perineural invasion ≥0.1mm
- Tumor invasion beyond subcutaneous fat

(Bone invasion automatic T3)

**Table II.** Brigham and Women's Hospital tumor staging system

| Stage | No. of high-risk factors* |
|---|---|
| T1 | 0 |
| T2a | 1 |
| T2b | 2-3 |
| T3 | ≥4 |

SKT Que, FO Zwald, CD Schmults. Cutaneous squamous cell carcinoma Incidence, risk factors, diagnosis, and staging *JAAD* 2018

# cSCC: Prognostic factors

**Location:** Area L (trunk/extremities)
Area M (cheek, forehead, scalp, neck, shin)
Area H ("mask", genitalia, hands/feet)

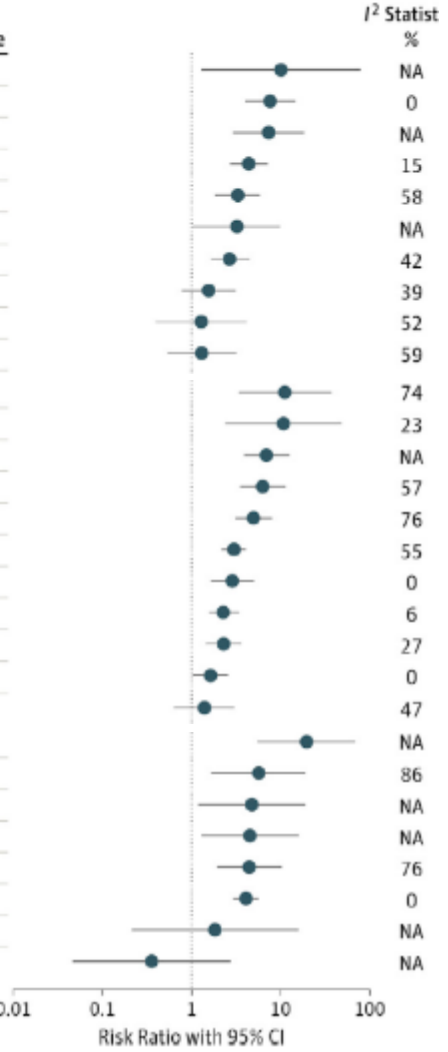
**Size:** Diameter: L ≥20mm, M ≥ 10 mm, H any
Depth (subcut or >6mm)

**Histology**:
Low: Keratoacanthoma, verrucous carcinoma

High: desmoplastic, adneosquamous, cSCC associated w/ scarring process (e.g. burn)

**Borders**
**Recurrent lesion**
**Growth rate**
**Neurologic symptoms**

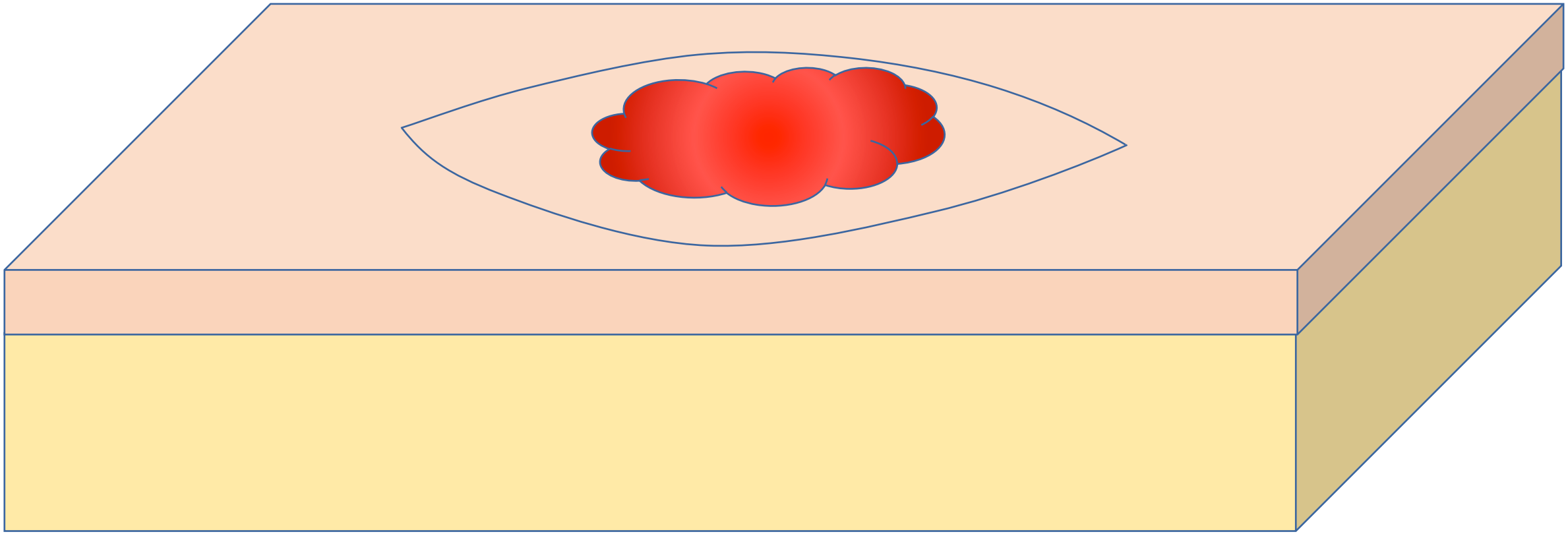
| Outcome | Risk Factor | No. of Studies | Risk Ratio | (95% CI) | *P* Value | $I^2$ Statist % |
|---|---|---|---|---|---|---|
| Recurrence | Breslow thickness >2 mm | 1 | 9.64 | 1.30-71.52 | .03 | NA |
| | Invasion beyond subcutaneous fat | 3 | 7.61 | 4.17-13.88 | <.01 | 0 |
| | Breslow thickness >6 mm | 1 | 7.13 | 3.04-16.72 | <.01 | NA |
| | PNI | 6 | 4.30 | 2.80-6.60 | <.01 | 15 |
| | Diameter >20 mm | 5 | 3.22 | 1.91-5.45 | <.01 | 58 |
| | Temple | 1 | 3.20 | 1.12-9.15 | .03 | NA |
| | Poor differentiation | 11 | 2.66 | 1.72-4.14 | <.01 | 42 |
| | Immunosuppression | 6 | 1.51 | 0.81-2.81 | .20 | 39 |
| | Lip | 4 | 1.28 | 0.41-3.97 | .67 | 52 |
| | Ear | 6 | 1.28 | 0.56-2.90 | .56 | 59 |
| Metastasis | Invasion beyond subcutaneous fat | 5 | 11.21 | 3.59-34.97 | <.01 | 74 |
| | Breslow thickness >2 mm | 3 | 10.76 | 2.55-45.31 | <.01 | 23 |
| | Breslow thickness >6 mm | 2 | 6.93 | 4.02-11.94 | <.01 | NA |
| | Diameter >20 mm | 8 | 6.15 | 3.56-10.65 | <.01 | 57 |
| | Poor differentiation | 18 | 4.98 | 3.30-7.49 | <.01 | 76 |
| | PNI | 12 | 2.95 | 2.31-3.75 | <.01 | 55 |
| | Temple | 7 | 2.82 | 1.72-4.63 | <.01 | 0 |
| | Ear | 13 | 2.33 | 1.67-3.23 | <.01 | 6 |
| | Lip | 13 | 2.28 | 1.54-3.37 | <.01 | 27 |
| | Immunosuppression | 6 | 1.59 | 1.07-2.37 | .02 | 0 |
| | Cheek | 5 | 1.30 | 0.61-2.77 | .49 | 47 |
| Disease-specific death | Diameter >20 mm | 1 | 19.10 | 5.80-62.95 | <.01 | NA |
| | Poor differentiation | 4 | 5.65 | 1.76-18.20 | <.01 | 86 |
| | Ear | 2 | 4.67 | 1.28-17.12 | .02 | NA |
| | Lip | 2 | 4.55 | 1.41-14.69 | .01 | NA |
| | Invasion beyond subcutaneous fat | 4 | 4.49 | 2.05-9.82 | <.01 | 76 |
| | PNI | 3 | 4.06 | 3.10-5.32 | <.01 | 0 |
| | Temple | 1 | 1.80 | 0.22-14.79 | .58 | NA |
| | Immunosuppression | 1 | 0.35 | 0.05-2.58 | .30 | NA |



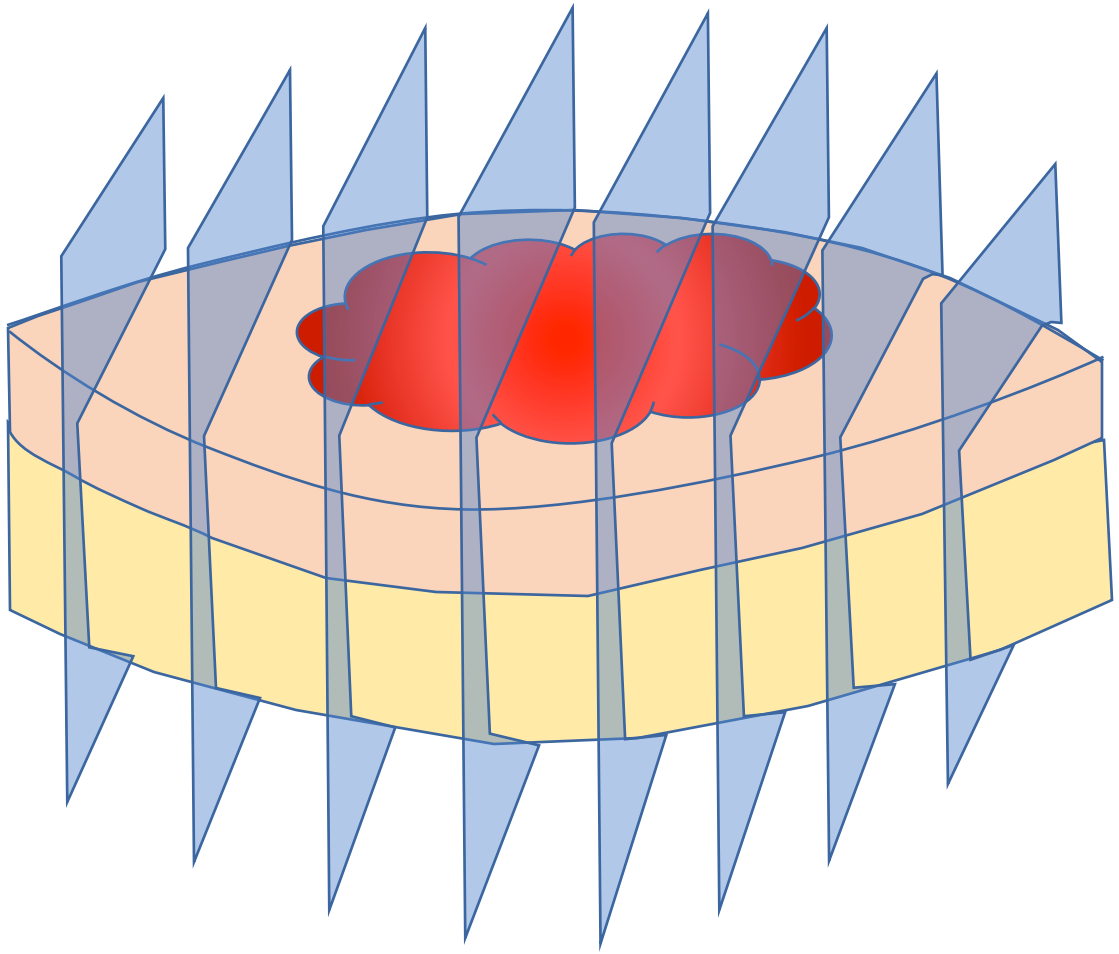

Working Group. NCCN Guidelines Version 1.2020 Squamous cell skin cancer.

SKT Que, FO Zwald, CD Schmults. Cutaneous squamous cell carcinoma Incidence, risk factors, diagnosis, and staging *JAAD* 2018

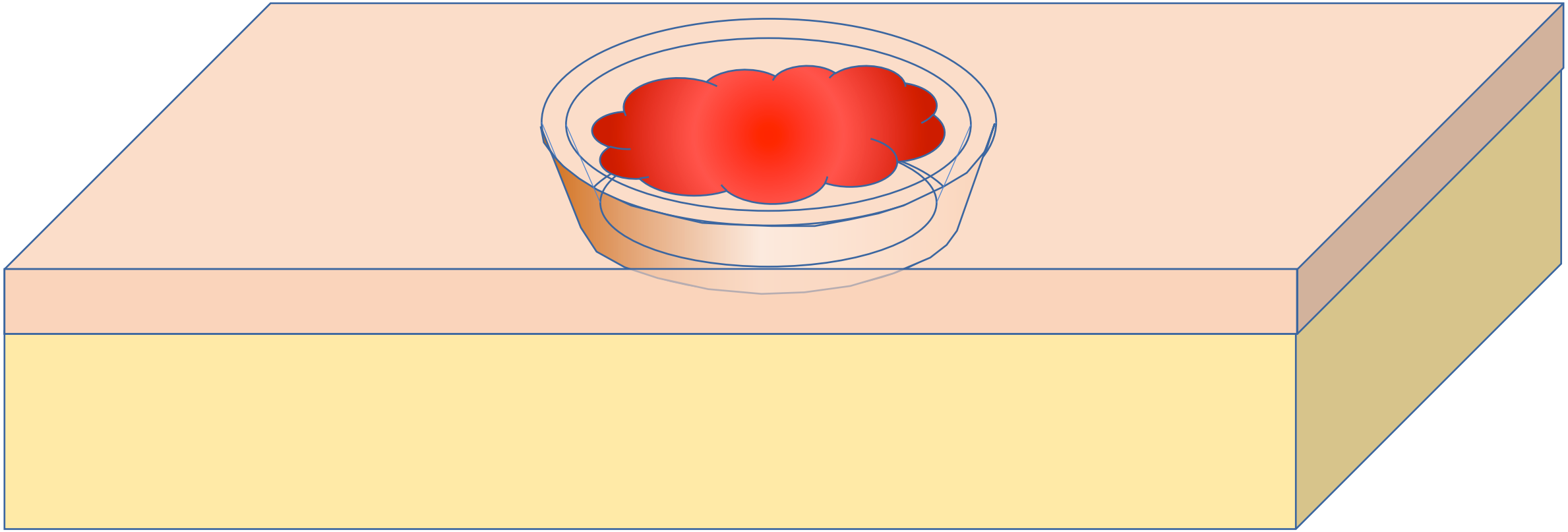
# cSCC: Mohs' vs. Excision Pathology



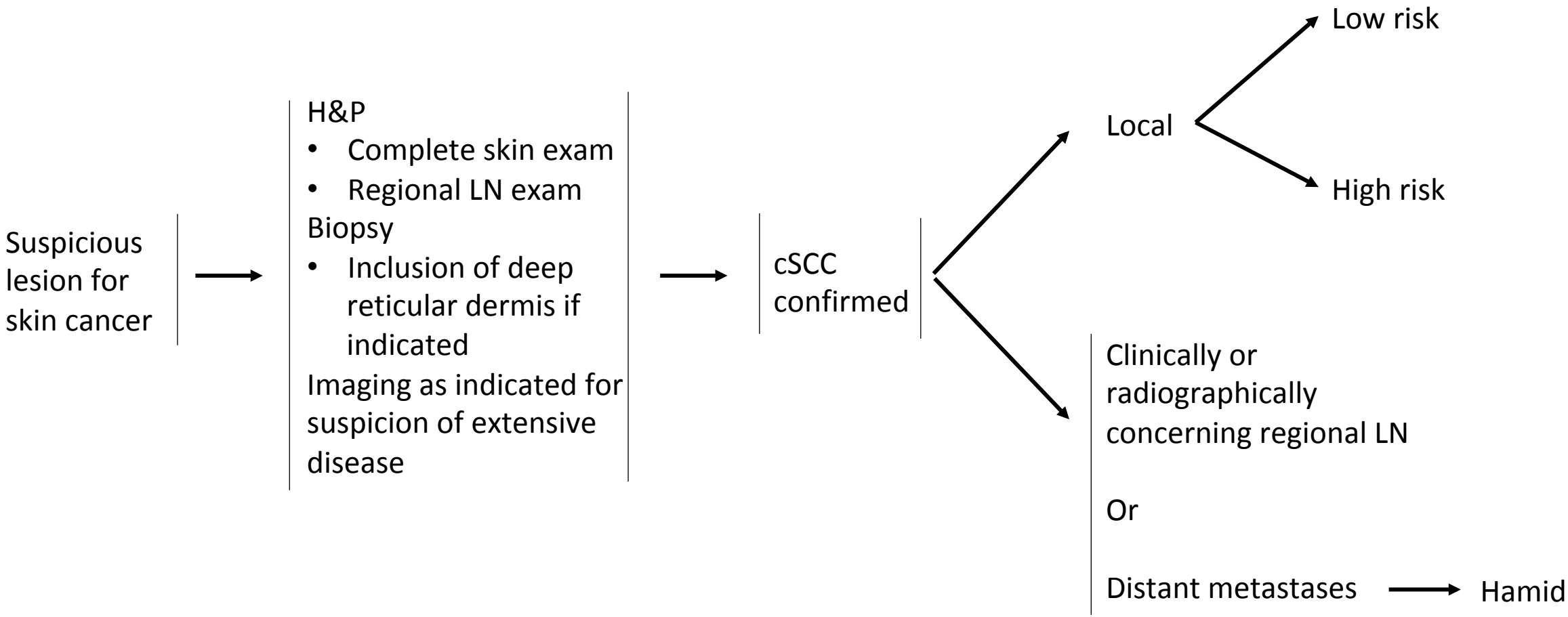
# cSCC: Pathology “Breadloaf”



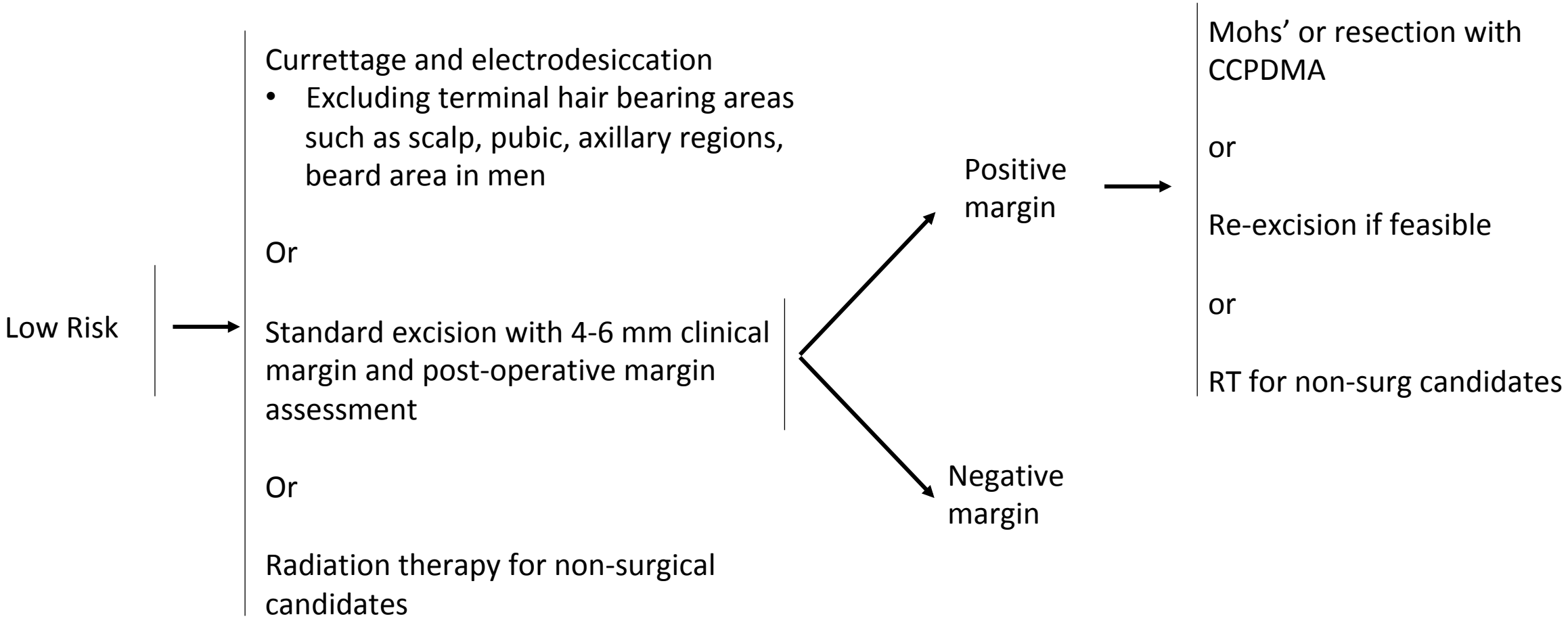
# cSCC: Pathology
# CCPDMA



# Primary Treatment (NCCN)

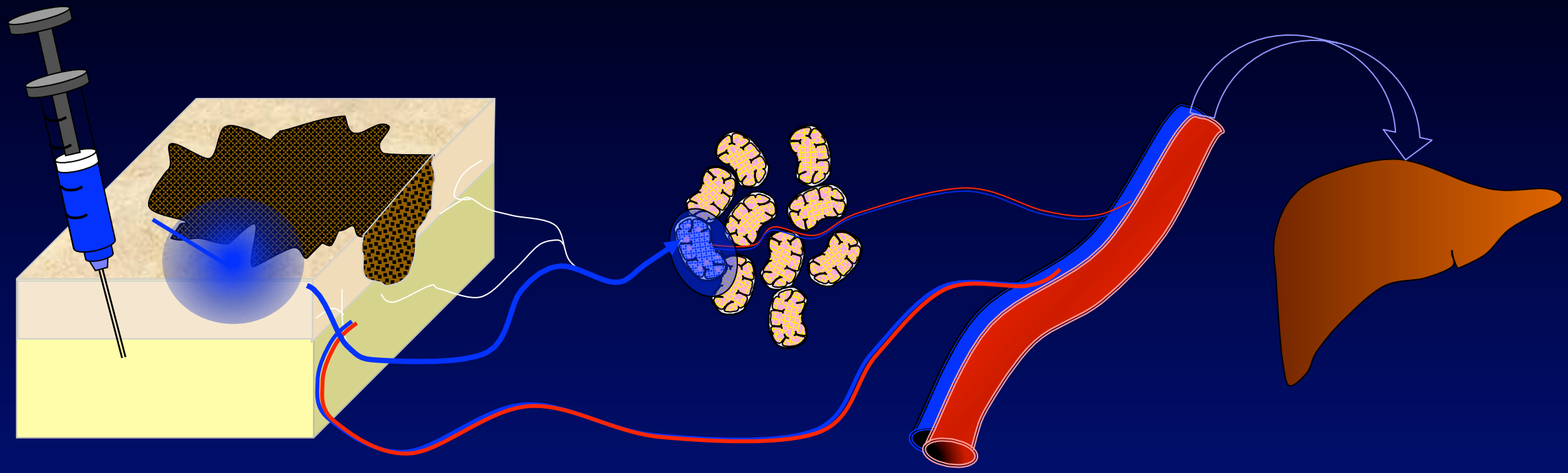


# Primary Treatment: Low Risk (NCCN)




Working Group. NCCN Guidelines Version 1.2020 Squamous cell skin cancer.

