Universität Rostock Traditio et innovatio

Universitätsmedizin Rostock

DOC 2024, Nürnberg, 21.06.2024

Zielgerichtete Therapieformen bei malignen Lidtumoren

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:
   Amgen, BMS, MSD, Novartis, LEO, ROCHE, Sanofi, Pierre-Fabre, Pfizer, Janssen, Abbvie, UCB, Almirall, Galderma, Mayne Genzyme Corporation, Malinckrodt, SUN Pharma, Oncobeta, SolGel, RheaCell, Teion und CINOGY.
3. Stocks:
   None
4. Financing of studies:
   None
5. Reviewer activities:
   Public/academic institutions, Occupation cooperatives, Transfer centers
6. Other financial associations:
   None

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Photokarzinogenese

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Mehrschrittiges Photokarzinogenese Modell

Tumorinitiation → DNA-Schäden

UV

Tumorpromotion → DNA Mutationen in Genomwächtern (p53)

UV

Tumorprogression → Weitere DNA-Mutationen durch Mutator-Phänotyp

UV

Sichtbarer Hautkrebs → Unkontrolliertes Zellwachstum

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Somatische Mutationsraten verschiedener Tumore

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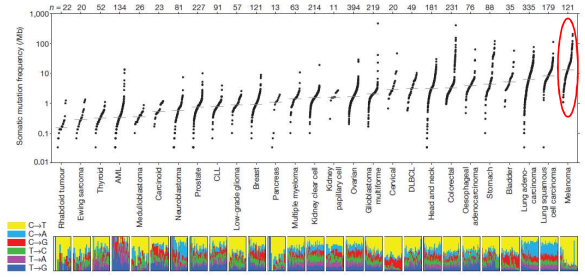

Tumore mit hoher Mutationslast
sind einer Immuntherapie zugänglicher

Modifiziert nach: Lawrence Nature 2013

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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.

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Basalzellkarzinome

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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

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Wuchsformen von BCC

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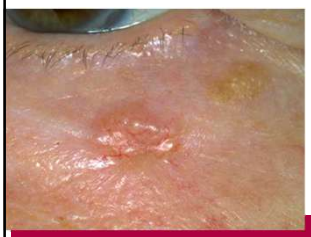
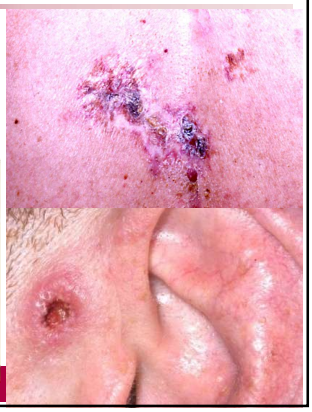
- Solid, knotiges BCC
- Sklerodermiformes BCC
- Multizentrisch-superfizielles BCC
- Ulzerierend-destruktives BBC
- Pigmentiertes BCC





Basalzellkarzinome

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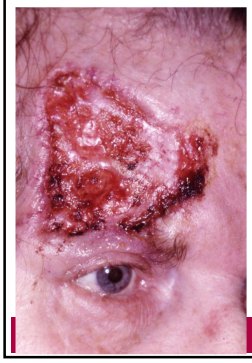
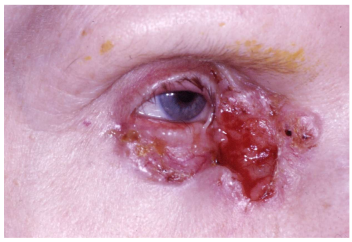
BCC: metastasierend oder chirurgisch schwer resezierbar





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BCC – Driver Mutationen UV-typisch (75%)

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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

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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.

