

# S3 guideline „actinic keratosis and cutaneous squamous cell carcinoma“ – update 2023, part 1: treatment of actinic keratosis, actinic cheilitis, cutaneous squamous cell carcinoma in situ (Bowen’s disease), occupational disease and structures of care

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For involved societies see long version at [www.awmf.org](http://www.awmf.org).

## Summary

Actinic keratosis (AK) are common lesions in light-skinned individuals that can potentially progress to cutaneous squamous cell carcinoma (cSCC). Both conditions may be associated with significant morbidity and constitute a major disease burden, especially among the elderly. To establish an evidence-based framework for clinical decision making, the guideline “actinic keratosis and cutaneous squamous cell carcinoma” was updated and expanded by the topics cutaneous squamous cell carcinoma *in situ* (Bowen’s disease) and actinic cheilitis. The guideline is aimed at dermatologists, general practitioners, ear nose and throat specialists, surgeons, oncologists, radiologists and radiation oncologists in hospitals and office-based settings, as well as other medical specialties, policy makers and insurance funds involved in the diagnosis and treatment of patients with AK and cSCC. A separate guideline exists for patients and their relatives. In

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this part, we will address aspects relating to AK, actinic cheilitis, Bowen's disease, occupational disease and care structures.

## INTRODUCTION

The guideline represents a short version of the complete guideline available at [www.awmf.org](http://www.awmf.org). Information on epidemiology and etiology, diagnostics, surgical and systemic treatment of cutaneous squamous cell carcinoma (cSCC), surveillance and prevention can be found in part 2 of the short version – update 2023 of the guideline or in the long version. A full list of references and the analysis of evidence underlying the recommendations and statements, along with the conflicts of interest of the authors involved in the present guideline, are available in the long version and in the guideline report. The guideline is an update of the previous version published in 2020.<sup>1,2</sup>

## METHODOLOGY

See long version at [www.awmf.org](http://www.awmf.org).

## TREATMENT OF ACTINIC KERATOSIS

### Indication for treatment and natural course of the disease

See long version at [www.awmf.org](http://www.awmf.org).

### General principles of treatment

See long version at [www.awmf.org](http://www.awmf.org).

### Treatment combinations

Evidence-based recommendation	Modified 2022
GoR <b>B</b>	Concurrent or sequential combinations of distinct field- or lesion-targeted treatments should be offered for actinic keratosis.
LoE <b>1</b>	1: De-novo-research
Strong consensus	

Abbr.: GoR, Grade of Recommendation; LoE, Level of Evidence

## Ablative and physical procedures

### Cryosurgery

See long version at [www.awmf.org](http://www.awmf.org).

### Surgical procedures

See long version at [www.awmf.org](http://www.awmf.org).

### Chemoexfoliation

Evidence-based recommendation	Modified 2022
GoR <b>0</b>	Chemoexfoliation by chemical peelings may be offered for single or multiple actinic keratoses and field cancerization.
LoE <b>3</b>	3: De-novo-research
Strong consensus	

### Potassium hydroxide

Evidence-based recommendation	New 2022
GoR <b>0</b>	Potassium hydroxide 5% solution may be offered for single or multiple actinic keratoses.
LoE <b>3</b>	3: De-novo-research
Strong consensus	

### Laser treatment

See long version at [www.awmf.org](http://www.awmf.org).

## Topical drugs

### Diclofenac

See long version at [www.awmf.org](http://www.awmf.org).

### 5-Fluorouracil

See long version at [www.awmf.org](http://www.awmf.org).

Evidence-based recommendation	New 2022
GoR <b>B</b>	5-Fluorouracil 4% cream should be offered for single or multiple actinic keratoses and field cancerization.
LoE <b>2</b>	2: De-novo-research
Strong consensus	

## 5-Fluorouracil with salicylic acid

See long version at [www.awmf.org](http://www.awmf.org).

## Ingenol mebutate

Evidence-based recommendation	Modified 2022
GoR <b>A</b>	Ingenol mebutate shall not be offered for actinic keratosis.
LoE <b>2</b>	2: De-novo-research
Strong consensus	

## Imiquimod

See long version at [www.awmf.org](http://www.awmf.org).

## Tirbanibulin

Evidence-based recommendation	New 2022
GoR <b>B</b>	Tirbanibulin 1% ointment should be offered for single or multiple actinic keratoses and field cancerization.
LoE <b>2</b>	2: De-novo-research
Strong consensus	

## Photodynamic therapy

See long version at [www.awmf.org](http://www.awmf.org).

