Universität Rostock Traditio et Innovatio

Universitätsmedizin Rostock

DOC 2022, Nürnberg, 23.06.2022

Zielgerichtete Therapie des Basalzellkarzinoms

Univ.-Prof. Dr. Steffen Emmert

Direktor der Klinik und Poliklinik für Dermatologie und Venerologie Universitätsmedizin Rostock

Disclosures

DUK

1. Director, Clinic for Dermatology and Venereology, University Medical Center Rostock

2. Advisory and Speaker‘s activities:
   Alle onkologische tätigen u.a. Pharmaindustrien: Amgen, BMS, MSD, Novartis, LEO, ROCHE, Sanofi, Sun Pharma, Pierre-Fabre, Almirall, Pfizer, Janssen, Abbvie, UCB, Mayne Genzyme Corporation und CINOGY.

3. Stocks:
   None

4. Financing of studies:
   Cinogy, Mayne, Lilly, DS Biopharma

5. Reviewer activities:
   Public/academic institutions, Occupation cooperatives, Transfer centers

6. Other financial associations:
   None

Basalzellkarzinom

- Epidemiologie und Klinik
- Molekularpathogenese
- Hedgehog Signaling
- Immuntherapie mit Checkpointinhibitoren
- Rhenium SCT

Basalzellkarzinome

Epidemiologie:

BCC sind die häufigsten menschlichen Tumore

BCC ist der häufigste Hautkrebs (65%; 10x SCC)

Prävalenz: 50 pro 100,000
in Deutschland: 17,000-20,000 Fälle pro Jahr

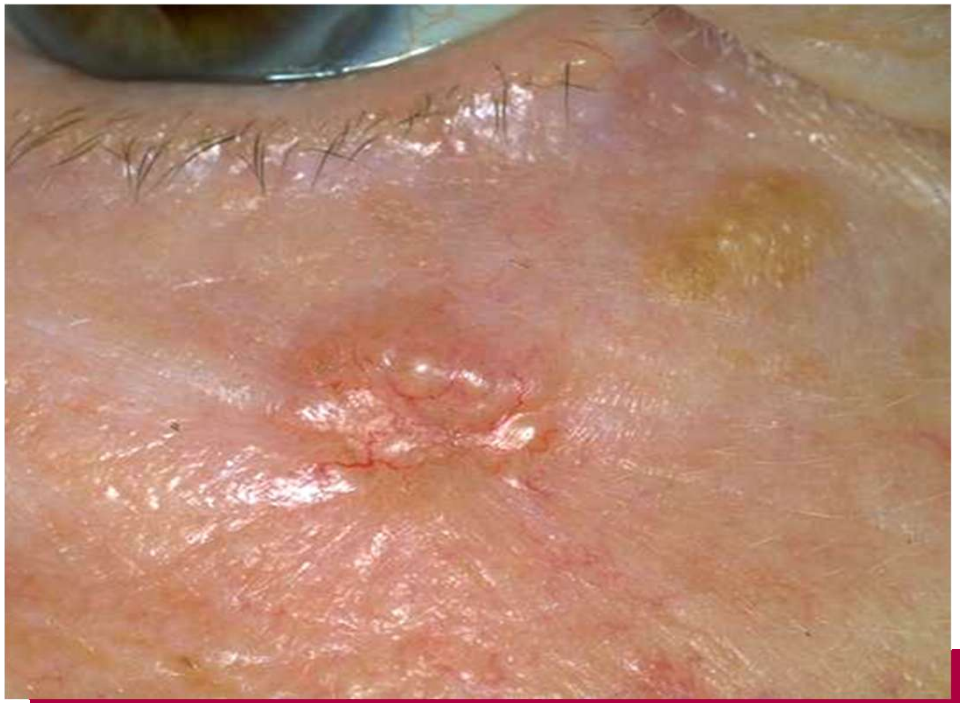
BCC ist ein Alterskrebs (zwischen 60-70 Jahren)

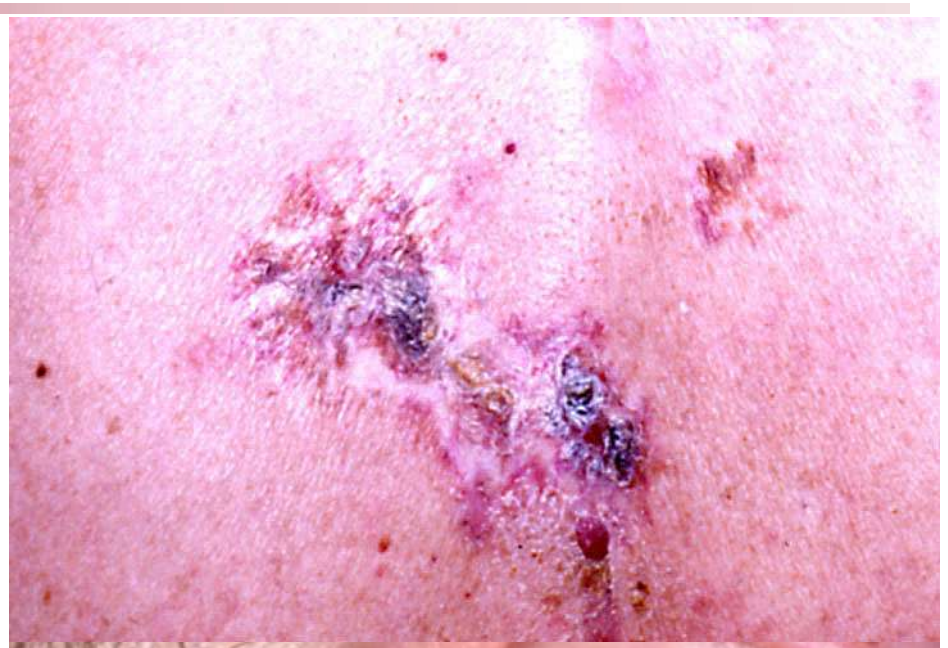
Die Inzidenz steigt mit dem Alter

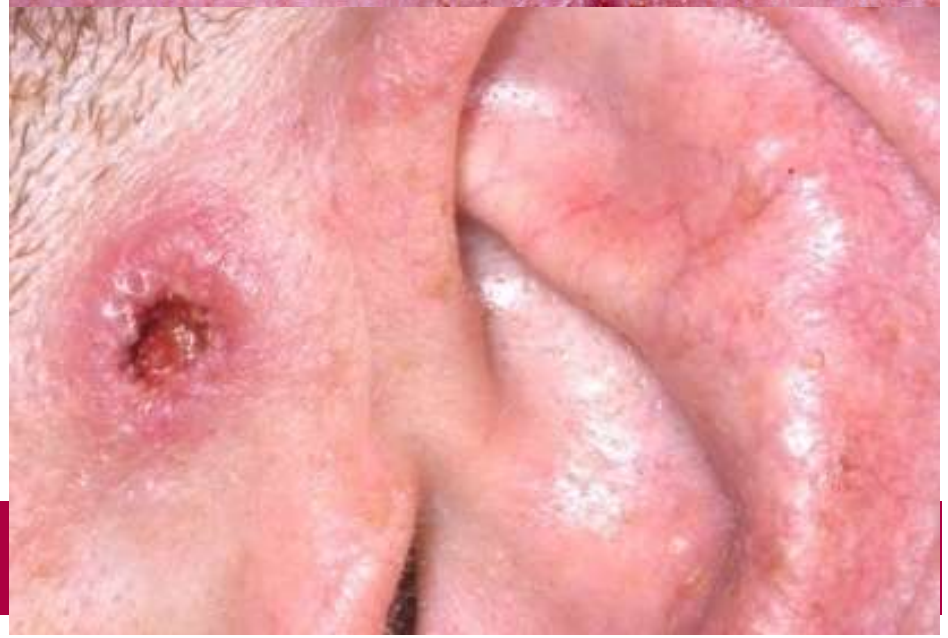
Wuchsformen von BCC

DUK

- Solid, knotiges BCC
- Sklerodermiformes BCC
- Multizentrisch-superfizielles BCC
- Ulzerierend-destruktives BBC
- Pigmentiertes BCC



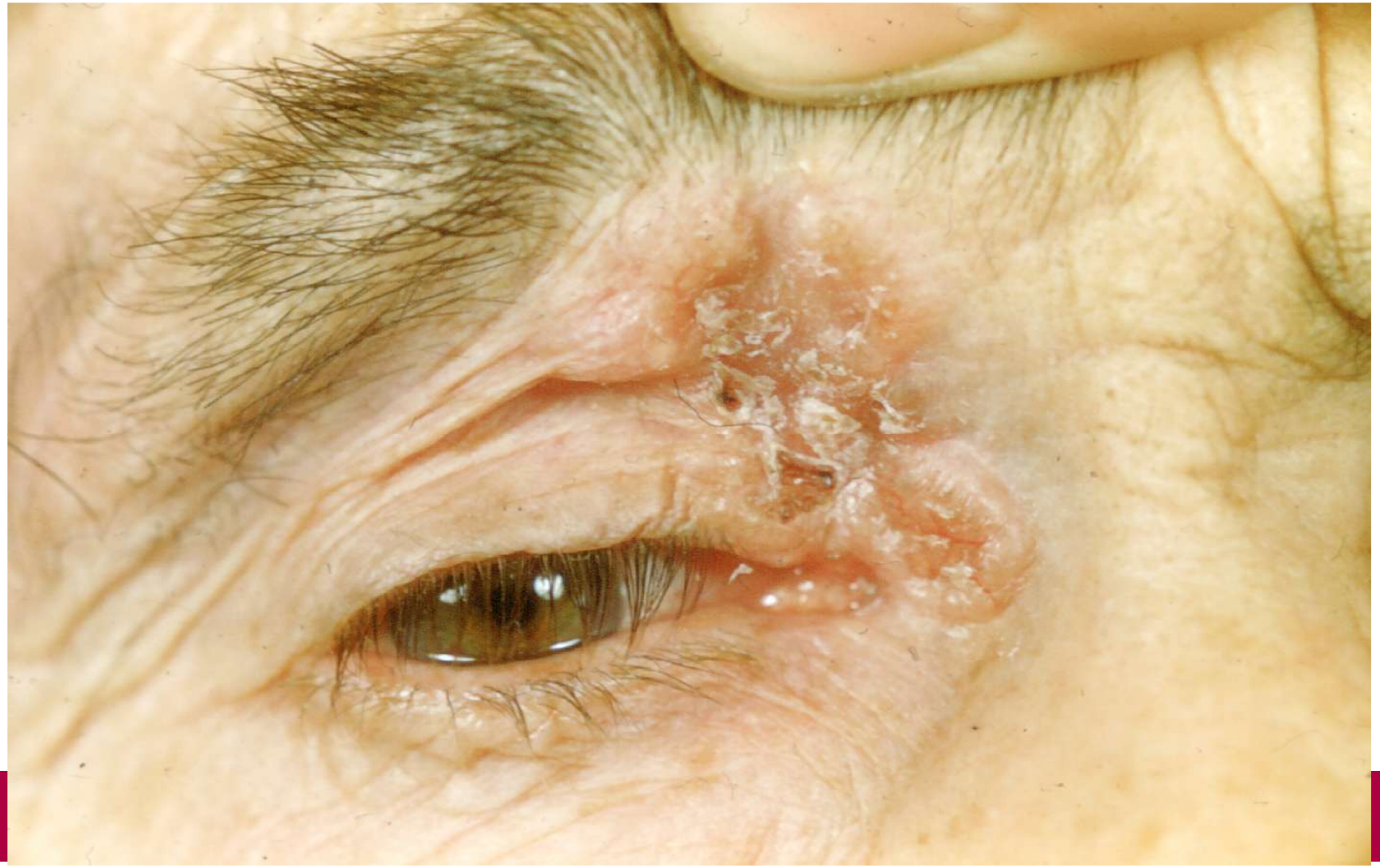




Basalzellkarzinome

DUK

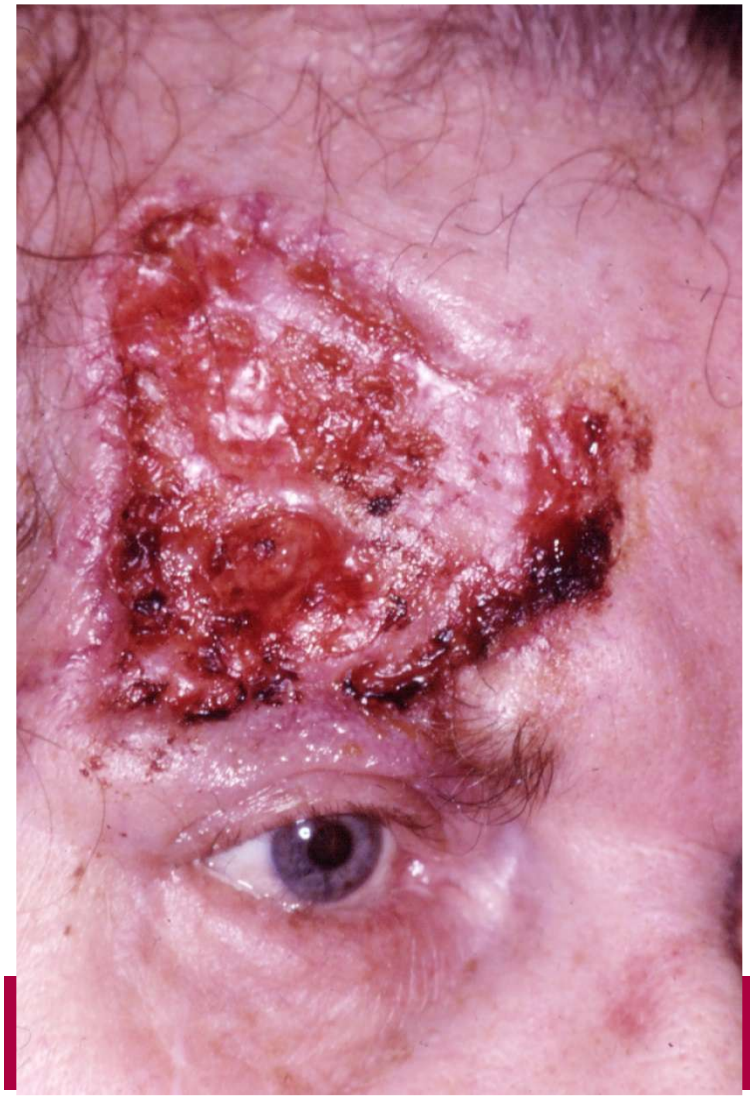
BCC: metastasierend oder chirurgisch schwer resezierbar

