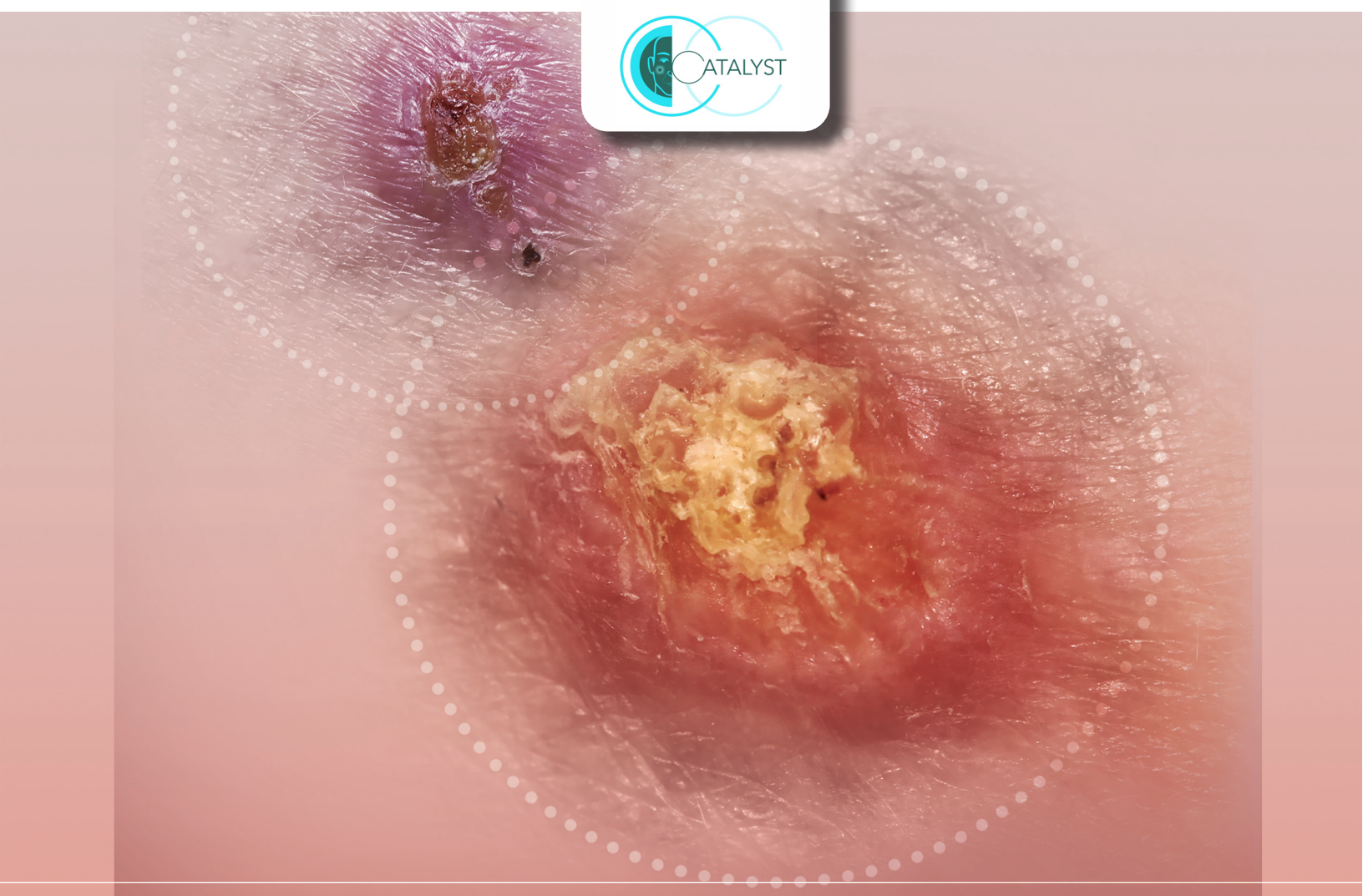

# COMPLEMENTARY THERAPEUTIC APPROACHES:

## Mohs Micrographic Surgery and Immunotherapy in Non-Melanoma Skin Cancer

**MONDAY, JUNE 26, 2023**

**Virtual Symposium**

7:00 PM - 8:00 PM ET | 6:00 PM – 7:00 PM CT | 5:00 PM - 6:00 PM MT | 4:00 PM – 5:00 PM PT

### FACULTY

**Vishal Anil Patel, MD**
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Director of Dermatologic Surgery
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This activity is provided by Med Learning Group.
This activity is co-provided by AMEDCO.
This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc.


**AGENDA**

I. **Surgical and Nonsurgical Approaches to the Treatment of Patients with NMSCs**
   a. Mohs micrographic surgical techniques
      i. High-risk basal cell
      ii. High-risk cutaneous squamous cell
   b. Rationale for targeting the immune system to treat NMSCs
   c. Identifying patients for either new systemic therapies or Mohs surgery – to cut or not to cut

II. **Systemic Anti-Cancer Therapy – Early to Advanced NMSCs**
   a. Clinical trials data for immunotherapy
      i. Neo-adjuvant and adjuvant setting
         1. Efficacy and safety findings of immune-checkpoint inhibition
      ii. Advanced setting
         1. Efficacy and safety data of immune-checkpoint inhibition

III. **Multidisciplinary Team Approach - Individualizing Care for Patients with NMSCs**
   a. Multidisciplinary team
      i. Collaboration of Mohs surgeons, dermatologists, pathologists and oncologists, head/neck surgeons
         1. Role of Mohs surgeon on team – care coordination, consultation, and referral
         2. What works to advance coordination of care?
         3. Tools and processes to enhance interdisciplinary communication
      ii. Patient outcomes
         1. Improvement in quality of life
         2. Psychosocial functioning and surgical intervention

IV. **Complex Case Studies**

V. **Conclusions**

VI. **Questions and Answers**

# Complementary Therapeutic Approaches: Mohs Micrographic Surgery and Immunotherapy in Non-Melanoma Skin Cancer

**FACULTY PRESENTERS**

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**Vishal Anil Patel, MD**
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Associate Professor of Dermatology and Medicine/Oncology
George Washington University
School of Medicine & Health Sciences
Washington, DC

**PROGRAM OVERVIEW**
This program is designed to meet the targeted educational needs of surgical dermatologists, Mohs surgeons, dermatologists, and other healthcare practitioners who care for patients with advanced metastatic basal cell carcinoma (mBCC) or cutaneous squamous cell carcinoma (cSCC). This education will help healthcare providers to better examine clinical trials data supporting the use of new systemic immunotherapies for the treatment of patients with advanced nonmelanoma skin cancers (NMSCs), failing or not amenable to surgery or radiation; describe risk-assessment of patients with NMSCs who may derive greater benefit from new systemic therapies as opposed to Mohs surgery; and review the coordination and collaboration of multidisciplinary team members in the management of patients with advanced NMSCs failing or not amenable to surgery or radiation.

**TARGET AUDIENCE**
This initiative is designed to meet the educational needs of surgical dermatologists, Mohs surgeons, dermatologists, and other healthcare practitioners who care for patients with advanced/mBCC or cSCC.

**LEARNING OBJECTIVES**
Upon the completion of this program, attendees should be able to:

- Examine clinical trials data supporting the use of new systemic immunotherapy for the treatment of patients with advanced NMSCs failing or not amenable to surgery or radiation
- Describe risk-assessment of patients with NMSCs who may derive greater benefit from new systemic therapies as opposed to Mohs surgery
- Review the coordination and collaboration of multidisciplinary team members in the management of patients with advanced NMSCs failing or not amenable to surgery or radiation

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|---|---|
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| **Vishal Anil Patel, MD** | Dr. Patel serves as a paid consultant for Almirall, Jounce Therapeutics, PHD Biosciences, and Regeneron; he serves on the speaker bureau for Regeneron and Sanofi and has ownership interest in Science 37. |

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# *Complementary Therapeutic Approaches: Mohs Micrographic Surgery and Immunotherapy in Non-Melanoma Skin Cancer*

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- During the course of this lecture, the faculty may mention the use of medications for both US Food and Drug Administration (FDA)-approved and non-FDA-approved indications

All relevant financial relationships have been mitigated.

**This activity is supported by an independent medical education grant from**

**Regeneron Pharmaceuticals, Inc.**

## Learning Objectives

- Examine clinical trials data supporting the use of new systemic immunotherapy for the treatment of patients with advanced NMSCs failing or not amenable to surgery or radiation
- Describe risk assessment of patients with NMSCs who may derive greater benefit from new systemic therapies as opposed to Mohs surgery
- Review the coordination and collaboration of multidisciplinary team members in the management of patients with advanced NMSCs failing or not amenable to surgery or radiation

NMSC = non-melanoma skin cancer.

# Non-Melanoma Skin Cancer Overview

## Non-Melanoma Skin Cancer

- About 64,000 people worldwide die of NMSC every year[1]
- Basal cell carcinoma
  - Most common skin cancer[2]
  - About 80% of all skin cancers[3]
  - Increasing rates, particularly in young women due to tanning[2]
- Cutaneous squamous cell carcinoma
  - Second most common form of skin cancer[4]
  - Lifetime risk of 9% to 14% for men and 4% to 9% for women[5]

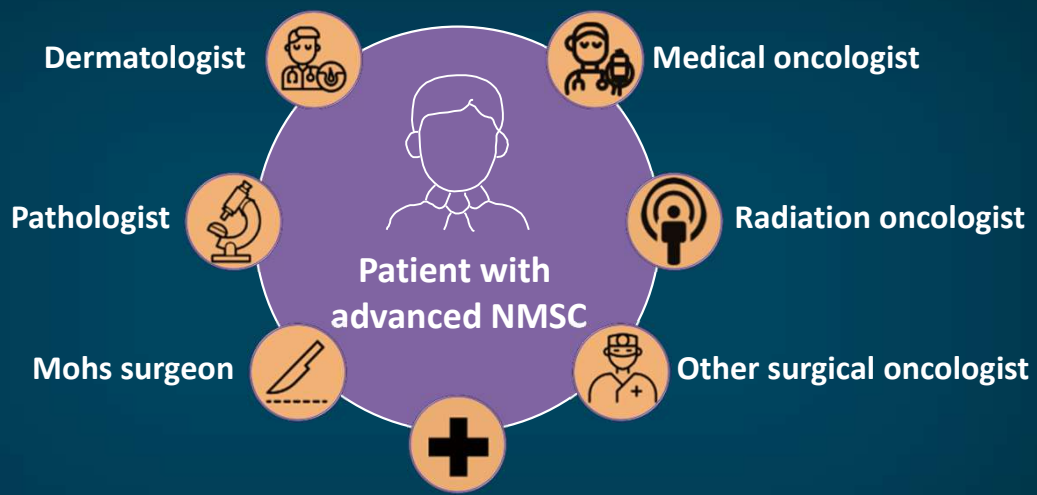
NMSC = non-melanoma skin cancer.