Evidence-based recommendation	Modified 2022
GoR <b>B</b>	Photodynamic therapy using natural or simulated daylight with 5-aminolevulinic acid (ALA) or its methyl ester (MAL) should be offered for single or multiple actinic keratoses and field cancerization.
LoE <b>1</b>	1: De-novo-research
Strong consensus	

## Treatment on chronic immunosuppression and in organ transplant recipients

See long version at [www.awmf.org](http://www.awmf.org).

## Other interventions

See long version at [www.awmf.org](http://www.awmf.org).

### Synopsis of interventions for actinic keratosis (balance sheet)

Intervention	TA	Type and application of the intervention	Anatomical location	Clearance rates <sup>1</sup>	Side-effects and tolerability <sup>2</sup>	Cosmesis <sup>3</sup>	Duration of the treatment <sup>4</sup>	Practicability <sup>6</sup>			Strength of recommendation and evidence base by subgroups <sup>7</sup>			
								Physician	Patient	Single AK (1-5)	Multiple AK (≥ 6)	Field cancerization	Immune suppression	
Cryosurgery	L	One to two freeze-thaw cycles with liquid nitrogen (-196°C)	Face, scalp	+++	+++	+/+++	∞	++++	+++	↑	↑	↑		
			Neck	Lesion-specific clearance rate: 41.9%–88%						2	2			
Surgical procedures <sup>6</sup>	L	Cold exposure of the target lesions for 15–60 seconds (whitening)	Trunk	+++	+++	+++	∞	+++	+++	↑	EC			
			Extremities	Patient-specific clearance rate: 25%–90.3%										
			Complete excision	(No data available from RCT) <sup>8</sup>										
Chemo-exfoliation	L+F	Ablation of superficial skin layers using chemical agents (e.g., trichloroacetic acid, Jessner's solution, phenol)	Face, Scalp	++	++	+++	∞	+++	++	↔	↔	↔		
			Neck	Lesion-specific clearance rate: 31.9%										
			Trunk	Patient-specific clearance rate: 11.8%–92%										
Dermabrasion <sup>6</sup>	L+F	Mechanical removal of the uppermost skin layers up to the dermoepidermal junction zone	Face, Scalp	+	+	++	∞	+/+++	+					
			Neck	(No data available from RCT) <sup>8</sup>										
			Trunk	Lesion-specific clearance rate: 69.9%–83%										
Potassium hydroxide 5% solution (Solcera <sup>®</sup> )	L	Single and well-defined lesions < 2 cm in diameter	Face, Scalp	++	+++	++	∞	+++	++++	↔	↔	↔		
			Neck	Lesion-specific clearance rate: 54.9%										
			Trunk	Patient-specific clearance rate: 54.9%										
Solcera <sup>®</sup>	L	Max. 10 lesions	Face, Scalp	+	+	++	∞	+++	+++	↔	↔	↔		
			Neck	Lesion-specific clearance rate: 54.9%										
			Trunk	Patient-specific clearance rate: 54.9%										
Solcera <sup>®</sup>	L	1 cycle: 2 x/day over 14 days, then 14 days treatment-free interval (max. 3 cycles = 12 weeks)	Face, Scalp	+	+	++	∞	+++	+++	↔	↔	↔		
			Neck	Lesion-specific clearance rate: 54.9%										
			Trunk	Patient-specific clearance rate: 54.9%										
Solcera <sup>®</sup>	L	Availability as a medical device	Face, Scalp	+	+	++	∞	+++	+++	↔	↔	↔		
			Neck	Lesion-specific clearance rate: 54.9%										
			Trunk	Patient-specific clearance rate: 54.9%										

(Continues)

Intervention	TA	Type and application of the intervention	Anatomical location	Clearance rates <sup>1</sup>	Side-effects and tolerability <sup>2</sup>	Cosmesis <sup>3</sup>	Duration of the treatment <sup>4</sup>	Practicability <sup>6</sup>			Strength of recommendation and evidence base by subgroups <sup>7</sup>		
								Physician	Patient	AK (1-5)	Single AK (≥ 6)	Multiple AK (≥ 6)	Field cancerization
Laser <sup>6</sup>	L+F	Ablative laser treatment (e.g., CO <sub>2</sub> laser, Er:YAG laser)	Face, Scalp Neck Trunk Extremities	++ Lesion-specific clearance rate: 72.4%–91.1% Patient-specific clearance rate: 8%–65.3%	++	+++	€–€€	+++	++	⇔ 2–3	⇔ 2–3	⇔ 2–3	⇔ 2–3
	L	Non-ablative laser procedures <sup>6</sup> (e.g., Nd:YAG laser, fractional 1540 nm laser)	Face, Scalp Neck Trunk Extremities	++ (No data available from RCT) <sup>8</sup>	+++ (No data available from RCT) <sup>8</sup>	++ (No data available from RCT) <sup>8</sup>	€–€€	+++	+++	⇔ EC	⇔ EC		