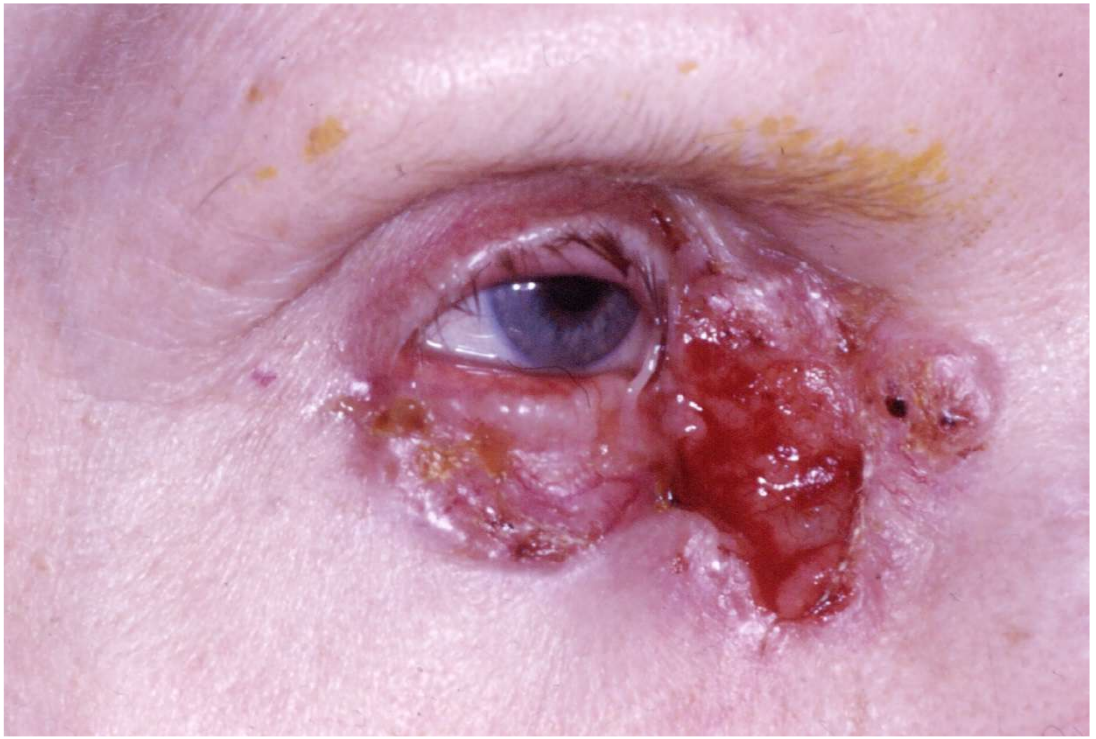


Basalzellkarzinome

DUK

BCC: metastasierend oder chirurgisch schwer resezierbar





Basalzellkarzinom

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- Immuntherapie mit Checkpointinhibitoren
- Rhenium SCT

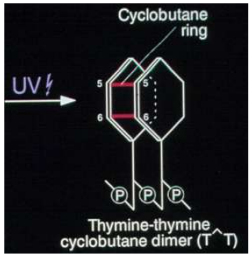
Molekularpathogenese

DUK

Mehrschrittiges Photokarzinogenese Modell

Tumorinitiation

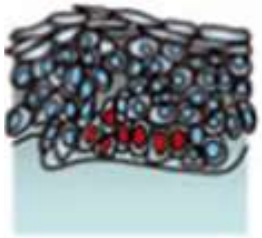
UV



DNA-Schäden

Tumorpromotion

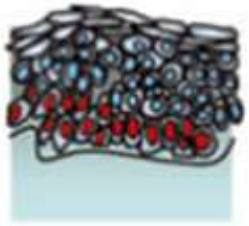
UV



DNA Mutationen in Genomwächtern (p53)

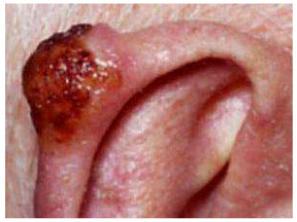
Tumorprogression

UV



Weitere DNA-Mutationen durch Mutator-Phänotyp

Sichtbarer Hautkrebs



Unkontrolliertes Zellwachstum

Nur onko-initiierte Stammzellen bilden Tumore

DUK

298 | NATURE | VOL 536 | 18 AUGUST 2016

ARTICLE

doi:10.1038/nature19069

Defining the clonal dynamics leading to mouse skin tumour initiation

Adriana Sánchez-Danés[1]*, Edouard Hannezo[2,3,4]*, Jean-Christophe Larsimont[1], Mélanie Liagre[1], Khalil Kass Youssef[1], Benjamin D. Simons[2,3,4] & Cédric Blanpain[1,5]

The changes in cell dynamics after oncogenic mutation that lead to the development of tumours are currently unknown. Here, using skin epidermis as a model, we assessed the effect of oncogenic hedgehog signalling in distinct cell populations and their capacity to induce basal cell carcinoma, the most frequent cancer in humans. We found that only stem cells, and not progenitors, initiated tumour formation upon oncogenic hedgehog signalling. This difference was due to the hierarchical organization of tumour growth in oncogene-targeted stem cells, characterized by an increase in symmetric self-renewing divisions and a higher p53-dependent resistance to apoptosis, leading to rapid clonal expansion and progression into invasive tumours. Our work reveals that the capacity of oncogene-targeted cells to induce tumour formation is dependent not only on their long-term survival and expansion, but also on the specific clonal dynamics of the cancer cell of origin.

BCC – Driver Mutationen UV-typisch (75%)

DUK

ORIGINAL ARTICLE

Mutational Landscape of Basal Cell Carcinomas by Whole-Exome Sequencing

Shyam S. Jayaraman[1], David J. Rayhan[2], Salar Hazany[2] and Michael S. Kolodney[1]

Recent advances in sequencing technology allow genome-scale approaches to cancer mutation discovery. Such data-intensive methods have been applied to cutaneous squamous cell carcinomas (SCCs) and melanomas but have not, to our knowledge, been applied to basal cell carcinomas (BCCs). We used whole-exome sequencing to characterize the mutational landscape of sporadic BCCs. We show that BCCs are the most mutated type of human cancer. Tumors from anatomical regions with chronic UV exposure were associated with higher mutation rates than those with intermittent exposure. The majority of all mutations (75.7%) were UV signature. Using a conventional binomial probability model, several genes were found mutated significantly. However, this model assumes a uniform distribution of mutations throughout the genome. We also used a more stringent approach called InVEx that uses a permutation-based framework to pick drivers from passengers. After correction for multiple hypothesis testing, InVEx identified only *PTCH1* (*Patched 1*) as having a significant functional mutation burden. We also found three genes, *STAT5B*, *CRNKL1*, and *NEBL*, with mutational hot spots at a single base in 3 of 12 tumors sequenced. Our findings support the central role of *PTCH1* mutations in BCCgenesis. Moreover, our discovery of the uniquely high number of mutations in this tumor may lend insight into its biological behavior.

Journal of Investigative Dermatology (2014) **134,** 213–220; doi:10.1038/jid.2013.276; published online 25 July 2013

Basalzellkarzinome – viele verschiedene Driver Mutationen

DUK

nature genetics

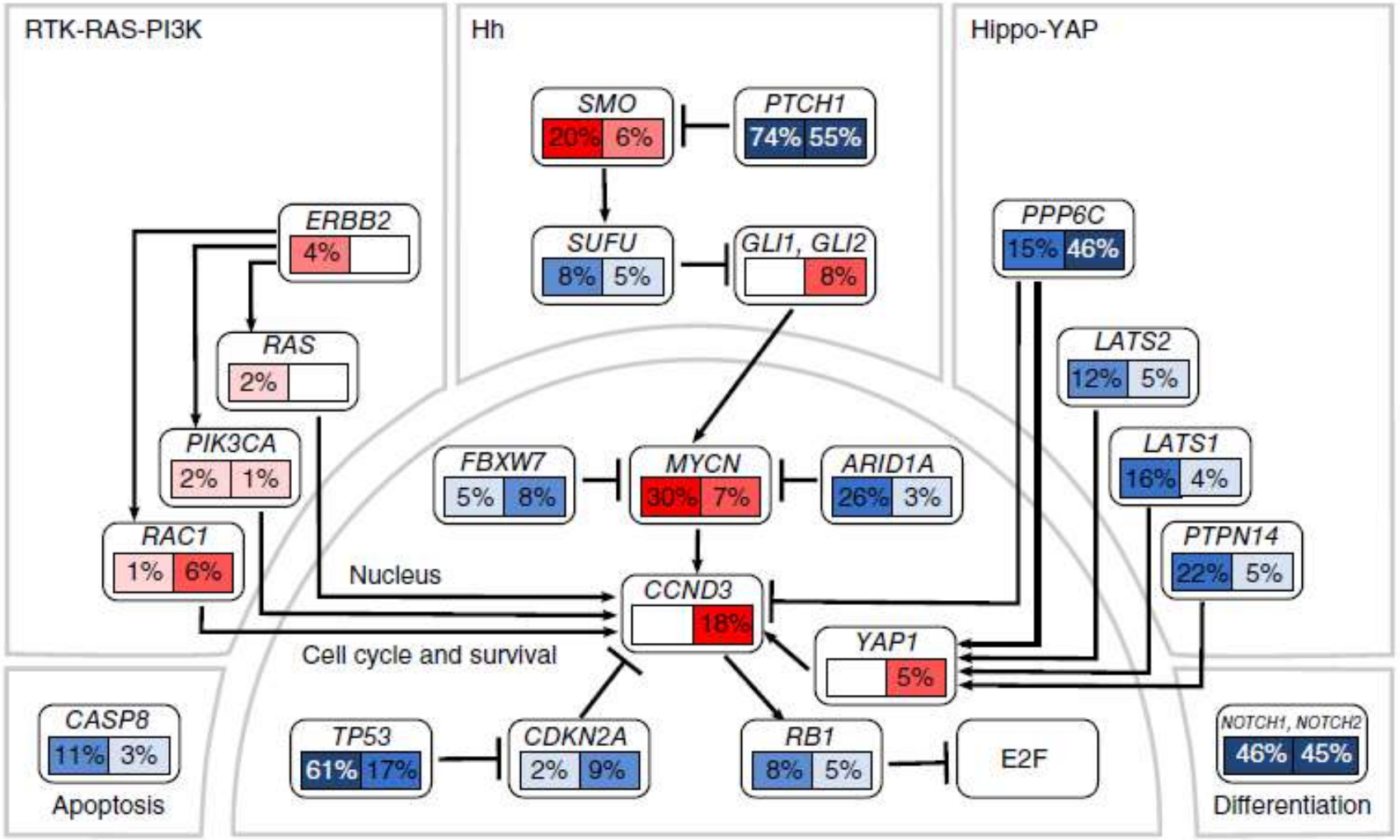
Genomic analysis identifies new drivers and progression pathways in skin basal cell carcinoma

Ximena Bonilla[1,19], Laurent Parmentier[2,19], Bryan King[3], Fedor Bezrukov[4,5], Gürkan Kaya[6], Vincent Zoete[7], Vladimir B Seplyarskiy[8–10], Hayley J Sharpe[11], Thomas McKee[12], Audrey Letourneau[1], Pascale G Ribaux[1], Konstantin Popadin[1], Nicole Basset-Seguin[13], Rouaa Ben Chaabene[1], Federico A Santoni[1,14], Maria A Andrianova[8–10], Michel Guipponi[14], Marco Garieri[1], Carole Verdan[12], Kerstin Grosdemange[6], Olga Sumara[15], Martin Eilers[15,16], Iannis Aifantis[3], Olivier Michielin[7,17], Frederic J de Sauvage[11], Stylianos E Antonarakis[1,14,18] & Sergey I Nikolaev[1,14]

Basal cell carcinoma (BCC) of the skin is the most common malignant neoplasm in humans. BCC is primarily driven by the Sonic Hedgehog (Hh) pathway. However, its phenotypic variation remains unexplained. Our genetic profiling of 293 BCCs found the highest mutation rate in cancer (65 mutations/Mb). Eighty-five percent of the BCCs harbored mutations in Hh pathway genes (*PTCH1*, 73% or *SMO*, 20% ($P = 6.6 \times 10^{-8}$) and *SUFU*, 8%) and in *TP53* (61%). However, 85% of the BCCs also harbored additional driver mutations in other cancer-related genes. We observed recurrent mutations in *MYCN* (30%), *PPP6C* (15%), *STK19* (10%), *LATS1* (8%), *ERBB2* (4%), *PIK3CA* (2%), and *NRAS*, *KRAS* or *HRAS* (2%), and loss-of-function and deleterious missense mutations were present in *PTPN14* (23%), *RB1* (8%) and *FBXW7* (5%). Consistent with the mutational profiles, N-Myc and Hippo-YAP pathway target genes were upregulated. Functional analysis of the mutations in *MYCN*, *PTPN14* and *LATS1* suggested their potential relevance in BCC tumorigenesis.

