CUTANEOUS SQUAMOUS CELL CARCINOMAS (CSCC)

Epidemiology, surgery, radiotherapy, systemic treatment & guidelines

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SKIN CANCER AND CSCC EPIDEMIOLOGY
SKIN CANCER INCIDENCE

Overall skin cancer incidence¹

- NMSC: 80%
- Other skin cancer cases: 20%

Non-melanoma skin cancer¹

- BCC: 70%
- CSCC: 20%
- Other*: 10%

*Other includes a variety of rare tumours such as DFSP, primary cutaneous B-cell lymphoma, Kaposi sarcoma, carcinosarcoma and MCC²
BCC, basal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; DFSP, dermatofibrosarcoma protuberans; MCC, Merkel cell carcinoma; NMSC, non-melanoma skin cancer
## Skin Cancers Incidence and Lifetime Risk

**Estimation for 2010-2020**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Incidence</th>
<th>Lifetime Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>20/100,000/year</td>
<td>1:70</td>
</tr>
<tr>
<td>BCC</td>
<td>200/100,000/year</td>
<td>1:7</td>
</tr>
<tr>
<td>CSCC</td>
<td>50/100,000/year</td>
<td>1:25</td>
</tr>
<tr>
<td>Actinic Keratosis</td>
<td>350/100,000/year</td>
<td>1:3</td>
</tr>
</tbody>
</table>
INCIDENCE OF NONMELANOMA SKIN CANCER (NMSC)

Age-standardised incidence rates according to the European standard population

- Between 1999 and 2012, the NMSC age-standardised incidence rate in the male population increased from 125 to 170 and in the female population from 92 to 134 cases per 100,000 persons per year.

CRUDE INCIDENCE RATES OF EPITHELIAL SKIN CANCER
In Schleswig-Holstein, projected to 2030

- 2000: 140 cases/100,000 cases
- 2030: 400 cases/100,000 cases
- Increase: ~3-fold over 18 years

Cancer Registry Schleswig-Holstein, Courtesy of Claus Garbe, Tübingen, Germany.
CRUDE INCIDENCE RATES OF EPITHELIAL SKIN CANCER
Throughout Germany from 1950 to 2030

<table>
<thead>
<tr>
<th>Year</th>
<th>CIR</th>
<th>Instances</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>5/100,000 (estimated)</td>
<td>4,000/year</td>
</tr>
<tr>
<td>1970</td>
<td>15/100,000 (Saarland)</td>
<td>12,000/year</td>
</tr>
<tr>
<td>1990</td>
<td>80/100,000 (Saarland)</td>
<td>64,000/year</td>
</tr>
<tr>
<td>2010</td>
<td>220/100,000 (Germany)</td>
<td>176,000/year</td>
</tr>
<tr>
<td>2030</td>
<td>400/100,000 (Germany)</td>
<td>320,000/year</td>
</tr>
</tbody>
</table>

Courtesy of Prof Claus Garbe, Tübingen, Germany
CSCC: DEVELOPMENT FROM PRECANCEROUS LESIONS AND CLINICAL FEATURES
ACTINIC KERATOSIS WITH ATYPICAL BASAL CELLS (AK I) IS THE MOST COMMON LESION ASSOCIATED WITH INVASIVE SQUAMOUS CELL CARCINOMA OF THE SKIN

Features of the epidermis overlying iSCCs and at the edge of iSCCs, distributed according to the degree of involvement and the presence of ulceration (number of cases and corresponding percentages of total)

<table>
<thead>
<tr>
<th></th>
<th>AK I</th>
<th>AK II</th>
<th>AK III</th>
<th>Normal</th>
<th>Not evaluable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of lesion overlying iSCC</td>
<td>125 (63.8%)</td>
<td>35 (17.9%)</td>
<td>36 (18.4%)</td>
<td>0</td>
<td>0</td>
<td>196</td>
</tr>
<tr>
<td>Type of lesion at iSCC edges</td>
<td>141 (77.9%)</td>
<td>12 (6.6%)</td>
<td>15 (8.3%)</td>
<td>13 (7.2%)</td>
<td>15 (8.1%)</td>
<td>196</td>
</tr>
<tr>
<td>Foci of ulceration over iSCC</td>
<td>40 (32%)</td>
<td>10 (28.6%)</td>
<td>12 (33.3%)</td>
<td>-</td>
<td>-</td>
<td>62</td>
</tr>
</tbody>
</table>
AKTINIC KERATOSES: MORE THAN A RISK FACTOR FOR CSCC!

Swedish registry cohort study on 17,651 pts
2,893 AK pts und 14,668 pts without AKs
Significant risk for CSCC (5.1-fold ↑), BCC (4.4-fold) und melanoma (2.7-fold elevated)
Long follow-up: 10.6 years!
However, it is still unclear if these SCCs are developing on pre-existing AKs or de novo on unaffected skin?
What is the true risk of a transformation of AKs to invasive CSCCs?
It is unpredictable for immunocompetent individuals!

SHORT SUMMARY FACTS ABOUT CSCC

Second most frequent NMSC (after BCC) – 20% of all cutaneous malignancies

Incidence rate increases have been recorded (50 - 200%) in last 30 years

The majority occur on the head and neck (80-90%)

Usually develops from precursor lesions (actinic keratoses), but also de novo

>90% of cases have excellent prognosis

Courtesy of Prof A. Hauschild
AKS: CSCC ON ACTINIC KERATOSES

Courtesy of Prof A. Hauschild
MULTIPLE ACTINIC KERATOSES WITH ULCERATED CSCC
PRIMARY TUMOUR AND CUTANEOUS METASTASIS

Courtesy of Prof Rolf-Markus Szeimies, Recklinghausen, Germany
CSCC: RISK FACTORS FOR INFERIOR PROGNOSIS
Characteristics for LN mets and CSCC-related death

Tumour diameter > 2 cm (HR: 7.0 for LN-mets and 15.9 for death)

Low differentiation grade (HR: 6.1 and 6.7)

Deeper invasion than subcutaneous fat (HR: 9.3 and 13.0)

Localisation on ears or lip (HR: 3.8 and 5.9)

Perineural invasion (HR for death: 3.6)

Anogenital localisations

HR, Hazard Ratio
<table>
<thead>
<tr>
<th>Clinical scenarios/Key questions</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US 2018</strong></td>
<td><strong>Canada 2015</strong></td>
</tr>
<tr>
<td><strong>UK 2015</strong></td>
<td><strong>Europe 2015</strong></td>
</tr>
<tr>
<td><strong>Italy/Europe 2018</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Definition of high-risk SCC</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
</tr>
<tr>
<td>trunk/extremities ≥20 mm</td>
<td>trunk/extremities ≥20 mm</td>
</tr>
<tr>
<td>cheeks, forehead, scalp, neck,</td>
<td>cheeks, forehead, scalp, neck,</td>
</tr>
<tr>
<td>pretibial ≥10 mm</td>
<td>pretibial ≥10 mm</td>
</tr>
<tr>
<td>central face, eyelids, eyebrows,</td>
<td>central face, eyelids, eyebrows,</td>
</tr>
<tr>
<td>periorbital skin, nose, lips,</td>
<td>periorbital skin, nose, lips,</td>
</tr>
<tr>
<td>chin, mandible, preauricular</td>
<td>chin, mandible,</td>
</tr>
<tr>
<td>and postauricular skin/ulcer,</td>
<td>preauricular and postauricular</td>
</tr>
<tr>
<td>temple, ear, genitilia, hands,</td>
<td>skin/ulcer, temple, ear,</td>
</tr>
<tr>
<td>and feet</td>
<td>genitilia, hands, and feet</td>
</tr>
<tr>
<td>poorly defined borders</td>
<td>poorly defined clinical margins</td>
</tr>
<tr>
<td>recurrent</td>
<td>recurrence</td>
</tr>
<tr>
<td>immunosuppression</td>
<td>immunosuppression</td>
</tr>
<tr>
<td>site of prior radiation therapy</td>
<td>site of prior radiation</td>
</tr>
<tr>
<td>or chronic inflammatory process</td>
<td>therapy or chronic inflammatory process</td>
</tr>
<tr>
<td>rapidly growing tumor</td>
<td>rapidly growing tumor</td>
</tr>
<tr>
<td>neurologic symptoms</td>
<td>neurologic symptoms</td>
</tr>
<tr>
<td>Pathologic</td>
<td>Pathologic</td>
</tr>
<tr>
<td>poorly differentiated</td>
<td>poorly differentiated</td>
</tr>
<tr>
<td>high-risk histologic subtype</td>
<td>high-risk histologic subtype</td>
</tr>
<tr>
<td>≥2 mm depth/Clark level IV, V</td>
<td>≥2 mm depth/Clark level IV, V</td>
</tr>
<tr>
<td>perineural, lymphatic, or</td>
<td>perineural invasion</td>
</tr>
<tr>
<td>vascular involvement</td>
<td>vascular involvement</td>
</tr>
</tbody>
</table>