<sup>1</sup>Semiquantitative assessment taking into account lesion- and patient-related response rates: + little effective, ++ moderately effective, +++ effective, ++++ very effective  
<sup>2</sup>Semiquantitative assessment taking into account frequency and severity of treatment-related side effects: + poorly tolerated/ many side effects, ++ moderately tolerated, +++ well tolerated, ++++ very well tolerated  
<sup>3</sup>Semiquantitative assessment taking into account investigator- and patient-assessed endpoints such as dyspigmentation, improvement of hyperkeratosis, global assessment: + poor, ++ moderate, +++ good, ++++ excellent  
<sup>4</sup>Short (< 1 week), Medium (1–6 weeks), Long (> 6 weeks)  
<sup>5</sup>< 100 Euro, €€ 100–500 Euro, €€€ > 500 Euro; only direct treatment costs per cycle performed were considered; topical drugs were based on the public pharmacy dispensing prices in Germany (as of August 2021); procedural procedures were based on the assessments of the Gebührenordnung für Ärzte (GOÄ, as of August 2021).  
<sup>6</sup>Taking into account expert assessments  
<sup>7</sup>Strength of recommendation: Can ⇔ Should ↑, Shall ↑↑  
<sup>8</sup>When applying the mentioned search strategy and inclusion and exclusion criteria  
<sup>9</sup>Abbri.: L, lesion-directed; F, field-directed; AK, actinic keratosis; EC, expert consensus; FK, field cancerization; RCT, randomized controlled trial; TA, therapeutic approach

		Strength of recommendation and evidence base by subgroups <sup>7</sup>												
		Practicability <sup>6</sup>		Immune suppression										
Intervention	TA	Mechanism of action	Recommended max. area of the treatment field	Approval for anatomical location	Efficacy <sup>1</sup>	Side-effects and tolerability <sup>2</sup>	Cosmesis <sup>3</sup>	Duration of treatment <sup>4</sup>	Immediate treatment costs per cycle <sup>5</sup>	Doctor	Patient	Single AK (1-5)	Multiple AK (≥6)	Field cancerization
Diclofenac sodium 3% gel (Solaraze <sup>®</sup> ) (Diclofenac acis <sup>®</sup> ) (Diclofenac AbZ <sup>®</sup> ) (Diclofenac-ratiopharm <sup>®</sup> )	F	Cyclooxygenase-2 inhibitors 2 x daily for 60-90 days	8 g/d or max. 200 cm <sup>2</sup>	Face and scalp	++ Lesion-specific clearance rate: 51.8%-81.0% Patient-specific clearance rate: 27%-50%	+++ / +++++	+ / + + + +	∞∞∞	€-€€	+++++	++	↑	↑	↑
5-Fluorouracil 5% cream (Efudix <sup>®</sup> )	F	Cytostatic agent 2 x daily until erosion stage (usually 2-4 weeks) Application with finger cloth or glove No nucleoside analogues (e.g., brivudine, sorivudine) for at least 4 weeks	500 cm <sup>2</sup> (approx. 23 x 23 cm)	Face and scalp Neck Trunk Extremities	+++ / +++++ Lesion-specific clearance rate: 47%-94% Patient-specific clearance rate: 38%-96%	++	++ / +++++	∞∞	€	+++	+++	↑	↑	↑
5-Fluorouracil 4% cream (Tolak <sup>®</sup> )	F	Cytostatic agent 1 x daily for 4 weeks No nucleoside analogues (e.g., brivudine, sorivudine) for at least 4 weeks	None (in studies 240-961 cm <sup>2</sup> )	Face and scalp	+++ Patient-specific clearance rate: 80.5%	+++	+++	∞∞	€	+++	+++	↑	2	↑
5-Fluorouracil 0.5% with salicylic acid 10% in solution (Actikerall <sup>®</sup> )	F+L	Cytostatic and keratolytic agent 1 x daily until the lesions have cleared completely (max. 12 weeks) No nucleoside analogues (e.g., brivudine, sorivudine) for at least 4 weeks	25 cm <sup>2</sup>	Face and scalp Neck Trunk Extremities	+++ Lesion-specific clearance rate: 39.4%-98.7% Patient-specific clearance rate: 55.4%	+++	+++	∞∞∞	€	+++	+++	↑	2	↑
Ingenol mebutate gel (Picato <sup>®</sup> )	F	Garden spray extract (cytotoxic) 0.015% (face and scalp); 1 x daily for 3 consecutive days 0.050% (trunk, extremities); 1 x daily for 2 consecutive days	25 cm <sup>2</sup>	Face and scalp Neck Trunk Extremities	+++ Face/scalp: Lesion-specific clearance rate: 62.9%-87.2% Patient-specific clearance rate: 36.4%-61.6% Extremities/trunk: Lesion-specific clearance rate: 73%-100% Patient-specific clearance rate: 22%-54.4%	+	++	∞	€	+++	+++	↑	2	↑