# Sentinel Lymph Node



# SLN in cSCC:

Nodal staging of high-risk cutaneous squamous cell carcinoma

M Fox, M Brown, N Golda, D Goldberg, C Miller, M Pugliano-Mauro, C Schmults, T Shin, T Stasko, YG Xu, K Nehal, High Risk SCC Workgroup, Dermatol Surg Section of Assoc Prof Derm

*J AM ACAD DERMATOL* VOLUME 81, NUMBER 2, 2019

| Study | Year | Design | Tumor site | SLN + (14.5%) | False - (5.1%) | Other: |
|---|---|---|---|---|---|---|
| Navarrete-Dechent | 2015 | System review | Various | 13.9% (32/231) | 4.6% (10/215) (24%) | |
| Gore | 2016 | Prospective | cSCC | 14% (8/57) | | |
| Krediet | 2015 | Case series | Head / neck, legs, trunk | 11.7% (2/17) | 35.2% (6/17) | |
| Schmitt | 2014 | System review | Various | 12.3% | | BWH T2b/T3: 34.7% (8/23) |
| Ahmed | 2014 | Systemreview | Various | 13% | | 100%/NPV 92.5% |
| Fukushima | 2014 | Prosp case series | Head/neck, extrem, trunk, genitalia | 7.4% (4/54) | | T2 and above: 12.9% |
| Takahashi | 2014 | Case series | Head/neck, extrem, trunk, genitalia | 23.1 % (6/26) | 0/26 | |
| Kwon | 2011 | Case series | Head, extremities, perineum | 0% (0/6) | | |
| Rastrelli | 2010 | Case series | Head and neck, extrem, trunk | 5% (1/20) | 2/20 | |
| Renzi | 2007 | Prosp case series | Not specified | 4.5% (1/22) | | |
| Resendiz-Colosia | 2007 | Prosp case series | Head and neck, extrem, trunk | 20% (4/20) | 0/20 | |
| Ross | 2006 | System review | Various | 21%/ | 4% | |
| Cecchi | 2006 | Case series | Head, extremities | 16.6% (1/6) | 0/6 | |
| Hatta | 2005 | Prosp case series | Lower extremity | 0% (0/4) | 0/4 | |
| Nouri | 2004 | Prosp case series | Head and neck | 12% (1/8) | 0/8 | |
| Eastman | 2004 | Prosp case series | Extremities | 80% (4/5) | 0/5 | |
| Wagner | 2004 | Prosp case series | Head and neck, extrem, perineum, vulva | 29.4% (5/17) | 1/17 | |
| Reschly | 2003 | Prosp case series | Head and neck, extrem, trunk | 44.4% (4/9) | 0/9 | |
| Michl | 2003 | Case series | Head/neck, trunk, extrem, genitalia | 18.1% (2/11) | 0/11 | |
| Altinyollar | 2002 | Prosp case series | Lower lip | 16.6% (3/18) | 0/18 | |

# Sentinel Lymph Node in cSCC

High-risk cutaneous squamous cell carcinoma and the emerging role of sentinel lymph node biopsy: A literature review

C Navarrete-Dechent, MJ Veness, N Droppelmann, P Uribe

*J Am Acad Dermatol* 2015;73:127-37

Ave SLN +: Depth 10.7mm
Diam. 4.6 cm

Survival:
(Takahashi et al, *Eur J Surg Oncol* 2014)
3-yr OS SLN– 100%
SLN+ 20.8%

**Table I.** Summary of high-risk features and clinical implications

| Factors* | Rate of local recurrence†; relative risk (RR) | Rate of metastasis‡; relative risk or hazard risk |
|---|---|---|
| Size: >2 cm | 15.2%; RR = 2 | 30.3%-42.5%; RR = 3 |
| Depth: Breslow >2-4 mm§ or Clark IV, V | 17.2%; RR = 2 | 4.0%-45.7%; RR = 5 |
| Recurrent tumor | 10%-27.5%; RR = 3‖ | 16.3%-45%; RR = 4 |
| Poorly differentiated in histology | 28.6%; RR = 2 | 32.8%-57.9%; RR = 3 |
| Perineural invasion¶ | 47.2%; RR = 5 | 15%-50%; RR = 5 |
| Site: | | |
| Lip | 10.5%; RR = 2 | 13.7%; RR = 4 |
| External ear | 18.7%-53%; RR = 2 | 11%; RR = 3 |
| Lymphovascular invasion# | — | 40%; RR = 7 |
| Histologic subtype (mainly desmoplastic) | 24% Desmoplastic; RR = 16 | 21.4%-44.4% Desmoplastic; RR = 3 |
| Incomplete excision | 50%; — | — |
| De novo cSCC** | — | 20%-38%; — |
| Immunosuppression: | | |
| Solid organ transplantation†† | 13%-39%; — | 8%-12.9%;— |
| CLL | 15% | 14% |

# Sentinel Lymph Node in cSCC

**Staging for Cutaneous Squamous Cell Carcinoma as a Predictor of Sentinel Lymph Node Biopsy Results**
Meta-analysis of AJCC and a Proposed Alternative System

AR Schmitt, JD Brewer, JS Bordeaux, CL Baum

**JAMA Dermatology** January 2014 Volume 150, Number 1

**Risk Factors**:

- ≥2 cm diameter,
- Poor Differentiation
- Perineural invasion
- invasion beyond subcut fat (except bone which =T3)

Table 2. Alternative Tumor Staging System for cSCC[a]

| Primary Tumor | Criteria[b] |
|---|---|
| T0 | In situ squamous cell carcinoma |
| T1 | 0 Risk factors |
| T2a | 1 Risk factor |
| T2b | 2-3 Risk factors |
| T3 | 4 Risk factors or bone invasion |

Table 4. SLN+ by T Stage in Patients With Nonanogenital cSCC in 2 Staging Systems

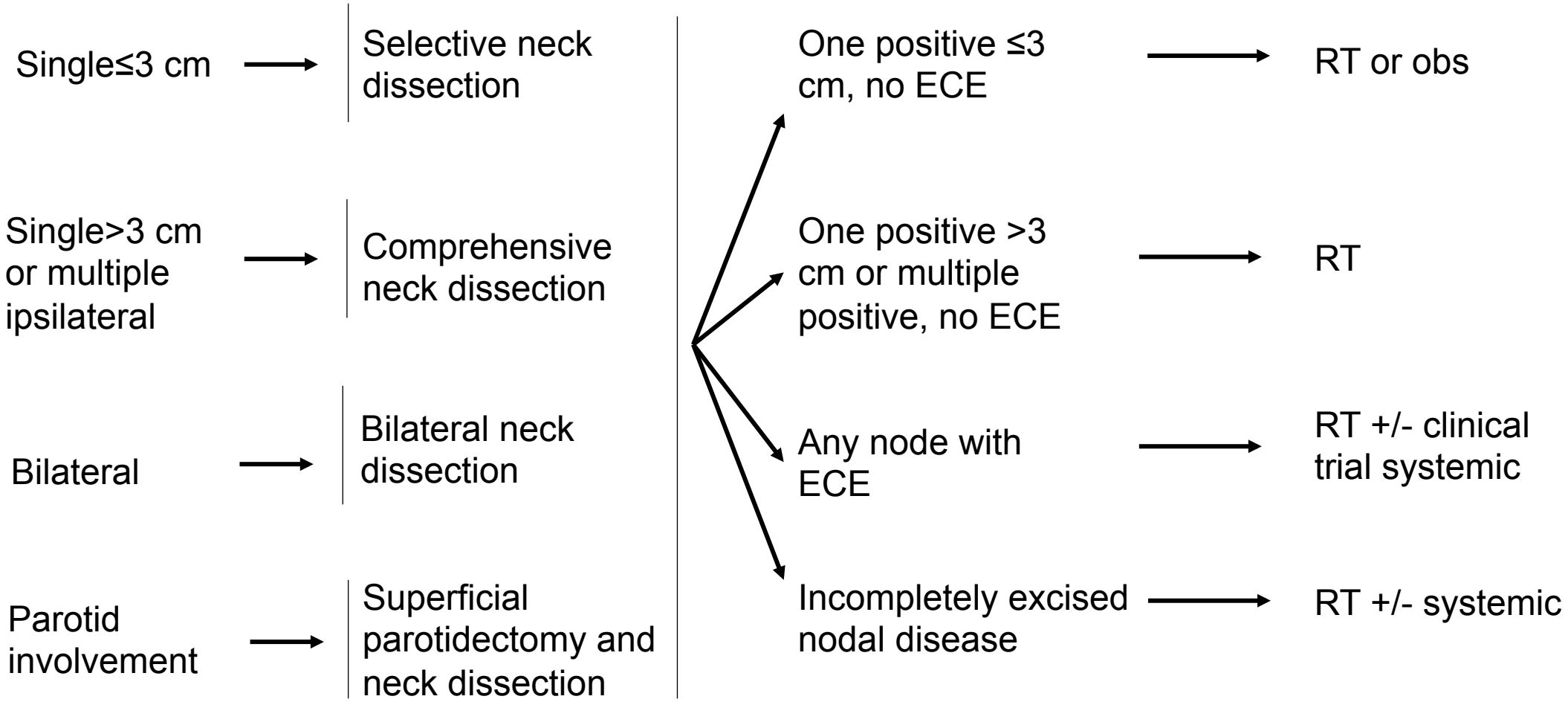
| T Stage | No. of SLN+ Tumors/Total No. of Tumors (%) |
|---|---|
| AJCC staging system[a] | |
| T1 | 0/9 |
| T2 | 13/116 (11.2) |
| T3 | 0/0 |
| T4 | 3/5 (60.0) |
| Alternative staging system[b] | |
| T0 | Not included |
| T1 | 0/9 |
| T2a | 6/85 (7.1) |
| T2b | 5/17 (29.4) |
| T3 | 3/6 (50.0) |

# Sentinel Lymph Node in cSCC

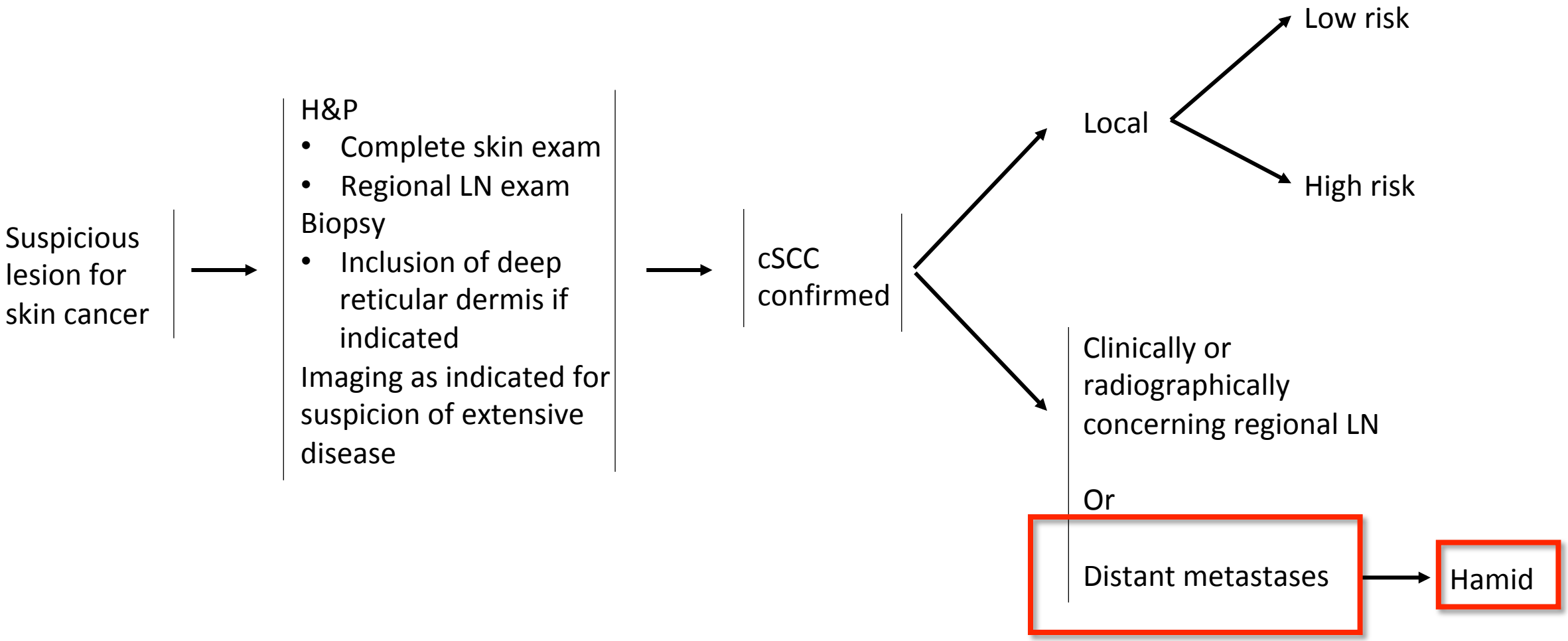
- Rationale?
  - Therapy: Guide for CLND or XRT
    - Essentially no data

- NCCN
  - No specific recommendation:
    - “In certain high-risk lesions, consider sentinel lymph node mapping, although benefit of and indication for this technique has yet to be proven.”

# Regional Nodes



# Unresectable or Metastatic cSCC



# Lifestyles of the Rich and Squamous: Recent cSCC Data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TheAngelesClinic
AND RESEARCH INSTITUTE
A CEDARS-SINAI AFFILIATE

# Disclosures

- **The more conflicts of interest for the speaker, the more balanced the talk . . . . . Hauschild 2015**

- Pfizer
- Rinat
- Genentech
- Roche
- BMS
- Merck
- Merck Serano
- Immunocore
- Medimmune
- Tesaro

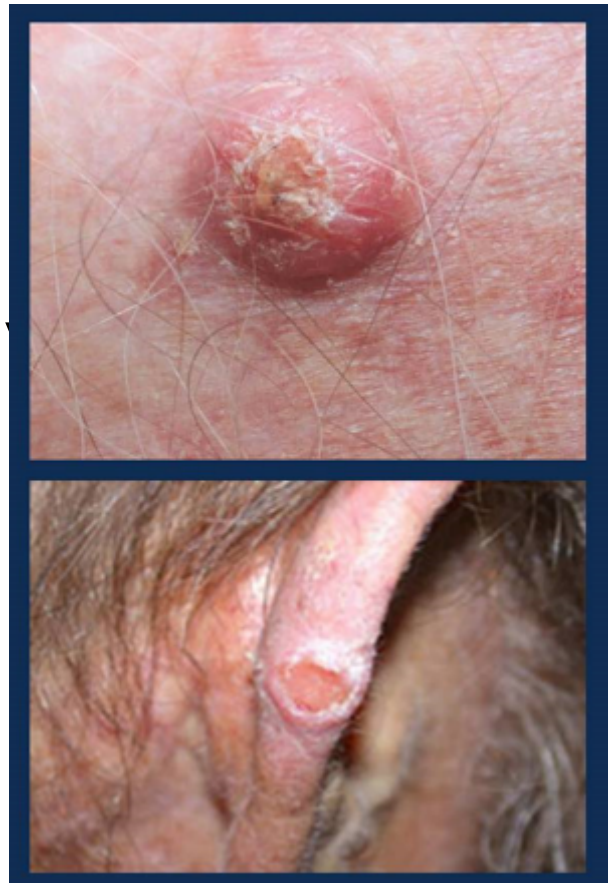
- Astra Zeneca
- Novartis
- Celldex
- Incyte
- Esai
- Eli Lilly
- Cytomx
- Curis
- Aduro
- Regeneron

# General Facts About Cutaneous SCC

- 2nd most frequent NMSC (after BCC) – 20% of all cutaneous malignancies
- Incidence rate increases have been recorded (50-200%) in last 30 years
- The majority occur on the head and neck (80-90%)
- Usually develops from precursor lesions (actinic keratosis), but also de novo
- > 90% of cases have excellent prognosis
- 700,000 new cases
- 2000 deaths per year
- Most cSCCs are curable with surgery or radiation

# cSCC: Background

- 5% metastasize
  - treated typically with platinum-based chemotherapy and
  - EGFR inhibitors
  - Overall response rates (ORR) of only10-20%
  - No current treatments have been shown to improve survi
- Risk factors:
  – UV radiation, immunosuppression
- Lifetime risk:
  – Men: 9%-14%; Women: 4%-9%
- Risk of nodal metastases: 2%-5.8%
- Disease-specific death rate: 1.5%
- Lifetime risk : M-9-14%. W- 4-9%



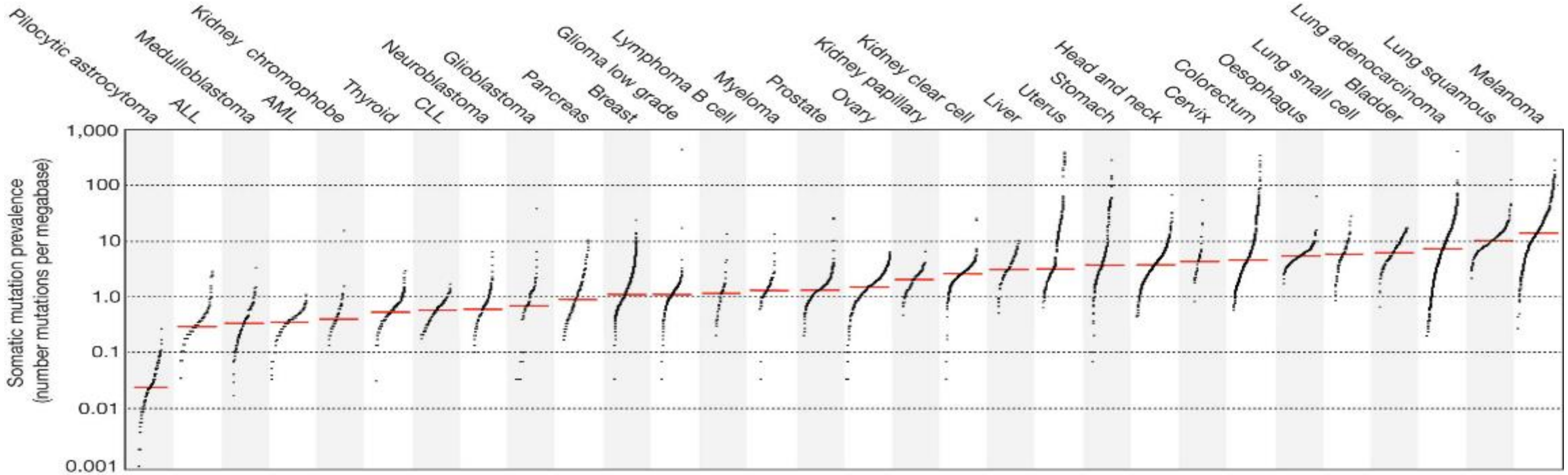
1.Work Group. *J Am Acad Dermatol.* 2018;78:560-578; Rogers HW, et al. *JAMA Dermatol*. 2015;151:1081-086; Karia PS, et al. *J Clin Oncol*. 2014;32:327–334; Karia PS, et al. *J Am Acad Dermatol.* 2013;68:957-966.

# Locally Advanced and Metastatic SCC

- Radiotherapy
- Cisplatin-based chemotherapy
  - No established standard regimen
  - short-lived remissions (average duration: 3 months) up to 60%
  - toxic
- Mutation-driven targeted therapies: ⇨ **EGFR/pan-HER inhibitors**
  - Cetuximab: 28% RR, 69% DCR
  - Panitumumab: 31% RR, 68% DCR
  - Dacomitinib (pan-HER inhibitor): 28% RR, 86% DCR
- Immunotherapies
  - Change of immunosuppression in OTRs – toward mTOR inhibitors
  - PD-1 antibodies

1. Maubec et al, J Clinc Oncol, 2011; 2. Foote et al, Ann Oncol, 2014; 3. Bossi, ASCO 2017

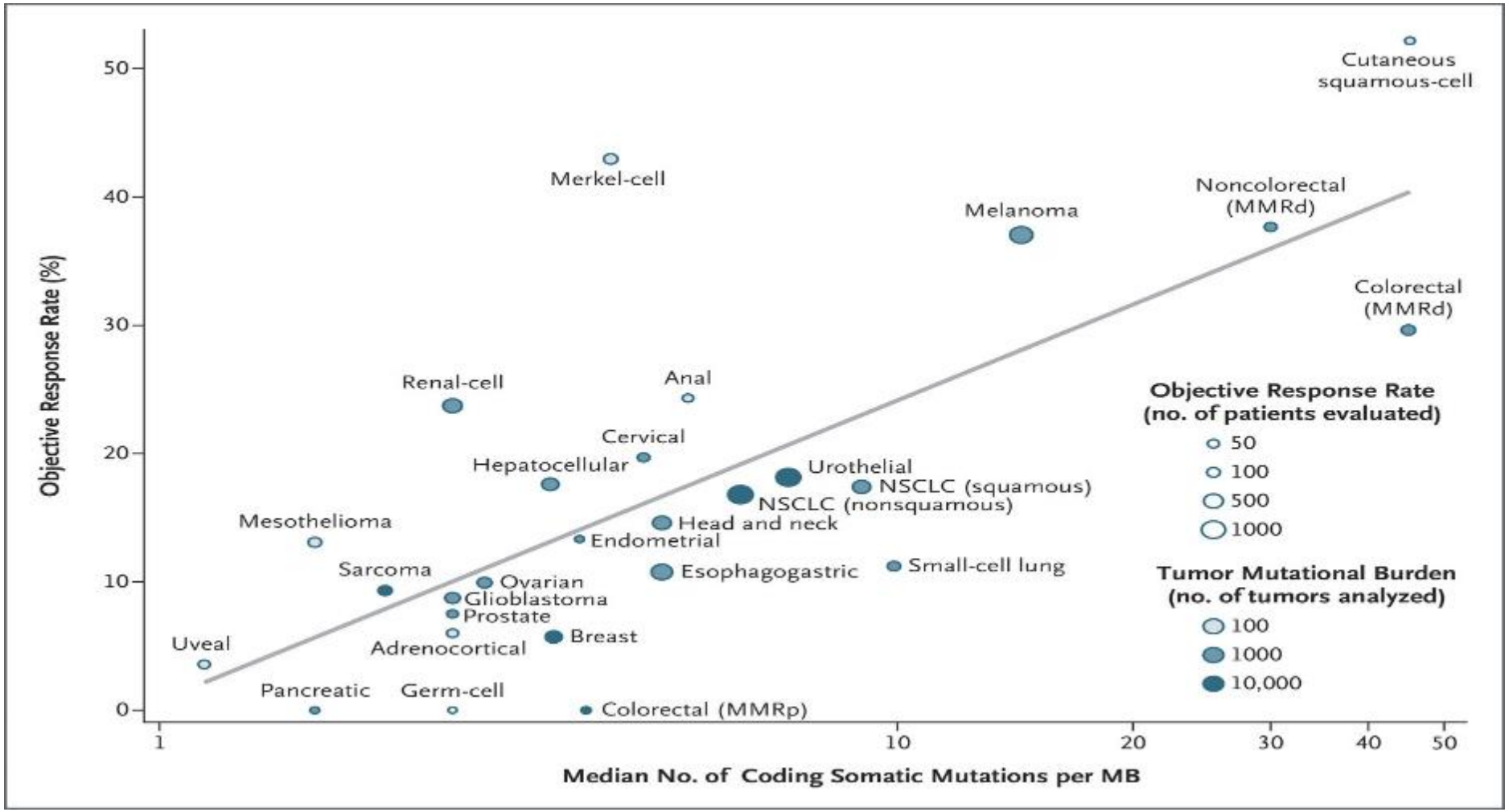
# The prevalence of somatic mutations across human cancer types.