### External ears, lips, scalp
- external ears, lips, scalp
- size: diameter ≥2 cm
- depth: ≥0.2 cm or Clark level IV or V
- poorly differentiated; Broders grade 3 or 4
- immunosuppression
- perineural involvement
- recurrence
- rapid growth
- originating from chronic wound or scar
- size >2 cm
- failure of previous treatment
- immunosuppression
- depth or invasion ≥2 mm thickness
- Clark level ≥4
- perineural invasion
- primary site ear or hair-bearing lip
- poorly differentiated or undifferentiated
- tumor diameter: more than 2 cm
- earlip, non-sun exposed sites
  - SCC arising in radiation sites, scars, burns
  - chronic inflammatory conditions
  - recurrent SCCs
  - more than 6 mm invasion beyond subcutaneous fat
    - moderately, or poorly differentiated grade
    - acantholytic, spindle, desmoplastic subtype
    - perineural invasion
    - surgical margins: incomplete excision
    - immunosuppressed (organ transplant recipients, chronic immunosuppression)
    - immunosuppressive disease or treatment

### Clinical
- trunk/extremities ≥20 mm
- cheeks, forehead, scalp, neck, pretibial ≥10 mm
- central face, eyelids, eyebrows, periorbital skin, nose, lips, chin, mandible, preauricular and postauricular skin/ulcer, temple, ear, genitilia, hands, and feet
- poorly defined clinical margins
- recurrence
- immunosuppression
- radiotherapy or chronic inflammatory sites
- fast-growing tumor
- neurologic symptoms

### Histology
- poorly differentiated histologic grade
- histologic subtype: acantholytic, desmoplastic, adeno-squamous
- tumor thickness ≥2 mm or Clark level IV, V
- perineural, lymphatic or vascular invasion

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PATIENTS WHO ARE IMMUNOSUPPRESSED ARE AT HIGHER RISK OF CSCC, RECURRENCE AND RISK OF DEATH

Cumulative incidence of mortality and dermatologic cancers after heart transplant (N=312)¹

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Cumulative incidence</th>
<th>10-year risk, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, %</td>
<td>18.4 (13.6, 23.0)</td>
<td>37.9 (30.5, 44.5)</td>
</tr>
<tr>
<td></td>
<td>63.5 (51.5, 72.5)</td>
<td>78.7 (57.7, 89.3)</td>
</tr>
<tr>
<td>SCC, %</td>
<td>5.4</td>
<td>32.3</td>
</tr>
<tr>
<td></td>
<td>38.2</td>
<td>nr</td>
</tr>
<tr>
<td>BCC, %</td>
<td>10.3</td>
<td>19.2</td>
</tr>
<tr>
<td></td>
<td>31.6</td>
<td>nr</td>
</tr>
<tr>
<td>Any skin cancer, %</td>
<td>0.4</td>
<td>37.5</td>
</tr>
<tr>
<td></td>
<td>46.4</td>
<td>nr</td>
</tr>
</tbody>
</table>

Number of CSCCs elevates risk of recurrence²

<table>
<thead>
<tr>
<th>CSCCs No.</th>
<th>Patients No.</th>
<th>10-year risk, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>727</td>
<td>3.0 (2.0, 4.5)</td>
</tr>
<tr>
<td>2–9</td>
<td>239</td>
<td>6.7 (4.2, 10.6)</td>
</tr>
<tr>
<td>≥10</td>
<td>19</td>
<td>36.8 (19.2, 59.0)</td>
</tr>
</tbody>
</table>

Patients with ≥10 CSCCs (who are often immunosuppressed) have a high 10-year risk of recurrence and nodal metastases

nr, not reported; BCC basal cell carcinoma; SCC, squamous cell carcinoma

### POSTTRANSPLANT SKIN CANCER: HIGHEST RISK FOR CSCC

Incidence rates (cases PWE 100,000 person-years)

<table>
<thead>
<tr>
<th>Type</th>
<th>OTR</th>
<th>US population</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMSC</td>
<td>1,436</td>
<td>449</td>
</tr>
<tr>
<td>SCC</td>
<td>1,355</td>
<td>38</td>
</tr>
<tr>
<td>MM</td>
<td>125</td>
<td>18</td>
</tr>
<tr>
<td>MCC</td>
<td>3.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

36-fold higher incidence in OTRs (SCC:BCC = 4:1)
Aggressive biologic behaviour; poor outcome
CSCC: STANDARD SURGERY
CSCC: MOST PATIENTS ARE EASY TO TREAT BY LOCAL SURGERY

>98% Treated surgically

CSCC patient population

~1 to 3% Ineligible for surgery/radiotherapy

Poor outcomes

Previously, no approved therapies

Small population, great medical need
INVASIVE CSCC: MICROGRAPHIC SURGERY

Surgical removal of CSCC

Histology

Re-excision

Incomplete

In sano (complete)

Wound defect closure

Courtesy of Prof Andreas Dietz (Leipzig, Germany)
SURGERY PROVIDES A HIGH CURE RATE FOR THE MAJORITY OF CSCC PATIENTS

5-Year clinical outcomes of patients with invasive CSCC treated with MMS

Relapse/metastasis risk by tumour thickness

MMS, Mohs Micrographic Surgery
LOCALLY ADVANCED AND METASTATIC CSCC
Harbouring two different groups of patients with different features and response criteria

- **Locally advanced disease** (typically one very large or multiple primary tumours)
- **Metastatic disease** with regional or distant metastases

- Risk factors in complex cases: comorbidities, negligence, immunosuppression (i.e. CLL pts, organ transplant recipients)
PROGNOSIS OF CSCC PATIENTS WITH LYMPH NODE METASTASES

N1 Disease

92% 5-year cure for N1 disease with lymphadenectomy

- N1: Single node, <3 cm tumour focus, no ECS

N2 Disease

Fares worse: 68% vs 42% surviving based on immune status (CLL, organ transplant)

- 68% is better than anti-PD1 response rate so surgery still plays a role, but it is a good group in whom to study adjuvant therapy

CLL, chronic lymphocytic leukaemia.

INTERDISCIPLINARY PATIENT CARE IN ADVANCED AND DIFFICULT TO TREAT SCC

- Plastic surgeon
- Radio-oncologist
- Psycho-oncologist/psychiatrist
- Pathologist
- Oncologist/derm-oncologist
- Derm-surgeon
- Head and neck surgeon
DETERMINING INELIGIBILITY FOR SURGERY/RADIOThERAPY

PROCEDURAL/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

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?

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

SPREAD
Has the tumour spread to multiple lymph nodes or distant organs?