1. Sung H, et al. *CA Cancer J Clin*. 2021:71:209-249. 2. Verkouteren JAC, et al. *Br J Dermatol*. 2017;177:359-372. 3. Karia PS, et al. *J Am Acad Dermatol*. 2013;68:957-966. 4. Weinberg AS, et al. *Dermatol Surg*. 2007;33:885-899. 5. Alam M, et al. *J Am Acad Dermatol*. 2018;78(3):560-578.

## *When Surgery Is Not Enough or Not Possible*

# Multidisciplinary Need for Treatment for Advanced NMSC

## Multidisciplinary Team




NMSC = non-melanoma skin cancer.

Negbenebor NA. *Cutis*. 2021;107:E22-E23.

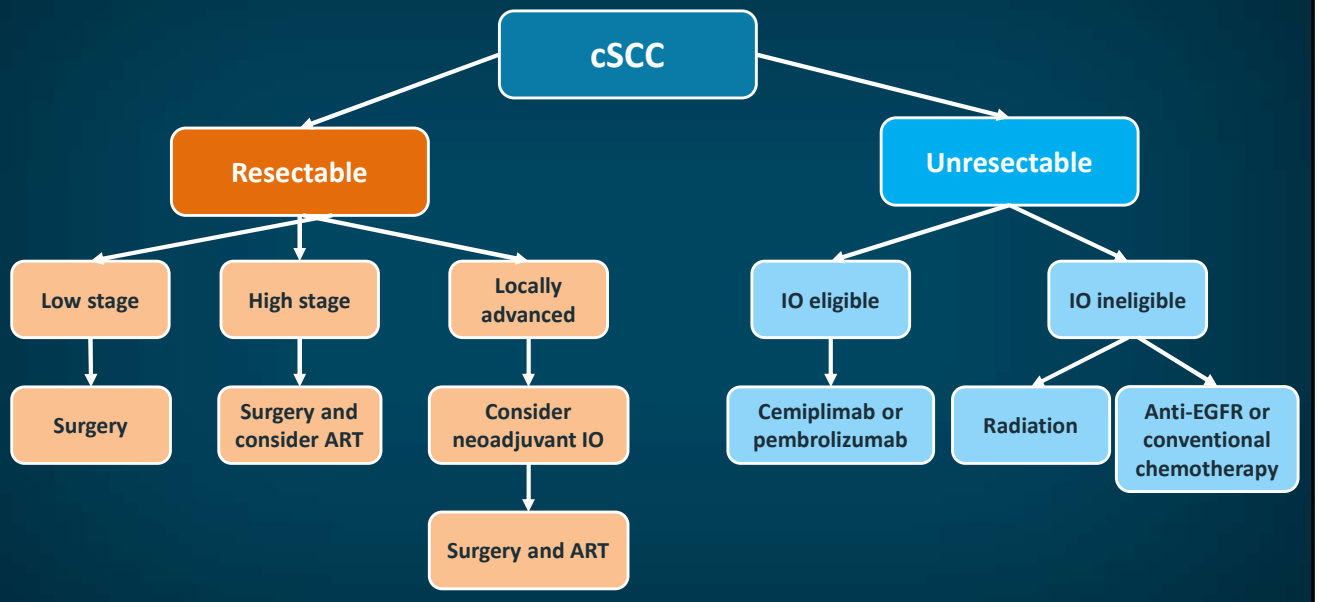
## The Need for a Multidisciplinary Approach

- Advanced cSCC and BCC (particularly locally advanced) are multifaceted
- Wide range of presentations and responses to treatment
- Multidisciplinary care is critical to optimal patient management
- Requires skills and expertise across many subspecialists who need to work in coordination
- Patient perspective is important to ensure treatment choices match patient goals of therapy

BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma.

Negbenebor NA. *Cutis*. 2021;107:E22-E23.

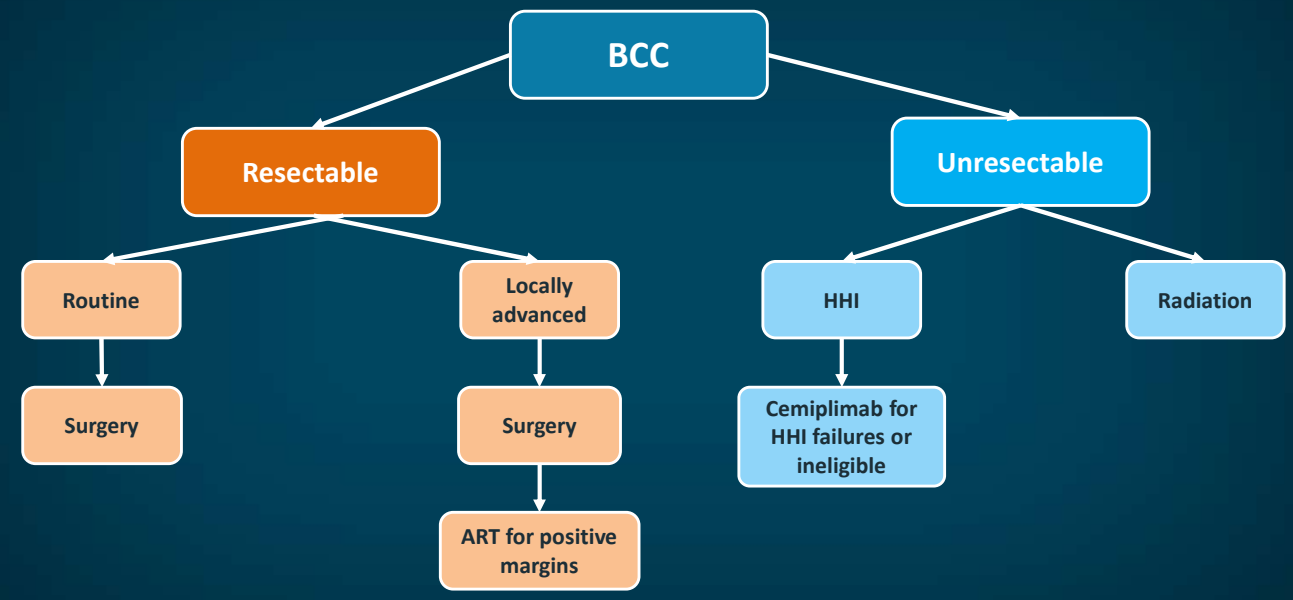
## Proposed Treatment Algorithm: cSCC




ART = adjuvant radiation therapy; cSCC = cutaneous squamous cell carcinoma; EGFR = epidermal growth factor receptor; IO = immunotherapy.

*Flowchart courtesy of Dr Emily Ruiz.*

## Proposed Treatment Algorithm: BCC




ART = adjuvant radiation therapy; BCC = basal cell carcinoma; HHI = hedgehog inhibitor.
*Flowchart courtesy of Dr Emily Ruiz.*

## Radiation Therapy

## Definitive/Salvage RT in BCC and cSCC

- Locoregional control of 58% for tumors ≥T2 and/or node-positive[1]

| Tumor characteristic[2] | Cure rate with RT |
|---|---|
| Size <1.0 cm, low-risk, nonaggressive | 97.8% |
| Size 1.0 to 3.0 cm | 80%-90% |
| Incidental perineural invasion | 80% |
| >3.0 cm or recurrent tumors | 50%-88% |
| Locally advanced | 55% |

BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma; RT = radiation therapy.

1. Kwan W, et al. *Int J Radiat Oncol Biol Phys*. 2004;60:406-411. 2. Adapted from Parikh SA, et al. *F1000Prime Rep*. 2014;6:70.

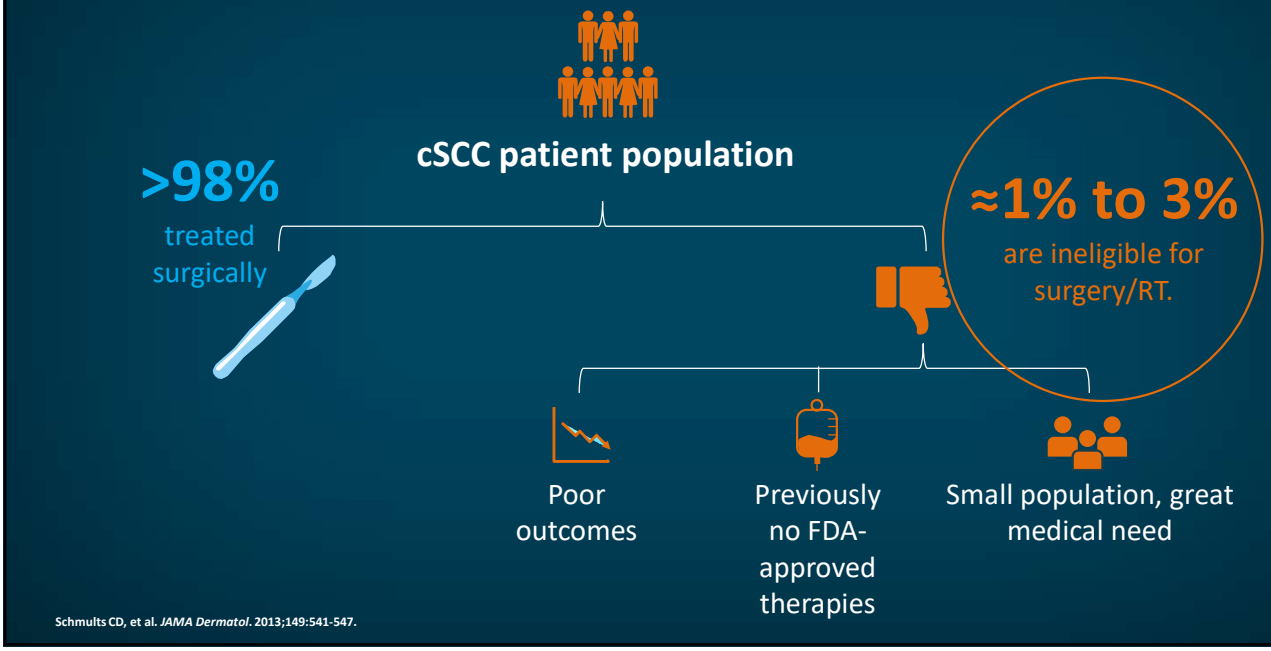
## Polling Question

What percentage of patients with cSCC do you believe are ineligible for surgery/RT?

a) 0% to 0.5%
b) 0.5% to 1%
c) 1% to 3%
d) 3% to 5%
e) 5% to 10%

cSCC = cutaneous squamous cell carcinoma; RT = radiation therapy.

## Ineligible for Surgery or RT




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

## Determining Ineligibility for Surgery or RT

**Procedural and clinical logistics**

Can the patient tolerate the procedure and reconstruction?