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Basalzellkarzinome – viele verschiedene Driver Pathways

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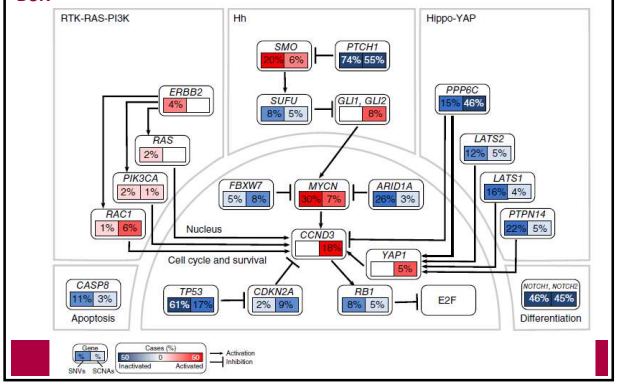

Kleine Moleküle (Inhibitoren) der Hedgehog-Signalkaskade

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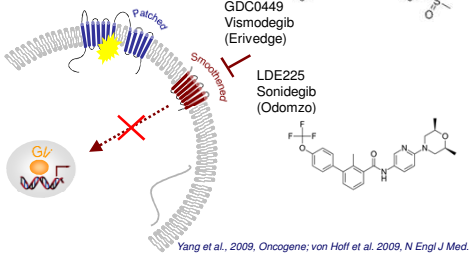
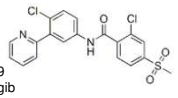
Basalzellnävussyndrom



GDC0449
Vismodegib
(Erivedge)



LDE225
Sonidegib
(Odomzo)

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

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Basalzellkarzinome – neue therapeutische Optionen

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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,[h] Sarah T. Arron, MD, PhD,[i] Philip A. Friedlander, MD, PhD,[j,k] Ellen Marmur, MD,[l] Charles M. Rudin, MD, PhD,[1] Anne Lynn S. Chang, MD,[m] Luc Dirix, MD, PhD,[n] Jeannie Hsu, 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

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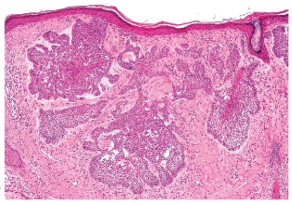

The FDA approved sonidegib, another SMO inhibitor, based on results from the **phase II BOLT study**, which compared two doses (200 mg and 800 mg per day, given orally) in 194 patients with locally advanced BCC who were ineligible for surgery or radiation. Sonidegib showed durable antitumor activity,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

Cancer Discovery 2015;5:1011.

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

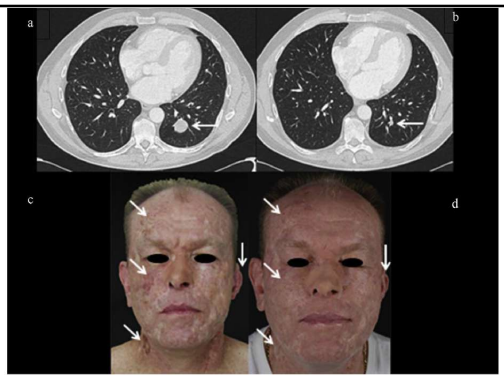

Fig. 1. Lung metastases of the right upper lobe (a) and non-melanoma skin cancers of the sun-damaged skin in the face (c) before pembrolizumab treatment and in the follow-up after six months (b and d). Arrows indicate NMSC as target lesions.

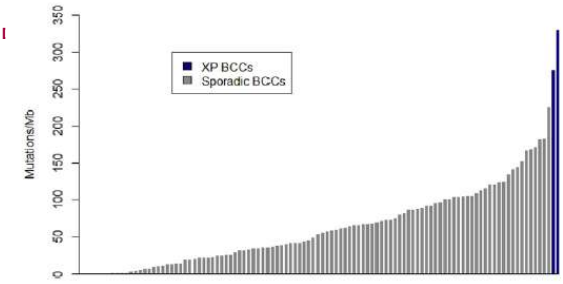

Fig. 2. Mutational burden per megabase of XP-associated BCCs of our patient (blue bars) compared to published data on 100 sporadic BCCs (grey bars). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Cemiplimab (REGN2810)

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U.S. National Library of Medicine
ClinicalTrials.gov

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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 Program 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)

SANOFI

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.