RADIOThERAPY
Does the patient have any contraindications for radiotherapy?
LOCALLY ADVANCED CSCC:
NOT A CANDIDATE FOR SURGERY OR IRRADIATION

Courtesy of Prof A. Hauschild
LOCALLY ADVANCED AND METASTATIC CSCC: TREATMENT OPTIONS
ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA
A retrospective analysis of patient profiles and treatment patterns –
Results of a non-interventional study of the DeCOG

LOCALLY ADVANCED AND METASTATIC SCC

Radiotherapy

Platinum-based chemotherapy

- No established standard regiment, short-lived remissions (average duration: 3 months) up to 60%

Mutation-driven targeted therapies

- EGFR/pan-HER inhibitors: Cetuximab (RR: 28%), Panitumumab (31%), Dacomitinib (ASCO 2017: 28%)

Immunotherapies with PD1 antibodies: Cemiplimab (EMA- and FDA-approved) and Pembrolizumab (only FDA-approved)

Change of immunosuppressive treatment in organ transplanted patients (OTR) towards mTOR inhibitors
SYSTEMIC THERAPY FOR LOCALLY ADVANCED OR METASTATIC CSCC

Before immune checkpoint inhibitor

Conventional cytotoxic chemotherapy (Cisplatin or carboplatin + 5-FU or paclitaxel)+
  - Tumour responses usually short duration
  - Poorly tolerated

Anti-EGFR cetuximab
Single arm trial (n=36)²
  - ORR: 28%
  - Median OS: 8.1 months

CETUXIMAB FOR MCSCC

August 2010

December 2010

Courtesy of Prof A. Hauschild
WHY IMMUNOTHERAPIES FOR ADVANCED CSCC?
UV-EXPOSURE AS AN IMPORTANT CARCINOGEN IS DRIVING MOST MUTATIONS IN SKIN CANCERS
TUMOUR MUTATIONAL BURDEN

Tumour mutational burden versus response

HIGH MUTATIONAL BURDEN IN CSCC

Mutation frequencies

![Graph showing mutation frequencies for different cancer types.]

Mutation types

![Bar chart showing mutation types for different cancer types.]

LOCALLY ADVANCED AND METASTATIC CSCC: PD1-ANTIBODIES
MECHANISM: PD-(L)1 INHIBITION

Without treatment:

- **T cell** interacts with **PD-1** on the **Cancer Cell**.
- **PD-L1** is expressed on the **Cancer Cell**.

- T cell is inactivated by PD-L1, leading to cancer proliferation.

With treatment:

- **PD-1 inhibitor** blocks the interaction between T cell and PD-L1.
- T cell is prevented from being inactivated.

- T cell is now able to attack the cancer cell, leading to its destruction.

T cell is prevented from being inactivated by the cancer cell, cancer is attacked by immune system.
PHASE 2 STUDY OF CEMIPLIMAB
In patients with advanced cutaneous squamous cell carcinoma (CSCC): Longer follow-up

Danny Rischin,1 Nikhil I. Khushalani,2 Chrysalyne D. Schmults,3 Alexander Guminski,4
Anne Lynn S. Chang,5 Karl D. Lewis,6 Annette M. Lim,1 Leonel Hernandez-Aya,7 Brett G.M. Hughes,8
Dirk Schadendorf,9 Axel Hauschild,10 Elizabeth Stankevich,11 Jocelyn Booth,11 Suk-Young Yoo,11
Zhen Chen,12 Emmanuel Okoye,13 Israel Lowy,12 Matthew G. Fury,12 Michael R. Migden14

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CANDIDATES FOR IMMUNOTHERAPY FOR ADVANCED CSCC

Patients with advanced CSCC

- Locally advanced/metastatic disease

Patients who have failed prior surgeries

Patients who are not surgical candidates due to morbidity/potential disfigurement or low confidence of clear margins

Patients not candidates for radiotherapy

CSCC, cutaneous squamous cell carcinoma.
OBJECTIVES

Primary objective was to evaluate ORR by ICR per RECIST 1.1 (for scans)1 and modified WHO criteria (for photos)

Key secondary objectives were to investigate:

- ORR per INV
- DOR by ICR and INV
- PFS by ICR and INV
- OS
- Complete response rate by ICR
- Safety and tolerability
- Assessment of health-related quality of life
- Durable disease control rate, defined as the proportion of patients with response or stable disease for at least 105 days

Here, we present up to 3-year follow-up (median duration of follow-up for all patients: 15.7 months) from the largest and most mature prospective data set in advanced CSCC

CSCC, cutaneous squamous cell carcinoma; DOR, duration of response; ICR, independent central review; INV, investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria In Solid Tumours version 1.1; WHO, World Health Organisation.

EMPOWER-CSCC-1 is an open-label, non-randomised, multicentre, International Phase 2 study of patients with advanced CSCC.

The data cut-off was October 11, 2019.

**Group 1**
- Adult patients with metastatic (nodal and/or distant) CSCC (n=59)

**Group 2**
- laCSCC (n=78)

**Group 3**
- Adult patients with metastatic (nodal and/or distant) CSCC (n=56)

**Primary objective:**
- ORR by ICR per RECIST 1.1 (for scans) and modified WHO criteria (for photos)

<table>
<thead>
<tr>
<th>Group</th>
<th>Metastatic CSCC Details</th>
<th>Advanced CSCC (n=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median age, years (range)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male, n (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ECOG performance status, n (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary CSCC site: head and neck, n (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>131 (67.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mCSCC, n (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>laCSCC, n (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients with cemiplimab as first-line therapy, n (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients with prior systemic therapy, n (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median duration of exposure to cemiplimab, weeks (range)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median number of doses of cemiplimab administered (range)</td>
</tr>
</tbody>
</table>

CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; ICR, independent central review; laCSCC, locally advanced CSCC; IV, intravenous; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; RECIST 1.1, Response Evaluation Criteria In Solid Tumours version 1.1. WHO, World Health Organisation.\(^\text{a}\)Settings for prior lines of therapy included metastatic disease, adjuvant, chemotherapy with concurrent radiation, or other and the most common types of prior systemic therapy were platinum compounds (n=46/65 [70.8%]) and monoclonal antibodies (n=18/65 [27.7%]).

