Methods and Results Report

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Evidence and consensus based (S3) Guidelines for the Treatment of Actinic Keratosis

International League of Dermatological Societies in cooperation with the European Dermatology Forum

R.N. Werner[1], A. Jacobs[1], S. Rosumeck[1], R. Erdmann[1], B. Sporbeck[1], A. Nast[1]

1 Division of Evidence Based Medicine (dEBM), Department of Dermatology, Venerology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany

Abbreviations

5-FU	5-fluorouracil
AK, AKs	actinic keratosis, actinic keratoses
ALA-PDT	5-aminolevulinic acid-photodynamic therapy
CI	confidence interval
EADV	European Academy of Dermatology and Venereology
EDF	European Dermatology Forum
GP	general practitioner(s)
HA	hyaluronic acid
ILDS	International League of Dermatological Societies
MAL-PDT	methylaminolevulinate-photodynamic therapy
NMSC	Non melanoma skin cancer
SA	salicylic acid
SCC	squamous cell cancer of the skin
SoF table	summary of findings table
UEMS	European Union of Medical Specialists
UV, UVR	ultraviolet, ultraviolet radiation

Guidelines Development Group Members

Name	Role / Function
Steering group	
Alexander **Nast**	Chairman, structured moderation of the consensus conference, coordination; consultant dermatologist and head of the Division of Evidence based Medicine (dEBM), Department of Dermatology, Venerology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany
Ricardo N. **Werner**	Coordination, systematic literature assessment; resident in dermatology; dEBM, Department of Dermatology, Venerology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany
Anja **Jacobs**	Systematic literature assessment; scientist; dEBM, Department of Dermatology, Venerology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany
Stefanie **Rosumeck**	Systematic literature assessment; scientist; dEBM, Department of Dermatology, Venerology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany
Birte **Sporbeck**	Systematic literature assessment; resident in dermatology; dEBM, Department of Dermatology, Venerology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany
Ricardo **Erdmann**	Organization; health data manager; dEBM, Department of Dermatology, Venerology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany
Expert panel	
Eggert **Stockfleth**	Chairman of the guidelines, Consultant dermatologist, Professor of dermatology and assistant medical director, Department of Dermatology, Venerology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany; now: Department of Dermatology, Venereology and Allergology, St. Josef-Hospital, Universitätsklinikum der Ruhr-Universität Bochum, Bochum, Germany
Suzanne M. **Connolly**	Professor of Dermatology, Mayo Clinic; Scottsdale, Arizona, USA
Osvaldo **Correia**	Clinical Director of Centro Dermatologia Epidermis, Instituto CUF, Porto; Affiliate Professor of Faculty of Medicine, University of Porto, Portugal
Peter **Foley**	Associate Professor of Dermatology, The University of Melbourne, Skin & Cancer Foundation, Melbourne, Victoria, Australia
Aditya K. **Gupta**	Consultant dermatologist, London, Canada; Professor, Department of Medicine, Univeristy of Toronto, Toronto, Canada
Heinz-Joachim **Kahrs**	Patient representative; Berlin, Germany
Helmut **Kerl**	Professor of dermatology, Chairman emerit. Department of Dermatology, University of Graz, Austria
Henry W. **Lim**	Chairman and C.S. Livingood Chair, Department of Dermatology, Henry Ford Hospital, Detroit, Michigan, USA
George **Martin**	Consultant dermatologist, Dermatology and Laser Center of Maui; Maui, Hawaii, USA
Maryse **Paquet**	Consultant health care researcher; scientist; Mediprobe Research Inc., London, Canada
David M. **Pariser**	Professor of dermatology, Department of Dermatology, Eastern Virginia Medical School; Consultant dermatologist, Pariser Dermatology Specialists, Ltd; Norfolk, Virginia, USA
Hans-Joachim **Röwert-**	Head of the Division of Dermatopathology, Department of

Huber	Dermatology, Venerology and Allergology, Charité - Universitätsmedizin Berlin; Berlin, Germany
Anshoo **Sahota**	Consultant Dermatologist; Whipps Cross University Hospital, The Royal London Hospital, London, UK
Omar P. **Sangueza**	Professor of Dermatology, Pathology and Anatomic Pathology; Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, USA
Stephen **Shumack**	Clinical Associate Professor of Dermatology, Northern Medical School, University of Sydney, NSW, Australia
Neil A. **Swanson**	Consultant dermatologist; Dermatology, Surgery, and Otolaryngology, Oregon Health and Science University; Surgical and Cosmetic Dermatology and Clinical Operations, Oregon Health and Science University Knight Cancer Institute; Portland, Oregon, USA
Luis **Torezan**	Assistant professor of dermatology at Universidade de Sao Paulo Medical School, Sao Paulo, Brazil

Methods Report

Results report, see page 29

List of tables

1 Introduction

Nast / Werner

This document is the methods report of the

Evidence and consensus based (S3) Guidelines for the Treatment of Actinic Keratosis - International League of Dermatological Societies (ILDS) in cooperation with the European Dermatology Forum (EDF).

Detailed results of the guidelines development are available in the long version and in the results report of the guidelines, both available online. For clinical guidance on the clinical background, assessment and treatment of actinic keratosis (AK), please consider the long version or the original guidelines publication.

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These guidelines encompass different clinical aspects related to AK. The primary goal of the guidelines was the development of treatment recommendations appropriate for different subgroups of patients presenting with AK. This was subject to a systematic literature review and a formalized consensus conference of the members of the guidelines' expert panel.

A secondary aim of these guidelines is the implementation of knowledge relating to the clinical background of AK, including recommendations for the histopathological definition of the disease and for the diagnosis and assessment of patients presenting with AK. Clinical background texts were written by the steering group and subgroups of the expert panel, based on a narrative literature review. Some of these aspects (diagnosis, histopathology, assessment of patients with AK) were formally consented as recommendations during the consensus conference.

The guidelines were elaborated along adapted recommendations by the WHO guidelines review committee[1] and the quality criteria for guidelines as suggested by the Appraisal of Guidelines Research and Evaluation (AGREE II) Instrument[2] were incorporated into the methodological development of the guidelines. For the planning and elaboration of the underlying systematic literature review on interventions for AK, the methodology suggested by the Cochrane Handbook for Systematic Reviews of Interventions[3], the GRADE working group[4] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[5] was adapted.

1.1 Remarks on the use of guidelines / Disclaimer

These evidence- and consensus-based guidelines contain recommendations that were developed to assist clinicians in the care of patients in specific clinical conditions. The recommendations are based on the best available evidence and their development followed a pre-specified, standardized process. Nevertheless, guidelines do not replace the clinicians' knowledge and skills, since guidelines never encompass therapy specifications for all medical decision-making situations. Guidelines should not be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. Deviation from the recommendations may be justified or inevitable in specific situations. The ultimate judgment regarding patient care must be individualized and must be made by the physician and patient in light of all presenting circumstances.

Safety aspects that were considered within these guidelines do not represent a comprehensive assessment of all available safety information for the included interventions. They are limited to those aspects chosen for evaluation and the information available in the included clinical trials. Readers must carefully check the information in these guidelines and determine whether the recommendations (e.g. regarding dose, dosing regimens, contraindications, or drug interactions) are complete, correct, up-to-date and appropriate.

International guidelines are intended to be adapted to national or regional circumstances (regulatory approval and availability of treatments, health care provider and insurance systems). Particularly, the mode of application of the different treatment options has to be adapted to national approval of the interventions. Thus, the national medical societies associated with the International League of Dermatological Societies (ILDS) will be responsible for the adoption and implementation of the guidelines on a national level.

1.2 Objectives of the guidelines

Improvement in the care of patients with actinic keratosis

The provision of recommendations that are based on a systematic review of the external evidence and consented by clinical experts during a structured and formalized process aims at improving the medical care of patients presenting with AK. The choice of an adequate evidence-based treatment strategy – adapted to the individual demands – will be facilitated by the provision of recommendations that take into account frequent clinical scenarios.

Improvement of the knowledge on the treatment necessity and on treatment options

The description of the clinical background, histopathological features and assessment of AK intends to raise awareness of the treatment necessity in a broader range of medical specialties and advance concepts of AK towards a more widely accepted definition.

Reduction of percentage of patients with AKs progressing to invasive squamous cell carcinoma

The use of lesion- and field-directed interventions should be optimized by using the most appropriate treatment regarding the extent and type of AK. Along with a clearance of AK lesions and prevention of their recurrence, the provision of evidence-based treatment algorithms intends to decrease the percentage of patients with progression from AK to invasive squamous cell carcinoma (SCC).

Promotion of adherence

Adherence to the therapeutic regimen is a basic element for the treatment success. Knowledge on the suggested interventions, including expectable effects, adverse effects, duration and possible alternatives is indispensable in the communication with patients. These evidence-based guidelines can help patients to make informed decisions and, consequently, improve the patient compliance to their therapeutic regimen.

1.3 Target population

Health care professionals

The primary goal of these guidelines is to assist health care professionals in the choice of the optimal treatment strategy for their patients with consideration of the severity of the disease and the specific circumstances of the individual patient. Target groups include all health care professionals involved in the assessment and treatment of patients with AK, primarily dermatologists, histopathologists and general practitioners (GP). Due to the international focus of these guidelines and different organizational structures of health care services in different countries, target groups may vary correspondingly.

Patients
Patients who have AK are mainly adult patients, often of advanced age, and treated in outpatient settings. To take frequent clinical situations into account, different patient subgroups were defined, according to the severity of the disease and the medical history of the patients. The primary focus of these guidelines is the assessment and therapy of patients presenting with single AK lesions, multiple lesions or field cancerization. Patients with concomitant immunosuppression are included as a target group requiring a differential therapeutic approach.

1.4 Pharmacoeconomic considerations

There might be significant variability from country to country, not only in regulatory approval and the availability of interventions, but also in terms of health care providers and insurance systems. Thus, these international guidelines are intended to be adapted to the national or regional conditions. Pharmacoeconomic considerations were therefore not considered as part of the reasoning behind the recommendations concerning interventions. These aspects and possible prioritization of certain interventions should be considered when these guidelines are adapted for implementation at a national level.

2 Methods

Werner

2.1 Groups involved in the guidelines development

The steering group of the guidelines project was composed by experts in the field of guidelines development. It consisted of members of the Division of Evidence-based Medicine (dEBM) from the Department of Dermatology, Venerology and Allergology, Charité – Universitätsmedizin, Berlin, Germany. The group assisted the guidelines development process with organization of the guidelines process, development of methodology and the conduction of a systematic review of the literature on interventions for AK. Members of the steering group participated in the consensus conference, but were not entitled to vote on recommendations.

Members of the expert panel were dermatologists and histopathologists. They were officially nominated by the International League of Dermatological Societies (ILDS). The expert panel members were selected by virtue of their clinical experience and/or research expertise in the field of keratinocytic skin lesions. Participation of general practitioners (GP) was highly desirable and the World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians (WONCA) was officially requested to nominate GP members for participation in the expert panel. Unfortunately, no official GP nominations were received. The external review was performed also following the European Dermatology Forum (EDF) Guidelines SOPs. Final approval included ILDS, EDF, (European Academy of Dermatology and Venereology (EADV) and European Union of Medical Specialists (UEMS). Further details of the external review process are described below.

An international patient organization to nominate a representative for patients affected by AK could not be identified, and thus patient participation was difficult to realize. Various attempts to include the patient perspective into the guidelines were made: One patient from the Charité – Universitätsmedzin Berlin, Berlin, Germany with large personal experience with different AK treatments was invited to participate in the expert panel. Patient reported outcomes such as Participants' satisfaction and Participants' preference were considered as an important outcome and studies reporting on these endpoints were included into the systematic literature review. Patients were invited to take part in the external review and to comment the drafted guidelines document.

The expert panel was responsible for the selection of relevant patient subgroups, interventions and outcomes. During the consensus conference, experts were responsible for the appraisal and interpretation of the external evidence supplied by the steering group, considering the overall balance of the benefits and harms of interventions and their clinical expertise. No financial incentives or reimbursement for the participation in the expert panel were administered. A full list of the guidelines steering group and expert panel members is supplied at the beginning of the document.

2.2 Funding of the guidelines project and management of conflicts of interest

The guidelines project has kindly been supported by the European Skin Cancer Foundation (ESCF). The financial support did not influence the guidelines development. Assessment and synthesis of the evidence were done independently from industrial interest. Key questions to be answered and outcomes were chosen in accordance to consensus of the members from the expert panel. Recommendations on diagnostic means and interventions for the management of AK were exclusively based on the consensus of the members from the

expert panel in the consensus conference, according to the clinical expertise and external evidence (systematic literature review of the available data on interventions for AK).

A declaration of conflicts of interest (COI) was required for the participation in the guidelines development. The form used to assess the individual interests is presented in the appendix of this document (see chapter 7.1). At the beginning of the formalized consensus conference on the interventions for AK, each member was offered to update his or her declaration. COI were discussed and one member decided to abstain from voting on recommendations concerning methyl-aminolevulinic acid photodynamic therapy (MAL-PDT) due to conflicting interests. The expert panel did not see any substantial conflicts of interest and there were no further comments or remarks. COI of each person involved in the guidelines development are presented in the publication and in the long version of these guidelines.

2.3 Generation of evidence-based recommendations on interventions for AK

2.3.1 Selection of key questions to be answered

The selection of key questions to be answered by guidelines depends on the definition of subgroups of patients, the selected interventions and their comparators, and finally on the outcomes to be considered. The respective decisional steps for the preparation of the systematic literature review were performed via electronic mail contacts and consented in an online kick-off conference with the members of the expert panel.

A consensus of ≥75% of the members of the expert panel served as relevant cut-off for the confirmation of each decided aspect and its inclusion in the systematic literature review and in the formalized consensus conference.

Definition of subgroups of patients presenting with AK
Different subgroups of patients presenting with AK, requiring differential therapeutic approaches were defined in order to address the demands of clinical practice. The definitions were based on suggestions of the steering group and clinical expertise of the expert panel members. The defined categories served as basis for separate assessment of the interventions during the systematic literature review and the formalized consensus conference. For details on the chosen subgroups of patients see chapter 3.

Selection of included interventions
Multiple lesion- and field-directed interventions are available for the treatment of AK. The options are further extended by the availability of different formulations and treatment schemes. For the selection of the relevant interventions to be included in the guideline, all members of the expert panel were consulted. Interventions could be chosen from a list supplied by the steering group or be proposed by each member of the expert group. The fact that certain interventions were not included does not necessarily imply that it may not be an appropriate treatment for AK. For details on the interventions selected for evaluation see chapter 4.

Selection and rating of outcomes
The evaluation of the interventions was based on efficacy, cosmetic, patient reported and safety outcomes. Expert panel members were asked to rate outcomes with respect to their relevance for clinical decisions concerning the choice of treatment of AK. Rating was performed on a scale from 1 to 9 with 1 representing irrelevant and 9 representing critical outcomes. Mean values of the ratings from the experts served to rank the importance of the selected outcomes when grading the available evidence. A mean score of 7-9 rated an outcome as critical for a decision, 4-6 rated an outcome as important but not critical for

decision-making, and a mean score of 1-3 indicated that the respective outcome was of limited importance[6]. The selection of outcomes to be considered was additionally based on the availability of reported outcomes in the available evidence. For details on the chosen outcomes and their rating see chapter 5.

2.3.2 Literature search: Search for guidelines and systematic reviews

A systematic search for existing guidelines and systematic reviews on Interventions for AK in Medline, Embase, the Cochrane Library, the Guidelines International Network (G-I-N) database, and National guidelines clearinghouse was conducted at the beginning of the project. Relevant hits were evaluated independently by two assessors (SR, RNW) using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool[2] or the SIGN Methodology Checklist 1: Systematic Reviews and Meta-analyses[7]. A relevant and recent high quality systematic review was identified[8]. More details are presented in the results part (see results report of the guidelines). The identified Cochrane Review was used as basis of the body of evidence.

2.3.3 Literature search: Update search for primary literature

A systematic literature search was performed to update the included Cochrane review using the databases Cochrane Library, Medline, Medline in Process and Embase, and covered the periods from March 2011 through the date of the search (January 25th, 2013). The search strategies corresponded to the strategies used in the Cochrane review[8]. Detailed electronic search strategies for the different databases are presented in the appendix (see chapter 7.2).

Titles and abstracts of the update search were individually checked for eligibility by two independent assessors (RNW, BS). Full texts of potentially relevant studies were similarly checked for eligibility by two independent assessors (RNW, AJ). In the case of disagreement during the screening of abstracts and full texts, a third assessor (AN) was involved and the conflict solved by discussion.

2.3.4 Eligibility criteria

Criteria for the eligibility of studies for inclusion in the systematic review were similar to those of the Cochrane review on interventions for actinic keratosis.[8] Eligible studies for inclusion were RCTs (including parallel group and intraindividual designs as well as crossover trials) reporting on participants with a clinical or histological diagnosis of at least one AK lesion at baseline. Randomization had to refer to participants or to body parts of participants (e.g. left versus right side), not to individual AK lesions. Publication language was not restricted. Studies reporting on participants with a particular predisposition for developing sun exposure-related skin lesions (e. g. Xeroderma pigmentosum, Albinism) were excluded. Additional criteria were defined by the expert panel concerning the selection of interventions and the selection of outcomes to be considered. For a list of the selected interventions and outcomes please see chapters 4 and 5.

2.3.5 Data extraction

Data collection of the update search results was done independently by two assessors (RNW, AJ), using a standardized data extraction form (Microsoft® Excel worksheet). The original Review Manager[9] file from the Cochrane review[8] was kindly made available by the authors. This file was updated along the selected eligibility criteria and the update search by two independent assessors (AJ, SR / RNW). Discrepancies of the extracted data were reviewed and discussed.

2.3.6 Categorization of the literature along subgroups of patients

Included studies were categorized according to the AK severity in the participants at baseline. As there is no pre-existing, widely accepted method for classification of AK severity, the subgroups of patients as defined by the expert panel were used.

The studies were categorized on the basis of the inclusion criteria of each individual trial. If disease severity as inclusion criterion was not reported or if the inclusion criteria of the trial overlapped the defined categories of patients, studies were classified in accordance to the mean AK lesion counts and standard deviation at baseline. If studies could not be classified into a singular category, the data were taken into account for both respective patient subgroups and GRADE quality ratings with respect to directness were adapted.

2.3.7 Qualitative assessment of the evidence

The available evidence and its quality were summarized according to the system recommended by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group[4] for each available outcome in each comparison.

Using the GRADE profiler[10], GRADE evidence profiles were developed for each available comparison of interventions, based on the rated outcomes (see chapters 2.3.1 and 5). The quality of the evidence for each key question was categorized into one of four categories, from 'very low' to 'high'.[11]

Table 1 summarizes the different quality levels of evidence and the approach used to grade the quality of evidence as suggested by the GRADE working group.[11]

Table 1: Summary of the approach used to grade the quality of evidence for each outcome of interest and the quality levels of evidence as suggested by the GRADE working group[11]

Source of body of evidence and Initial rating of quality of a body of evidence		**Factors that may decrease the rating**	**Factors that may increase the rating**	**Final quality of the body of evidence for a certain recommendation and implications**	
RCT	High	1. Limitations to study quality 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias	1. Large effect 2. Dose-response 3. All plausible confounding would have reduced the demonstrated effect	High (++++)	We are very confident that the true effect lies close to that of the estimate of effect.
				Moderate (+++)	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Observational studies	Low			Low (++)	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Any other evidence	Very low			Very low (+)	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

The following criteria, as defined by the GRADE working group were applied to decrease or increase the quality ratings for each key question, intervention and outcome:

Limitations to the study quality: The Cochrane risk of bias tool[3] was used to assess limitations to the study quality on a study level. The following domains were assessed: random sequence generation, allocation concealment, incomplete outcome data, selective

reporting, blinding of participants and personnel, blinding of outcome assessment, and other sources of bias. Overall study quality depended on the limitations of the contributing studies. A downgrading of 1 ('serious limitations') or 2 points ('very serious limitations') was possible.[12]

Inconsistency: Overall quality of evidence was downgraded by 1 point ('important inconsistency'), when the study results were heterogeneous with respect to the direction or the size of the effect. The main criteria for downgrading were: widely varying point estimates across the studies, minimal or no overlap of the confidence intervals (CI), large I^2 (I^2 is a statistical test quantifying the variation of the point estimate between the studies).[13] Inconsistency could not be assessed in case of only one contributing study.

Indirectness: When differences between the effect size in the populations recruited for the study participation and the patient subgroup to make a recommendation for were expected (due to significant and important differences of the studied populations to the target population), overall study quality was downgraded by 1 ('some') or 2 points ('major uncertainty about the directness').[14] Here, study quality was downgraded, when the study inclusion criteria or the patient characteristics at baseline did not match exclusively one of the predefined patient subgroups.

Imprecision: The main criterion for determining the precision of the pooled effect size is the width and position of the 95% confidence interval (CI)[15]: the overall study quality was downgraded for imprecision if the CI was very wide (range of >100), crossed the threshold of minimal important difference (defined as the line of no effect ±0.25) or if the CI crossed the line of no effect and the threshold of minimal important difference. For continuous outcomes such as the mean reduction in AK lesion counts, the minimal important difference was calculated as the line of no effect ±0.5*SD of the control group.