(Continues)

		Strength of recommendation and evidence base by subgroups <sup>5,7</sup>													
Intervention	TA	Mechanism of action	Recommended max. area of the treatment field	Approval for anatomical location	Efficacy <sup>1</sup>	Side-effects and tolerability <sup>2</sup>	Cosmesis <sup>3</sup>	Duration of treatment <sup>4</sup>	Immediate treatment costs per cycle <sup>5</sup>	Practicality <sup>6</sup>	Strength of recommendation and evidence base by subgroups <sup>7</sup>				
										Doctor	Patient	Single AK (1-5)	Multiple AK (≥ 6)	Field cancerization	Immune suppression
Imiquimod 3.75% cream (Zyclara <sup>®</sup> )	F	Toll-like receptor 7 agonist 1 x daily for 2 weeks, 2 weeks treatment-free interval, 1 x daily for 2 weeks (interval therapy), apply in the evening before going to bed. per application up to 2 sachets of 250 mg imiquimod cream per sachet	None The treatment area is the entire face or the entire hairless scalp.	Face and scalp	+++ Lesion-specific clearance rate: 34.0%–81.8%	+++ Lesion-specific clearance	+++ Cosmesis	€€	€€	+++	+++	↑	2	1	
Imiquimod 5% cream (Aldara <sup>®</sup> )	F	Toll-like receptor 7 agonist 3 times a week for 4 weeks, in case of residual lesions for additional 4 weeks (max. 8 weeks), apply in the evening before going to bed (leave for at least 8 h).	Maximum dose is the contents of one sachet (250 mg)	Face and scalp	+++ Lesion-specific clearance rate: 45.1%–93.6% Patient-specific clearance rate: 24%–85%	+++ Lesion-specific clearance	+++	€€	€€	+++	+++	↑	1	1	↔ 2 OLU
ALA red light PDT: ALA nanoemulsion (Ameluz <sup>®</sup> )	F	Precursor of protoporphyrin (photosensitizer) Pre-treatment, application of ALA, drying for 10 min, light-protective dressing, incubation for 3 h, illumination with suitable red light sources, second cycle after 12 weeks if necessary	Layer thickness approx. 1 mm Lesion or entire cancerized fields of up to 20 cm <sup>2</sup>	Face and scalp Neck Trunk Extremities	+++ / +++++ Lesion-specific clearance rate: 58.0%–94.3% Patient-specific clearance rate: 50%–91%	++ Lesion-specific clearance	++	€€–€€€	€€–€€€	++	++	↑	1	1	
ALA red light PDT: ALA patch (Alacare <sup>®</sup> )	L	Precursor of protoporphyrin (photosensitizer) Apply patch for 4 h, illuminate with red light (37 J/cm <sup>2</sup> ), no St. John's wort for at least 2 weeks, second cycle if no clearance per treatment after 12 weeks	1 patch 4 cm <sup>2</sup> (with 8 mg ALA) Lesion max. 1.8 cm diameter (max. 6 patches per treatment session)	Face and scalp	+++ / +++++ Lesion-specific clearance rate: 63%–89% Patient-specific clearance rate: 62%–67%	++ Lesion-specific clearance	+++ / +++++	€€€–€€	€€€–€€	+++	+++	↑	1	1	
MAL red light PDT (Metvix <sup>®</sup> )	F	Precursor of protoporphyrin (photosensitizer) Pre-treatment, application of MAL, occlusive dressing for 3 h, illumination with suitable red light sources, second cycle after 12 weeks if necessary	Layer thickness approx. 1 mm Lesion, for field cancerization up to approximately 20 cm <sup>2</sup>	Face and scalp	+++ / +++++ Lesion-specific clearance rate: 67.1%–90.3% Patient-specific clearance rate: 31.4%–78%	++ Lesion-specific clearance	+++ / +++++	€€€–€€	€€€–€€	++	+++ / +++++	↑	1	1	↑ 3

