John Strasswimmer MD, PhD

MIAMI CANCER 2018: NOVEL THERAPIES FOR BCC AND SCC OF SKIN AND MERKEL CELL CARCINOMA.

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John Strasswimmer, MD, PhD

Novel Therapies for BCC and SCC of Skin and Merkel Cancer

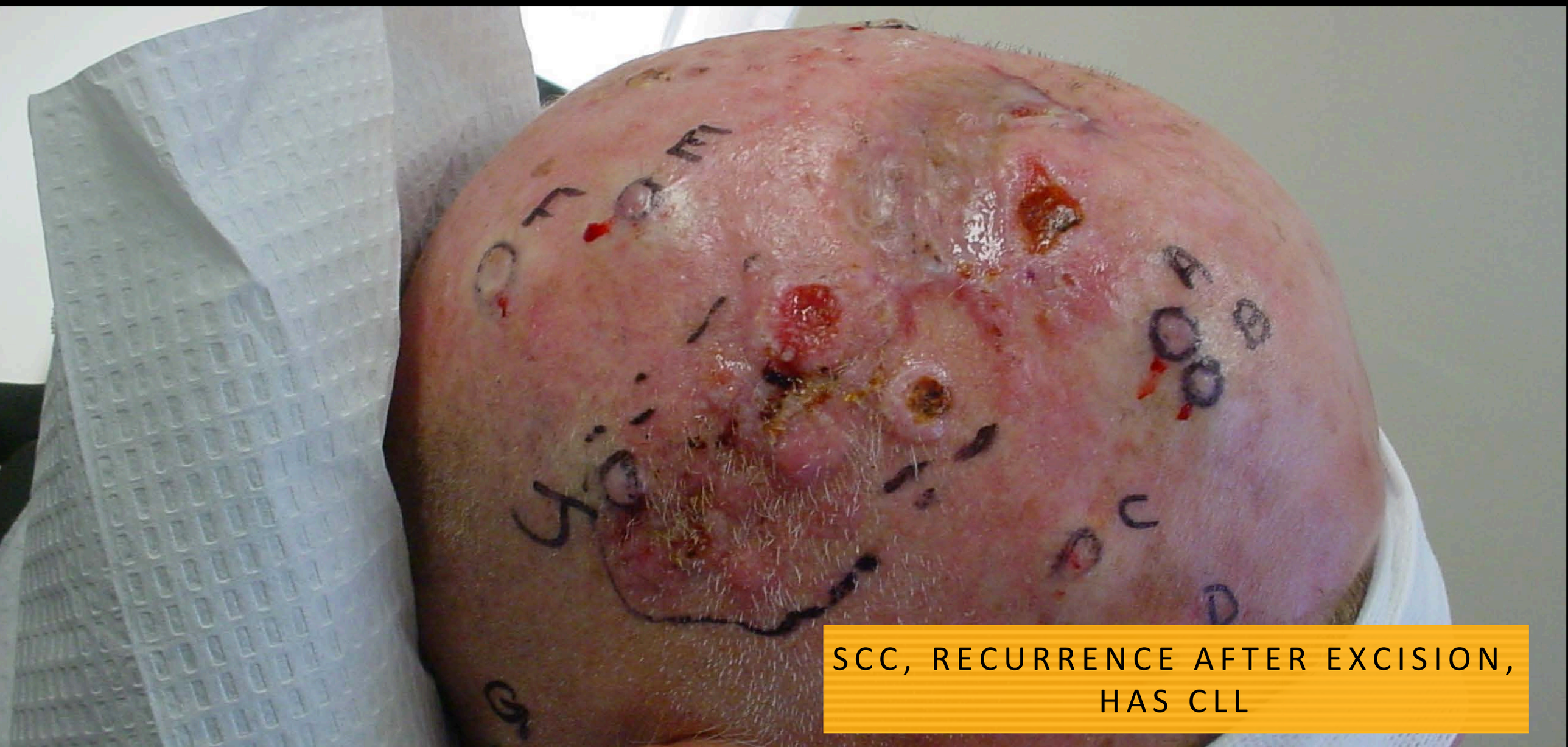
Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Speakers Bureau: Genentech, Sun Pharmaceuticals

The speaker will directly disclosure the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.

“why I am a mohs surgeon”

–JOHN STRASSWIMMER MD, PHD



SCC, RECURRENCE AFTER EXCISION, HAS CLL

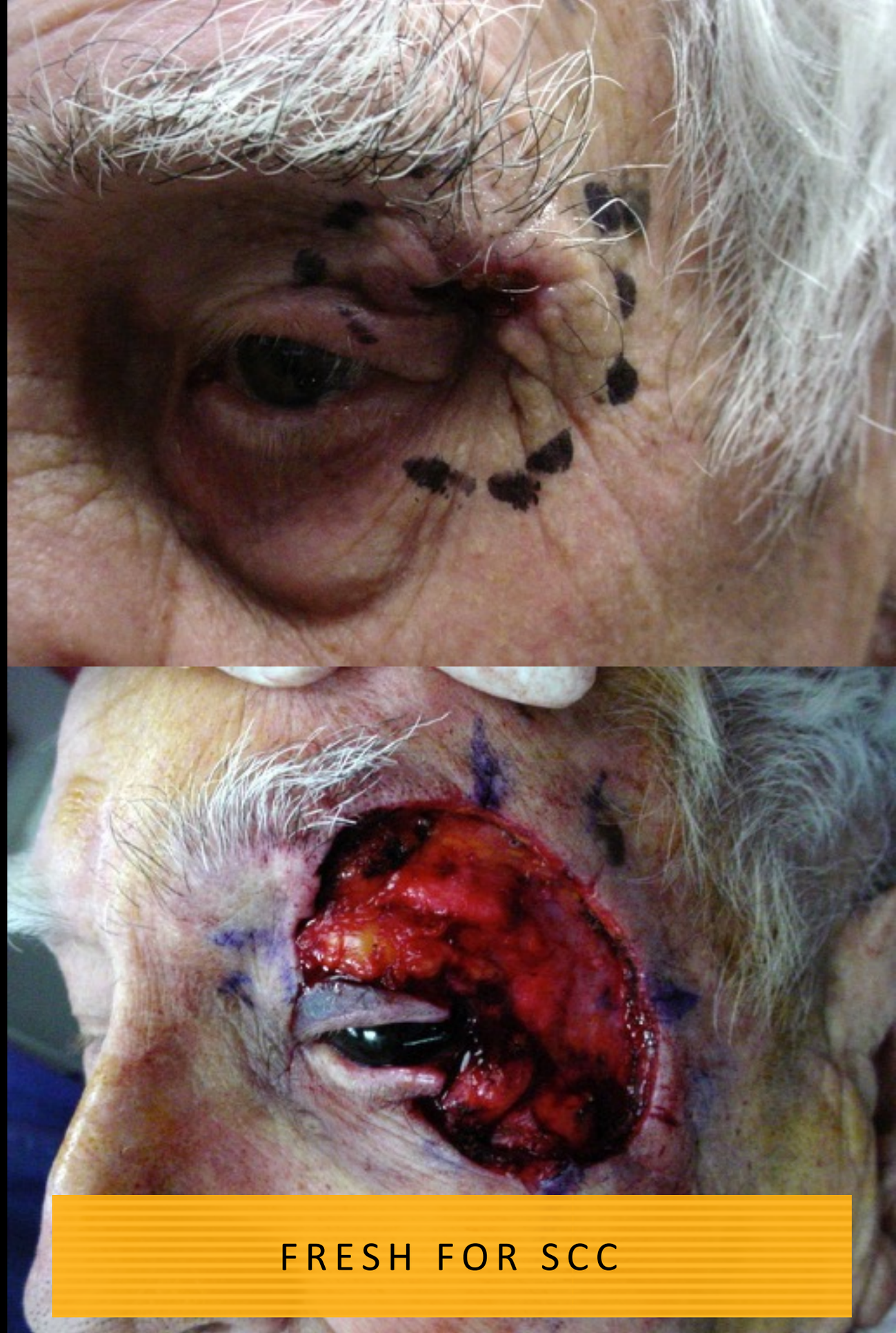
“why I am a mohs surgeon”

–JOHN STRASSWIMMER MD, PHD

13 MONTHS LATER, HE TOOK ME SCUBA DIVING

MOHS IN 2018: CURATIVE SURGERY NOT "FROZEN SECTIONS"

- fresh technique: <1% -5% recurrence vs 3-25% for excision (BCC, SCC)
- "staged" permanent technique:
  - <3% recurrence vs 15% (melanoma in situ)
  - <5% recurrence vs 20% DFSP (dermato-fibro-sarcoma-protuberans)



FRESH FOR SCC

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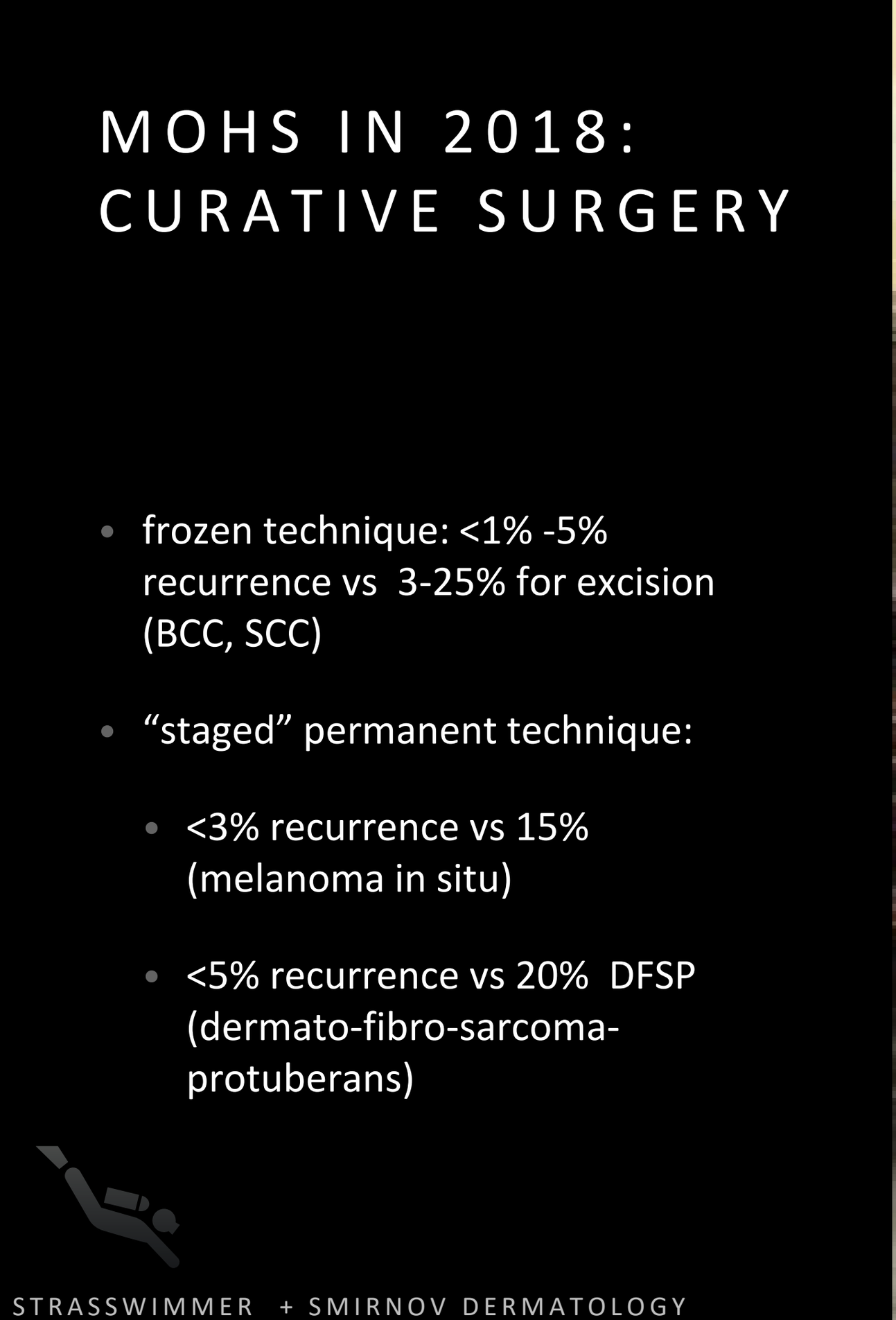

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MIAMI CANCER 2018: NOVEL THERAPIES FOR BCC AND SCC OF SKIN AND MERKEL CELL CARCINOMA.

Goals: understand three tumors

- MERKEL CELL CARCINOMA -
  THE DERMATOLOGIST'S ROLE IN AN ONCOLOGY CHALLENGE

SQUAMOUS CELL CARCINOMA:
  A DERMATOLOGIST'S AND ONCOLOGISTS' SHARED CHALLENGE

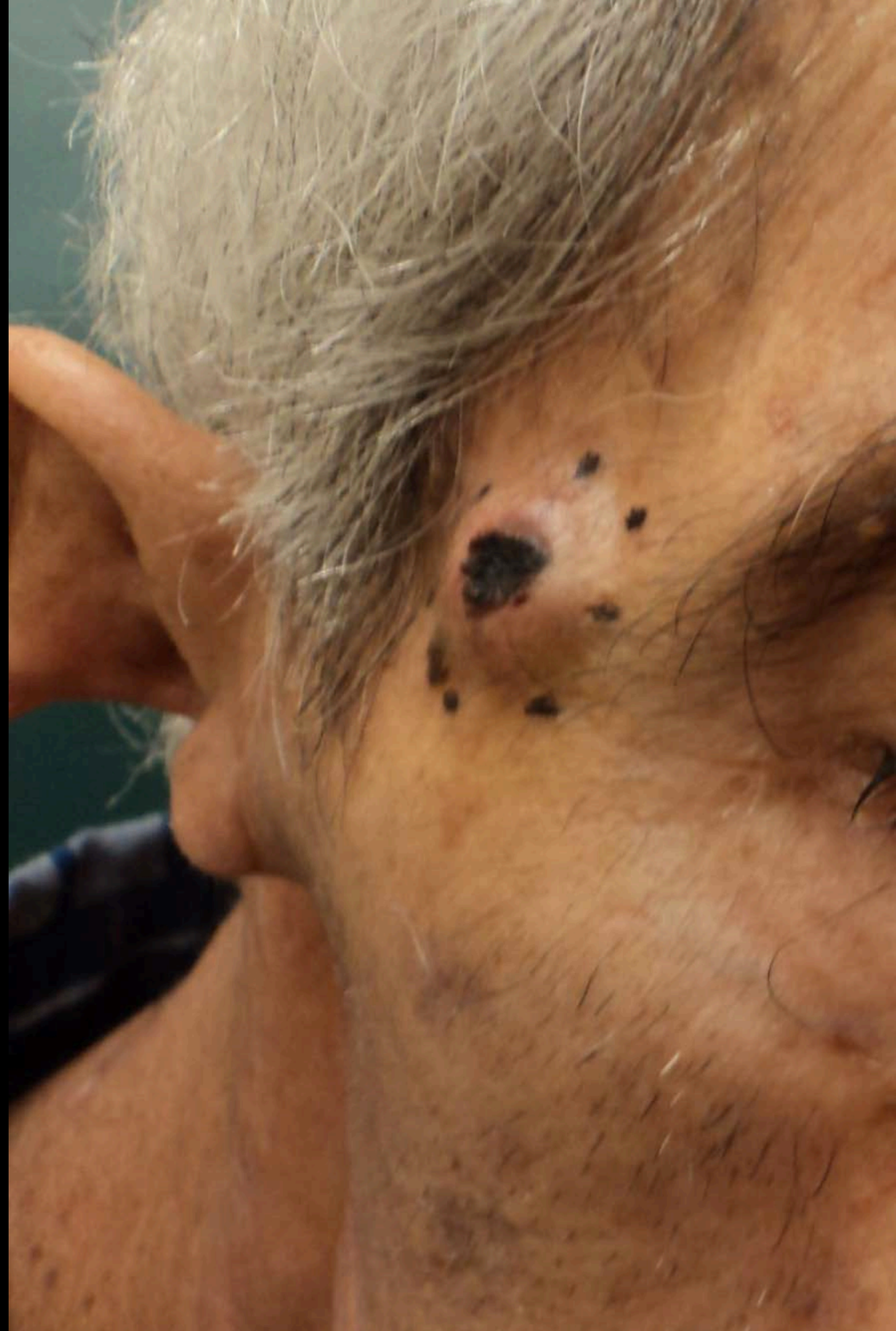
BASAL CELL CARCINOMA-
  AN ONCOLOGIST'S ROLE IN A DERMATOLOGY CHALLENGE

Goals: understand three cutaneous tumors

	MERKEL (MCC)	SQUAMOUS (SCC)	BASAL (BCC)
INCIDENCE	RARE (2488)	COMMON (1,000,000)	COMMON (5,000,000)
METASTATIC POTENTIAL	20-30% (1000)	LOW (10,000)	RARE (1,000 EST)
SYSTEMIC THERAPY	PD-1/PD-L1	NO	HEDGEHOG PATHWAY