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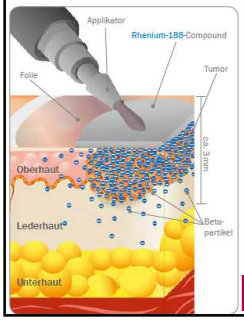
Rhenium SCT

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**

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Rhenium SCT

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Carpoulen gefüllt mit Rhenium-188-compound

Der mit einer Carpoule geladene Applikator

Behandlungseinheit der Rhenium SCT®

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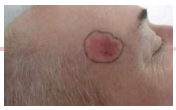
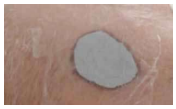
Rhenium SCT

DUK

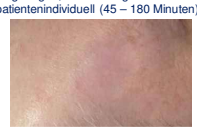
- **Zulassung als Medizinprodukt**
- **Strahlentherapie (Betastrahler)**
- **1-2 h Einwirkzeit,**
- **Lokale NW: Rötung, Radiodermatitis**
- **Keine systemischen NW**
- **Sehr gute kosmetische Ergebnisse**
- **Komplette Heilungsrate: 89% nach einmaliger Applikation**
- **1,5% Rezidivrate nach 12-78 Monaten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

Patientin 1

DUK

- 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

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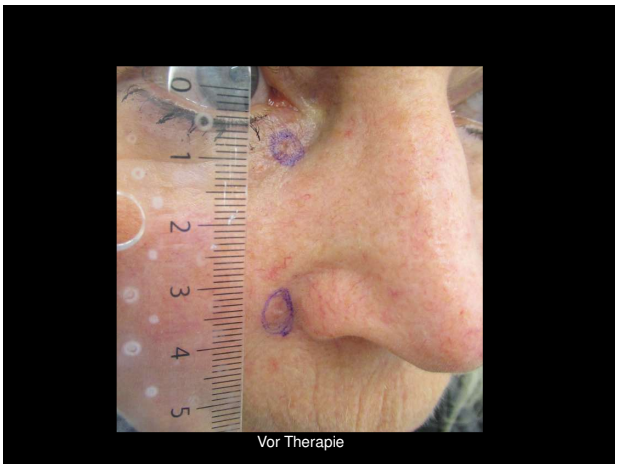
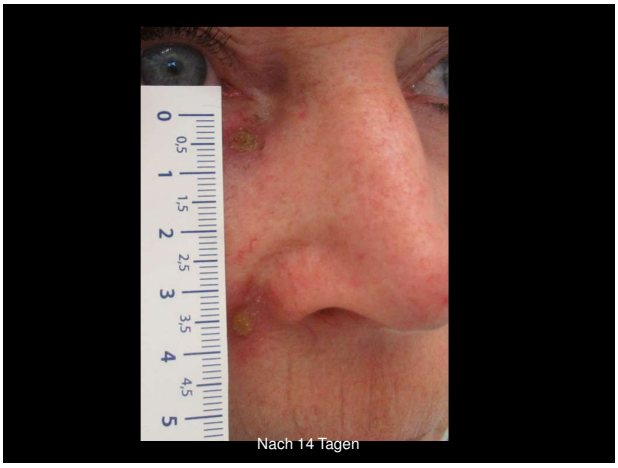
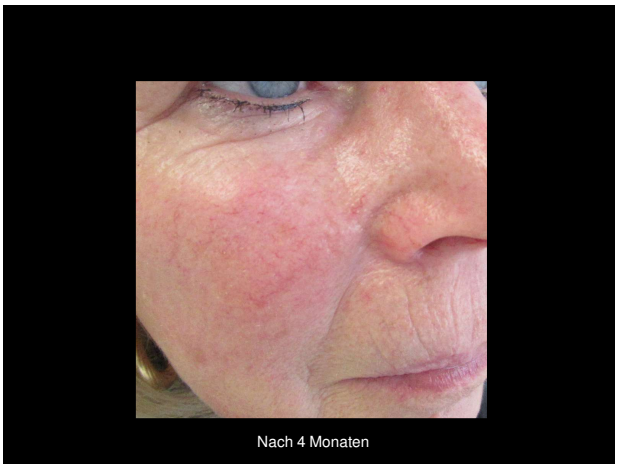

Vor Therapie


Nach 14 Tagen


Nach 4 Monaten

Rhenium SCT

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.