EMPOWER-CSCC-1: PHASE 2 CEMIPLIMAB STUDY

Duration of follow-up and tumour response to cemiplimab per ICR

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (mCSCC)</th>
<th>Group 2 (laCSCC)</th>
<th>Group 3 (mCSCC)</th>
<th>Total (n=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of follow-up, months (range)</td>
<td>18.5 (11.1 – 36.1)</td>
<td>15.5 (0.8 – 35.6)</td>
<td>17.3 (0.6 – 26.3)</td>
<td>15.7 (0.6 – 36.1)</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>50.8 (37.5 – 64.1)</td>
<td>44.9 (33.6 – 56.6)</td>
<td>42.9 (29.7 – 56.8)</td>
<td>46.1 (38.9 – 53.4)</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
<td>12 (20.3)</td>
<td>10 (12.8)</td>
<td>9 (16.1)</td>
<td>31 (16.1)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>18 (30.5)</td>
<td>25 (32.1)</td>
<td>15 (26.8)</td>
<td>58 (30.1)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>9 (15.3)</td>
<td>27 (34.6)</td>
<td>10 (17.9)</td>
<td>46 (23.8)</td>
</tr>
<tr>
<td>Non-complete response/non-progressive disease, n (%)</td>
<td>3 (5.1)</td>
<td>0</td>
<td>2 (3.6)</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>10 (16.9)</td>
<td>10 (12.8)</td>
<td>14 (25.0)</td>
<td>34 (17.6)</td>
</tr>
<tr>
<td>Not evaluable, n (%)</td>
<td>7 (11.9)</td>
<td>6 (7.7)</td>
<td>6 (10.7)</td>
<td>19 (9.8)</td>
</tr>
<tr>
<td>Disease control rate, % (95% CI)</td>
<td>71.2 (57.9 – 82.2)</td>
<td>79.5 (68.8 – 87.8)</td>
<td>64.3 (50.4 – 76.6)</td>
<td>72.5 (65.7 – 78.7)</td>
</tr>
<tr>
<td>Durable disease control rate†, % (95% CI)</td>
<td>61.0 (47.4 – 73.5)</td>
<td>62.8 (51.1 – 73.5)</td>
<td>57.1 (43.2 – 70.3)</td>
<td>60.6 (53.3 – 67.6)</td>
</tr>
<tr>
<td>Median observed time to response, months (IQR)‡</td>
<td>1.9 (1.8 – 2.0)</td>
<td>2.1 (1.9 – 3.8)</td>
<td>2.1 (2.1 – 4.2)</td>
<td>2.1 (1.9 – 3.7)</td>
</tr>
<tr>
<td>Median observed time to complete response, months (IQR)‡</td>
<td>11.1 (7.5 – 18.4)</td>
<td>10.5 (7.4 – 12.9)</td>
<td>12.4 (8.2 – 16.6)</td>
<td>11.2 (7.4 – 14.8)</td>
</tr>
<tr>
<td>Median DOR, months (range)‡</td>
<td>NR (20.7, NE)</td>
<td>NR (18.4, NE)</td>
<td>NR (NE, NE)</td>
<td>NR (28.8, NE)</td>
</tr>
<tr>
<td>Kaplan–Meier 12-month estimate of patients with ongoing response, % (95% CI)</td>
<td>89.5 (70.9 – 96.5)</td>
<td>83.2 (64.1 – 92.7)</td>
<td>91.7 (70.6 – 97.8)</td>
<td>87.8 (78.5 – 93.3)</td>
</tr>
<tr>
<td>Kaplan–Meier 24-month estimate of patients with ongoing response, %</td>
<td>68.8 (46.9 – 83.2)</td>
<td>62.5 (38.4 – 79.4)</td>
<td>NE (NE, NE)</td>
<td>69.4 (55.6 – 79.6)</td>
</tr>
</tbody>
</table>

Per ICR, ORR was 48.4% and 41.5% among those who had not received prior anticancer systemic therapy (n=128) and those who had received prior anticancer systemic therapy (n=65), respectively. Overall, the observed time to response was 2 months for 41 (46.1%) patients, 2–4 months for 29 (32.6%) patients, 4–6 months for 8 (9.0%) patients, and >6 months for 11 (12.4%) patients.

†Defined as the proportion of patients without progressive disease for at least 105 days. Based on number of patients with confirmed complete or partial response. ORR per INV was 54.4% (95% CI: 47.1 – 61.6) for all patients; 50.8% (95% CI: 37.5 – 64.1) for Group 1, 56.4% (95% CI: 44.7 – 67.6) for Group 2, and 55.4% (95% CI: 41.5 – 68.7) for Group 3. ORR per INV was 71.2% (95% CI: 50.4 – 76.6) among treatment-naïve patients and 47.7% (95% CI: 35.1 – 60.5) among previously treated patients. CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; DOR, duration of response; ICR, independent central review; INV, investigator review; IQR, interquartile range; laCSCC, locally advanced CSCC; mCSCC, metastatic CSCC; NE, not evaluable; NR, not reached; ORR, objective response rate; Q2W, every 2 weeks; Q3W, every 3 weeks.
Among 89 responders, median time to complete response was 11.2 months (IQR, 7.4–14.8)

Among 23 laCSCC patients who were included in the pre-specified Group 2 interim analysis, there were no complete responses.

CSCC, cutaneous squamous cell carcinoma; ICR, independent central review; IQR, interquartile range; laCSCC, locally advanced CSCC; mCSCC, metastatic CSCC; Q2W, every 2 weeks; Q3W, every 3 weeks.

JULY TO DEC 2019

Courtesy of Dr. Laura Lusok, Bochum, Germany
JULY 2018 (POST MULTIPLE SURGERIES): BEFORE ANTI-PD1

Courtesy of Prof A. Hauschild
OCTOBER 2018 (AFTER 3 MON. PD1 ANTIBODIES): ALMOST CR

Courtesy of Prof A. Hauschild
FEBRUARY 2019:
ONGOING CR (LAST VISIT: SEPTEMBER 2021)

Courtesy of Prof. A. Hauschild
FEBRUARY 2020:
BEFORE CEMIPLIMAB TREATMENT

Courtesy of Prof A. Hauschild
EMPOWER-CSCC-1: PHASE 2 CEMIPLIMAB STUDY

Kaplan–Meier curves for DOR per ICR

- Median DOR has not been reached (observed DOR range: 1.9–34.3 months)
- In responding patients, the estimated proportion of patients with ongoing response at 24 months was 69.4% (95% CI: 55.6–79.6)

Data cut-off date: October 11, 2019. Median duration of follow-up among all patients: 15.7 months (range: 0.6–36.1).
CSCC, cutaneous squamous cell carcinoma; CI, confidence interval; DOR, duration of response; ICR, independent central review; laCSCC, locally advanced CSCC; mCSCC, metastatic CSCC; Q2W, every 2 weeks; Q3W, every 3 weeks.
EMPOWER-CSCC-1: PHASE 2 CEMIPLIMAB STUDY

Kaplan–Meier curves for PFS & OS

---

**KM Curves for PFS by ICR**

Estimated median PFS (all patients): 18.4 months (95% CI 10.3–24.3)
- Estimated probability of PFS at 24 months: 44.2% (95% CI 36.1–52.1)

**KM Curves for OS by ICR**

Median OS (all patients): not reached
- Estimated probability of OS at 24 months: 73.3% (95% CI 66.1–79.2)

---

CSCC, cutaneous squamous cell carcinoma; CI, confidence interval; laCSCC, locally advanced CSCC; mCSCC, metastatic CSCC; OS, overall survival; Q2W, every 2 weeks; Q3W, every 3 weeks.

EMPOWER-CSCC-1: PHASE 2 CEMIPLIMAB STUDY

Treatment-emergent adverse events

<table>
<thead>
<tr>
<th>TEAEs regardless of attribution</th>
<th>Advanced CSCC (n=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>Any grade</td>
</tr>
<tr>
<td>Any</td>
<td>192 (99.5)</td>
</tr>
<tr>
<td>Led to discontinuation</td>
<td>19 (9.8)</td>
</tr>
</tbody>
</table>

Most common TEAEs by any grade were fatigue (n=67, 34.7%), diarrhea (n=53, 27.5%), and nausea (n=46, 23.8%)

Grade ≥3 TRAEs were reported in 33 (17.1%) patients, with the most common being pneumonitis (n=5, 2.6%), autoimmune hepatitis (n=3; 1.6%), anemia, colitis, and diarrhea (all n=2; 1.0%)

No new TEAEs resulting in death were reported compared to previous reports\(^1-3\)

Data cut-off date: October 11, 2019. Median duration of follow-up among all patients: 15.7 months (range: 0.6–36.1).

1TEAEs reported in ≥10% of patients, ordered by frequency of any grade. CSCC, cutaneous squamous cell carcinoma; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

EMPOWER-CSCC-1: PHASE 2 CEMIPLIMAB STUDY

Longitudinal analysis on quality of life (QLQ-C30)

Among the symptom scales and items, a marked improvement in pain score was observed as early as cycle 2.