MERKEL CELL CARCINOMA

- Rare: 0.7 per 100,000 15.5 per 100,000 for ≥85 years
- -
- -



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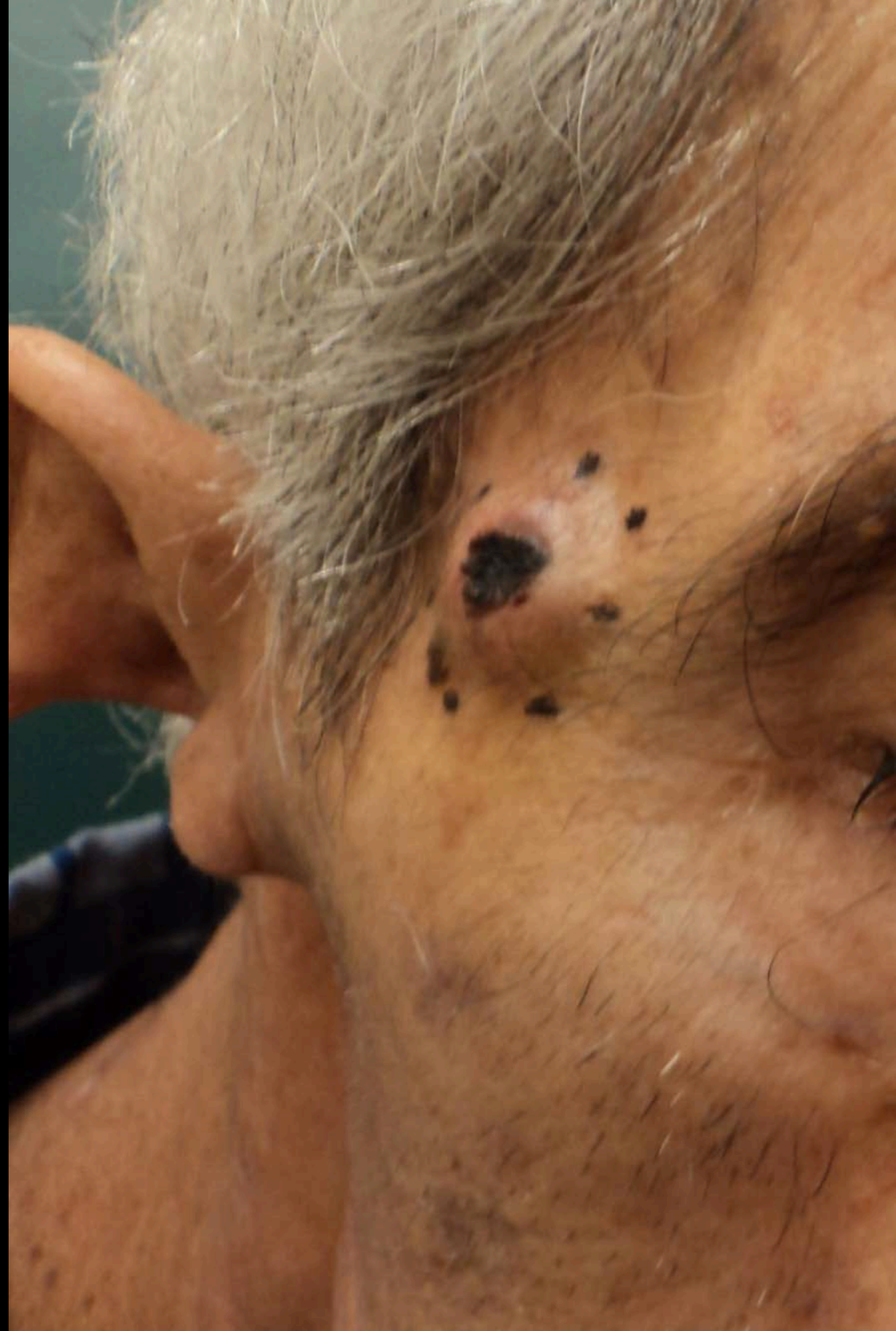
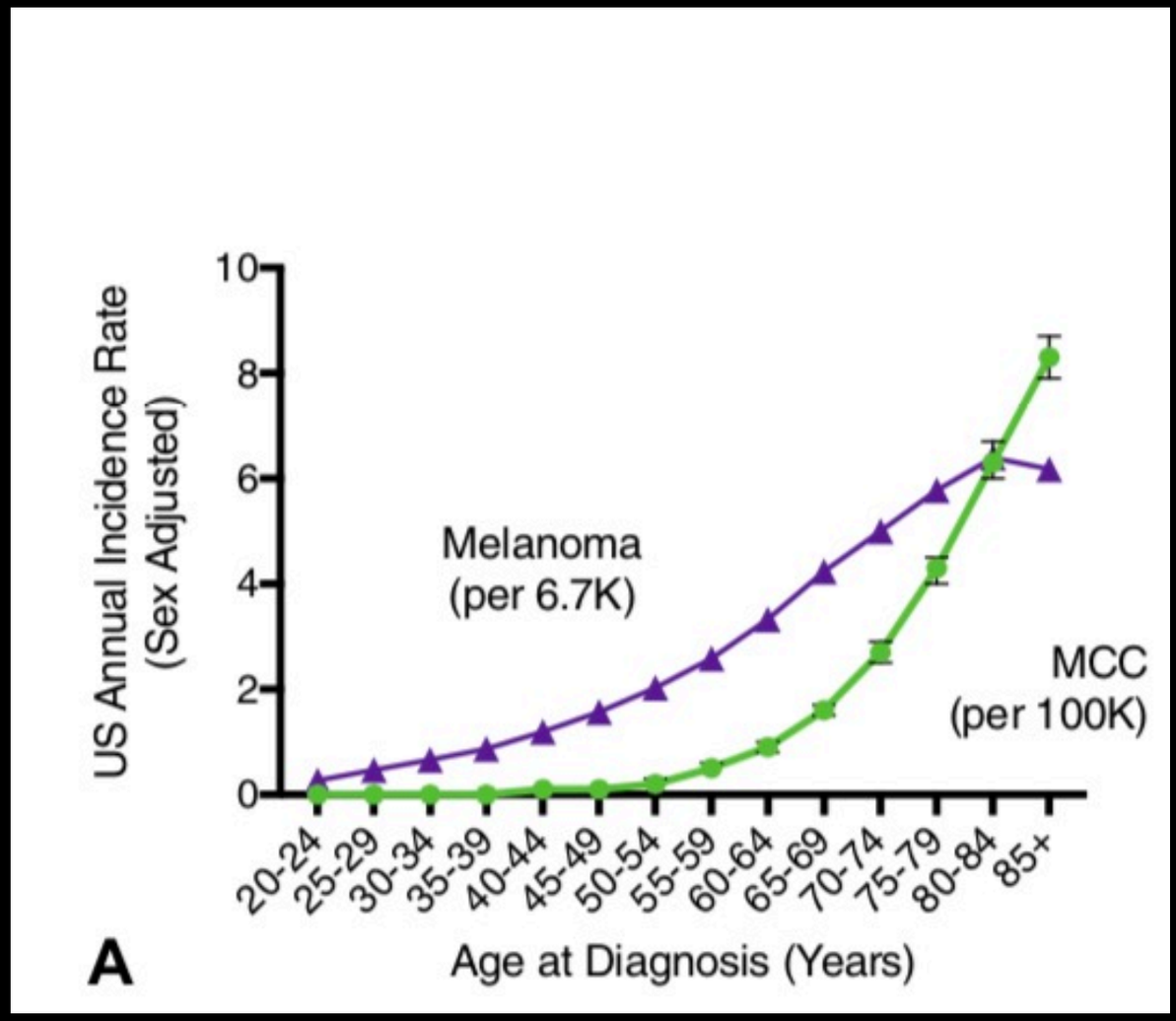
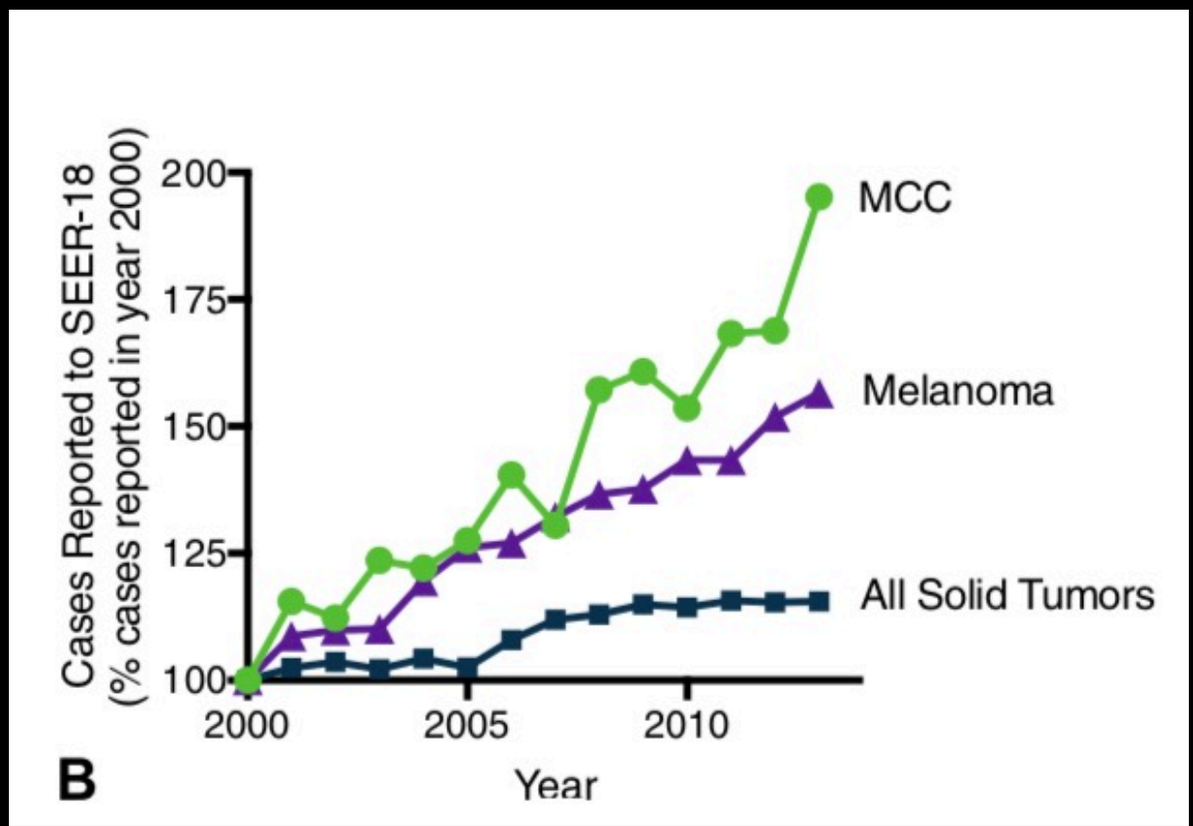


MERKEL CELL CARCINOMA

- Rare: 0.7 per 100,000 15.5 per 100,000 for ≥85 years
- -Very age dependent
- predict >3000 by 2025

REF: PAULSON ET AL:J. AMER ACAD. DERM 78 (3) NOVEMBER 2017





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- Etiology: UV and virus
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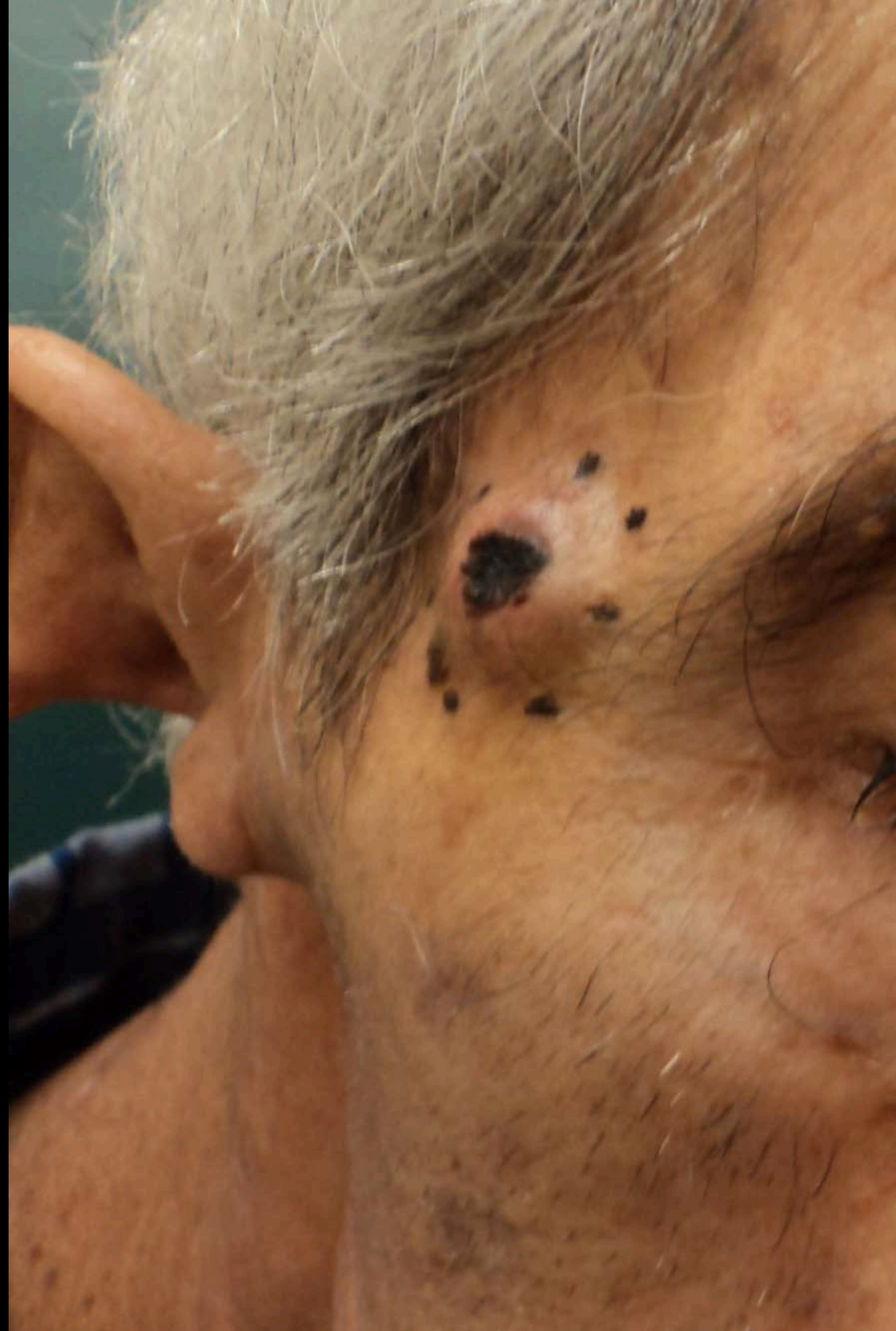

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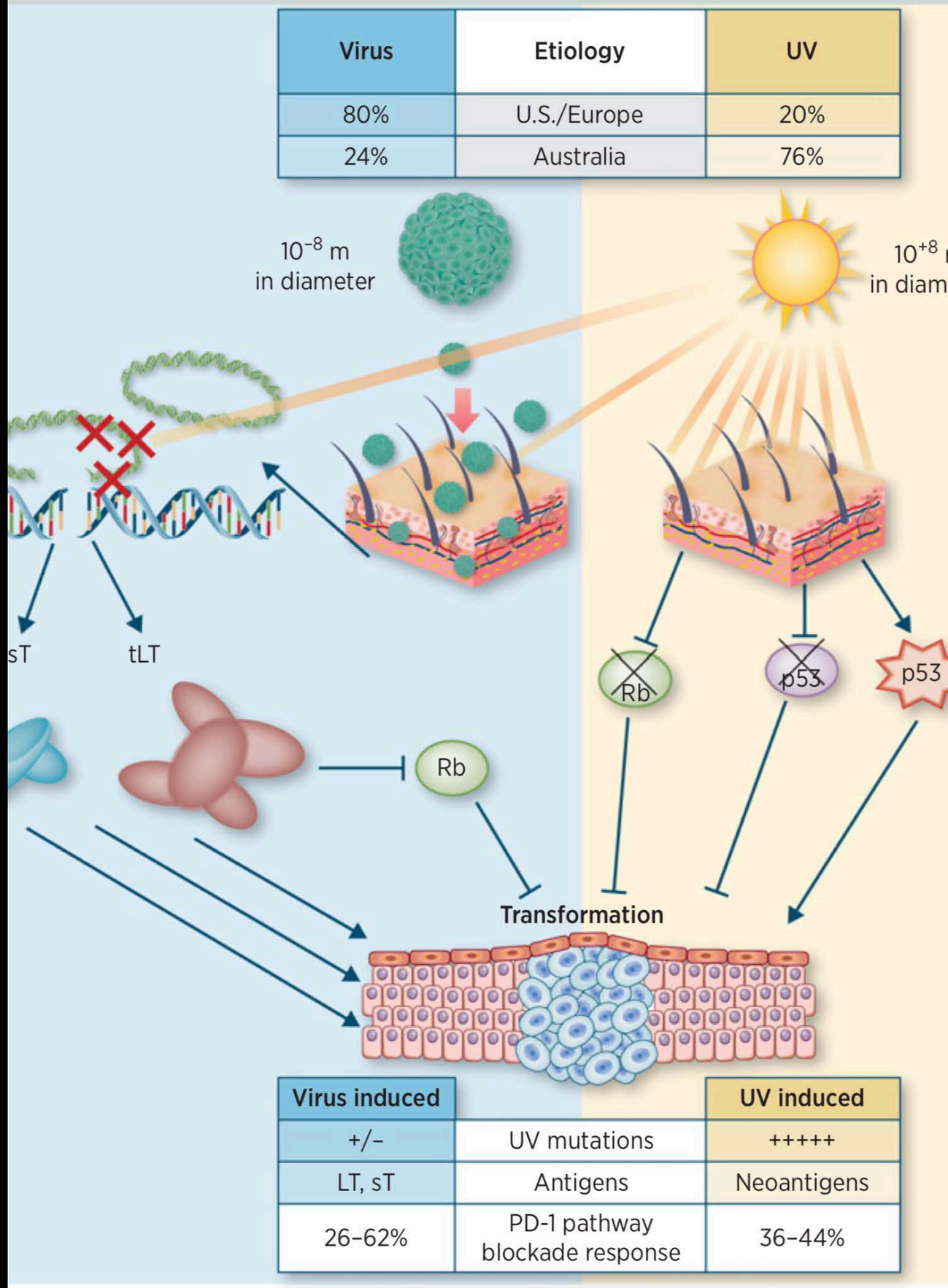
REF: NGHEIM ET AL: CLINICAL CANCER RES. DECEMBER 2017