ONCOBETA® epidermal radioisotope therapy Internationale Studie EPIC-Skin

DUK

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

Universitätsmedizin Rostock

Basalzellkarzinom

DUK

- **Hedgehog Signaling**
- **Immuntherapie mit Checkpointinhibitoren**
- **Rhenium SCT**

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Aktinischen Keratosen und Plattenepithel-Ca

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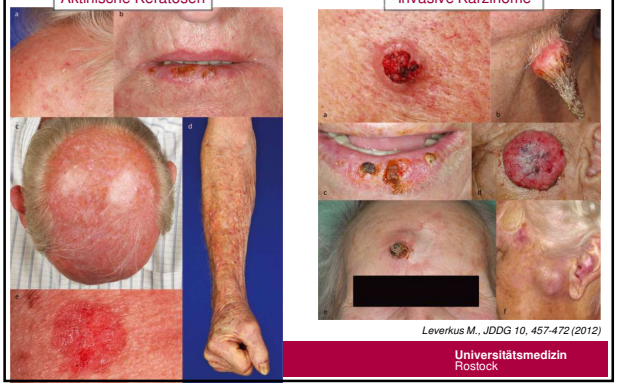
Aktinische Keratosen | Invasive Karzinome



Leverkus M., JDDG 10, 457-472 (2012)

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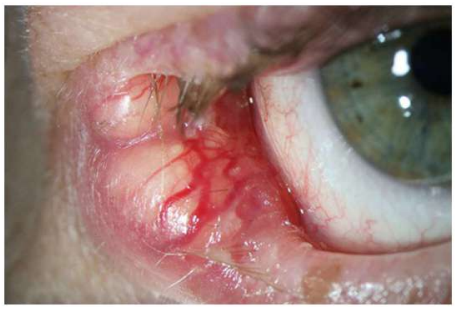
PECA – OP Herausforderung am Auge

DUK



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Auslöser von Plattenepithel-Ca

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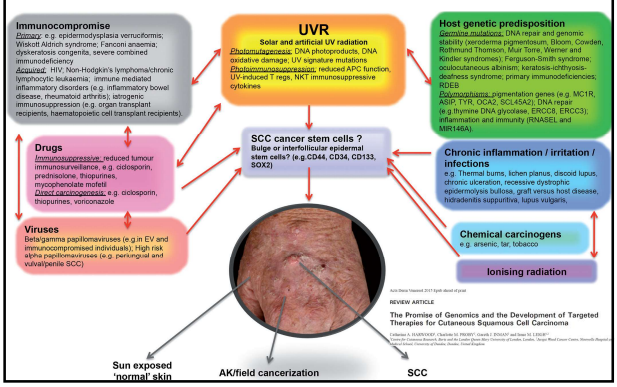

Driver Mutationen bei Plattenepithel-Ca

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Table 1. Genes most frequently mutated in SCC of the skin

Gene name	% Mutated in cSCC	cSCC tested
NOTCH1	60.00	25
NOTCH2	41.67	24
TP53	35.32	705
CDKN2A	18.30	388
STK11	8.82	34
PTCH1	8.22	73
HRAS	6.71	507
PIK3R1	5.88	17
SMO	4.55	22
NFE2L2	4.17	24
PTEN	3.39	59
NRAS	2.40	375
KRAS	2.38	378
PIK3CA	2.18	229

cSCC, cutaneous squamous cell carcinoma.
Mutation data were obtained from the Sanger Institute Catalogue Of Somatic Mutations In Cancer (COSMIC; http://www.sanger.ac.uk/cosmic) (9).

Experimental Dermatology, 2014, **23**, 143–146

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Driver Pathways bei Plattenepithel-Ca

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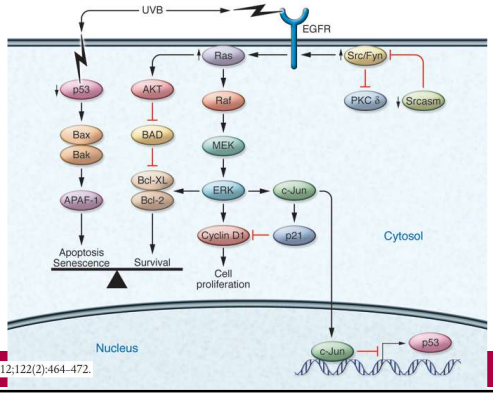

J Clin Invest. 2012;122(2):464–472.