The initial clinically meaningful improvement (≥10 points) in pain score at cycle 3 (LS mean [SE] change –11.5 [1.9]; P<0.0001) was maintained during study treatment to cycle 12 (LS mean [SE] change –14.3 [3.1]; P<0.0001)

HRQL, health-related quality of life; LS, least squares; QLQ-C30, Quality of Life Questionnaire-Core 30; SD, standard deviation; SE, standard error.

EMPOWER-CSCC-1: ONGOING CEMIPLIMAB PIVOTAL PHASE 2 CSCC STUDY IN ACSCC

Clinical trial design

**Primary endpoint:**
ORR

**Key secondary endpoints:**
DOR, PFS, OS, CR, PK, safety and tolerability

**Estimated enrollment N=433**

- **Group 1**
  - Metastatic (nodal or distant) CSCC
  - 3 mg/kg IV cemiplimab every 14 days (up to 96 weeks)

- **Group 2**
  - Locally advanced CSCC (not candidates for surgery or radiation)
  - 350 mg IV cemiplimab every 21 days (up to 54 weeks)

- **Group 3**
  - Metastatic (nodal or distant) CSCC
  - 600 mg IV cemiplimab every 28 days (up to 48 weeks)

- **Group 4**
  - Advanced CSCC (metastatic or locally advanced)
  - 350 mg IV cemiplimab every 21 days (up to 108 weeks)

- **Group 6**
  - Advanced CSCC (metastatic or locally advanced)
  - 350 mg IV cemiplimab every 21 days (up to 108 weeks)

CR, complete response; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PK, pharmacokinetics

NCT02760498 available at: https://clinicaltrials.gov/ct2/show/NCT02760498 accessed July 2020
CEMIPLIMAB 600 MG EVERY 4 WEEKS IN PATIENTS WITH ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA

Primary analysis of Group 4 Phase 2 results

Danny Rischin,1 Brett GM Hughes,2 Nicole Basset-Séguin,3 Dirk Schadendorf,4 Samantha Bowyer,5 Sabiha Trabelsi,6 Friedegund Meier,7,8 Thomas Eigentler,9 Victoria Casado Echarren,10 Michael R Migden,11 Axel Hauschild,12 Chrysalyne D Schmults,13 Suk-Young Yoo,14 Anne Paccaly,14 John Davis,14 Suzanne Green,14 Frank Seebach,14 Scott Drutman,14 Jocelyn Booth,14 David Weinreich,14 George Yancopoulos,14 Israel Lowy,14 Matthew G Fury,14 Alexander Guminski15

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Verbatim presentation of poster presented at ESMO 2021. Conclusions and opinions expressed are those of the authors only. Poster number: 1066P. MAT-GLB-2104213 v1.0. Approval Date: 09/2021.
PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

A total of 63 patients with mCSCC (n=39) or laCSCC (n=24) were enrolled in Group 4, treated with cemiplimab, and included in this analysis.

- 10 patients (15.9%) completed treatment
- 29 patients (46.0%) discontinued treatment
  - 16 patients (25.4%) have entered follow-up
- 24 patients (38.1%) treatment is ongoing

The median number of doses was 9 (range, 1–18) and the median duration of exposure was 36.4 weeks (range, 4.0–71.9)

At the time of data cut-off, median duration of follow-up was 9.2 months (range, 1.0–16.5)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Advanced CSCC (Group 4; N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>74 (23–94)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>53 (84)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>25 (40)</td>
</tr>
<tr>
<td>1</td>
<td>38 (60)</td>
</tr>
<tr>
<td>Extent of disease, n (%)</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>39 (62)</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>24 (38)</td>
</tr>
<tr>
<td>Prior cancer-related systemic therapy, n (%)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Prior cancer-related radiotherapy, n (%)</td>
<td>38 (60)</td>
</tr>
</tbody>
</table>

CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; laCSCC, locally advanced CSCC; mCSCC, metastatic CSCC.

Verbatim presentation of poster presented at ESMO 2021. Conclusions and opinions expressed are those of the authors only.
Among 55 patients who had optional baseline PET as an exploratory endpoint, centrally reviewed ORR was 61.8% and the complete metabolic response was 25.5%.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Conventional imaging (primary endpoint) (advanced CSCC, Group 4, N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)†</td>
<td>58.7 (45.6–71.0)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>11 (17.5)</td>
</tr>
<tr>
<td>Partial response</td>
<td>26 (41.3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (14.3)</td>
</tr>
<tr>
<td>Noncomplete response/ nonprogressive disease</td>
<td>3 (4.8)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>9 (14.3)</td>
</tr>
<tr>
<td>Not evaluable‡</td>
<td>5 (7.9)</td>
</tr>
</tbody>
</table>

†For conventional imaging, ORR is defined as complete response plus partial response; Clopper-Pearson exact CI. ‡Includes missing and unknown tumour response. CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; ICR, independent central review; ORR, overall response rate; PET, positron emission tomography.

Verbatim presentation of poster presented at ESMO 2021. Conclusions and opinions expressed are those of the authors only.
Median PFS per ICR, median OS, and median duration of response had not been reached at data cut-off

- KM estimate of the proportion of patients with ongoing response at 12 months was 89.4% (95% CI, 70.0–96.6%; see Supplementary Figure 1)
- KM estimation of PFS and probability of OS at 12 months were 64.7% (95% CI, 49.2–76.6%) and 79.6 (95% CI, 66.8–87.9%), respectively

The durable disease control rate was 76.2% (95% CI, 63.8–86.0%)

CSCC, cutaneous squamous cell carcinoma; CI, confidence interval; ICR, independent central review; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; Q4W, every 4 weeks.

Verbatim presentation of poster presented at ESMO 2021. Conclusions and opinions expressed are those of the authors only.

With permission from Prof D. Rischin.
TREATMENT-EMERGENT ADVERSE EVENTS

The most common Grade ≥3 TEAEs reported in >2 patients were hypercalcaemia and anaemia (n=3 each; 4.8%)

Any TEAEs were reported in 50 patients (79.4%) of which 12.7% of patients (n=8) reported serious TEAEs with 4 of these events reported as Grade ≥3 (n=1 each; bullous dermatitis, immune-mediated pneumonitis and hepatitis, peripheral neuropathy); 7 patients (11.1%) experienced TEAEs leading to discontinuation (see Supplementary Table 1)

Investigator-assessed Grade ≥3 irAEs occurred in 8 patients (12.7%; see Supplementary Table 2)

Four patients (6.3%) experienced TEAEs with an outcome of death:
- 2 patients developed infections (infectious pneumonia, sepsis), 1 patient had a cerebrovascular accident, and 1 patient had a lung disorder on study, all with fatal outcomes
- None of the deaths were considered treatment related by investigators

†TEAEs reported in >10% of patients, ordered by frequency of any grade.

The severity of TEAEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

AE, adverse event; CSCC, cutaneous squamous cell carcinoma; irAE, immune-related adverse event; TEAE, treatment-emergent adverse event.

Verbatim presentation of poster presented at ESMO 2021. Conclusions and opinions expressed are those of the authors only.