Basalzellkarzinome – viele verschiedene Driver Pathways

DUK

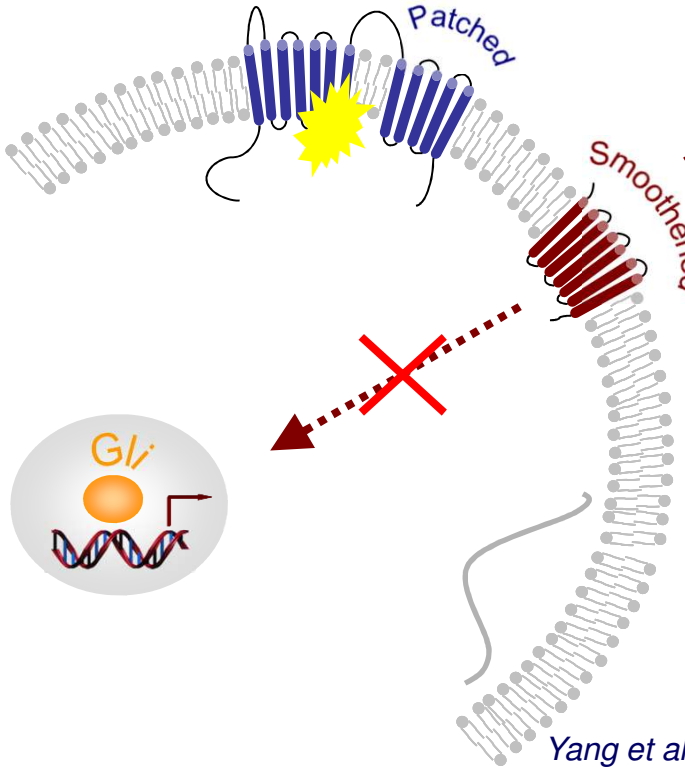


Basalzellkarzinom

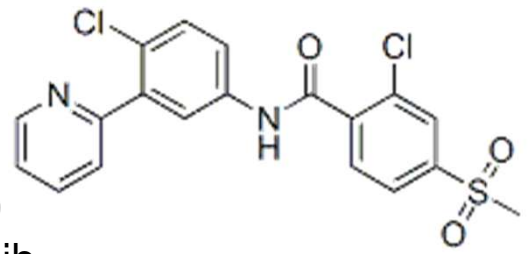
- Epidemiologie und Klinik
- Molekularpathogenese
- Hedgehog Signaling
- Immuntherapie mit Checkpointinhibitoren
- Rhenium SCT

Kleine Moleküle (Inhibitoren) der Hedgehog-Signalkaskade

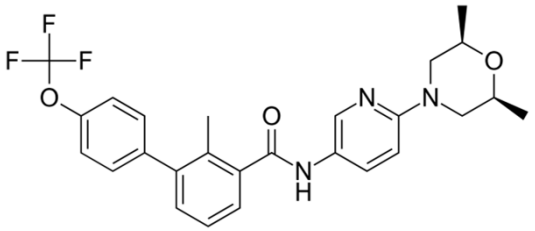
Basalzellnävussyndrom



GDC0449
Vismodegib
(Erivedge)



LDE225
Sonidegib
(Odomzo)



Yang et al., 2009, Oncogene; von Hoff et al. 2009, N Engl J Med.

Basalzellkarzinome – neue therapeutische Optionen

DUK

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inhibition of the Hedgehog Pathway in Advanced Basal-Cell Carcinoma

Daniel D. Von Hoff, M.D., Patricia M. LoRusso, D.O., Charles M. Rudin, M.D., Ph.D., Josina C. Reddy, M.D., Ph.D., Robert L. Yauch, Ph.D., Raoul Tibes, M.D., Glen J. Weiss, M.D., Mitesh J. Borad, M.D., Christine L. Hann, M.D., Ph.D., Julie R. Brahmer, M.D., Howard M. Mackey, Ph.D., Bertram L. Lum, Pharm.D., Walter C. Darbonne, M.S., James C. Marsters, Jr., Ph.D., Frederic J. de Sauvage, Ph.D., and Jennifer A. Low, M.D., Ph.D.

CONCLUSIONS

GDC-0449, an orally active small molecule that targets the hedgehog pathway, appears to have antitumor activity in locally advanced or metastatic basal-cell carcinoma. (ClinicalTrials.gov number, NCT00607724.)

N ENGL J MED 361;12 NEJM.ORG SEPTEMBER 17, 2009

Basalzellkarzinome – systemische Vismodegib-Gabe

DUK

J Am Acad Dermatol
June 2015

Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC

Aleksandar Sekulic, MD,[a] Michael R. Migden, MD,[b] Karl Lewis, MD,[c] John D. Hainsworth, MD,[d] James A. Solomon, MD, PhD,[e,f,g] Simon Yoo, MD,[b] Sarah T. Arron, MD, PhD,[i] Philip A. Friedlander, MD, PhD,[j,k] Ellen Marmur, MD,[k] Charles M. Rudin, MD, PhD,[l] Anne Lynn S. Chang, MD,[m] Luc Dirix, MD, PhD,[n] Jeannie Hou, MD,[o] Huibin Yue, PhD,[o] and Axel Hauschild, MD,[p] on behalf of the ERIVANCE BCC investigators

Scottsdale, Arizona; Houston, Texas; Denver, Colorado; Nashville, Tennessee; Ormond Beach and Orlando, Florida; Urbana and Evanston, Illinois; San Francisco, Palo Alto, and South San Francisco, California; Boston, Massachusetts; New York, New York; Baltimore, Maryland; Antwerp, Belgium; and Kiel, Germany

CAPSULE SUMMARY

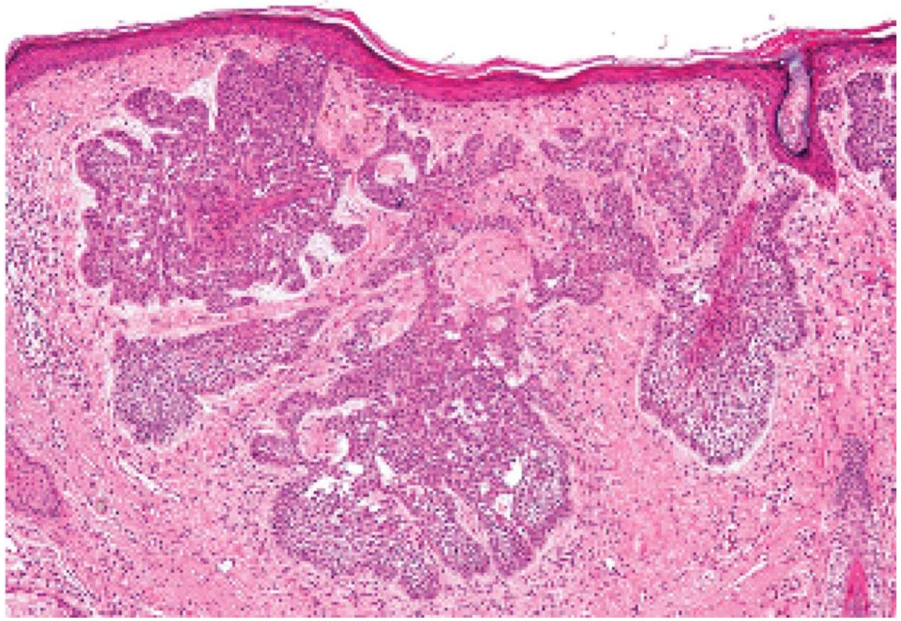
- Vismodegib is approved for adults with advanced basal cell carcinoma (BCC) that has recurred after surgery or who are not candidates for surgery or radiation.
- We provide an additional 12 months of follow-up from the ERIVANCE BCC study.
- Durability of efficacy and confirmed safety of vismodegib is demonstrated in patients with advanced BCC.

METHODS:
This was a multinational, multicenter, nonrandomized, 2-cohort study in patients with measurable and histologically confirmed locally advanced or metastatic BCC taking **oral vismodegib (150 mg/d)**. Primary outcome measure was objective response rate (complete and partial responses) assessed by independent review facility.

RESULTS:
After 12 months of additional follow-up, median duration of **exposure to vismodegib was 12.9 months**. Objective **response rate** increased from **30.3% to 33.3%** in patients with metastatic disease, and from **42.9% to 47.6%** in patients with the locally advanced form. Median **duration of response** in patients with locally advanced BCC increased from **7.6 to 9.5 months**. No new safety signals emerged with extended treatment duration.

Basalzellkarzinome – systemische Sonidegib-Gabe

DUK



The FDA approved sonidegib, another SMO inhibitor, based on results from the **phase II BOLT study**, which compared two doses (200 mg and 800 mg per day, given orally) in 194 patients with locally advanced BCC who were ineligible for surgery or radiation. Sonidegib showed durable antitumor activity, with **58% of the patients given the 200 mg dose achieving an objective response**.

Cancer Discovery 2015;5:1011.

Basalzellkarzinom

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- Rhenium SCT

European Journal of Cancer 77 (2017) 84–87

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Letter to the Editor

Regression of melanoma metastases and multiple non-melanoma skin cancers in xeroderma pigmentosum by the PD1-antibody pembrolizumab☆

Axel Hauschild*, Julia Eichstaedt, Lena Möbus, Katharina Kähler, Michael Weichenthal, Thomas Schwarz, Stephan Weidinger

Department of Dermatology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany

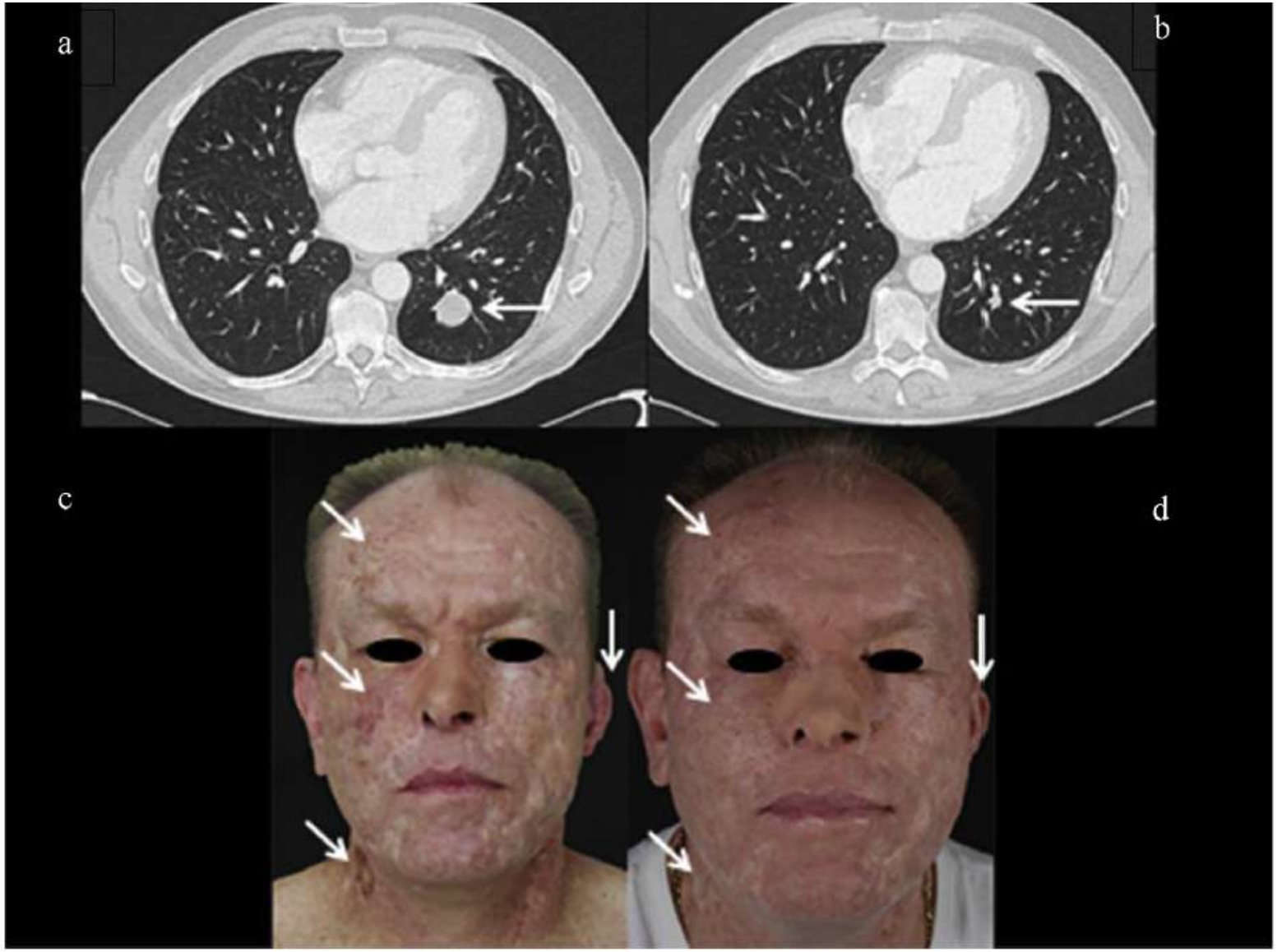

Fig. 1. Lung metastases of the right upper lobe (a) and non-melanoma skin cancers of the sun-damaged skin in the face (c) before pembrolizumab treatment and in the follow-up after six months (b and d). Arrows indicate NMSC as target lesions.