- For example, craniectomy or free-flap reconstruction in patients with significant comorbidities can be too challenging

**Location and functionality**

Is the tumor large or deep such that surgery will lead to significant morbidity (eg, vision loss)?

**Confidence**

Is there low confidence in obtaining clear margins? Would a new surgical approach lead to cure? What is the effect of surgery on in-transit metastasis?

**Spread**

Has the tumor spread to multiple lymph nodes or distant organs?

**Radiation therapy**

Does the patient have any contraindications for RT?

RT = radiation therapy.

1. Boutros A, et al. *Front Oncol*. 2021;11:733917. 2. National Comprehensive Cancer Network (NCCN). Guidelines for squamous cell skin cancer. 2023 (https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf). Accessed 5.19.2023.

# *Systemic Therapy for Advanced/Metastatic NMSC*

## Pre-Immune Checkpoint Inhibitor (ICI) Systematic Therapies for cSCC

# (Pre-ICI) cSCC Treatment Landscape

- Until recently, there has not been an FDA-approved or guideline-recommended standard of care for nonoperable advanced or distant metastatic cSCC[1]
- Standard of care provided with cisplatinum monotherapy, cisplatinum plus 5-FU, taxanes, or EGFR inhibitors such as cetuximab[1,2]

**5-FU, cetuximab, bleomycin and cisplatin are not FDA-approved for this indication.*

5-FU = 5-fluorouracil; cSCC = cutaneous squamous cell carcinoma; EGFR = epidermal growth factor receptor; FDA = United States Food and Drug Administration; ICI = immune checkpoint inhibitor; NCCN = National Comprehensive Cancer Network.

1. Boutros A, et al. *Front Oncol.* 2021;11:733917. 2. NCCN. Guidelines for squamous cell skin cancer. 2023 (https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf). Accessed 5.19.2023.

# Classic Chemotherapy

## Prospective studies of systemic therapies in advanced cSCC or mcSCC

| Reference | Trial design | Patients | Chemotherapy | RR | Comments |
|---|---|---|---|---|---|
| **Chemotherapy** | | | | | |
| **Cartei et al (2000)** | Prospective observational | 14 | Oral 5-FU* 175 mg/m$^2$ for 3 weeks every 5 weeks | 2 PR (14.3%)<br>7 SD (50%) | Aggressive, multiple, recurrent SCCs in aged patients |
| **Sadek et al (1990)** | Prospective observational | 14/13 evaluable | Cisplatin* bolus injection; 5-FU* and bleomycin* continuous 5-day infusion | 4 CR (30%)<br>7 PR (54%)<br>2 SD (16%) | Advanced SCC of the skin or lip |
| **Guthrie et al (1990)** | Prospective observational | 12 | Cisplatin* and doxorubicin (n = 7)<br>Neoadjuvant to surgery or radiation (n = 5) | 4 CR (33%)<br><br>3 PR (25%) | None |
| **Khansur et al (1991)** | Prospective observational | 7 | Cisplatin* and 5-FU* every 21 days | 3 CR (43%)<br>3 PR (43%)<br>1 SD (14%) | None |
| **No authors listed, 1976** | Phase 3 randomized control trial | 70 advanced SCC; 6 cSCCs | Bleomycin* twice weekly vs other cytotoxic drugs | 39% RR | Only 3 patients with cSCC in the treatment arm |

5-FU = 5-fluorouracil; CR = complete response; cSCC = cutaneous squamous cell carcinoma; mcSCC = metastatic cSCC; PR = partial response; RR = response rate; SD = stable disease.

*Not FDA-approved for this indication.

Adapted from Stratigos A, et al. *Eur J Cancer*. 2015;51:1989-2007.

# "Druggable" Driver Mutation in cSCC?

## NO

Benign → Cancer

| CSD skin | AK/SCCIS | Invasive SCC | Metastatic SCC |
|---|---|---|---|
| **Frequently mutated genes** | | | |
| TP53 NOTCH1 NOTCH2 CDKN2A HRAS KNSTRN CARD11 | TP53 NOTCH1 NOTCH2 CDKN2A HRAS EGFR KNSTRN CARD11 | TP53 ATM NOTCH1 NOTCH2 PIK3CA CDKN2A CCND1 HRAS EGFR AJUBA FBXW7 KMT2C ERBB4 CASP8 PTCH1 FAT1 NF1 PARD3 TERT RASA1 p300 KMT2D PTEN BRCA2 CARD11 NFkB | TP53 CDKN2A NOTCH1 NOTCH2 PIK3CAHRAS EGFR BRAF KRAS FGFR3 KIT ERBB4 MTOR EZH2 HGF CARD11 |
| **Differentially expressed miRNAs** | | | |
| | | **Upregulation** of let-7a, miR-365, miR-9, miR-21, miR-135b, miR-424, miR-766, miR-31, and miR-223<br>**Downregulation** of miR-125b, miR-34, miR-124, miR-483-3p, miR-193b/365a, miR-30a*, miR-378, miR-145, miR-140-3p, miR-30a, miR-26a MiRNA-125a, let-7b, let-7c let-7d, let-7f, let-7g, miR-99a, miR-99b, miR-100, miR-101, and miR-143 | **Upregulation** of miR-4286, miR-200a-3p, miR-148a-3p<br>**Downregulation** of miR-1915-3p, miR-205-5p, miR-4516, and miR-150-5p |
| **Cytogenetic alterations** | | | |
| | | **Gains** of 3q, 7, 8q, 9, 9q, 11q, 14, and 20<br>**Loss** of 2q, 3p, 4, Sa, 8p, 9p, 11, 13, 17p, 18, 19, and 21<br>**Allelic gain** on 3q, 8q, and 11q<br>**Isochromosomes** 3q, 8q, and 9q<br>**Microdeletion** of 9p23, 9p21.2 or 9p21.3, 3p14.2 | **Gains** of 3q, 7, 8q, 9, 9q, 11q, 14, and 20<br>**Loss** of 2q, 3p, 4, 5q, 8p, 9p, 11, 13, 17p, 18, 19, and 21<br>**Microdeletion** of 9p23, 9p21.2 or 9p21.3 |
| **Epigenetic changes** | | | |
| **Methylation** of DAPK1 | **Methylation** of DAPK1 | **Methylation** of CDH13, CDKN2A | **Hypermethylation** of 9923, TFAP2C, and ASCL2<br>**Hypomethylation** of ACTG2 |

AK = actinic keratosis; CSD = cumulative sun damage; cSCC = cutaneous squamous cell carcinoma; miRNA = microRNA; SCCIS = SCC in situ.

Personal communication from Mike Wong, MD.

# Targeted Therapies

## Clinical trials of targeted therapies in cSCC

| Drug | Treatment | Conditions | NCT code |
|---|---|---|---|
| **Cetuximab*** | Alone | lacSCC and mcSCC surgically unresectable | NCT00240682 |
| | Alone | lacSCC and mcSCC surgically unresectable | NCT03325738 |
| | Alone (neoadjuvant therapy) | Aggressive lacSCC | NCT02324608 |
| | Combination with postoperative radiation | Locally advanced head and neck cSCC | NCT01979211 |
| | Combination with pembrolizumab | Recurrent/metastatic cSCC | NCT03082534 |
| | Combination with lenvatinib | Advanced cSCC | NCT03524326 |
| | Combination with avelumab | Advanced cSCC | NCT03944941 |
| **Gefitinib*** | Alone (neoadjuvant therapy) | Locally advanced/recurrent cSCC | NCT00126555 |
| | Alone | Metastatic or locoregional recurrent | NCT00054691 |
| **Erlotinib*** | Alone | Recurrent/metastatic cSCC | NCT01198028 |
| | Combination with RT | Advanced head and neck cSCC | NCT00369512 |
| | Alone (before surgery) | Head and neck cSCC | NCT00954226 |
| **Cobimetinib*** | Combination with atezolizumab* | cSCC | NCT03108131 |

cSCC = cutaneous squamous cell carcinoma; lacSCC = locally advanced cSCC; mcSCC = metastatic cSCC; NCT = National Clinical Trial; RT = radiation therapy.

*Not FDA-approved for this indication.

Corchado-Cobos R, et al. *Int J Mol Sci.* 2020;21:2956.

# IacSCC and mcSCC

**Radiation therapy**

**Cisplatin-based chemotherapy***

- No established standard regimen, short-lived responses, toxic[1-3]

**Molecular targeted therapies**

- Cetuximab*: ORR = 28%, DCR = 69%, median PFS = 4.1 months[3]
- Panitumumab*: ORR = 31%, DCR = 69%[4]
- Dacomitinib* (pan-HER inhibitor): ORR = 28%, DCR = 86%[5]
- Gefitinib* and erlotinib* (selective EGFR TKIs): ORR = 16% and 10%, respectively[6,7]
- Lapatinib* (dual EGFR TKI inhibitor): Reduction in tumor size in 2 of 8 patients with neoadjuvant therapy[8]

**Immunotherapies**

- Change of immunosuppressive medications in OTRs to mTOR inhibitors[2]
- PD-1 antibodies[1,9]

cSCC = cutaneous squamous cell carcinoma; DCR = disease control rate; EGFR = epiderma growth factor receptor; laSCC = locally advanced cSCC; mcSCC = metastatic cSCC; mTOR = mammalian target of rapamycin; ORR = objective response rate; OTR = organ transplant recipient; PD-1 = programmed cell death 1; PFS = progression- free survival; TKI = tyrosine kinase inhibitor.

*Not an FDA-approved indication.

1. Alam M, et al. *J Am Acad Dermatol*. 2018;78(3):560-578. 2. NCCN. Guidelines for squamous cell skin cancer. 2023 (https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf). Accessed 5.19.2023. 3. Maubec E, et al. *J Clin Oncol*. 2011;29:3419-3426. 4. Foote MC, et al. *Ann Oncol*. 2014;25:2047-2052. 5. Bossi P, et al. American Society of Clinical Oncology (ASCO) 2017; Abstract 9543. 6. William WN Jr, et al. *J Am Acad Dermatol*. 2017;77: 1110-1113.e2. 7. Gold KA, et al. *Cancer*. 2018;124:2169-2173. 8. Jenni D, et al. *ESMO Open*. 2016;1:e000003. 9. Boutros A, et al. *Front Oncol*. 2021;11:733917.

# IacSCC and mcSCC: Systemic Therapy Guideline Recommendations

- Cemiplimab and pembrolizumab are recommended for patients with lacSCC or mcSCC who are not candidates for curative surgery or curative RT[1]
  - Given the risk of organ rejection in solid OTRs, weigh risks and benefits[1]
- Limited evidence (may be combined with radiation) for off-label use of
  - Cetuximab (EGFR inhibitor)[1,2]
  - Platinum-based chemotherapy (eg, cisplatin or carboplatin) as single agent or with 5-FU[1,2]

5-FU = 5-fluorouracil; cSCC = cutaneous squamous cell carcinoma; EGFR = epidermal growth factor receptor; laSCC = locally advanced cSCC; mcSCC = metastatic cSCC; OTR = organ transplant recipient; RT = radiation therapy.