Therapieansätze bei Plattenepithel-Ca

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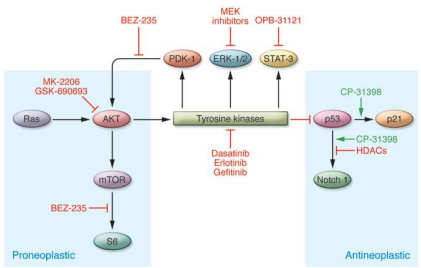
EGFR monoclonal antibody inhibitors. Cetuximab

EGFR tyrosine kinase inhibitors. Currently approved EGFR tyrosine kinase inhibitors include gefitinib (non-small cell lung cancer), erlotinib (non-small cell lung and pancreatic cancer) and lapatinib (breast cancer).



J Clin Invest. 2012;122(2):464–472.

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Cemiplimab beim Plattenepithel-Ca

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Michael R. Migden,[1] Danny Rischin,[2] Chrysalyne D. Schmults,[3] Alexander Guminski,[4] Axel Hauschild,[5] Karl D. Lewis,[6] Christine H. Chung,[7] Leonel Hernandez-Aya,[8] Annette M. Lim,[9] Anne Lynn S. Chang,[10] Guilherme Rabinowits,[11] Aiesha A. Thai,[12] Lara A. Dunn,[13] Brett G.M. Hughes,[13] Nikhil I. Khushalani,[14] Badri Modi,[15] Dirk Schadendorf,[16] Bo Gao,[17] Frank Seebach,[18] Siyu Li,[17] Jingjin Li,[17] Melissa Mathias,[18] Jocelyn Booth,[17] Kosalai Mohan,[18] Elizabeth Stankevich,[17] Hani M. Babiker,[19] Irene Brana,[20] Marta Gil-Martin,[21] Jade Homsi,[22] Melissa L. Johnson,[23] Victor Moreno,[24] Jiaxin Niu,[25] Tapfeek K. Owonikoko,[26] Kyriakos P. Papadopoulos,[27] George D. Yancopoulos,[18] Israel Lowy,[18] Matthew G. Fury[18]

[1]*Departments of Dermatology and Head and Neck Surgery, University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [2]*Department of Medical Oncology, Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia;* [3]*Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;* [4]*Department of Medical Oncology, Royal North Shore Hospital, St Leonards, Australia;* [5]*Schleswig-Holstein University Hospital, Kiel, Germany;* [6]*University of Colorado Denver, School of Medicine, Aurora, CO, USA;* [7]*Department of Head and Neck-Endocrine Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA;* [8]*Division of Medical Oncology, Department of Medicine, Washington University School of Medicine, St Louis, MO, USA;* [9]*Department of Medical Oncology, Sir Charles Gairdner Hospital, Perth, Australia;* [10]*Department of Dermatology, Stanford University School of Medicine, Redwood City, CA, USA;* [11]*Formerly of Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA;* [12]*Department of Medicine, Head and Neck Medical Oncology, Memorial Sloan Kettering Cancer Center, New York City, NY, USA;* [13]*Royal Brisbane & Women's Hospital and University of Queensland, Brisbane, Australia;* [14]*Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL, USA;* [15]*Division of Dermatology, City of Hope, Duarte, CA, USA;* [16]*University Hospital Essen, Essen and German Cancer Consortium, Germany;* [17]*Regeneron Pharmaceuticals Inc., Basking Ridge, NJ, USA;* [18]*Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA;* [19]*University of Arizona Cancer Center, Tucson, AZ, USA;* [20]*Medical Oncology Department, Vall D'Hebron University Hospital, Barcelona, Spain;* [21]*Institut Català D'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain;* [22]*Formerly of Banner MD Anderson Cancer, Gilbert, AZ, USA;* [23]*Sarah Cannon Research Institute, Nashville, TN, USA;* [24]*START Madrid-FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain;* [25]*Department of Medical Oncology, Banner MD Anderson Cancer Center, Gilbert, AZ, USA;* [26]*Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA;* [27]*START, San Antonio, TX, USA.*

Migden MR, Rischin D, et al. *N Engl J Med.* 2018. doi:10.1056/NEJMoa1805131 (epub ahead of print).