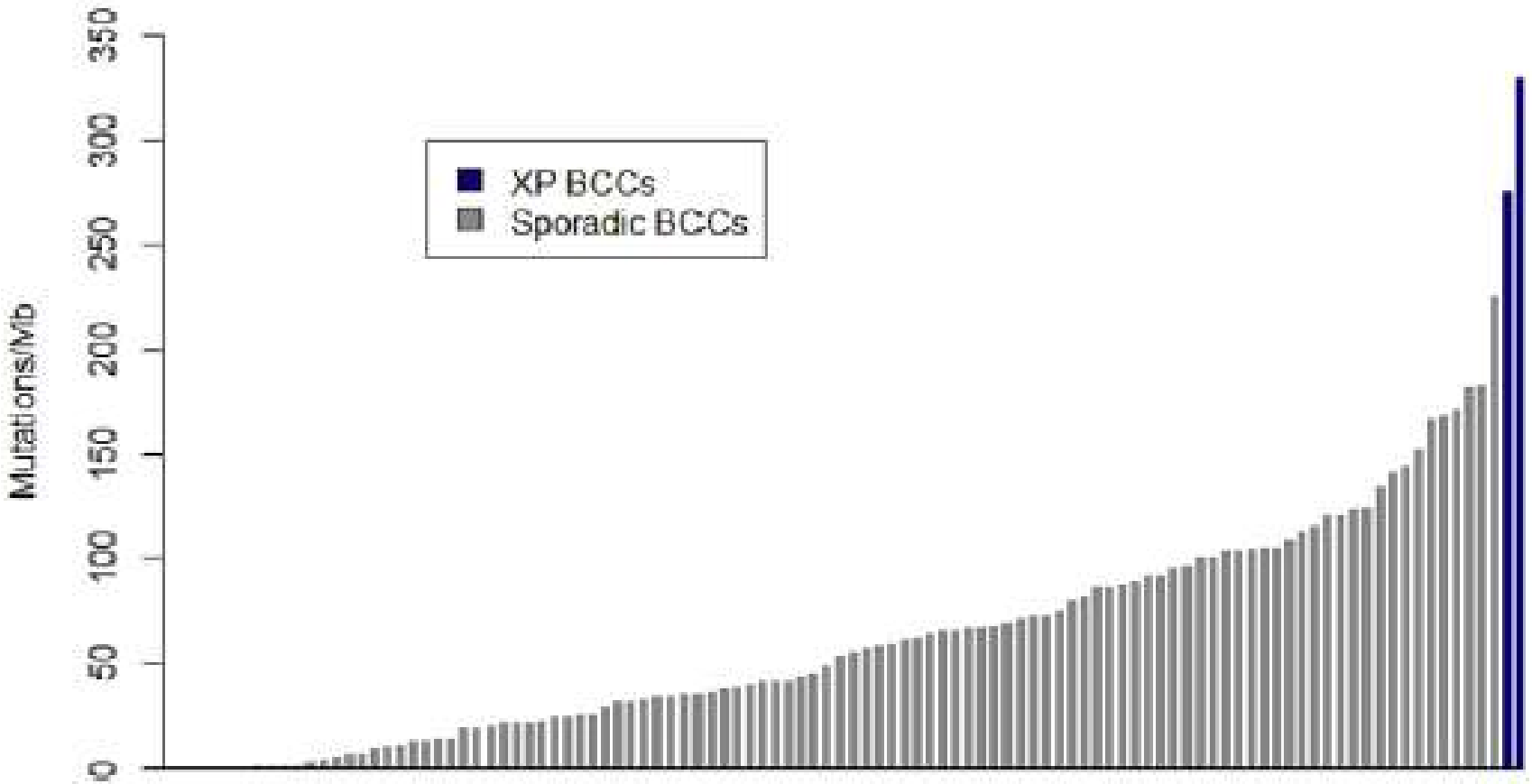

Fig. 2. Mutational burden per megabase of XP-associated BCCs of our patient (blue bars) compared to published data on 100 sporadic BCCs (grey bars). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Cemiplimab (REGN2810)

DUK

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site

Home > Search Results > Study Record Detail

Save this study

PD-1 in Patients With Advanced Basal Cell Carcinoma Who Experienced Progression of Disease on Hedgehog Pathway Inhibitor Therapy, or Were Intolerant of Prior Hedgehog Pathway Inhibitor Therapy

A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1, in Patients With Advanced Basal Cell Carcinoma Who Experienced Progression of Disease on Hedgehog Pathway Inhibitor Therapy, or Were Intolerant of Prior Hedgehog Pathway Inhibitor Therapy

Study Design

Study Type:	Interventional (Clinical Trial)
Estimated Enrollment:	137 participants
Allocation:	Non-Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programm Pathway Inhibitor Therapy, or Were Intolerant of Prior Hedgehog Pathway Inhibito
Actual Study Start Date:	June 30, 2017
Estimated Primary Completion Date:	July 2018
Estimated Study Completion Date:	December 2020

Cemiplimab (REGN2810)

DUK

PARIS and TARRYTOWN, NY – June 25, 2021 – The European Commission (EC) has approved Sanofi and Regeneron's PD-1 inhibitor Libtayo® (cemiplimab) to treat adults with locally advanced or metastatic basal cell carcinoma (BCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).

The EC approval in BCC is based on data from the largest prospective clinical trial (n=119) in patients with advanced BCC previously treated with an HHI to date. Libtayo-treated patients with locally advanced BCC experienced an objective response rate (ORR) of 32% (95% confidence interval [CI]: 22-43) (25% partial response, 7% complete response) by independent central review. Libtayo-treated patients with metastatic BCC demonstrated an ORR of 29% (95% CI: 15-46) (26% partial response, 3% complete response) by investigator assessment. In addition, approximately 90% of patients across both groups had a duration of response (DOR) of 6 months or longer per Kaplan Meier estimates, and the median DOR has not been reached for either group. Median duration of follow-up was 16 months for locally advanced BCC and 9 months for metastatic BCC.

Basalzellkarzinom

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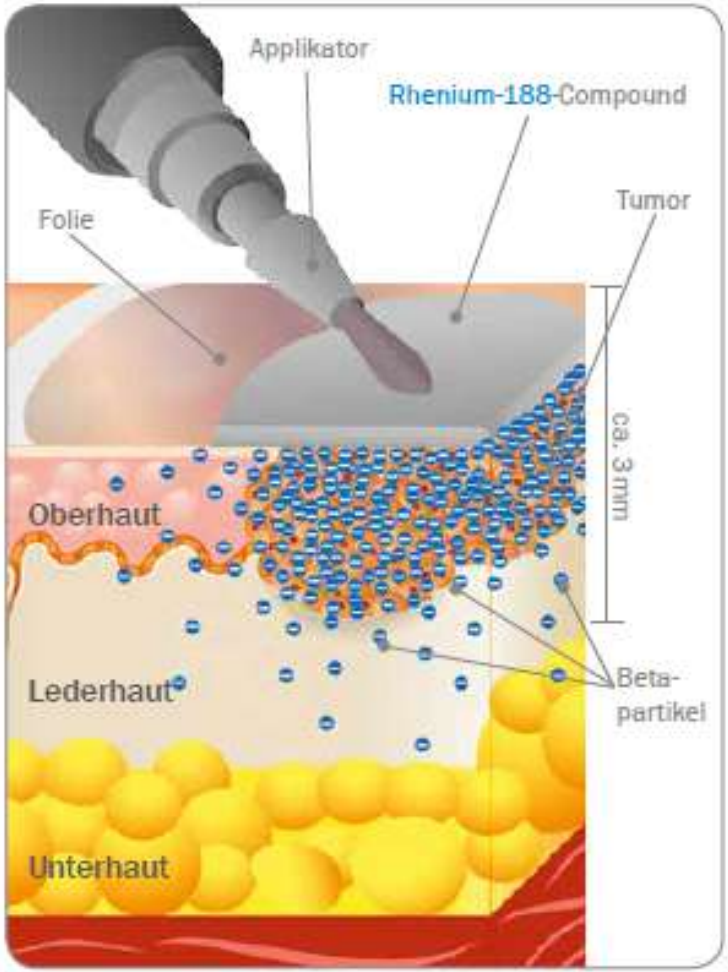
- Rhenium SCT

Rhenium SCT

DUK

Epidermale Radioisotopen-Therapie zur Behandlung dünner Basalzell- und Plattenepithelkarzinome



- Rhenium-188 ist ein speziell für medizinische Zwecke hergestelltes Radioisotop (Betastrahler)
- Eindringtiefe ca. 2-3 mm (92% der Dosis bis 3 mm)
- Rhenium-SCT geeignet für dünne BCC und SCC inkl. M. Bowen

Rhenium SCT

DUK

Carpoulen gefüllt mit Rhenium-188-Compound

Der mit einer Carpoule geladene Applikator

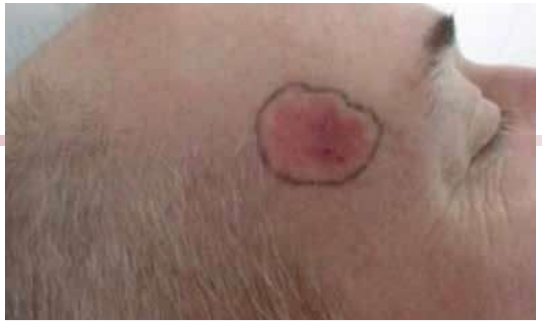
Behandlungseinheit der Rhenium-SCT®

smedizin

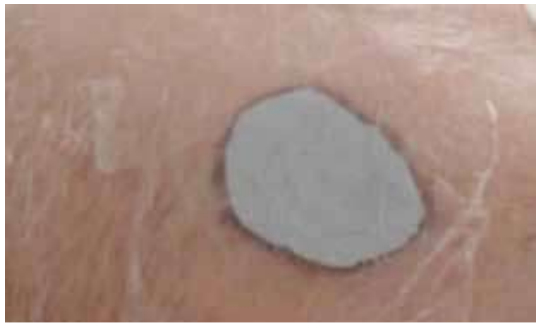
Rhenium SCT

DUK

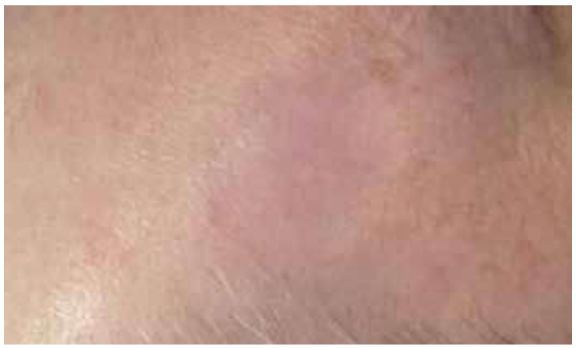
- **Zulassung als Medizinprodukt**
- **Strahlentherapie (Betastrahler)**
- **1-2 h Einwirkzeit,**
- **Lokale NW: Rötung, Radiodermatitis**
- **Keine systemischen NW**
- **Sehr gute kosmetische Ergebnisse**
- **Komplette Heilungsrate: 89% nach einmaliger Applikation**
- **1,5% Rezidivrate nach 12-78 Monaten Follow-Up**



Markierung der Läsion und Vorbereitung der Behandlungsfläche



Rhenium-188-Compound wird auf Folie aufgetragen, Behandlungszeit patientenindividuell (45 – 180 Minuten)



Heilungsprozess und Bildung von neuem Gewebe nach 30 – 180 Tagen

Erste Studienergebnisse zur Behandlung von Nicht-Melanozytärem Hautkrebs mit der Rhenium-SCT®- Eine Alternative zur OP?