<table>
<thead>
<tr>
<th>Advanced CSCC (Group 4; N=63)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>Any grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>63 (100)</td>
<td>30 (47.6)</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>29 (46.0)</td>
<td>22 (34.9)</td>
</tr>
<tr>
<td>TEAE leading to treatment discontinuation</td>
<td>10 (15.9)</td>
<td>7 (11.1)</td>
</tr>
<tr>
<td>TEAE leading to death</td>
<td>4 (6.3)</td>
<td>4 (6.3)</td>
</tr>
<tr>
<td>Most common TEAEs†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>15 (23.8)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>15 (23.8)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (22.2)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>12 (19.0)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>11 (17.5)</td>
<td>0</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>7 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>7 (11.1)</td>
<td>3 (4.8)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>7 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>7 (11.1)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Skin infection</td>
<td>7 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7 (11.1)</td>
<td>0</td>
</tr>
</tbody>
</table>
Pembrolizumab monotherapy for recurrent or metastatic cutaneous squamous cell carcinoma: A single-arm Phase II trial (KEYNOTE-629)
### Summary of tumour response in all patients as treated

<table>
<thead>
<tr>
<th>Response</th>
<th>Pembrolizumab (N = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate, % (95% CI)(^a)</td>
<td>34.3 (25.3 to 44.2)</td>
</tr>
<tr>
<td>Disease control rate, % (95% CI)(^b)</td>
<td>52.4 (42.4 to 62.2)</td>
</tr>
<tr>
<td><strong>Best overall response</strong></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>4.0 (3.8)</td>
</tr>
<tr>
<td>Partial response</td>
<td>32.0 (30.5)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>31.0 (29.5)</td>
</tr>
<tr>
<td>Stable disease ≥12 weeks</td>
<td>19.0 (18.1)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>28.0 (26.7)</td>
</tr>
<tr>
<td>Not evaluable(^c)</td>
<td>2.0 (1.9)</td>
</tr>
<tr>
<td>Not assessed(^d)</td>
<td>8.0 (7.6)</td>
</tr>
</tbody>
</table>

\(^a\)Includes complete and partial responses.
\(^b\)Includes stable disease ≥12 weeks, partial responses, and complete responses.
\(^c\)Postbaseline assessment available but not evaluable.
\(^d\)No postbaseline assessment available for response evaluation.

All patients had at least one postbaseline assessment of target lesion(s) (n=76). Symbols for complete response (CR), partial response (PR), and progressive disease depict the first response to pembrolizumab. Symbols depict the timing of first objective response unless otherwise indicated.

*Discontinued or ongoing refers to status in relation to study treatment. †Patient achieved a best overall response (BOR) of CR

PEMBROLIZUMAB FOR ADVANCED CSCC (KN-029)

Kaplan-Meier estimates of (A) PFS by blinded independent central review using RECIST v1.1 and (B) OS in all patients as treated.

NR, not reached.

PEMBROLIZUMAB IN ADVANCED CSCC (KEYNOTE-629 TRIAL)
EFFICACY OF PD1-ANTIBODIES

CEMIPLIMAB

Metastatic disease
Response Rate: 47% to 49%\textsuperscript{1,2}

Locally advanced disease
Response Rate: 43% to 50%\textsuperscript{1,3}

PEMBROLIZUMAB

Locally advanced or metastatic disease
Response Rate: 34% to 40%\textsuperscript{4-6}

Approximately 75% of patients took pembrolizumab second-line after chemotherapy, resulting in slightly lower response rates.\textsuperscript{6}
MULTICENTRIC PHASE II OF NIVOLUMAB IN CSCC

Patients with metastatic and/or locally advanced cSCC.

24 pts received nivolumab at the dose of 3 mg/kg Q2W

Primary endpoint: bORR at 24w as per RECIST criteria

<table>
<thead>
<tr>
<th>Best response at 24 weeks – N (%)</th>
<th>N=22 (evaluable for response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>12 (54.5%)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>5 (22.7%)</td>
</tr>
<tr>
<td>Disease control rate (CR+PR+SD)</td>
<td>17 (77%)</td>
</tr>
<tr>
<td>Progression of disease</td>
<td>5 (22.7%)</td>
</tr>
</tbody>
</table>
FIRST REAL LIFE COHORT FROM AN EARLY ACCESS PROGRAM IN ADVANCED CSCC

Patients treated with cemiplimab: French experience

Patient eligibility
Histologically confirmed CSCC
la/m SCCS not amenable to surgery
Age ≥18 years

Retrospective study conducted in 58 French centres
Patients were enrolled between 08/18 and 10/19; N=245

Cemiplimab 3 mg/kg Q2W until unacceptable toxicity or disease progression
Response evaluation according to the standard of care in each center
Efficacy and safety evaluated in patients who received ≥ 1 cemiplimab infusion; N=240

Primary endpoint: To assess the best response rate (RR) in patients with la/m CSCCs treated with cemiplimab
Secondary endpoints: Progression-free survival (PFS), overall survival (OS), duration of response (DOR) and safety

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 245</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (± SD)</td>
<td>77.1 ± 13.3</td>
</tr>
<tr>
<td>Males n (%)</td>
<td>178 (73)</td>
</tr>
<tr>
<td>ECOG performance status 0 or 1, n (%)</td>
<td>178 (73)</td>
</tr>
<tr>
<td>Immunocompromised*, n (%)</td>
<td>59 (24)</td>
</tr>
<tr>
<td>Genodermatosis§, n (%)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Chronic dermatitis*, n (%)</td>
<td>28 (12)</td>
</tr>
<tr>
<td>Primary CSCC site, n (%)</td>
<td></td>
</tr>
<tr>
<td>Head or neck</td>
<td>164 (68)</td>
</tr>
<tr>
<td>Other</td>
<td>79 (32.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=245</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>85 (35)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>159 (65)</td>
</tr>
<tr>
<td>Previous systemic therapy, n (%)</td>
<td>121 (49)</td>
</tr>
<tr>
<td>Previous radiotherapy, n (%)</td>
<td>144 (59)</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>12.6</td>
</tr>
<tr>
<td>Median number of infusions (IQR)</td>
<td>10 (4–22)</td>
</tr>
</tbody>
</table>

*Among the cohort: HIV (3%), organ transplants (3%), CLL (8%), others hematologic malignancies (7%), under immunosuppressive drugs (2%), others (1%).
§Inherited epidermolysis bullosa (n=2), Muir Torre syndrome (n=2), ichthyosis (n=2), xeroderma pigmentosum (n=1).
*Burns (n=2), scars (n=4), lichen (n=2), ulcers (n=8), condyloma (n=3), arsenic keratosis (n=2), radiodermatitis (n=2), and SOS (squamous cell carcinoma of the skin)

CSCC, cutaneous squamous cell carcinoma; la, locally advanced; m, metastatic; Q2W, every 2 weeks; SOS, squamous cell carcinoma of the skin

1. Hober C. Presented at the ESMO Congress; September 19-21, 2020. P1086. MAT-GLB-2100691 v1.0. Approval Date: 03/2021
Annals of Oncology (2020) 31 (suppl_4): S672-S710. 10.1016/annonc/annonc280 © 2020 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved.
FIRST REAL LIFE COHORT FROM AN EARLY ACCESS PROGRAM IN ADVANCED CSCC

Patients treated with cemiplimab: Evaluation of response

<table>
<thead>
<tr>
<th>Best overall response, n (%) unless otherwise stated</th>
<th>Advanced CSCC Patients; N=240</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response rate, n [% (95% CI)]</td>
<td>121 [50.4 (43.9, 56.9)]</td>
</tr>
<tr>
<td>Complete response</td>
<td>51 (21.3)</td>
</tr>
<tr>
<td>Duration of response</td>
<td>Not reached</td>
</tr>
<tr>
<td>Treatment-related adverse events (TRAE)</td>
<td>75 (31)</td>
</tr>
<tr>
<td>Cemiplimab discontinuation for TRAE</td>
<td>16 (7)</td>
</tr>
<tr>
<td>Experienced ≥1 grade 3–4 TRAE</td>
<td>22 pts (9)</td>
</tr>
</tbody>
</table>

The safety profile was consistent with previous cemiplimab studies

The median OS was not reached.