1. NCCN. Guidelines for squamous cell skin cancer. 2023 (https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf). Accessed 5.19.2023. 2. Alam M, et al. *J Am Acad Dermatol*. 2018;78:560-578.

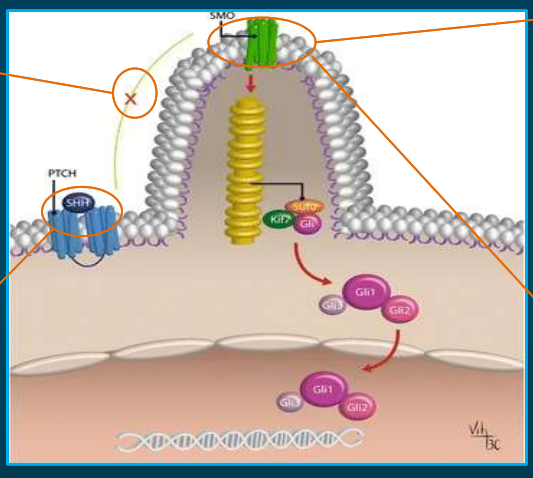
# Pre-ICI Systemic Therapies for BCC

We will now watch an animation on the pathogenesis of BCC and how the hedgehog and immune pathways can be targeted for treatment.

# Sonic Hedgehog Pathway: Common Mutation in BCC

2 In response to this binding, PTCH no longer inhibits SMO

1 Pathway activation occurs when SHH binds to PTCH at cell membrane




3 SMO accumulates at primary cilium and initiates downstream signaling cascade

4 Therefore, inhibiting SMO deactivates carcinogenesis cascade

BCC = basal cell carcinoma; PTCH = patched (multitransmembrane protein); SHH = sonic hedgehog; SMO = smoothened (key transmembrane protein).

Carballo GB, et al. *Cell Commun Signal.* 2018;16:11.

## Vismodegib: Hedgehog-Pathway Inhibitor

- Indications[1]
  - mBCC
  - laBCC that has recurred following surgery or in those who are not candidates for surgery/radiation
- Dosage: Oral, 150 mg once daily[1]
- Contraindications: None[1]
- Boxed warning: Embryo-fetal toxicity[1]

| | mBCC (n = 33) | laBCC (n = 63) |
|---|---|---|
| ORR[2] | 30% | 43% |
| CR | 0% | 21% |
| PR | 30% | 22% |
| Median DOR | 7.6 months | 7.6 months |

BCC = basal cell carcinoma; CR = complete response; DOR = duration of response; laBCC = locally advanced BCC; mBCC = metastatic BCC; ORR = overall response rate; PR = partial response.

1. Vismodegib (Erivedge®) PI 2023 (https://www.gene.com/download/pdf/erivedge_prescribing.pdf). Accessed 5.19.2023. 2. Sekulic A, et al. *N Engl J Med*. 2012;366:2171-2179.

## Sonidegib: Hedgehog-Pathway Inhibitor

- Indications[1]
  - laBCC that has recurred following surgery or in those who are not candidates for surgery/radiation
- Dosage: Oral, 200 mg once daily[1]
- Contraindications: None[1]
- Boxed warning: Embryo-fetal toxicity[1]

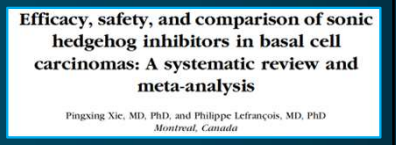
| | laBCC (n = 66) |
|---|---|
| ORR[2] | 56.1% |
| CR | 4.5% |
| PR | 51.5% |
| Median DOR | 26.1 months |

BCC = basal cell carcinoma; CR = complete response; DOR = duration of response; laBCC = locally advanced BCC; ORR = overall response rate; PR = partial response.

1. Sonidegib (Odomzo®) PI 2022 (https://www.odomzo.com/themes/custom/odomzo/global/pdfs/pi.pdf). Accessed September 6, 2022. 2. Lear JT, et al. *J Eur Acad Dermatol Venereol*. 2018;32:372-381.

## Summary: Sonic Hedgehog Inhibitors in BCC

- 16 studies: Quantitative meta-analysis of safety and efficacy
- **laBCC**
  - ORR: Vismodegib and sonidegib comparable (69% vs 57%)
  - CR rate: Higher with vismodegib than sonidegib (31% vs 3%)
- **mBCC**
  - ORR: Higher with vismodegib than sonidegib (39% vs 15%)
- Side effects (pooled prevalence)
  - 67%, 54%, and 58% for muscle spasms, dysgeusia, and alopecia, respectively; comparable between sonidegib and vismodegib
  - More upper gastrointestinal distress with sonidegib than with vismodegib
- Vismodegib favored over sonidegib in clinical practice


Efficacy, safety, and comparison of sonic hedgehog inhibitors in basal cell carcinomas: A systematic review and meta-analysis

Pingxing Xie, MD, PhD, and Philippe Lefrançois, MD, PhD
*Montreal, Canada*

BCC = basal cell carcinoma; CR = complete response; laBCC = locally advanced BCC; mBCC = metastatic BCC; ORR = overall response rate.

Xie P, Lefrançois P. *J Am Acad Dermatol*. 2018;79:1089-1100.e17.

## SHH Inhibitor Side Effects

- HHI side effects are not life-threatening but are nearly universal and often severe[1-5]
- High rate of discontinuation due to AEs in clinical trials (12% to 38%)[1-4]
  - Debilitating muscle pain/cramping[1-5]
  - Loss of taste leading to major weight loss[1-5]
  - Hair loss is often extensive[1-5]
- Alternatives to daily dosing are often used (though minimally studied)[5]
  - Impact on efficacy is unknown but such modifications are often needed to remain on treatment[3,5]

AE = adverse event; HHI = hedgehog pathway inhibitor; SHH = sonic hedgehog.

1. Migden MR, et al. *Lancet Oncol*. 2015;16:716-728. 2. Dummer R, et al. *Br J Dermatol*. 2020;182:1369-1378. 3. Sekulic A, et al. *BMC Cancer*. 2017;17:332. 4. Sekulic A, et al. *N Engl J Med*. 2012;366:2171-2179. 5. Villani A, et al. *Dermatol Ther* (Heidelb). 2020;10:401-412.

## Interval Q & A

## Immunotherapy in NMSC

We will now watch an animation on the pathogenesis of cSCC and targeting the PD-1/PD-L1 pathway with immunotherapy to overcome cytotoxic T-cell suppression by tumor cells.

# Immunotherapeutic Options for Advanced/Metastatic NMSCs

## FDA-Approved Immunotherapy Agents for Advanced NMSC

| | Cemiplimab | Pembrolizumab | Avelumab | Retifanlimab |
|---|---|---|---|---|
| Locally advanced and metastatic cSCC | ✓ | ✓ | | |
| Metastatic MCC | | ✓ | ✓ | ✓ |
| Locally advanced MCC | | ✓ | | ✓ |
| Unresectable/metastatic solid tumors—MSI high or MMR-deficient | | ✓ | | |
| Solid tumors—TMB high | | ✓ | | |
| Locally advanced/ metastatic BCC | ✓ | | | |

BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma; FDA = United States Food and Drug Administration; lacSCC = locally advanced cSCC; MCC = Merkel cell carcinoma; mcSCC = metastatic cSCC; MMR = mismatch repair; MSI = microsatellite instability; NMSC = non-melanoma skin cancer; TMB = tumor mutation burden.

Adapted from Shalhout SZ, et al. *Curr Oncol Rep.* 2021;23:125. US FDA. FDA grants accelerated approval to retifanlimab-dlwr for metastatic or recurrent locally advanced Merkel cell carcinoma. 3.22.2023 (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-retifanlimab-dlwr-metastatic-or-recurrent-locally-advanced-merkel). Accessed 5.19.2023.

# Final Analysis From EMPOWER-CSCC-1 Groups 1, 2, and 3

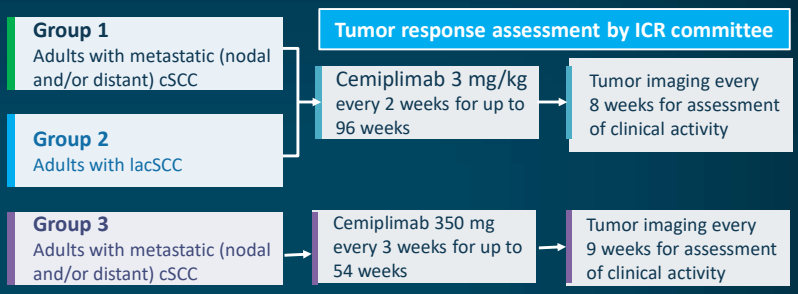
## *Phase 2 Study of Cemiplimab in Patients With Advanced cSCC*

### Key inclusion criteria

- ECOG PS of 0 to 1
- Adequate organ function
- Groups 1 and 3
  - At least 1 measurable lesion by RECIST
- Group 2
  - At least 1 lesion by digital medical photography
  - cSCC lesion not amenable to surgery or radiation therapy per investigator's assessment

### Key exclusion criteria

- Ongoing or recent (within 5 years) autoimmune disease requiring systemic immunosuppression
- Prior treatment with anti-PD-1 or anti-PD-L1 therapy
- History of solid organ transplant, concurrent malignancies, or hematologic malignancies




**Primary objective:** To assess clinical benefits of cemiplimab as measured by ORR per ICR

**Key secondary objectives:** DOR, PFS, OS, CRR, safety, and tolerability

CRR = complete response rate; cSCC = cutaneous squamous cell carcinoma; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; ICR = independent central review; lacSCC = locally advanced CSCC; ORR = overall response rate; OS = overall survival; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PS = performance status; RECIST = Response Evaluation Criteria in Solid Tumors.

Migden MR, et al. European Society for Medical Oncology (ESMO) Congress 2022; Presentation 814P.