LB Alexandrov *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12477

nature

# Correlation Between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PD-L1 Therapy in 27 Tumor Types

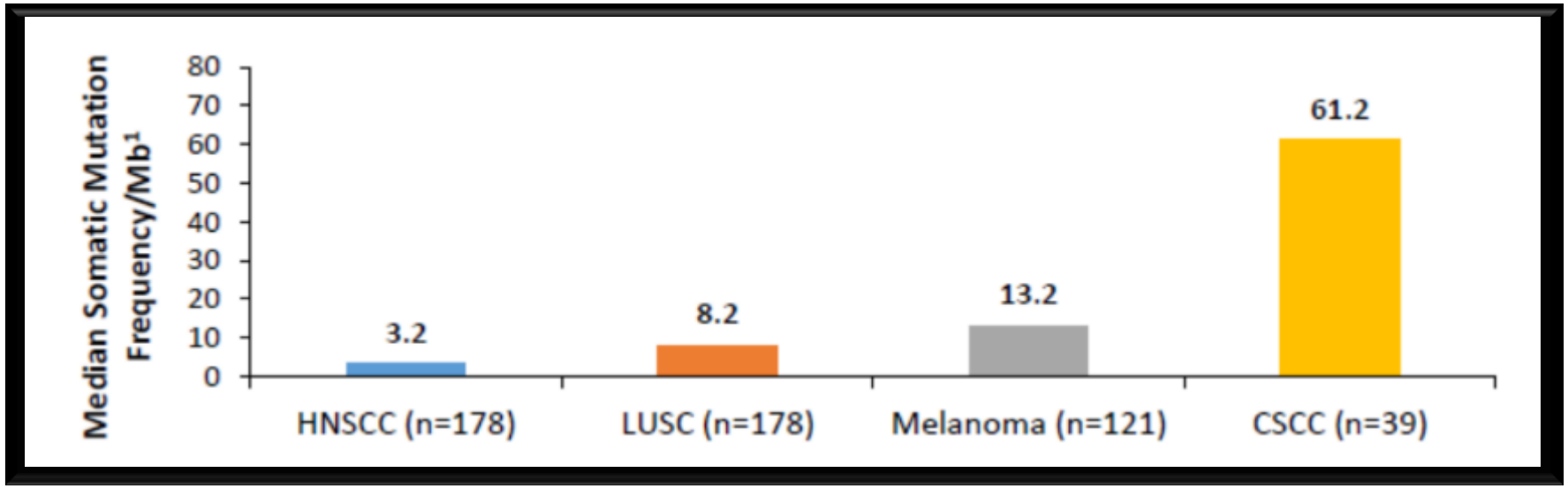



Yarchoan M et al. N Engl J Med 2017;377:2500-2501.

The NEW ENGLAND JOURNAL of MEDICINE

# Rationale for PD-1 Inhibition in CSCC

- Higher mutation burden than any tumor type in The Cancer Genome Atlas (TCGA)[1]
- Mutation burden exceeded by that of BCC[2]




- Immunosuppression is a well-described risk factor for CSCC, especially in solid organ transplant patients[3]
- PD-L1 expression has been associated with high-risk disease[4]
- In the phase I dose escalation study of cemiplimab (REGN2810), **a durable radiologic complete response** to cemiplimab was achieved in a CSCC patient[5,6]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

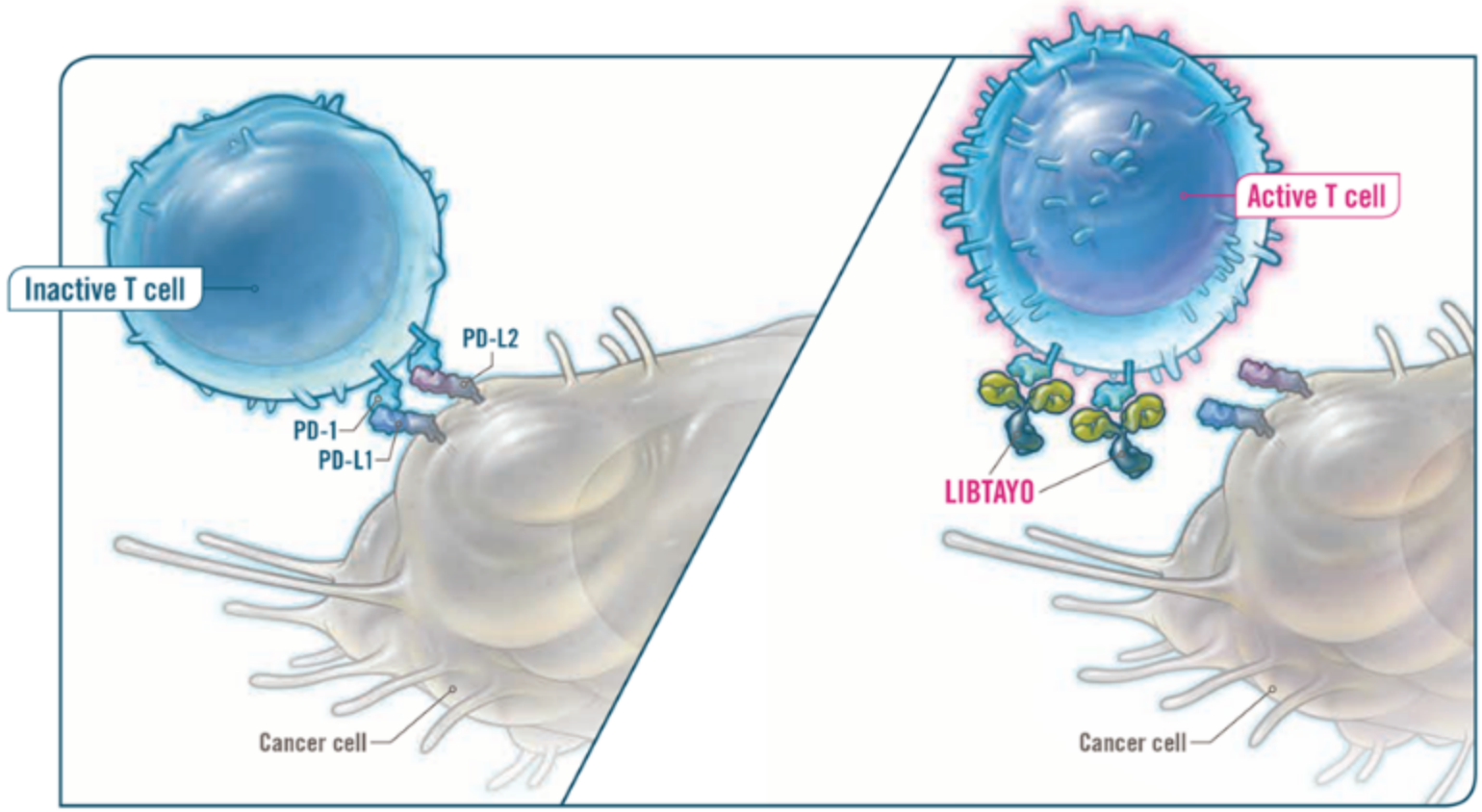
M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, A. Hauschild, K.D. Lewis, C.H. Chung, L. Hernandez-Aya, A.M. Lim, A.L.S. Chang, G. Rabinowits, A.A. Thai, L.A. Dunn, B.G.M. Hughes, N.I. Khushalani, B. Modi, D. Schadendorf, B. Gao, F. Seebach, S. Li, J. Li, M. Mathias, J. Booth, K. Mohan, E. Stankevich, H.M. Babiker, I. Brana, M. Gil-Martin, J. Homsi, M.L. Johnson, V. Moreno, J. Niu, T.K. Owonikoko, K.P. Papadopoulos, G.D. Yancopoulos, I. Lowy, and M.G. Fury

## ABSTRACT

### BACKGROUND

No systemic therapies have been approved for the treatment of advanced cutaneous squamous-cell carcinoma. This cancer may be responsive to immune therapy, because the mutation burden of the tumor is high and the disease risk is strongly associated with immunosuppression. In the dose-escalation portion of the phase 1 study of cemiplimab, a deep and durable response was observed in a patient with metastatic cutaneous squamous-cell carcinoma.

# Binds to PD-1 and Blocks its Interaction with PD-L1 and PD-L2




monoclonal antibody.

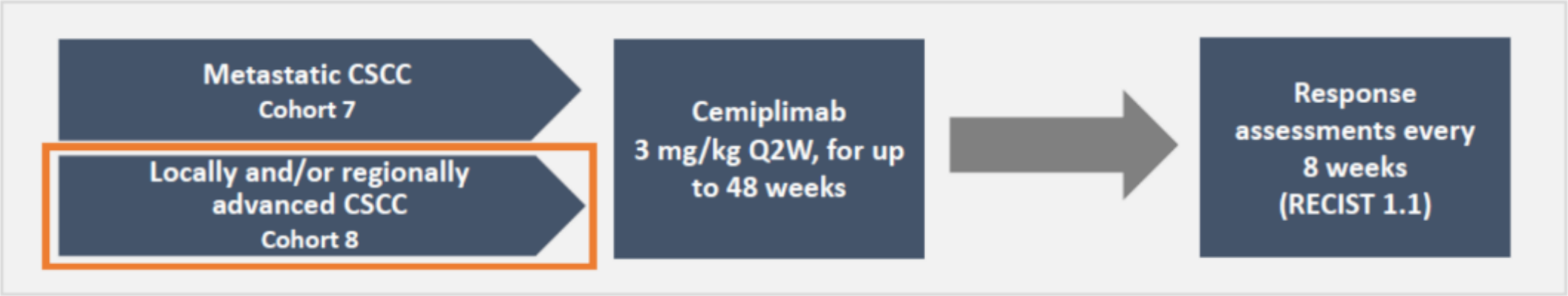
Binds to PD-1 and blocks its interaction with PD-L1 and PD-L2.

Releases PD-1 pathway–mediated inhibition of the immune response, including the anti-tumor immune response.

In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

# Phase I Open-Label Cemiplimab Study: CSCC Expansion Cohorts (NCT0238212)

## Study Design: Phase I Expansion Cohorts



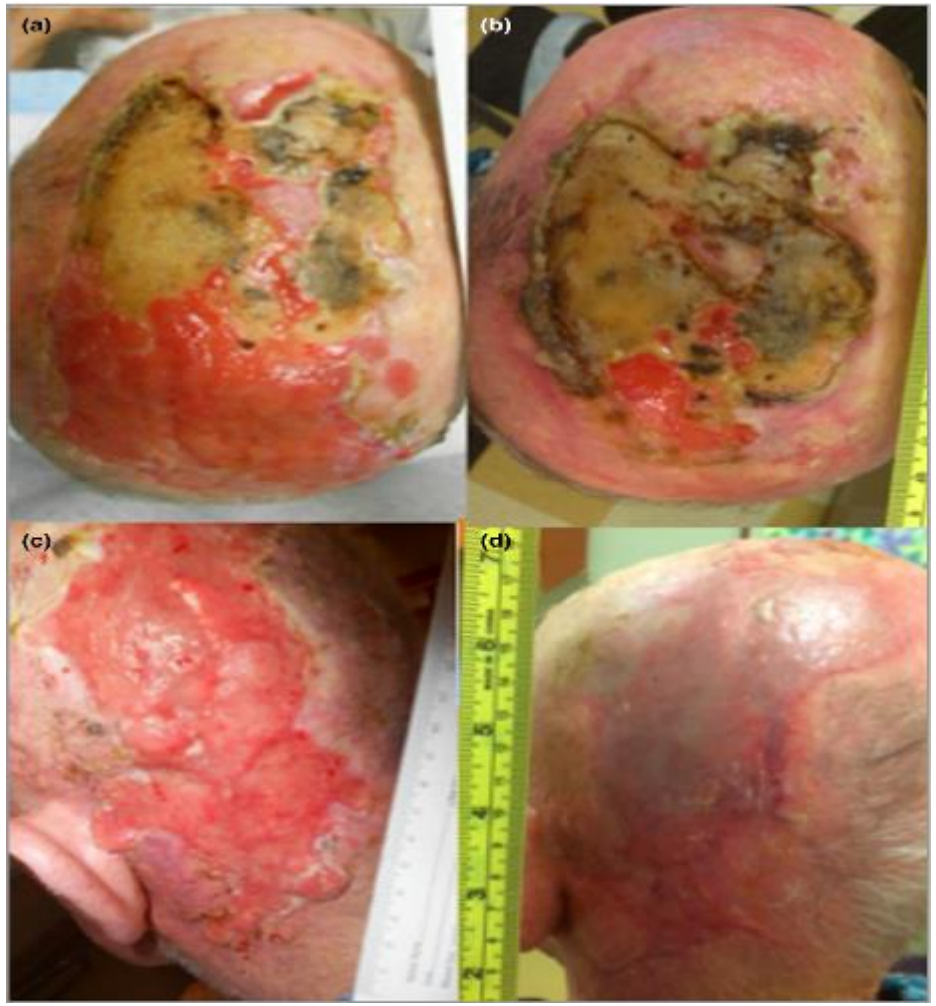

**Co-primary objectives:**

- To characterize the safety and tolerability of IV cemiplimab, 3 mg/kg Q2W
- To evaluate the efficacy of cemiplimab by measuring ORR

Papadopoulos KP. REGN2810, A Human Anti-PD-1 Monoclonal Antibody, for Patients with Unresectable Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC): Initial Safety and Efficacy. Presented at the 2017 Annual Meeting of the American Society of Clinical Oncology; 2017 Jun 2-6; Chicago, IL.

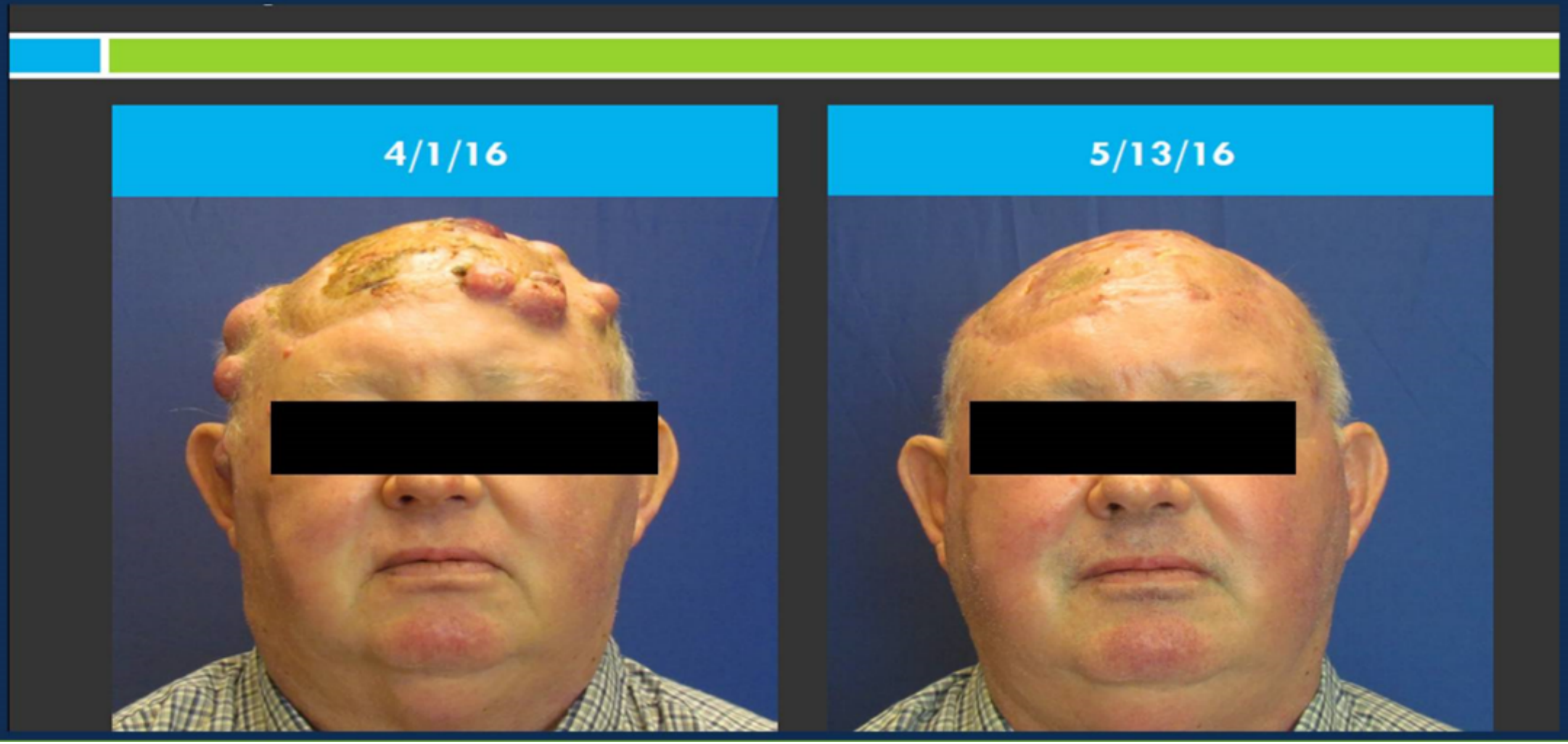
# PD1 antibodies in SCC patients

*Borradori et al., Br J Dermatol,2016. 175: 1382–1386*

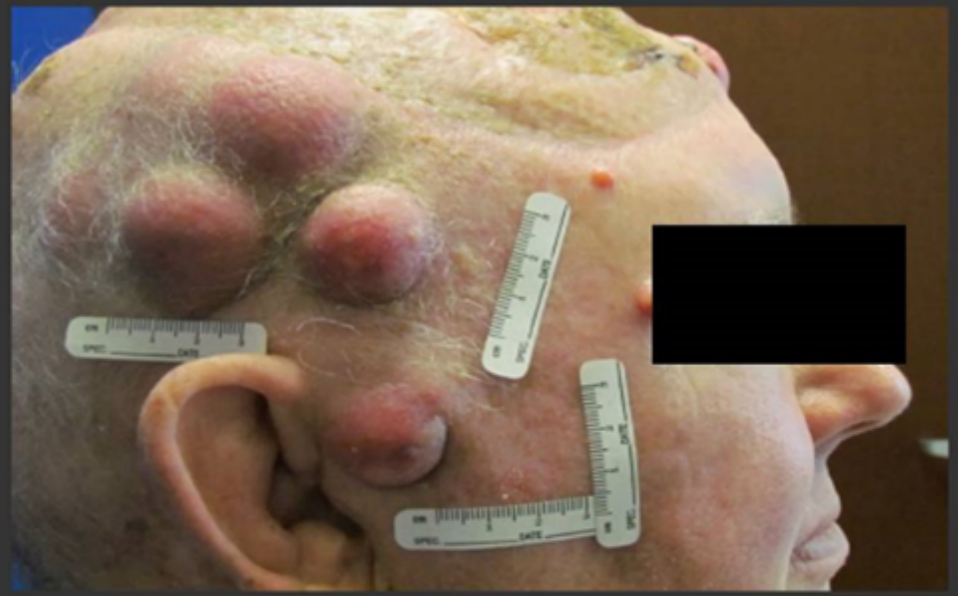
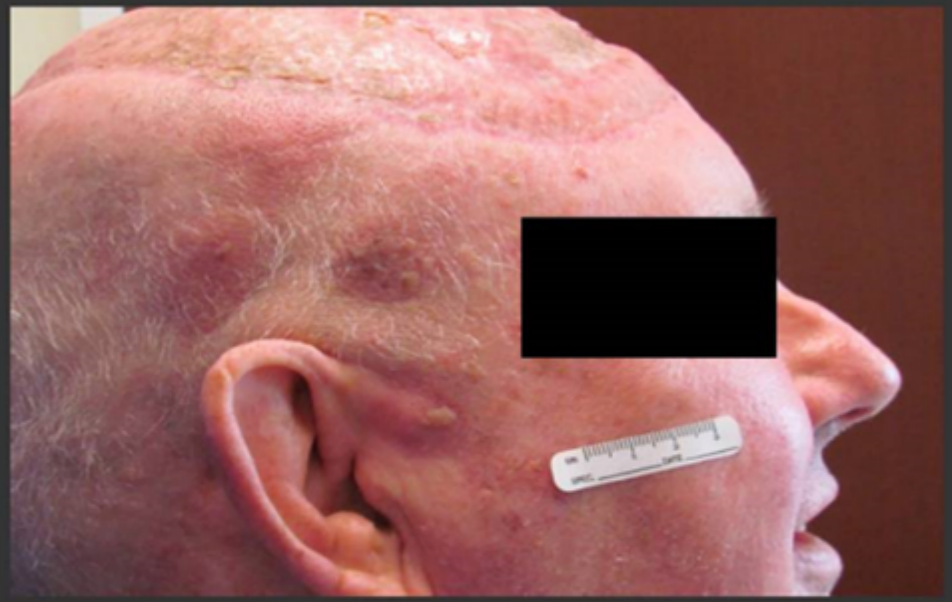


# CSCC EXPANSION COHORTS WERE OPENED IN THE PHASE 1 STUDY OF REGN2810

)



# CSCC EXPANSION COHORTS WERE OPENED IN THE PHASE 1 STUDY OF REGN2810

| 4/1/16 | 5/13/16 |
| --- | --- |
|  |  |

# Cemiplimab is Active Across All PD-L1 Strata in CSCC (Tumor PD-L1 Expression by Immunohistochemistry; Dako 22C3 Clone)

**91% (10/11) of evaluated tumors were positive (≥1%) for tumor expression of PD-L1 by IHC**

| Tumor PD-L1 | Total | CR | PR | SD | PD | NE | ORR† |
|---|---|---|---|---|---|---|---|
| | Number of Patients | | | | | | |
| ≥50% | 5 | 0 | 1 | 2 | 2 | 0 | 20% (1/5) |
| ≥1–49% | 5 | 1 | 2 | 0 | 1 | 1 | 60% (3/5) |
| <1% | 1 | 0 | 0 | 1 | 0 | 0 | 0 |

**No apparent association between PD-L1 IHC results and objective responses**

Papadopoulos KP. REGN2810, A Human Anti-PD-1 Monoclonal Antibody, for Patients with Unresectable Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC): Initial Safety and Efficacy. Presented at the 2017 Annual Meeting of the American Society of Clinical Oncology; 2017 Jun 2-6; Chicago, IL.

# Defined Population per Study Design

| Metastatic cSCC[a] | Locally advanced cSCC[a] |
|---|---|
| • Nodal metastasis<br>• Distant metastasis | • Locally advanced cSCC patients who were not candidates for curative surgery or curative radiation |

**Recurrence**

- cSCC that has recurred in the same location after 2 or more surgical procedures and curative resection is deemed unlikely

**Location of disease**

- cSCC in anatomically challenging locations for which surgery may result in severe disfigurement or dysfunction (eg, removal of all or part of a facial structure, such as nose, ear, or eye; or requirement for limb amputation)

**Invasive disease**

- cSCC with significant local invasion that precludes complete resection

**Other**

- Other conditions deemed to be contraindicating for surgery

Not a candidate for curative surgery:

Factors to consider[a]

- a. Midgen MR, et al. *N Engl J Med*. 2018;379:341-351.