Julia K. Tietze[1], Sarah Schwarzenböck[2], Jens Kurth[2], Martin Heuschkel[2], Maila Krönert[1], Gregor Ojak[1], Pawel Grünwald[1], Joachim Röwer[1], Paulina Troitsch[1], Anna-Liisa Riedmiller-Schraaven[1], Miriam Dörschner[1], Bernd J. Krause[2], Steffen Emmert[1]

[1]Klinik und Poliklinik für Dermatologie und Venerologie, Universitätsmedizin Rostock, Rostock, Deutschland

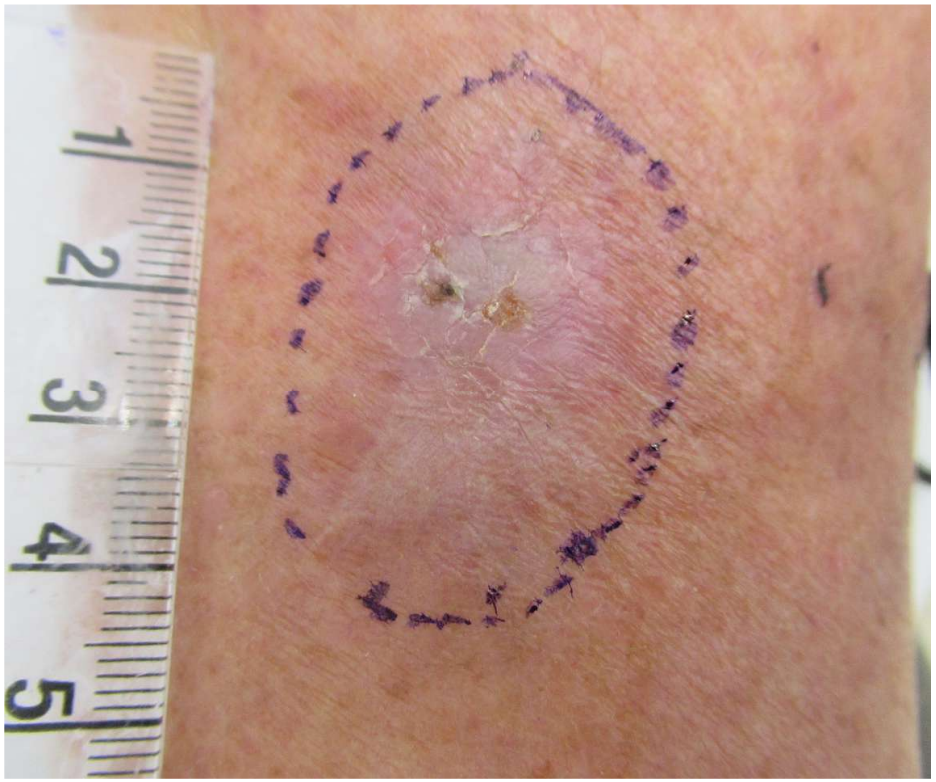
[2]Klinik und Poliklinik für Nuklearmedizin, Universitätsmedizin Rostock, Rostock, Deutschland

Einschlusskriterien der OncoBetaStudie

DUK

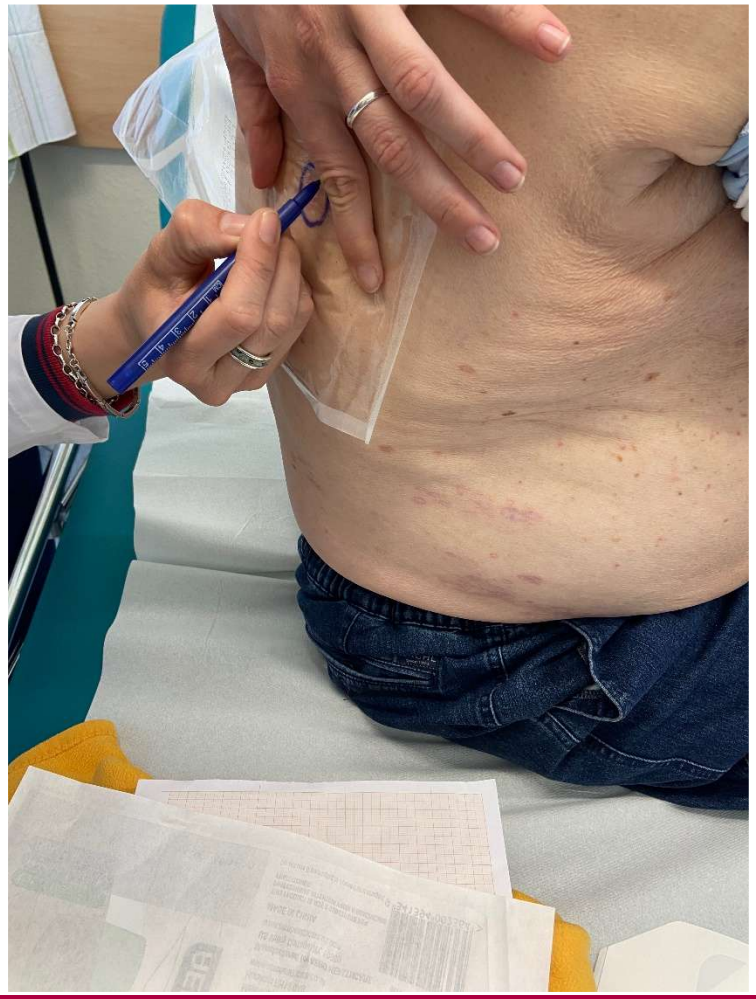
- histologisch gesichertes M. Bowen, SCC oder BCC, Fläche geringer 5 cm^2, Tumordicke nach Kürettage kleiner 3 mm
- Alter ≥ 18 Jahre
- Patienten, die aufgrund ihrer Komorbiditäten nicht für eine chirurgische Entfernung in Frage kommen, sowie Patienten, bei denen aufgrund der anatomischen Lage bei chirurgischer Entfernung mit keinem befriedigenden Ergebnis zu rechnen ist.
- Patienten, bei denen chirurgische Verfahren misslungen sind und bei denen es sich um eine Ultima Ratio Behandlung handelt
- Patienten, die ein chirurgisches Verfahren ablehnen
- 20 Patienten sollten eingeschlossen werden
- 24 Patienten aufgeklärt, 22 Patienten mit 41 Läsionen behandelt

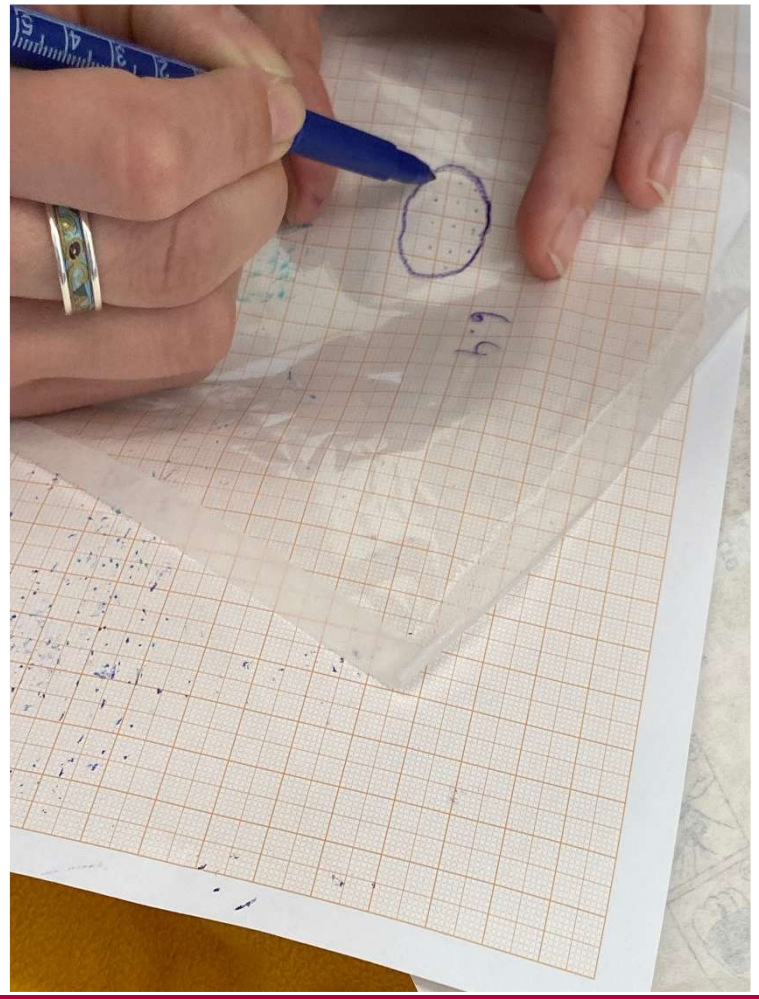
Ablauf der Therapie: Markierung der Läsion



- Markierung des mit der Rhenium-SCT® zu behandelnden Areals vom Dermato-Onkologen.
- Gegebenenfalls Vorbereitung der Behandlungsfläche
  - Entfernung von Krusten
  - Entfernung von Blut
- Flächenbestimmung der Läsion.
- Fotodokumentation
- Überweisung und Aufnahme in der Nuklearmedizin.

Präzise Ausmessung der Größe und Berechnung der aufzutragenden Aktivität





Aktivitätsmessung

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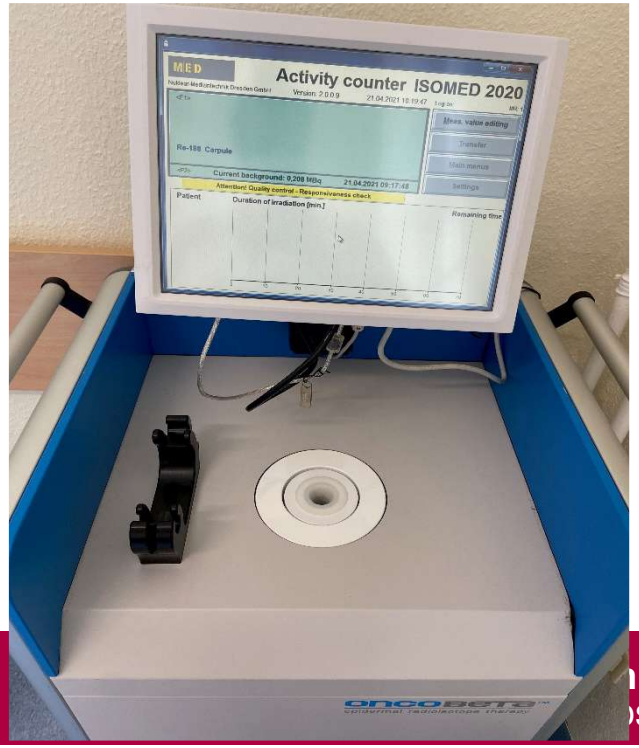
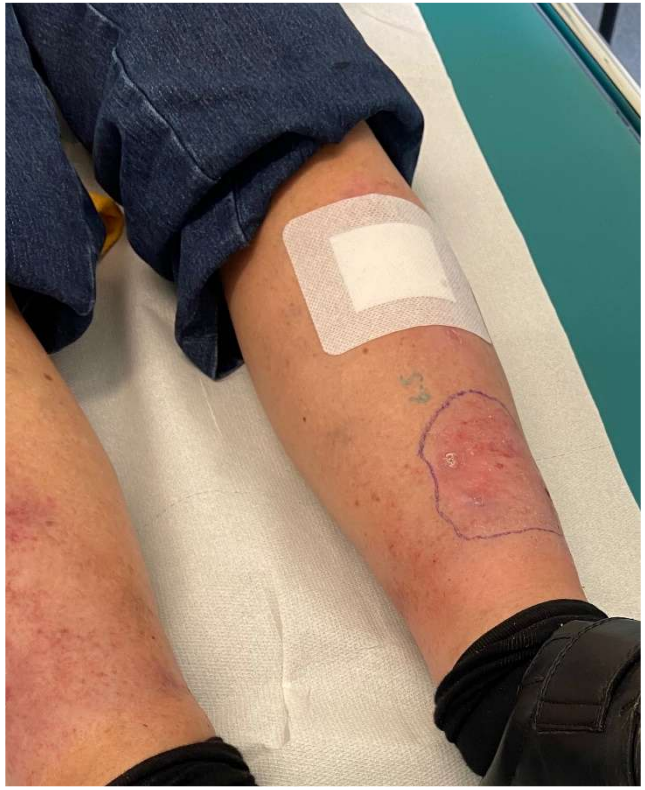
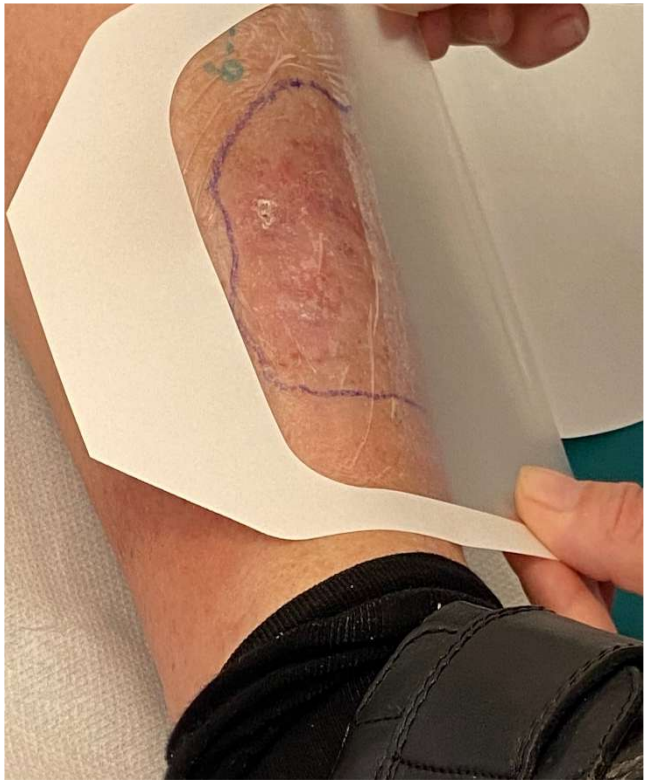
- Messen der initialen Aktivität des Rhenium-188-Compound in der Carpoule.
- Eine Carpoule reicht für etwa 25cm^2 Tumor