# EMPOWER-CSCC-1
# Tumor Response per ICR

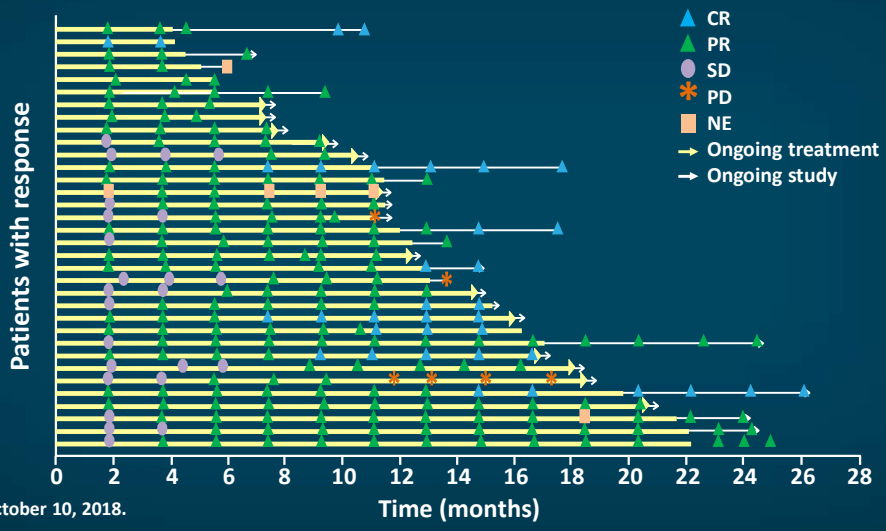
| | Group 1 (mcSCC) 3 mg/kg every 2 weeks (n = 59) | Group 2 (lacSCC) 3 mg/kg every 2 weeks (n = 78) | Group 3 (mcSCC) 350 mg every 3 weeks (n = 56) | Total (n = 193) |
|---|---|---|---|---|
| Median duration of follow-up, months (range) | 18.5 (1.1-41.0) | 15.5 (0.8-43.2) | 17.3 (0.6-43.4) | 15.7 (0.6-43.4) |
| ORR, % (95% CI) | 50.8 (37.5, 64.1) | 44.9 (33.6, 56.6) | 46.4 (33.0, 60.3) | 47.2 (39.9, 54.4) |
| CR, n (%) | 12 (20.3) | 10 (12.8) | 11 (19.6) | 33 (17.1) |
| PR, n (%) | 18 (30.5) | 25 (32.1) | 15 (26.8) | 58 (30.1) |
| Median DOR, months (95% CI) | NR (20.7, NE) | 41.9 (20.5, 54.6) | 41.3 (40.8, 46.3) | 41.3 (38.8, 46.3) |
| Median PFS, months (95% CI) | 18.4 (7.3, 53.2) | 18.5 (11.1, 43.8) | 21.7 (3.8, 43.3) | 22.1 (10.4, 32.3) |
| Median OS, months (95% CI) | 57.7 (29.3, NE) | NR (58.3, NE) | 48.4 (29.5, NE) | NR (56.0, NE) |

CR = complete response; mcSCC = metastatic cSCC; NE = not evaluable; NR = not reached; PR = partial response.

Migden MR, et al. ESMO Congress 2022; Presentation 814P.

# Cemiplimab in lacSCC: DOR

## Time to and duration of response in lacSCC



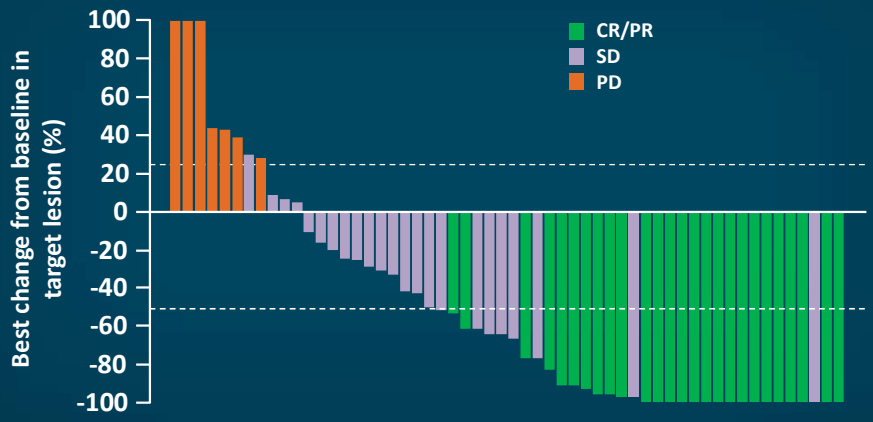

Data cut-off date: October 10, 2018.

CR = complete response; DOR = duration of response; lacSCC = locally advanced cutaneous squamous cell carcinoma; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Migden MR, et al. *Lancet Oncol.* 2020;21:294-305.

# Cemiplimab in lacSCC

## lacSCC response to cemiplimab (response by medical photography using modified WHO criteria)




Data cut-off date: October 10, 2018.

CR = complete response; lacSCC = locally advanced cutaneous squamous cell carcinoma; PD = progressive disease; PR = partial response; SD = stable disease; WHO = World Health Organization.

Migden MR, et al. *Lancet Oncol.* 2020;21:294-305.

# Cemiplimab: Adverse Events

| TEAEs (regardless of attribution) in lacSCC (N = 78)[1] | Any grade n (%) | Grade ≥3 n (%) |
|---|---|---|
| Any | 77 (99.0) | 39 (50.0) |
| Led to discontinuation | 6 (7.7) | 5 (6.4) |
| Death as outcome | 2 (2.6) | 2 (2.6) |

| TEAEs (regardless of attribution) in mcSCC (N = 59)[2] | Any grade n (%) | Grade ≥3 n (%) |
|---|---|---|
| Any | 59 (100.0) | 30 (50.8) |
| Serious | 24 (40.7) | 20 (33.9) |
| Led to discontinuation | 6 (10.2) | 4 (6.8) |

AE = adverse event; cSCC = cutaneous squamous cell carcinoma; lacSCC = locally advanced cSCC; mcSCC = metastatic cSCC; TEAE = treatment-emergent AE.

1. Migden MR, et al. *Lancet Oncol*. 2020;21:294-305. 2. Rischin D, et al. *J Immunother Cancer*. 2020;8:e000775.

# Cemiplimab: Adverse Events

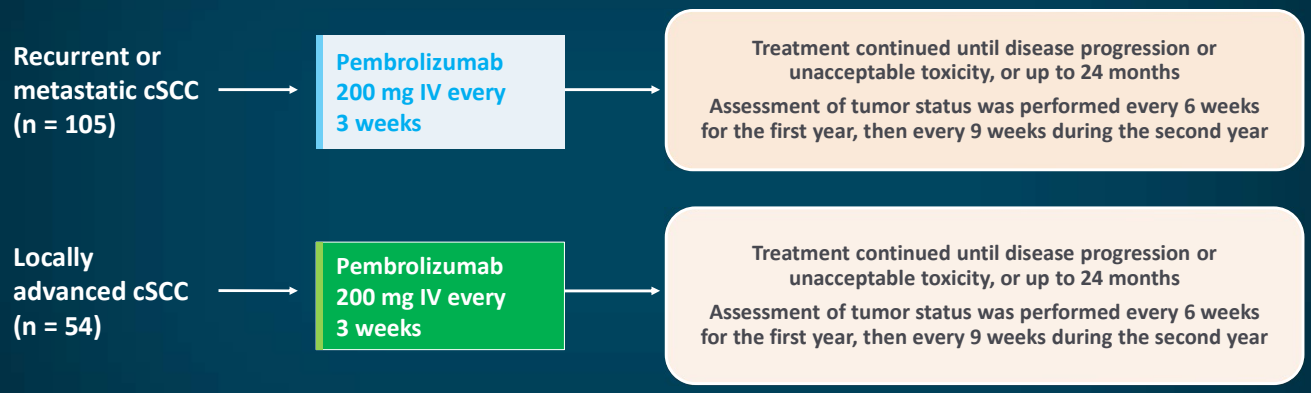
| TEAEs (regardless of attribution) in lacSCC (N = 78)[1] | Any grade, n (%) | Grade ≥3, n (%) |
|---|---|---|
| Any | 77 (99.0) | 39 (50.0) |
| Serious | 23 (29.5) | 19 (24.4) |
| Led to discontinuation | 6 (7.7) | 5 (6.4) |
| Death as outcome | 2 (2.6) | 2 (2.6) |
| **Occurred in ≥7 patients by any grade** | | |
| Fatigue | 32 (41.0) | 1 (1.3) |
| Diarrhea | 21 (26.9) | 0 |
| Pruritus | 21 (26.9) | 0 |
| Nausea | 17 (21.8) | 0 |
| Cough | 15 (19.2) | 0 |
| Abdominal pain | 11 (14.1) | 0 |
| Rash | 10 (12.8) | 0 |
| Vomiting | 9 (11.5) | 1 (1.3) |
| Actinic keratosis | 8 (10.3) | 0 |
| Anemia | 8 (10.3) | 1 (1.3) |
| Back pain | 8 (10.3) | 0 |
| Constipation | 8 (10.3) | 0 |
| Dry skin | 8 (10.3) | 0 |
| Hypothyroidism | 8 (10.3) | 0 |
| Maculopapular rash | 8 (10.3) | 0 |
| Arthralgia | 7 (8.9) | 1 (1.3) |
| BCC | 7 (8.9) | 1 (1.3) |

| TEAEs (regardless of attribution) in mcSCC (N = 59)[2] | Any grade, n (%) | Grade ≥3, n (%) |
|---|---|---|
| Any | 59 (100.0) | 30 (50.8) |
| Serious | 24 (40.7) | 20 (33.9) |
| Led to discontinuation | 6 (10.2) | 4 (6.8) |
| **Occurred in ≥6 patients by any grade** | | |
| Diarrhea | 17 (28.8) | 1 (1.7) |
| Fatigue | 15 (25.4) | 1 (1.7) |
| Nausea | 14 (23.7) | 0 |
| Headache | 11 (18.6) | 0 |
| Constipation | 10 (16.9) | 1 (1.7) |
| Pruritus | 10 (16.9) | 0 |
| Rash | 10 (16.9) | 0 |
| Arthralgia | 9 (15.3) | 0 |
| Cough | 9 (15.3) | 0 |
| Decreased appetite | 8 (13.6) | 0 |
| Maculopapular rash | 8 (13.6) | 0 |
| Anemia | 7 (11.9) | 2 (3.4) |
| Dizziness | 7 (11.9) | 0 |
| Dry skin | 6 (10.2) | 0 |
| Dyspnea | 6 (10.2) | 2 (3.4) |
| Hypothyroidism | 6 (10.2) | 0 |
| Oropharyngeal pain | 6 (10.2) | 0 |
| Pneumonitis | 6 (10.2) | 3 (5.1) |
| URTI | 6 (10.2) | 0 |
| Vomiting | 6 (10.2) | 0 |

BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma; lacSCC = locally advanced cSCC; mcSCC = metastatic cSCC; TEAE = treatment emergent adverse event; URTI = upper respiratory tract infection.