(Continues)

		Strength of recommendation and evidence base by subgroups <sup>7</sup>											
		Practicability <sup>6</sup>			Side-effects and tolerability <sup>2</sup>			Cosmesis <sup>3</sup>			Immune suppression		
Intervention	TA	Mechanism of action	Recommended max. area of the treatment field	Approval for anatomical location	Efficacy <sup>1</sup>	Duration of treatment <sup>4</sup>	Immediate treatment costs per cycle <sup>5</sup>	Doctor	Patient	Single AK (1–5)	Multiple AK (≥ 6)	Field cancerization	Immune suppression
ALA daylight PDT (Ameletuz <sup>®</sup> )	F	Precursor of protoporphyrin (photosensitizer) Application of chemical light protection filter, after 15 min pre-treatment, application of ALA without occlusion, within 30 min exposure to natural daylight for 2 h, second cycle after 12 weeks if necessary	None (apply thin layer) Lesion or entire cancerized fields	Face and scalp	+++ Patient-specific clearance rate: 27.5%–42.9% Lesion-specific clearance rate: 79.7%–79.8%	≈	€€	++	++++	↑	↑	↑	
MAL daylight PDT (Metvix <sup>®</sup> ) (Luxerm <sup>®</sup> )	F	Precursor of protoporphyrin (photosensitizer) Application of chemical light protection filter, after pre-treatment drying, application of MAL without occlusion, within 30 min exposure to natural or simulated daylight (Metvix <sup>®</sup> only) for 2 h, second cycle after 12 weeks if necessary	None (apply thin layer) Lesion and/or field cancerization	Face and scalp	+++ Patient-specific clearance rate: 27.5%–38.8% Lesion-specific clearance rate: 77.2%–89.2%	≈	€€	++	++++	↑	↑	↑	
Tirbanitulin (Klisyri <sup>®</sup> )	F	Topical microtubule inhibitor 1 X/d over 5 consecutive days	25 cm <sup>2</sup>	Face and scalp	+++ Patient-specific clearance rate: 44%–54% Lesion-specific clearance rate: 76%–82%	≈	≈	+++	+++	↑	↑	↑	

1 Semiquantitative assessment taking into account lesion- and patient-related response rates: + little effective, ++ moderately effective, +++ effective, ++++ very effective  
 2 Semiquantitative assessment taking into account frequency and severity of therapy-mediated side effects: + poorly tolerated/ many side effects, ++ moderately tolerated, +++ well tolerated  
 3 Semiquantitative assessment considering investigator- and patient-assessed endpoints such as dyspigmentation, improvement of hyperkeratosis, global assessment: + poor, ++ moderate, +++ good, ++++ excellent  
 4 ≈ short (< 1 week), ≈ medium (1–6 weeks), ≈ long (> 6 weeks)  
 5 € < 100 Euro, 100–500 Euro, € > 500 Euro; only direct treatment costs per cycle performed were considered; topical drugs were based on the public pharmacy dispensing prices in Germany (as of August 2021); procedural procedures were based on the assessments of the GEM (Germanische Dermatologische Gesellschaft), as of August 2021.  
 6 Taking into account expert opinions  
 7 Strength of recommendation: May ⇌, Should ↑, Shall ↑↑, indication of evidence levels according to Oxford 2011  
 Abbv.: L, lesion-directed; F, field-directed; AK, actinic keratosis; OLU, off-label use; TA, treatment approach



## Treatment of actinic cheilitis

### Indication for treatment and natural course of the disease

#### Consensus-based recommendation **New 2022**

- EC** The indication for the treatment of actinic cheilitis should be made based on the clinical presentation, risk factors (e.g., immunosuppression, cumulative UV exposure, involvement of the entire lower lip, involvement also of the upper lip), comorbidities, life expectancy, and patient desire.

Strong consensus

#### Consensus-based recommendation **New 2022**

- EC** Prior to treatment, a biopsy should be obtained for diagnostic confirmation and to exclude invasive squamous cell carcinoma of the lip.

Consensus

#### Consensus-based recommendation **New 2022**

- EC** A biopsy should be obtained if there is clinical evidence of a lack of response or incomplete response to treatment.