The studies were funded by Regeneron Pharmaceuticals, Inc. and Sanofi

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Cemiplimab beim Plattenepithel-Ca

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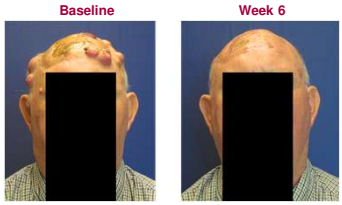
Phase 1 cSCC Expansion Cohorts



62-year-old patient at baseline and after 6 weeks of treatment with Cemiplimab.

Migden MR, Rischin D, et al. *N Engl J Med.* 2018. doi:10.1056/NEJMoa1805131 (epub ahead of print).

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Cemiplimab beim Plattenepithel-Ca

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Outcome	Phase 1 cSCC Expansion Cohorts (N = 26)	Phase 2 Metastatic cSCC (N = 59)
Best overall response, n (%)		
Complete response	0	4 (7)
Partial response	13 (50)	24 (41)
Stable disease	6 (23)	9 (15)
Progressive disease	3 (12)	11 (19)
Could not be evaluated*	3 (12)	7 (12)
Nontarget lesions only†	1 (4)	4 (7)
Objective response, % (95% CI)	50 (30–70)	47 (34–61)
Durable disease control, % (95% CI)‡	65 (44–83)	61 (47–74)
Median observed time to response (range), months§	2.3 (1.7–7.3)	1.9 (1.7–6.0)

Median duration of response had not been reached at the time of this analysis

- In the Phase 1 cSCC expansion cohorts, **duration of response exceeded 6 months in 54% (7/13) of patients who had a response**
- In the Phase 2 metastatic cSCC cohort, **the duration of response exceeded 6 months in 57% (16/28) of patients who had a response; 82% (23/28) of patients who had a response continued to have a response and to receive cemiplimab**

In subgroup analyses of the Phase 2 study, similar response was observed in patients with **regional metastasis (6 of 14 patients; 43%; 95% CI, 18 to 71)** and **distant metastasis (22 of 45 patients; 49%; 95% CI, 34 to 64)**.

Migden MR, Rischin D, et al. *N Engl J Med.* 2018. doi:10.1056/NEJMoa1805131 (epub ahead of print).

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Plattenepithelkarzinom

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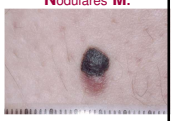
- Immuntherapie mit Checkpointinhibitoren
- Rhenium SCT

Melanom

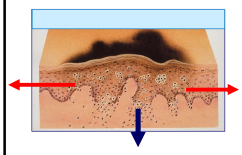
DUK

SSM
Superficial Spreading M.

NM
Noduläres M.

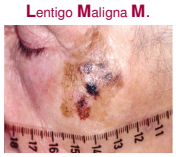


Wachstumsrichtungen

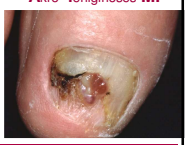


Vertikales Wachstum
prognostisch ungünstig

LLM
Lentigo Maligna M.



ALM
Akro- lentiginöses M.



Melanom – OP Herausforderung am Auge

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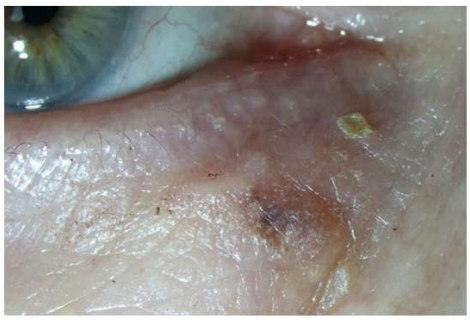

Driver Mutationen beim Melanom

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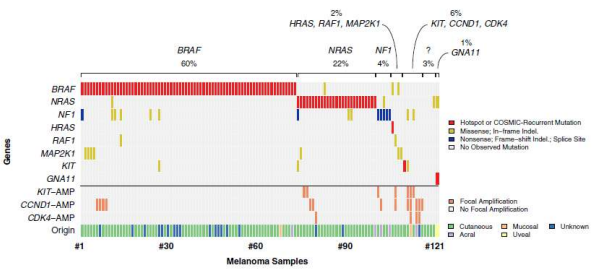