1. Migden MR, et al. *Lancet Oncol*. 2020;21:294-305. 2. Rischin D, et al. *J Immunother Cancer*. 2020;8:e000775.

# KEYNOTE-629: Single-Arm Phase 2 Trial of Pembrolizumab Monotherapy for Locally Advanced and Recurrent or Metastatic cSCC




**Endpoints:**
Primary: ORR, defined as percentage of patients with a CR or PR by BICR per RECIST 1.1
Secondary: DOR, DCR, PFS, OS, and safety and tolerability

BICR = blinded independent central review; CR = complete response; DCR = disease control rate; PR = partial response.

Hughes BGM, et al. *Ann Oncol*. 2021;32:1276-1285.

# KEYNOTE-629: Pembrolizumab in cSCC

- ORR was 34.3% (3.8% achieved CR, 30.5% achieved PR)
- Median PFS was 6.9 months
- 12-month PFS rate of 32.4%
- Treatment-related AEs occurred in 66.7% of patients
  - 5.7% of patients experienced grade 3-5 treatment-related AEs
  - 1 patient died of treatment-related cranial nerve neuropathy
  - Most common treatment-related AEs were pruritis (14.3%), asthenia (13.3%), and fatigue (12.4%)

AE = adverse event; CR = complete response; cSCC = cutaneous squamous cell carcinoma; ORR = overall response rate; PFS = progression-free survival; PR = partial response.

Grob J-J, et al. *J Clin Oncol*. 2020;38:2916-2925.

# Anti–PD-1 Clinical Trial Data in cSCC

| | Cemiplimab[1,2] | CARSKIN Pembrolizumab[3,4] | KEYNOTE-629 Pembrolizumab[5,6] |
|---|---|---|---|
| **Phase (design)** | 2 (3 cohorts: locally advanced and metastatic) | 2 (single arm: locally advanced and metastatic) | 2 (single arm: recurrent and/or metastatic) |
| **Patients, n** | 193 | 39 + 18 extension | 105 |
| **Extent of disease** | Locally advanced, 40%; metastatic, 60% | Locally advanced, 12%; regional, 63%; distant, 25% | Locally advanced, 45%; distant only, 24%; locoregional and distant, 31.4% |
| **Primary endpoint** | ORR (RECIST v.1.1) | ORR at 15 weeks (RECIST v.1.1) | ORR (RECIST v.1.1) |
| **Follow-up, median, months** | 15.7 | 22.4 | 11.4 |
| **ORR, %** | 46.1 | 42 | 34.3 |
| **CR, %** | By cohort: 20.3, 12.8, 16.1 | 7 | 3.8 |
| **PR, %** | 30.1 | 35 | 30.5 |

CR = complete response; cSCC = cutaneous squamous cell carcinoma; ORR = overall response rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

1. Rischin D, et al. ASCO 2020; Abstract 10018. 2. Rischin D, et al. *J Immunother Cancer.* 2021;9:e002757. 3. Maubec E, et al. ASCO 2019; Abstract 9547. 4. Maubec E, et al. *J Clin Oncol.* 2020;38:3051-3061. 5. Grob J-J, et al. ESMO 2019; Abstract 3622. 6. Grob J-J. *J Clin Oncol.* 2020;38:2916-2925.

# Neoadjuvant Immunotherapy

# Neoadjuvant Cemiplimab

## Open-label, phase 2 Study of stage II-IV (M0) cSCC

- Cemiplimab* 350 mg IV every 3 weeks for up to 4 doses pre-surgery
- Data cutoff date: December 1, 2021; n = 79, median age 73 years, predominantly male (n = 67)
- 70 patients underwent surgery (3 declined, 2 LTFU, 2 inoperable, 2 due to AE)
- Primary endpoint (pCR) met: **pCR + MPR 63.3% by ICPR**

| Response | Number of patients (%) | 95% CI |
|---|---|---|
| pCR | 40 (50.6%) | 39-62 |
| MPR | 10 (13%) | 6-22 |
| ORR | 54 (68%) | 57-78 |
| CR | 5 (6%) | |
| PR | 49 (62%) | |
| Stable disease | 16 (20%) | |
| Progressive disease | 8 (10%) | |
| Not evaluable | 1 (1%) | |

| Adverse events | Number of patients (%) |
|---|---|
| Grade ≥3 | 14 (18%) |
| Death due to AE† | 4 (5%) |
| Most common AEs (all grades) | |
| Fatigue | 24 (30%) |
| Maculopapular rash | 11 (14%) |
| Diarrhea | 11 (14%) |
| Nausea | 11 (14%) |

† *1 due to exacerbation of cardiac failure, 2 MI, 1 COVID-19 pneumonia.*

AE = adverse event; CI = confidence interval; CR = complete response; cSCC = cutaneous squamous cell carcinoma; ICPR = independent central pathologic review; IV = intravenously; LTFU = lost to follow-up; MPR = major pathologic response (≤10% viable tumor); MI = myocardial infarction; ORR = overall response rate; pCR = pathologic CR; PR = partial response.

Gross N, et al. ESMO 2022; Abstract 789O. Gross ND, et al. *N Engl J Med.* 2022;387:1557-1568.

**Cemiplimab is not FDA-approved for neoadjuvant cSCC.*

# Immunotherapy for Advanced BCC

## Cemiplimab for Advanced BCC

- First FDA-approved immunotherapy for BCC (locally advanced/metastatic cases previously treated with HHI or for whom HHI not appropriate)[1]
- Also indicated for mcSCC and lacSCC[2]

| Cemiplimab in patients not tolerating or progressing on HHI[1,2] | | |
|---|---|---|
| | laBCC (n = 84) | mBCC (n = 28) |
| ORR, % | 29 | 21 |
| CR, % | 6 | 0 |
| PR, % | 23 | 21 |
| DOR, months | NR (2.1-21.4+) | NR (9.0-23.0+) |

BCC = basal cell carcinoma; CR = complete response; DOR = duration of response; FDA = United States Food and Drug Association; HHI = hedgehog inhibitor; laBCC = locally advanced BCC; lacSCC = locally advanced cutaneous squamous cell carcinoma; mBCC = metastatic BCC; mcSCC = metastatic cutaneous squamous cell carcinoma; NR = not reached; ORR = overall response rate; PR = partial response.

1. US FDA. Cemiplimab approval for BCC. 2.9.2021 (www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-cemiplimab-rwlc-locally-advanced-and-metastatic-basal-cell-carcinoma). 2. Cemiplimab (Libtayo®) PI 2022 (https://www.regeneron.com/downloads/libtayo_fpi.pdf). URLs accessed 5.19.2023.

## Cemiplimab: Phase 2 Trial in laBCC

- No specific predictors of response
  - TMB
    - Median baseline TMB: 58 (responding; n = 18) and 23 (nonresponding; n = 38) mutations/mb
    - Responses occurred at all TMB levels
  - MHC
    - Downregulation of MHC-I expression may be an immune evasion mechanism in nonresponding BCCs with high TMB
- AEs
  - No new safety signals: Fatigue (30%), diarrhea (24%), pruritus (21%)
  - 11% of patients discontinued due to AEs

AE = adverse event; laBCC = locally advanced basal cell carcinoma; mb = megabase; MHC = major histocompatibility complex; TMB = tumor mutation burden.

Stratigos AJ, et al. *Lancet Oncol.* 2021;22:848-857 and supplement.

## Pembrolizumab ± Vismodegib for Advanced BCC

| | All participants (N = 16) | Pembrolizumab* (n = 9) | Pembrolizumab* + vismodegib (n = 7) |
|---|---|---|---|
| ORR | 38% | 44% | 29% |
| Probability | | | |
| 1-year PFS | 70% | 62% | 83% |
| 1-year OS | 94% | 89% | 100% |

- No life-threatening AEs or deaths during study
- 3 grade 3 AEs occurred out of 98 AEs from 16 participants (1 case of hyponatremia attributed to pembrolizumab)
- Total of 23 irAEs (grade 1 or 2 dermatitis and fatigue most common)

AE = adverse event; BCC= basal cell carcinoma; irAE = immune-related AE; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

Chang AL, et al. *J Am Acad Dermatol*. 2019;80:564-566.

*Pembrolizumab is not currently FDA-approved for BCC.

## Guidelines on Use of Immunotherapy in NMSC

# NCCN Systemic Treatment Guidelines for cSCC

National Comprehensive Cancer Network®

**NCCN Guidelines Version 1.2022**
**Squamous cell skin cancer**

## PRINCIPLES OF SYSTEMIC THERAPY WITH MULTIDISCIPLINARY TEAM CONSULTATION

### Local disease (including multiple primaries) amenable to curative surgery

- Systemic therapy is not recommended

### Primary and recurrent locally advanced disease in nonsurgical candidates

- Residual disease where further surgery is not feasible, recommend RT, consider concurrent systemic therapy in select cases
- Complicated cases of locally advanced disease in which curative surgery and curative RT are not feasible, consider systemic therapy alone

### New regional disease

- For most cases of fully resected regional disease, adjuvant systemic therapy is not recommended, unless within a CT
- Resected high-risk regional disease, consider RT ± systemic therapy
- Unresectable, inoperable, or incompletely resected disease, consider
  - RT + systemic therapy
  - Systemic therapy alone if curative RT not feasible

### Regional recurrence or distant metastatic disease

- For regional recurrence or distant metastases, multidisciplinary team can consider systemic therapy alone or in combination with RT

Cisplatin, 5-FU, cetuximab, carboplatin, paclitaxel, and capecitabine are not FDA-approved for this indication.

cSCC = cutaneous squamous cell carcinoma; CT = clinical trial; RT = radiation therapy.

NCCN. Guidelines for squamous cell skin cancer. V1.2023 (https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf). Accessed 5.19.2023.

# NCCN Systemic Treatment Guidelines for cSCC

National Comprehensive Cancer Network®

**NCCN Guidelines Version 1.2022**
**Squamous cell skin cancer**

## PRINCIPLES OF SYSTEMIC THERAPY WITH MULTIDISCIPLINARY TEAM CONSULTATION

| Systemic therapy options for use with RT | | |
|---|---|---|
| **Preferred regimens**<br>• Cisplatin<br>• Clinical trial | **Other recommended regimens**<br>• None | **Useful in certain circumstances**<br>• EGFR inhibitors (eg, cetuximab)<br>• Cisplatin + 5-FU<br>• Carboplatin + paclitaxel |
| **Options for systemic therapy alone** | | |
| **Preferred regimens**<br>• Cemiplimab-rwlc (if curative RT or surgery is not feasible for locally advanced, recurrent, or metastatic disease)<br>• Pembrolizumab (if curative RT or surgery is not feasible for locally advanced, recurrent, or metastatic disease)<br>• Clinical trial | **Other recommended regimens**<br>• If ineligible for or progressed on immune checkpoint inhibitors and clinical trials, consider<br>▶ Carboplatin + paclitaxel | **Useful in certain circumstances**<br>• If ineligible for or progressed on immune checkpoint inhibitors and clinical trials, consider<br>▶ EGER inhibitors (eg, cetuximab)<br>▶ Capecitabine<br>▶ Cisplatin<br>▶ Cisplatin + 5-FU<br>▶ Carboplatin |

Cisplatin, 5-FU, cetuximab, carboplatin, paclitaxel, and capecitabine are not FDA-approved for this indication.