# Cemiplimab for Advanced cSCC

- Phase I
  - Response in 13 of 26 patients
  - RR: 50% (95% CI, 30 to 70)
- Phase II
  - Response in 28 of 59 patients
  - RR: 47%  (95% CI, 34 to 61)
  - Median follow-up: 7.9 months
  - Response duration > 6 months in 57%
  - 82% continued response on treatment

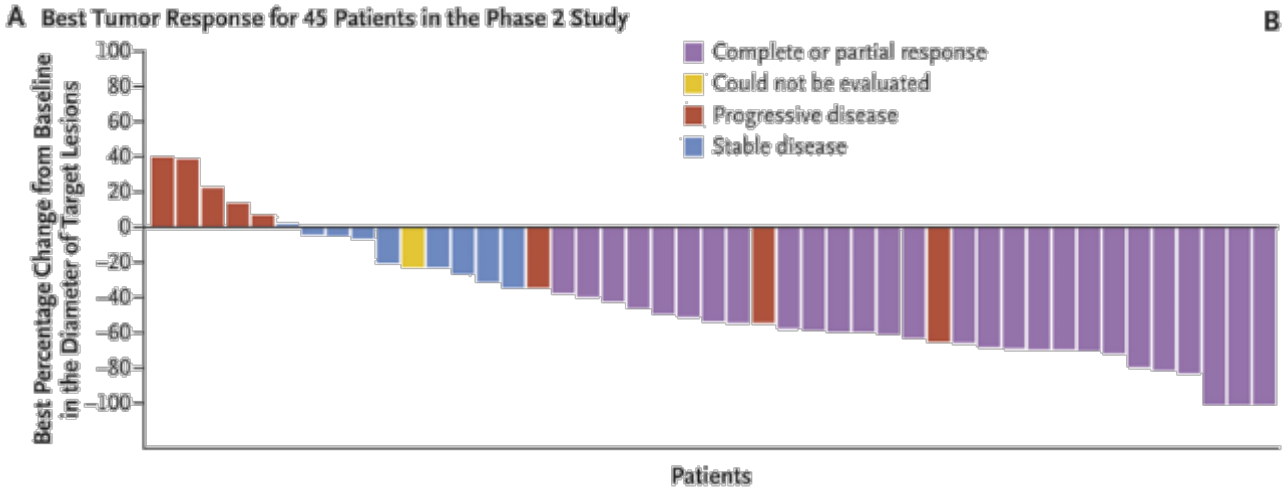

- Midgen MR et al. *N Engl J Med.* 2018;379:341-351.

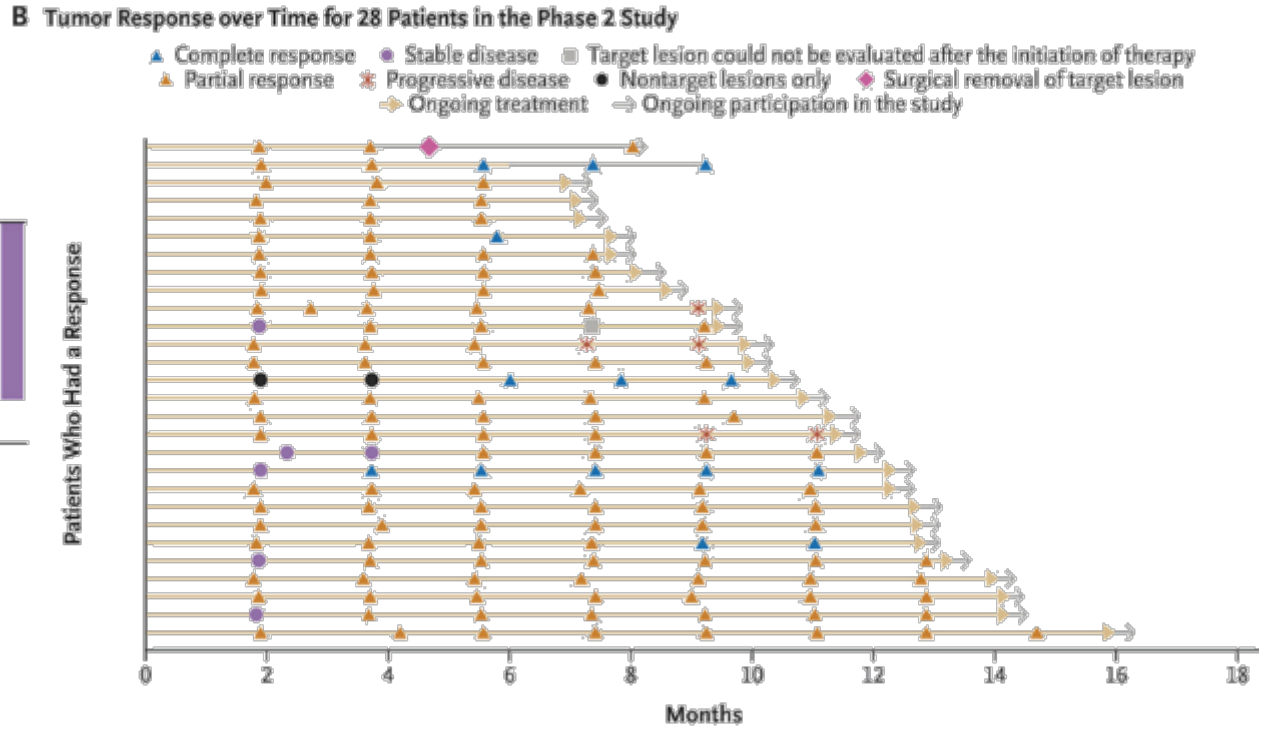
# Tumor Response to Cemiplimab, as Assessed by Independent Central Review

**Table 2. Tumor Response to Cemiplimab, as Assessed by Independent Central Review.***

| Outcome | Expansion Cohorts of the Phase 1 Study (N = 26) | Metastatic-Disease Cohort of the Phase 2 Study (N = 59) |
|---|---|---|
| Best overall response — no. (%)† | | |
| Complete response | 0 | 4 (7) |
| Partial response | 13 (50) | 24 (41) |
| Stable disease | 6 (23) | 9 (15) |
| Progressive disease | 3 (12) | 11 (19) |
| Could not be evaluated‡ | 3 (12) | 7 (12) |
| Nontarget lesions only§ | 1 (4) | 4 (7) |
| Objective response — % (95% CI) | 50 (30–70) | 47 (34–61) |
| Durable disease control — % (95% CI) | 65 (44–83) | 61 (47–74) |
| Median observed time to response (range) — mo¶ | 2.3 (1.7–7.3) | 1.9 (1.7–6.0) |

# Tumor Response to Cemiplimab Among Patients in the Phase 2 Study Who Had Metastatic Cutaneous Squamous-Cell Carcinoma

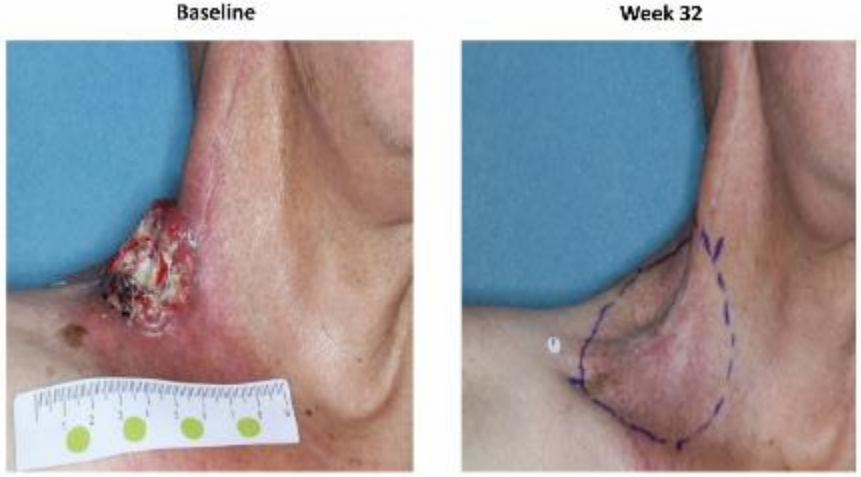


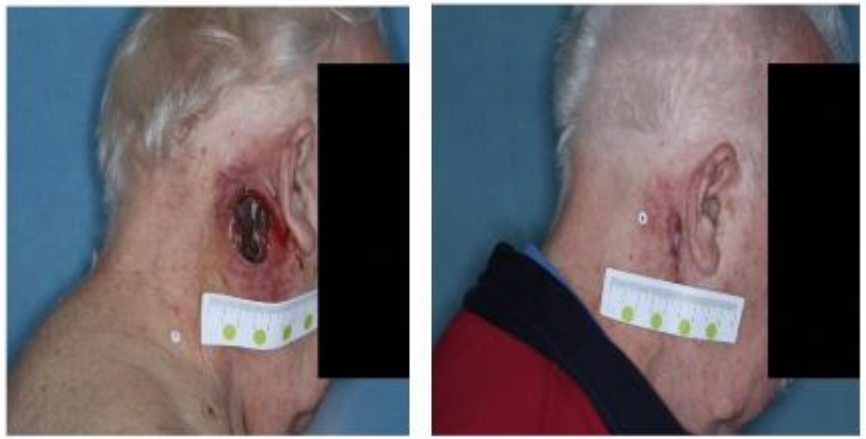

- Midgen MR et al. *N* Engl *J Med* 2018;379:341-351.

# Examples of Reductions in Visible CSCC Lesions Following Treatment with Cemiplimab

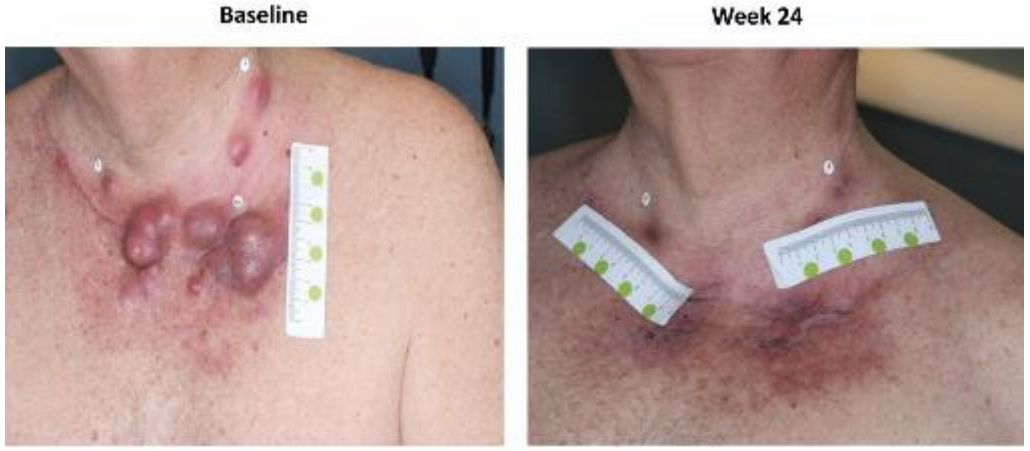
A




B



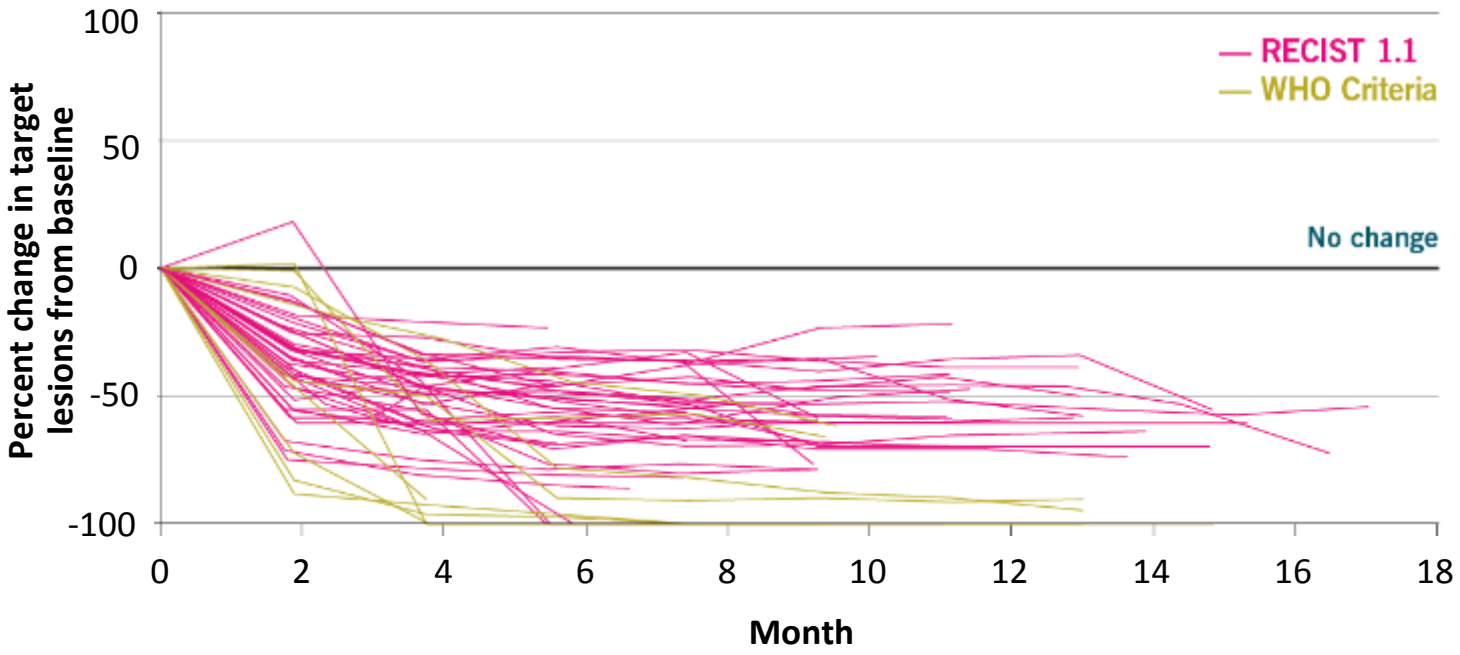

C




- Upper left: 85-year-old man with supraclavicular lesion who had received prior RT.
- Upper right: 66-year-old man with anterior chest wall lesions who had received prior cisplatin.
- Lower left: 83-year-old-man with multiple prior surgeries for CSCC.

- The patient in panel A is an 85-year-old man with supraclavicular lesion who had received prior radiotherapy. The patient in panel B is an 83-year-old-man with multiple prior surgeries for CSCC. The patient in panel C is a 66-year-old man with anterior chest wall CSCC lesions who had received prior cisplatin.

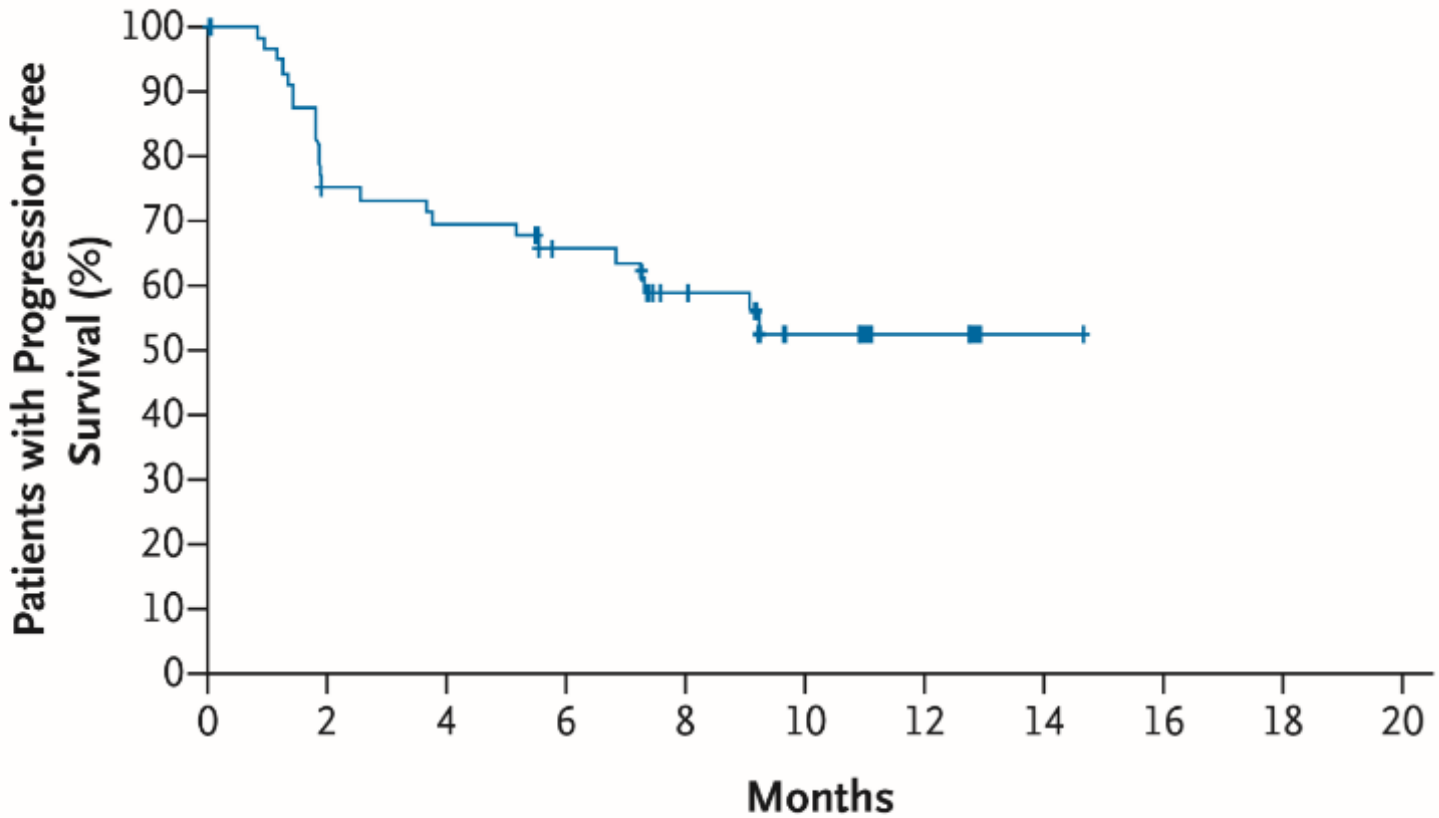
# Target Lesion Percent Change from Baseline Among Responders (N=49)[1]




Median duration of follow-up for all patients included in the efficacy analysis was 8.1 months for metastatic CSCC, 10.2 months for locally advanced CSCC, and 8.9 months for combined CSCC (N=108).[2]

- Each line represents the individual percent change in target lesions from baseline among the 49 responders who reached a complete or partial response.[1]
- For a patient to be assessed as at least a partial response (PR), for target lesion evaluation, there had to be at least 30% reduction in the sum of target lesion diameters by RECIST 1.1 and at least 50% reduction by WHO.[1]
- Patients with new lesions or unequivocal progression of non-target lesions were characterized as non-responders.[1]
- At the time of data cutoff, among the responders included in the figure, 4 patients had disease progression—at 7.3, 8.2, 9.1, and 9.2 months of study, respectively—and 6 patients had their response duration censored for the following reasons: withdrawal of consent (2), not evaluable for last response assessment (2), tumor resection (1), and AEs resulting in study discontinuation (1) at 2.8, 3.7, 14.7, 9.1, 4.6, and 9.2 months, respectively.[1]

# Progression-free Survival among Patients in the Phase 2 Study Who Had Metastatic Cutaneous Squamous-Cell Carcinoma




MR Migden et al. N Engl J Med 2018;379:341-351

# Cemiplimab Phase II Study: Adverse Events

| Event | Metastatic-Disease Cohort of the Phase 2 Study (N=59) | |
|---|---|---|
| | Any Grade | Grade ≥3 |
| | *no. of patients (%)* | |
| Any | 59 (100) | 25 (42) |
| Serious | 21 (36) | 17 (29) |
| Led to discontinuation of treatment | 4 (7) | 3 (5) |
| Associated with an outcome of death | 3 (5) | 3 (5) |

| Event | Metastatic-Disease Cohort of the Phase 2 Study (N=59) | |
|---|---|---|
| | Any Grade | Grade ≥3 |
| | *no. of patients (%)* | |
| Occurred in ≥5 patients | | |
| Diarrhea | 16 (27) | 1 (2) |
| Fatigue | 14 (24) | 1 (2) |
| Nausea | 10 (17) | 0 |
| Constipation | 9 (15) | 1 (2) |
| Rash | 9 (15) | 0 |
| Cough | 8 (14) | 0 |
| Decreased appetite | 8 (14) | 0 |
| Pruritus | 8 (14) | 0 |
| Headache | 8 (14) | 0 |
| Dry skin | 6 (10) | 0 |
| Maculopapular rash | 6 (10) | 0 |
| Vomiting | 6 (10) | 0 |
| Anemia | 5 (8) | 1 (2) |
| Hypothyroidism | 5 (8) | 0 |
| Increased alanine aminotransferase | 5 (8) | 0 |
| Pneumonitis | 5 (8) | 2 (3) |

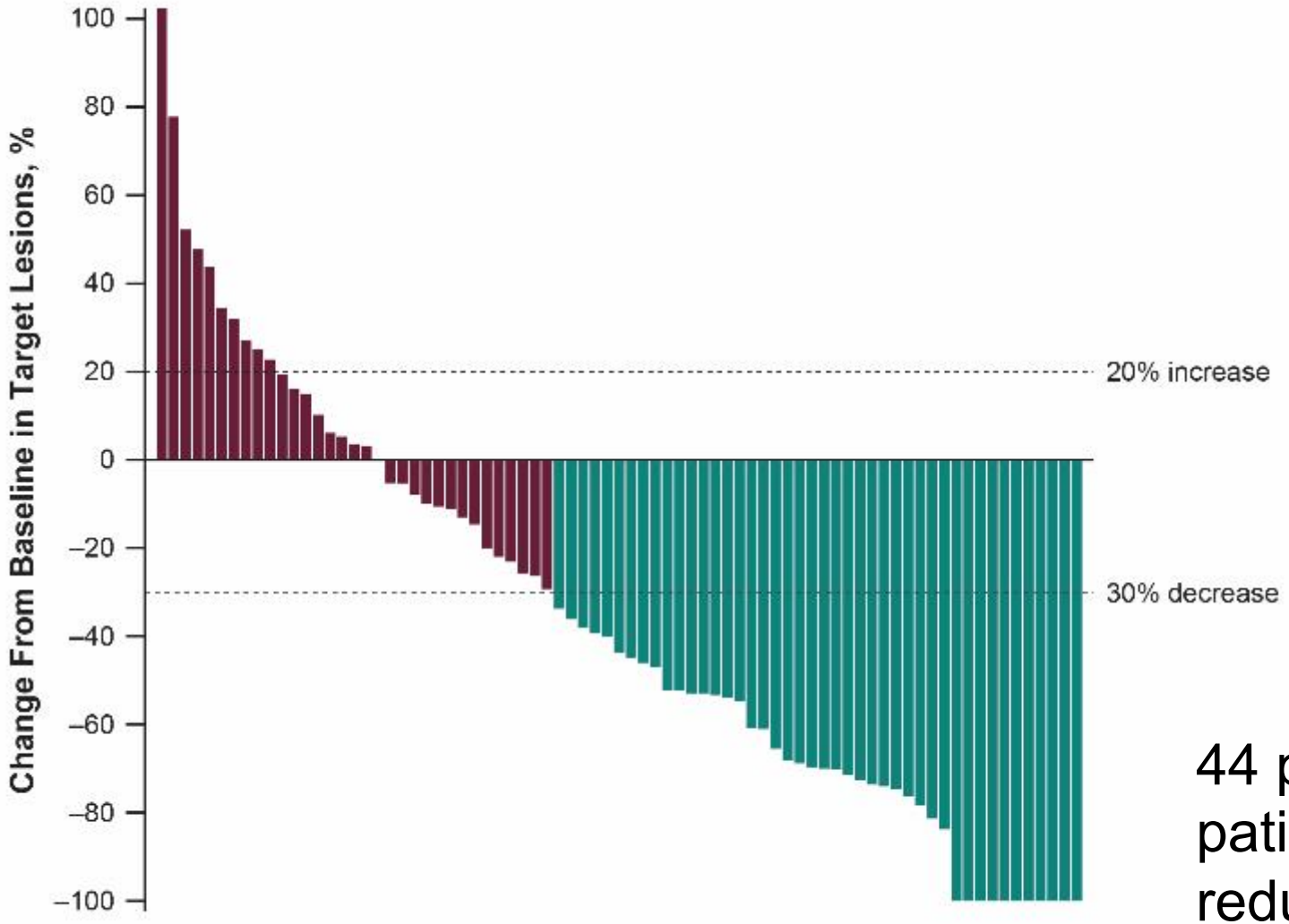
Migden MR, et al. N Engl J Med. 2018;379:341-351.