MERKEL CELL CARCINOMA

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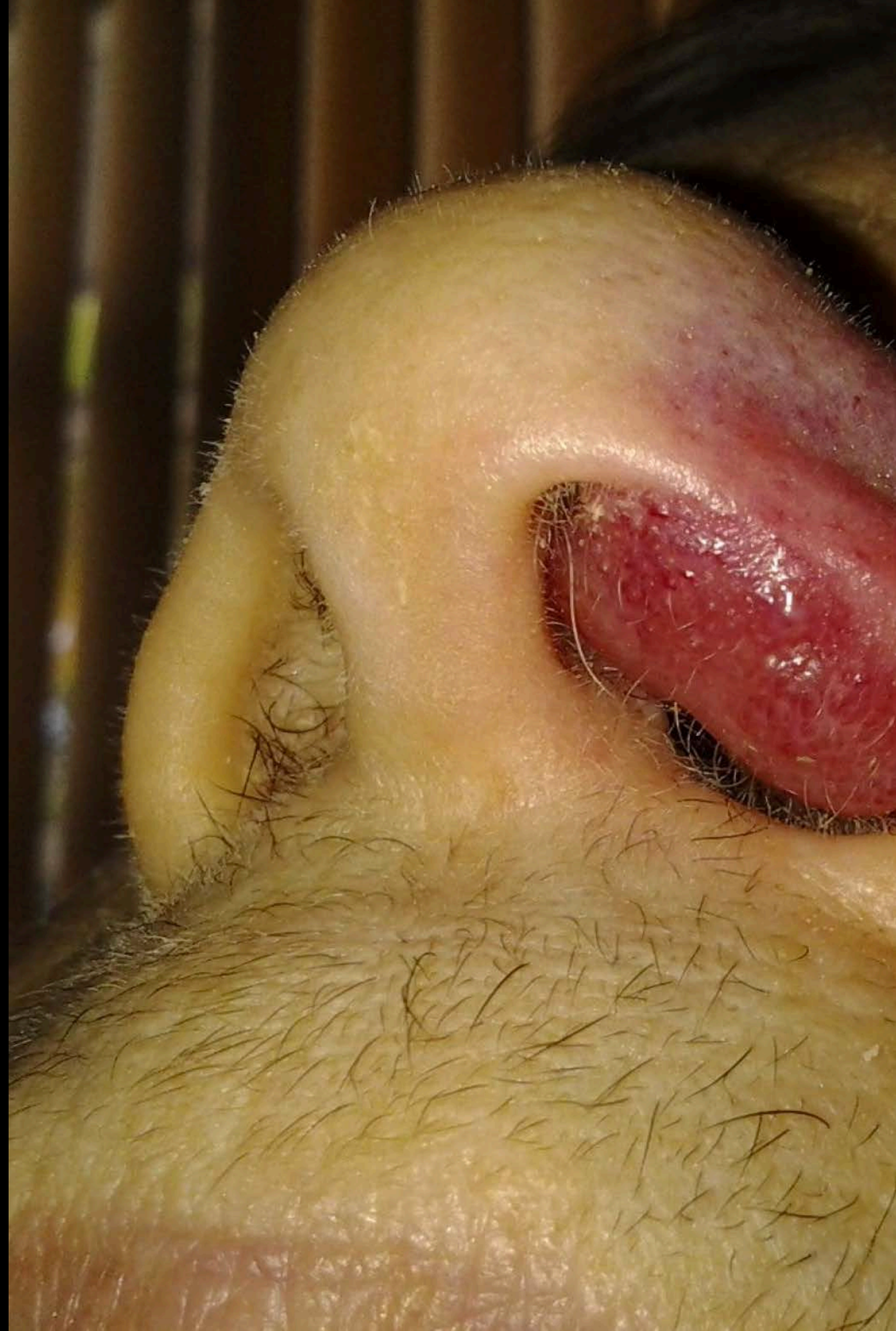

STRASSWIMMER + SMIRNOV DERMATOLOGY

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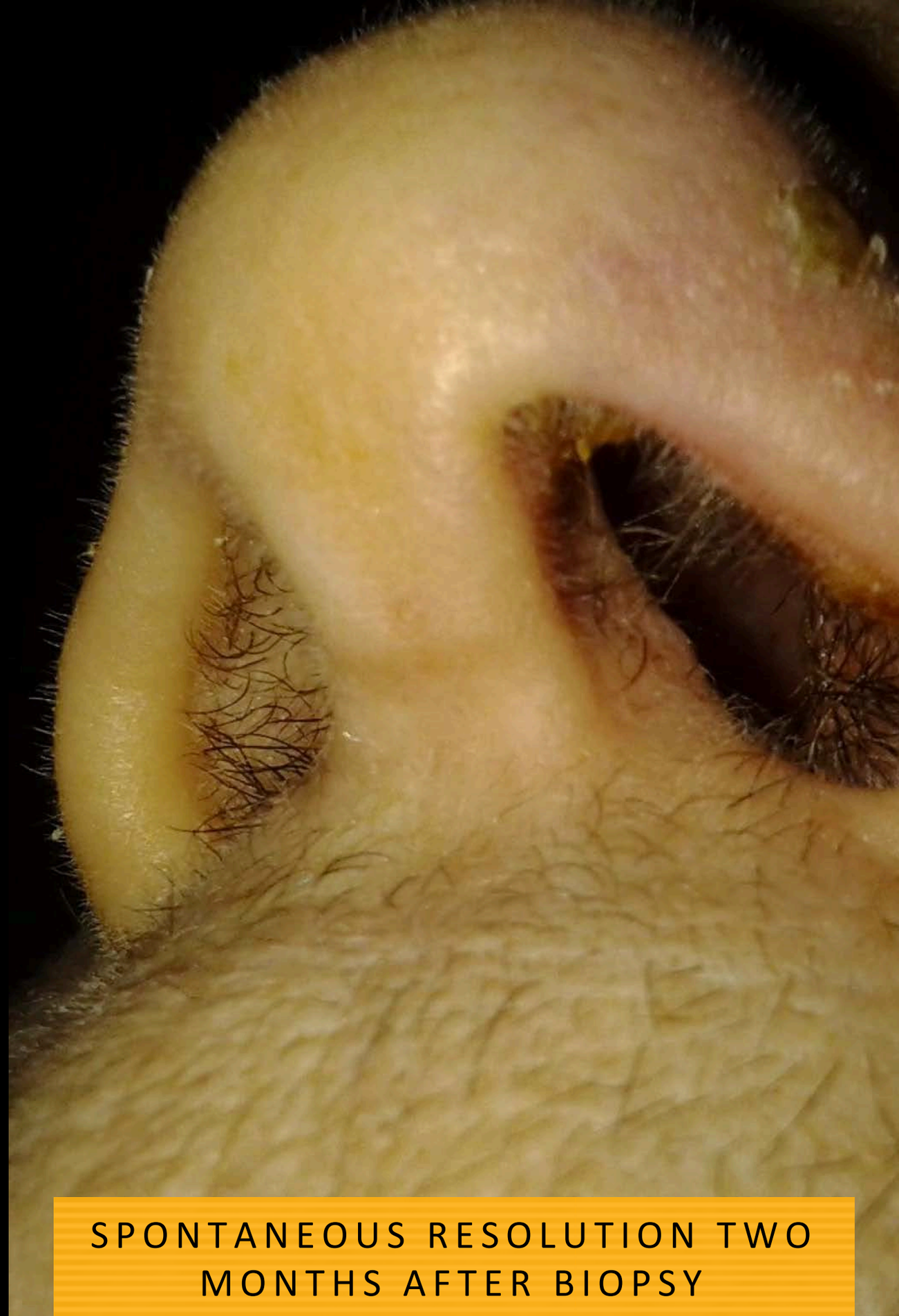

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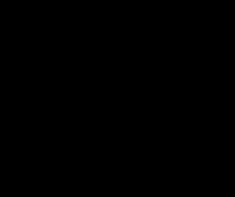
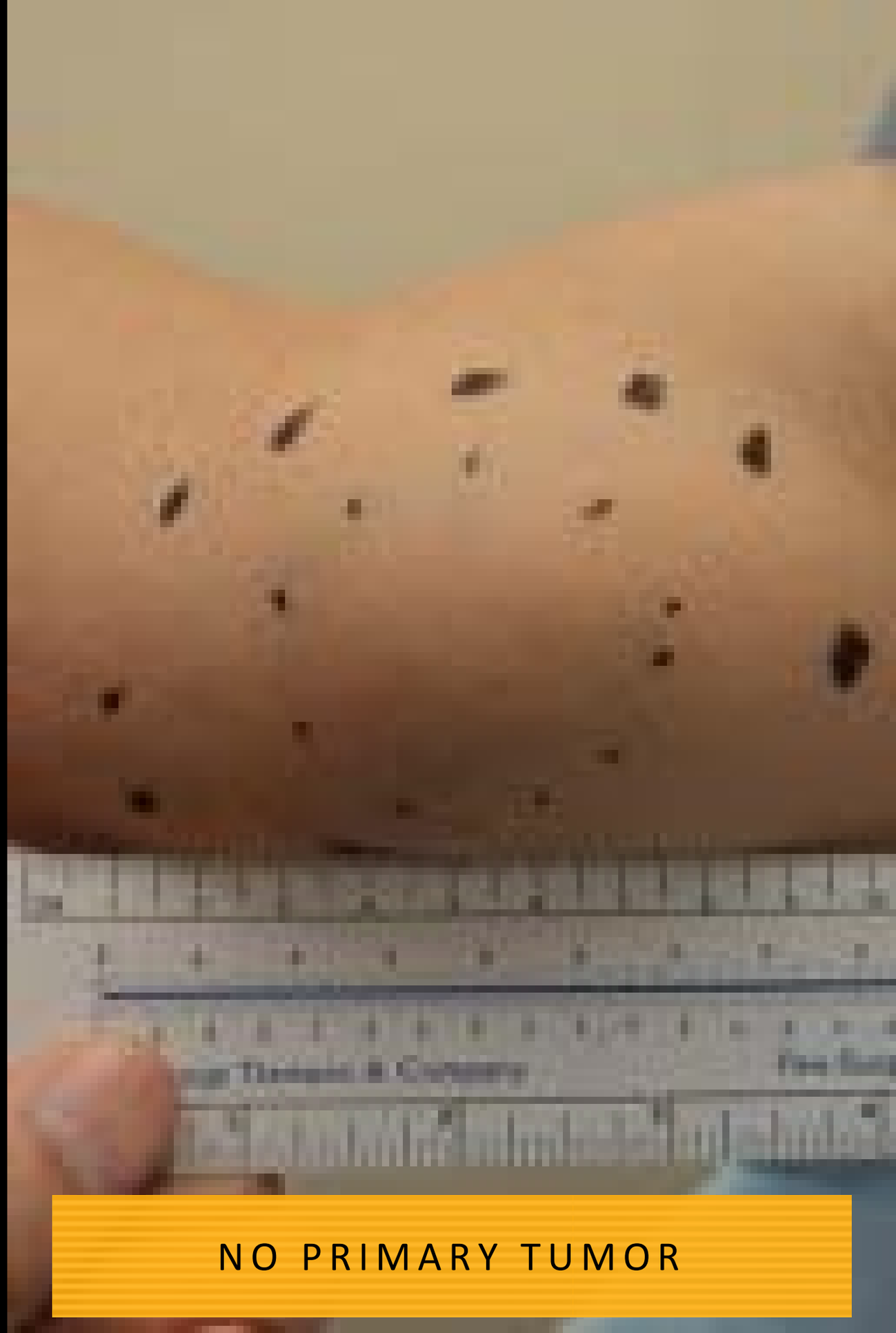
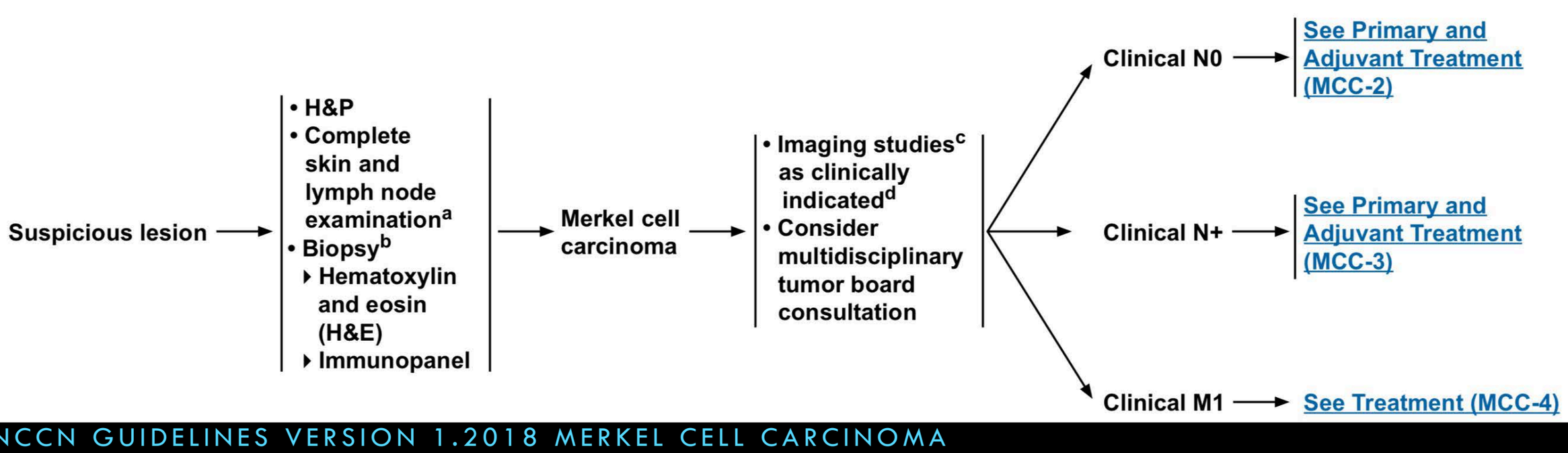


STRASSWIMMER + SMIRNOV DERMATOLOGY



Staging Merkel Cell New 2018



NCCN GUIDELINES VERSION 1.2018 MERKEL CELL CARCINOMA

- ROLE OF VIRUS (MVPV)
  - QUANTITATION OF MCPV ANTIBODIES:PATIENT STATUS”
    - SERONEGATIVE: MAY PREDICT HIGHER RECURRENCE
    - SEROPOSITIVE: RISING TITRE MAY EARLY INDICATE RECURRENCE

- 2018 AJCC STAGING CHANGES INCLUDE
  - PATIENTS WITH UNKNOWN PRIMARY = NEARLY 2X INCREASED SURVIVAL
  - STAGING OF NODE DISEASE BY PATHOLOGY VS CLINICAL EACH STAGE

How to treat Merkel Cell ?