5-FU = 5-fluorouracil; cSCC = cutaneous squamous cell carcinoma; EGFR = epidermal growth factor receptor; RT = radiation therapy.

NCCN. Guidelines for squamous cell skin cancer. V1.2023. (https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf). Accessed 5.19.2023.

# NCCN Guidelines: BCC

National Comprehensive Cancer Network®

**NCCN Guidelines Version 2023**
**Basal cell skin cancer**

**Approach[1]**

- Systemic therapy may be considered for laBCC and mBCC; it is not used where topical therapy, surgery, or RT is likely to be curative
  - Locally advanced disease is defined by those that have primary or recurrent local disease that are not amenable to surgery or RT
- Systemic therapy may be considered for cases of nodal or distant metastatic disease, especially if surgery and RT are not feasible
- Multidisciplinary consultation may be required to determine the best treatment approach and deem the tumor not amenable to surgery or radiation

**Based on the review of the data in the noted reference, and the recent FDA approval, the panel consensus was to include cemiplimab-rwlc as a systemic therapy option for[2]**

- laBCC if curative surgery and curative RT are not feasible in patients previously treated with an HHI or for whom an HHI is not appropriate; category 2A recommendation
- As a systemic therapy option for patients with nodal or distant mBCC previously treated with an HHI or for whom an HHI is not appropriate; category 2A recommendation

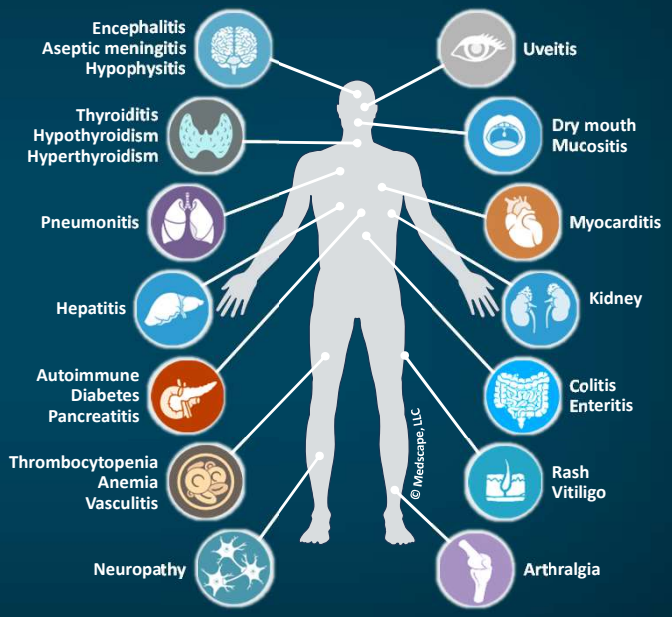
FDA = United States Food and Drug Administration; HHI = hedgehog inhibitor; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; RT = radiation therapy.

1. NCCN. Guidelines for basal cell skin cancer. V1.2023 (https://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf). Accessed 5.19.2023. 2. Stratigos AJ, et al. *Ann Oncol.* 2020;31:S1175-S1176.

# Beyond the Guidelines: Factors That Complicate Treatment Decision-Making

## Immune-Related AEs

- Most commonly occurring irAEs affect
  - Skin, gut, endocrine organs, liver, and lungs[1,2]
- Majority of irAEs occur early
  - Within weeks to months after initiation of ICIs[1]
- First onset of irAEs has been documented as long as 1 year after discontinuation of ICI[1]




AE = adverse event; ICI = immune checkpoint inhibitor; irAE = immune-related adverse event.

1. Haanen JBAG, et al. *Ann Oncol.* 2017;28(suppl 4):iv119-iv142. 2. Postow MA, et al. *N Engl J Med*. 2018;378:158-168.

## Summary

- Advanced NMSC is best managed by a multidisciplinary team
- BCC and cSCC that are advanced resectable, unresectable, and metastatic may benefit from systemic therapy
- Immunotherapy is approved for both BCC and cSCC
  - Pembrolizumab and cemiplimab are approved for cSCC that is unresectable/ metastatic
  - Cemiplimab is approved for BCC that progresses on HHI, is intolerant to HHI, or in patients in which HHI is inappropriate as first-line treatment

BCC = basal cell carcinoma; cSCC = cutaneous squamous cell carcinoma; HHI = hedgehog inhibitor; NMSC = non-melanoma skin cancer.

# *Case Studies*

## Case Study 1:

**67-year-old male with chronic lymphocytic leukemia (CLL) and cSCC with regional metastases**

## Case 1

- A 67-year-old male with CLL on ibrutinib presents with a 3-cm poorly differentiated cSCC on the right temple
- Two 2- to 3-cm parotid lymph nodes are palpated on exam
- Neck computerized tomography scan demonstrated multiple level II to IV cervical nodes as well as supraclavicular nodes, concerning for additional involvement
- Computerized tomography scan of the chest, abdomen, and pelvis revealed numerous ~1-cm nodes in his bilateral axilla and mediastinum consistent with the patient's known CLL
- Fine needle aspiration (FNA) of a level IV lymph node is positive for carcinoma

## Case 1: Question 1


What treatment would you recommend as first-line therapy?

a. Surgical excision of primary with completion lymphadenectomy
b. Primary/definitive radiation
c. Primary/definitive chemoradiation
d. Anti–PD-1 therapy
e. Other

## Case 1 (continued)

- The patient signs consent to start pembrolizumab
- The patient does well for 3 cycles
- During Cycle 4 he develops a grade 2 lichenoid eruption involving the skin of his trunk and upper extremities

## Case 1: Question 2


What would be your next steps in management?

a. Start a class V topical steroid
b. Start oral antihistamine
c. Start oral antihistamine and a class V topical steroid
d. Start oral antihistamine and a class I topical steroid

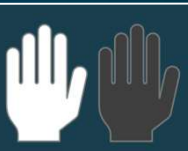
# Clinical Case #2

**55-year-old female with locally advanced BCC on right shoulder**

## Case #2

- A 55-year-old-female presented to the clinic with a 14-cm ulcerated BCC on the right shoulder
- The lesion has been slowly growing for 10 years
- The lesion has not previously been treated
- She has no other comorbidities
- Computed tomography scan of her torso demonstrated no evidence of regional or metastatic disease, but the lesion invades into the scapula and clavicle
- She continues to have the use and function of her right arm

## Case 2: Question 1



Would you consult with, or refer to, other healthcare professionals before making treatment recommendations/ initiating treatment?

a. Dermatology and Medical Oncology
b. Radiation Oncology and Medical Oncology
c. Surgical Oncology and Medical Oncology
d. Surgical Oncology, Medical Oncology, and Radiation Oncology

## Case 2: Question 2

What treatment would you not recommend?

a. Surgical excision
b. Radiation
c. Smoothened inhibitor
d. Anti–PD-1 therapy
e. Other

## Case 2: Question 2

What treatment would you recommend?

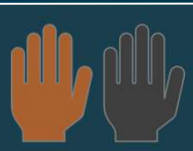
Given that the lesion is locally advanced, but with no evidence of regional or distant disease, surgical therapy would likely offer the best chance of cure. However, given the extensive involvement of both muscle and bone, surgery would likely entail a forequarter amputation. Thus, a patient-centered decision would need to be made regarding patient preferences and priorities. Radiation treatment would be reasonable, though the likelihood of cure given the extent of the disease would be low. Treatment with upfront systemic therapy would be reasonable. If the patient desired systemic therapy, a smoothened inhibitor as first-line treatment would be standard, reserving anti–PD-1 therapy for the refractory setting.

## Case 2: Decision-Making

- Treatment options were discussed with the patient, who inquires as to the percentage of patients that achieved a complete response in the clinical trial that led to the FDA approval of vismodegib
- It is shared that in the ERIVANCE trial, 32% of patients with locally advanced disease treated with vismodegib achieved a complete response
- The patient is started on vismodegib; after 2 months of daily dosing the patient has disease progression, and at this time she would like to avoid a forequarter amputation

## Case 2: Question 3

What would you recommend as next steps for treatment?

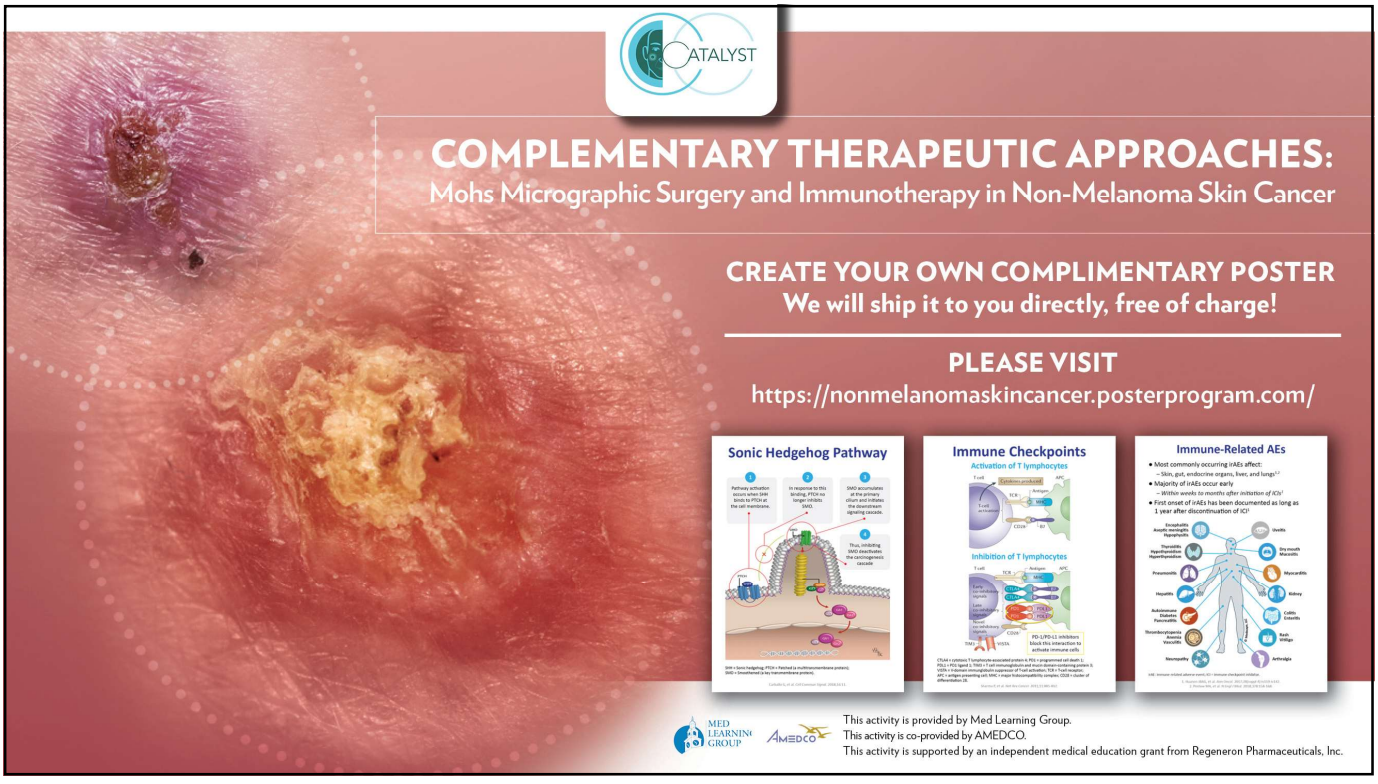


a. Radiation
b. Change to another smoothened Inhibitor
c. Anti–PD-1 therapy
d. Other

## Case 2: Follow-Up

The patient is transitioned to cemiplimab. Over the next year she has slowly improving disease. She tolerates therapy well and is treated to a complete response at 18 months. Cemiplimab is stopped, and she remains disease free today.