# Pembrolizumab for Recurrent/Metastatic Cutaneous Squamous Cell Carcinoma: Efficacy and Safety Results From the Phase 2 KEYNOTE-629 Study

J.-J. Grob[1]; R. Gonzalez Mendoza[2]; N. Basset-Seguin[3]; O. Vornicova[4]; J. Schachter[5]; A. Joshi[6]; N. Meyer[7]; F. Grange[8]; J. M. Piulats[9]; J. R. Bauman[10]; P. Zhang[11]; B. Gumuscu[11]; R. F. Swaby[11]; B. G. M. Hughes[12,13]

[1]AIX-Marseille University, Marseille, France; [2]Centro Estatal de Cancerologiade Chihuahua, Chihuahua, Mexico; [3]Hôpital Saint-Louis, Paris, France; [4]Rambam Health Care Campus, Haifa, Israel; [5]Sheba Medical Center at Tel Hashomer, Ramat Gan, Israel; [6]Townsville Cancer Centre, Townsville, Queensland, Australia; [7]IUCT–Oncopole, Toulouse, France; [8]CHU Reims–Hôpital Robert Debre, Reims, France; [9]Hospital Duran i Reinals ICO de Hospitalet, Barcelona, Spain; [10]Fox Chase Cancer Center, Philadelphia, PA, USA; [11]Merck & Co., Inc., Kenilworth, NJ, USA; [12]Royal Brisbane and Women's Hospital, Herston, Queensland, Australia; [13]University of Queensland, Brisbane, Queensland, Australia

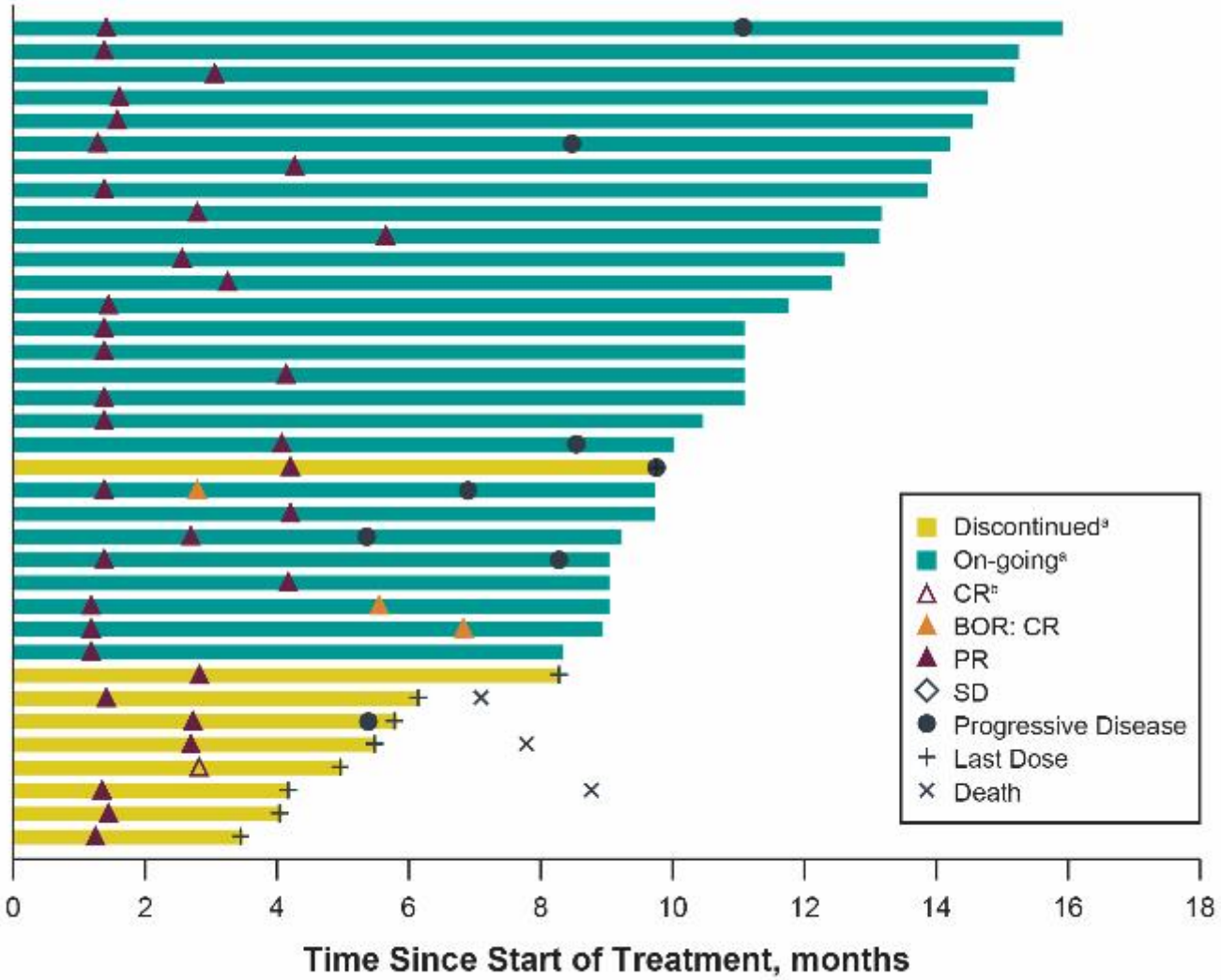
# Best Percentage Change From Baseline in Target Lesion in the R/M Cohort




44 patients (57.9%) patients had ≥30% reduction

Database cutoff date: April 8, 2019.

# Response Duration and PFS and OS in the R/M Cohort




Median[c] PFS: 6.9 months (95% CI, 3.1-8.5)

6-month rate: 50.4%

12-month rate: 32.4%

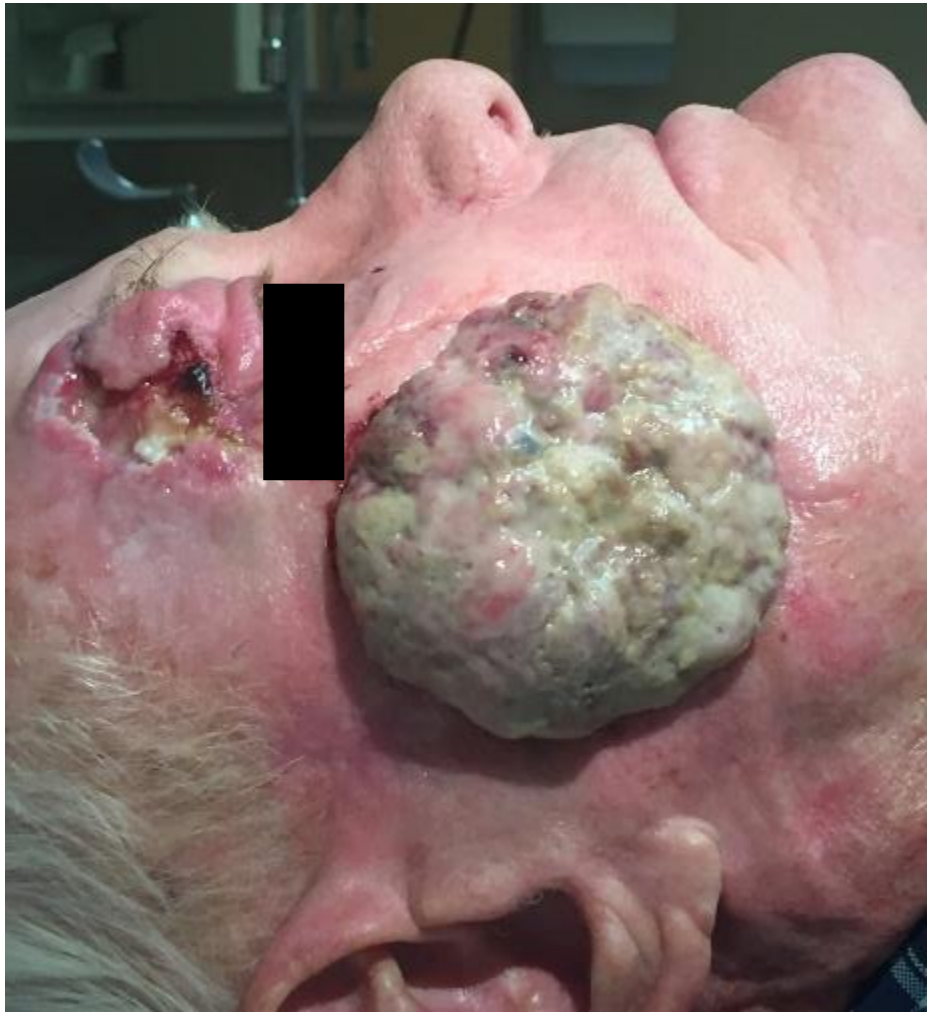
Median[c] OS: NR (95% CI, 10.7-NR)

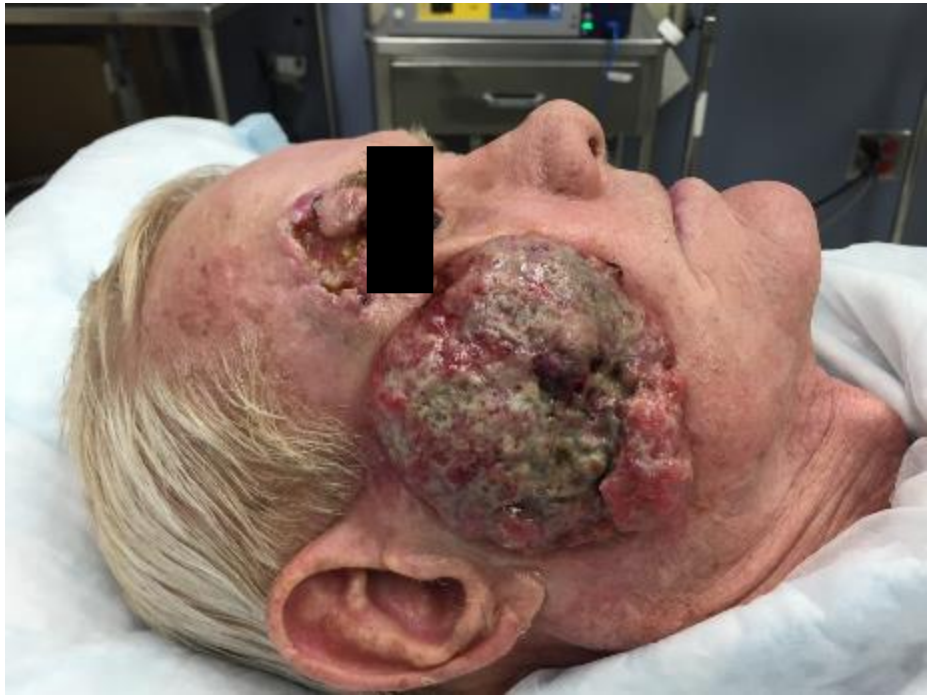
6-month rate: 79.0%

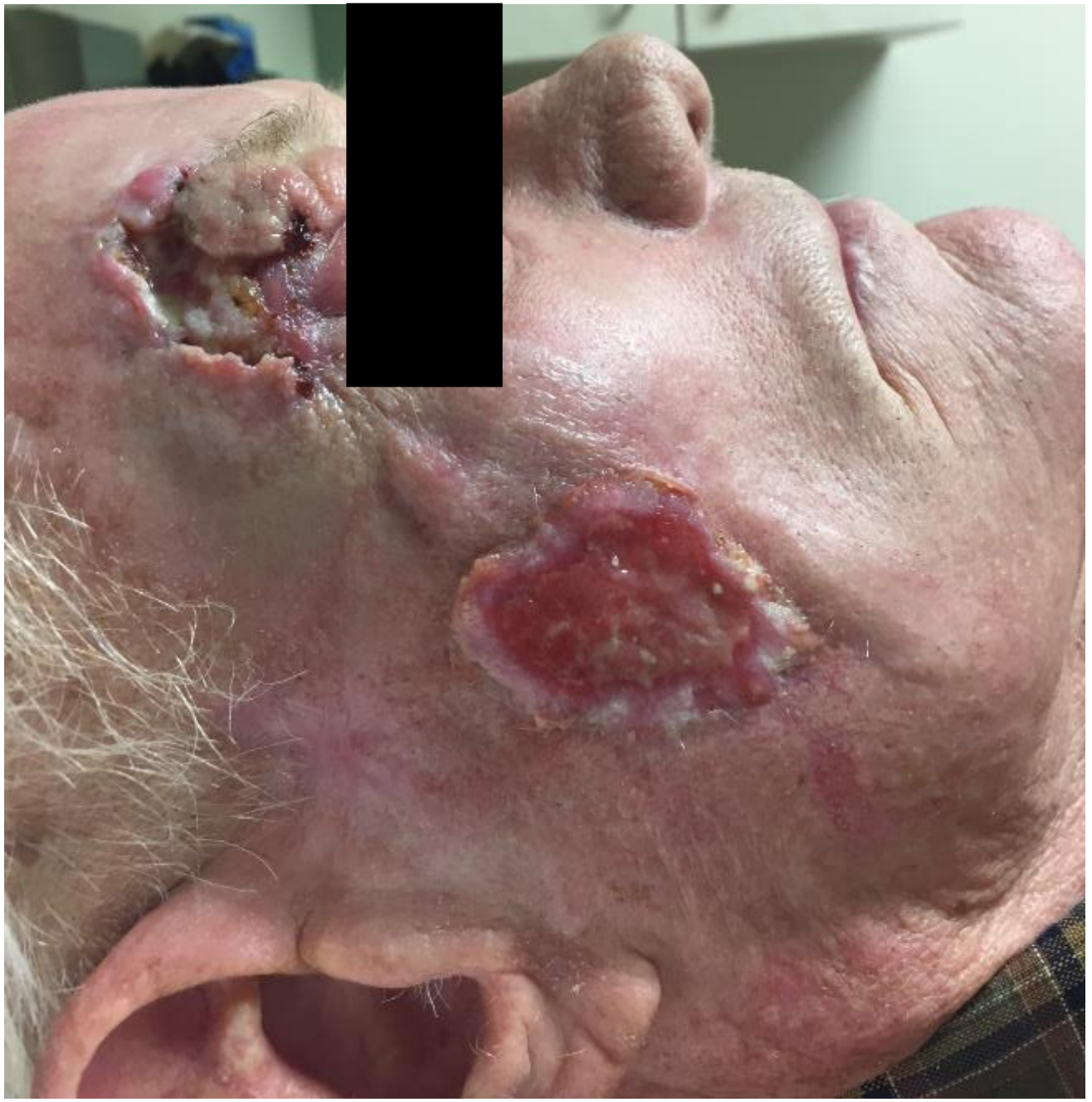
12-month rate: 60.3%

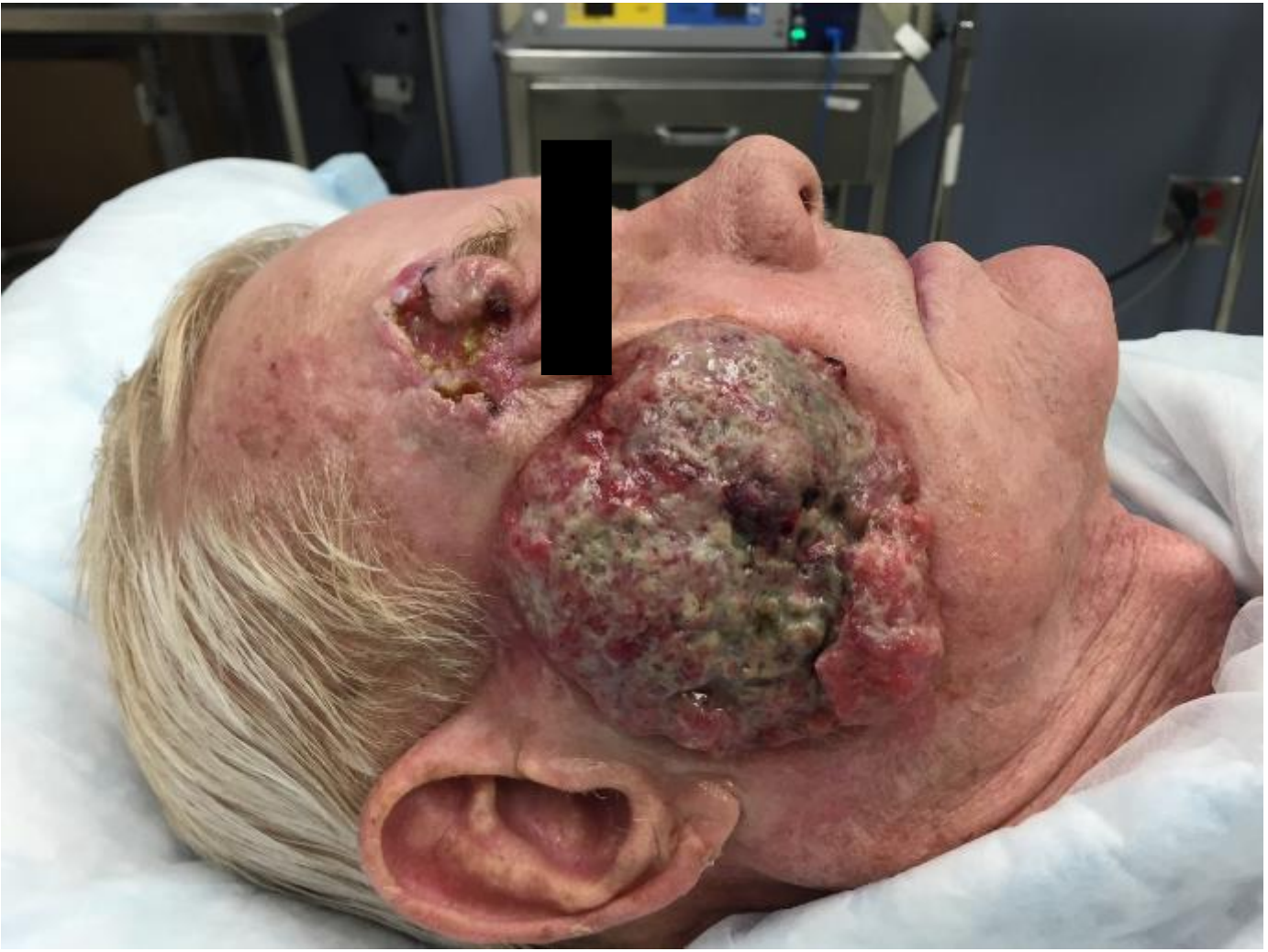
BOR, best overall response; CR, complete response; NR, not reached; PR, partial response; SD, stable disease. Database cutoff date: April 8, 2019. Response was based on blinded independent central review per RECIST v1.1; confirmed responses are shown. [a]Discontinued or ongoing refers to status in relation to study treatment. [b]This patient achieved a best overall response of CR. [c]Per Kaplan-Meier estimate

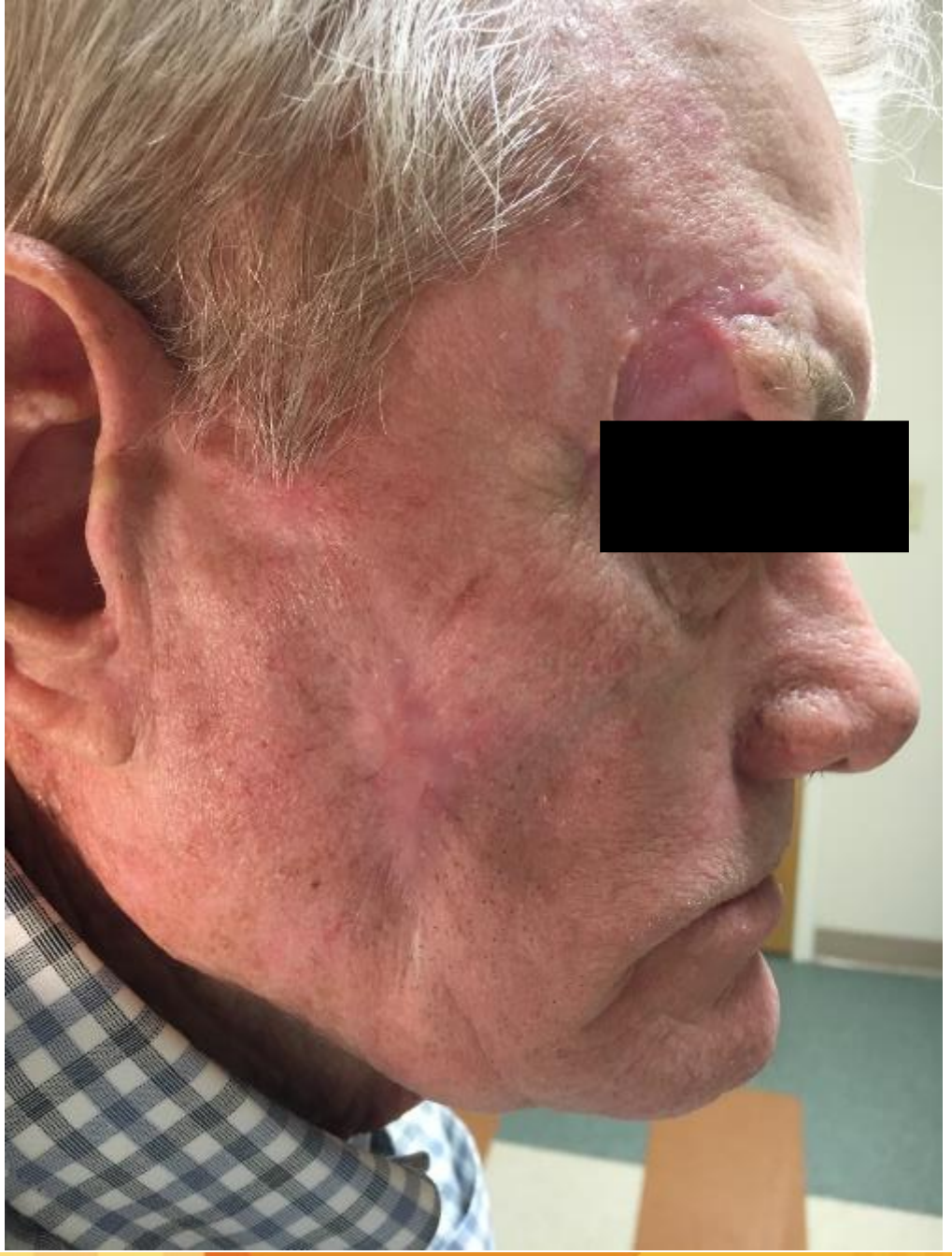
# NEOAdjuvant Approach







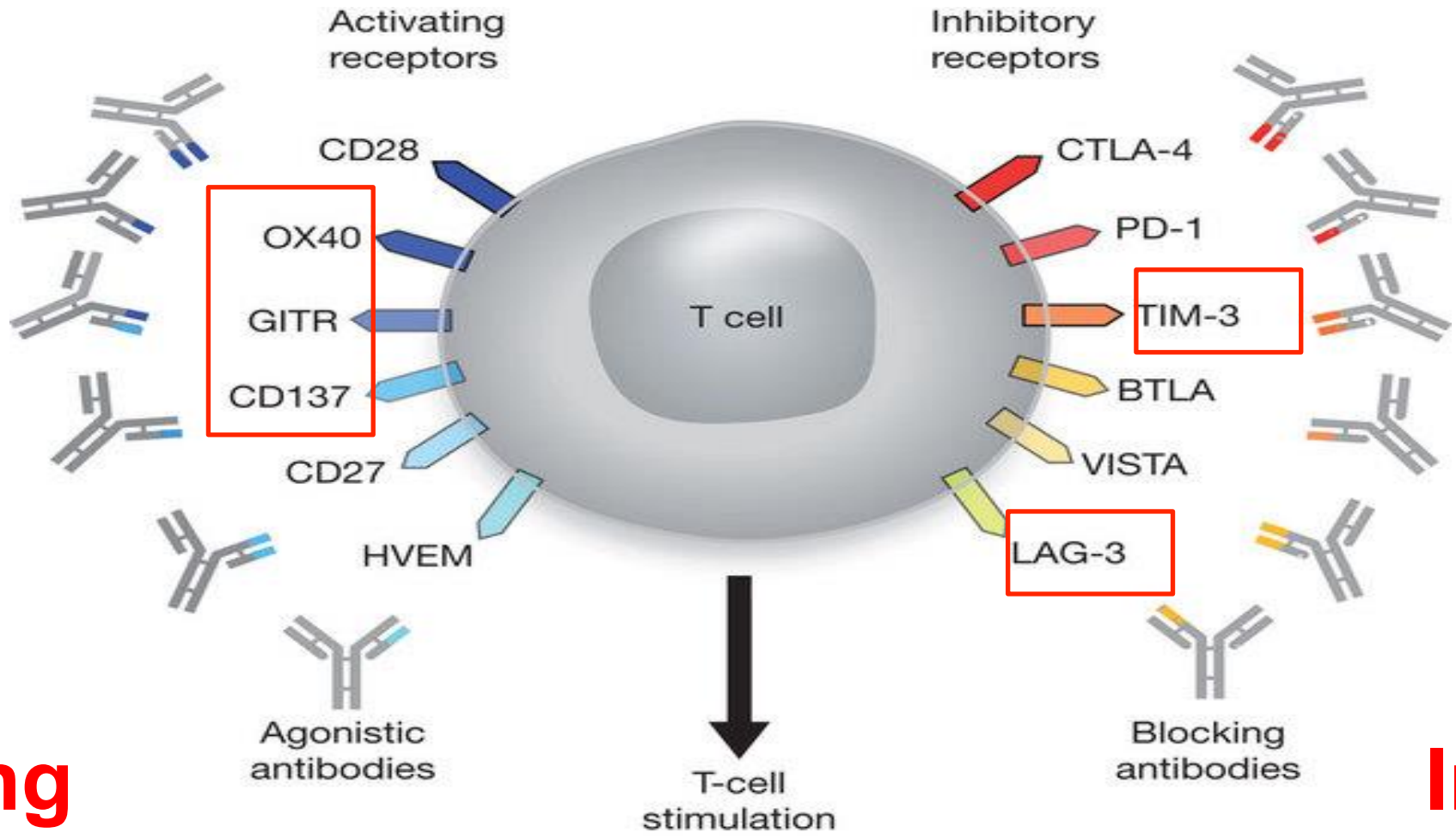




# Immune Modulatory Receptors

## Turning up The Activating

## Blocking the Inhibiting




**Activating**

**Inhibiting**

Mellman *et al*. Nature, 2011

# Durable Response of Metastatic Squamous Cell Carcinoma of the Skin to Ipilimumab Immunotherapy.

- A 72-year-old male patient was receiving second-line chemotherapy for metastatic squamous cell carcinoma of the skin (SCCS) when he was diagnosed with concurrent metastatic melanoma (BRAF mutant).
- Chemotherapy was ceased and he was treated with 4 cycles of ipilimumab immunotherapy. T
- he patient experienced clinical benefit and durable remission in both malignancies and remains free of cancer progression 8 months after the last cycle of ipilimumab.
- Response of SCCS to ipilimumab has not been previously described,
- pembrolizumab efficacy confirm the critical role of the immune system in SCCS pathogenesis and
- suggest further exploration of checkpoint immunotherapy for the treatment of this disease.