Publication bias: When publication bias was expected to influence the size or direction of the effect, study quality was downgraded by 1 point[16]. Due to the low number of contributing trials for each comparison, no formal testing (e.g. visual characterization of funnel plots) could be performed.

Large effect / evidence of a dose response gradient / confounders that would have decreased the effect: Rating up the quality of evidence due to the mentioned reasons is generally recommended only to be applied to results from observational studies or nonrandomized trials[17]. As the systematic literature search was restricted to randomized controlled trials, no upgrading of the overall study quality was performed.

The quality of the evidence was evaluated by two assessors (AJ, SR) after discussion of each aspect. In case of dissent of the assessors, a third assessor (RNW) was involved and the conflict solved as a majority decision. Comments to justify the ratings are supplied in case of downgrading.

2.3.8 Presentation of the results of the systematic review

For each intervention or comparison of interventions, a short text summarizing the available evidence and a GRADE summary of findings table is presented (see results report and long version of these guidelines). The summary of findings (SoF) tables encompass a detailed summary of the findings and their interpretation[18]. Data are presented as risk ratios (dichotomous outcomes)[19] or mean differences (continuous outcomes)[20].

The risk ratio (RR) refers to the relative risk of an event occurring in the interventional group compared with the control group. For continuous data (e.g. the mean reduction in AK lesions counts), the mean difference relative to the control group is presented.

2.3.9 Development of recommendations/ Consensus process

All recommendations were consented during the consensus conference, moderated by Alexander Nast, MD, head of the steering group and certified moderator for the German Association of Scientific Medical Societies (AWMF). Formal consensus methodology (nominal group technique) was used to agree upon the recommendations[21]. All expert panel members without critical conflicts of interest were entitled to vote on the recommendations. The consensus conference was performed as an online consensus conference, using a regular telephone conference for the sound and the online platform Adobe® Connect™ for the presentation of the evidence data from the systematic literature review and voting on recommendations.

The results from the systematic literature review (summary of findings tables and textual summaries) were supplied to the members of the expert panel prior to the consensus conference. During the consensus conference, the results of the systematic literature review were presented for each intervention prior to the discussion and voting on the recommendation for the respective intervention. When evaluating the evidence, the balance of benefits and harms, considering the predefined ranking of the importance of the outcomes, and the quality of the evidence were taken into consideration. Besides the evidence from the systematic review of the literature, expert opinion and experience was included, particularly if the body of evidence was insufficient and if further aspects such as time and costs, additional side effects, quality of life, resource use, etc. had to be considered. Additional reasoning was required to be discussed and explicitly stated in the case of aberration from the external evidence.

2.3.10 Structure and presentation of the recommendations

To simplify the identification of consented recommendations, all consented recommendations are highlighted throughout the guidelines documents (grey boxes). In order to avoid ambiguity, a standardized language was used to classify the direction and strength of each recommendation.

Based on the GRADE approach, five strengths of recommendations were differentiated: strong recommendations for or against the use of an intervention, weak recommendations for or against the use of an intervention, and no recommendation.[22] The strength is expressed by the wording and symbols as shown in Table 2. The strength of a recommendation had to be based on the quality of the evidence as shown above (high / moderate / low / very low) and the balance of expected undesirable and desirable outcomes.[23] If expert opinion without external evidence was incorporated into the reasoning for making a certain recommendation, the rationale was provided.

Table 2: Strength of recommendations: wording, symbols and implications[23]

Strength	Wording	Symbols	Implications
Strong recommendation for the use of an intervention	"We recommend …"	↑↑	We believe that all or almost all informed people would make that choice. Clinicians will have to spend less time on the process of decision making, and may devote that time to overcome barriers to implementation and adherence. In most clinical situations, the recommendation may be adopted as a policy.
Weak recommendation for the use of an intervention	"We suggest …"	↑	We believe that most informed people would make that choice, but a substantial number would not. Clinicians and health care providers will need to devote more time on the process of shared decision making. Policy makers will have to involve many stakeholders and policy making requires substantial debate.

No recommendation with respect to an intervention	"We cannot make a recommendation with respect to …"	0	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e.g. no evidence data available, conflicting outcomes, etc.)
Weak recommendation against the use of an intervention	"We suggest not to …"	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
Strong recommendation against the use of an intervention	"We recommend not to …"	↓↓	We believe that all or almost all informed people would make a choice against that intervention. This recommendation can be adopted as a policy in most clinical situations.

For each recommendation, the quality of consensus in terms of percentage of agreement was measured and documented. Three levels of consensus were defined and distinguished. A 'strong consensus' (agreement of at least 90% of the expert panel members participating in the conference) was generally aimed at. In cases where only lower values of agreement were achieved, these were defined as 'consensus' (75 to 89% agreement) or 'weak consensus' (50 to 74% agreement).

2.4 Peer review and piloting

Before publication, the guidelines draft underwent an extensive internal and external review. Internal review was accomplished at the beginning of the guidelines development to confirm the selection of key questions (kick-off conference), prior to the consensus conference for a preliminary review of the results from the systematic literature review, after the consensus conference to confirm the completed recommendations, and after the external review to confirm changes before publication.

The external review took place from 24th of March through 5th of May 2014. All ILDS member societies, the European Dermatology Forum (EDF), European Union Of Medical Specialists (UEMS), European Academy of Dermatology and Venereology (EADV), and European Association of Dermato-Oncology (EADO) were officially invited. Furthermore, the Skin Cancer Foundation, American Cancer Society and European Skin Cancer Foundation were invited to participate in the external review. The review took place using an open-access internet platform (www.crocodoc.com), and comments could directly be integrated in the guidelines documents. The comment function was open to every interested individual. In total, 103 comments were posted on the online platform (38 on the short version of the guidelines and 65 on the long version of the guidelines). We received 9 additional letters from different institutions. Each comment was assessed individually and categorized according to the required consequences. A document summarizing all comments, individual responses and their handling is available at the Division of Evidence based Medicine (Charité - Universitätsmedizin Berlin, Berlin, Germany).

The guidelines were approved by the ILDS, the EDF, the EADV and the UEMS.

During the phase of external review, the members of the expert panel piloted the drafted guidelines within their own practices and were encouraged to comment on the practicability and results during the second internal review. International guidelines are intended to be adapted to the national circumstances of each health system. Therefore, a formalized piloting of the recommendations will have to take place in each country and the national societies are responsible for the planning, realization, and evaluation of piloting projects.

2.5 Implementation, evaluation, updating

International guidelines are intended to be adapted to national or regional circumstances (regulatory approval and availability of treatments, health care provider and insurance systems). Thus, the national medical societies associated to the ILDS will be responsible for the adaption and implementation of the guidelines on a national level. In order to assist implementation, additional material such as a short version of the guidelines will be supplied. The original guidelines publication and a long version of the guidelines, this methods report and the results report including detailed data on the methodology and results will be published online. Evaluation strategies with respect to the awareness of the treatment necessity amongst patients and physicians, the treatment adhesion and treatment success should be pursued at a national level.

Due to the increasing amount of publications, guidelines need to be continually updated to reflect the recent state of evidence. After July 31, 2018 these guidelines will expire. Should important changes occur in the meantime, such as new available interventions, new important evidence or withdrawal of drug licensing, the information contained in the guidelines will be outdated earlier. In these cases, an update issue of the guidelines is needed earlier. The ILDS will be responsible to initiate an update.

3 Subgroups of patients presenting with AK

Werner

A widely agreed upon definition of degrees of the overall severity of AK could not be identified. Different subgroups of patients presenting with AK, requiring differential therapeutic approaches were defined at the beginning of the guidelines development in order to address the demands of clinical practice. The definitions were discussed and consented during the kick-off consensus conference (Table 3).

Table 3: Recommendations for a classification of patients according to the severity of AK

Recommendations for a classification of patient subgroups:	**Evidence**	**Percentage of agreement**
The following subgroups of patients should be considered separately: • Patients with single AK lesions • Patients with multiple AK lesions • Patients with field cancerization • Patients with concomitant immunosuppression	expert consensus	≥90%
Definition of patients presenting with single AK lesions: At least one and not more than five palpable or visible AK lesions per field or affected body region	expert consensus	≥90%
Definition of patients presenting with multiple AK lesions: At least 6 distinguishable AK lesions in one body region or field	expert consensus	≥90%
Definition of patients presenting with field cancerization: At least 6 AK lesions in one body region or field, and contiguous areas of chronic actinic sun damage and hyperkeratosis	expert consensus	≥90%
Definition of immunosuppressed patients with AK: AK at any of the above-mentioned severity degrees and concomitant immunosuppression (e. g. due to chronic immunosuppressive medication or specific diseases affecting the function of the immune system, such as malignant hematologic disorders)	expert consensus	≥90%

4 Available treatment options

The following treatment options were selected as relevant interventions for actinic keratosis by the authors of these guidelines in consensus with ≥ 75% of the expert panel members to be included in the assessment and evaluation. The selection of interventions and their mode of application served as inclusion criteria for the systematic literature assessment. Other interventions and other application modes for the selected interventions were not included into the systematic literature review. This does not imply that other interventions are not possibly suitable for the treatment of AK. Modes of application of the listed interventions might have to be adapted when implementing the guidelines in the national context. When deciding for using certain interventions, users of this guidelines must carefully check the treatment option and its mode of application, e.g. regarding approval status, dose, dosing regimen, adverse effects, contraindications, or drug interactions.

Lesion-directed treatment options for AK aim at the physical destruction or removal of atypical keratinocytes that constitute a singular AK lesion. These treatments are directed towards the clinically manifest (visible or palpable) AK lesions. Field-directed treatment options for AK similarly aim at the destruction, removal or remission of atypical keratinocytes. Here, therapy of latent, subclinical areas of atypical keratinocytes within a field of chronic sun damaged skin and not only a reduction of manifest areas of AK is intended. Classification of the interventions along these categories is difficult in some cases. For the recommendations, all listed interventions were considered for all types of patients.

Table 4 shows a list of treatment options for AK that were selected for evaluation within these clinical guidelines. Please note that the stated mode of application does not imply guidance for the mode of use of the listed interventions, but solely reflects the criteria that had to be fulfilled for inclusion into the systematic review.

Table 4: Treatment options selected for evaluation

Intervention	**Mode of application**
Curettage	Once, repeated up to 2 times
Cryotherapy	Once, repeated up to several times
Carbon dioxide (CO2) laser	Once, repeated up to several times
Er:YAG laser	Once, repeated up to several times
0.5% 5-fluorouracil + 10% salicylic acid	Once daily application for 6 to 12 weeks
5-aminolaevulinic acid photodynamic therapy (ALA-PDT)*	Different concentrations, light sources and application modes of ALA-PDT were included, incubation time had to be at least 1 hour
Methylaminolevulinate photodynamic therapy (MAL-PDT)*	Different light sources and application modes of MAL-PDT were included, incubation time had to be at least 2.5 hours
3% diclofenac in 2.5% hyaluronic acid gel	Twice daily application for 60 to 90 days
0.5% 5-fluorouracil (0.5% 5 FU)	Once daily for 1 to 4 weeks
5% 5-fluorouracil (5% 5 FU)	Once or twice daily for 2 to 4 weeks
2.5% Imiquimod	Once daily application for 2 weeks followed by a rest period of two weeks (One or two treatment cycles)
3.75% Imiquimod	Once daily application for 2 weeks followed by a rest period of two weeks (One or two treatment

	cycles)
5% Imiquimod	Once daily application at 2 or 3 days per week for a time period of 4-16 weeks; continuously or intermittent.
0.015% Ingenol mebutate for lesions on the face or scalp	Once daily application for 3 days
0.05% Ingenol mebutate for lesions on the trunk or extremities	Once daily application for 2 days

* PDT often included pretreatment of the AK lesions, e.g. with curettage or other topical interventions. These were not classified as 'combination treatments' (see chapter 4.1), unless the combination included one of the other selected interventions (except for curettage). For information on the specific mode of application of PDT in the included studies, see results report (online supplement).

4.1 Combined treatment options

The expert panel suggested different (sequential) combinations of interventions for the treatment of AK. Although these were initially intended to be assessed within the systematic literature review, the expert panel and steering group decided not to include combined treatment options into the systematic literature assessment: For a substantial number of combinations, no data were eligible for the inclusion in the review and within the eligible data, application modes were heterogeneous and comparability very limited. A systematic literature assessment would not have been capable of reflecting the actual possibilities of combined treatments.

A subgroup from the expert panel summarized the available evidence (not exclusively based on the systematic literature assessment) regarding reasonable combinations that may increase the efficacy through synergistic effects (see guidelines publication or long version of these guidelines).

4.2 Interventions not included into this guideline

The fact that certain interventions were not included into the evaluation within these guidelines does not necessarily imply that it may not be an appropriate treatment for AK. The following interventions were identified as having been studied for their efficacy in the treatment of AK, but were not included in the systematic assessment: topical masoprocol, topical adapalene, topical trichloracetic acid, 2-2-(Difluoromethyl)-dl-ornithine (DFMO), oral tretinoin, oral etretinate, aretinoid methyl sulfone, betulin-based oleogel, calcipotriol, colchicine, systemic diclofenac, topical tretinoin, ß-1,3-D-glucan, nicotinamide, resiquimod, and DL-α-tocopherol (vitamin E).

5 Assessment of treatment options/ rating of outcomes

To be included into the systematic review, studies had to report at least one of the selected outcomes. Outcomes had to be reported as events per patients in case of dichotomous outcomes (the number of events and the number of patients at the time of assessment had to be reported) or as mean difference in case of continuous outcomes (the mean and standard deviation had to be reported). Otherwise studies could not be considered. Efficacy assessment was accomplished for all comparisons. Safety outcomes, patient reported outcomes, and cosmetic outcomes were only assessed for head-to-head comparisons (RCTs with active control).

5.1 Efficacy

The selection of efficacy outcomes was based on the rating of outcomes by the expert panel members according to the GRADE methodology (see chapter 2.3.1, 'Selection of key questions to be answered') and on the primary outcomes chosen for the Cochrane review of interventions for AK.[8] Table 5 shows the selected efficacy outcomes and assigned rating of importance.

Table 5: Efficacy outcomes and assigned rating of importance

Outcome	Importance
Mean reduction in lesion counts from baseline to assessment (absolute values [preferred] or percentages)	Critical outcome
Participant complete clearance (CC, rate of participants with a complete clearance of all lesions within a predefined field)	Critical outcome
Participant partial clearance (PC, rate of participants with at least a 75% reduction of the AK lesion counts within a predefined field)	Critical outcome
Investigator global improvement index (IGII, rate of participants rated as 'completely improved' by the investigator)	Critical outcome
Participants global improvement index (PGII, rate of participants self-assessed as 'completely improved')	Critical outcome

For reasons of feasibility and to allow for comparability, the efficacy outcomes had to be reported 2 months after the end of treatment or whatever was closest, not more than 6 months after the end of treatment. Studies examining longer treatment periods were not included in the systematic review.

5.2 Tolerability/ safety

The selection of safety outcomes was similarly based on the rating of outcomes by the expert panel members according to the GRADE methodology (see chapter 2.3.1, 'Selection of key questions to be answered') and on the outcomes chosen for the Cochrane review of interventions for AK.[8] Withdrawals due to adverse events and skin irritation were assessed for every head-to-head comparison. For all head-to-head comparisons, members of the expert panel could choose three further safety outcomes. The expert panel was supplied with a list of safety outcomes that were available in the identified studies. Experts were asked to evaluate which of the respective outcomes were treatment-associated and rate their importance. Among the 'treatment-associated' outcomes, three outcomes with the highest

ranking were selected for evaluation. Table 6 gives an overview of a selection of the chosen safety outcomes and the assigned rating of importance.

Table 6: Example of safety outcomes and the assigned rating of importance

Outcome	Importance
Withdrawals due to adverse events	Critical outcome
Skin irritation	Critical outcome
Erosion/ulceration*	Important outcome
Infection*	Important outcome
Blister formation*	Important outcome

* The importance of these outcomes refers to the rating of outcomes for the comparison of cryotherapy with 5% imiquimod. All safety outcomes that were selected for other specific comparisons were rated as important outcomes.

The rate of events for all safety outcomes refers to events that occurred from baseline until the end of the study. Apart from 'withdrawals due to adverse events' and 'skin irritation', all safety outcomes that were selected for evaluation were rated as 'important outcome'.

5.3 Patient reported outcomes

The selection of patient reported outcomes was equally based on the rating of outcomes by the expert panel members according to the GRADE methodology (see chapter 2.3.1, 'Selection of key questions to be answered') and on the outcomes assessed for the Cochrane review of interventions for AK.[8] Patient reported outcomes were assessed for head-to-head-comparisons. Table 7 shows the selected patient reported outcomes and the assigned rating of the importance.

Table 7: Patient reported outcomes and the assigned rating of importance

Outcome	Importance
Participant's satisfaction (rate of participants 'satisfied' or 'very satisfied)	Critical outcome
Participant's preference (rate of participants preference)*	Critical outcome
Compliance	Critical outcome

* Participant's preference could only be assessed in split-patient trials.

If more than one assessment of patient reported outcomes was performed in a study, the final assessment was chosen for evaluation.

5.4 Cosmetic outcomes

The selection of cosmetic outcomes was equally based on the rating of outcomes by the expert panel members according to the GRADE methodology (see chapter 2.3.1, 'Selection of key questions to be answered'). For all head-to-head comparisons, members of the expert

panel could choose three cosmetic outcomes. The expert panel was supplied with a list of cosmetic outcomes that were available in the identified studies. The three patient reported outcomes with the highest ranking were selected for evaluation. Table 8 gives an overview of a selection of the chosen cosmetic outcomes and the assigned rating of importance.

Table 8: Example of cosmetic outcomes and the assigned rating of importance

Outcome	Importance
Improvement in global response*	Important outcome
Improvement in tactile roughness*	Important outcome
Improvement in mottled hyperpigmentation*	Important outcome

* The importance of these outcomes refers to the rating of outcomes for the comparison of ALA-PDT with 0.5% 5-fluorouracil.

If more than one assessment of cosmetic outcomes was performed in a study, the final assessment was chosen for evaluation. Apart from ‘excellent global cosmetic outcome’ for the comparisons of cryotherapy with 5% 5-fluorouracil and cryotherapy with 5% imiquimod (both rated as ‘critical outcome’), all cosmetic outcomes that were selected for evaluation were rated as ‘important outcome’.

5.5 Other considerations

Other considerations could be included into the reasoning for making recommendations for specific interventions. These could include expert experience concerning resource use, practicability, adherence or other reasons. These considerations were not assessed systematically. They were discussed during the consensus conference and stated for each recommendation as ‘additional reasoning’.

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7 Appendix

7.1 Form used to assess conflicts of interest (COI)

Conflicts of interests:

Family name, first name

The Work Under Consideration for Publication		
1	Grant	
2	Consulting fee or honorarium	
3	Support for travel to meetings for the study or other purposes	
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	
5	Payment for writing or reviewing the manuscript	
6	Provision of writing assistance, medicines, equipment, or administrative support	
7	Other	

Relevant financial activities outside the submitted work		
1	Board membership	
2	Consultancy	
3	Employment	
4	Expert testimony	
5	Grants/grants pending	
6	Payment for lectures including service on speakers bureaus	
7	Payment for manuscript preparation	
8	Patents (planned, pending or issued)	
9	Royalties	
10	Payment for development of educational	

	presentations	
11	Stock/stock options	
12	Travel/accommodations/meeting expenses unrelated to activities listed*	
13	Other (err on the side of full disclosure)	

* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships		
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	

Date

Signature

7.2 Electronic search strategies used for the update search

Cochrane Central Register of Controlled Trials

Search dates: 2011 – January 25th, 2013

ID	Search
#1	actinic and keratos* (Word variations have been searched)
#2	"solar" and keratos* (Word variations have been searched)
#3	"senile" and keratos* (Word variations have been searched)
#4	hyperkeratos* (Word variations have been searched)
#5	MeSH descriptor: [Keratosis, Actinic] explode all trees
#6	#1 or #2 or #3 or #4
#7	#5 or #6 from 2011 to 2013

Pubmed/Medline via OVID SP

Search dates: 2011 – January 25th, 2013

ID	Search
#1	randomized controlled trial.pt.
#2	controlled clinical trial.pt.
#3	randomized.ab.
#4	placebo.ab.
#5	clinical trials as topic.sh.
#6	randomly.ab.
#7	trial.ti.
#8	1 or 2 or 3 or 4 or 5 or 6 or 7
#9	(animals not (human and animals)).sh.
#10	8 not 9
#11	actinic keratos$.mp.
#12	exp Keratosis, Actinic/
#13	solar keratos$.mp.
#14	senile keratos$.mp.
#15	hyperkeratos$.mp.
#16	11 or 12 or 13 or 14 or 15
#17	10 and 16
#18	limit 17 to yr="2011 -Current"

Medline in Process

Search dates: 2011 – January 25th, 2013

ID	Search
#1	"trial*".ab,ti.
#2	"placebo*".ab,ti.
#3	"random*".ab,ti.
#4	1 or 2 or 3
#5	"keratos*".ab,ti.
#6	"hyperkeratos*".ab,ti.
#7	5 or 6
#8	4 and 7
#9	limit 8 to yr="2011 -Current"

Embase via OVID SP

Search dates: 2011 – January 25th, 2013

ID	Search
#1	random$.mp.
#2	factorial$.mp.
#3	(crossover$ or cross-over$).mp.
#4	placebo$.mp.
#5	exp placebo/
#6	(doubl$ adj blind$).mp.
#7	(singl$ adj blind$).mp.
#8	(assign$ or allocat$).mp.
#9	volunteer$.mp.
#10	exp volunteer/
#11	exp crossover procedure/
#12	exp double blind procedure/
#13	exp randomized controlled trial/
#14	exp single blind procedure/
#15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
#16	actinic keratos$.mp.
#17	exp actinic keratosis/
#18	solar keratos$.mp.
#19	senile keratos$.mp.
#20	hyperkeratos$.mp.
#21	16 or 17 or 18 or 19 or 20
#22	15 and 21
#23	limit 22 to yr="2011 -Current"

Results Report

List of figures

List of tables

1 Introduction

Nast / Werner

This document is the results report, providing a comprehensive description of the results from the evidence report (systematic literature review and meta-analyses) of the

Evidence and consensus based (S3) Guidelines for the Treatment of Actinic Keratosis - International League of Dermatological Societies (ILDS) in cooperation with the European Dermatology Forum (EDF).