Strong consensus

Abbr.:EC, expert consensus.

## General principles of treatment

See long version at [www.awmf.org](http://www.awmf.org).

## Surgical procedures

#### Evidence-based recommendation **New 2022**

- GoR A** Surgical treatment of actinic cheilitis (e.g., by vermilionectomy or lip shave with histologic assessment and analysis of resection margins) shall be offered for extensive involvement of the lip.

**LoE 1** 1: De-novo-research

Consensus

## Ablative procedures

### Laser treatment

#### Evidence-based recommendation **New 2022**

- GoR 0** Ablative laser treatment (e.g., CO<sub>2</sub>, Er:YAG) may be offered for actinic cheilitis.

**LoE 1** 1: De-novo-research

Strong consensus

#### Consensus-based statement **New 2022**

- EC** No recommendation for non-ablative laser treatment of actinic cheilitis can be made due to insufficient data.

Strong consensus

## Cryosurgery

#### Consensus-based statement **New 2022**

- EC** The data available on cryosurgery do not allow a conclusive recommendation for the treatment of actinic cheilitis.

Strong consensus

## Chemoexfoliation

#### Consensus-based recommendation **New 2022**

- EC** Chemical peelings should not be used for the treatment of actinic cheilitis due to a lack of evidence for clinical benefit.

Strong consensus

## Topical drugs

### Diclofenac

#### Evidence-based recommendation **New 2022**

- GoR 0** Diclofenac sodium 3% gel may be offered for the treatment of actinic cheilitis.

**LoE 2** 2: De-novo-research

Strong consensus

### 5-Fluorouracil

#### Consensus-based statement **New 2022**

- EC** No evidence-based recommendation for the treatment of actinic cheilitis with 5-fluorouracil can be made due to insufficient data.

Strong consensus

### Imiquimod

#### Consensus-based statement **new 2022**

- EC** No evidence-based recommendation for the treatment of actinic cheilitis with imiquimod 5% and 3.75% cream can be made due to insufficient data.

Strong consensus

## Photodynamic therapy

### Evidence-based recommendation

**New 2022**

GoR **B** Photodynamic therapy with illumination by red light and 5-aminolevulinic acid (ALA) or its methyl ester (MAL) should be offered for the treatment of actinic cheilitis.

LoE **1** 1: De-novo-research

Strong consensus

### Evidence-based recommendation

**New 2022**

GoR **B** Methyl aminolevulinate (MAL) in combination with illumination by natural or simulated daylight (MAL daylight PDT) should be offered for the treatment of actinic cheilitis.

LoE **3** 3: De-novo-research

Strong consensus

## Treatment combinations

See long version at [www.awmf.org](http://www.awmf.org).