6-months OS (CI 95%) was 73.8% (68.3, 79.7)
12-months OS (CI 95%) was 63.1% (56.8, 70.1)

13 patients (5.4%) were not evaluable; One cemiplimab related death due to Toxic epidermal necrolysis (TEN)
CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; TRAE, treatment-related adverse events
1. Hober C. Presented at the ESMO Congress; September 19-21, 2020. P1086. MAT-GLB-2100691 v1.0. Approval Date: 03/2021
Annals of Oncology (2020) 31 (suppl_4): S672-S710. 10.1016/annonc/annonc280 © 2020 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved
HIGH-RISK CSCC: ADJUVANT RADIOTHERAPY
## Indications for adjuvant radiotherapy according to European, US and Australian guidelines

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Substantial perineural invasion</td>
<td>Extensive perineural invasion or invasion of large-caliber nerves Positive margins</td>
<td>Perineural invasion of large- and small-caliber nerves Positive margins Margins &lt;5 mm Lymphovascular invasion T4 Rapid growth Recurrent squamous cell carcinoma</td>
</tr>
<tr>
<td>Positive margins (if surgery is not possible)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


DFS AND OS FOR ADJUVANT RADIOTHERAPY IN CSCC

Disease-free survival among patients with regional disease

Overall survival among patients with regional disease

No. at risk
Surgery and radiation therapy
Surgery alone

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery and radiation therapy</td>
<td>87</td>
<td>70</td>
<td>68</td>
<td>61</td>
<td>57</td>
<td>55</td>
<td>53</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>31</td>
<td>23</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>

HR, 0.36 (95% CI, 0.15-0.84)

No. at risk
Surgery and radiation therapy
Surgery alone

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery and radiation therapy</td>
<td>87</td>
<td>79</td>
<td>70</td>
<td>57</td>
<td>52</td>
<td>49</td>
<td>44</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>31</td>
<td>19</td>
<td>15</td>
<td>12</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

HR, 0.30 (95% CI, 0.15-0.61)
ADJUVANT RADIOTHERAPY IN CSCC: NO IMPACT ON OS

Comparison of surgery vs surgery plus adjuvant radiation therapy – OS

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>1.0</td>
<td>0.8</td>
<td>0.6</td>
<td>0.4</td>
<td>0.2</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Log-rank $P = .83$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. at risk
- Surgery and radiation therapy: 176, 167, 142, 123, 107, 100, 88
- Surgery alone: 173, 152, 128, 103, 88, 86, 78

Cox proportional hazards regression multivariate analysis\textsuperscript{a}

<table>
<thead>
<tr>
<th>Factor</th>
<th>DFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age $\geq$ 70 y</td>
<td>1.50 (0.92-2.45)</td>
<td>1.80 (1.20-2.67)</td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td>0.89 (0.32-2.52)</td>
<td>2.17 (1.12-4.17)</td>
</tr>
<tr>
<td>Periorbital primary</td>
<td>2.48 (1.00-6.16)</td>
<td>1.47 (0.62-3.52)</td>
</tr>
<tr>
<td>PNI-positive disease</td>
<td>1.90 (1.12-3.19)</td>
<td>1.32 (0.87-2.00)</td>
</tr>
<tr>
<td>N2 or greater disease</td>
<td>2.16 (1.13-4.16)</td>
<td>2.43 (1.42-4.17)</td>
</tr>
<tr>
<td>Postoperative radiation therapy</td>
<td>0.67 (0.40-1.15)</td>
<td>0.59 (0.38-0.90)</td>
</tr>
</tbody>
</table>

PNI, perineural invasion.

\textsuperscript{a}Results were controlled for recurrent tumour, lymphovascular invasion, differentiation, and T stage. Reference groups were age younger than 70 years, other primary site, and NO disease. Harris B, et al. JAMA Otolaryngology Head Neck Surg 2019;145:153–8.
PNI ADJUVANT RADIOTHERAPY IN CSCC
Subset analysis of patients with perineural invasion (PNI) and regional disease

Disease-free survival among patients with PNI-positive disease

OS among patients with PNI-positive disease

**POSTOPERATIVE RADIOTHERAPY VS. CHEMORADIOTHERAPY IN CSCC**

Randomised Phase 3 TROG 05.01 Trial

---

**Hazard Ratio (95% CI)**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>310</td>
<td>0.84</td>
<td>.58</td>
</tr>
<tr>
<td>Primary margin status*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>32</td>
<td>0.89</td>
<td>.88</td>
</tr>
<tr>
<td>Close or clear</td>
<td>51</td>
<td>0.81</td>
<td>.46</td>
</tr>
<tr>
<td>Extracapsular extension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>115</td>
<td>0.78</td>
<td>.61</td>
</tr>
<tr>
<td>Present</td>
<td>165</td>
<td>1.10</td>
<td>.81</td>
</tr>
<tr>
<td>No. of positive nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>254</td>
<td>0.51</td>
<td>.07</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>56</td>
<td>3.25</td>
<td>.06</td>
</tr>
<tr>
<td>Size of largest positive node†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 3 cm</td>
<td>226</td>
<td>0.54</td>
<td>.11</td>
</tr>
<tr>
<td>&gt; 3 cm</td>
<td>58</td>
<td>1.89</td>
<td>.36</td>
</tr>
</tbody>
</table>

---

**Disease-Free Survival**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Time Since Random Assignment (months)</th>
<th>Disease-Free Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT</td>
<td>0, 12, 24, 36, 48, 60</td>
<td>100, 95, 90, 85, 80</td>
</tr>
<tr>
<td>RT</td>
<td>0, 12, 24, 36, 48, 60</td>
<td>100, 95, 90, 85, 80</td>
</tr>
</tbody>
</table>

**OS by treatment arm**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Time Since Random Assignment (months)</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT</td>
<td>0, 12, 24, 36, 48, 60</td>
<td>100, 95, 90, 85, 80</td>
</tr>
<tr>
<td>RT</td>
<td>0, 12, 24, 36, 48, 60</td>
<td>100, 95, 90, 85, 80</td>
</tr>
</tbody>
</table>

---

HIGH-RISK CSCC: ADJUVANT AND NEOADJUVANT PD1-ANTIBODIES
NEOADJUVANT AND ADJUVANT THERAPY
Aim to increase treatment success and decrease recurrence risk

Cancer treatment

Neoadjuvant therapy (before primary therapy)
Primary treatment
Adjuvant therapy (after primary therapy)

Purpose of treatment

Reduce tumour size and eliminate any metastasised cells\(^1,2\)
Remove tumour\(^1,2\)
Eliminate any remaining cancer cells and prevent recurrence\(^2\)

**PHASE II STUDY OF CEMIPLIMAB PRIOR TO SURGERY IN ADV STAGE, RESECTABLE CSCC**

Single institution, single arm phase 2 study

N=20 Stage III/IV (M0) CSCC patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial clinic visit</td>
<td></td>
</tr>
<tr>
<td>REGN2810 IV 2 cycles (6 weeks)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Radiation +/- chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathologic Complete Response (pCR)</th>
<th>11/20</th>
<th>55%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Pathologic Response (MPR)</td>
<td>3/20</td>
<td>15%</td>
</tr>
<tr>
<td>Total</td>
<td>14/20</td>
<td>70%</td>
</tr>
</tbody>
</table>

Median follow up of 3.8 months (range: 1.5-11.2). (Data cutoff 1-Aug-2019).