Table 1. Selected data for chemotherapy and anti-PD1/PD-L1 in MCC

	Chemotherapy		Nivolumab	Avelumab	Pembrolizumab
Line	**1st line**	**2nd line**	**≥1st line**	**≥2nd line**	**1st line**
Cohort size	62–67	20–30	22	88	25
Agent	Etoposide and platinum-based agent[b]	Topotecan[b]	Anti–PD-1	Anti–PD-L1	Anti–PD-1
ORR	31%–55%	9%–23%	68%	32%	56%
9-month PFS[a]	15%–26%	0%–3%	N/A[c]	33%	56%
Publications	Becker, 2017[d] (46); Cowey, 2017 (45); Iyer, 2016 (44)		Topalian, 2017 (52)	Kaufman, 2016 (54)	Nghiem, 2016 (50)

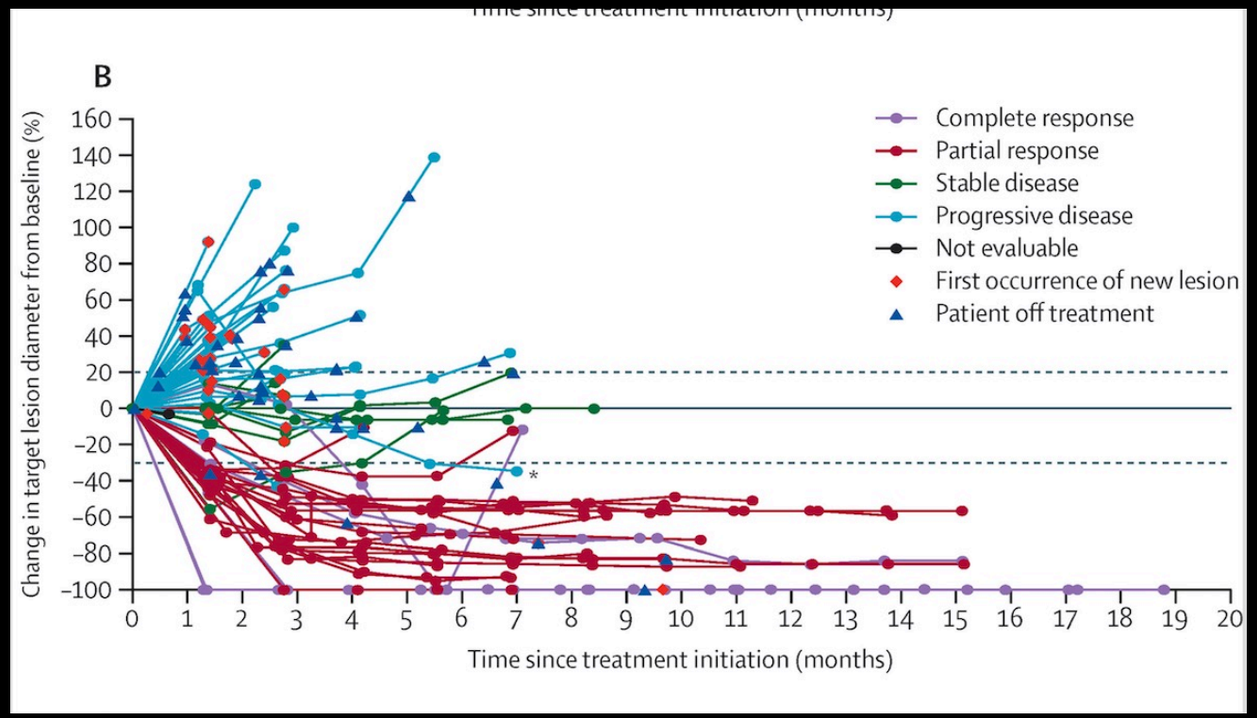
[a]Values estimated from charts.
[b]Most commonly used agents.
[c]9-Month PFS is not yet available; however, 3-month median PFS is 82%.
[d]Data for second-line chemotherapy only.

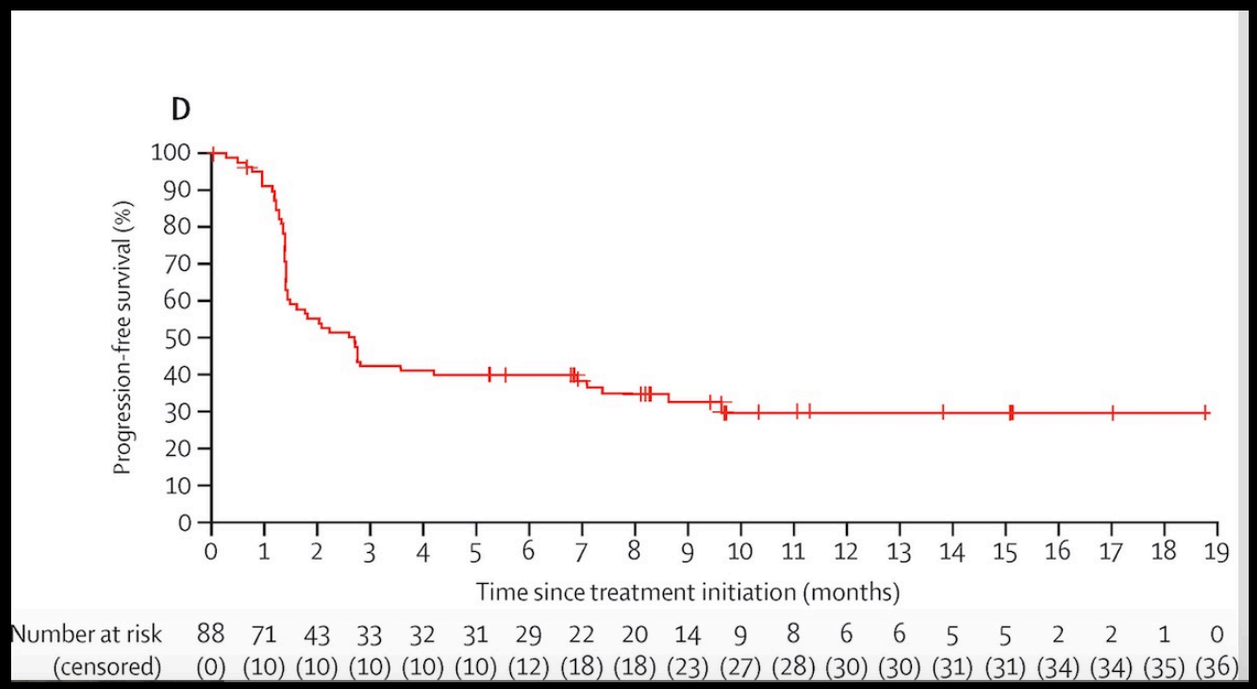
REF: NGHEIM ET AL: CLINICAL CANCER RES. DECEMBER 2017

- PD-(L)-1 BLOCKADE AVELUMAB FDA-APPROVED MARCH 2017
  - 40% DONT GET INITIAL RESPONSE
  - SECONDARY RESISTANCE CAN APPEAR
  - PATIENT LIMITATION: IMMUNOSUPPRESSED, AUTOIMMUNE
- TRIALS
  - NIVOLUMAB+IPILIMUMAB+/- SBRT
  - PEMBROLIZUMAB WITH OR WITHOUT STEREOTACTIC BODY RADIATION
  - T-VEC (TALIMOGENE LAHERPAREPVEC) WITH OR WITHOUT RADIOTHERAPY

JAVELIN Merkel 200 trial

- Avelumab (PD-L1 blockade) approved March 2017 for >12 year old for metastatic MCC
- Administration:
  - 10mg.kg q2 weeks
  - AE: pneumonitis, hepatitis, coitis, endocrinopathies, nephritis
  - embryo and fetotoxic
- Study: Phase 2, open label, single arm
  - RECIST v1.1
  - : 88 patients ORR= 33% (11% CR; 21% PR)
  - estimate: 74% of responders wil have duration ?12 months

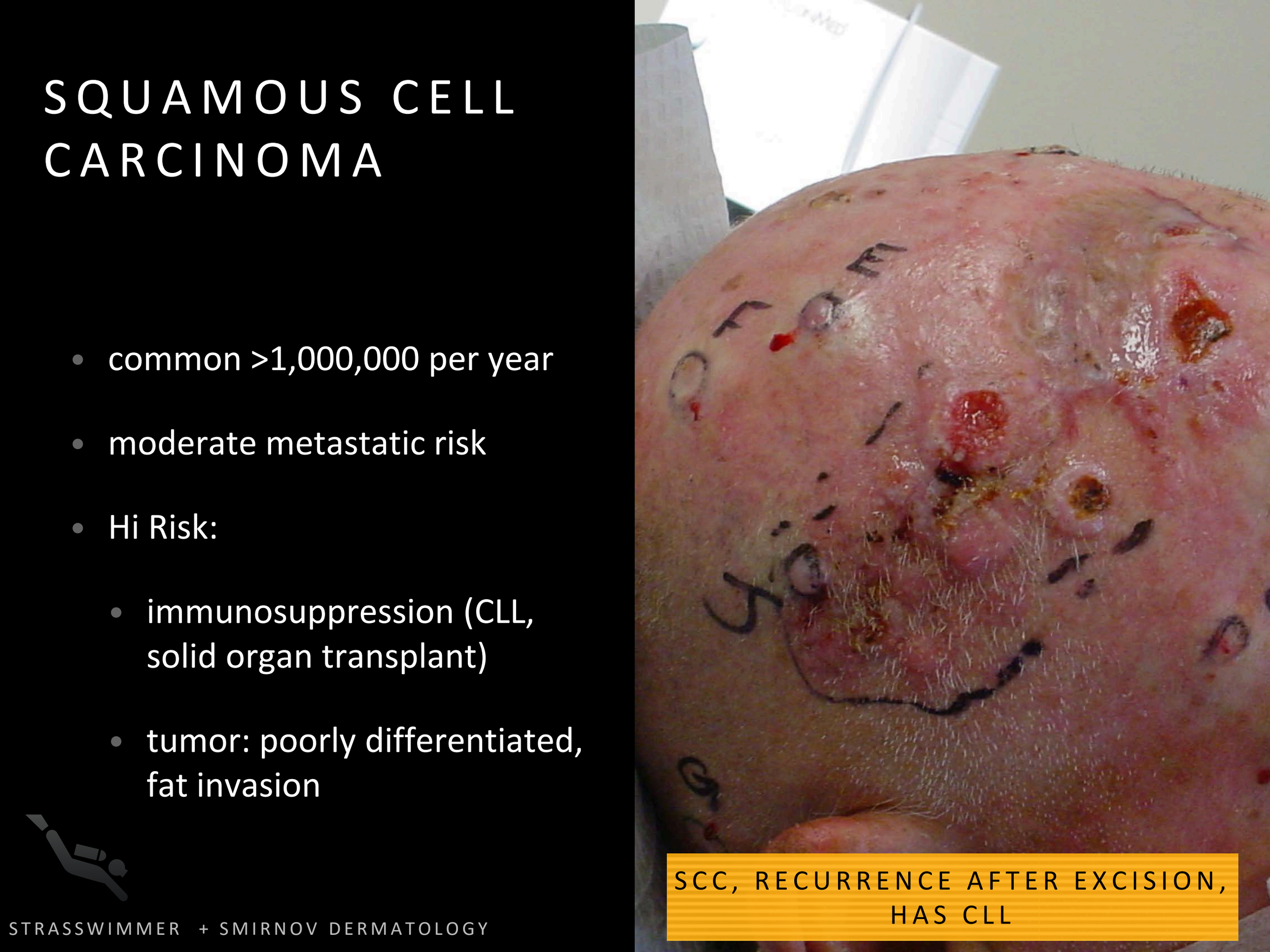




REF: KAUFMAN ET AL: LANCET ONCOLOGY OCTOBER 2016 AND KAUFMAN ET AL J. IMMUNOTHERAPY CANCER 2018

SQUAMOUS CELL CARCINOMA

- common >1,000,000 per year
- moderate metastatic risk
- Hi Risk:
  - immunosuppression (CLL, solid organ transplant)
  - tumor: poorly differentiated, fat invasion



SCC, RECURRENCE AFTER EXCISION, HAS CLL

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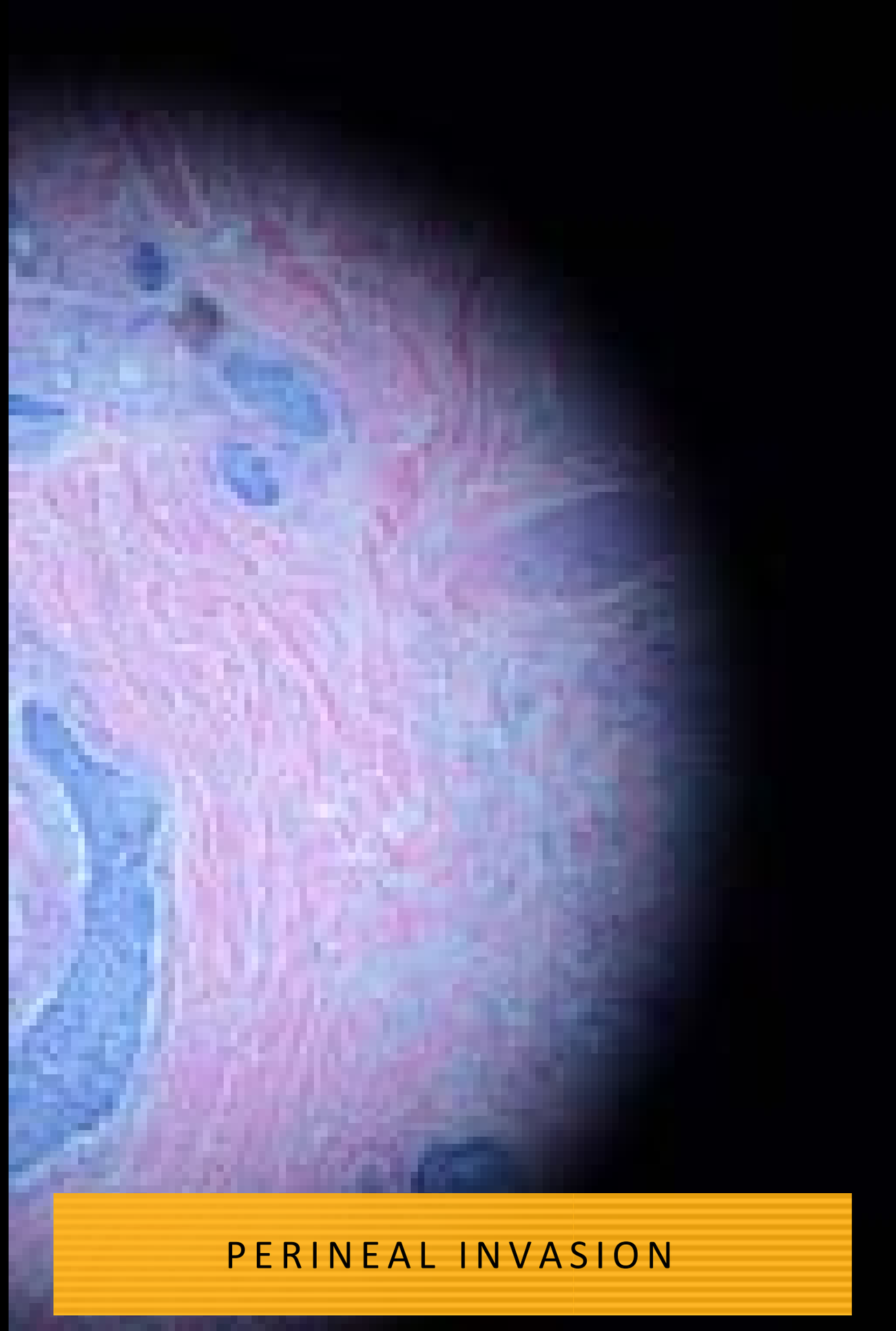

How to treat cSCC?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Squamous Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

FOLLOW-UP

Local disease:

- H&P[u,v]
  - Every 3–12 mo for 2 y, then every 6–12 mo for 3 y, then annually for life
- Patient education
  - Sun protection
  - Self examination of skin

Regional disease:

- H&P[u,v,w]
  - Every 1–3 mo for 1 y, then every 2–4 mo for 1 y, then every 4–6 mo for 3 y, then every 6–12 mo for life
- Patient education
  - Sun protection
  - Self examination of skin and lymph nodes

RECURRENCE

- Local → See Primary Treatment for local disease (SCC-1)
- New regional disease → See Primary Treatment for regional disease (SCC-4)
- Regional recurrence or distant metastases → Multidisciplinary tumor board consultation[x]

"THERE ARE NO DRUGS APPROVED BY THE US FOOD AND DRUG ADMINISTRATION (FDA) SPECIFICALLY FOR THE TREATMENT OF CSCC. " 2018 J. AMER ACAD DERMATOL.

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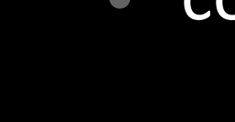
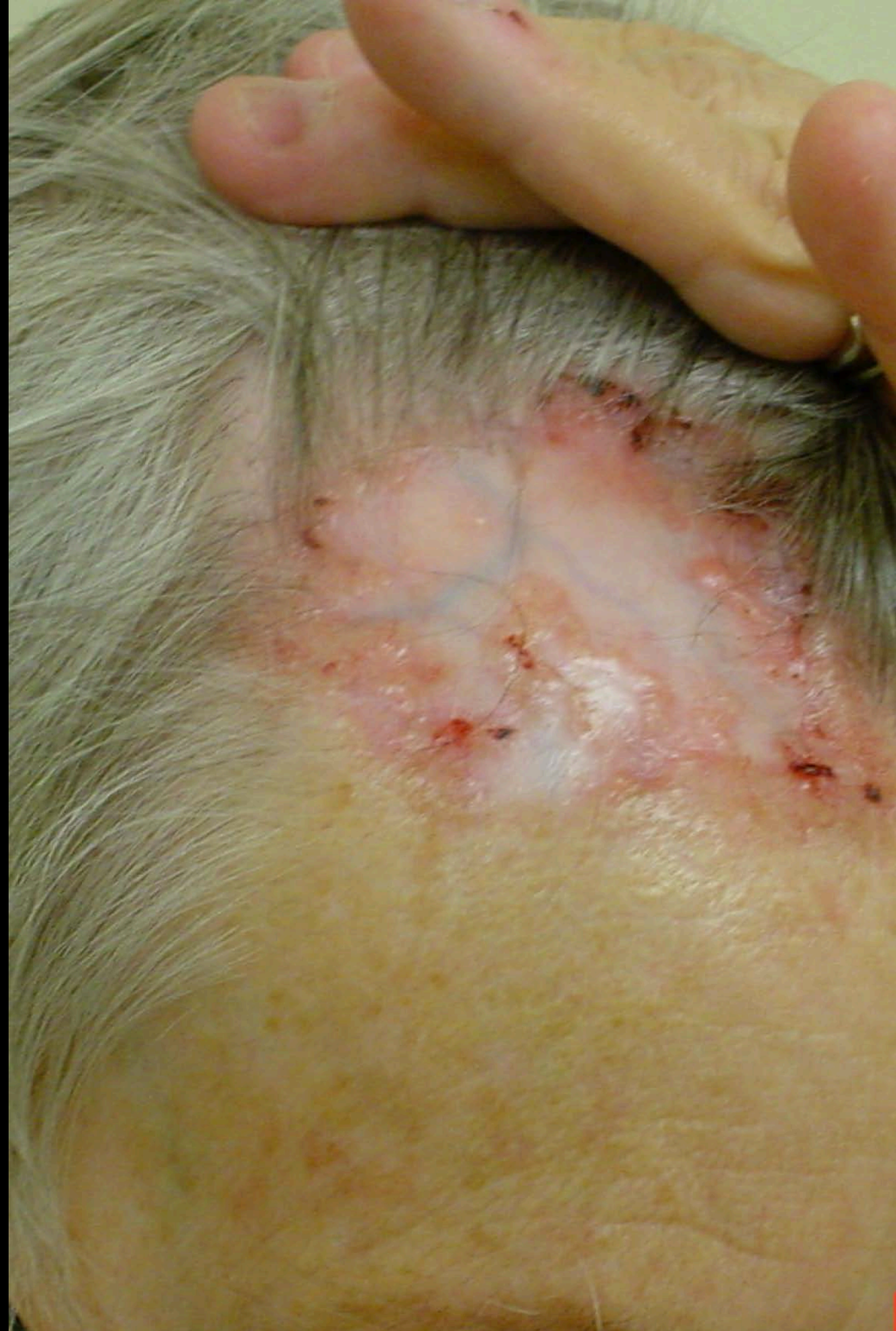
How to treat cSCC?