Day F, J Immunother. 2017 Jan;40(1):36-38. PubMed PMID: 27684455.

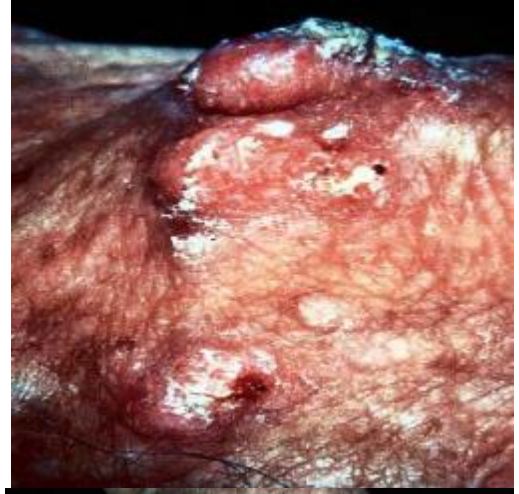
## Genomic profiling of squamous malignancies across anatomic sites. 2017 #11512

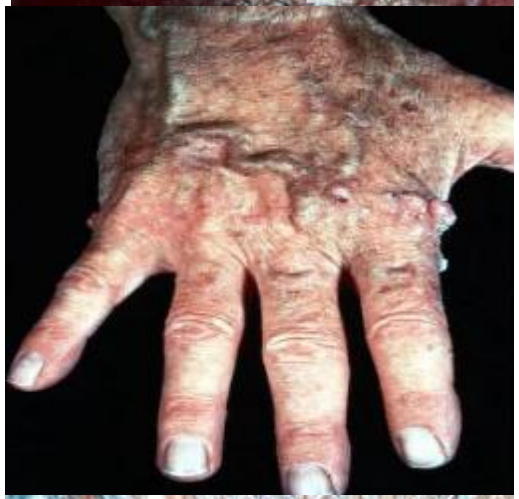
- HPV driven SCC have similar genomic profiles regardless of of site origin, and have a significantly lower median TMB than HPV negative SCC.
- site independent genomic predictors of therapy response.
- Sites of origin were head and neck (HNSCC, n = 1300), cervical (cSCC; n = 318), anal (aSCC, n = 248), esophageal (n = 242), lung (lSCC, n = 2386), and cutaneous (sSCC, n = 289) SCC cases.
- TMB of all SCC cases was significantly different ($p < 10^{-12}$) when stratified by HPV status
- In sSCC, the most common GA were in *TP53* (85.5%), *CDKN2A* (54.3%), and *TERT*(44.0%), and mean TMB was 59.5 with HPV in 3.1% of cases.

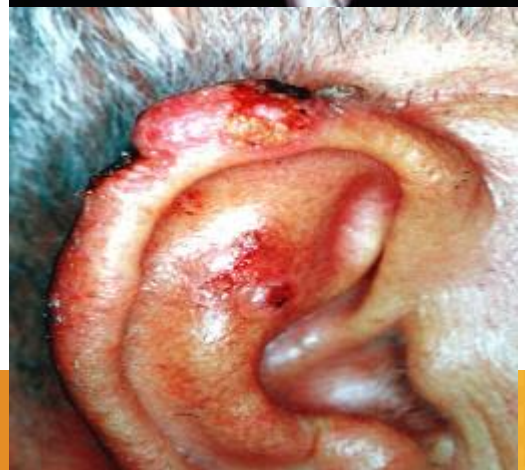
# Post Transplant Skin Cancer

- 36-fold higher incidence in OTRs (SCC:BCC = 4:1)
- Aggressive biological behavior; poor outcomes
- Incidence rates (cases per 100,000 person-years)

| Post Transplant Skin Cancer | OTR | US population |
|---|---|---|
| NMSC | 1,436 | 449 |
| SCC | 1,355 | 38 |
| MM | 125 | 18 |
| MCC | 3.3 | 0.1 |



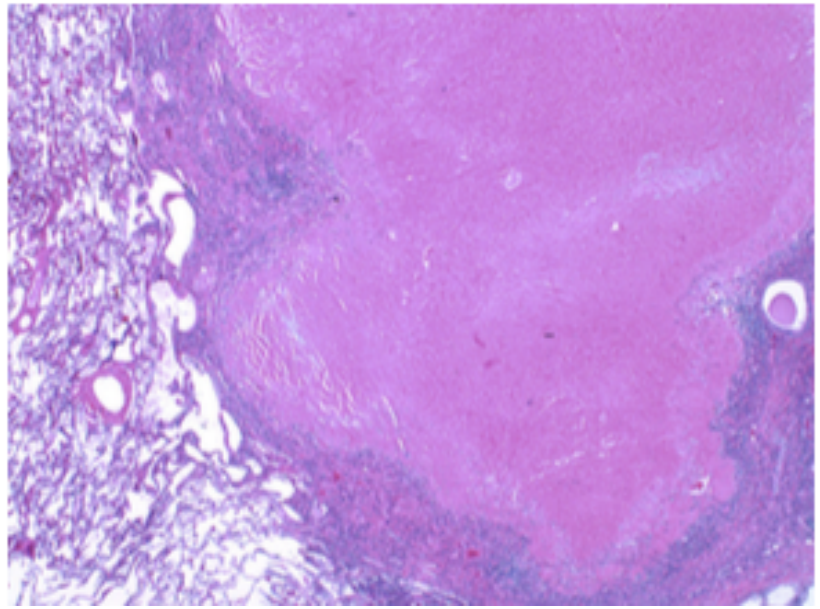


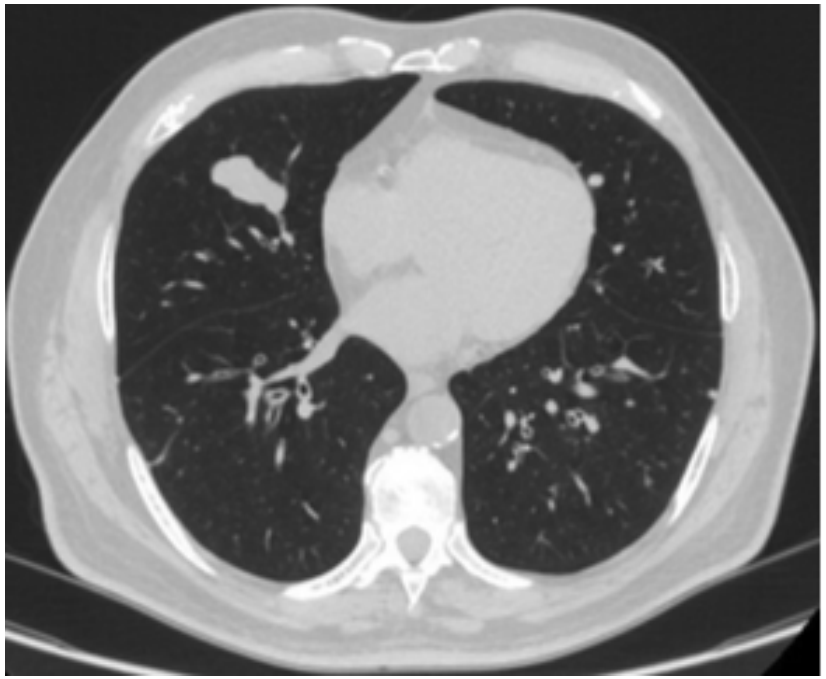


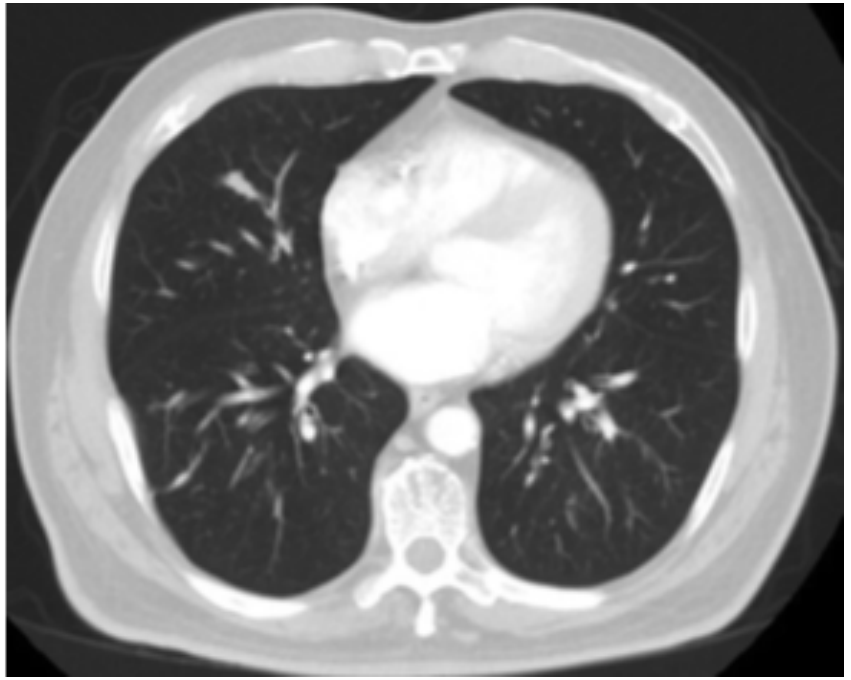
Garrett et al, JAMA Dermatol 153; 296-303, 2017.

# Complete pathologic response of metastatic cutaneous squamous cell carcinoma and allograft rejection after treatment with combination immune checkpoint blockade

David M. Miller, MD, PhD,[a,b] Beverly E. Faulkner-Jones, MD, PhD,[c] James R. Stone, MD, PhD,[d] and Reed E. Drews, MD[a]
*Boston, Massachusetts*



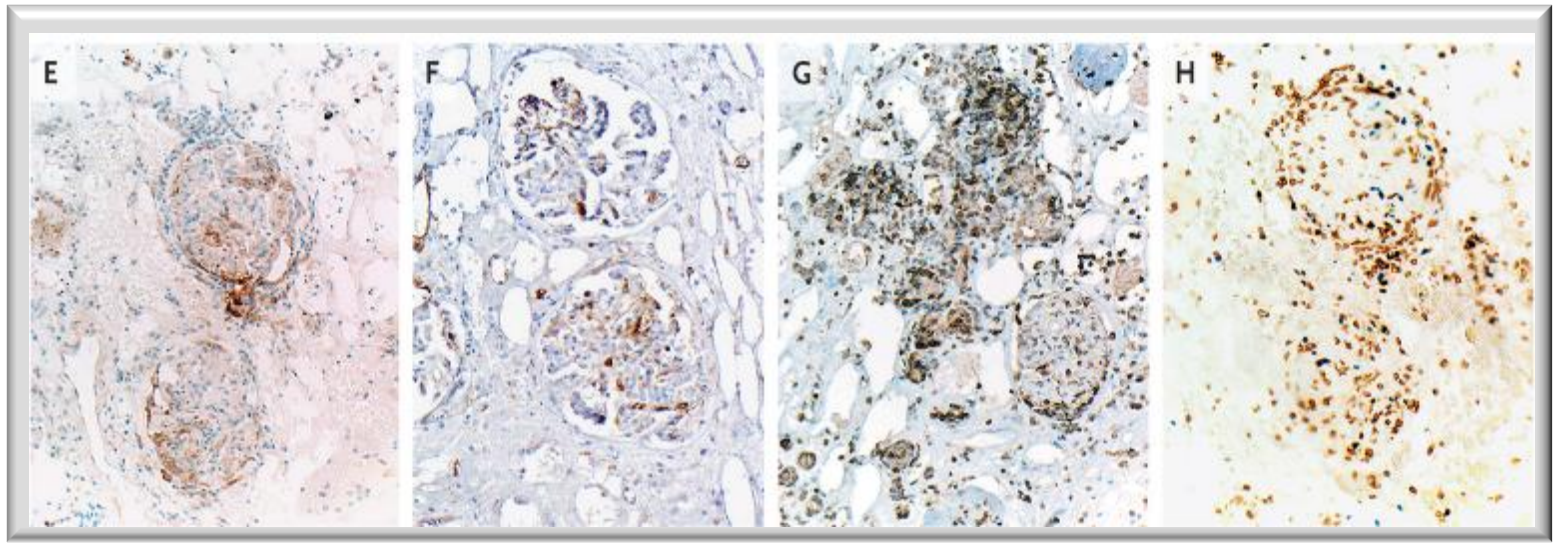




# Pembrolizumab for Metastatic CSCC in Organ-Transplant Patient

- Sept 2014 – started off-label pembrolizumab
- Nov 2014 – irreversible organ rejection: dense T-cell infiltrate with PD-L1 expression
- 85% reduction in metastatic tumor burden
- Pembro continued with dialysis

Explanted renal allograft




PD-L1 expression on endothelial cells and infiltrating immune cells

Infiltrating T-cells express PD-1

Immune cells are CD8-+

Lipson et al N Engl J Med;374, 2016.

CASE REPORT Open Access

# Safe and effective administration of T-VEC in a patient with heart transplantation and recurrent locally advanced melanoma

Gustavo Schvartsman[1], Kristen Perez[2], Jill E. Flynn[3], Jeffrey N. Myers[3] and Hussein Tawbi[2,4*]

**Abstract**

**Background:** Immunotherapy plays a key role in the treatment of metastatic melanoma. Patients with autoimmune conditions and/or on immunosuppressive therapy due to orthotropic transplants, however, are systematically excluded from clinical trials. Talimogene laherparepvec (T-VEC) is the first oncolytic virus to be approved by the FDA for cancer therapy. To our knowledge, this is the first report of T-VEC being administered in the setting of an organ transplant recipient.

**Case presentation:** Here we present the case of a patient with recurrent locally advanced cutaneous melanoma receiving salvage T-VEC therapy in the setting of orthotropic heart transplantation. After 5 cycles of therapy, no evidence of graft rejection has been observed to date, and the patient achieved a complete remission, and is currently off therapy.

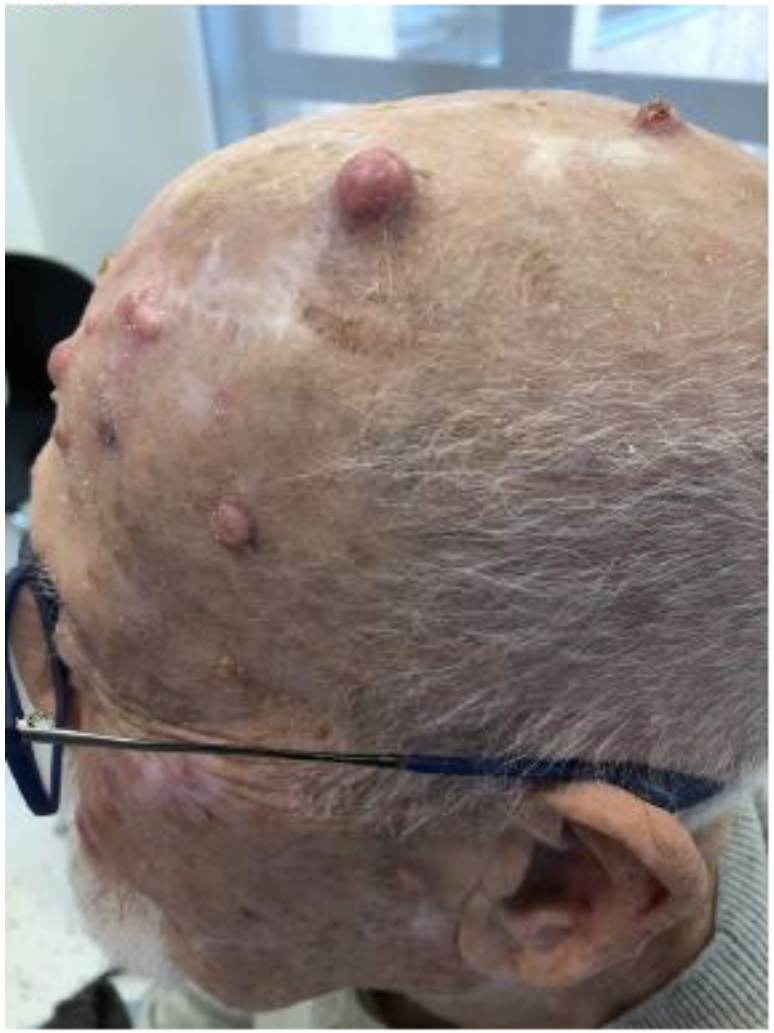
**Conclusion:** This case advocates for further investigation on the safety and efficacy of immunotherapeutic approaches, such as T-VEC, in solid organ transplant recipients.

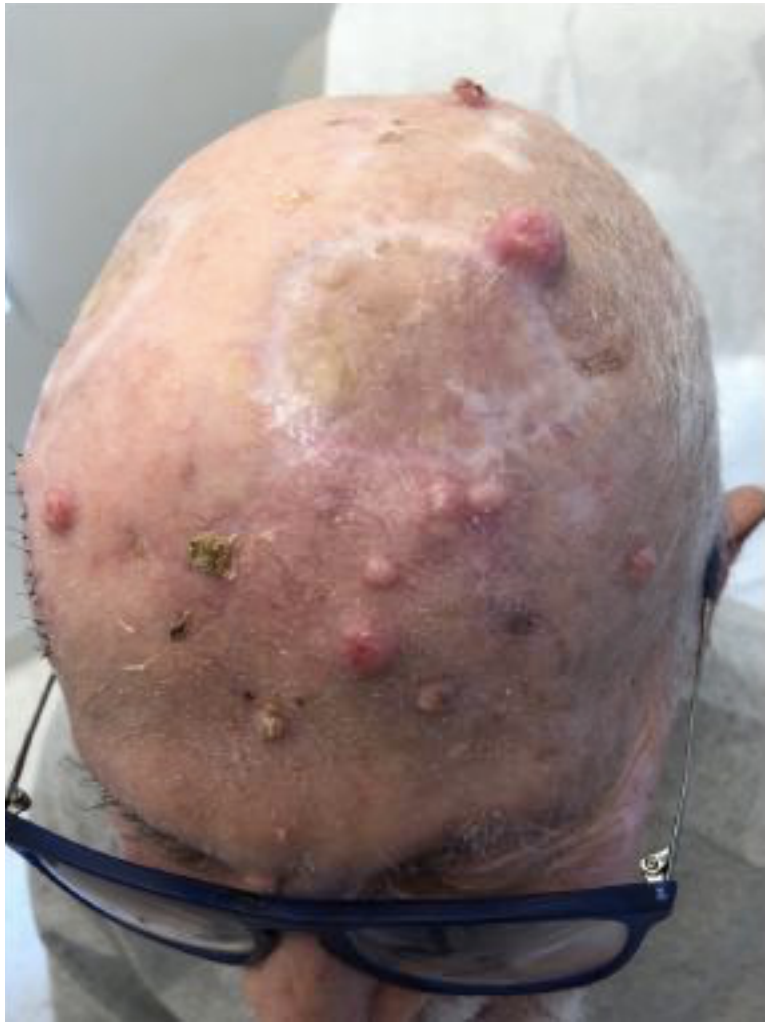
**Keywords:** Cancer, Melanoma, Immunotherapy, Allotransplant, Rejection, T-VEC

# AP -

- History of hepatitis B status post liver transplant (1993)
- multiple basal cell carcinomas, squamous cellcarcinoma
- neuroendocrine carcinoma and Merkel cell carcinoma
- Has received ----  for metastatic squamous cell carcinoma.