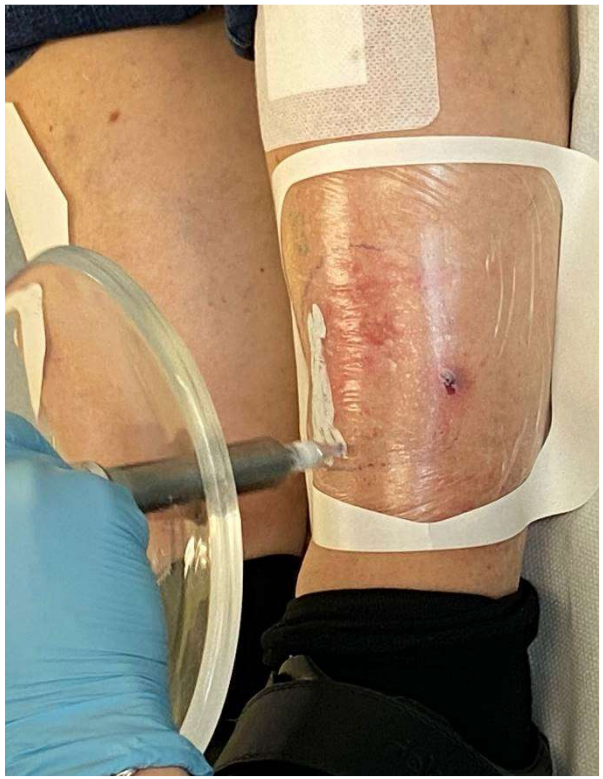


Aufkleben der Folie und Applikation des Rheniums

DUK







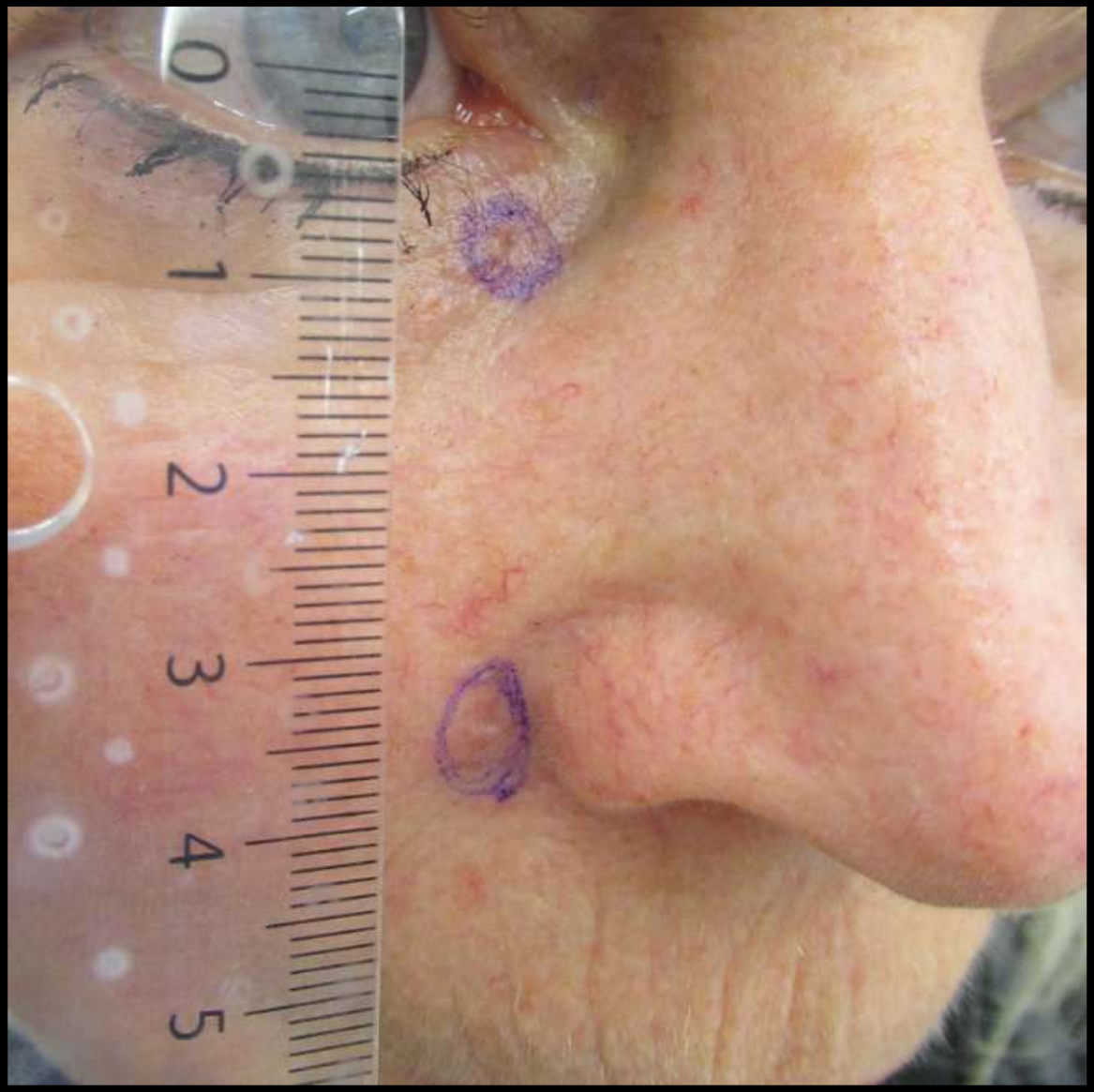
- Rhenium SCT ist eine Art eintrockende Paste
- Patient darf sich während Therapie bewegen
- Die Folie mit der Paste wird nach der Therapie fachgerecht entsorgt
- Nach Ende der Therapie Messung der Aktivität am Patienten

Nebenwirkungen

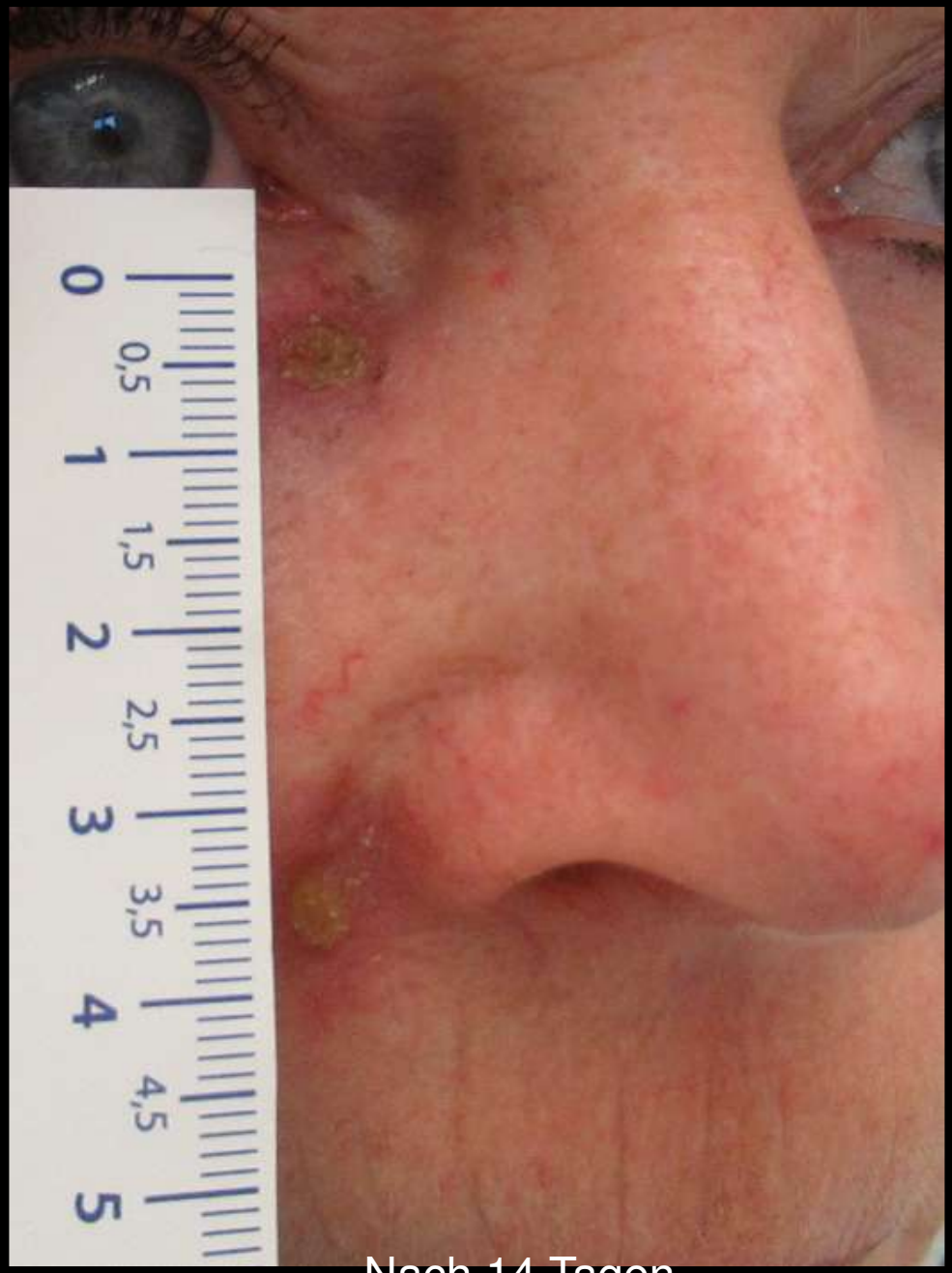
- Unter Therapie keine Nebenwirkungen, insbesondere keine Schmerzen
- Nach 14 Tagen litten 58% Patienten unter keinen Nebenwirkungen, in 35% der Fälle unter leichten Brennen und in 6% unter Juckreiz.
- Nach 4 Monaten waren keinerlei Nebenwirkungen mehr feststellbar

Patientin 1

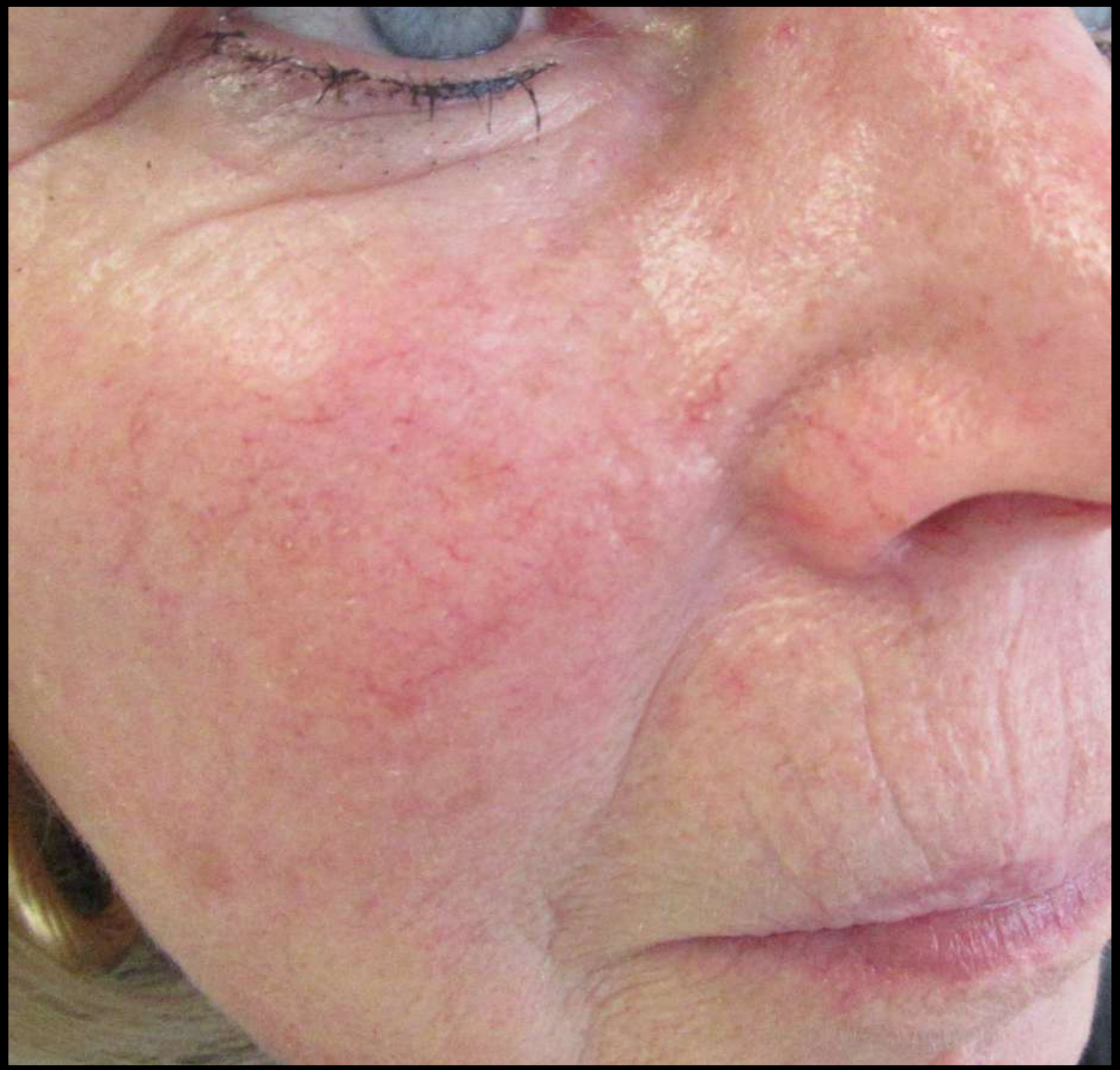
- Weiblich
- 51 Jahre
- Rechter Augeninnenwinkel, BCC, 0,04 cm^2 Größe, TD 1 mm
- Paranasal rechts, BCC, 0,04 cm^2 Größe, TD 1,2 mm