- EGFR MONOCLONAL ANTIBODIES
  - cetuximab 2011 Phase 2: nonresectable DCR 69% PR 35% CR 6% CR
  - cetuximab + /- platinum, 5-FU 2015 nonresectable neoadjuvant helps 92% become resectable
  - panitumumab 2014 Phase 2: nonresectable 31% ORR PR18% CR 12%
- EGFR SMALL MOLECULE INHIBITOR
  - Gefitinib 2017 Phase 2: nonresectable DCR 51% % ORR 16%
- PD-1 INHIBITOR
  - Cemiplimab
    - 2017 Phase 2: nonresectable ORR 16% PR 16%
    - Expanded axes study 2018: Regenron/Sanofi : “An Open-Label, Expanded Access Protocol of Cemiplimab in Patients With Metastatic or Locally Advanced Cutaneous Squamous Cell Carcinoma Who Are Not Candidates for Surgery”

BASAL CELL CARCINOMA

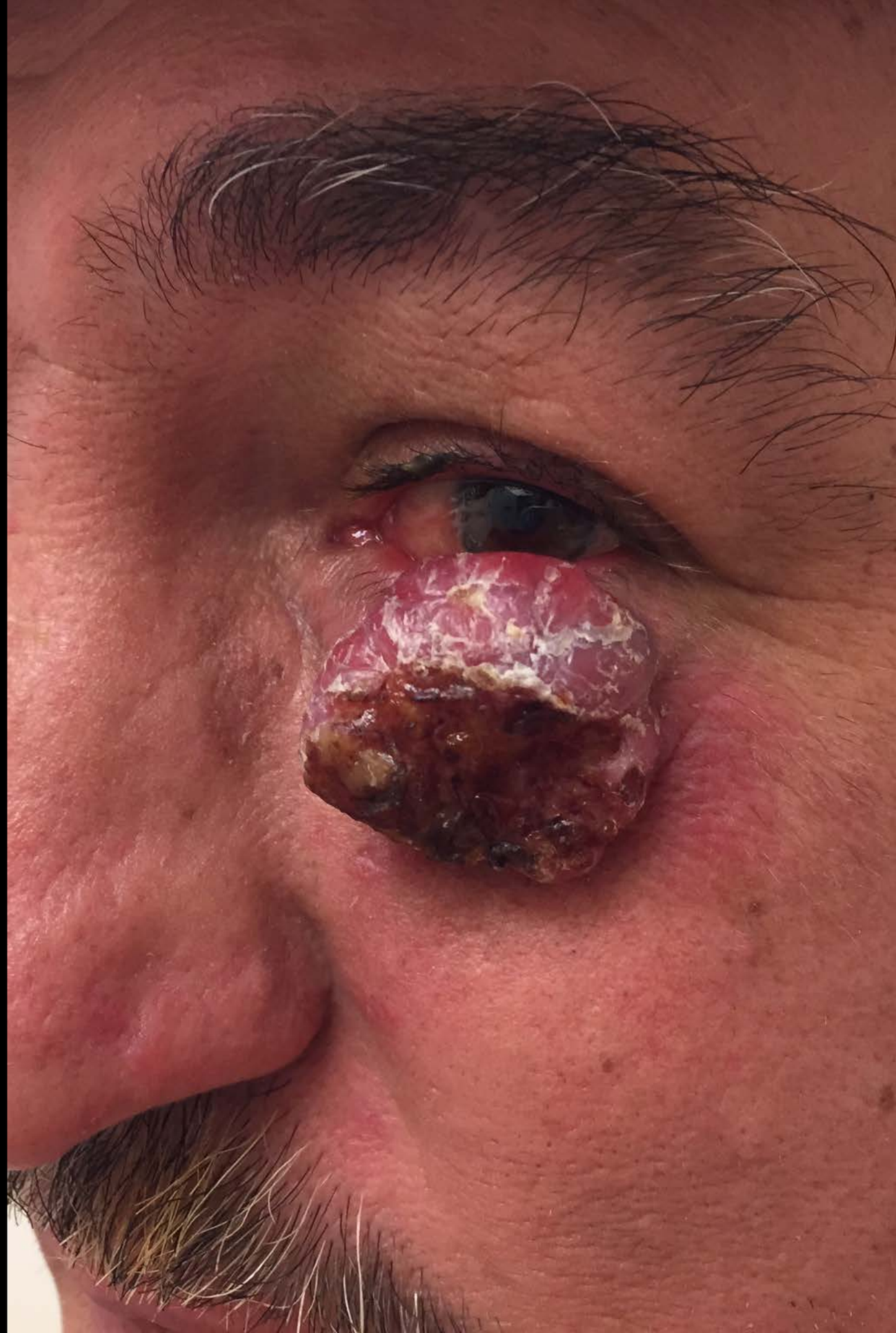
- common >5,000,000 per year
- extremely low metastatic risk
- hig risk for local morbidity
  - tumor type(size, location, histology)
  - perineurial invasion





ADVANCED BCC

- Locally Advanced (laBCC)
- Metastatic (mBCC)



STRASSWIMMER + SMIRNOV DERMATOLOGY

LOCALLY ADVANCED BCC

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2015
Basal Cell Skin Cancer

NCCN Guidelines Inde
Basal Cell TO(
Discussio

CLINICAL PRESENTATION | **WORKUP** | **RISK STATUS**

Suspicious lesion →

- H&P
- Complete skin exam
- Biopsy
  - If more than superficial lesion, inclusion of deep reticular dermis preferred[a]
- Imaging studies as indicated for suspicion of extensive disease[b]

High Risk

Area L ≥20 mm

Area M ≥10 mm

Area H ≥6 mm[1]

Poorly defined

Recurrent

Low risk[a] → See Primary Treatment of Low-Risk Basal Cell Skin Cancer (BCC-2)

High risk[a,c] → See Primary Treatment of High-Risk Basal Cell Skin Cancer (BCC-3)

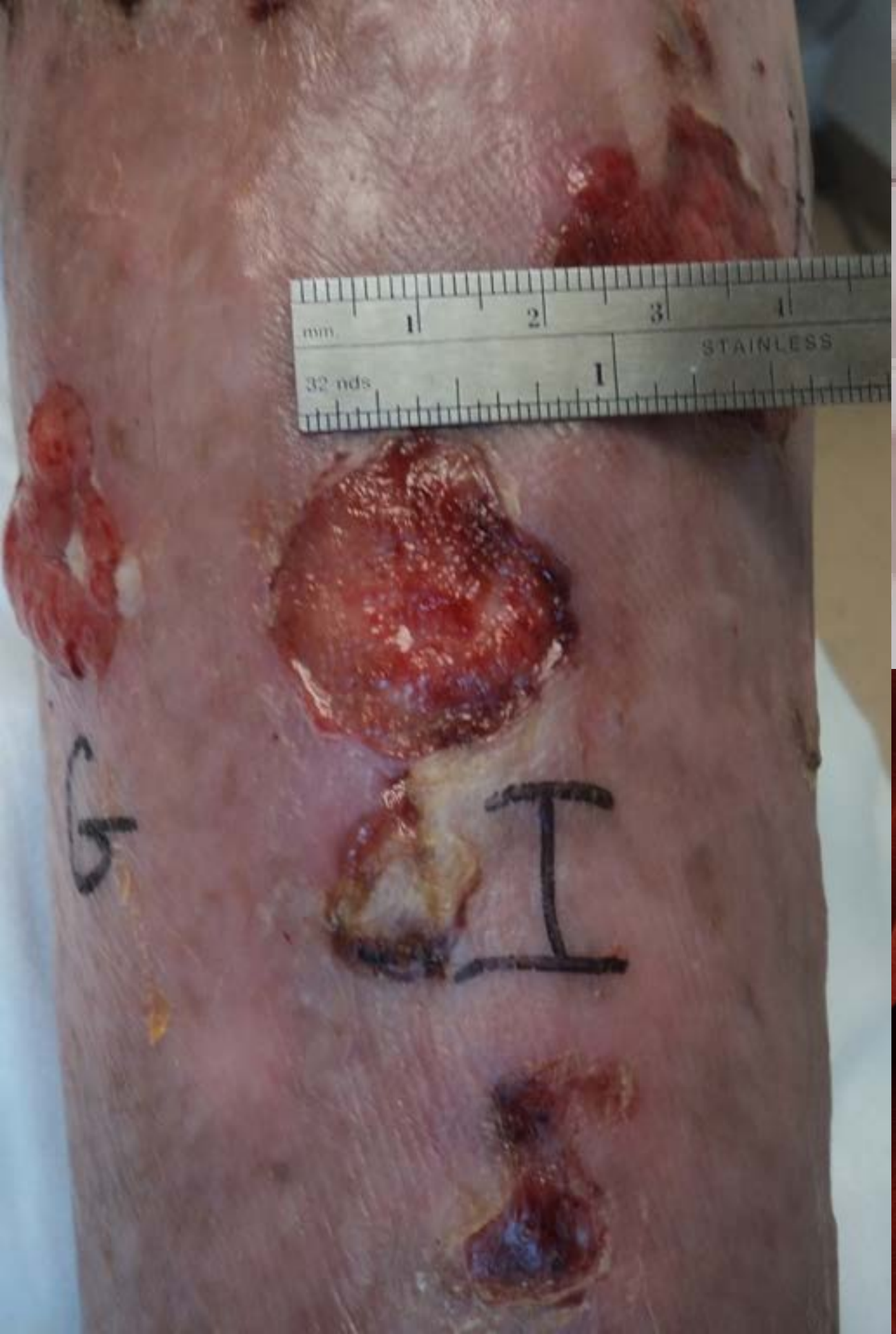
See Risk Factors for Recurrence (BCC-A).

Extensive disease includes deep structural involvement such as bone, perineural disease, and deep soft tissue. If perineural disease is suspected, MRI is preferred.

Any high-risk factor places the patient in the high-risk category.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

BCC-1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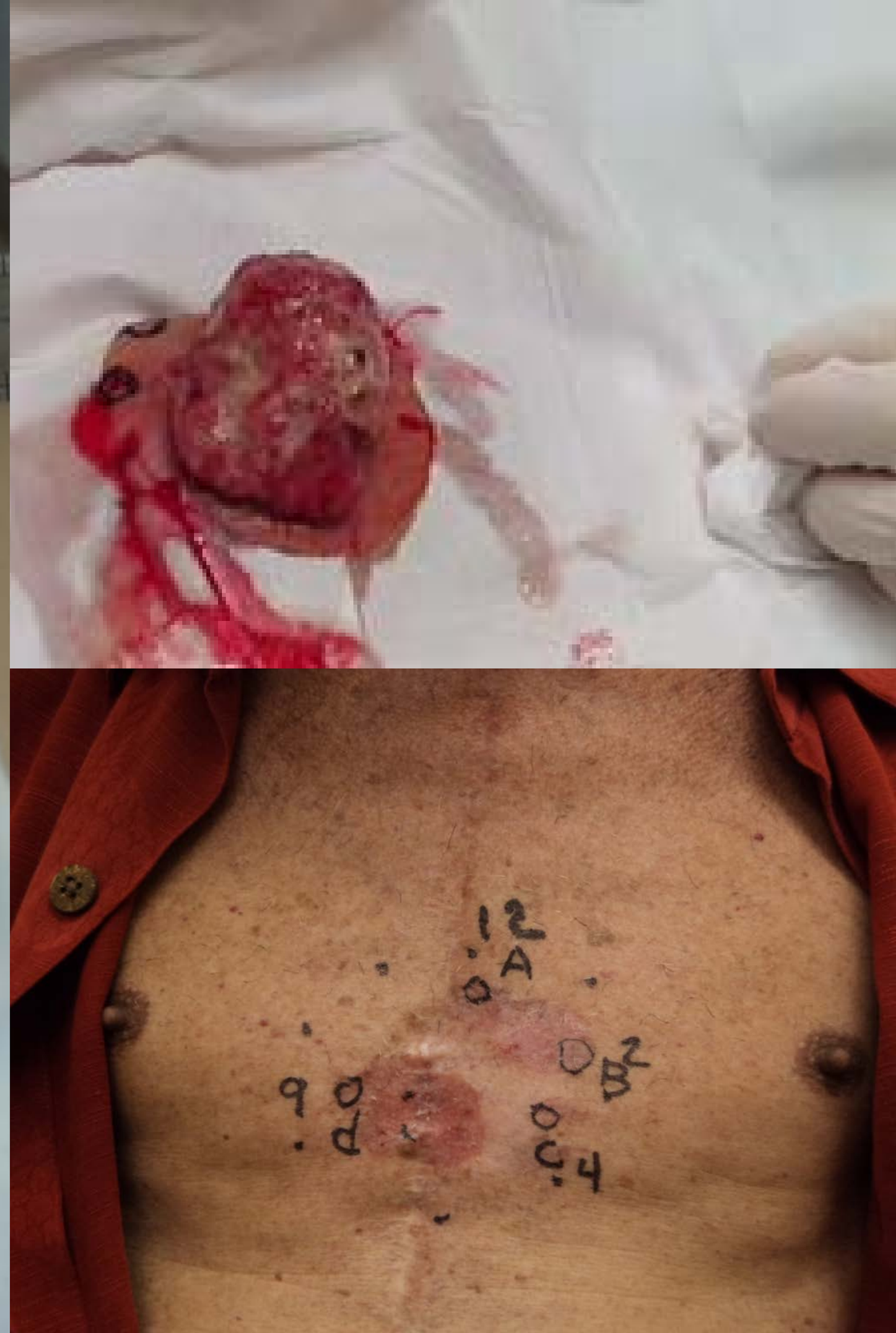

12
A
B
C
D

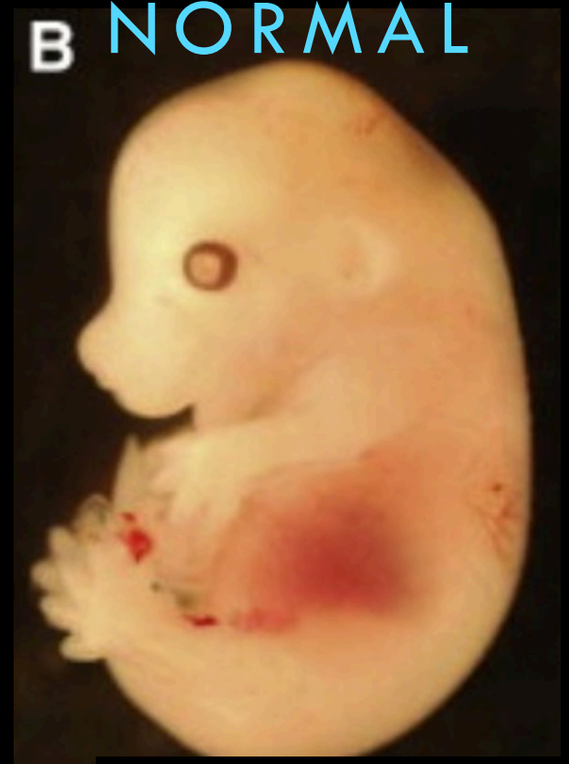
How to treat laBCC?