Please use the following reference when citing this document: JEADV DOI: 10.1111/jdv.13179.

In the present document, detailed results of the guidelines development process including a comprehensive description of the results from the systematic literature assessment are presented. A detailed description of the guidelines development process and methodology is available in the methods report of the guidelines. For clinical guidance on the clinical background, assessment and treatment of actinic keratosis (AK), please consider the original guidelines publication or the long version of these guidelines.

These guidelines encompass different clinical aspects related to AK. The primary goal of the guidelines was the development of treatment recommendations appropriate for different subgroups of patients presenting with AK. This was subject to a systematic literature review and a formalized consensus conference of the members of the guidelines' expert panel.

A secondary aim of these guidelines is the implementation of knowledge relating to the clinical background of AK, including recommendations for the histopathological definition of the disease and for the diagnosis and assessment of patients presenting with AK. Clinical background texts were written by the steering group and subgroups of the expert panel, based narrative literature reviews. Some of these aspects (diagnosis, histopathology, assessment of patients with AK) were formally consented as recommendations during the consensus conference.

The guidelines were elaborated along adapted recommendations by the WHO guidelines review committee[1] and the quality criteria for guidelines as suggested by the Appraisal of Guidelines Research and Evaluation (AGREE II) Instrument[2] were incorporated into the methodological development of the guidelines. For the planning and elaboration of the underlying systematic literature review on interventions for AK, the methodology suggested by the Cochrane Handbook for Systematic Reviews of Interventions[3], the GRADE working group[4] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[5] was adapted.

2 Disclaimer

Guidelines do not replace the clinicians' knowledge and skills, since guidelines never encompass therapy specifications for all medical decision-making situations. Guidelines should not be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. Deviation from the recommendations may be justified or inevitable in specific situations. The ultimate judgment regarding patient care must be individualized and must be made by the physician and patient in light of all presenting circumstances.

Safety aspects that were considered within these guidelines do not represent a comprehensive assessment of all available safety information for the included interventions. They are limited to those aspects chosen for evaluation and the information available in the included clinical trials. Readers must carefully check the information in these guidelines and determine whether the recommendations (e.g. regarding dose, dosing regimens, contraindications, or drug interactions) are complete, correct, up-to-date and appropriate.

International guidelines are intended to be adapted to national or regional circumstances (regulatory approval and availability of treatments, health care provider and insurance systems). Particularly, the mode of application of the different treatment options has to be adapted to national approval of the interventions. Thus, the national medical societies associated with the International League of Dermatological Societies (ILDS) will be responsible for the adoption and implementation of the guidelines on a national level.

3 Results from the systematic literature review (meta-data)

3.1 Existing reviews and guidelines

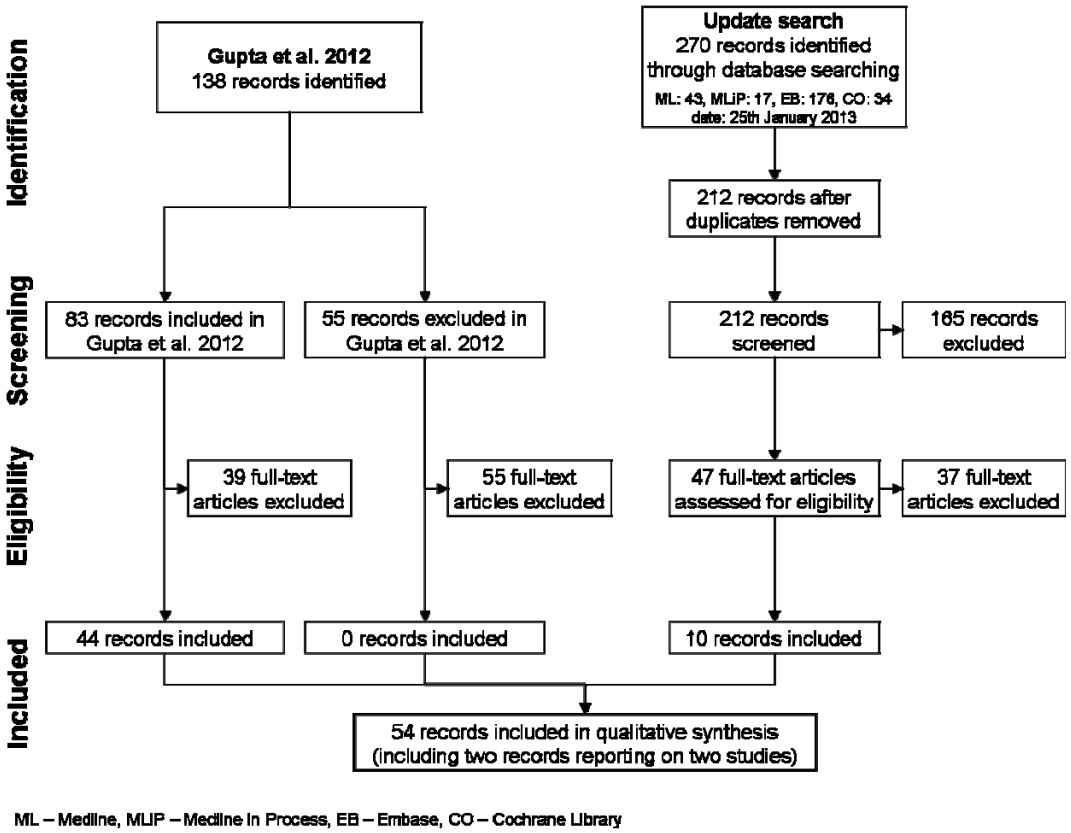
During the preparation of the guidelines, a recent and high-quality systematic review of interventions for actinic keratosis was identified.[6] The critical appraisal using the SIGN checklist for Systematic reviews[7] identified the Cochrane review as suitable to be used as basis of an update search for the guidelines' body of evidence.

3.2 Study selection

3.2.1 Selection of studies from the Cochrane review

In the original Cochrane review of interventions for AK,[6] 83 trials were included and 55 trials excluded after the full-text screening. The included studies were checked for eligibility for the guidelines, and 39 of these excluded. The trials that had been excluded in the Cochrane review due to reasons that did not necessarily correspond to the exclusion criteria of the present guidelines were reassessed for eligibility, but none of these was included. One of the included publications from the Cochrane review reports on results from two independent trials and is therefore referred to as two single studies in the following text (Hauschild 2009).[8] Figure 1 shows a PRISMA flowchart[5] of included and excluded publications. Reasons for the exclusion of studies that were included in the original Cochrane review are shown in the appendix (Chapter 8.1, 'Excluded studies: reasons for exclusion').

Figure 1: Flow of information through the different phases of the systematic literature review



ML – Medline, MLiP – Medline In Process, EB – Embase, CO – Cochrane Library

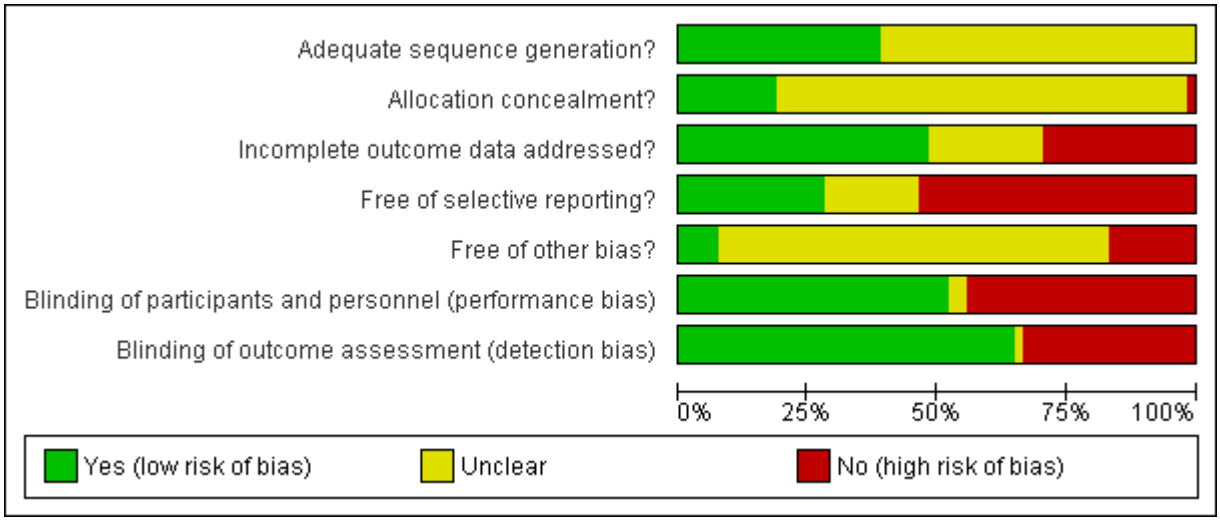
3.2.2 Selection of studies from the update search

The update search, conducted on January 25th, 2013, yielded 270 hits (Medline: 43, Medline in Process: 17, Embase: 176, Cochrane Central Library: 34). After removal of duplicates, 212 single records remained. 165 studies were excluded during the titles and abstract screening, and full texts of the 47 remaining studies were assessed. 10 of these were included into the evaluation for the systematic review. One of the included publications from the update search reports on results from four trials on two different interventions (ingenol mebutate at a concentration of 0.015% for lesions on the face or scalp and ingenol mebutate at a concentration of 0.05% for lesions on the trunk or extremities) and is therefore referred to as two studies in the following text (Lebwohl 2012).[9] Figure 1 shows a PRISMA flowchart[5] of included and excluded publications. Reasons for the exclusion of studies from the update search are shown in the appendix (Chapter 8.1, 'Excluded studies: reasons for exclusion').

3.3 Risk of bias within studies

Figure 2 shows a summary of the evaluation of the included studies for each risk of bias item.

Figure 2: Summary of the evaluation of the included studies for each risk of bias item



Concerning randomization, 21 of the included studies stated the method used for the sequence generation ('low risk of bias') and 33 did not explicitly state how randomization was performed ('unclear risk of bias'). Most frequently, a computer-generated randomization schedule was used. Because randomization was an inclusion criterion, no studies had a 'high risk of bias' with respect to the adequacy of the sequence generation.

The mode of the allocation concealment was reported in 10 of the included studies ('low risk of bias') and not reported in 43 studies ('unclear risk of bias'). For one split-patient trial[10], the judgment concerning allocation concealment was 'high risk of bias', because the generation of the random allocation sequence, enrolment of patients and assignment of procedures to body half were conducted by the same investigator.

Incomplete outcome data were addressed in 26 of the included studies by using intention-to-treat-analysis (ITT). The risk of bias for this item was rated as 'high', if no or unclear data on dropouts were provided or the analysis was based on the per-protocol-population and it was not possible to convert the data into an ITT analysis. This was the case in 16 of the included

studies. In 12 further studies, the risk of bias with respect to incomplete outcome data was judged as ‘unclear’.

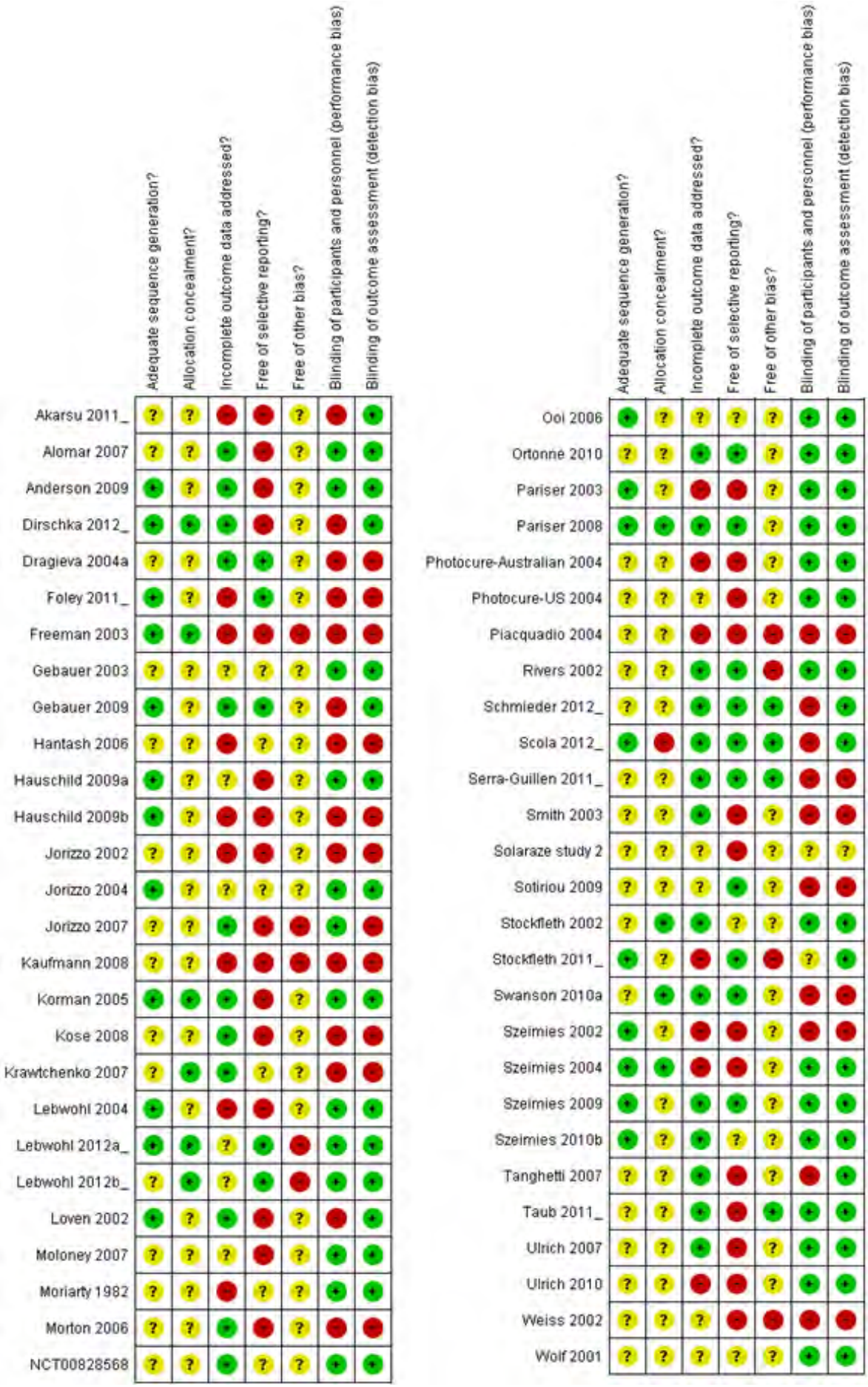
A ‘high risk of bias’ concerning selective reporting was assigned to the studies, if selective data were not reported according to the protocol or the stated methods report, or when the reporting methods remained unclear or inconsistent. With 29 studies, this was the case in the majority of the included studies. Selective reporting was judged as introducing a ‘low risk of bias’ in 15 studies, and an ‘unclear risk of bias’ in 10 of the included studies.

In 9 of the included studies, the other bias item was rated as ‘high risk of bias’, because there was a specific risk of bias that was not assessed within the other items of the risk of bias assessment. With 41 studies, the majority of studies remained unclear concerning other risks of bias, and in 4 studies, this item was judged as introducing a ‘low risk of bias’.

The majority of studies were judged as at ‘low risk of bias’ concerning an adequate blinding of the participants and personnel (28 studies) and blinding of the outcome assessment (35 studies). 24 studies were not or inadequately blinded towards participants and personnel and 18 studies were not or inadequately assessor-blinded. In two studies, the blinding of participants and personnel remained unclear[11, 12] and in one study, the blinding of the assessor was unclear.[11]

Figure 3 shows the risk of bias evaluation for each included study.

Figure 3: Risk of bias evaluation for each included study


Adequate sequence generation?
Allocation concealment?
Incomplete outcome data addressed?
Free of selective reporting?
Free of other bias?
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Akarsu 2011_
Alomar 2007
Anderson 2009
Dirschka 2012_
Dragieva 2004a
Foley 2011_
Freeman 2003
Gebauer 2003
Gebauer 2009
Hantash 2006
Hauschild 2009a
Hauschild 2009b
Jorizzo 2002
Jorizzo 2004
Jorizzo 2007
Kaufmann 2008
Korman 2005
Kose 2008
Krawtchenko 2007
Lebwohl 2004
Lebwohl 2012a_
Lebwohl 2012b_
Loven 2002
Moloney 2007
Moriarty 1982
Morton 2006
NCT00828568
Ooi 2006
Ortonne 2010
Pariser 2003
Pariser 2008
Photocure-Australian 2004
Photocure-US 2004
Piacquadio 2004
Rivers 2002
Schmieder 2012_
Scola 2012_
Serra-Guillen 2011_
Smith 2003
Solaraze study 2
Sotiriou 2009
Stockfleth 2002
Stockfleth 2011_
Swanson 2010a
Szeimies 2002
Szeimies 2004
Szeimies 2009
Szeimies 2010b
Tanghetti 2007
Taub 2011_
Ulrich 2007
Ulrich 2010
Weiss 2002
Wolf 2001

3.4 Risk of bias across studies

Publication bias (selective publication of results from the accomplished trials) is a major concern in evidence based approaches. In this systematic review, a minimization of publication bias was attempted by using the data from the Cochrane review that extensively searched for registered studies in trials registers and searched the U.S. Food and Drug Administration (FDA) website as well as pharmaceutical company websites.[6] The results from the recent update search were compared against the 'studies awaiting classification' category (ongoing trials or unpublished data) from the Cochrane review to check for completeness. One of the 12 studies listed in the Cochrane review as 'studies awaiting classification' was not found in the recent update search, this record[13] was excluded after full-text assessment because it reported a comparison not relevant to this literature review. An evaluation of funnel plots to check for the possibility of publication bias was not feasible due to the low number of trials contributing to the evidence for each comparison.

3.5 Categorization of studies along the predefined patient subgroups

Studies often included a mixed sample of participants from the different predefined patient subgroups so that quality ratings concerning directness of the data had to be adapted. The information reported in the included studies did not allow to distinguish between the subgroups of patients with multiple AK lesions and patients with field cancerization. Therefore, these two subgroups were generally pooled together in order to make treatment recommendations.

During the categorization of the studies with respect to study populations, studies that did not specify the enrolment of immunosuppressed patients were considered as enrolling immunocompetent participants, even though some of these studies did not contain immunosuppression as an explicit exclusion criterion.

4 Results and recommendations

4.1 Curettage

4.1.1 Additional reasoning and recommendations

No data were eligible for this intervention.

Curettage is particularly useful for treating hypertrophic AK of the extremities. It can be used in conjunction with shave excision, electrodessication (ED&C) or cryotherapy. If the possibility of an invasive SCC is suspected, a shave excision or biopsy of a suspicious lesion should be performed in conjunction with curettage. The disadvantage of curettage is that only a limited number of visible lesions can be treated, local anesthesia is required, healing times are prolonged especially on the lower extremities, prolonged hyperpigmentation can occur and depigmentation and scarring are expected.

Performing curettage for discrete hyperkeratotic lesions is a very common practice and especially in hyperkeratotic lesions, other interventions are less likely to work due to insufficient penetration into the skin. Despite the long experience with performing curettage, due to the missing external evidence a weak recommendation was made for the curettage of discrete, hyperkeratotic AK lesions in patients with single lesions and in immunosuppressed patients with AK.

Recommendation	Strength of recommendation	Percentage of agreement
We suggest using curettage for discrete, hyperkeratotic lesions in patients with single AK lesions.	↑	≥90%
We cannot make a recommendation with respect to curettage in patients with multiple AK lesions or field cancerization.	0	≥90%
We suggest using curettage for discrete, hyperkeratotic lesions in immunosuppressed patients.	↑	≥75%

4.2 Cryotherapy

4.2.1 Cryotherapy vs. placebo

No data were available for this comparison.

4.2.2 Cryotherapy vs. 5% 5-fluorouracil (5% 5-FU)

Study and patient characteristics:
One RCT[14] (N= 75, age 57 to 88 years, mean: 73) compared cryotherapy and 5% 5-fluorouracil in a sample of 49 patients with at least five AK lesions in an area of 50 cm². No studies including samples of patients with single AK lesions were eligible.
Interventions:
Cryotherapy was performed using liquid nitrogen for 20 to 40 seconds for each lesion. Treatment was repeated after two weeks in case of insufficient clearance after the first treatment. 5% 5-FU cream was applied twice daily during four weeks with a rest period of up to one week in case of inflammation.