Gross N, et al. Poster LBA74, ESMO 2019

Annals of Oncology (2019) 30 (suppl_5): v851-v934. 10.1093/annonc/mdz394 © 2019 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved.
NCT03565783: RESPONSE WITH NEOADJUVANT CEMIPLIMAB

A phase 2 study of neoadjuvant cemiplimab in patients with advanced-stage resectable CSCC of the head and neck

<table>
<thead>
<tr>
<th>Pathologic complete response</th>
<th>11/20</th>
<th>55%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major pathologic response</td>
<td>3/20</td>
<td>15%</td>
</tr>
<tr>
<td>Total</td>
<td>14/20</td>
<td>70%</td>
</tr>
</tbody>
</table>

Definitions
- Pathologic complete response: 0% viable
- Major pathologic response: ≤10% viable
- Pathologic partial response: 11% to 50% viable
- Pathologic stable/progressive disease: >50% viable

Before surgery
- Significant reduction in tumour allowed for less extensive surgery, sparing the orbit
- Final pathology revealed major pathologic response

Patient on study

After surgery
- Significant reduction in tumour allowed for less extensive surgery, sparing the orbit
- Final pathology revealed major pathologic response
NCT04154943: A PHASE 2 STUDY OF NEOADJUVANT CEMIPLIMAB
In patients with Stage II to IV CSCC (R2810-ONC-1901)

Part 1: neoadjuvant treatment (12 weeks)
- Neoadjuvant cemiplimab 350 mg IV q3w (4 doses)
  Estimated N=76
- Surgery

Part 2: adjuvant treatment (48 weeks)
- Adjuvant cemiplimab 350 mg IV q3w (16 doses)
- Adjuvant RT at investigator discretion
- Observation only

Follow-up (up to 3 years)

Key eligibility criteria:
- Age ≥18 years
- Stage II to IV (M0) CSCC for which surgery would be the recommended routine clinical practice
  - Stage II: lesion must be ≥3 cm at longest diameter
- At least 1 measurable lesion by RECIST v1.1
- ECOG PS 0 or 1
- No distant metastases
- No prior radiation therapy for CSCC

Primary endpoint:
- pCR rate (central)

Secondary endpoints:
- pCR rate (local)
- mPR rate (central and local)
- ORR
- EFS
- DFS
- OS
- Safety
TWO OPEN TRIALS RECRUITING IN ADJUVANT CSCC

Pembrolizumab
MK-3475-630¹

- A Phase 3, randomised, double-blind, placebo-controlled study to evaluate pembrolizumab versus placebo as adjuvant therapy following surgery and radiation of high-risk locally advanced cutaneous squamous cell carcinoma (LA CSCC)

Cemiplimab
R2810-ONC-1788 / C-POST trial²

- A randomised, placebo-controlled, double-blind study of adjuvant cemiplimab versus placebo after surgery and radiation therapy in patients with high risk cutaneous squamous cell carcinoma (CSCC)

1. NCT03969004 available at: https://clinicaltrials.gov/ct2/show/NCT03969004 accessed July 2020
2. NCT03833167 available at: https://clinicaltrials.gov/ct2/show/NCT03833167 accessed July 2020
ARE PD1-ANTIBODIES SAFE IN CSCC PATIENTS WITH CONCOMITANT COVID-INFECTIONS?
PATIENTS WITH LOCALLY ADVANCED AND METASTATIC CUTANEOUS SQUAMOUS CELL CARCINOMA TREATED WITH IMMUNOTHERAPY IN THE ERA OF COVID-19: Stop or go? Data from five Italian referral cancer centres

Patients with cancer seem to have a higher risk of contracting the infection and to have a worse course of the disease. The reasons can be many, including: advanced age (50% of cancer patients are >70 years of age); frequent visits to hospitals to receive treatments and a subsequent high risk of COVID-19 transmission between patients, infusion staff and medical system; their immunosuppressive status determined by the tumour itself and by anticancer treatments such as chemotherapy and radiotherapy.
Patients with cancer seem to have a higher risk of contracting the infection and to have a worse course of the disease. The reasons can be many, including: advanced age (50% of cancer patients are >70 years of age); frequent visits to hospitals to receive treatments and a subsequent high risk of COVID-19 transmission between patients, infusion staff and medical system; their immunosuppressive status determined by the tumour itself and by anticancer treatments such as chemotherapy and radiotherapy.

Stop or go treatment with cemiplimab in aCSCC? Go!
CONCLUSIONS ON PD1-ANTIBODIES AS THE NEW STANDARD OF CARE FOR ADVANCED CSCC
EGFR INHIBITORS

Erlotinib ORR: 10\%\textsuperscript{1}
Gefitinib ORR: 16\%\textsuperscript{2}
Cetuximab ORR: 21\%\textsuperscript{3}
Panitumumab ORR: 31\%\textsuperscript{4}

CHEMOTHERAPY

Platinum-based: 34\% ORR\textsuperscript{5}

PAN-HER INHIBITOR

Dacomitinib RR: 28\%\textsuperscript{6}

EGFR, estimated glomerular filtration rate; ORR, overall response rate


MAT-GLB-2100691 v1.0. Approval Date: 03/2021.
EFFICACY OF PD1 BLOCKING ANTIBODIES IN ADVANCED CSCC

**CEMIPLIMAB**

**Metastatic CSCC**
Response Rate: 47% to 49%\(^1,2\)

**Locally advanced CSCC**
Response Rate: 43% to 50%\(^1,3\)

**PEMBROLIZUMAB**

**Locally advanced or metastatic CSCC**
Response Rate: 34% to 40%\(^4-6\)

Approximately 75% of patients took pembrolizumab second-line after chemotherapy, resulting in slightly lower response rates.\(^6\)

No head-to-head studies have been conducted; it is unclear to what degree these study populations are comparable.

CEMIPLIMAB IN ADVANCED CSCC (PHASE 2, STUDY 1540): DURATION OF RESPONSES

Data cut-off date: October 11, 2019. Median duration of follow-up among all patients: 15.7 months (range: 0.6–36.1).

CSCC, cutaneous squamous cell carcinoma; CI, confidence interval; DOR, duration of response; ICR, independent central review; laCSCC, locally advanced CSCC; mCSCC, metastatic CSCC; Q2W, every 2 weeks; Q3W, every 3 weeks.


- Median DOR has not been reached (observed DOR range: 1.9–34.3 months)
- In responding patients, the estimated proportion of patients with ongoing response at 24 months was 69.4% (95% CI: 55.6–79.6)
THE HUGE DIFFERENCE IS THE DURATION OF RESPONSE!

4.5 Months
EGFR INHIBITORS

3 Months
CHEMOTHERAPY

Not reached
CHECKPOINT INHIBITORS

(69.4% still in response after 2 years)

CONCLUSIONS

Small population, great need

Surgery is generally curative for high-stage patients with CSCC, including those with early nodal disease, but it is not an option for a small subset of patients.

Previously, these patients were treated with chemotherapy and off-label EGFR inhibitors. Response rates averaged 20% between agents, with low durability and high recurrence risk.

Immunotherapy

PD-1 inhibitors have shown efficacy in patients with CSCC ineligible for surgery, mainly due to the high tumour mutational burden associated with CSCC.

Currently, cemiplimab is the only approved agent for unresectable CSCC in Europe. Response rates are around 40% to 50%, with high durability and lasting control.

Both cemiplimab and pembrolizumab are approved in the U.S.
Safety

Checkpoint inhibitors stimulate the immune system, which can be a problem for some patients, such as intentionally immunosuppressed patients. These include patients with organ transplants and autoimmune diseases.

Eligibility for immunotherapy should be evaluated on a case-by-case basis.

Immune-related Adverse Events

IrAEs can happen at any time and can affect any organ system. Corticosteroids are the cornerstone of management, along with treatment holidays and drug discontinuation in more severe cases.

Non-thyroid endocrine irAEs are usually permanent and affect about 1% of patients.

Due to rejection potential, determine eligibility of renal transplant patients for immunotherapy on a case-by-case basis.
FUTURE: COMBINATIONS OF PD1-ANTIBODIES WITH...

Irradiation
Targeted agents: cetuximab, lenvatinib
Intralesional agents like oncolytic viruses (TVEC or RP-1)
CTLA-4 antibodies
Chemo's (?)

High medical need particularly for PD1-refractory CSCC patients (in second-line)!

Multicentre studies in immunocompromised patients (CLL, etc)
THANK YOU!