Vor Therapie



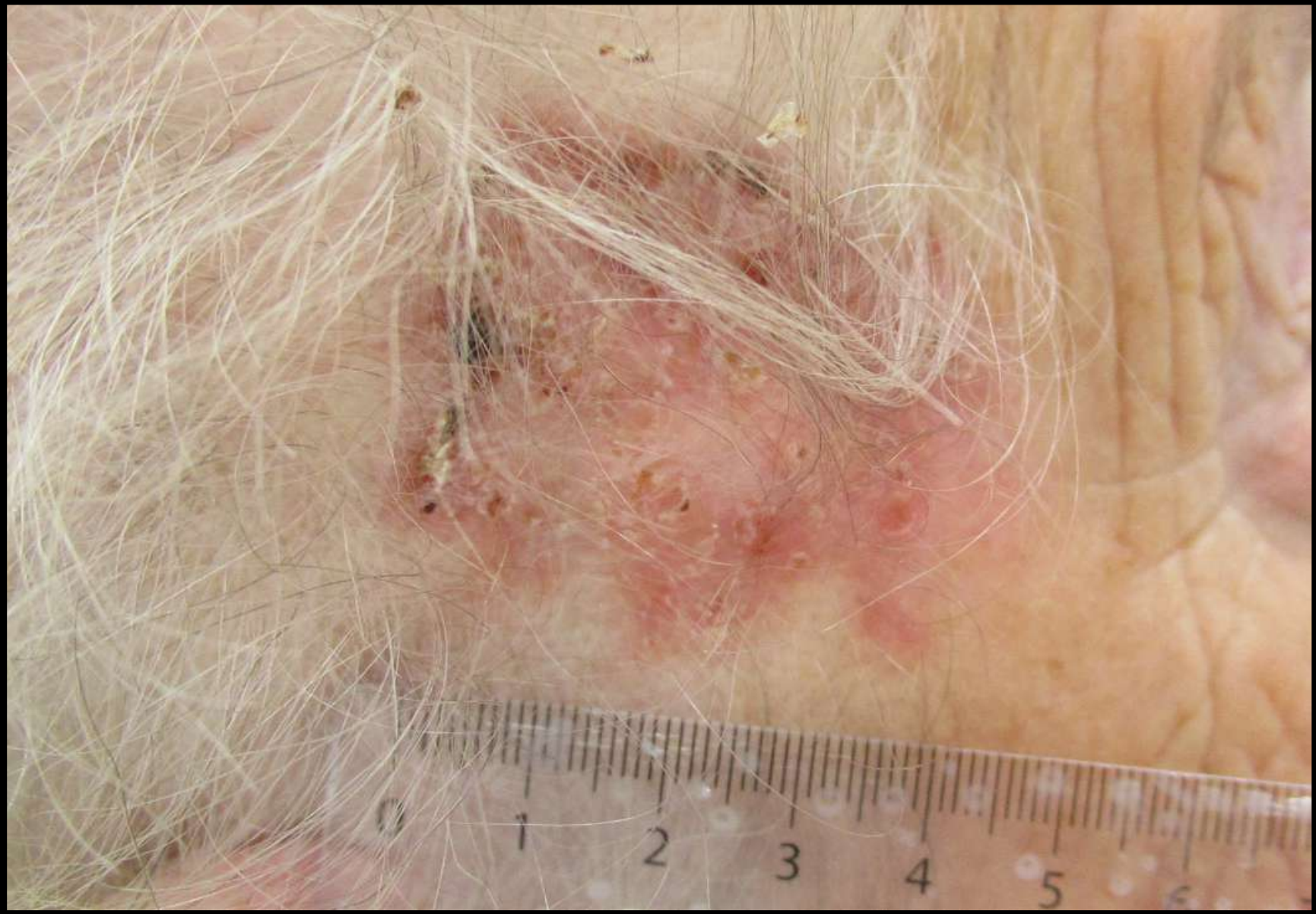
Nach 14 Tagen



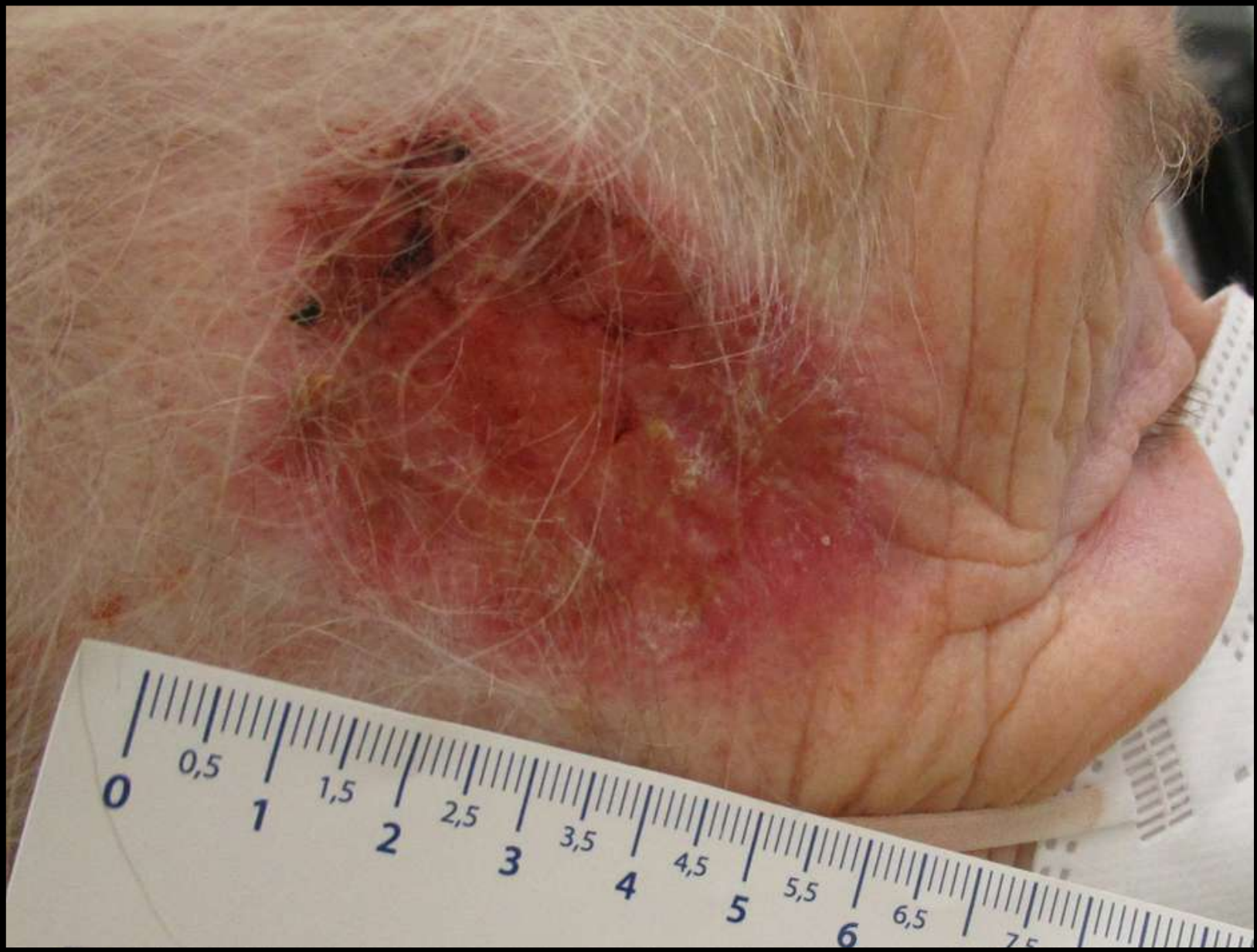
Nach 4 Monaten

Patientin 2

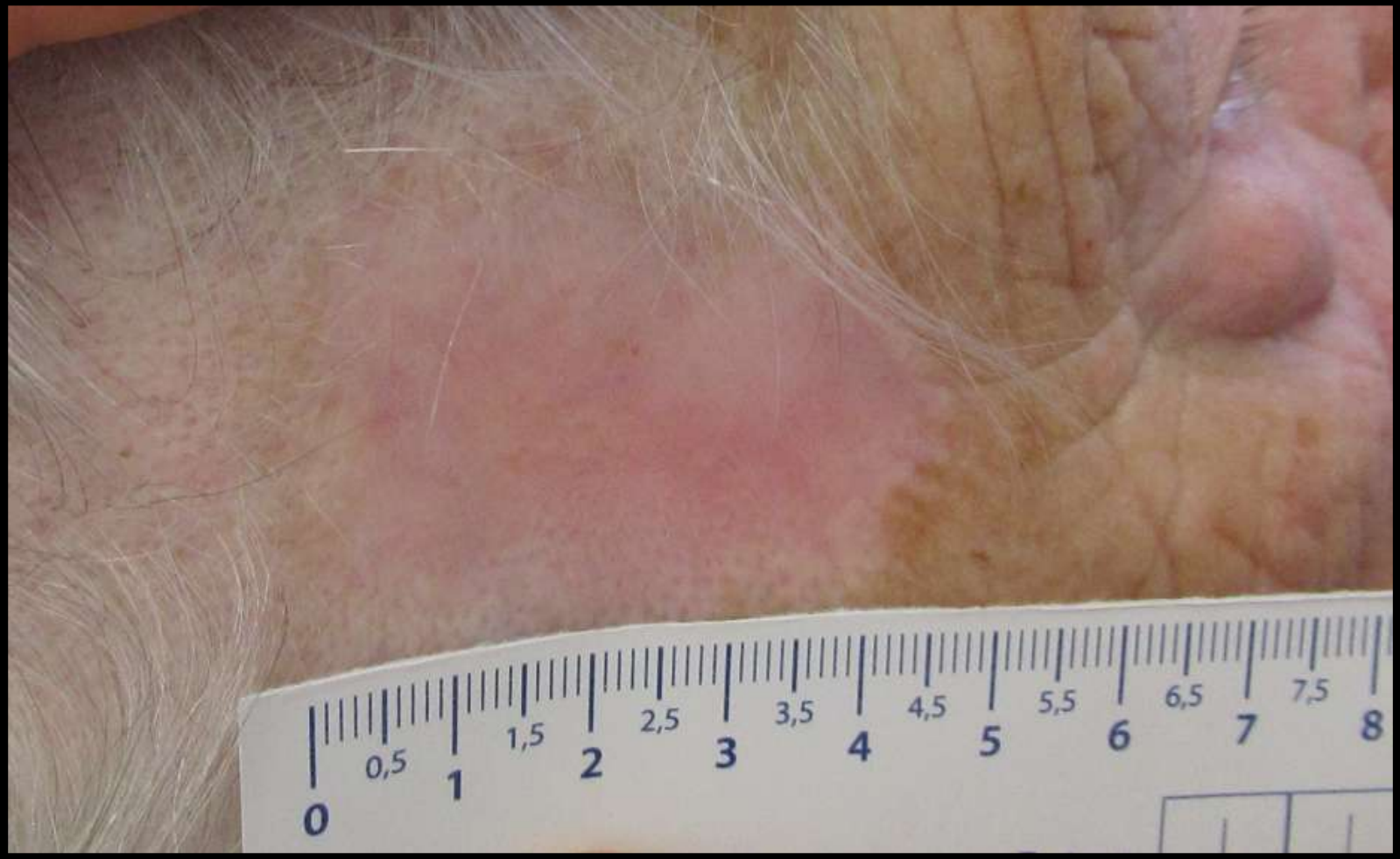
- Weiblich
- 86 Jahre
- Stirn rechts, SCC, 3,68 cm^2 Größe, TD 1,6 mm
- Linke Wange, SCC, Größe, 0,54 cm^2, TD 0,8 mm
- Rechte Schläfe, BCC, Größe, 16,8 cm^2, TD 1,2 mm