Outcomes:
The rate of participants' complete clearance, rate of participants with an "excellent cosmetic outcome", and rate of participants with "better skin appearance" was assessed 12 weeks after the treatment.
Results (see table below):
The study showed a statistically significant lower rate of participants' complete clearance for the cryotherapy treatment group (RR: 0.71; 95%-CI: 0.54 – 0.94; GRADE: low quality). With respect to the outcome of an "excellent cosmetic outcome", no statistically significant differences were seen (RR: 0.96; 95%-CI: 0.06 -14.5; GRADE: low quality), but the authors could demonstrate a statistically significant lower proportion of participants with "better skin appearance" in the cryosurgery group when compared to the 5% 5-FU group (RR: 0.27; 95%-CI: 0.11 – 0.72; GRADE: moderate quality).
Other results and comments:
The statistically significant difference with respect to the rate of complete clearance is of uncertain clinical importance due to the small effect size (confidence interval crosses the minimal important difference threshold line of 0.75).

Question: Should Cryotherapy vs 5% 5-Fluorouracil be used in patients with multiple AK / field cancerization?
Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 5% 5-Fluorouracil	With Cryotherapy		Risk with 5% 5-Fluorouracil	Risk difference with Cryotherapy (95% CI)
Participant complete clearance (CRITICAL OUTCOME)											
49 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	23/24 (95.8%)	17/25 (68%)	**RR 0.71** (0.54 to 0.94)	**958 per 1000**	**278 fewer per 1000** (from 58 fewer to 441 fewer)
Cosmetic outcomes: excellent global cosmetic outcome (CRITICAL OUTCOME)											
46 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊕⊖⊖ LOW[1,3] due to risk of bias, imprecision	1/24 (4.2%)	1/22 (4.5%)	**RR 0.96** (0.06 to 14.5)	**42 per 1000**	**2 fewer per 1000** (from 39 fewer to 563 more)
Cosmetic outcomes: better skin appearance (IMPORTANT OUTCOME)											
49 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ MODERATE[1] due to risk of bias	14/24 (58.3%)	4/25 (16%)	**RR 0.27** (0.11 to 0.72)	**583 per 1000**	**426 fewer per 1000** (from 163 fewer to 519 fewer)

[1] Unclear allocation concealment, no blinding
[2] CI crosses MID threshold (stat. sig. difference of uncertain clinical importance)
[3] CI crosses MID threshold and line of no effect (uncertain whether there is any diffference)

4.2.3 Cryotherapy vs. 5% imiquimod

Study and patient characteristics:
Two RCTs[14, 15] compared cryotherapy with 5% imiquimod. Krawtchenko et al. performed the study (N= 75, age 57 to 88 years, mean: 73) in a sample of 51 patients with at least five AK lesions in an area of 50 cm².[14] The study by Foley et al. was conducted in a sample of 71 patients with at least 10 AK lesions at baseline (mean age: 71.5, SD 1.23).[15] No studies including samples of patients with single AK lesions were eligible.
Interventions:
Cryotherapy was performed using liquid nitrogen for 20 to 40 seconds for each lesion[14] or measuring the 10-second freeze/thaw time.[15] Treatment was repeated after two weeks in case of insufficient clearance after the first treatment[14] or at the 3, 6, and 9 month post-treatment visits.[15]
5% imiquimod was applied to the target area three times per week for 8 hours during a period of 3 to 4 weeks (first treatment cycle), followed by three to four weeks without application. A second treatment cycle was performed, if lesions were still present. In case of inflammation, a resting period of 1 week was permitted.
Outcomes:

Participants' complete clearance, "excellent cosmetic outcome" and "better skin appearance" were assessed 12 weeks after treatment,[14] withdrawals due to adverse events, "erosion / ulceration", "blister formation" and "infection" were assessed during the observational period of the study (12 months).[15]

Results (see table below):

No statistically significant differences were seen with respect to complete clearance (RR: 0.80; 95%-CI: 0.59 – 1.10; GRADE: low quality), withdrawals due to adverse events (RR: 0.49; 95%-CI: 0.10 – 2.49; GRADE: moderate quality), erosion / ulceration (RR: 1.75; 95%-CI: 0.65 – 4.71; GRADE: low quality), and rates of infection (RR: 0.49; 95%-CI: 0.05 – 5.12; GRADE: low quality). A statistically significant higher rate of blister formation was seen in the cryotherapy group (RR: 20.43; 95%-CI: 1.24 – 335.9; GRADE: low quality). Regarding cosmetic outcomes, cryotherapy had statistically significant inferior values when compared to 5% imiquimod, with respect to the rate of an "excellent cosmetic outcome" (RR: 0.05; 95%-CI: 0.01 – 0.34; GRADE: moderate quality) and "better skin appearance" (RR: 0.19; 95%-CI: 0.08 – 0.47; GRADE: moderate quality).

Other results and comments:

None.

Question: Should Cryotherapy vs 5% imiquimod be used in patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 5% imiquimod	With Cryotherapy		Risk with 5% imiquimod	Risk difference with Cryotherapy (95% CI)
Participant complete clearance (CRITICAL OUTCOME)											
51 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁◯◯ LOW[1,2] due to risk of bias, imprecision	22/26 (84.6%)	17/25 (68%)	**RR 0.8** (0.59 to 1.1)	**846 per 1000**	**169 fewer per 1000** (from 347 fewer to 85 more)
Cosmetic outcomes: excellent global cosmetic outcome (CRITICAL OUTCOME)											
51 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[1] due to risk of bias	21/26 (80.8%)	1/25 (4%)	**RR 0.05** (0.01 to 0.34)	**808 per 1000**	**767 fewer per 1000** (from 533 fewer to 800 fewer)
Cosmetic outcomes: better skin appearance (IMPORTANT OUTCOME)											
51 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[1] due to risk of bias	22/26 (84.6%)	4/25 (16%)	**RR 0.19** (0.08 to 0.47)	**846 per 1000**	**685 fewer per 1000** (from 448 fewer to 778 fewer)
Withdrawal due to AE (CRITICAL OUTCOME)											
71 (1 study)	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[3] due to risk of bias	4/35 (11.4%)	2/36 (5.6%)	**RR 0.49** (0.1 to 2.49)	**114 per 1000**	**58 fewer per 1000** (from 103 fewer to 170 more)
Minor AE: erosion/ulceration (IMPORTANT OUTCOME)											
71 (1 study)	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁◯◯ LOW[2,3] due to risk of bias, imprecision	5/35 (14.3%)	9/36 (25%)	**RR 1.75** (0.65 to 4.71)	**143 per 1000**	**107 more per 1000** (from 50 fewer to 530 more)
Minor AE: blister formation (IMPORTANT OUTCOME)											
71 (1 study)	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⨁⨁◯◯ LOW[3,4] due to risk of bias, imprecision	0/35 (0%)	10/36 (27.8%)	**RR 20.43** (1.24 to 335.9)	**0 per 1000**	-
Minor AE: infection (IMPORTANT OUTCOME)											
71 (1 study)	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁◯◯ LOW[2,3] due to risk of bias, imprecision	2/35 (5.7%)	1/36 (2.8%)	**RR 0.49** (0.05 to 5.12)	**57 per 1000**	**29 fewer per 1000** (from 54 fewer to 235 more)

[1] Unclear randomization method, high risk in performance bias (blinding)

[2] CI crosses MID threshold and line of no effect (uncertain whether there is any difference)

[3] Unclear allocation concealment, no blinding, incomplete outcome data

[4] Very wide CI

4.2.4 Cryotherapy vs. ALA-PDT

Study and patient characteristics:
One RCT[8] compared cryotherapy and 5-aminolaevulinic acid-photodynamic therapy using red light (ALA-red light PDT) in a sample of 297 patients with an age ranging from 41 to 93 years (mean: 70.6 and 70.0) and a mean number of AK lesions at baseline of 5.4 (SD 1.57; cryotherapy group) and 5.8 (SD 1.64; PDT group). No studies including samples of patients solely with single AK lesions or solely with multiple AK lesions / field cancerization were eligible.
Interventions:
Cryotherapy was performed using liquid nitrogen open spraying with a freezing time between 5 and 10 seconds. Only one cycle of cryotherapy was performed. ALA-PDT was applied using four to eight self-adhesive 5-ALA patches, each patch covering one AK lesion. Incubation time was 4 hours and illumination performed with red light (37 J/cm² at 630 +/- 3nm).
Outcomes:
The rate of participants' complete clearance was assessed 12 weeks post-treatment, skin irritation one day after the treatment.
Results (see table below):
In the cryotherapy group, a statistically significant lower rate of complete clearances was seen (RR: 0.76; 95%-CI: 0.61 to 0.96; GRADE: very low quality). Statistically significant fewer participants had a skin irritation in the cryotherapy group, when compared to the ALA-PDT group (RR: 0.27; 95%-CI: 0.16 to 0.46; GRADE: low quality).
Additional results and comments:
The statistically significant difference with respect to the rate of participants' complete clearance is of uncertain clinical importance due to the small effect size (confidence interval crosses the minimal important difference threshold line of 0.75).

Question: Should Cryotherapy vs ALA-PDT be used in patients with single AK lesions and/or multiple AK lesions / field cancerization?
Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With ALA-PDT	With Cryotherapy		Risk with ALA-PDT / Risk difference with Cryotherapy (95% CI)
Participant complete clearance (CRITICAL OUTCOME)										
297 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	86/148 (58.1%)	66/149 (44.3%)	**RR 0.76** (0.61 to 0.96)	**581 per 1000** / **139 fewer per 1000** (from 23 fewer to 227 fewer)
Skin irritation: one day after treatment (CRITICAL OUTCOME)										
297 (1 study)	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁◯◯◯ LOW[1,2] due to risk of bias, indirectness	55/148 (37.2%)	15/149 (10.1%)	**RR 0.27** (0.16 to 0.46)	**372 per 1000** / **271 fewer per 1000** (from 201 fewer to 312 fewer)

[1] Unclear allocation concealment, no blinding, incomplete outcome data
[2] Study included participants with single and multiple lesions (range 1-8 lesions)
[3] CI crosses MID threshold (stat. sig. difference of uncertain clinical importance)

4.2.5 Cryotherapy vs. MAL-PDT

Study and patient characteristics:
Four RCTs compared cryotherapy with methyl-aminolaevulinic acid-photodynamic therapy (MAL-PDT).[16-19] The studies by Kaufmann et al.[17] and Morton et al.[18] were split-patient trials with intraindividual comparisons, with a sample of 121 patients with at least 4 comparable symmetrical AK lesions on each body side and a mean age of 69 years (range 39 to 89)[17] and with a sample of 119 patients with at least 3 AK on each side and a mean age of 75 years (range: 53 to 93).[18] The study by Freeman et al.[16] included a sample of 200 participants with at least one mild-to-moderate AK lesion and a mean age of 65 years (range:

33 – 86). Szeimies et al.[19] included a sample of 202 participants with a maximum of ten AK lesions per patient and with an age range from 42 to 89 years. No studies including samples of patients solely with single AK lesions or solely with multiple AK lesions / field cancerization were eligible.

Interventions:

Cryotherapy was performed with double freeze/thaw using liquid nitrogen for 16-20 seconds with a 1 to 2 mm frozen rim outside the marked outline of the respective lesion. One or two treatments were performed within a 12 week interval, depending on the response of the lesion after the first treatment.[17, 18] Szeimies et al.,[19] performed cryotherapy with a mean freeze time of 24 ± 18 seconds. In the study by Freeman et al.,[16] a single timed freeze-thaw cycle creating a 1 to 2 mm rim of frozen tissue beyond the marked outline was performed, using the following freeze times: for lesions with a diameter < 10 mm, a mean freeze time of 12 + 13 seconds was applied, for 10 to 20 mm lesions, a mean time of 16 + 15 seconds, and for lesions > 20 mm, 26 ± 11 seconds.

MAL-PDT was applied to individual AK lesions using a methyl aminolevulinate (MAL) cream at a concentration of 16%, 1 mm thick onto the lesions and covering 5 mm of the surrounding normal tissue.[17-19] One or two treatments were performed with an interval of 12 weeks between the treatments.[17, 18] In the study by Freeman et al., two treatments with an interval of 1 week were performed.[16] One treatment for lesions on the face and scalp, and two treatments at an interval of one week for other lesions were performed by Szeimies et al.[19] Before the treatment, crusts and scales were usually removed from the lesions. All studies used occlusive dressing over the MAL cream and incubated for three hours. The following technical parameters were used: 1) type of light: red light LED; light source: Aktilite CL128; wavelength (nm): 630; energy fluence (J/cm²): 37,[17, 18] or 2) type of light: red light, wavelength (nm): 570-670, energy fluence (J/cm²): 75, intensities (mW/cm²): 50 to 250, exposure time: 10 minutes,[16] or 3) type of light: red light, wavelength (nm): 570-670, energy fluence (J/cm²): 75, intensities (mW/cm²): 70 to 200, exposure time: 10 min.[19]

Outcomes:

For this comparison, the following outcomes were assessed: Withdrawals due to adverse events during the course of the study,[16, 19] photosensitivity reaction,[17] cold exposure injury,[17] proportion of participants with an “excellent or good” cosmetic outcome as rated by the investigator at week 24,[18, 19] proportion of participants with an “excellent or good” cosmetic outcome as rated by the participant 12 or 24 weeks after the treatment,[17, 19] participant’s satisfaction (proportion of participants satisfied with the treatment) after 24 weeks,[17] participant’s preference 24 weeks after the first treatment.[18]

Results (see table below):

With respect to withdrawals due to AE, no statistically significant differences were seen (RR: 1.06; 95%-CI: 0.16 – 7.16; GRADE: very low quality), as well as with respect to the participant’s rating of the cosmetic outcome as excellent or good (RR: 0.93; 95%-CI: 0.86 – 1.01; GRADE: low quality). For photosensitivity reaction, a lower rate was seen in the cryotherapy group, when compared to the MAL-PDT group (RR: 0.01; 95%-CI: 0 – 0.15; GRADE: very low quality). For the event ‘cold exposure injury’, a higher rate was seen in the cryotherapy group (RR: 151; 95%-CI: 9.47 – 2409; GRADE: very low quality). An “excellent or good cosmetic outcome” as rated by the investigator was seen in a lower proportion of participants who were assigned to the cryotherapy group (RR: 0.84; 95%-CI: 0.74 – 0.95; GRADE: very low quality). Participants from the intraindividual split-patient trial preferred MAL-PDT over cryotherapy (RR: 0.42; 95%-CI: 0.29 – 0.63; GRADE: low quality) and a lower proportion of patients was satisfied with the cryotherapy (RR: 0.41; 95%-CI: 0.27 – 0.61; GRADE: very low quality).

Additional results and comments:

The statistically significant difference with respect to the rate of participants with a cosmetic outcome that was rated as “excellent or good” by the investigator is of uncertain clinical importance due to the small effect size (confidence interval crosses the minimal important difference threshold line of 0.75).

For methodological reasons, data from intraindividual comparisons could not be included into the meta-analyses and GRADE profiles that similarly include data from interindividual comparisons. Morton et al.[18] also reported data on “excellent or good cosmetic outcome” as rated by the investigator: in the cryotherapy group the rate was 113/119 and in the MAL-PDT group 118/119. Kaufmann et al.[17] reported data on “excellent or good cosmetic outcome” as rated by the participants: in the cryotherapy group the rate was 111/121 and in the MAL-PDT group 119/121. Data on participants’ satisfaction, participants’ preference, ‘photosensitivity reaction’ and ‘cold exposure injury’ in the GRADE evidence profile (see below) refer to split-patient studies, and therefore to a sample size of 121 and 119 patients, respectively.

Question: Should Cryotherapy vs MAL-PDT be used in patients with single AK lesions and/or patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characistics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With MAL-PDT	With Cryotherapy		Risk with MAL-PDT	Risk difference with Cryotherapy (95% CI)
Withdrawal due to AE (CRITICAL OUTCOME)											
379 (2 studies)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	2/190 (1.1%)	2/189 (1.1%)	**RR 1.06** (0.16 to 7.16)	**11 per 1000**	**1 more per 1000** (from 9 fewer to 65 more)
Cosmetic outcomes: excellent or good by investigator (CRITICAL OUTCOME)											
122 (1 study)	serious[4]	no serious inconsistency	serious[5]	serious[6]	undetected	⨁◯◯◯ VERY LOW[4,5,6] due to risk of bias, indirectness, imprecision	52/54 (96.3%)	55/68 (80.9%)	**RR 0.84** (0.74 to 0.95)	**963 per 1000**	**154 fewer per 1000** (from 48 fewer to 250 fewer)
Cosmetic outcomes: excellent or good by participant (CRITICAL OUTCOME)											
122 (1 study)	serious[4]	no serious inconsistency	serious[5]	no serious imprecision	undetected	⨁◯◯◯ LOW[4,5] due to risk of bias, indirectness	53/54 (98.1%)	62/68 (91.2%)	**RR 0.93** (0.86 to 1.01)	**981 per 1000**	**69 fewer per 1000** (from 137 fewer to 10 more)
Participants satisfaction: satisfied with treatment (CRITICAL OUTCOME)											
242 (1 study)	very serious[7]	no serious inconsistency	serious[8]	no serious imprecision	undetected	⨁◯◯◯ VERY LOW[7,8] due to risk of bias, indirectness	59/121 (48.8%)	24/121 (19.8%)	**RR 0.41** (0.27 to 0.61)	**488 per 1000**	**288 fewer per 1000** (from 190 fewer to 356 fewer)
Participants preference (CRITICAL OUTCOME)											
238 (1 study)	serious[9]	no serious inconsistency	serious[10]	no serious imprecision	undetected	⨁◯◯◯ LOW[9,10] due to risk of bias, indirectness	59/119 (49.6%)	25/119 (21%)	**RR 0.42** (0.29 to 0.63)	**496 per 1000**	**288 fewer per 1000** (from 183 fewer to 352 fewer)
Minor AE: photosensitivity reaction (IMPORTANT OUTCOME)											
242 (1 study)	very serious[7]	no serious inconsistency	serious[8]	no serious imprecision	undetected	⨁◯◯◯ VERY LOW[7,8] due to risk of bias, indirectness	52/121 (43%)	0/121 (0%)	**RR 0.01** (0 to 0.15)	**430 per 1000**	**425 fewer per 1000** (from 365 fewer to 430 fewer)
Minor AE: cold exposure injury (IMPORTANT OUTCOME)											
242 (1 study)	very serious[7]	no serious inconsistency	serious[8]	serious[11]	undetected	⨁◯◯◯ VERY LOW[7,8,11] due to risk of bias, indirectness, imprecision	0/121 (0%)	75/121 (62%)	**RR 151** (9.47 to 2408.85)	**0 per 1000**	-

[1] No blinding, incomplete outcome data, 1 study with baseline differences
[2] Both studies included participants with single and multiple lesions (inclusion criteria 4-8 lesions), and more than 50% of patients had single lesions
[3] CI crosses MID threshold and line of no effect (uncertain whether there is any diffference)
[4] No blinding, incomplete outcome data
[5] Study included participants with single and multiple lesions (inclusion criteria 4-8 lesions), and more than 60% of patients had single lesions
[6] CI crosses MID threshold (stat. sig. difference of uncertain clinical importance)
[7] Unclear randomization method, no blinding, incomplete outcome data, selective reporting
[8] Study included participants with single and multiple lesions (inclusion criteria 4-8 lesions)
[9] Unclear randomization method and allocation concealment, no blinding
[10] study included participants with at least 3 AK in each treated field
[11] Very wide CI

4.2.6 Additional reasoning and recommendations

Cryotherapy is a widely used and long established treatment option and experts confirm a very good clinical efficacy for single lesions. The low costs (resource use), availability and good compliance (due to the treatment mode) are further arguments for the use of cryotherapy. Based on these considerations the expert group felt that a strong

recommendation for patients with single AK lesions is well justified. For the use of cryotherapy for discrete lesions in immunosuppressed patients, analogue considerations led to the weak recommendation.

Recommendation	Strength of recommendation	Percentage of agreement
We recommend using cryotherapy in patients with single AK lesions.	↑↑	≥75%
We suggest using cryotherapy in patients with multiple lesions, especially for multiple discrete lesions Cryotherapy is not suitable for the treatment of field cancerization.	↑	≥90%
We suggest using cryotherapy in immunosuppressed patients, especially for single lesions or multiple discrete lesions. Cryotherapy is not suitable for the treatment of field cancerization.	↑	≥75%

4.3 Carbon dioxide (CO_2) laser and Er:YAG laser

4.3.1 Carbon dioxide (CO_2) laser vs. placebo

No data were eligible for this comparison.

4.3.2 Er:YAG laser vs. placebo

No data were eligible for this comparison.

4.3.3 Carbon dioxide (CO_2) laser vs. 5% 5-fluorouracil (5% 5-FU)

For details on the study and participants' characteristics and on the results see chapter 4.6.4 (5% 5-fluorouracil (5% 5-FU) vs. carbon dioxide (CO_2) laser).