UV-induzierte Driver Mutationen beim Melanom

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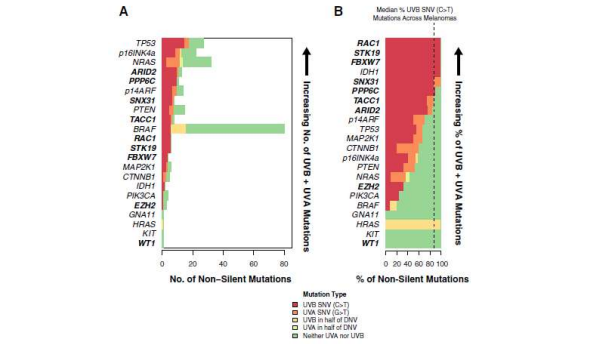

Driver Mutationen beim Melanom

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TABLE 1. Common Gene Mutations Associated With Melanoma Subtypes

Mutated Gene	Melanoma Subtypes	Gene Function and Mutation	Therapy
BRAF	40%-50% of cutaneous melanomas More commonly at sites of acute intermittent sun exposure Often superficial spreading or nodular melanomas	Kinase in Ras/Raf/MAPK cascade Activates MEK V600E point mutation most common (in activation segment) Mutation increases BRAF catalytic activity Downstream MAPK activation	Specific BRAF inhibitors (vemurafenib FDA-approved)
NRAS	15%-20% of cutaneous melanomas BRAF wild-type More commonly on extremities Often nodular melanomas	GTPase in Ras/Raf/MAPK cascade Activating mutations in codon 61 lead to downstream Raf, MAPK activation May also signal through PI3K and Racl	No effective direct inhibitors so far; some MEK inhibitors may be effective; possible combination therapies
KIT	Subset of melanomas in chronically sun-damaged skin (lentigo maligna melanoma) Mucosal melanomas Acral melanomas	Receptor tyrosine kinase Binds stem cell factor Signals through MAPK, PI3K, JAK/STAT pathways Mutations in region coding for juxtamembrane domain cause constitutive activation	Imatinib effective in subset of patients with KIT mutations
GNAQ *GNA11*	Uveal melanoma Blue nevi	Guanine nucleotide–binding proteins Link G protein-coupled receptors to intracellular pathways Mutations lead to constitutive activation	No direct inhibitors so far; MEK combination therapy and PKC inhibitors may be effective based on in vitro studies

Systemtherapien beim Melanom

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Melanom (adjuvant und metastasiert):

- CTLA-4-Abs (Ipilimumab) und PD-1 (Nivolumab, Pembrolizumab)
- BRAF Inhibition (Dabrafenib, Vemurafenib, BRAFTOVI)
- MEK Inhibition (Trametinib, Cobimetinib, MEKTOVI)
- Fusion protein: gp100 (presented by HLA A*0201 auf der Krebszelle) - anti-CD3 (auf T-Zellen) (**Tebentafusp**)

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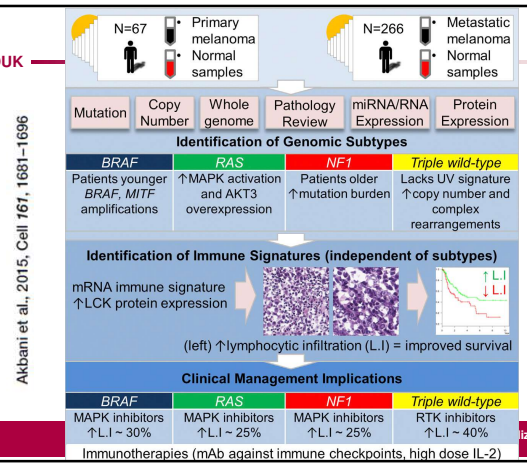

Akbani et al., 2015, Cell *161*, 1681–1696

Vielen Dank und sonnige Grüße aus Rostock !

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