HEDGEHOG PATHWAY (SMOOTHENED) INHIBITORS (HPI)

STRASSWIMMER + SMIRNOV DERMATOLOGY ASSOCIATES -DELRAY BEACH FL

HEDGHOG PATHWAY

- controls contact growth inhibition
- embryogenesis, others

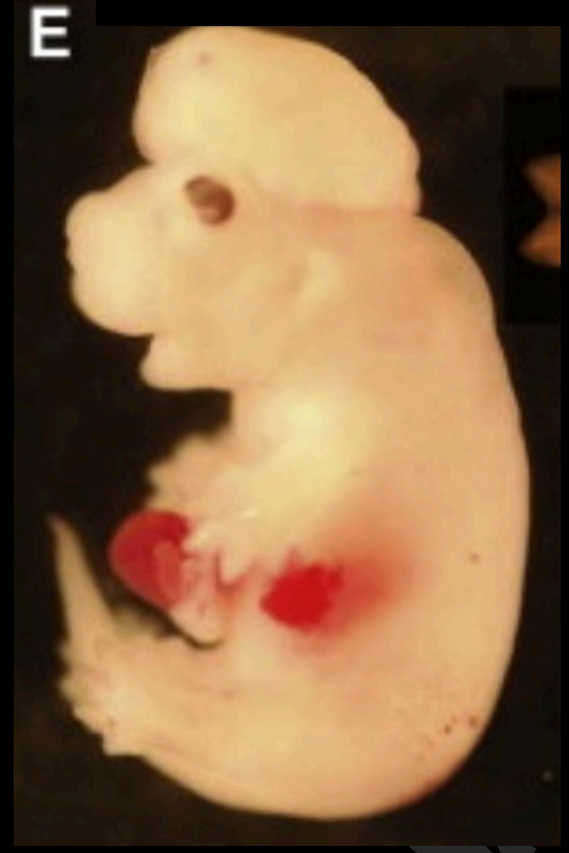


MAKE A “HEDGEHOG MUTATION”

OR

FEED THEM AN HPI

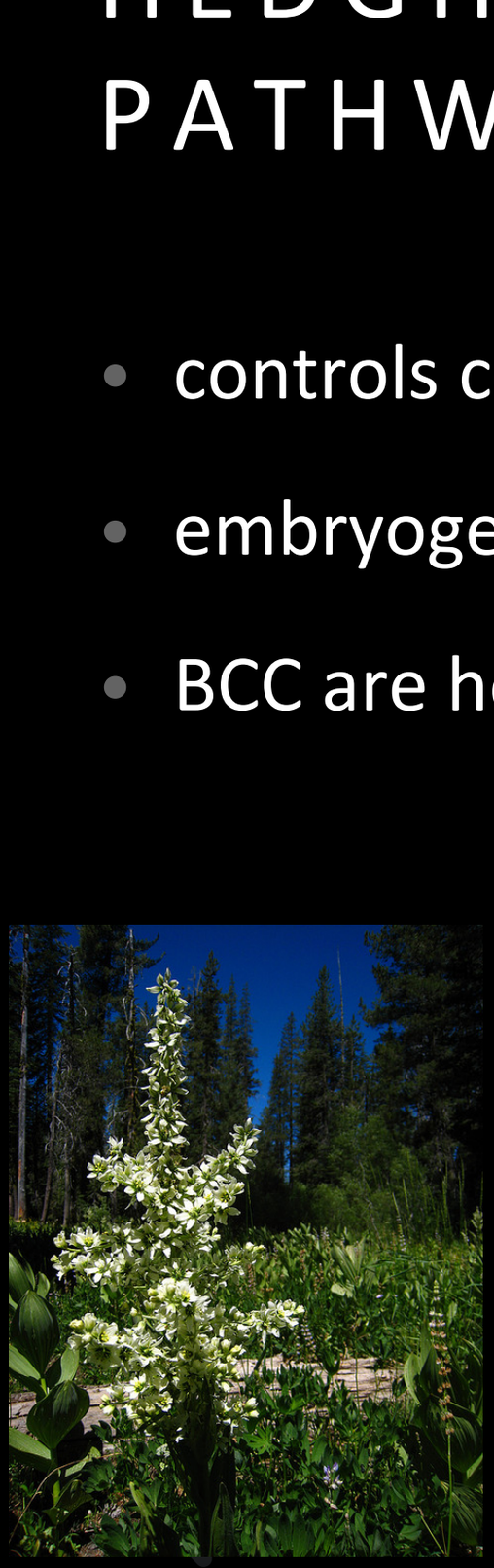
cylopamine (natural)



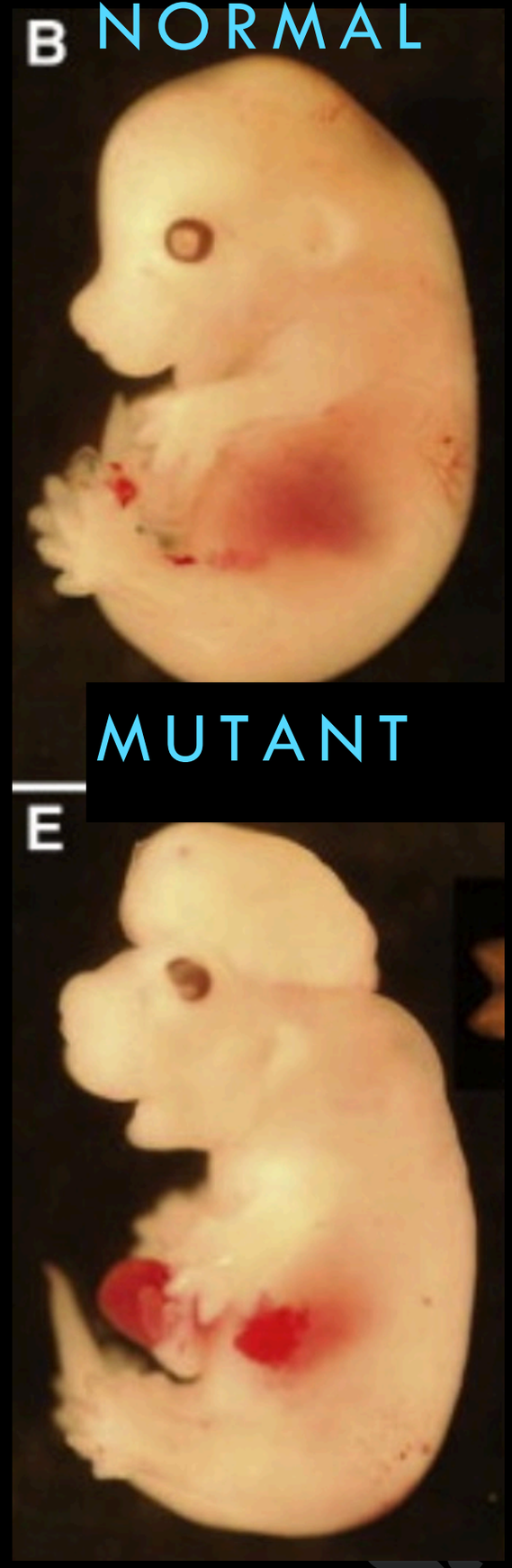
STRASSWIMMER + SMIRNOV DERMATOLOGY

HEDGHOG PATHWAY

- controls contact growth inhibition
- embryogenesis, others
- BCC are hedgehog mutants



cylopamine (natural) or
vismodegib / sonidegib



HEDGHOG PATHWAY

- controls contact growth inhibition
- embryogenesis, others
- BCC are “hedgehog mutants”

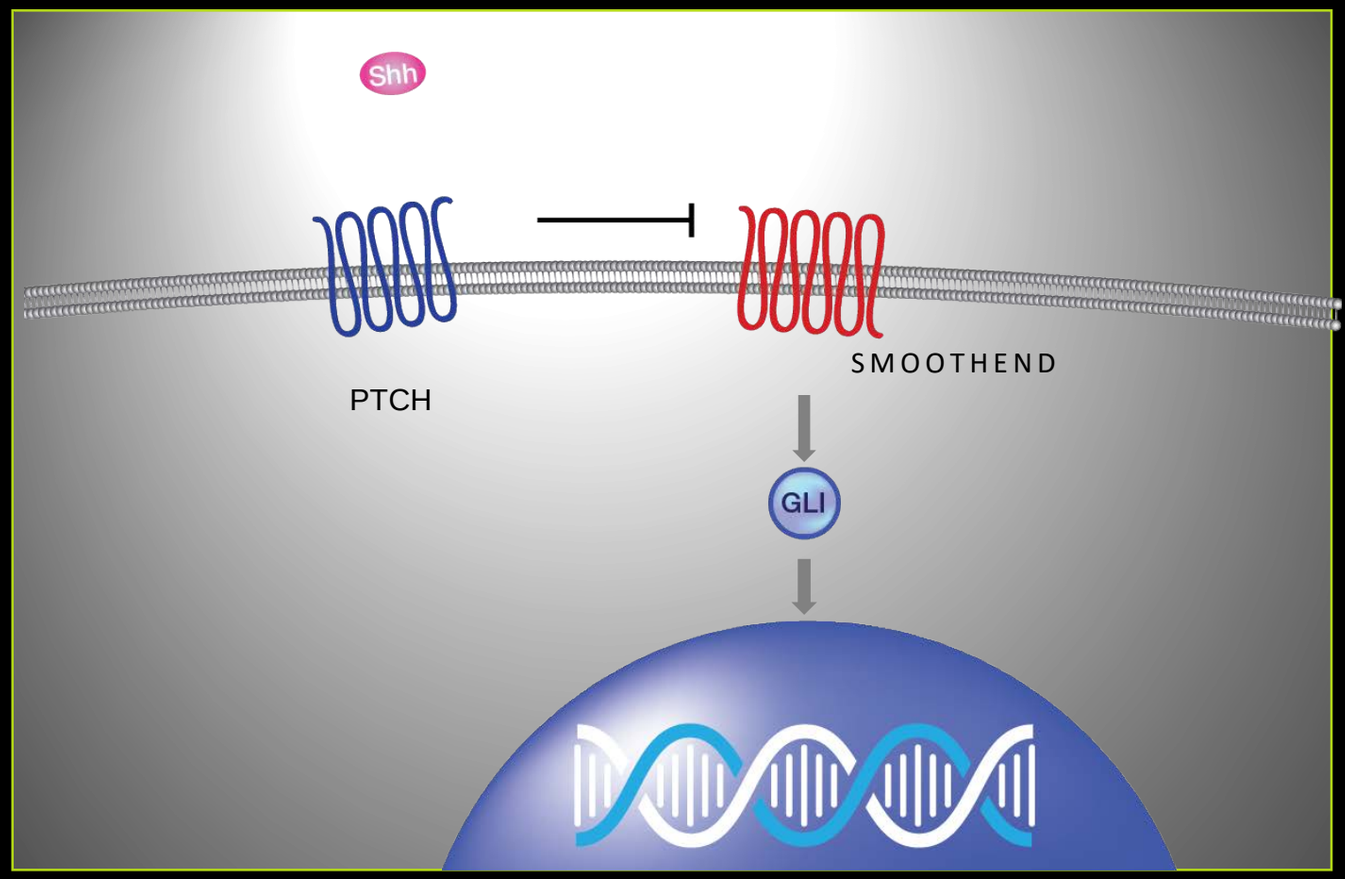
TREAT

BCC

FEED THEM AN HPI

What are HPIs?

SMALL MOLECULE INHIBITOR OF SMOOTHENED OF THE HEDGEHOG MULTISTEP PATHWAY



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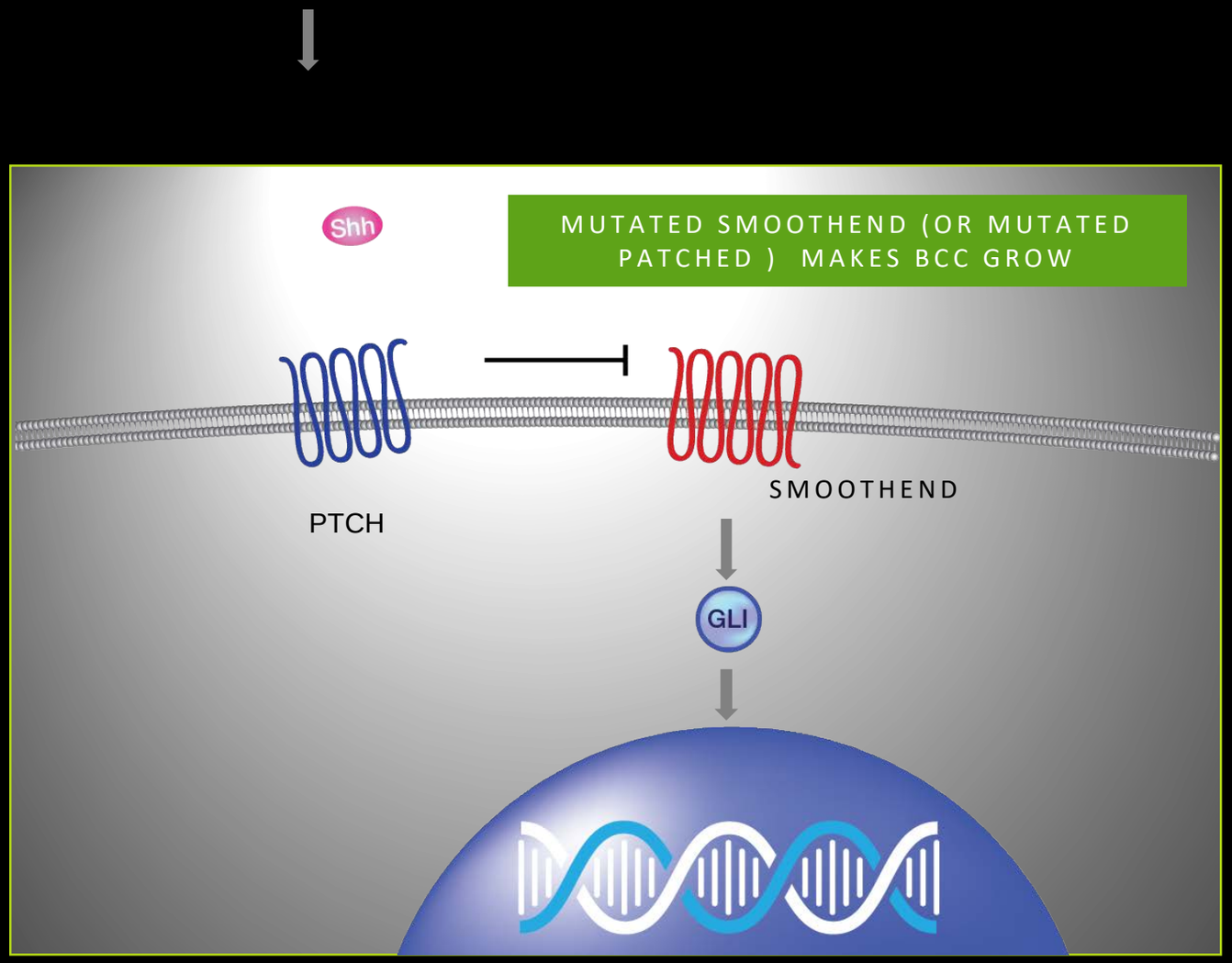