One RCT[20] compared carbon dioxide (CO_2) laser resurfacing with 5% 5-fluorouracil (5-FU), showing no statistically significant differences with respect to the mean percent reduction of AK lesion counts (GRADE: very low quality) and the number of withdrawals due to adverse events (GRADE: very low quality).

4.3.4 Carbon dioxide (CO_2) laser vs. ALA-PDT

For details on the study and participants' characteristics and on the results see chapter 4.11.3 (5-aminolevulinic acid (ALA)-photodynamic therapy (PDT) vs. carbon dioxide (CO_2) laser).

One intraindividual (split-patient) RCT[10] compared CO_2 laser with ALA-PDT, showing no statistically significant difference in the participants' preference (GRADE: very low quality).

4.3.5 Additional reasoning and recommendations

Experts evaluate CO_2 laser as an effective treatment with respect to long-term efficacy. Efficacy and safety of CO_2 laser depend on the user's experience due to a lack of

standardization of its application. Most common risks of using CO_2 laser are infections, scarring, and hyper-/hypopigmentation of the treated areas. Immunosuppressed patients are more susceptible to skin infections, and thus experts suggest not using CO_2 laser for the treatment of AK in immunosuppressed patients; in spot areas CO_2 laser might still be used.
For Er:YAG laser, experts decided to adapt the recommendations made for CO_2 laser. Two aspects should be considered: Er:YAG laser does not penetrate the epidermis as well as CO_2 laser does, hence it is not suitable for the treatment of hyperkeratotic lesions; furthermore Er:YAG laser does not provide coagulation and therefore the risk of bleeding is higher.

Recommendation	**Strength of recommendation**	**Percentage of agreement**
We cannot make a recommendation with respect to CO_2 laser and Er:YAG laser in patients with single AK lesions.	0	≥75%
We suggest using CO_2 laser or Er:YAG laser in patients with multiple AK lesions or field cancerization.	↑	≥50%*
We suggest not to use CO_2 laser or Er:YAG laser in immunosuppressed patients.	↓	≥75%
**Experts who did not agree to this recommendation voted for making no recommendation (0) for the use of this intervention in patients with multiple lesions or field cancerization.*		

4.4 3% diclofenac in 2.5% hyaluronic acid (HA) gel

4.4.1 3% diclofenac in 2.5% HA gel vs. vehicle (immunocompetent participants)

Study and patient characteristics:
Four RCTs compared 3% diclofenac in 2.5% hyaluronic acid gel vs. 2.5% hyaluronic acid gel in samples of immunocompetent patients.[11, 21-23] Gebauer et al.[21] included a sample of 150 participants with a mean age of 68 years (range: 27 to 87). Baseline AK lesion counts were 9.8 (SD 6.6) in the diclofenac group and 11.3 (SD 7.7) in the vehicle group[21]. Rivers et al.[22] studied the interventions in a sample of 195 participants with an age range from 34 to 90 years (mean ages in the different intervention groups: 65 to 70 years). The Solaraze study 2[11] encompassed 108 participants and the study by Wolf et al.[23] 118 participants, no data concerning the age of the participants were presented.[11] The participants had at least 5 AK lesions in the studies conducted by Rivers et al.,[22] Wolf et al.,[23] and in the Solaraze study 2.[11] No studies including samples of participants solely with single AK lesions were available.
Interventions:
In the studies, 0.25-0.5g of 3% diclofenac in 2.5% hyaluronic acid gel were applied twice daily with 6 hours between the treatments for a period of 60 to 90 days. The vehicle control intervention was performed with 2.5% hyaluronic acid gel twice daily for 60 to 90 days.
Outcomes:
Wolf et al.[23] and Rivers et al.[22] assessed the rate of Participant global improvement index (PGII) rated as 'completely improved' and the rate of Investigator global improvement index (IGII) rated as 'completely improved' 30 days after the treatment. The mean reduction of lesion counts at the 30 days follow up visit was assessed by Gebauer et al.[21] and Rivers et al.,[22] Gebauer et al.,[21] Rivers et al.,[22] Wolf et al.[23] and the authors of the Solaraze study 2[11] assessed the rate of complete clearance ("participant complete resolution rate", "rate of participants with a target lesion number score of 0", "complete clearing of lesions") at 30 days post-treatment.
Results (see table below):
When data from different treatment durations (60, 90 days) and different treatment areas are pooled, 3% diclofenac in 2,5% hyaluronic acid shows a statistically significant higher efficacy

than its vehicle alone, with respect to the rate of participants' complete clearance (RR: 2.35; 95%-CI: 1.65 - 3.34; GRADE: moderate quality), the mean reduction in AK lesion counts (mean difference: 3.00; 95%-CI: 1.64 - 4.36; GRADE: low quality), the rate of participants with a Participant global improvement index (PGII) rated as 'completely improved' (RR: 2.57; 95%-CI: 1.51 - 4.36; GRADE: moderate quality), and the rate of participants with an Investigator global improvement index (IGII) rated as 'completely improved' (RR: 2.65; 95%-CI: 1.60 - 4.39; GRADE: moderate quality).

Additional results and comments:

The results for the rate of complete clearance and mean reduction in lesions count refer to pooled data from trials assessing different treatment periods (60 and 90 days) and different affected areas (forehead, face, arm/forearm, back of the hand). Data concerning different treatment areas are heterogeneous[11, 22, 23] and subgroup analyses are partially underpowered to show statistically significant effects of diclofenac.[11, 23] With respect to the mean reduction in lesion counts, the pooled data show a statistically significant superiority of diclofenac versus its vehicle of unclear clinical importance (the confidence interval crosses the minimal clinical important difference threshold of 0+½ SD of the mean from the control group).

Question: Should 3% diclofenac in 2.5% HA vs 2.5% HA (vehicle) be used in patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 2.5% HA (vehicle)	With 3% diclofenac in 2.5% HA		Risk with 2.5% HA (vehicle)	Risk difference with 3% diclofenac in 2.5% HA (95% CI)
Investigator Global Improvement Indices-completely improved (CRITICAL OUTCOME)											
214 (2 studies)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[1] due to risk of bias	16/108 (14.8%)	42/106 (39.6%)	RR 2.65 (1.6 to 4.39)	148 per 1000	244 more per 1000 (from 89 more to 502 more)
Participant Global Improvement Indices-completely improved (CRITICAL OUTCOME)											
214 (2 studies)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[1] due to risk of bias	15/108 (13.9%)	38/106 (35.8%)	RR 2.57 (1.51 to 4.36)	139 per 1000	218 more per 1000 (from 71 more to 467 more)
Participant complete clearance (all lesions) (CRITICAL OUTCOME)											
472 (4 studies)	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[2] due to risk of bias	35/240 (14.6%)	81/232 (34.9%)	RR 2.35 (1.65 to 3.34)	146 per 1000	197 more per 1000 (from 95 more to 341 more)
Mean reduction of lesion counts, 30 day follow-up (CRITICAL OUTCOME; Better indicated by lower values)											
247 (2 studies)	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⨁⨁◯◯ LOW[1,3] due to risk of bias, imprecision	126	121	-		The mean mean reduction of lesion counts, 30 day follow-up in the intervention groups was 3 higher (1.64 to 4.36 higher)

[1] unclear randomisation methods in both studies

[2] unclear randomisation methods in all studies, no data on methodology for Solaraze study 2 (data extracted from product insert information)

[3] CI crosses MID treshold (0,5 * SD = 2,2) (stat. sig. difference of uncertain clinical importance)

4.4.2 3% diclofenac in 2.5% HA vs. vehicle (immunosuppressed participants)

Study and patient characteristics:

One RCT[24] compared 3% diclofenac in 2.5% hyaluronic acid gel with 2.5% hyaluronic acid gel (vehicle) in a sample of immunosuppressed organ transplant recipients. 32 organ transplant recipients (kidney, liver, heart transplantation within three years and stable status) with at least 3 AK lesions in a contiguous area of 50 cm² were included. Mean age of the participants was between 62 and 72 years in the different transplant type groups. No data concerning the mean number of AK lesions per participant were presented.

Interventions:

3% diclofenac sodium gel in 2.5% hyaluronic acid gel or vehicle was applied to a predefined treatment area twice daily for 16 weeks.

Outcomes:
Ulrich et al.[24] reported the rate of complete and partial clearance 4 weeks after the 16 weeks of treatment.
Results (see table below):
No statistically significant differences between the active and vehicle arm were found with respect to the rate of complete clearance (RR: 5.78; 95%-CI: 0.38 - 87.35; GRADE: very low quality) and the rate of partial clearance (RR: 3.55; 95%-CI: 0.57 - 21.94; GRADE: low quality).
Additional results and comments:
The results show a trend towards superiority of diclofenac, but due to the very small sample size, especially of the vehicle-treated group (n=6), results are not statistically significant.

Question: Should 3% diclofenac in 2.5% HA vs 2.5% HA (vehicle) be used in immunosuppressed patients with AK?
Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With 2.5% HA (vehicle)	With 3% diclofenac in 2.5% HA		Risk with 2.5% HA (vehicle) / Risk difference with 3% diclofenac in 2.5% HA (95% CI)
Participant complete clearance (CRITICAL OUTCOME)										
28 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	undetected	⨁◯◯◯ VERY LOW[1,2] due to risk of bias, imprecision	0/6 (0%)	9/22 (40.9%)	RR 5.78 (0.38 to 87.35)	0 per 1000 / -
Participant partial (>75%) clearance (CRITICAL OUTCOME)										
28 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⨁⨁◯◯ LOW[1,3] due to risk of bias, imprecision	1/6 (16.7%)	13/22 (59.1%)	RR 3.55 (0.57 to 21.94)	167 per 1000 / 425 more per 1000 (from 72 fewer to 1000 more)

[1] unclear randomization method and allocation concealment, incomplete outcome data
[2] CI crosses MID threshold and line of no effect, wide CI (uncertain whether there is any difference)
[3] CI crosses MID threshold and line of no effect (uncertain whether there is any difference)

4.4.3 3% diclofenac gel vs. 5% imiquimod (single AK lesions)

Study and patient characteristics:
Two RCTs compared 3% diclofenac gel with 5% imiquimod.[25, 26] Akarsu et al.[25] included a sample of 41 participants with one AK lesion each, mean age was 65.8 years. Kose et al.[26] included participants with at least three AK lesions, therefore the results from this study (Investigator and Participant global improvement indices, minor adverse events) are reported separately: see chapter 4.4.4 (3% diclofenac gel vs. 5% imiquimod: multiple AK lesions / field cancerization).
Interventions:
3% diclofenac sodium gel in 2.5% hyaluranon gel was used twice daily for 12 weeks; imiquimod 5% cream was used twice weekly for 16 weeks.
Outcomes:
Akarsu et al.[25] reported the rate of complete clearance and the rate of withdrawals due to adverse events.
Results (see table below):
No statistically significant differences were found with respect to the rate of complete clearance (RR: 0.95; 95%-CI: 0.27 - 3.30; GRADE: low quality).
Additional results and comments:
Effect size and confidence interval concerning the rate of withdrawals due to adverse events could not be calculated due to no events in both groups.

Question: Should 3% diclofenac in 2.5% HA vs 5% imiquimod be used in patients with single AK lesions?
Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 5% imiquimod	With 3% diclofenac in 2.5% HA		Risk with 5% imiquimod	Risk difference with 3% diclofenac in 2.5% HA (95% CI)
Participant complete clearance (at week 24) (CRITICAL OUTCOME)											
41 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ **LOW**[1,2] due to risk of bias, imprecision	4/20 (20%)	4/21 (19%)	**RR 0.95** (0.27 to 3.3)	**200 per 1000**	**10 fewer per 1000** (from 146 fewer to 460 more)
Withdrawal due to AE (CRITICAL OUTCOME)											
41 (1 study)	serious[1]	no serious inconsistency	no serious indirectness		undetected	See comment	0/20 (0%)	0/21 (0%)	-	See comment	-

[1] unclear randomization methods, only evaluator blinded
[2] wide CI, CI crosses MID threshold and line of no effect

4.4.4 3% diclofenac gel vs. 5% imiquimod (multiple AK lesions / field cancerization)

Study and patient characteristics:
Two RCTs compared 3% diclofenac gel with 5% imiquimod.[25, 26] Kose et al.[26] comprised a sample of 49 participants with a mean age of 56.4 years (range: 41-82) and with at least three AK lesions on the face and scalp. 79% in the diclofenac group and 76% in the imiquimod group were rated as being moderately ("many visible, small, moderately thick lesions or a few large thick, rough scaly lesions") or severely affected ("many thick, hyperkeratotic lesions which are clearly visible and palpable with well-defined borders"). Akarsu et al.[25] included participants with only one AK lesion, therefore the results from this study (rate of complete clearance, withdrawals due to adverse events) are reported separately: see chapter 4.4.3 (3% diclofenac in 2.5% hyaluronic acid vs. 5% imiquimod: single lesions).
Interventions:
3% diclofenac gel was applied to the AK lesions once daily for 12 weeks. 5% imiquimod cream was applied to the AK lesions three times a week.
Outcomes:
Kose et al.[26] assessed the rate of participants rated as 'completely improved' on the Investigator global improvement index (IGII) and on the Participant global improvement index (PGII) at the end of the 90 days treatment period. Furthermore, the rate of minor adverse events (erythema, crusting, scaling) during the study period was assessed.
Results (see table below):
No statistically significant differences were found with respect to the rate of participants with the Investigator global improvement index (IGII) rated as 'completely improved' (RR: 0.52; 95%-CI: 0.15 - 1.85; GRADE: very low quality) and with respect to the rate of participants with the Participant global improvement index (PGII) rated as 'completely improved' (RR: 1.22; 95%-CI: 0.48 - 3.10; GRADE: very low quality). With respect to the minor adverse events that were assessed during the study period, no statistically significant differences were seen: erythema (RR: 1.15; 95%-CI: 0.60 - 2.19; GRADE: very low quality), crusting (RR: 1.82; 95%-CI: 0.61 - 5.44; GRADE: very low quality), and scaling (RR: 0.69; 95%-CI: 0.13 - 3.80; GRADE: very low quality).
Additional results and comments:
None.

Question: Should 3% diclofenac in 2.5% HA vs 5% imiquimod be used in patients with multiple AK lesions / field cancerization?
Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 5% imiquimod	With 3% diclofenac in 2.5% HA		Risk with 5% imiquimod	Risk difference with 3% diclofenac in 2.5% HA (95% CI)
Investigator Global Improvement Indices-Complete improvement (CRITICAL OUTCOME)											
49 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⊟⊟⊟⊟ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	6/25 (24%)	3/24 (12.5%)	**RR 0.52** (0.15 to 1.85)	**240 per 1000**	**115 fewer per 1000** (from 204 fewer to 204 more)
Participant Global Improvement Indices-Complete improvement (CRITICAL OUTCOME)											
49 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⊟⊟⊟⊟ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	6/25 (24%)	7/24 (29.2%)	**RR 1.22** (0.48 to 3.1)	**240 per 1000**	**53 more per 1000** (from 125 fewer to 504 more)
Minor AE: Crusting (IMPORTANT OUTCOME)											
49 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⊟⊟⊟⊟ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	4/25 (16%)	7/24 (29.2%)	**RR 1.82** (0.61 to 5.44)	**160 per 1000**	**131 more per 1000** (from 62 fewer to 710 more)
Minor AE: Scaling (IMPORTANT OUTCOME)											
49 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⊟⊟⊟⊟ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	3/25 (12%)	2/24 (8.3%)	**RR 0.69** (0.13 to 3.8)	**120 per 1000**	**37 fewer per 1000** (from 104 fewer to 336 more)
Minor AE: Erythema (IMPORTANT OUTCOME)											
49 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⊟⊟⊟⊟ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	10/25 (40%)	11/24 (45.8%)	**RR 1.15** (0.6 to 2.19)	**400 per 1000**	**60 more per 1000** (from 160 fewer to 476 more)

[1] open study, randomization methods unclear
[2] no additional information on patient characteristics regarding type of AK, (inclusion of patients with >= 3 lesions --> probably single and multiple lesions)
[3] wide CI, CI crosses MID threshold and line of no effect

4.4.5 3% diclofenac in 2.5% HA vs. 0.5% 5-fluorouracil + 10% SA

For details on the study and participants' characteristics and the results please see chapter 4.13.2 (comparison 0.5% 5-fluorouracil + 10% SA vs. 3% diclofenac in 2.5% HA).

One RCT[12] compared 0.5% 5-fluorouracil in 10% salicylic acid (SA) with 3% diclofenac in 2.5% hyaluronic acid (HA) in a sample of 372 participants. 0.5% 5-fluorouracil in combination with 10% salicylic acid was statistically significantly more effective than diclofenac 3% in hyaluronic acid with respect to the rate of complete clearance (GRADE: low quality), the rate of participant's global assessment as "good/very good" (GRADE: very low quality) and the rate of physician's global assessment of the clinical improvement as "good/very good" (GRADE: very low quality). In the 0.5% 5-fluorouracil in 10% salicylic acid group, a statistically significantly higher rate of minor adverse events with respect to application-site irritation (GRADE: low quality), treatment emergent adverse events (GRADE: very low quality) and administration site reaction (GRADE: low quality) was seen. No statistically significant difference with respect to the rate of infections and infestations was seen (GRADE: very low quality).

Additional results and comments:

The statistically significant differences with respect to the rate of physician's and participant's global assessment as "good/very good" as well as with respect to the rate of treatment emergent adverse events are of uncertain clinical importance due to the small effect size (confidence interval crosses the minimal important difference threshold line).

4.4.6 Additional reasoning and recommendations

Experts perceive the long-term efficacy of 3% diclofenac in 2.5% hyaluronic acid as much poorer than long-term efficacy of other topical treatments. Diclofenac might be more effective in certain areas (e.g. face) than in others. Experts also perceive that the treatment duration of 60 to 90 days with twice daily use imposes a negative impact on the practicability and might affect the adherence, although there is some contradictory evidence to that from a randomized trial.

Recommendation	Strength of recommendation	Percentage of agreement
We cannot make a recommendation with respect to 3% diclofenac in 2.5% hyaluronic acid gel for patients with single AK lesions.	0	≥75%
We suggest using 3% diclofenac in 2.5% hyaluronic acid gel in patients with multiple AK lesions or field cancerization.	↑	≥75%
We cannot make a recommendation with respect to 3% diclofenac in 2.5% hyaluronic acid gel for immunosuppressed patients.	0	≥90%

4.5 0.5% 5-fluorouracil (0.5% 5-FU)

4.5.1 0.5% fluorouracil vs. vehicle

Study and patient characteristics:
Three studies[27-29] provided data for the comparison of 0.5% 5-fluorouracil with vehicle, with two studies containing a two week and a four week treatment arm,[27, 28] and one study reporting on a one-week treatment.[29] One hundred thirty-six participants with at least 5 AK lesions (mean number of AK lesions in the various treatment groups ranging from 14.6 to 15.8) were included into the study by Jorizzo et al.[27] No data on the age were provided. Weiss et al.[28] included a sample of 119 participants with a mean of 14.1 to 16.4 AK lesions and a mean age between 62.7 and 63.6 years (range 39-89). Jorizzo et al.[29] included a sample of 144 patients with at least 5 AK lesions and a mean age of 62.6 years. No studies including participants with single AK lesions were eligible.
Interventions:
0.5% fluorouracil cream or its vehicle was applied once daily to the affected areas for one, two or four weeks.
Outcomes:
The rate of complete clearance and mean reduction in AK lesion counts was assessed four weeks after completing the treatment.[27-29]
Results (see table below):
The rate of complete clearance from all AK lesions was statistically significantly higher in the 0.5% fluorouracil group than in the placebo group (RR: 8.86; 95%-CI: 3.67 - 21.40; GRADE: low quality). The mean reduction in lesion counts was only assessed for one week treatment, showing a statistically significant higher reduction for 0.5% 5-fluorouracil (mean difference: 5.40; 95%-CI: 2.94 - 7.86; GRADE: high quality.)
Additional results and comments:
Data for complete clearance were pooled from one, two and four week treatment. Data on the mean reduction in lesion counts only refer to a one week treatment.

Question: Should 0.5% 5-fluorouracil vs vehicle be used in patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Vehicle	With 0.5% 5-fluorouracil		Risk with Vehicle	Risk difference with 0.5% 5-fluorouracil (95% CI)
Participant complete clearance (CRITICAL OUTCOME)											
522 (3 studies)	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊏⊏⊏⊏ LOW[1] due to risk of bias	3/196 (1.5%)	99/326 (30.4%)	RR 8.86 (3.67 to 21.4)	15 per 1000	120 more per 1000 (from 41 more to 312 more)
Reduction in lesion counts (CRITICAL OUTCOME; Better indicated by higher values)											
142 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊏⊏⊏⊏ HIGH	70	72	-		The mean reduction in lesion counts in the intervention groups was 5.40 higher (2.94 to 7.86 higher)

[1] high risk in performance bias (blinding), unclear randomization, and selective reporting

4.5.2 0.5% fluorouracil vs. 5% fluorouracil

Study and patient characteristics:

One intraindividual split-patient RCT[30] compared different concentrations of fluorouracil cream (0.5% vs. 5%). The study comprised 21 patients with a mean age of 70.4 years and at least six visible or palpable AK lesions (mean number of AK lesions: 21.7). No studies including a sample of patients with single AK lesions were eligible.