# 7/16/18





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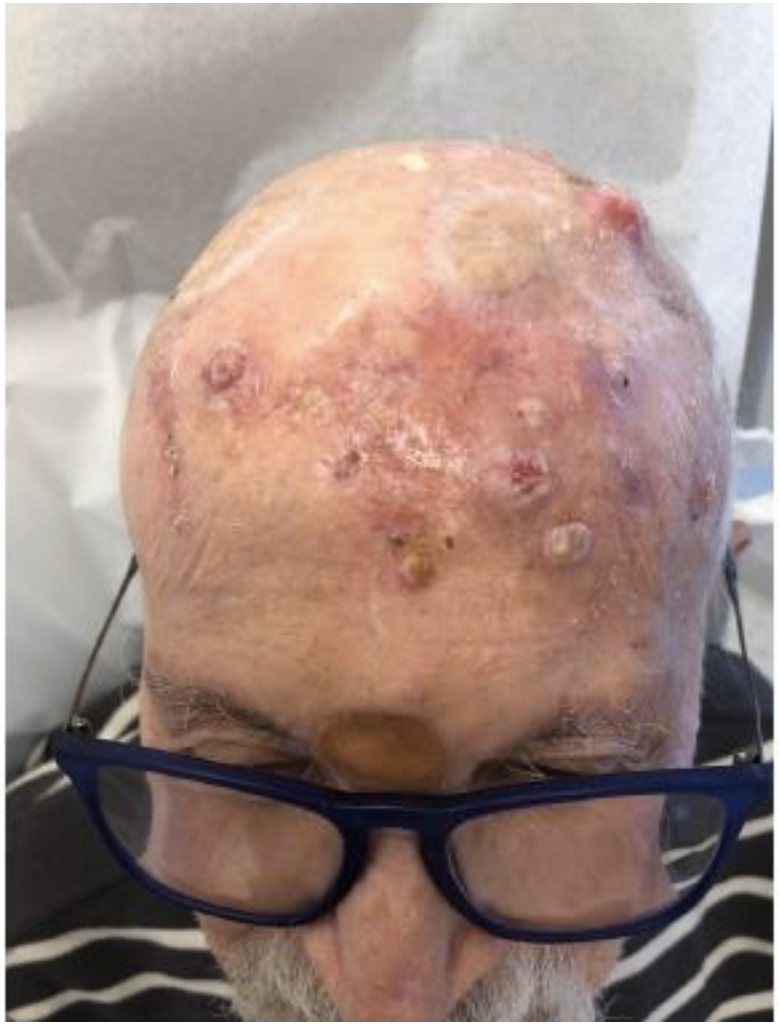

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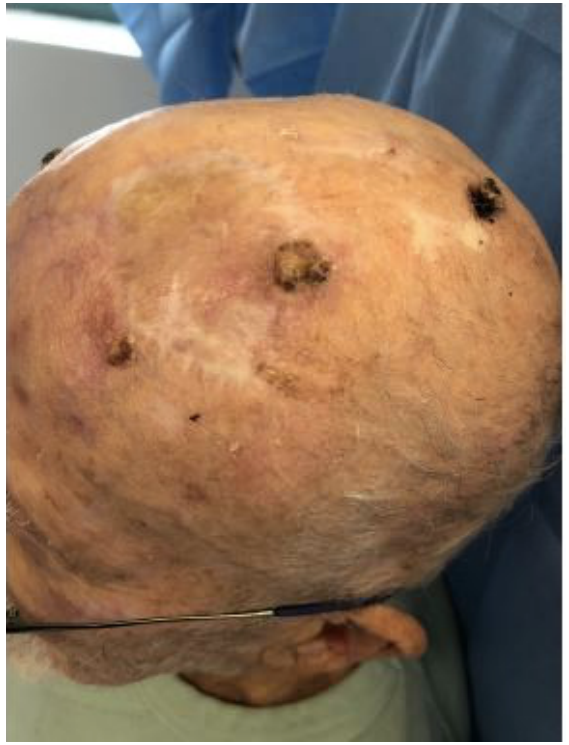

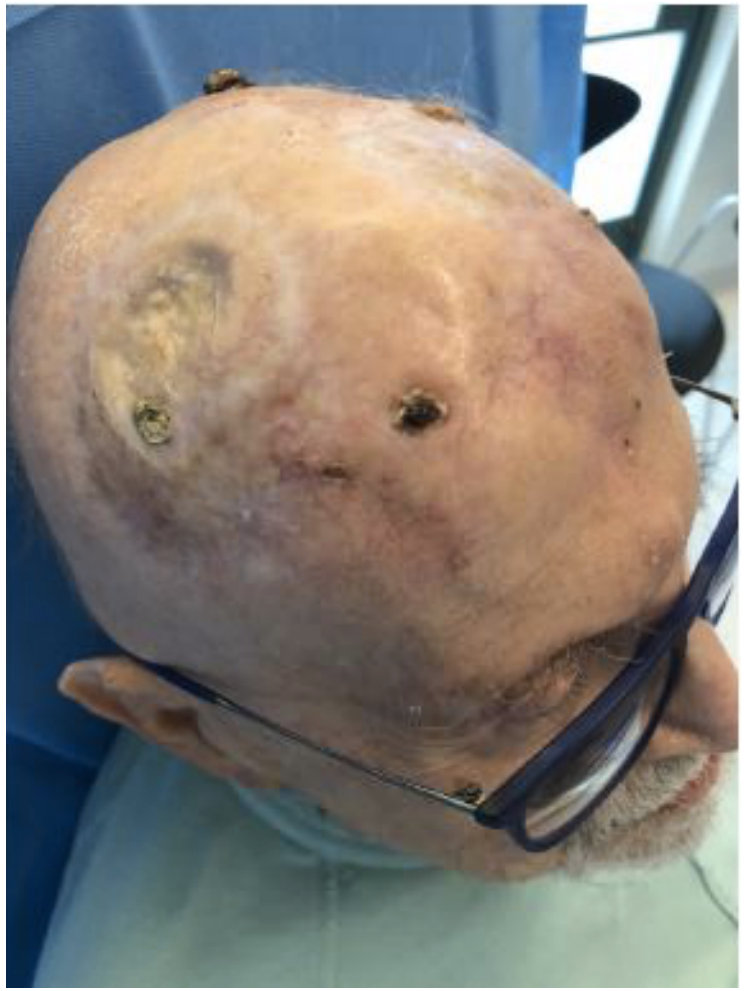

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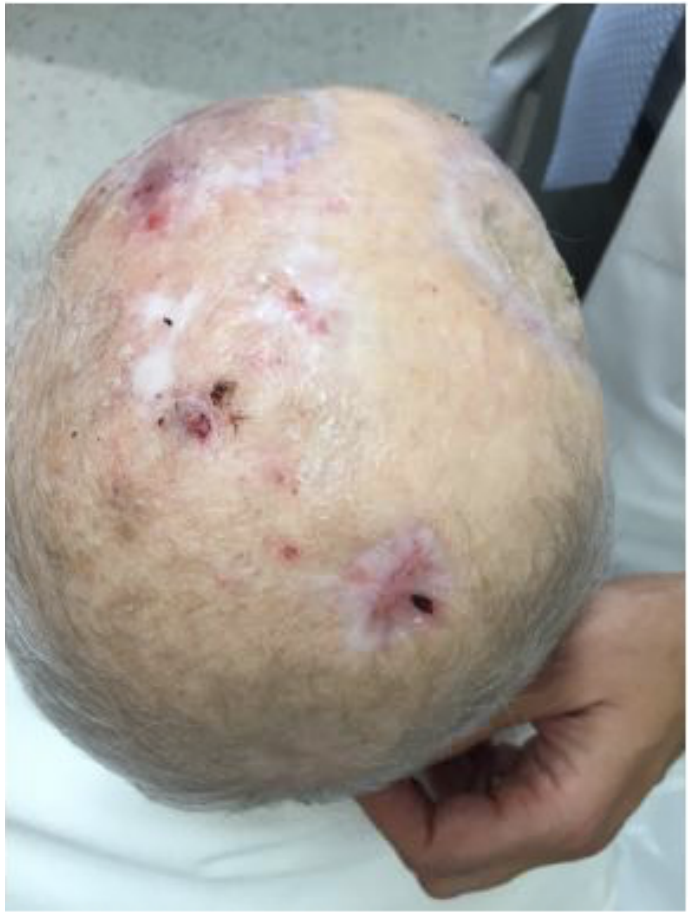
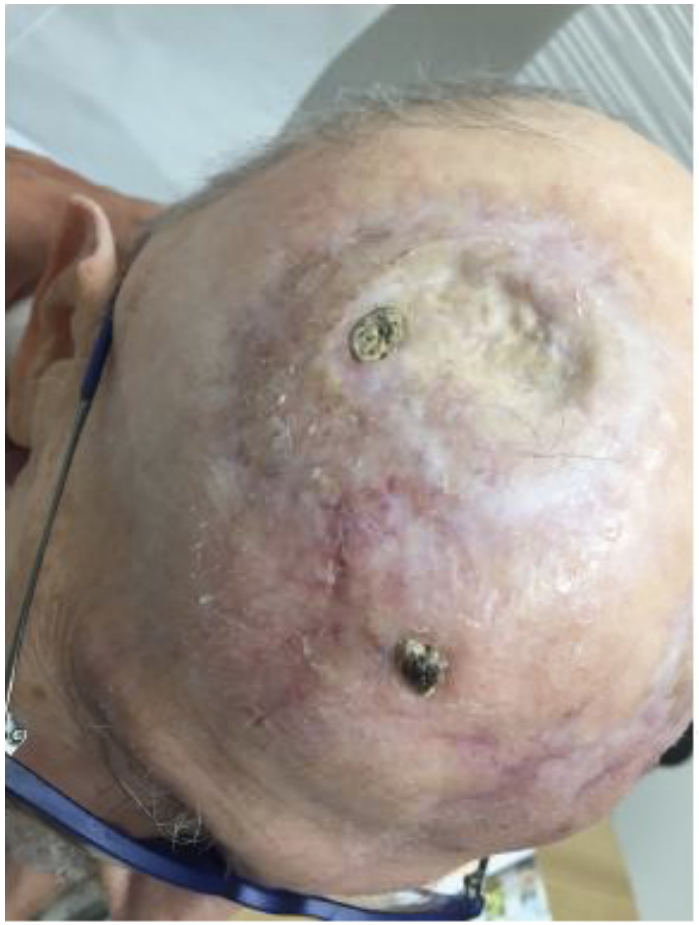
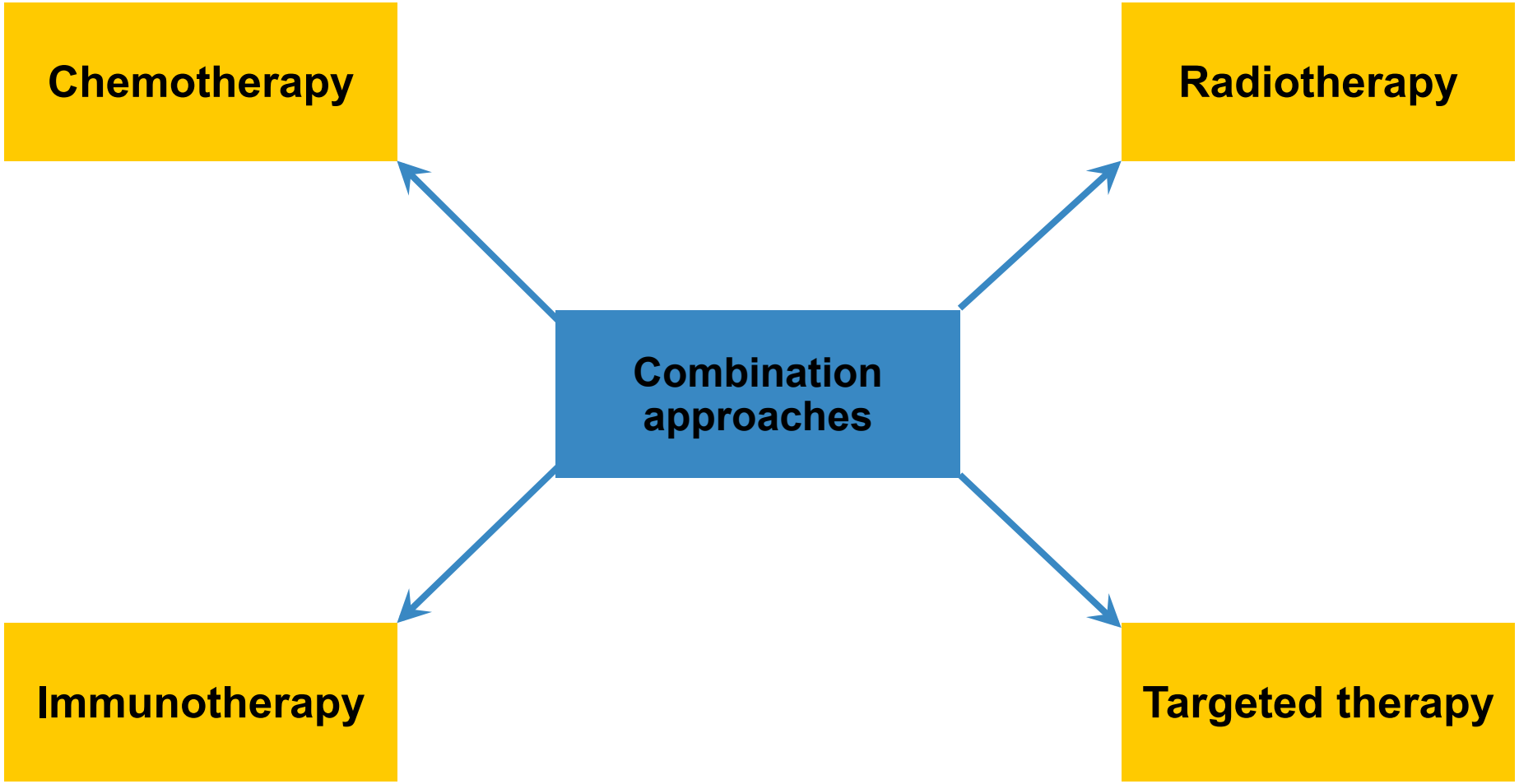
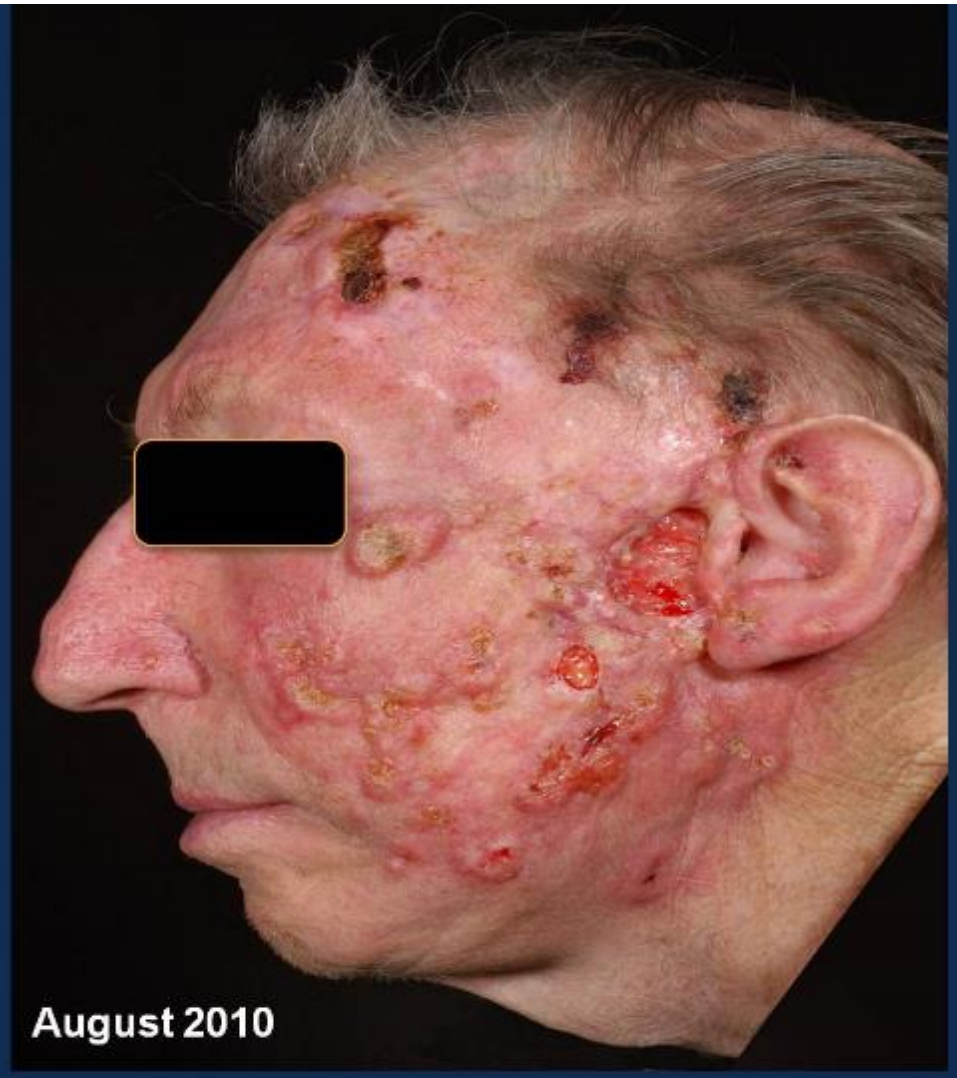




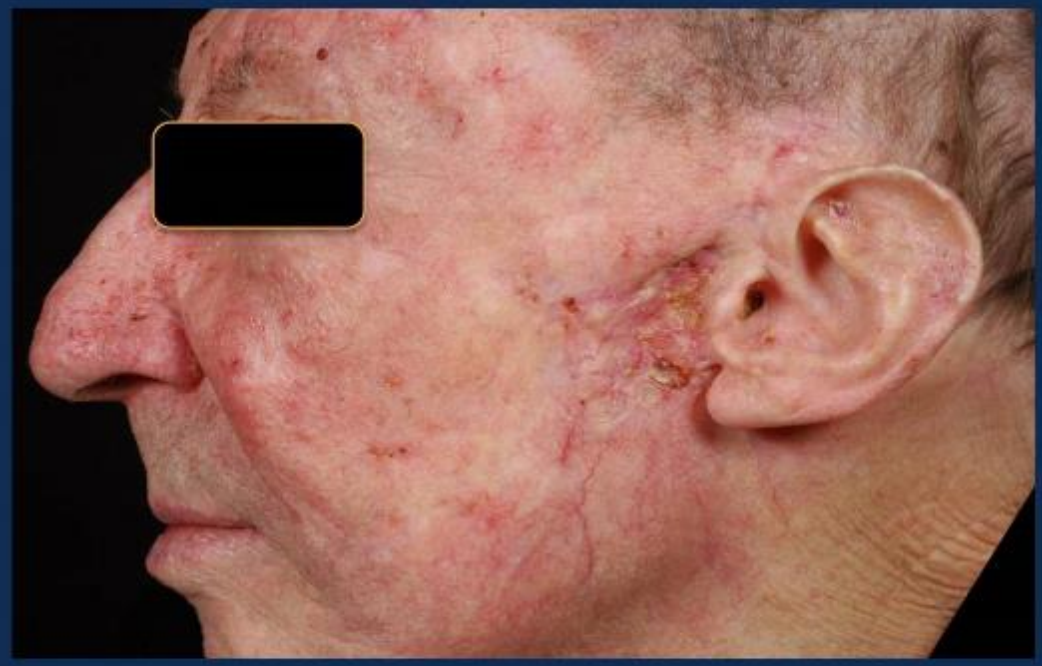
# Raising the bar ……



# Cetuximab in mSCC



August 2010



December 2010

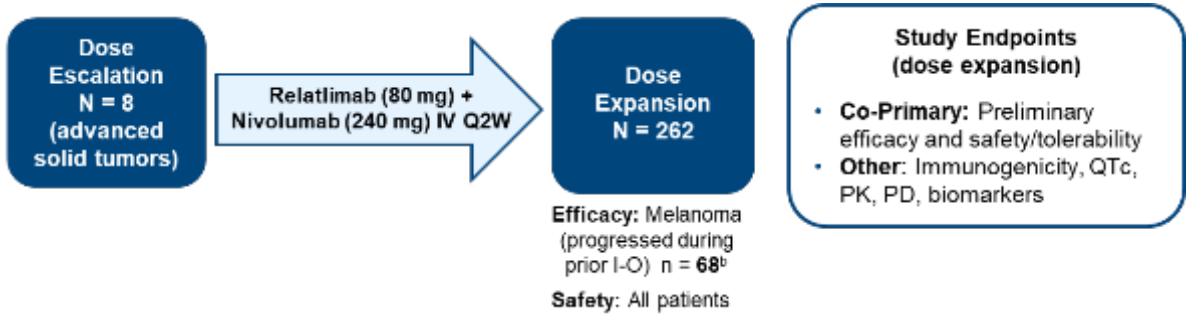
PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

# An open-label, non-randomized, multi-arm, phase II trial evaluating pembrolizumab combined with cetuximab in patients with recurrent/ metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): Results of the interim safety analysis #6037

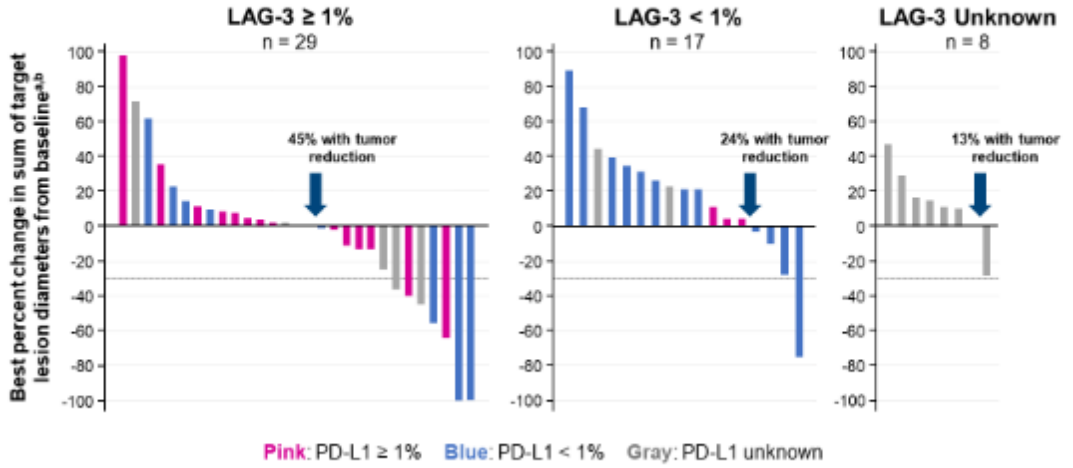
- This is the first trial to combine pembrolizumab with cetuximab to evaluate anti-tumor synergy. As this specific drug combination has not been previously tested, an interim safety analysis was completed per protocol.
- pembrolizumab at a fixed dose of 200mg IV on day 1 with cetuximab 400mg/m2 loading dose followed by 250mg/m2 weekly (21-day cycle).
- **Results:** Of the 10 patients included in the analysis, median age 58y (range 47-79y), M: F 5:5. 8 pts had mucosal (6 oral cavity, 1 oropharynx, 1 nasopharynx) and 2 had cutaneous HNSCC primaries.
- 65 adverse events (AEs) were reported in 9 pts; G1: 39, G2: 15, ≥G3: 11. Of the 11 ≥G3 AEs, only 1 was treatment-related (see Table). There were no treatment-related deaths or dose-limiting toxicities (DLTs).
- 3 pts discontinued treatment, none of which were due to toxicity (2 had disease progression, 1 withdrew from study).
- Pembrolizumab combined with cetuximab has a very tolerable safety profile, with no DLTs. Efficacy analysis of this combination will be performed.

2018 ASCO ANNUAL MEETING

# Initial Efficacy of Anti-Lymphocyte Activation Gene-3 (anti–LAG-3; BMS-986016) in Combination With Nivolumab in Patients With Melanoma Previously Treated With Anti–PD-1/PD-L1 Therapy




## Best Change in Target Lesion Size by LAG-3 and PD-L1 Expression




[a]Six patients with clinical progression prior to their first scan and 1 with PD due to a new symptomatic brain metastasis prior to getting full scans were not included.
[b]One patient with best change from baseline > 30% had a best response of SD.