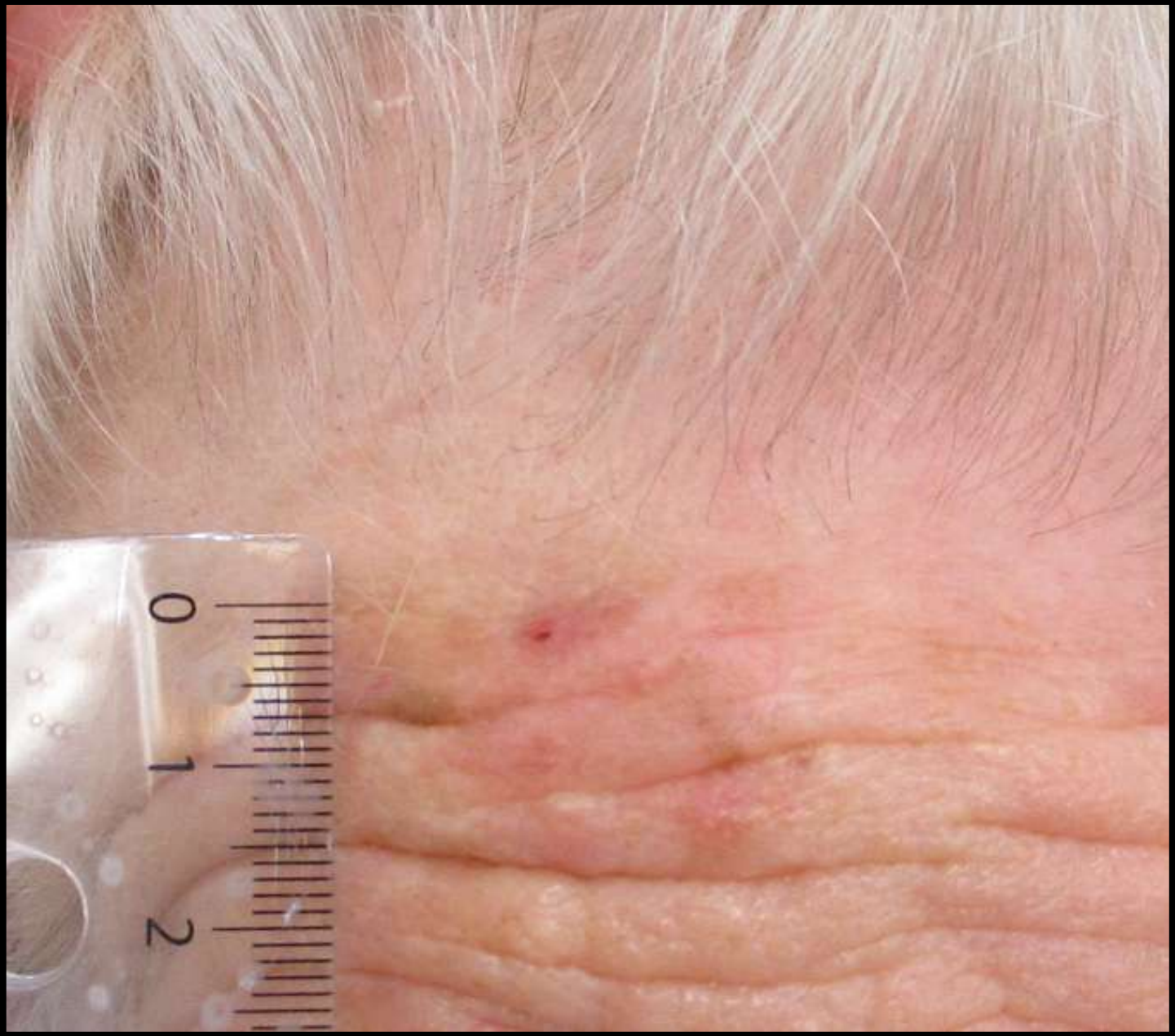
Vor Therapie



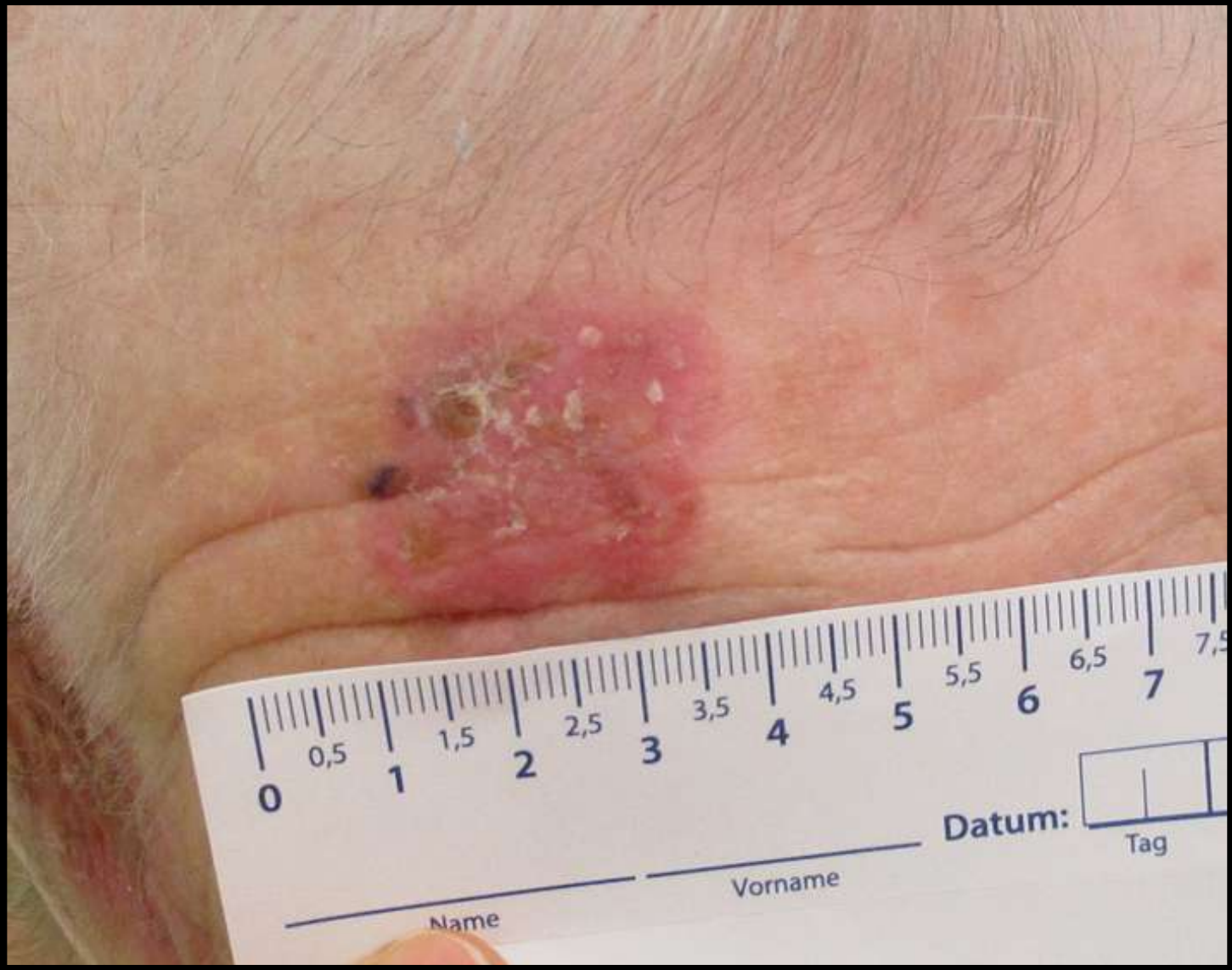
Nach 14 Tagen



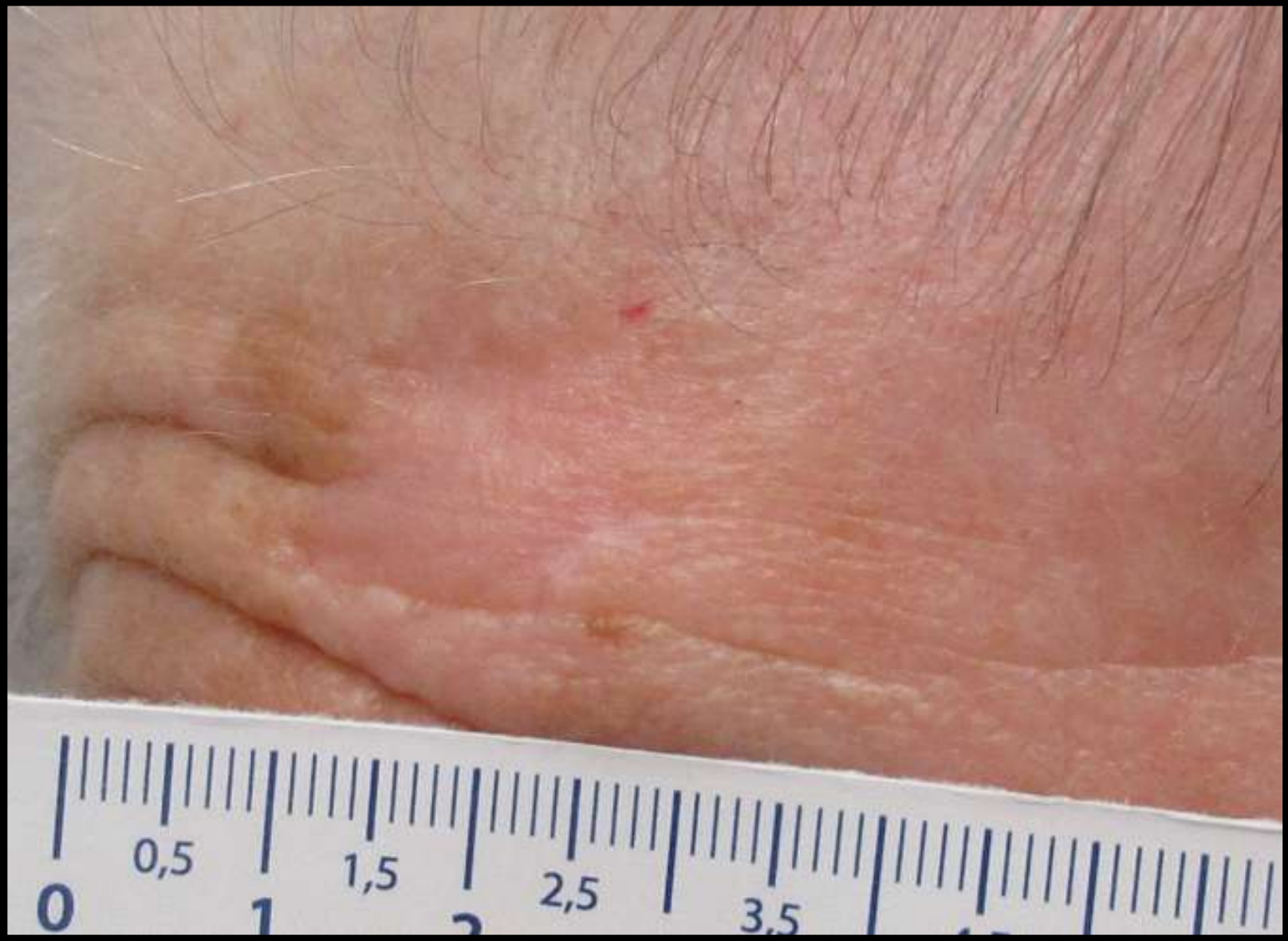
Nach 4 Monaten



Vor Therapie



Nach 14 Tagen



Nach 4 Monaten

Zusammenfassung

DUK

- Rhenium SCT Applikation ist eine vielversprechende Therapie für spezielle Fälle von weißem Hautkrebs:
  - Problemlokalisationen
  - Große Flächen
  - Bei stark voroperierten Gebieten
  - Bei multiplen Läsionen
  - Inoperablen Patienten
- Anwendung hat wenig Nebenwirkungen bei hoher Wirksamkeit

Fazit: Nach den vorläufigen Ergebnissen stellt die Therapie mit Rhenium SCT gerade bei ungünstig gelegenen und großen Tumoren bis 3mm Tumordicke eine valide Therapiealternative zur Operation dar.

RTL Punkt 12 vom 13.04.2022

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ONCOBETA® epidermal radioisotope therapy

Internationale Studie

EPIC-Skin

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Wirksamkeit der personalisierten Bestrahlung mit der Rhenium-Skin Cancer Therapy (SCT, Rhenium-Hautkrebstherapie) zur Behandlung von nicht-melanotischem Hautkrebs: multizentrische, internationale, unverblindete, einarmige Studie

Participating Sites	Principal Investigator	Site Status	
Tugun, Queensland, Australia	A/Professor Siddartha Baxi	Open	
North Shore Hub, St Leonards, New South Wales, Australia	Professor Angela Hong	Open	
Hollywood Private Hospital, Perth, Australia	A/Prof Joe Cardaci	Start up	
Clinic Ottakring, Vienna, Austria	Professor Siroos Mirzaei	Open	
Universitatsmedizin, Rostock, Germany	Dr Martin Heuschkel	Initiated	
King's College Hospital, London, U.K.	Dr Nicola Mullholland	Start up	

Vielen Dank und sonnige Grüße aus Rostock !

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