Interventions:

Fluorouracil cream at the two concentrations was applied to the AK lesions for four weeks. The 0.5% concentration was used once-daily, the 5% twice-daily. When needed, sunscreen/moisturizer was provided within the study. Due to irritation and other adverse events, the mean duration of the treatment was 19 days (range 9 – 28).

Outcomes:

The authors of the study[30] assessed participants' preference at the end of the four week posttreatment period, and minor adverse events (erythema, erosion, and pain) during the study period.

Results (see table below):

The participants of the trial preferred the 0.5% fluorouracil concentration to the 5% concentration (RR: 5.67; 95%-CI: 1.96 - 16.35; GRADE: moderate quality). No statistically significant differences were found with respect to the minor adverse events erythema (RR: 1.00; 95%-CI: 0.91 - 1.09; GRADE: moderate quality), erosion (RR: 0.85; 95%-CI: 0.68 - 1.07; GRADE: low quality), and pain (RR: 0.75; 95%-CI: 0.40 - 1.39; GRADE: low quality).

Additional results and comments:

The efficacy with respect to the rate of complete clearance was 43% in both study groups. With respect to the mean change of lesion counts from baseline to the end of the study, the 0.5% fluorouracil concentration had a higher efficacy. Due to missing data concerning N (sample size used in the analysis) and the standard deviation, these data could not be integrated into this evaluation.

Question: Should 0.5% 5-FU vs 5% 5-FU be used in patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With 5% 5-FU	With 0.5% 5-FU		Risk with 5% 5-FU / Risk difference with 0.5% 5-FU (95% CI)
Participants preference (CRITICAL OUTCOME)										
40 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊟⊟⊟⊟ MODERATE[1] due to risk of bias	3/20 (15%)	17/20 (85%)	**RR 5.67** (1.96 to 16.35)	**150 per 1000** / **701 more per 1000** (from 144 more to 1000 more)
Minor AE: erythema (IMPORTANT OUTCOME)										
42 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊟⊟⊟⊟ MODERATE[1] due to risk of bias	21/21 (100%)	21/21 (100%)	**RR 1.00** (0.91 to 1.09)	**1000 per 1000** / **0 fewer per 1000** (from 90 fewer to 90 more)
Minor AE: erosion (IMPORTANT OUTCOME)										
42 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊟⊟⊟⊟ LOW[1,2] due to risk of bias, imprecision	20/21 (95.2%)	17/21 (81%)	**RR 0.85** (0.68 to 1.07)	**952 per 1000** / **143 fewer per 1000** (from 305 fewer to 67 more)
Minor AE: pain (IMPORTANT OUTCOME)										
42 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊟⊟⊟⊟ LOW[1,2] due to risk of bias, imprecision	12/21 (57.1%)	9/21 (42.9%)	**RR 0.75** (0.4 to 1.39)	**571 per 1000** / **143 fewer per 1000** (from 343 fewer to 223 more)

[1] selective reporting (no exact data for clearance rated); performance bias, allocation concealment unclear

[2] CI crosses MID threshold and line of no effect

4.5.3 0.5% 5 fluorouracil vs. ALA-PDT

For details on the study and participants' characteristics and the results please see chapter 4.11.4 (comparison 5-aminolaevulinic acid-photodynamic therapy (ALA-PDT) vs. 0.5% 5-fluorouracil).

One RCT[31] compared 0.5% fluorouracil with aminolaevulinic acid (ALA)-photodynamic therapy (PDT), using two different light sources (blue light in one group and pulsed dye laser in another study group).
The following results refer to a comparison of 0.5% fluorouracil with the pooled data from the ALA-PDT arms (blue light and pulsed dye laser). No statistically significant differences were seen with respect to the rate of complete clearance (GRADE: very low quality), partial clearance (GRADE: very low quality), withdrawals due to adverse events (GRADE: very low quality), improvement in global response (GRADE: very low quality), improvement in tactile roughness (GRADE: very low quality), and improvement in mottled hyperpigmentation (GRADE: very low quality).
The efficacy of the blue light ALA-PDT was higher than the efficacy of pulsed dye laser ALA-PDT with respect to the rate of complete and partial clearance.[31] Nevertheless, in this study, separate analyses of the different light sources vs. 0.5% fluorouracil did not show statistically significant differences with respect to the rate of complete and partial clearance, withdrawals due to adverse events, improvement in the global response, tactile roughness and mottled hyperpigmentation.

4.5.4 Additional reasoning and recommendations

For patients with single AK lesions, indirect evidence from the good data on the efficacy of 0.5% 5-FU in multiple lesions patients was drawn to make a weak recommendation; additionally with regards to the evidence for the multiple lesions treatment, experts highlighted data from a network analysis showing the good efficacy of 5-FU compared to the other interventions for complete clearance.[32]

Recommendation	Strength of recommendation	Percentage of agreement
We suggest using 0.5% fluorouracil in patients with single AK lesions.	↑	≥75%
We recommend using 0.5% fluorouracil in patients with multiple AK lesions or field cancerization.	↑↑	≥50%*
We cannot make a recommendation with respect to 0.5% fluorouracil for immunosuppressed patients.	0	≥75%
** Experts who did not agree voted for making a weak recommendation (↑) for the use of 0.5% 5-fluorouracil in patients with multiple lesions or field cancerization.*		

4.6 5% 5-fluorouracil (5% 5-FU)

4.6.1 5% 5-fluorouracil vs. vehicle

No data were eligible for this comparison.

4.6.2 5% 5-fluorouracil vs. 0.5% 5-fluorouracil

For details on the study and participants' characteristics and on the results please see comparison 4.5.2 (0.5% fluorouracil vs. 5% fluorouracil).

One intraindividual split-patient RCT[30] compared different concentrations of fluorouracil cream (0.5% vs. 5%). The participants of the trial preferred the 0.5% fluorouracil concentration to the 5% concentration (GRADE: moderate quality). No statistically significant differences were found with respect to the minor adverse events erythema (GRADE: moderate quality), erosion (GRADE: low quality), and pain (GRADE: low quality).

4.6.3 5% 5-fluorouracil vs. cryotherapy

For details on the study and participants' characteristics and the results see comparison 4.2.2 (cryotherapy vs. 5% 5-fluorouracil).

One RCT[14] compared 5% 5-fluorouracil and cryotherapy, showing a statistically significant superiority of 5% 5-FU with respect to complete clearance (small effect size, uncertain clinical importance; GRADE: low quality) and the cosmetic outcome of "better skin appearance" (GRADE: moderate quality). No difference was seen with respect to the "excellent cosmetic outcome" (GRADE: low quality).

4.6.4 5% 5-fluorouracil (5% 5-FU) vs. carbon dioxide (CO_2) laser

Study and patient characteristics:
One RCT[20] compared carbon dioxide (CO_2) laser resurfacing with 5% 5-fluorouracil (5-FU) in a sample of 17 patients with an age ranging from 54 to 91 years (mean: 72.8) and a mean number of AK lesions at baseline of 61.8 (SD 22.4; 5% 5-FU group) and 78.0 (SD 29.2; CO_2 laser group). No studies including a sample of patients with single AK lesions were available.
Interventions:

CO_2 laser resurfacing was performed under local anesthesia with 2 passes. The first pass was made at a setting of 6 W, the second pass at 5W. During one month before and three weeks after the procedure, participants applied 0.05% tretinoin to the face at night. Two days before and through postoperative day ten, the participants were instructed to use valacyclovir hydrochloride, 500 mg twice daily. After the procedure, patients received an occlusive dressing and ciprofloxacin, 500 mg twice per day, for infection prophylaxis. Acetaminophen with or without hydrocodone bitartrate was provided as needed for pain. 5% 5-fluorouracil cream was self-administered twice daily for a time period of 3 weeks. After the 3 weeks of treatment, a low-potency corticosteroid preparation was used for 1 to 2 weeks.
All participants were instructed to use sunscreen and apply 0.05% tretinoin cream after the treatment.
Outcomes:
For this comparison, the mean percent reduction in lesion counts from baseline to the 3 months follow-up visit and withdrawals due to adverse events were assessed.
Results (see table below):
With respect to the mean percent reduction of the AK lesion counts, no statistically significant differences were seen between 5% 5-FU and CO_2 laser (mean difference -8.8%; 95%-CI: -20.7% - 3.16%; GRADE: very low quality). No statistically significant differences were seen regarding the number of withdrawals due to AE (RR: 0.18; 95%-CI: 0.01 - 3.27; GRADE: very low quality).
Additional results and comments: None.

Question: Should 5% 5-FU vs CO2 laser be used in patients with multiple AK lesions / field cancerization?
Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)	Relative effect (95% CI)	Anticipated absolute effects	
							With CO2 laser / With 5% 5-FU		Risk with CO2 laser	Risk difference with 5% 5-FU (95% CI)
Mean percentage of reduction of lesion counts (CRITICAL OUTCOME; Better indicated by lower values)										
14 (1 study)	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊟⊟⊟⊟ **VERY LOW**[1,2] due to risk of bias, imprecision	6 / 8	-		The mean mean percentage of reduction of lesion counts in the intervention groups was **8.8 lower** (20.76 lower to 3.16 higher)
Withdrawal due to AE (CRITICAL OUTCOME)										
17 (1 study)	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊟⊟⊟⊟ **VERY LOW**[1,2] due to risk of bias, imprecision	2/8 (25%) / 0/9 (0%)	**RR 0.18** (0.01 to 3.27)	**250 per 1000**	**205 fewer per 1000** (from 248 fewer to 567 more)

[1] Unclear randomization method and allocation concealment, no blinding, incomplete outcome data, very low number of participants
[2] CI crosses MID threshold and line of no effect (uncertain whether there is any difference)

4.6.5 5% 5-fluorouracil vs. 5% imiquimod

For details on the study and participants' characteristics and on the results please see comparison 4.9.6 (5% imiquimod vs. 5% fluorouracil).

Two RCTs compared 5% 5-fluorouracil and 5% imiquimod.[14, 33] With respect to the rate of complete clearance, no statistically significant difference between the interventions (GRADE: very low quality). 5% imiquimod was significantly more frequently associated with an 'excellent' cosmetic outcome as rated by the investigator (GRADE: low quality) and with a normal skin surface (GRADE: low quality). The statistically significant difference with respect to the rate of participants with 'normal skin surface' is of uncertain clinical importance due to the small effect size (confidence interval crosses the minimal important difference threshold line and touches the line of no effect). Concerning the withdrawals due to adverse events, no effect estimate could be calculated (no events in both study groups).

4.6.6 Additional reasoning and recommendations

The weak recommendation for using 5% 5-fluorouracil cream in patients with single and multiple AK lesions and patients with field cancerization is based on clinical long-term experience through wide-spread use in many countries and the non-inferiority of topical 5% 5-FU with respect to head-to-head comparison with imiquimod 5%, cryotherapy and CO_2 laser.
With respect to immunosuppressed patients, the weak recommendation is similarly based on clinical long-term experience through the wide-spread use in many countries. Additionally, there is a good expert agreement that the cytotoxic mechanism of action without direct modulation of the immune system is safer for the use in immunosuppressed patients than e.g. imiquimod.

Recommendation	**Strength of recommendation**	**Percentage of agreement**
We suggest using 5% fluorouracil in patients with single AK lesions.	↑	≥50%*
We suggest using 5% fluorouracil in patients with multiple AK lesions or field cancerization.	↑	≥50%**
We suggest using 5% fluorouracil in immunosuppressed patients.	↑	≥75%
** Experts who did not agree voted for making a strong recommendation (↑↑) or no recommendation (0) for the use of 5% 5-fluorouracil in patients with single AK lesions.*		
*** Experts who did not agree voted for making a strong recommendation (↑↑) for the use of 5% 5-fluorouracil in patients with multiple lesions or field cancerization.*		

4.7 2.5% Imiquimod

4.7.1 2.5% imiquimod vs. vehicle

Study and patient characteristics:
One RCT[34] compared a 2.5% concentration of imiquimod with its vehicle in a sample of 319 participants with five to 20 visible or palpable AK lesions within a field of 25cm². Participants had a mean number of 10.9 and 11.3 AK lesions (2.5% imiquimod and vehicle group) and a mean age of 64.3 years in both groups. No studies including participants with single AK lesions were eligible.
Interventions:
Up to 0.25g of 2.5% imiquimod or vehicle were applied to the treatment area once daily overnight (approximately eight hours, then washed off) during two weeks. After a rest period of two weeks, another two week treatment cycle was performed.
Outcomes:
The authors assessed the rate of complete clearance and partial clearance eight weeks after the last application.
Results (see table below):
2.5% imiquimod cream had a higher efficacy when compared to its vehicle on a statistically significant level with respect to the rate of complete clearance (RR: 4.87; 95%-CI: 2.59 - 9.27; GRADE: high quality) and the rate of partial clearance (RR: 2.13; 95%-CI: 1.53 - 2.95; GRADE: high quality).
Additional results and comments: None.

Question: Should 2.5% Imiquimod vs vehicle be used in patients with multiple AK lesions / field cancerization?
Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With Vehicle	With 2.5% Imiquimod		Risk with Vehicle	Risk difference with 2.5% Imiquimod (95% CI)
Participant complete clearance (CRITICAL OUTCOME)											
319 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ HIGH	10/159 (6.3%)	49/160 (30.6%)	**RR 4.87** (2.59 to 9.27)	**63 per 1000**	**243 more per 1000** (from 100 more to 520 more)
Participant partial (>75%) clearance (CRITICAL OUTCOME)											
319 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ HIGH	36/159 (22.6%)	77/160 (48.1%)	**RR 2.13** (1.53 to 2.95)	**226 per 1000**	**256 more per 1000** (from 120 more to 442 more)

4.7.2 2.5% imiquimod vs. 3.75% imiquimod

Study and patient characteristics:
One RCT[34] compared a 2.5% concentration of imiquimod with a 3.75% imiquimod formulation in a sample of 320 participants with five to 20 visible or palpable AK lesions within a field of 25cm². Participants had a mean number of 10.9 and 11.0 AK lesions and a mean age of 64.3 and 64.5 years (2.5% and 3.75% imiquimod group, respectively). No studies including participants with single AK lesions were eligible.
Interventions:
Up to 0.25g of 2.5% or 3.75% imiquimod were applied to the treatment area once daily overnight (approximately eight hours, then washed off) during two weeks. After a rest period of two weeks, another two week treatment cycle was performed.
Outcomes:
The authors assessed the rate of complete clearance and partial clearance eight weeks after the last application. Additionally, the authors reported the rate of withdrawals due to adverse events during the study period, and the rates of application site pruritus, application site irritation, application site pain and application site swelling.
Results (see table below):
With respect to the rate of complete clearance, no statistically significant differences were seen between 2.5% and 3.75% imiquimod concentration (RR: 0.86; 95%-CI: 0.63 - 1.18; GRADE: moderate quality). With respect to the rate of partial clearance, the confidence interval touches the line of no effect (RR: 0.81; 95%-CI: 0.66 - 1.00; GRADE: moderate quality). No statistically significant differences were seen concerning the withdrawals due to adverse events (RR: 0.50; 95%-CI: 0.05 - 5.46; GRADE: moderate quality), application site irritation (RR: 0.80; 95%-CI: 0.22 - 2.92; GRADE: moderate quality), application site pruritus (RR: 0.86; 95%-CI: 0.29 - 2.49; GRADE: moderate quality), application site pain (RR: 0.40; 95%-CI: 0.08 - 2.03; GRADE: moderate quality), and application site swelling (RR: 0.20; 95%-CI: 0.01 - 4.13; GRADE: moderate quality).
Additional results and comments: None.

Question: Should 2.5% imiquimod vs 3.75% imiquimod be used in patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 3.75% imiquimod	With 2.5% imiquimod		Risk with 3.75% imiquimod	Risk difference with 2.5% imiquimod (95% CI)
Participant complete clearance (CRITICAL OUTCOME)											
320 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊟⊟⊟⊟ MODERATE[1] due to imprecision	57/160 (35.6%)	49/160 (30.6%)	**RR 0.86** (0.63 to 1.18)	**356 per 1000**	**50 fewer per 1000** (from 132 fewer to 64 more)
Participant partial (>75%) clearance (CRITICAL OUTCOME)											
320 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊟⊟⊟⊟ MODERATE[1] due to imprecision	95/160 (59.4%)	77/160 (48.1%)	**RR 0.81** (0.66 to 1)	**594 per 1000**	**113 fewer per 1000** (from 202 fewer to 0 more)
Withdrawals due to AE (CRITICAL OUTCOME)											
320 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊟⊟⊟⊟ MODERATE[1] due to imprecision	2/160 (1.3%)	1/160 (0.63%)	**RR 0.50** (0.05 to 5.46)	**12 per 1000**	**6 fewer per 1000** (from 12 fewer to 56 more)
Minor AE: Application site irritation (CRITICAL OUTCOME)											
320 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊟⊟⊟⊟ MODERATE[1] due to imprecision	5/160 (3.1%)	4/160 (2.5%)	**RR 0.80** (0.22 to 2.92)	**31 per 1000**	**6 fewer per 1000** (from 24 fewer to 60 more)
Minor AE: Application site pruritus (IMPORTANT OUTCOME)											
320 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊟⊟⊟⊟ MODERATE[1] due to imprecision	7/160 (4.4%)	6/160 (3.8%)	**RR 0.86** (0.29 to 2.49)	**44 per 1000**	**6 fewer per 1000** (from 31 fewer to 65 more)
Minor AE: Application site pain (IMPORTANT OUTCOME)											
320 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊟⊟⊟⊟ MODERATE[1] due to imprecision	5/160 (3.1%)	2/160 (1.3%)	**RR 0.40** (0.08 to 2.03)	**31 per 1000**	**19 fewer per 1000** (from 29 fewer to 32 more)
Minor AE: Application site swelling (IMPORTANT OUTCOME)											
320 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	undetected	⊟⊟⊟⊟ MODERATE[1] due to imprecision	2/160 (1.3%)	0/160 (0%)	**RR 0.20** (0.01 to 4.13)	**12 per 1000**	**10 fewer per 1000** (from 12 fewer to 39 more)

[1] CI crosses MID threshold and line of no effect

4.7.3 Additional reasoning and recommendations

Because of limited experience with this concentration of imiquimod and the lower efficacy concerning partial clearance rates when compared to the 3.75% concentration of imiquimod, a weak recommendation was made for patients with multiple AK lesions or field cancerization.

Recommendation	**Strength of recommendation**	**Percentage of agreement**
We cannot make a recommendation with respect to 2.5% imiquimod for patients with single AK lesions.	0	≥90%
We suggest using 2.5% imiquimod in patients with multiple AK lesions or field cancerization.	↑	≥75%
We cannot make a recommendation with respect to 2.5% imiquimod for immunosuppressed patients.	0	≥90%

4.8 3.75% Imiquimod

4.8.1 3.75% imiquimod vs. vehicle

Study and patient characteristics:
One RCT[34] compared a 3.75% concentration of imiquimod with its vehicle in a sample of 319 participants with five to 20 visible or palpable AK lesions within a field of 25cm². Participants had a mean number of 11.0 and 11.3 AK lesions and a mean age of 64.5 and 64.3 years (3.75% imiquimod and vehicle group, respectively). No studies including participants with single AK lesions were eligible.
Interventions:
Up to 0.25g of 3.75% imiquimod or vehicle were applied to the treatment area once daily overnight (approximately eight hours, then washed off) during two weeks. After a rest period of two weeks, another two week treatment cycle was performed.
Outcomes:
The authors assessed the rate of complete clearance and partial clearance eight weeks after the last application.
Results (see table below):
3.75% imiquimod cream had a higher efficacy when compared to its vehicle on a statistically significant level with respect to the rate of complete clearance (RR: 5.66; 95%-CI: 3.00 - 10.69; GRADE: high quality) and the rate of partial clearance (RR: 2.62; 95%-CI: 1.91 - 3.59; GRADE: high quality).
Additional results and comments: None.

Question: Should 3.75% imiquimod vs vehicle be used in patients with multiple AK lesions / field cancerization?
Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Vehicle	With 3.75% imiquimod		Risk with Vehicle	Risk difference with 3.75% imiquimod (95% CI)
Participant complete clearance (CRITICAL OUTCOME)											
319 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⨁ HIGH	10/159 (6.3%)	57/160 (35.6%)	**RR 5.66** (3 to 10.69)	**63 per 1000**	**293 more per 1000** (from 126 more to 609 more)
Participant partial (>75%) clearance (CRITICAL OUTCOME)											
319 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⨁ HIGH	36/159 (22.6%)	95/160 (59.4%)	**RR 2.62** (1.91 to 3.59)	**226 per 1000**	**367 more per 1000** (from 206 more to 586 more)

4.8.2 3.75% imiquimod vs. 2.5% imiquimod

For details on the study and participants' characteristics and on the results please see comparison 4.7.2 (2.5% imiquimod vs. 3.75% imiquimod).

One RCT[34] compared a 2.5% concentration of imiquimod with a 3.75% imiquimod formulation. With respect to the rate of complete clearance, no statistically significant differences were seen between 2.5% and 3.75% imiquimod concentration (GRADE: moderate quality). With respect to the rate of partial clearance, the confidence interval touches the line of no effect (GRADE: moderate quality). No statistically significant differences were seen concerning the withdrawals due to adverse events (GRADE: moderate quality), application site irritation (GRADE: moderate quality), application site pruritus (GRADE: moderate quality), application site pain (GRADE: moderate quality), and application site swelling (GRADE: moderate quality).