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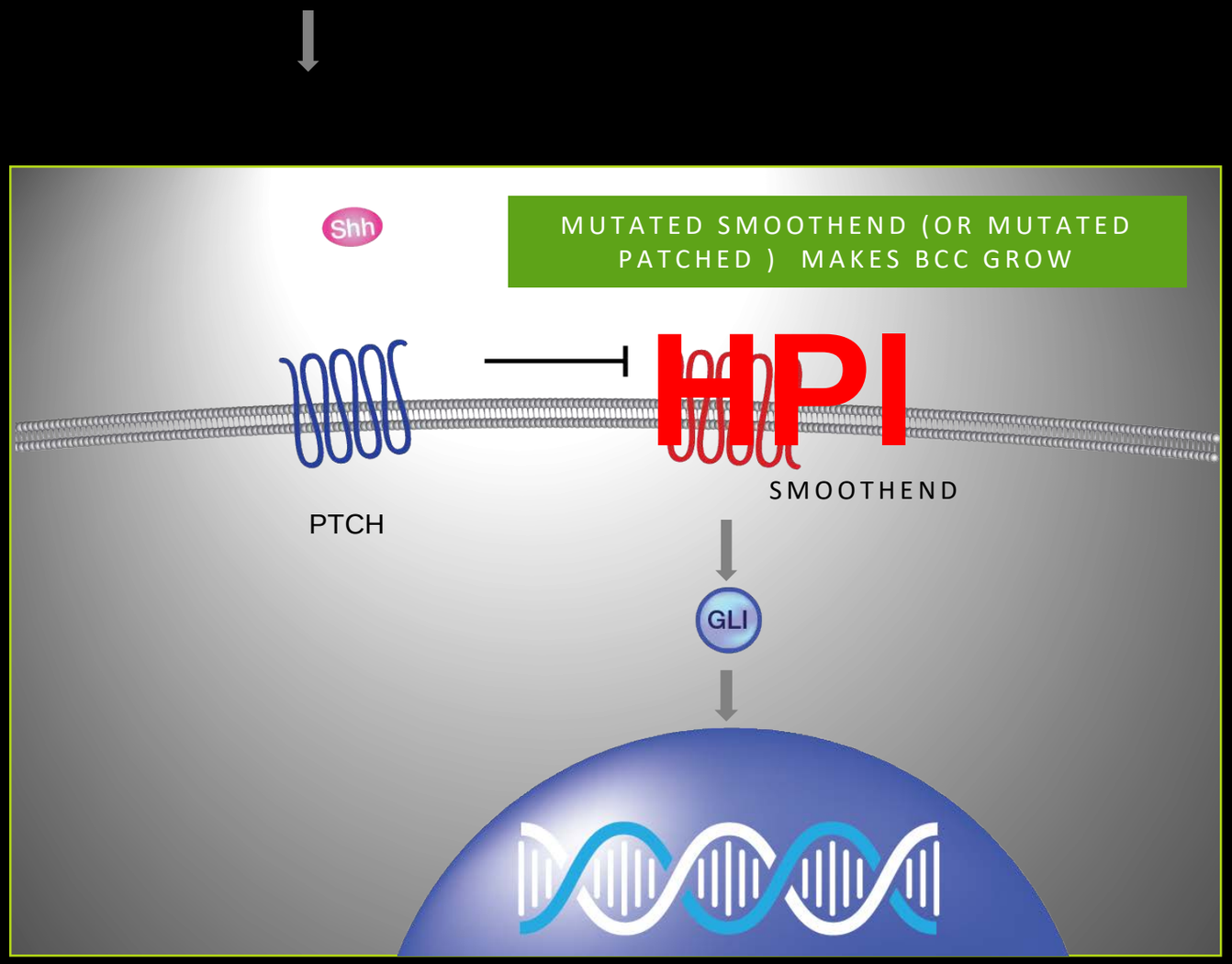
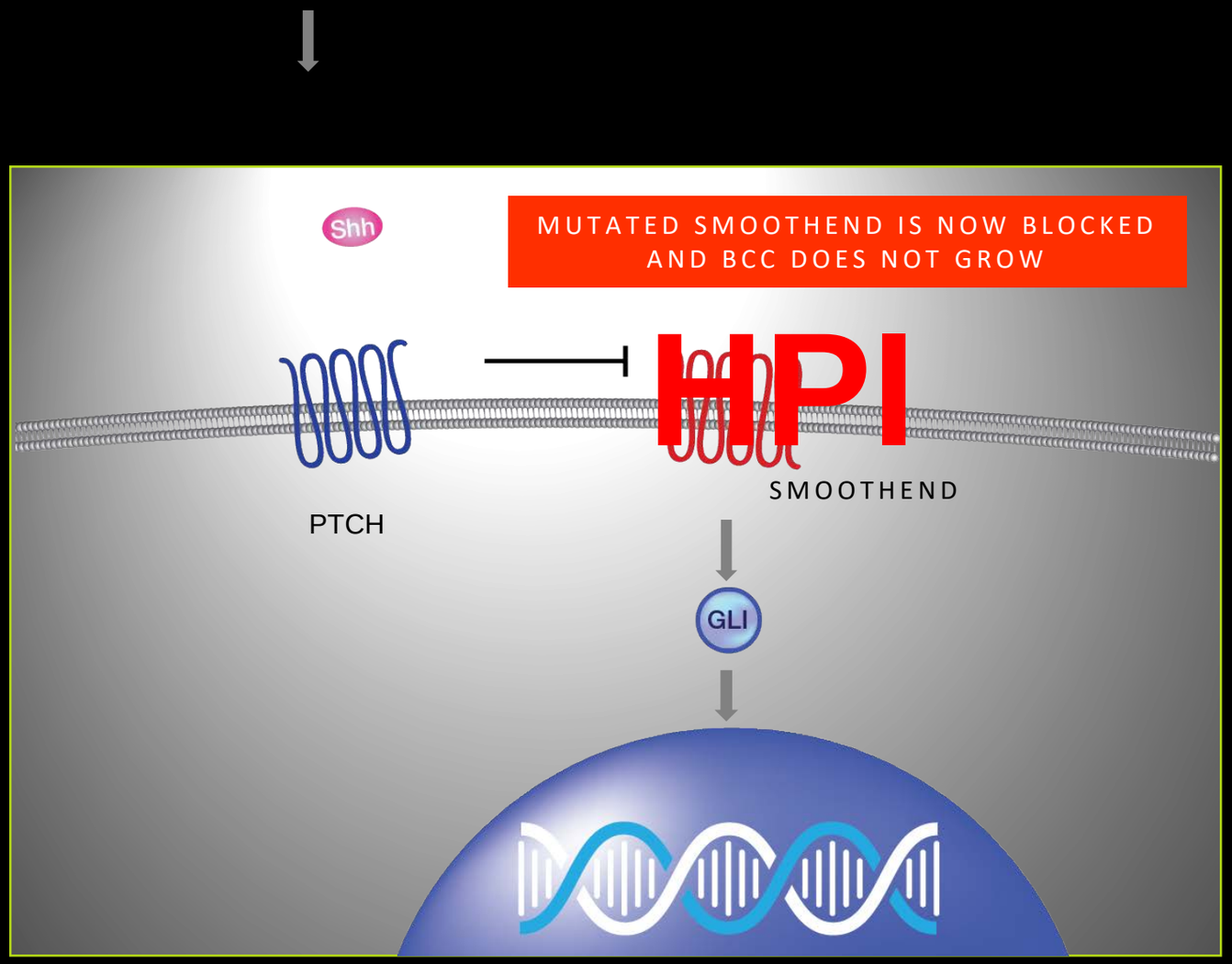


What are HPIs?

SMALL MOLECULE INHIBITOR



HPI for laBCC

- Reversible inhibitors of smoothened molecule in the hedgehog pathway
- Both requite pregnancy control “black box” as teratogen
- Both indicated to treat as long as tolerated or until progression
  - vismodegib: FDA approved for both laBCC and metastatic (mBCC) 2012 daily dose 150mg
  - sonidegib FDA approved for laBCC 2015 daily dose 200 mg

Goals

- WHAT ARE HEDGEHOG PATHWAY INHIBITORS (HPI)?

DO THEY WORK?

HOW LONG DO YOU NEED TO TREAT?

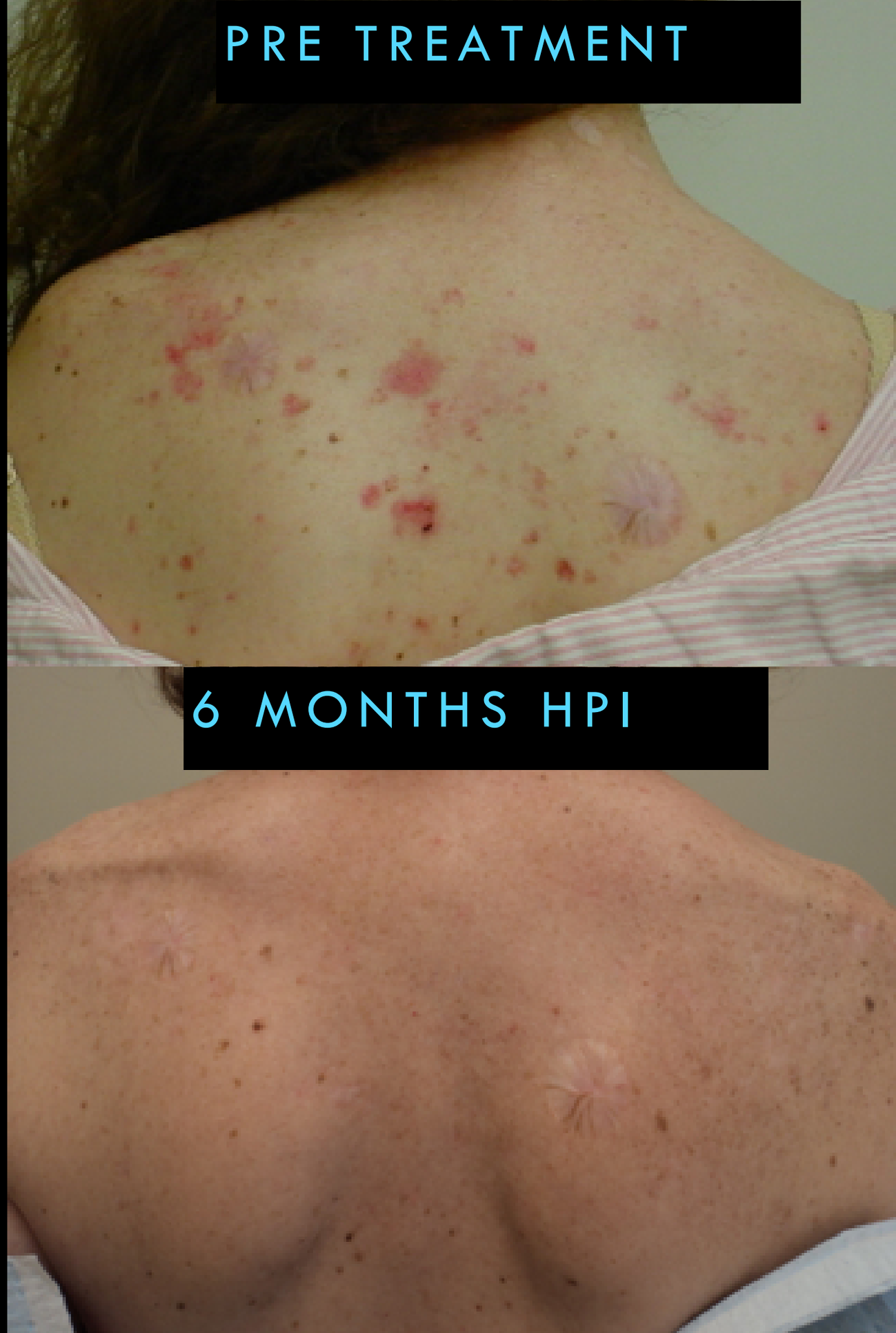
DO THEY HELP WITH SURGERY OR RADIATION TREATMENT?

HOW TO MANAGE “SIDE EFFECTS”

HOW TO MANAGE RESISTANCE?

HPI for laBCC

- work quickly



HPI for laBCC

- work quickly
- potential for cure
- How long to treat?

2 WEEK PULSE

Fig 1. A Hispanic man presented with a large BCC, which was previously treated with radiation. He was started on vismodegib, but treatment abruptly ended after only

Spontaneous resolution of advanced basal cell carcinoma after short-pulse treatment with hedgehog pathway inhibitor.

Jacobsen AA, **Strasswimmer** J.

JAAD Case Rep. 2016 Aug 30;2(4):360-1. doi: 10.1016/j.jdcr.2016.06.010. eCollection 2016 Jul. No abstract available.

HPI for laBCC

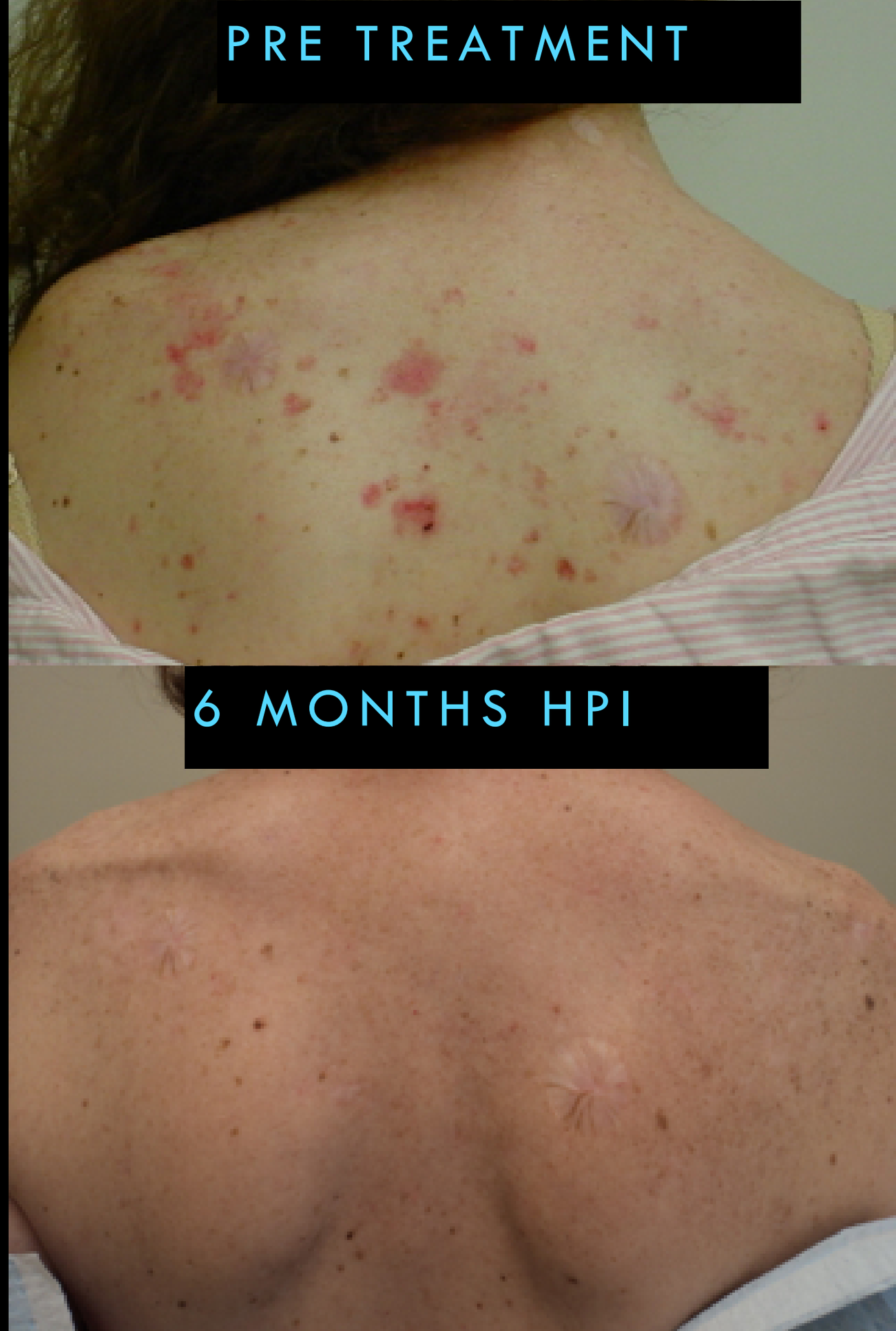
- work quickly

6 YEARS CONTINUOUS THERAPY

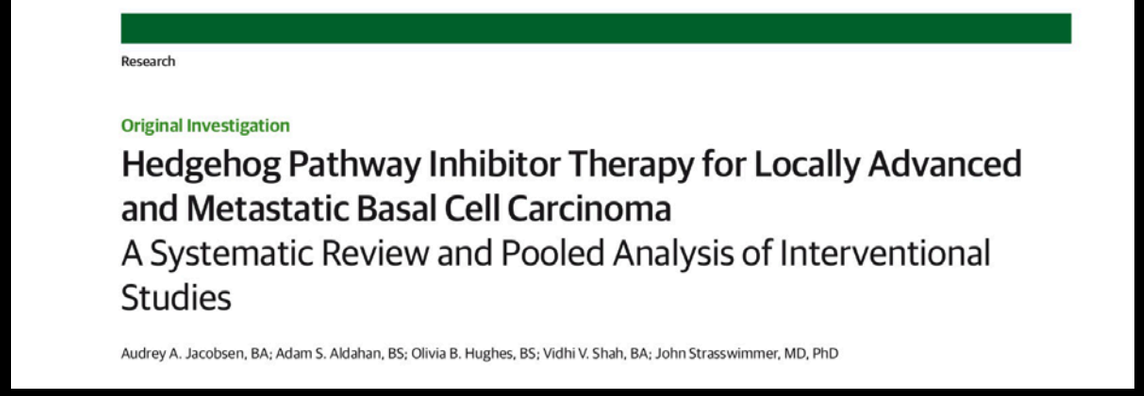
Four-year experience with vismodegib hedgehog inhibitor therapy

To the Editor: Vismodegib for basal cell carcinoma (BCC) is indicated until treatment failure. Long-term administration remains a concern. Two prospective studies report follow-up of only 10[1] and 5.5 months.[2] In another series, more than 33% could not tolerate vismodegib beyond 3 months,[3] and the longest patient series did not report tolerability.[4] We describe our 4-year experience.