## Synopsis of interventions for actinic cheilitis (balance sheet)

Intervention	TA	Mechanism of action & application	Efficacy <sup>1</sup>	Side effects and tolerability <sup>2</sup>	Cosmesis <sup>3</sup>	Duration of the treatment <sup>4</sup>	Direct treatment costs per cycle <sup>5</sup>	Practicability <sup>6</sup>			Strength of recommendations and evidence base <sup>7</sup>	
								Physician	Patient			
<b>Ablative procedures</b>												
Cryosurgery	L	1 to 2 freeze-thaw cycles with liquid nitrogen (-196°C) Cold exposure of the target lesions for 15–60 seconds "whitening" Open spray method Contact method (cryo stamp, cryo probe)	+++/+++ (No data available from RCT) <sup>8</sup>	++	+	∞	€	++++	+++	+++	~ EC	
Surgical procedures with histological assessment <sup>6</sup>	F	Complete excision, vermillionectomy, lip shave	+++ (No data available from RCT) <sup>8</sup>	++ (No data available from RCT) <sup>8</sup>	++ (No data available from RCT) <sup>8</sup>	∞	€–€€	+++	++	++	↑↑ 1–3	
Surgical procedures without histological assessment <sup>6</sup>	F	Electrodesiccation, dermabrasion	+ (No data available from RCT) <sup>8</sup>	+ (No data available from RCT) <sup>8</sup>	+/+++ (No data available from RCT) <sup>8</sup>	∞	€–€€	+/+++	+	+	~ EC	
Chemoexfoliation	F	Ablation of superficial skin layers using chemical agents (e.g., 50% trichloroacetic acid)	+ Clearance rate: 30%	+/+++	++	∞	€–€€	++	++	++	~ 1–4	
Laser treatment <sup>6</sup>	F	Ablative laser treatment (e.g., CO <sub>2</sub> ; Erbium YAG laser)	+++ Clearance rate: 93.4%	++	+/+++	∞	€€€	+++	+++	+++	↔ 2–3	
		Non-ablative laser treatments <sup>6</sup> (e.g., Nd:YAG laser, fractional 1540 nm laser)	+ (No data available from RCT) <sup>8</sup>	++ (No data available from RCT) <sup>8</sup>	++ (No data available from RCT) <sup>8</sup>	∞	€€€	+++	+++	+++	~ EC	
<b>Topical drugs and drug-based procedures</b>												
Diclofenac sodium 3% gel (Solaraze <sup>®</sup> ), (Solacutan <sup>®</sup> ), (diclofenac acis <sup>®</sup> ), (Diclofenac AbZ <sup>®</sup> ), (Diclofenac-ratiopharm <sup>®</sup> ) Off-label use	F	Cyclooxygenase-2 inhibitor 2 x daily for 60–90 days; max. 8 g/d for up to 200 cm <sup>2</sup>	++ Clearance rate: 45.2%	+++/++++ ++++	+/+++	∞	€€–€	++++	++	++	↔ 2–3	
5-Fluorouracil 5% cream (Efudix <sup>®</sup> ) Off-label use	F	Cytostatic drug 2 x daily for max. 4 weeks; max. 500 cm <sup>2</sup> (approx. 23 x 23 cm)	+++/+++++ Clearance rate: 50%–68.2%	++	+/+++++	∞	€€–€	+++	+++	+++	~ EC	
Imiquimod 3.75% cream (Zyclara <sup>®</sup> ) Off-label use	F	Toll-like receptor 7 agonist 1 x daily for 2 weeks, 2 weeks treatment-free interval, 1x daily for 2 weeks (interval therapy) per application up to 2 sachets of 250 mg imiquimod cream per sachet	+	++	+++	∞	€€	+++	+++	+++	~ EC	

(Continues)

Intervention	TA	Mechanism of action & application	Efficacy <sup>1</sup>	Side effects and tolerability <sup>2</sup>	Cosmesis <sup>3</sup>	Duration of the treatment <sup>4</sup>	Direct treatment costs per cycle <sup>5</sup>	Practicability <sup>6</sup>			Strength of recommendations and evidence base <sup>7</sup>
								Physician	Patient	EC	
Imiquimod 5% cream (Aldara <sup>®</sup> ) Off-label use	F	Toll-like receptor 7 agonist 3 x weekly for 4 weeks Recommended maximum dose is the contents of one sachet	++ Clearance rate: 40%–73.3%	++	+++	☹☹☹	€€	+++	+++	+++	~ EC
ALA red light PDT (Alacare <sup>®</sup> )	F, L	Prodrug of protoporphyrin (photosensitizer) Application of ALA-containing patch for 4 h, illumination with red light for approx. 10–20 min, if necessary, repeat after 4–12 weeks Alacare <sup>®</sup> 4 cm <sup>2</sup> (max. 6 patches)	+++ / +++++ Clearance rate: 66.6%–84.2%	++	+++ / +++++	☹	€€–€€€	+++ / +++++	+++	++	↑ 2–3
ALA red light PDT (Ameluz <sup>®</sup> ) Off-label use	F	Prodrug of protoporphyrin (photosensitizer) Application of ALA, light-protective bandage for 3 h, illumination with red light for approx. 10–20 min, if necessary repeat after 4–12 weeks	+++ / +++++ Clearance rate: 58.0%–80%	++	+++ / +++++	☹	€€–€€€	++ / +++	+++	++	↑ 2–3
MAL red light PDT (Metvix <sup>®</sup> )	F	Prodrug of protoporphyrin (photosensitizer) Application of MAL, light protection and occlusive dressing for 3 h, illumination with red light for approx. 10–20 min, repeat after 4–12 weeks if necessary	+++ / +++++ Clearance rate: 47%–62.5%	++	+++ / +++++	☹	€€–€€€	++ / +++	+++	++	↑ 2–3
MAL daylight-PDT (Luxerm <sup>®</sup> ), (Metvix <sup>®</sup> )	F	Prodrug of protoporphyrin (photosensitizer) Application of chemical photoprotective filter and MAL. Daylight exposure for 2 h Conditions: > 10°C outdoor temperature, cloudless to overcast sky, no rain	+++ Clearance rate: 80%–91%	++++	+++	☹	€€	+++	++	+++	↑ 3