# Thank you!
# Questions and Answers




CATALYST
COMPLEMENTARY THERAPEUTIC APPROACHES:
Mohs Micrographic Surgery and Immunotherapy in Non-Melanoma Skin Cancer
VISIT
https://catalyst-skincancers.com/
for more resources and
additional CME programming!
This activity is provided by Med Learning Group.
This activity is co-provided by AMEDCO.
This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc.

## *Complementary Therapeutic Approaches: Mohs Micrographic Surgery and Immunotherapy in Non-Melanoma Skin Cancer*

| Resource | Address |
|---|---|
| **Boutros A, Cecchi F, Tanda ET, et al. Immunotherapy for the treatment of cutaneous squamous cell carcinoma. *Front Oncol.* 2021;11:733917.** | https://pubmed.ncbi.nlm.nih.gov/34513710/ |
| **Carballo GB, Honorato JR, Farias de Lopes GPF, Spohr TCLSE. A highlight on Sonic hedgehog pathway. *Cell Commun Signal*. 2018;16:11.** | https://pubmed.ncbi.nlm.nih.gov/29558958/ |
| **Chang ALS, Tran DC, Cannon JGD, et al. Pembrolizumab for advanced basal cell carcinoma: An investigator-initiated, proof-of-concept study. *J Am Acad Dermatol*. 2019;80:564-566.** | https://www.jaad.org/article/S0190-9622(18)32471-X/fulltext |
| **Corchado-Cobos R, García-Sancha N, González-Sarmiento R, Pérez-Losada J, Cañueto J. Cutaneous squamous cell carcinoma: From biology to therapy. *Int J Mol Sci*. 2020;21:2956.** | https://pubmed.ncbi.nlm.nih.gov/32331425/ |
| **Dummer R, Guminksi A, Gutzmer R, et al. Long-term efficacy and safety of sonidegib in patients with advanced basal cell carcinoma: 42-month analysis of the phase II randomized, double-blind BOLT study. *Br J Dermatol*. 2020;182:1369-1378.** | https://pubmed.ncbi.nlm.nih.gov/31545507/ |
| **Foote MC, McGrath M, Guminski A, et al. Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma. *Ann Oncol*. 2014;25:2047-2052.** | https://pubmed.ncbi.nlm.nih.gov/25091317/ |
| **Gold KA, Kies MS, William WN Jr, et al. Erlotinib in the treatment of recurrent or metastatic cutaneous squamous cell carcinoma: A single-arm phase 2 clinical trial. *Cancer*. 2018;124:2169-2173.** | https://pubmed.ncbi.nlm.nih.gov/29579331/ |
| **Grob JJ, Gonzalez R, Basset-Seguin N, et al. Pembrolizumab monotherapy for recurrent or metastatic cutaneous squamous cell carcinoma: A single-arm phase II trial (KEYNOTE-629). *J Clin Oncol*. 2020;38:2916-2925.** | https://pubmed.ncbi.nlm.nih.gov/32673170/ |
| **Gross ND, Miller DM, Khushalani NI, et al. Neoadjuvant cemiplimab for stage II to IV cutaneous squamous-cell carcinoma. *N Engl J Med.* 2022;87:1557-1568.** | https://pubmed.ncbi.nlm.nih.gov/36094839/ |
| **Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017;28(suppl 4):iv119-iv142.** | https://pubmed.ncbi.nlm.nih.gov/28881921/ |
| **Hughes BGM, Munoz-Couselo E, Mortier L, et al. Pembrolizumab for locally advanced and recurrent/metastatic cutaneous squamous cell carcinoma (KEYNOTE-629 study): An open-label, nonrandomized, multicenter, phase II trial. *Ann Oncol*. 2021;32:1276-1285.** | https://pubmed.ncbi.nlm.nih.gov/34293460/ |

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|---|---|
| **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.** | https://pubmed.ncbi.nlm.nih.gov/23375456/ |
| **Kwan W, Wilson D, Moravan V. Radiotherapy for locally advanced basal cell and squamous cell carcinomas of the skin. *Int J Radiat Oncol Biol Phys*. 2004;60:406-411.** | https://pubmed.ncbi.nlm.nih.gov/15380573/ |
| **Lear JT, Migden MR, Lewis KD, et al. Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study. *J Eur Acad Dermatol Venereol*. 2018;32:372-381.** | https://pubmed.ncbi.nlm.nih.gov/28846163/ |
| **Maubec E, Boubaya M, Petrow P, et al. Phase II study of pembrolizumab as first-line, single-drug therapy for patients with unresectable cutaneous squamous cell carcinomas. *J Clin Oncol*. 2020;38:3051-3061.** | https://pubmed.ncbi.nlm.nih.gov/32730186/ |
| **Migden MR, Guminski A, Gutzmer R, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): A multicentre, randomised, double-blind phase 2 trial. *Lancet Oncol*. 2015;16:716-728.** | https://pubmed.ncbi.nlm.nih.gov/25981810/ |
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| **National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology. Squamous Cell Skin Cancer. Version 1.2023.** | https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf |
| **Negbenebor NA. The power of a multidisciplinary tumor board: Managing unresectable and/or high-risk skin cancers. *Cutis*. 2021;107:E22-E23.** | https://pubmed.ncbi.nlm.nih.gov/34288865/ |
| **Parikh SA, Patel VA, Ratner D. Advances in the management of cutaneous squamous cell carcinoma. *F1000Prime Rep*. 2014;6:70.** | https://pubmed.ncbi.nlm.nih.gov/25165569/ |
| **Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378:158-168.** | https://pubmed.ncbi.nlm.nih.gov/29320654/ |
| **Rischin D, Migden MR, Lim AM, et al. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: Primary analysis of fixed-dosing, long-term outcome of weight-based dosing. *J Immunother Cancer*. 2020;8:e000775.** | https://pubmed.ncbi.nlm.nih.gov/32554615/ |
| **Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: A 10-year, single-institution cohort study. *JAMA Dermatol*. 2013;149:541-547.** | https://pubmed.ncbi.nlm.nih.gov/23677079/ |

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| **Sekulic A, Migden MR, Basset-Seguin N, et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: Final update of the pivotal ERIVANCE BCC study. *BMC Cancer*. 2017;17:332.** | https://bmccancer.biomedcentral.com/articles/10.1186/s12885-017-3286-5 |
| **Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Eng J Med*. 2012;366:2171-2179.** | https://www.nejm.org/doi/full/10.1056/nejmoa1113713 |
| **Shalhout SZ, Emerick KS, Kaufman HL, Miller DM. Immunotherapy for non-melanoma skin cancer. *Curr Oncol Rep*. 2021;23:125.** | https://pubmed.ncbi.nlm.nih.gov/34448958/ |
| **Stratigos A, Garbe C, Lebbe C, et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. *Eur J Cancer*. 2015;51:1989-2007.** | https://pubmed.ncbi.nlm.nih.gov/26219687/ |
| **Stratigos AJ, Sekulic A, Peris K, et al. Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: An open-label, multi-centre, single-arm, phase 2 trial. *Lancet Oncol*. 2021;22:848-857.** | https://pubmed.ncbi.nlm.nih.gov/34000246/ |
| **Stratigos AJ, Sekulic A, Peris K, et al. LBA47 Primary analysis of phase II results for cemiplimab in patients (pts) with locally advanced basal cell carcinoma (laBCC) who progress on or are intolerant to hedgehog inhibitors (HHIs). *Ann Oncol*. 2020;31(suppl 4):S1175-S1176.** | https://www.annalsofoncology.org/article/S0923-7534(20)42359-2/abstract |
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| **William WN Jr, Feng L, Ferrarotto R, et al. Gefitinib for patients with incurable cutaneous squamous cell carcinoma: A single-arm phase II clinical trial. *J Am Acad Dermatol*. 2017;77:1110-1113.e2.** | https://pubmed.ncbi.nlm.nih.gov/28964539/ |
| **Work Group; Invited Reviewers, Kim JYS, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 2018;78:560-578.** | https://pubmed.ncbi.nlm.nih.gov/29331386/ |
| **Xie P, Lefrançois P. Efficacy, safety, and comparison of sonic hedgehog inhibitors in basal cell carcinomas: A systematic review and meta-analysis. *J Am Acad Dermatol*. 2018;79:1089-1100.e17.** | https://pubmed.ncbi.nlm.nih.gov/30003981/ |

**Resources and Societies**

| Resource | Address |
|---|---|
| **American Academy of Dermatology Association (AAD). Skin Cancer.** | https://www.aad.org/media/stats-skin-cancer |
| **American Cancer Society (ACS). Basal and Squamous Cell Skin Cancer.** | https://www.cancer.org/cancer/basal-and-squamous-cell-skin-cancer.html |
| **American College of Mohs Surgery (ACMS)** | https://www.mohscollege.org/ |
| **American Society of Clinical Oncology (ASCO)** | https://www.asco.org/ |
| **Centers for Disease Control and Prevention (CDC). What Is Skin Cancer?** | https://www.cdc.gov/cancer/skin/basic_info/what-is-skin-cancer.htm |
| **National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology. Basal Cell Skin Cancer. Version 1.2023.** | https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1416 |
| **National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology. Squamous Cell Skin Cancer. Version 1.2023.** | https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1465 |
| **Skin Cancer Foundation. Basal Cell Carcinoma Overview.** | https://www.skincancer.org/skin-cancer-information/basal-cell-carcinoma/ |
| **Skin Cancer Foundation. Squamous Cell Carcinoma Overview.** | https://www.skincancer.org/skin-cancer-information/squamous-cell-carcinoma/ |

**All URLs accessed June 7, 2023**