4.8.3 Additional reasoning and recommendations

Due to the long-term experience with the 3.75% imiquimod cream concentration and drawing indirect evidence from the efficacy of 3.75% imiquimod in patients with multiple AK lesions, a weak recommendation was made for patients with single AK lesions although no trials including this population were eligible.

Recommendation	Strength of recommendation	Percentage of agreement
We suggest using 3.75% imiquimod in patients with single AK lesions.	↑	≥90%
We recommend using 3.75% imiquimod in patients with multiple AK lesions or field cancerization.	↑↑	≥90%
We cannot make a recommendation with respect to 3.75% imiquimod for immunosuppressed patients.	0	≥90%

4.9 5% Imiquimod

4.9.1 5% imiquimod vs. vehicle in immunocompetent participants

Study and patient characteristics / Interventions / Outcomes:
Ten RCTs[35-44] compared 5% imiquimod with its vehicle or placebo cream. Study and participants' characteristics, the mode of intervention and outcomes are shown in Table 1. No studies solely including samples of participants with single lesions were eligible.

Table 1: 5% imiquimod vs. vehicle - study and participants' characteristics, intervention and outcomes

Study	N	Incl. criteria	Mean AK	Mean age (years)	Intervention	Outcome
Alomar 2007[35]	259	5-9 AK lesions within a contiguous 25cm² area	No data	70.3 (imiquimod group) 71.9 (vehicle group)	5% imiquimod was applied once daily 3 times per week for 4 weeks (course1), followed by a 4-week posttreatment period. Patients without complete clearance at four weeks post-treatment accomplished a second treatment course.	Complete and partial clearance rates eight weeks after treatment
Gebauer 2009[36]	89	10-50 AK	No data	71	5% imiquimod was applied once daily on two or three days per week, each application with 0,5-1,5g overnight during around 8 h, then washed off, eight weeks of treatment. The study contained different active arms. Here, data from two arms conforming the inclusion criteria were pooled vs. vehicle.	Complete and partial clearance rates eight weeks after treatment
Jorizzo 2007[37]	246	4-8 clinically typical, visible AK lesions within a contiguous 25cm² area	Median 6	No data	5% imiquimod was applied once daily 3 times per week for 4 weeks (course 1), followed by a 4-week posttreatment period. Patients without complete clearance at four weeks post-treatment accomplished a second treatment course.	Complete and partial clearance rates 4 weeks post-treatment.
Korman 2005[38]	492	4-8 clinically diagnosed AK lesions within a 25cm² contiguous	No data	66.7 (imiquimod group) and 65.9	5% imiquimod was applied once daily 3 times per week for 16 weeks, rest periods were allowed at the discretion of the	Rate of complete and partial clearance at 8 weeks post-

		area		(vehicle group)	investigator	treatment follow-up
Lebwohl 2004[39]	436	4-8 clinically diagnosed AK lesions within a 25cm² contiguous area	Median 6	66.6 (imiquimod group) and 65.5 (vehicle group)	5% imiquimod cream was applied on two days per week for 16 weeks	Rate of complete and partial clearance at 8 weeks post-treatment follow-up
NCT00828568[40]	422	4-8 clinically diagnosed, non-hyperkeratotic AK lesions within a 25cm² contiguous area	No data	67.2	5% imiquimod was applied to the treatment area on two days each week for 16 weeks (the study assessed two active arms – Aldara 5% imiquimod and Imiquimod 5% manufactured by Taro. Here, data from both active arms were pooled vs. vehicle).	Rate complete clearance 8 weeks after the end of treatment
Ooi 2006[41]	18	6-15 clinically diagnosed AK	No data	68	5% imiquimod was applied on the lesions once daily, three times per week until all lesions cleared or for up to 16 weeks	Rate of complete clearance at the end-of-treatment visit
Ortonne 2010[42]	12	At least 5 clinically diagnosed non-hyperkeratotic, non-hypertrophic AK lesions in a treatment area of 20 cm²	5.9	66	5% imiquimod was applied once daily 3 times per week for 4 weeks, followed by a 4-week posttreatment period (course 1). A second, similar course was performed consecutively.	Reduction in AK lesion counts from baseline to the 4 weeks post-treatment follow up.
Stockfleth 2002[43]	52	3 to 10 AK lesions in a treatment area of 20cm²	No data	68	5% imiquimod was applied on the lesions once daily, three times per week until all lesions cleared or for up to 12 weeks	Rate of complete and partial clearance at 2 weeks post-treatment follow-up
Szeimies 2004[44]	286	5 to 9 clinically diagnosed and histologically confirmed AK lesions located within a contiguous 25-cm² treatment area	No data	71.1 (imiquimod group) and 70.9 (vehicle group)	5% imiquimod was applied to the treatment area once daily 3 times per week for 16 weeks, using 0.25g of cream each day	Rate of complete and partial clearance at 8 weeks post-treatment follow-up

Results (see table below):

5% imiquimod was statistically significantly more effective than vehicle cream with respect to the rate of complete clearance (RR: 8.55; 95%-CI: 4.80 - 15.23; GRADE: low quality) and the rate of partial clearance (RR: 6.53; 95%-CI: 3.54 - 12.03; GRADE: low quality). In one study with a sample size of 12 participants, that assessed the mean reduction of AK lesion counts from baseline to the end of the study[42], no statistically significant difference between the study groups could be seen (mean difference 2.2 lesions; 95%-CI: -1.05 to +5.45; GRADE: low quality).

Additional results and comments: None.

Question: Should 5% Imiquimod vs vehicle be used in patients with single AK lesions and/or patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Vehicle	With 5% Imiquimod		Risk with Vehicle	Risk difference with 5% Imiquimod (95% CI)
Participant complete clearance (CRITICAL OUTCOME)											
2277 (9 studies)	no serious risk of bias	serious[1]	serious[2]	no serious imprecision	undetected	⊕⊕⊕⊕ LOW[1,2] due to inconsistency, indirectness	55/969 (5.7%)	602/1308 (46%)	RR 8.55 (4.8 to 15.23)	57 per 1000	429 more per 1000 (from 216 more to 808 more)
Participant partial (>75%) clearance (CRITICAL OUTCOME)											
1808 (6 studies)	no serious risk of bias	serious[3]	serious[4]	no serious imprecision	undetected	⊕⊕⊕⊕ LOW[3,4] due to inconsistency, indirectness	102/892 (11.4%)	562/916 (61.4%)	RR 6.53 (3.54 to 12.03)	114 per 1000	632 more per 1000 (from 290 more to 1000 more)
Reduction in lesion counts (CRITICAL OUTCOME; Better indicated by lower values)											
12 (1 study)	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	undetected	⊕⊕⊕⊕ LOW[5,6] due to risk of bias, imprecision	3	9	-		The mean reduction in lesion counts in the intervention groups was 2.2 higher (1.05 lower to 5.45 higher)

[1] Effect estimates of 3 studies are out CI of other studies; I^2 = 70%

[2] 5 out of 9 studies included participants with single and multiple lesions (inclusion criteria 4-8 or 3-10 lesions)

[3] Effect estimates of 3 studies are out CI of other studies; I^2 = 87%

[4] 3 out of 6 studies included participants with single and multiple lesions (inclusion criteria 4-8 lesions)

[5] Unclear randomization method and allocation concealment, low number of participants

[6] CI crosses MID threshold and line of no effect (uncertain whether there is any difference)

4.9.2 5% imiquimod vs. vehicle in immunosuppressed participants

Study and patient characteristics:

One RCT[45] compared 5% imiquimod cream with its vehicle cream in a sample of immunosuppressed organ transplant recipients. Ulrich et al.[45] included 43 organ transplant recipients (kidney, liver, heart transplantation within three years, stable status) with 4 to 10 AK lesions in a contiguous area of 100 cm². Mean age of the participants was between 60.7 and 65.5 years. No data concerning the mean number of AK lesions per participant were presented.

Interventions:

500mg imiquimod 5% cream or vehicle cream was applied to the treatment area for eight hours overnight on 3 days per week for 16 weeks.

Outcomes:

Ulrich et al.[45] reported the rate of complete and partial clearance 8 weeks after the 16 weeks of treatment.

Results (see table below):

Participants randomized to the imiquimod 5% treatment arm had a statistically significantly higher rate of complete clearance (RR: 18.50; 95%-CI: 1.19 - 286.45; GRADE: low quality) and of partial clearance (RR: 23.50; 95%-CI: 1.53- 360.94; GRADE: low quality).

Additional results and comments:

None.

Question: Should 5% imiquimod vs vehicle be used in immunosuppressed patients with AK?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Vehicle	With 5% imiquimod		Risk with Vehicle	Risk difference with 5% imiquimod (95% CI)
Participant complete clearance (CRITICAL OUTCOME)											
43 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁◯◯ LOW[1,2] due to risk of bias, imprecision	0/14 (0%)	18/29 (62.1%)	RR 18.5 (1.19 to 288.45)	0 per 1000	-
Participant partial (>75%) clearance (CRITICAL OUTCOME)											
43 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁◯◯ LOW[1,2] due to risk of bias, imprecision	0/14 (0%)	23/29 (79.3%)	RR 23.5 (1.53 to 360.94)	0 per 1000	-

[1] unclear randomization method and allocation concealment

[2] very wide CI

4.9.3 5% imiquimod vs. cryotherapy

For details on the study and participants' characteristics and the results see comparison 4.2.3 (cryotherapy vs. 5% imiquimod).

Two RCTs compared 5% imiquimod and cryotherapy.[14, 15] No statistically significant differences were seen with respect to the rate of complete clearance (GRADE: low quality), withdrawals due to adverse events (GRADE: moderate quality), erosion / ulceration, and infection (GRADE: low quality). 5% imiquimod was superior to cryotherapy with respect to the rate of blister formation (GRADE: low quality), "excellent cosmetic outcome" (GRADE: moderate quality) and "better skin appearance" (GRADE: moderate quality).

4.9.4 5% imiquimod vs. 3% diclofenac gel (single AK lesions)

For details on the study and participants' characteristics and on the results see comparison 4.4.3 (3% diclofenac gel vs. 5% imiquimod: single AK lesions).

One RCT[25] compared 5% imiquimod with 3% diclofenac gel in a sample of participants with single AK lesions.
No statistically significant differences were found with respect to the rate of complete clearance (GRADE: low quality). Effect size and confidence interval concerning the rate of withdrawals due to adverse events could not be calculated due to no events in both groups.

4.9.5 5% imiquimod vs. 3% diclofenac gel (multiple AK lesions / field cancerization)

For details on the study and participants' characteristics and the results see comparison 4.4.4 (3% diclofenac gel vs. 5% imiquimod: multiple AK lesions / field cancerization).

One RCT[26] compared 5% imiquimod with 3% diclofenac gel in participants with single or multiple AK lesions / field cancerization.
No statistically significant differences were found with respect to the rate of participants with the Investigator global improvement index (IGII) rated as 'completely improved' (GRADE: very low quality) and with respect to the rate of participants with the Participant global improvement index (PGII) rated as 'completely improved' (GRADE: very low quality). With respect to the minor adverse events that were assessed during the study period, no

statistically significant differences were seen: Erythema (GRADE: very low quality), crusting (GRADE: very low quality), and scaling (GRADE: very low quality).

4.9.6 5% imiquimod vs. 5% 5-fluorouracil

Study and patient characteristics:
Two RCTs compared 5% imiquimod and 5% 5-fluorouracil.[14, 33] The study by Krawtchenko et al.[14] included a sample of 50 participants with at least 5 AK lesions (mean 7.9 AK lesions in the imiquimod group and 8.3 in the 5-FU group) and a mean age of 73 years (range: 57 to 88). Tanghetti et al.[33] included a sample of 39 participants with at least four AK lesions within a 25cm² area, no age data were presented. No studies including solely participants with single AK lesions were eligible.
Interventions:
5% imiquimod was applied to the treatment area twice weekly for eight hours overnight during a period of 16 weeks[33] or three times per week (0.25g of cream for eight hours overnight) during a period of four weeks, followed by four weeks without treatment. If lesions were still present after the first course, another course of four weeks treatment and four weeks of rest was performed.[14]
5% 5-fluorouracil cream was used twice daily for two to four weeks[33] or for four weeks with a rest period of up to one week in case of acute inflammation.[14]
Outcomes:
The authors of the studies assessed the rate of complete clearance in the participants four weeks after the last application of 5-FU and eight weeks after the last application of imiquimod[14] and at week 24 in both study groups.[33] Tanghetti et al. also reported the rate of withdrawals due to adverse events during the study period[33] and Krawtchenko et al. additionally reported the rate of participants with a 'normal skin surface' and the rate of participants with the investigator cosmetic outcome rated as 'excellent'.[14]
Results (see table below):
With respect to the rate of complete clearance, no statistically significant difference between the interventions (RR: 0.54; 95%-CI: 0.12 - 2.43; GRADE: very low quality). 5% imiquimod was significantly more frequently associated with an 'excellent' cosmetic outcome as rated by the investigator (RR: 19.38; 95%-CI: 2.82 - 133.26; GRADE: low quality) and with a normal skin surface (RR: 1.45; 95%-CI: 1.00 - 2.11; GRADE: low quality; statistically significant result of uncertain clinical importance). With respect to the withdrawals due to adverse events, no effect estimate could be calculated (no events in both study groups).
Additional results and comments:
The statistically significant difference with respect to the rate of participants with 'normal skin surface' is of uncertain clinical importance due to the small effect size (confidence interval crosses the minimal important difference threshold line and touches the line of no effect).

Question: Should 5% imiquimod vs 5% 5-fluorouracil be used in patients with single AK lesions and/or patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 5% 5-fluorouracil	With 5% imiquimod		Risk with 5% 5-fluorouracil	Risk difference with 5% imiquimod (95% CI)
Participant complete clearance (CRITICAL OUTCOME)											
89 (2 studies)	serious[1]	serious[2]	serious[3]	serious[4]	undetected	⨁◯◯◯ VERY LOW[1,2,3,4] due to risk of bias, inconsistency, indirectness, imprecision	40/44 (90.9%)	27/45 (60%)	**RR 0.54** (0.12 to 2.43)	**909 per 1000**	**418 fewer per 1000** (from 800 fewer to 1000 more)
Cosmetic outcome: Investigator cosmetic outcome "excellent" (IMPORTANT OUTCOME)											
50 (1 study)	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	undetected	⨁◯◯◯ LOW[5,6] due to risk of bias, imprecision	1/24 (4.2%)	21/26 (80.8%)	**RR 19.38** (2.82 to 133.26)	**42 per 1000**	**766 more per 1000** (from 76 more to 1000 more)
Cosmetic outcome: normal skin surface (IMPORTANT OUTCOME)											
50 (1 study)	serious[5]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⨁◯◯◯ LOW[4,5] due to risk of bias, imprecision	14/24 (58.3%)	22/26 (84.6%)	**RR 1.45** (1 to 2.11)	**583 per 1000**	**262 more per 1000** (from 0 more to 647 more)
Withdrawal due to AE (CRITICAL OUTCOME)											
39 (1 study)	serious[7]	no serious inconsistency	serious[8]		undetected	See comment	0/20 (0%)	0/19 (0%)	-	See comment	-

[1] Unclear randomization methods; high risk in performance bias (blinding), 1 study with selective reporting

[2] Effect estimates are out CI of the other study; I^2 = 93%, but heterogenity can be partially explained by different intervention duration

[3] one of the two studies included patients with at least 4 AK lesions

[4] CI crosses MID threshold and line of no effect (uncertain whether there is any difference)

[5] Unclear randomization methods; high risk in performance bias (blinding: physically distinct interventions and topical treatments with different application regimens)

[6] very wide CI

[7] Unclear randomization method; high risk in performance bias (blinding of participants); selective reporting

[8] study included participants with at least 4 AK lesions

4.9.7 5% imiquimod vs. ALA-PDT

For details on the study and participants' characteristics and the results see comparison 4.11.5 (5 aminolevulinic-photodynamic therapy (ALA-PDT) vs. 5% imiquimod).

One intraindividual (split-patient) RCT[46] compared ALA-PDT with 5% imiquimod.
Participants preferred ALA-PDT over 5% imiquimod cream on a statistically significant level (GRADE: moderate quality). No statistically significant differences were seen with respect to the minor adverse event "erythema" (GRADE: moderate quality). Statistically significantly less minor adverse events occurred in the imiquimod treated areas, with respect to "burning" (GRADE: moderate quality), "pain" (GRADE: low quality), and "oedema" (GRADE: moderate quality).

4.9.8 5% imiquimod vs. MAL-PDT

For details on the study and participants' characteristics and the results see comparison 4.12.4 (methylaminolevulinate-photodynamic therapy (MAL-PDT) vs. 5% imiquimod).

Two RCTs[47, 48] compared MAL-PDT with 5% imiquimod cream. There was no statistically significant difference between the interventions concerning efficacy: complete clearance (GRADE: low quality) and partial clearance rates (GRADE: low quality). A statistically significantly lower rate of participants was "very satisfied" with 5% imiquimod than with MAL-PDT (GRADE: moderate quality).

4.9.9 Additional reasoning and recommendations

For patients with multiple AK lesions / field cancerization, a weak recommendation was made (as compared to the strong recommendation for the 3.75% concentration of imiquimod cream). Besides the lower quality of evidence for 5% imiquimod, experts perceive the tolerability of 3.75% imiquimod as better due to the shorter duration and lower intensity of side effects.

Recommendation	**Strength of recommendation**	**Percentage of agreement**
We suggest using 5% imiquimod in patients with single AK lesions.	↑	≥75%
We suggest using 5% imiquimod in patients with multiple AK lesions or field cancerization.	↑	≥75%
We suggest using 5% imiquimod in immunosuppressed patients with AK.*	↑	≥50%**
** For immunosuppression, different clinical situations may exist, e.g. iatrogenic medical immunosuppression after organ transplantation, iatrogenic medical immunosuppression because of autoimmune disorders, immunosuppression due to other reasons (hematologic disorders, AIDS etc). Depending on the underlying disease, special care has to be given to the selection of the treatment to avoid (auto-) immunstimulation that may lead to a worsening of the underlying condition.* *** Experts who did not agree voted for making a strong recommendation (↑↑) for the use of 5% imiquimod in immunosuppressed patients.*		

4.10 Ingenol mebutate

4.10.1 Ingenol mebutate 0.015% vs. vehicle

Study and patient characteristics:
A publication[49] reported on two RCTs comparing the efficacy of 0.015% ingenol mebutate with its vehicle, in a sample of 547 participants with 4-8 clinically typical, visible, and discrete AK lesions within a 25cm² contiguous area on the face or scalp. 47.3% of the participants had four or five AK lesions and 52.7% of the participants had six to eight AK lesions. Mean age was 64.2 and 64.0 years in the verum and placebo group, respectively. No studies including solely participants with single AK lesions or multiple AK / field cancerization were eligible.
Interventions:
Ingenol mebutate at a concentration of 0.015% or its vehicle was applied to the treatment area once daily at three consecutive days.
Outcomes:
The authors of the studies assessed the rate of complete and partial clearance and the mean percent change of lesion counts at day 57.
Results (see table below):
Ingenol mebutate 0.015% was statistically significantly more effective for treating AK lesions on the face and scalp when compared to its vehicle gel with respect to the rate of complete clearance (RR: 11.40; 95%-CI: 6.11 - 21.28; GRADE: moderate quality), partial clearance (RR: 8.63; 95%-CI: 5.61 - 13.27; GRADE: moderate quality), and percent reduction in AK lesion counts (mean difference: 58.06; 95%-CI: 52.52 – 63.60; GRADE: moderate quality).
Additional results and comments: None.

Question: Should Ingenol mebutate 0.015% vs vehicle be used in patients with single AK lesions and/or patients with multiple AK lesions / field cancerization [lesions on the face and scalp]?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Vehicle	With Ingenol mebutate 0.015%		Risk with Vehicle	Risk difference with Ingenol mebutate 0.015% (95% CI)
Participant complete clearance of all lesions (CRITICAL OUTCOME)											
547 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[1] due to indirectness	10/270 (3.7%)	117/277 (42.2%)	**RR 11.4** (6.11 to 21.28)	**37 per 1000**	**385 more per 1000** (from 189 more to 751 more)
Participant partial clearance of all lesion (CRITICAL OUTCOME)											
547 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[1] due to indirectness	20/270 (7.4%)	177/277 (63.9%)	**RR 8.63** (5.61 to 13.27)	**74 per 1000**	**565 more per 1000** (from 341 more to 909 more)
Percent reduction in AK lesion counts (CRITICAL OUTCOME; Better indicated by higher values)											
542 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[1] due to indirectness	269	273	-		The mean percent reduction in ak lesion counts in the intervention groups was **58.06 higher** (52.52 to 63.60 higher)

[1] Study included participants with single and multiple lesions (inclusion criteria 4-8 lesions)

4.10.2 Ingenol mebutate 0.05% vs. vehicle

Study and patient characteristics:

Three RCTs[49, 50] compared the efficacy of 0.05% ingenol mebutate with its vehicle. Lebwohl et al.[49] reported two RCTs including a sample of 458 participants with 4-8 clinically typical, visible, and discrete AK lesions within a 25cm² contiguous area on the trunk or extremities. 55.0% of the participants had four or five AK lesions and 45.0% of the participants had six to eight AK lesions. Mean age was 66.4 and 66.0 years in the verum and placebo group, respectively..Anderson et al.[50] comprised a sample of 115 participants, equally with 4-8 clinically typical, visible, and discrete AK lesions within a 25cm² contiguous area on the trunk or extremities, but also including lesions on the scalp. Participants had a mean age of 67 years (range: 43 – 85), mean numbers of baseline AK lesions were not presented. No studies including solely participants with single AK lesions or multiple AK / field cancerization were eligible.