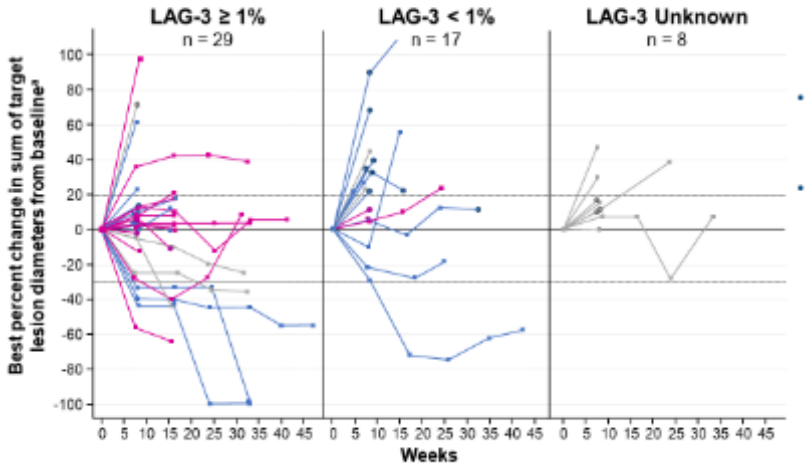
## Safety of Relatlimab 80 mg + Nivolumab 240 mg Q2W

| | All Patients[a] N = 270 | |
|---|---|---|
| | Any Grade n (%) | Grade 3–4 n (%) |
| Any TRAE[b] | 137 (51) | 27 (10) |
| TRAEs in ≥ 5% of patients | | |
| Fatigue | 30 (11) | 0 |
| Pruritus | 19 (7.0) | 0 |
| Diarrhea | 18 (6.7) | 3 (1.1) |
| Arthralgia | 17 (6.3) | 0 |
| Infusion-related reaction | 15 (5.6) | 0 |
| Any serious TRAE[b] | 18 (6.7) | 12 (4.4) |
| Serious TRAEs in > 1 patient | | |
| Colitis | 4 (1.5) | 3 (1.1) |
| Pneumonitis | 2 (0.7) | 2 (0.7) |
| Myocarditis[c] | 2 (0.7) | 0 |
| Pyrexia | 2 (0.7) | 0 |
| Any TRAE leading to discontinuation[b] | 11 (4.1) | 8 (3.0) |

- The safety profile of the melanoma prior PD-(L)1 cohort was similar to that of the overall population
- No treatment-related deaths were reported[d]

TRAE, treatment-related adverse event.
[a]Patients treated with relatlimab 80 mg + nivolumab 240 mg in the dose-escalation and -expansion phases as of the June 15, 2017, data cutoff.
[b]Safety evaluated per CTCAE v4.0 during treatment and up to 135 days after discontinuation. [c]There were a total of 4 myocarditis events (1.5%), all of which were grade 1, and 2 of which were serious AEs. [d]One TRAE of grade 5 myocarditis was observed with relatlimab 240 mg + nivolumab 240 mg Q2W.

## Depth and Duration of Response by LAG-3 and PD-L1 Expression




- Responses were more likely in patients with LAG-3 expression ≥ 1%
- PD-L1 expression did not appear to enrich for response

Pink: PD-L1 ≥ 1%
Blue: PD-L1 < 1%
Gray: PD-L1 unknown
○: Appearance of new lesions

[a]Six patients with clinical progression prior to their first scan and 1 patient with PD due to a new symptomatic brain metastasis prior to getting full scans were not included.

# T-VEC + pembrolizumab

## Phase 1b Study Schema

**N=21**

- Unresectable stage III or IV melanoma
- Treatment naive
- Injectable lesions
- No clinically active brain mets
- No active herpetic skin lesions or prior complications from herpetic infection

**T-VEC intralesional**
- Up to 4 mL per treatment
- 1st dose $10^6$ PFU/mL
- Then $10^8$ PFU/mL Q2W

T-VEC Intralesional

Pembrolizumab 200mg IV Q2W

Wk -5 | Wk -2 | Wk 0 | DLT Window | Wk 6

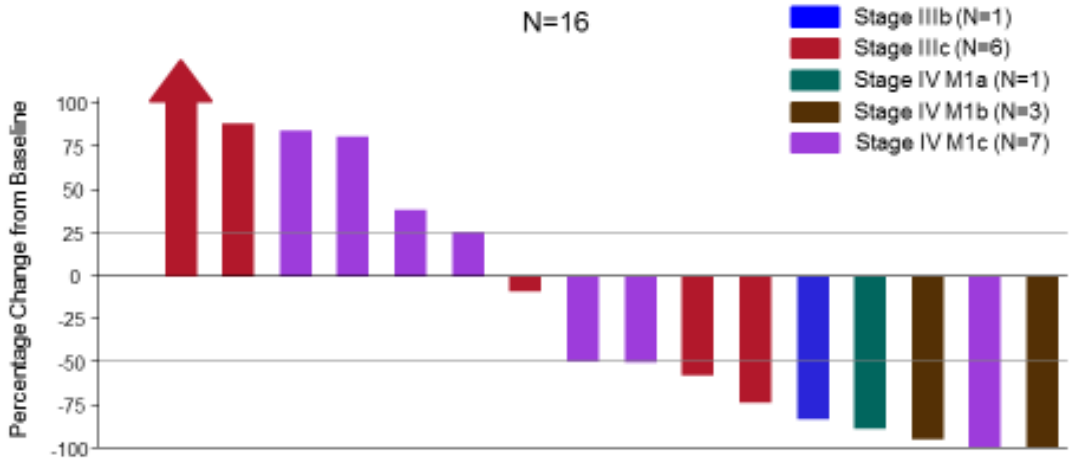
SAFETY FOLLOW-UP

30 (+7) days after end of treatment

**Treatment until whichever occurs first:**
- Progressive disease (PD) per irRC
- Intolerance
- All injectable tumors disappeared (T-VEC only)
- 2 Years

T-VEC: talimogene laherparepvec

## MASTERKEY-265 (pembro+T-Vec) Best Change in Tumor Burden




Includes all patients who received at least 1 dose of talimogene laherparepvec or pembrolizumab.
Include patients who had at least 2 assessments with bi-dimensional measurements.

Long et al SMR 2015

# Current Approaches to Squamous Cell Carcinoma Skin

| ClinicalTrials.Gov | | | | |
|---|---|---|---|---|
| NCT02268747 | Efficacy and Safety of Dacomitinib in the Treatment of Skin Squamous Cell Cancer | II | Pan-HER inhibitor, | Coexpression of EGFR, HER2 and HER3 |
| NCT00423397 | Gefitinib and PEG-Interferon Alfa-2a in Treating Patients With Unresectable or Metastatic Skin Cancer | I/II | Immuno/Immuno Combination | |
| NCT02978625 | Talimogene Laherparepvec and Nivolumab in Treating Patients With Refractory Lymphomas or Advanced or Refractory Non-melanoma Skin Cancers | II | Immuno/Immuno Combination | Locall Oncolytic and Systemic Immunotherapy |
| NCT02218164 | Capecitabine or 5-FU With Pegylated Interferon Alpha-2b in Unresectable/Metastatic Cutaneous Squamous Cell Carcinoma | II | Chemo/Immuno Combination | |
| NCT03291002 | Study of Intratumoral CV8102 in cMEL, cSCC, hnSCC, and ACC | I | Intratumoral Therapy | RNAdjuvant |
| NCT03108131 | Cobimetinib and Atezolizumab in Advanced Rare Tumors | II | Targeted Immuno Combination | |

# Factors Predictive of Recurrence / Death

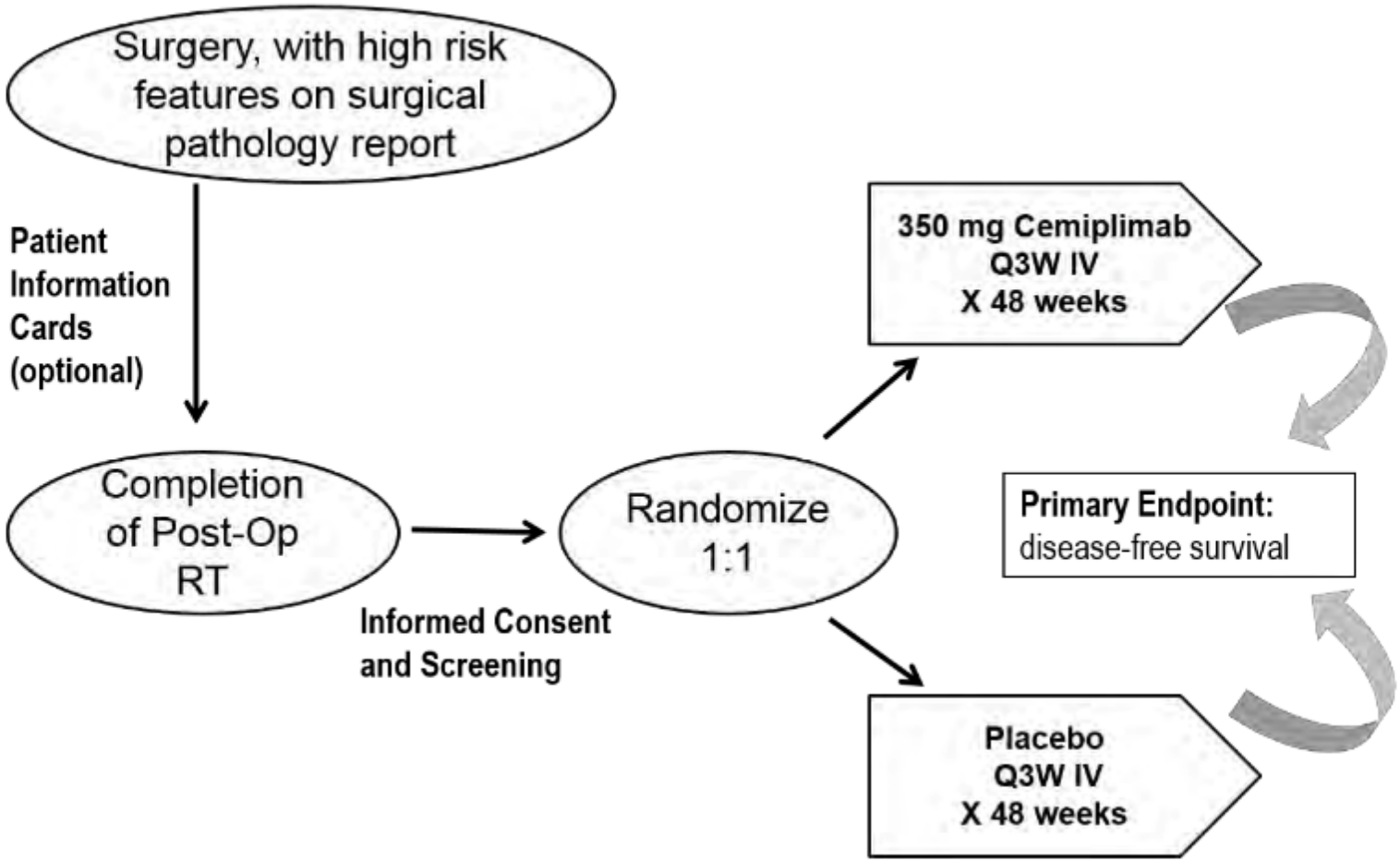
| | Nodal Metastases | Disease- Specific Death | Overall Death |
|---|---|---|---|
| Diameter ≥2 cm | ✔ | ✔ | |
| Poor differentiation | ✔ | ✔ | ✔ |
| Invasion beyond fat | ✔ | ✔ | ✔ |
| Ear/temple location | ✔ | ✔ | |
| Anogenital location | | ✔ | |
| Perineural invasion | | ✔ | |

**3.7% risk of metastases; 2.1% DSD**

Schmults CD, et al. *JAMA Dermatol.* 2013; 149:541-547

# Adjuvant trials

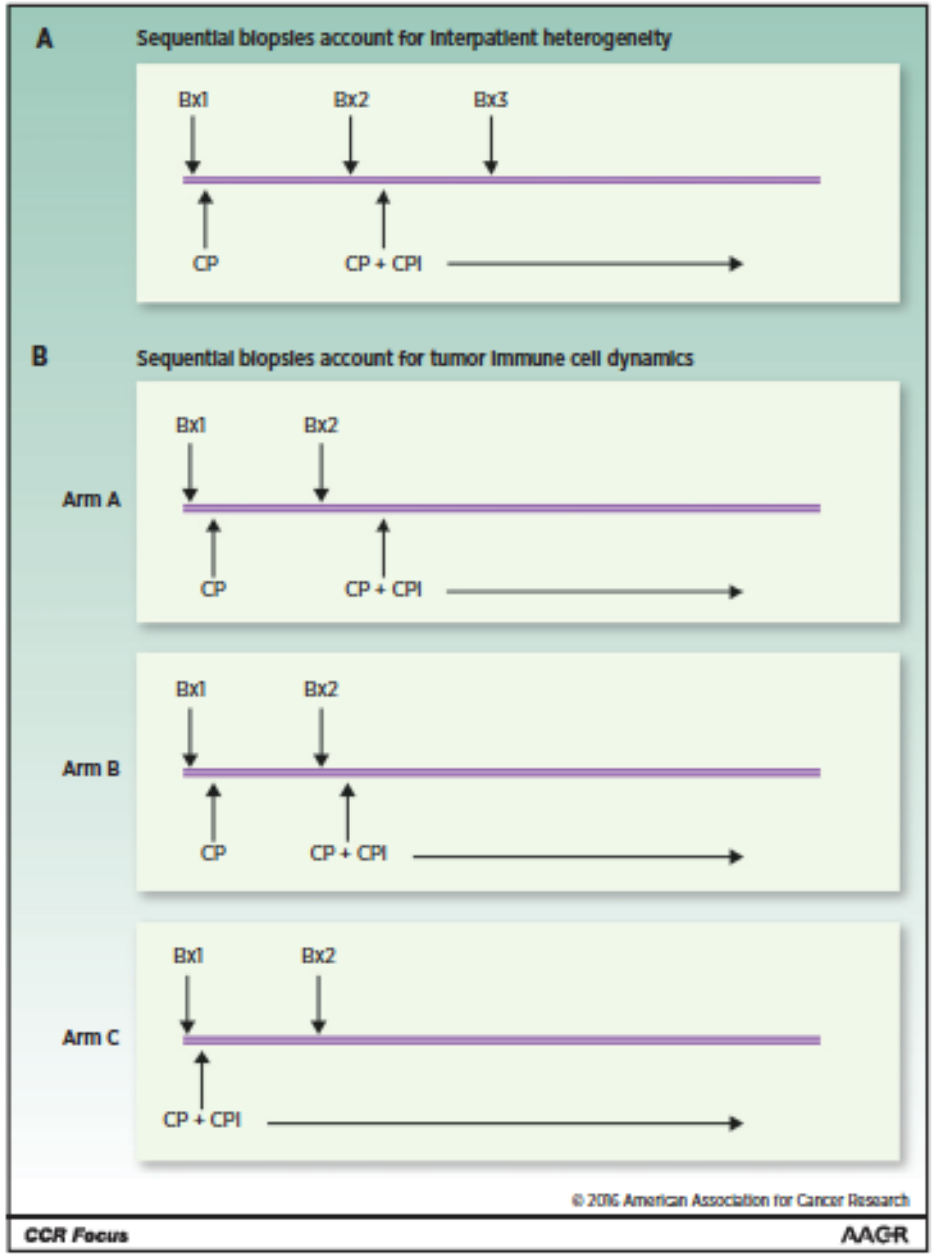
**Figure 1: Study Schematic for Part 1 the Study (blinded for primary analysis)**



# The Where, the When, and the How of Immune Monitoring for Cancer Immunotherapies in the Era of Checkpoint Inhibition

Priti S. Hegde[1], Vaios Karanikas[2], and Stefan Evers[2]

Trial design considerations for combination therapies. A, a commonly employed trial design for interrogation of drug mechanism of action employs multiple biopsies (Bx) from the same individual with the combining partner (CP) alone or the combination of CP with checkpoint inhibitors (CPI). B, tumor immune modulation is a dynamic process. Trial designs that incorporate sequential biopsies keeping the time between biopsies constant for each agent enable comparison of the impact of each combining partner on tumor immune microenvironment.




Clin Cancer Res; 22(8); 1865–74. !2016 AACR.

## The Where, the When, and the How of Immune Monitoring for Cancer Immunotherapies in the Era of Checkpoint Inhibition

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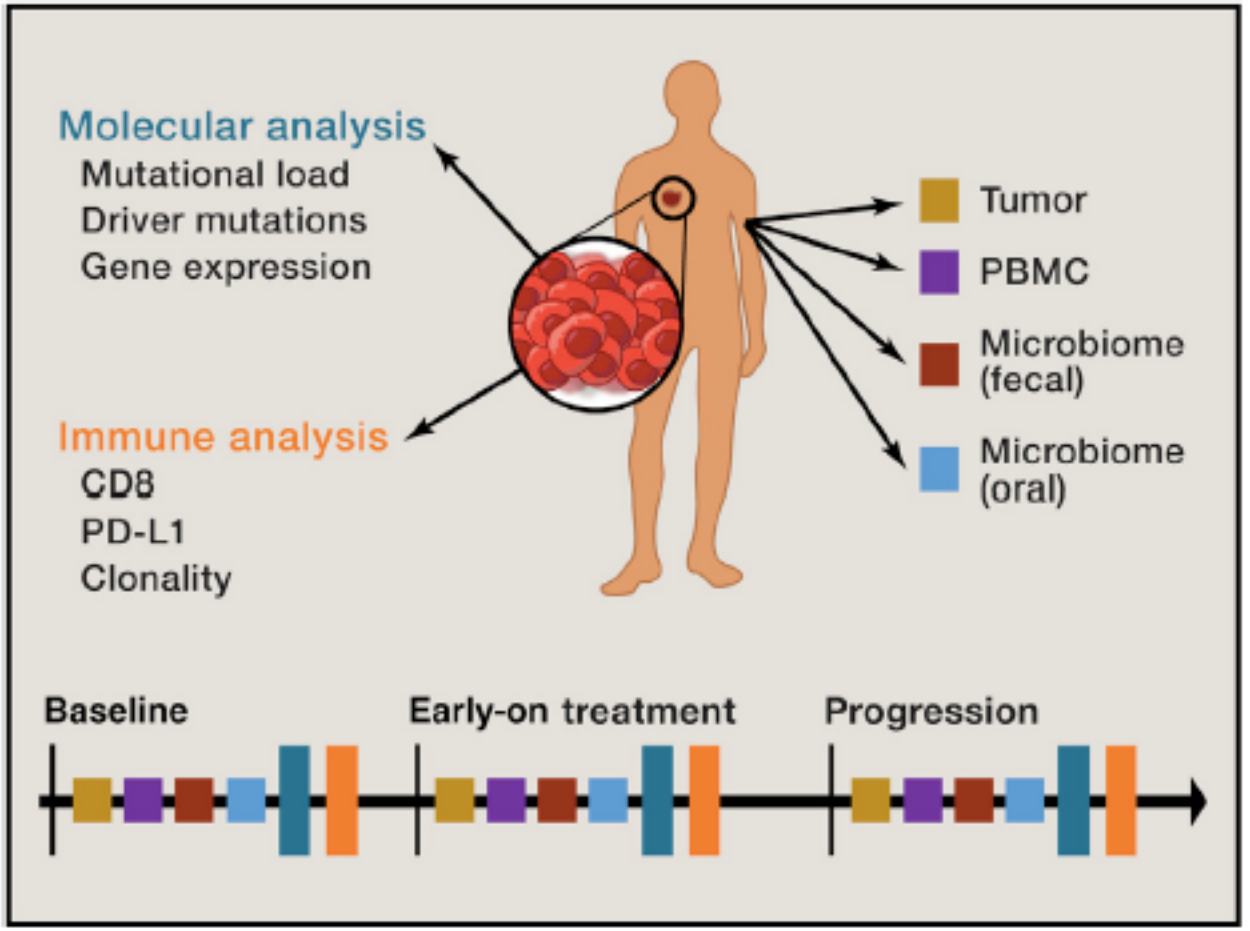
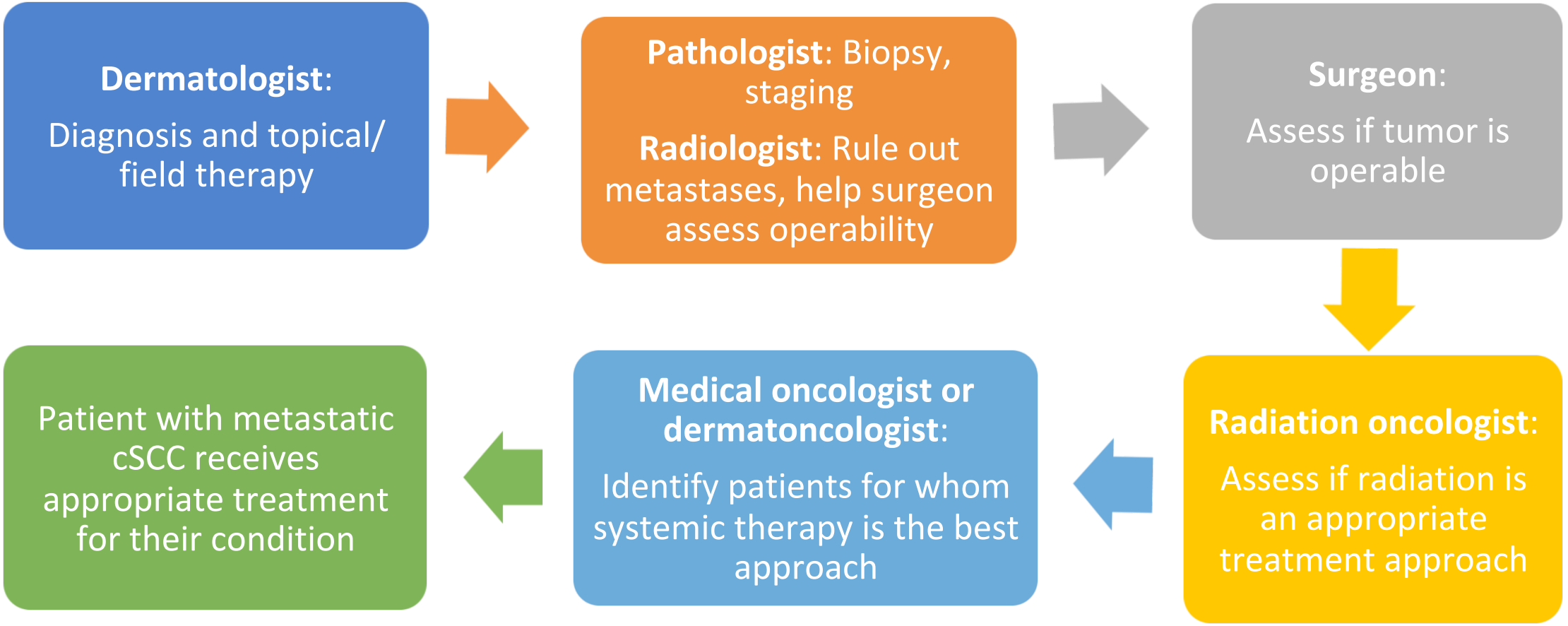



Clin Cancer Res; 22(8); 1865–74. !2016 AACR.

Sharma et al, Cell 168, February 9, 2017

# Importance of Multidisciplinary Collaboration

## NCCN Guidelines




NCCN Guidelines. Squamous Cell Skin Cancer. Version 2.2019.

# Conclusion

- Dramatic advances have been made in the molecular understanding of cSCC
- Early data suggest rapid and (possibly) durable responses to anti-PD-1 therapy in advanced cSCC
- This sets the stage for investigation into combination therapy
- Identifying biomarkers of response is key
- Work to do
- Clinical trials, clinical trials, clinical trials …..

# Thank You

@OmidHamidMD

clinicaltrials@theangelesclinic.org

310-294-0438

**This lecture will be made available as an on-demand webinar.**

# For more information about this project:

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*Assistant Director, Education Programs*

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