<sup>1</sup>Semiquantitative assessment taking into account lesion- and patient-related response rates (+ = little effective, ++ = moderately effective, +++ = effective, ++++ = very effective)  
<sup>2</sup>Semiquantitative assessment taking into account frequency and severity of treatment-mediated side effects (+ = poorly tolerated/moderately tolerated, ++ = well tolerated, +++ = very well tolerated)  
<sup>3</sup>Semiquantitative assessment considering investigator- and patient-assessed outcomes such as dyspigmentation, improvement of hyperkeratosis, global assessment (+ = predominantly poor, ++ = predominantly moderate, +++ = predominantly good, ++++ = predominantly excellent).  
<sup>4</sup>☹ = short (< 1 week), ☹☹ = medium (1–6 weeks), ☹☹☹ = long (> 6 weeks)  
<sup>5</sup>€ = < 100 Euro, €€ = 100–500 Euro, €€€ = > 500 Euro; only direct treatment costs per cycle performed were considered; public pharmacy dispensing prices in Germany (as of August 2021) were used as the basis for topical drug procedures; procedural procedures were based on the valuations of the Gebührensordnung für Ärzte (GOÄ, as of August 2021)  
<sup>6</sup>Taking into account expert opinions  
<sup>7</sup>Strengths of recommendation: May = ⇔; Should = ↑; Shall = ↑↑; ~ no recommendation if data / evidence base is unclear; indication of evidence levels according to Oxford 2011  
<sup>8</sup>When applying the mentioned search strategy and inclusion and exclusion criteria  
 Abbr.: L, lesion-directed; F, field-directed; AK, actinic keratosis; EC, expert consensus; RCT, randomized controlled trial; TA, treatment approach

## TREATMENT OF CUTANEOUS SQUAMOUS CELL CARCINOMA IN SITU (BOWEN'S DISEASE)

### Clinical presentation and natural course of the disease

See long version at [www.awmf.org](http://www.awmf.org).

### Indication for treatment and treatment approaches

#### Consensus-based recommendation

New 2022

- EC** Prior to treatment of Bowen's disease, a biopsy should be obtained to exclude invasive squamous cell carcinoma of the skin, other skin neoplasms, or inflammatory conditions. If there is clinical evidence of a lack of response or incomplete response to treatment, a biopsy with histologic assessment should be performed.

Strong consensus

### Surgical procedures

#### Consensus-based recommendation

New 2022

- EC** Surgical removal of Bowen's disease (e.g., by shave excision or complete excision) should be offered for single lesions.

Strong consensus

### Ablative procedures

#### Cryosurgery

#### Consensus-based recommendation

New 2022

- EC** Cryosurgery may be offered for the treatment of Bowen's disease.

Consensus

#### Ablative laser treatment

#### Evidence-based recommendation

New 2022

- GoR 0** Ablative laser treatment may be offered for the treatment of Bowen's disease.

**LoE 2** 2: De-novo-research

Consensus

### Topical drugs

#### 5-Fluorouracil

#### Evidence-based recommendation

New 2022

- GoR B** 5-Fluorouracil 5% cream should be offered for the treatment of Bowen's disease.

**LoE 2** 2: De-novo-research

Consensus

#### Imiquimod

#### Evidence-based recommendation

New 2022

- GoR 0** Imiquimod 5% cream may be offered for the treatment of Bowen's disease in immunocompetent patients. The lack of approval for this indication should be considered.

**LoE 2** 2: De-novo-Recherche

Consensus

### Photodynamic therapy

#### Evidence-based recommendation

New 2022

- GoR B** Photodynamic therapy with illumination by red light should be offered for the treatment of Bowen's disease, performed as two treatment cycles within 4 weeks.

**LoE 1** 1: De-novo-research

Strong consensus

#### Evidence-based recommendation

New 2022

- GoR 0** Pretreatment (e.g., with ablative fractional laser, microneedling) may be offered prior to photodynamic therapy with illumination by red light to enhance drug penetration.

**LoE 2** 2: De-novo-research

Strong consensus

## OCCUPATIONAL DISEASES OF ACTINIC KERATOSIS AND CUTANEOUS SQUAMOUS CELL CARCINOMA

See long version at [www.awmf.org](http://www.awmf.org).

## Structures of care

### Certified skin cancer centers

See long version at [www.awmf.org](http://www.awmf.org).

### Quality indicators

See long version at [www.awmf.org](http://www.awmf.org).

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