Twelve patients (median age, 63 years; range, 34-94 years) with BCC commenced vismodegib therapy (Table I). Three (25%) terminated therapy within 6 months due to adverse events (AE). All others had sustained improvement (mean, 25 months; range, 13-42 months). Two required "medication holidays," and 2 others discontinued after 13 and 17 months due to worsening AEs despite clinical improvement. One



Evidence



Research

Original Investigation

Hedgehog Pathway Inhibitor Therapy for Locally Advanced and Metastatic Basal Cell Carcinoma

A Systematic Review and Pooled Analysis of Interventional Studies

Audrey A. Jacobsen, BA; Adam S. Aldahan, BS; Olivia B. Hughes, BS; Vidhi V. Shah, BA; John Strasswimmer, MD, PhD

- VISMODEGIB
  - ERIVANCE 2012- Phase 2, FDA approval for laBCC (43% ORR) and mBCC (30% ORR)
  - STEVIE 2017 open label 1215 patients 8.9 month duration 68% ORR laBCC 37% mBCC
- SONIDEGIB
  - BOLT 2015 2012- Phase 2, FDA approval for laBCC (43% ORR)
- POOLED ANALYSIS JAMA DERMATOLOGY 2016
  - Audrey A. Jacobsen BS, ; Adam S. Aldahan, BS; Olivia B. Hughes,; Vidhi V. Shah, BA1; John Strasswimmer, MD, PhD
  - ORR 64% (vismodegib) 3 most common adverse effects were muscle spasms (66.4%), alopecia (61.1%) and dysguesia (57.3%) Recommend CPK monitoring for class of medications

PART2 : METHODS TO MANAGE ADVERSE EVENTS

USERS MANUAL FOR HPI

JACOBSEN ET AL PRACTICAL MANAGEMENT OF ADVERSE EVENTS OF HPI THERAPY JAAD 76 (4) 2016

- Molecules active in :
  - hair follicles, GI tract, ovaries
  - probably elsewhere
- Adverse events are in groups:
  - The anticipated, treatment limiting discomforts (alopecia, dysgeusia, leg gramps, fatigue, amenorrhea)
  - medical adverse events (high CPK, electrolyte disturbance, CHF, pregnancy)
  - ? SCC risk

Table 1. Mechanism of Action and Proposed Management for Adverse Effects Due to Hedgehog Pathway Inhibitors

Adverse Effect	Mechanism	Proposed Management
Alopecia	Shh inhibition leads to telogen arrest in the hair follicle cycle[14]	Concealment measures and minoxidil 2-5% continued 6 months post-therapy[12]
Amenorrhea	Reversible FSH inhibition[23]	Counsel on reversibility Early family planning in Gorlin Syndrome cases Monitor for other menopause-like state conditions
Dysguesia and weight loss	HPIs may inhibit taste cell turnover[18]	Early nutritional evaluation and counseling[17] Eliminate extraneous factors of taste alteration[12]
Elevated CPK and muscle spasms	Shh may cause altered calcium transport leading to impaired muscle function[21]	Supportive care Calcium channel blockers (amlodipine) may help[22]
New onset SCC	Possible dedifferentiation of basilosquamous tumors, chronic inflammation (similar to a Marjolin ulcer), and/or SCC collision tumor with the original BCC site[32]	Biopsy for new or persistent ulceration, nodule, or erythema[32] Skin exams during and after therapy for distant SCC

PART2 : METHODS TO MANAGE ADVERSE EVENTS

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- New recognized adverse events are appearing

Table 2. New and/or rare adverse effects due to vismodegib treatment reported in the literature

Amenorrhea due to reversible FSH inhibition[23]
Cholestatic hepatic injury[34] and hepatoxicity[33]
Drug hypersensitivity syndrome[37]
Elevated International Normalized Ratio (INR)[38]
Epidermal cyst formation and hyperkeratosis[39]
New onset congestive heart failure[40]
New onset keratoacanthomas[41]
Persistent alopecia[13]
Squamous cell carcinoma[32,42-46]
Trichodysplasia spinulosum in a Gorlin syndrome patient[47]

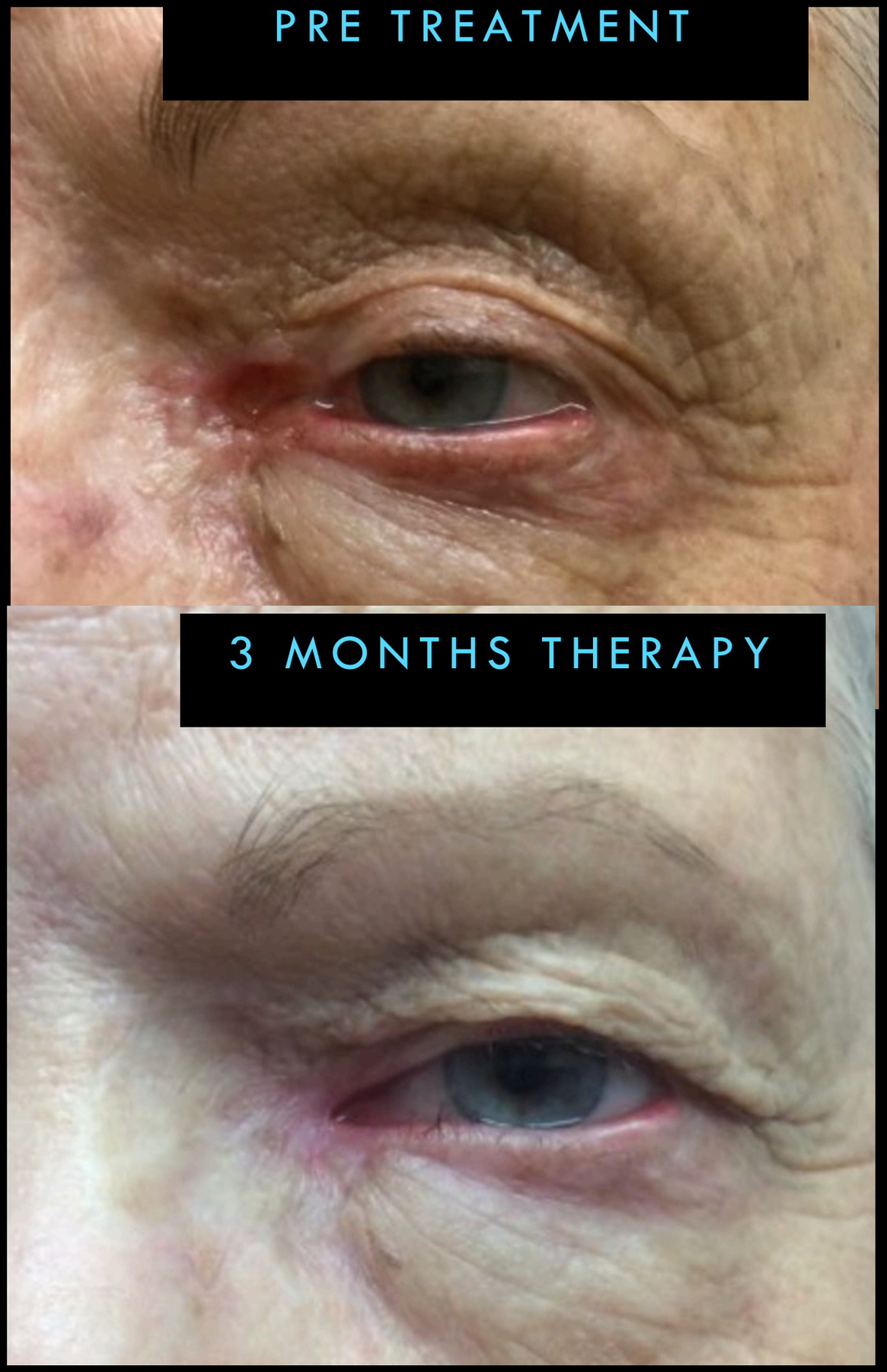
PART 3: RESISTANCE

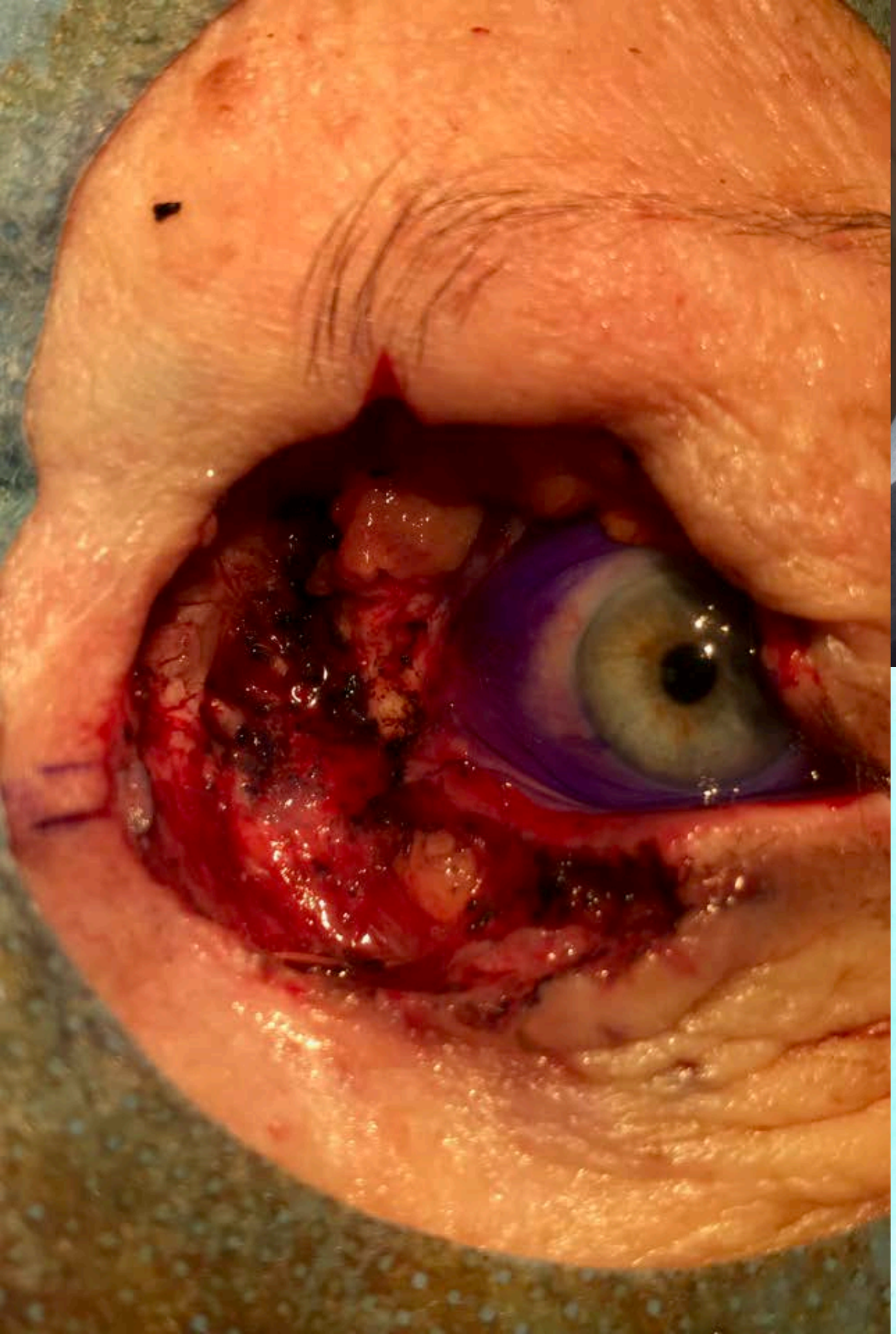
USERS MANUAL FOR HPI

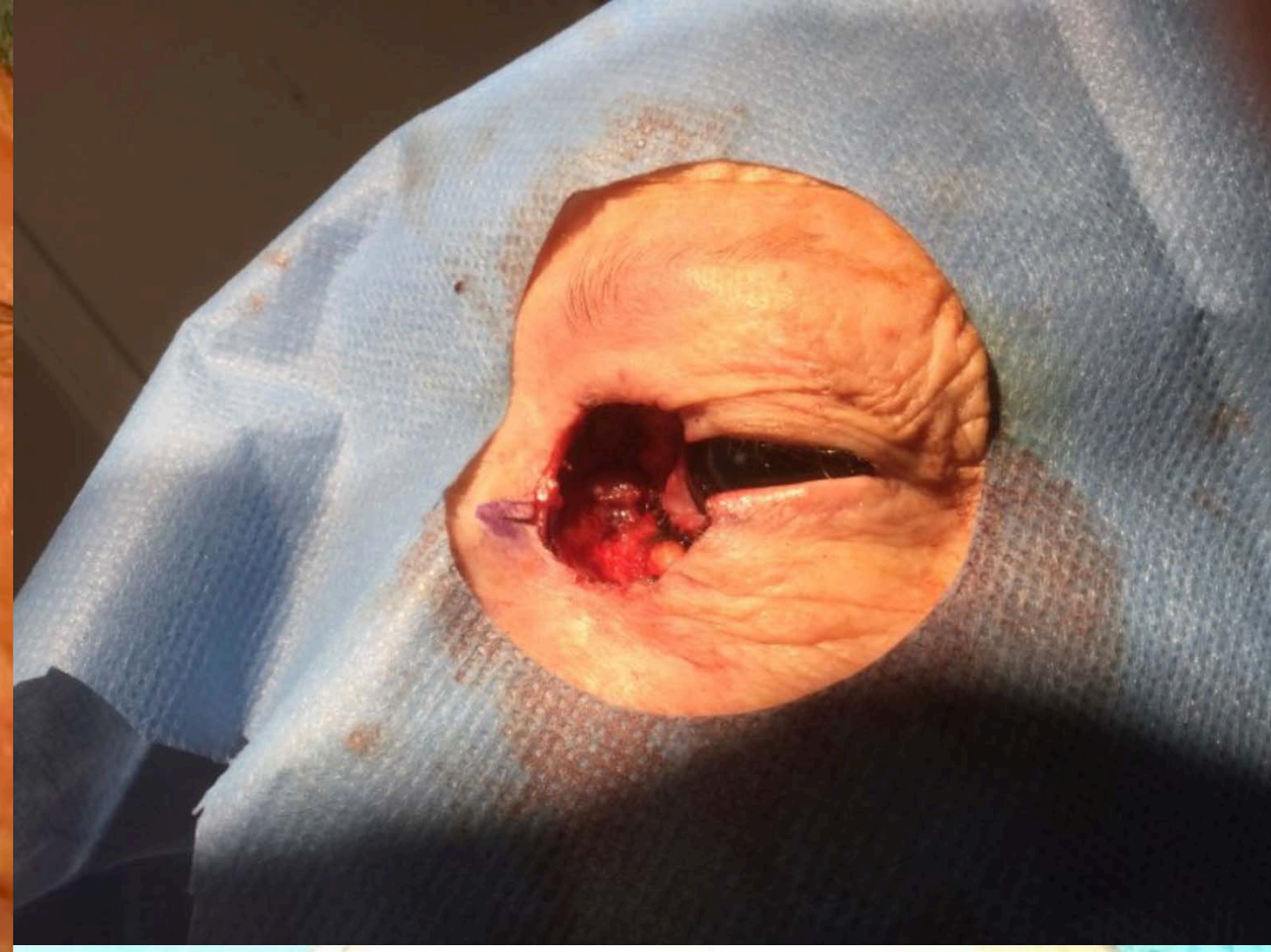
CLINICAL RESISTANCE VS OCCULT RESISTANCE

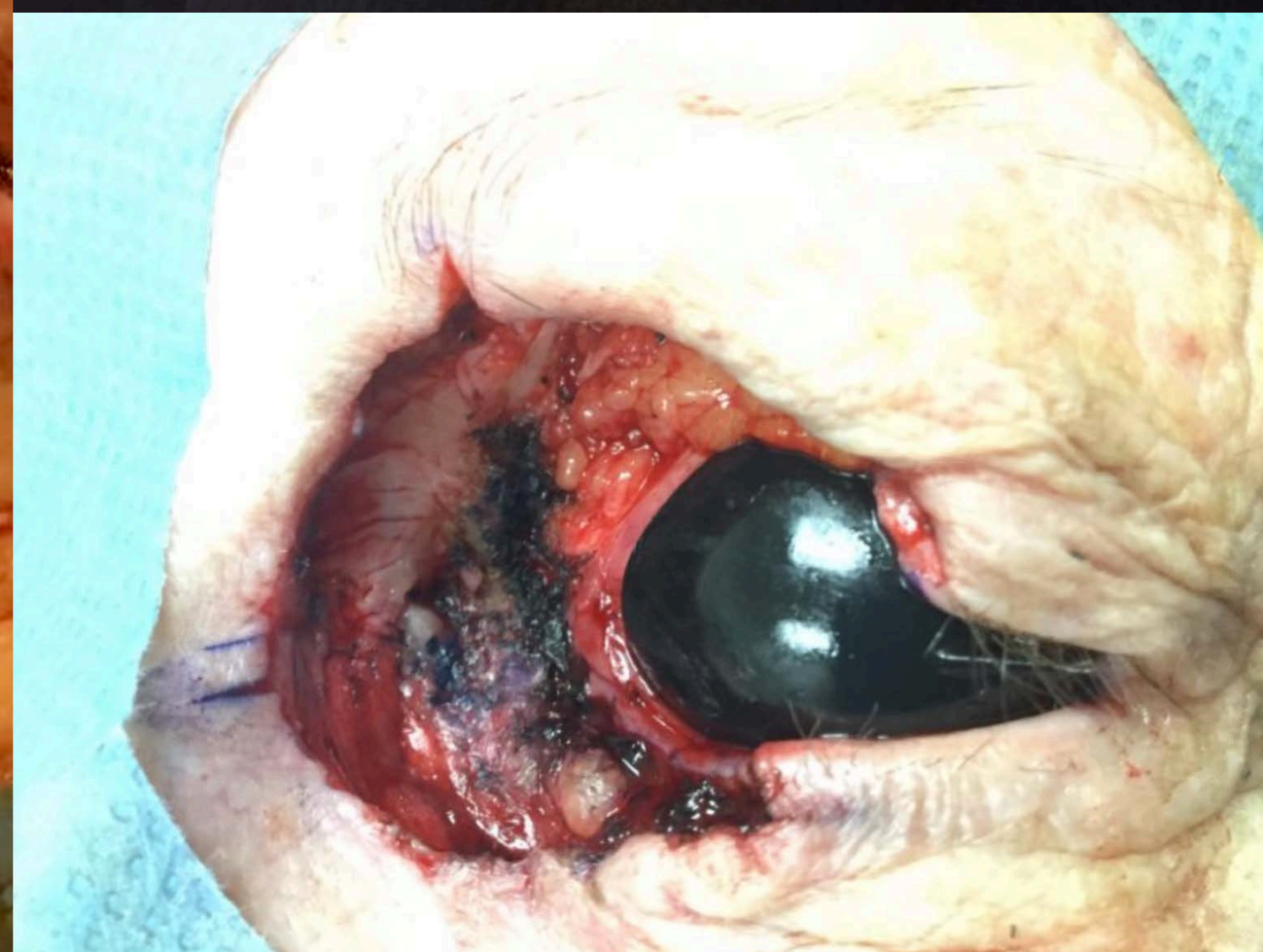
Occult Resistance

- Failed Mohs twice over 5 years
- MRI of orbit = limited
- Repeat MRI = no change









“Time to finish”

MELANOMA 5K APRIL 2018 BOCA RATON

Thank you

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