Interventions:

Ingenol mebutate at a concentration of 0.05% or its vehicle was applied to the treatment area once daily at two consecutive days.

Outcomes:

The authors of the studies assessed the rate of complete and partial clearance at day 57.

Results (see table below):

Ingenol mebutate 0.05% was statistically significantly more effective for treating AK lesions when compared to its vehicle gel with respect to the rate of complete clearance (RR: 5.40; 95%-CI: 2.84 - 10.27; GRADE: moderate quality) and partial clearance (RR: 7.12; 95%-CI: 4.36 - 11.64; GRADE: moderate quality).

Additional results and comments: None.

Question: Should ingenol mebutate 0.05% vs vehicle be used for patients with single AK lesions and/or patients with multiple AK lesions / field cancerization [lesions on the trunk and extremities]?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Vehicle	With Ingenol mebutate 0.05%		Risk with Vehicle	Risk difference with Ingenol mebutate 0.05% (95% CI)
Participant complete clearance of all lesions (CRITICAL OUTCOME)											
573 (2 studies)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⊟⊟⊟⊟ MODERATE[1] due to indirectness	18/292 (6.2%)	101/281 (35.9%)	**RR 5.40** (2.84 to 10.27)	**62 per 1000**	**271 more per 1000** (from 113 more to 571 more)
Participant partial clearance of all lesion (CRITICAL OUTCOME)											
458 (1 study)	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	undetected	⊟⊟⊟⊟ MODERATE[2] due to indirectness	16/232 (6.9%)	111/226 (49.1%)	**RR 7.12** (4.36 to 11.64)	**69 per 1000**	**422 more per 1000** (from 232 more to 734 more)

[1] Both studies included participants with single and multiple lesions (inclusion criteria 4-8 lesions)

[2] Study included participants with single and multiple lesions (inclusion criteria 4-8 lesions)

4.10.3 Additional reasoning and recommendations

Initially, a weak recommendation was made for the use of ingenol mebutate in patients with multiple AK lesions / field cancerization, mainly due to the fact that the treatment option had been on the market for just a short period of time with limited experience on the side of the experts. Now, with 10 months of further experience the experts felt more comfortable to support a strong recommendation for this newly available treatment. The adherence to the treatment due to the short treatment regimen of 2 / 3 days is assumed to be superior to other topical interventions for AK, supplying a further argument for the use of ingenol mebutate. No recommendation was made for immunosuppressed patients due to missing data and experience concerning this patient group.

Recommendation	**Strength of recommendation**	**Percentage of agreement**
In patients with single AK lesions, we suggest using ingenol mebutate 0.015% for lesions on the face or scalp and ingenol mebutate 0.05% for lesions on the trunk or extremities.	↑	≥90%
In patients with multiple AK lesions or field cancerization, we recommend using ingenol mebutate 0.015% for lesions on the face or scalp and ingenol mebutate 0.05% for lesions on the trunk or extremities.	↑↑	≥50%*
We cannot make a recommendation with respect to ingenol mebutate for immunosuppressed patients.	0	≥90%
** Experts who did not agree voted for making a weak recommendation (↑) for the use of ingenol mebutate in patients with multiple AK lesions or field cancerization.*		

4.11 5-aminolevulinic acid photodynamic therapy (ALA-PDT)

4.11.1 ALA-PDT vs. placebo-PDT

Study and patient characteristics / Intervention / Outcomes:

Seven RCTs[8, 51-55] reported data on the comparison of 5-aminolaevulinic acid (ALA)-photodynamic therapy (PDT) with placebo-PDT. Table 2 lists details on the study and participants' characteristics, the interventions used and outcomes of the studies. No studies included participants solely with single AK lesions.

Table 2: ALA-PDT vs. placebo-PDT - Study and participants' characteristics, interventions and outcomes

Study	N	Incl. criteria	Mean AK	Mean age (years)	Mode of ALA-PDT	Outcome
Dirschka 2012[51]	324	4 to 8 mild to moderate actinic keratoses, 1 lesion confirmed histologically	6.1 (ALA-PDT group) and 6.4 (placebo-PDT group)	70.2 (ALA-PDT group) and 71.5 (placebo-PDT group)	BF-200 ALA-PDT with 10% gel concentration; 1 or 2 treatments, second treatment in case of remaining lesions 12 weeks after first PDT; interval between treatments: 12 weeks; incubation: occlusive, light-tight dressing over cream for 3 hours; type of light: red light; light source: Aktilite CL 128, Omnilux PDT, PhotoDyn 750 505, and Waldmann PDT 1200L; wavelength (nm): 580 – 1400; energy fluence (J/cm²): 37 - 170	Rate of complete clearance 12 weeks after PDT
Hauschild 2009a[8]	103	Mild to moderate grade actinic keratoses with a minimum diameter of 1.8 cm and an interlesional distance of at least 1 cm	5.8 (ALA-PDT group) and 5.5 (placebo-PDT group)	70.4 (ALA-PDT group) and 71.4 (placebo-PDT group)	3 to 8 self-adhesive patches of PD P506A ALA-PDT (patches containing 8 mg); 1 treatment; incubation: 4 hours; type of light: red light LED; light source: Aktilite CL 128 or Omnilux; wavelength (nm): 630; energy fluence (J/cm²): 37	Rate of complete clearance 12 weeks after PDT
Hauschild 2009b[8]	197	Mild to moderate grade actinic keratoses with a minimum diameter of 1.8 cm and an interlesional distance of at least 1 cm	5.8 (ALA-PDT group) and 5.9 (placebo-PDT group)	70.0 (ALA-PDT group) and 71.6 (placebo-PDT group)	4 to 8 self-adhesive patches of PD P506A ALA-PDT (patches containing 8 mg); 1 treatment; incubation: 4 hours; type of light: red light LED; light source: Aktilite CL 128 or Omnilux; wavelength (nm): 630; energy fluence (J/cm²): 37	Rate of complete clearance 12 weeks after PDT
Piacquadio 2004[52]	243	4 to 15 actinic keratoses, grade 1 or 2 lesions	No data	67.1 (ALA-group) and 64.5 (vehicle group)	ALA-PDT with 20% cream concentration; 1 or 2 treatments with an interval of 8 weeks; incubation time: 14 to 18 hours; type of light: blue light; light source: Blu-U; wavelength (nm): 417 ± 5; energy fluence (J/cm²): 10; intensities (mW/cm²): 10; exposure time: 1000 seconds (16 minutes)	Rate of complete clearance and partial clearance at 8 weeks (1 treatment) or 12 weeks (2 treatments)
Schmieder 2012[53]	70	At least 4 AK lesions, grade 1 or 2	Median: 12 to 13	64	ALA-PDT with 20% cream concentration; 1 or 2 treatments with an interval of 8 weeks; incubation: 3 hours, with or without occlusive dressing; type of light: blue light; light source: Blu-U; wavelength (nm): 417; energy fluence (J/cm²): 10; intensities (mW/cm²): 10; exposure time: 16 minutes, 40 seconds	Rate of complete and partial clearance at 8 weeks (1 treatment) or 12 weeks (2 treatments)
Szeimies 2010b[54]	122	4 to 8 actinic keratoses, mild to moderate lesions, 0.5 to 1.5 cm in diameter, with a minimum of 1.0 cm interlesional distance	5.6	70.5	ALA- PDT with BF-200 gel; 1 or 2 treatments with an interval of 12 weeks; application of cream: air dry for 10 min; incubation for 3 hours with an occlusive dressing; type of light: red light; light source: Aktilite CL 128 or PhotoDyn 750; wavelength (nm): 590-670 (Aktilite), 595-1400 (PhotoDyn); energy fluence (J/cm²): 37 (Aktilite), 170 (PhotoDyn); intensities (mW/cm²): 50-70 (Aktilite), 196 (PhotoDyn); exposure time: 15 minutes (PhotoDyn)	Rate of complete clearance at 12 weeks after the last PDT session
Taub 2011[55]	15	at least 4 AK lesions on the dorsal sides of both	Median: 12 and 13	55.8	ALA-PDT with 20% cream concentration; 2 treatments with an interval of 8 weeks (first	mean percent of lesion count reduction from

		hands and forearms (intraindividual comparison)			session: ALA applied to lesions, second session: ALA applied to field); incubation: 2 hours, with occlusive dressing; type of light: blue light; wavelength (nm): 417; energy fluence (J/cm²): 10; intensities (mW/cm²): 10; exposure time: 16 minutes, 40 seconds	baseline to 4 weeks posttreatment

Results (see table below):

When compared to placebo-PDT, ALA-PDT had a statistically significantly superior efficacy concerning complete clearance (RR: 5.95; 95%-CI: 4.22 - 8.40; GRADE: low quality), partial clearance (RR: 6.77; 95%-CI: 3.91 - 11.71; GRADE: moderate quality), and mean percent reduction of lesions count from baseline to the end of the study (mean difference: 33.60%; 95%-CI: 18.27 - 48.93; GRADE: moderate quality).

Additional results and comments:

Taub et al.[55] reported data on complete clearance and partial clearance from a split-patient trial: in the ALA-PDT side the rate was 1/15 and 3/15, respectively, and in the placebo-PDT side 0/15 and 1/15, respectively. For methodological reasons, data from intraindividual comparisons could not be included into GRADE profiles that similarly include data from interindividual comparisons. Data on the mean reduction of lesion counts refer to the study by Taub et al., the number of participants was 15, not 30 as shown in the GRADE profile due to methodological reasons (see below).

Schmieder et al.[53] had two active treatment groups in their study: one using an occlusive dressing and one without. Here, data from these two groups were pooled. Rates of complete clearance were 12/35 and 7/35 and rates of partial clearance were 21/35 and 15/35 participants in the group with occlusion and in the group without occlusion, respectively.

Question: Should ALA-PDT vs placebo-PDT be used in patients with single AK lesions and/or multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With Placebo-PDT	With ALA-PDT		Risk with Placebo-PDT / Risk difference with ALA-PDT (95% CI)
Participant complete clearance [1 or 2 treatments] (CRITICAL OUTCOME)										
1129 (6 studies)	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⊕⊕⊕⊖ LOW[1,2] due to risk of bias, indirectness	29/332 (8.7%)	498/797 (62.5%)	**RR 5.95** (4.22 to 8.4)	**87 per 1000** / **432 more per 1000** (from 281 more to 646 more)
Participant partial (>75%) clearance [1 or 2 treatments] (CRITICAL OUTCOME)										
383 (2 studies)	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ MODERATE[3] due to risk of bias	12/132 (9.1%)	169/251 (67.3%)	**RR 6.77** (3.91 to 11.71)	**91 per 1000** / **525 more per 1000** (from 265 more to 974 more)
Mean percentage lesion count reduction [2 treatments] (CRITICAL OUTCOME; Better indicated by lower values)										
30 (1 study)	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ MODERATE[4] due to risk of bias	15	15	-	The mean mean percentage lesion count reduction [2 treatments] in the intervention groups was **33.6 higher** (18.27 to 48.93 higher)

[1] Hauschild 2009b and Piacquadio 2004 with severe quality bias, other studies with low bias

[2] 2 studies included participants with single and multiple lesions (range 1-8 lesions)

[3] 1 study with severe quality bias, 1 study with moderate quality bias

[4] Unclear randomization method and allocation concealment, selective reporting

4.11.2 ALA-PDT vs. cryotherapy

For details on the study and participants' characteristics and the results see comparison 4.2.4 (cryotherapy vs. 5-aminolaevulinic acid-photodynamic therapy (ALA-PDT)).

One RCT[8] compared 5-aminolaevulinic acid-photodynamic therapy using red light (ALA-red light PDT) and cryotherapy, showing a statistically significant superiority of ALA-red light PDT with respect to the rate of complete clearance (small effect size, uncertain clinical importance; GRADE: very low quality). With respect to "skin irritation", a statistically significant higher rate of events was seen in the ALA-red light PDT group (GRADE: low quality).

4.11.3 ALA-PDT vs. carbon dioxide (CO_2) laser

Study and participants' characteristics:
One intraindividual (split-patient) RCT[10] compared ALA-PDT with CO_2 laser in a sample of 21 participants with a mean age of 74 years (range: 55 to 84) and a median number of baseline AK lesions of 6 (ALA-PDT side) and 8 (CO_2 laser side). No studies including a sample of participants solely with single AK lesions were eligible.
Interventions:
ALA-PDT was performed in a single course, using a cream concentration of 20% at an incubation time of 4 hours. Red light at a wavelength of 570 to 670nm from a distance of 20 cm with an energy fluence of 76 J/cm² and an exposure time of 20 minutes was applied. CO_2 laser ablation was performed on the lesions and 2mm border with an ultrapulsed CO_2 laser (Coherent UltraPulse 5000c, Palo Alto, CA, U.S.A.; 150 mJ, 1Æ5 W, 10 Hz, pattern 1, size 1, density 1, 10 600 nm, 2 mm spot). In advance, mepivacaine 1% was used for local anaesthesia. After the treatment, a soothing dressing with dexpanthenol 50 mg/g cream and octenidine 0.1% phenoxyethanol 2.0% solution was administered.
Outcomes:
Participants' preference was assessed at four weeks after the treatment.
Results (see table below):
No statistically significant difference was seen in the participants' preference (RR: 2.0; 95%-CI: 0.94 - 4.27; GRADE: very low quality).
Additional results and comments: None.

Question: Should ALA-PDT vs CO2 laser be used for patients with single AK lesions and / or patients with multiple AK lesions / field cancerization?
Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With CO2 laser	With ALA-PDT		Risk with CO2 laser / Risk difference with ALA-PDT (95% CI)
Patients preference at 4 weeks posttreatment (CRITICAL OUTCOME)										
40 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	6/20 (30%)	12/20 (60%)	RR 2 (0.94 to 4.27)	300 per 1000 / 300 more per 1000 (from 18 fewer to 981 more)

[1] High risk in selection bias (inadequate allocation concealment) and in performance bias (unblinded participants and personnel (subjective outcome))
[2] Median number of baseline AK lesions was 6 and 8 on the ALA-PDT treated side and on the CO2-laser treated side, respectively.
[3] CI crosses MID threshold and line of no effect (uncertain whether there is any diffference)

4.11.4 ALA-PDT vs. 0.5% 5-fluorouracil

Study and patient characteristics:
One RCT[31] compared aminolevulinic acid-photodynamic therapy (ALA-PDT), using two different light sources (blue light in one group and pulsed dye laser in another study group), with 0.5% fluorouracil. The sample consisted of 36 participants with at least 4 non-hyperkeratotic AK lesions and a mean age of 61 years. No studies including a sample of participants solely with single AK lesions were eligible.
Interventions:

Aminolevulinic acid (ALA)-photodynamic therapy (PDT) was applied, using a 20% cream concentration with an incubation time of 1 hour, either using blue light (Blu-U Photodynamic Therapy Illuminator, Exposure time: 1000 sec) or pulsed dye laser (Wavelength (nm): 595; Energy fluence (J/cm²): 7.5; Exposure time: 10 ms; two full passes). Two treatments at an interval of 30 days were performed. 0.5% 5-fluorouracil cream was applied once or twice daily for a treatment duration of four weeks.

Outcomes:

The authors assessed the rate of complete and partial clearance, the improvement in global response, improvement in tactile roughness, and improvement in mottled hyperpigmentation at the four weeks follow-up visit. Withdrawals due to adverse events during the study period were recorded.

Results (see table below):

The following results refer to a comparison of the pooled data from the ALA-PDT arms (blue light and pulsed dye laser) with 0.5% fluorouracil. Separate analyses of the different light sources are presented below (see 'additional results and comments'). No statistically significant differences were seen with respect to the rate of complete clearance (RR: 0.58; 95%-CI: 0.25 - 1.35; GRADE: very low quality), partial clearance (RR: 0.78; 95%-CI: 0.49 - 1.24; GRADE: very low quality), withdrawals due to adverse events (RR: 0.17; 95%-CI: 0.01 - 3.96; GRADE: very low quality), improvement in global response (RR: 0.74; 95%-CI: 0.44 - 1.25; GRADE: very low quality), improvement in tactile roughness (RR: 0.92; 95%-CI: 0.52 - 1.61; GRADE: very low quality), and improvement in mottled hyperpigmentation (RR: 0.65; 95%-CI: 0.34 - 1.26; GRADE: very low quality).

Additional results and comments:

A differentiation of the light source for PDT has not been scope of this guideline. Therefore the results for the different light sources for PDT applied in the study by Smith et al.[31] as given above have been pooled. The efficacy of the blue light ALA-PDT was higher than the efficacy of pulsed dye laser ALA-PDT with respect to the rate of complete and partial clearance.[31] Nevertheless, in this study, separate analyses of the different light sources vs. 0.5% fluorouracil did not show statistically significant differences with respect to the rate of complete and partial clearance, withdrawals due to adverse events, improvement in the global response, tactile roughness, and mottled hyperpigmentation. Results from these separate analyses are also presented in a GRADE evidence table (see the second table below).

Question: Should ALA-PDT vs 0.5% 5-fluorouracil be used in patients with single AK lesions and / or patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 0.5% 5-fluorouracil	With ALA-PDT		Risk with 0.5% 5-fluorouracil	Risk difference with ALA-PDT (95% CI)
Participant complete clearance - Combined (CRITICAL OUTCOME)											
36 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ **VERY LOW**[1,2,3] due to risk of bias, indirectness, imprecision	6/12 (50%)	7/24 (29.2%)	**HR 0.58** (0.25 to 1.35)	**500 per 1000**	**169 fewer per 1000** (from 341 fewer to 108 more)
Participant partial (>75%) clearance - Combined (CRITICAL OUTCOME)											
36 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ **VERY LOW**[1,2,3] due to risk of bias, indirectness, imprecision	9/12 (75%)	14/24 (58.3%)	**RR 0.78** (0.49 to 1.24)	**750 per 1000**	**165 fewer per 1000** (from 382 fewer to 180 more)
Withdrawal due to AE - Combined (CRITICAL OUTCOME)											
36 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ **VERY LOW**[1,2,3] due to risk of bias, indirectness, imprecision	1/12 (8.3%)	0/24 (0%)	**RR 0.17** (0.01 to 3.96)	**83 per 1000**	**69 fewer per 1000** (from 82 fewer to 247 more)
Cosmetic outcome: improvement in global response - Combined (IMPORTANT OUTCOME)											
35 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ **VERY LOW**[1,2,3] due to risk of bias, indirectness, imprecision	8/11 (72.7%)	13/24 (54.2%)	**RR 0.74** (0.44 to 1.25)	**727 per 1000**	**189 fewer per 1000** (from 407 fewer to 182 more)
Cosmetic outcome: improvement in tactile roughness - Combined (IMPORTANT OUTCOME)											
35 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ **VERY LOW**[1,2,3] due to risk of bias, indirectness, imprecision	7/11 (63.6%)	14/24 (58.3%)	**RR 0.92** (0.52 to 1.61)	**636 per 1000**	**51 fewer per 1000** (from 305 fewer to 388 more)
Cosmetic outcome: improvement in mottled hyperpigmentation - Combined (IMPORTANT OUTCOME)											
35 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ **VERY LOW**[1,2,3] due to risk of bias, indirectness, imprecision	7/11 (63.6%)	10/24 (41.7%)	**RR 0.65** (0.34 to 1.26)	**636 per 1000**	**223 fewer per 1000** (from 420 fewer to 165 more)

[1] Unclear randomization method and allocation concealment, no blinding, selective reporting

[2] study included participants with at least 4 AK lesions

[3] CI crosses MID thereshold and line of no effect (uncertain whether there is any difference)

Question: Should ALA-PDT (separate analyses for blue light and pulsed dye laser) vs 0.5% 5-FU be used in patients with single AK lesions and / or patients with multiple AK / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 0.5% 5-FU	With ALA-PDT (separate analyses for blue light and pulsed dye laser)		Risk with 0.5% 5-FU	Risk difference with ALA-PDT (separate analyses for blue light and pulsed dye laser) (95% CI)
Participant complete clearance - Blue light (CRITICAL OUTCOME)											
24 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	6/12 (50%)	6/12 (50%)	RR 1 (0.45 to 2.23)	500 per 1000	0 fewer per 1000 (from 275 fewer to 615 more)
Participant complete clearance - Pulsed dye laser (CRITICAL OUTCOME)											
24 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	6/12 (50%)	1/12 (8.3%)	RR 0.17 (0.02 to 1.18)	500 per 1000	415 fewer per 1000 (from 490 fewer to 90 more)
Participant partial (>75%) clearance - Blue light (CRITICAL OUTCOME)											
24 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	9/12 (75%)	9/12 (75%)	RR 1 (0.63 to 1.59)	750 per 1000	0 fewer per 1000 (from 278 fewer to 443 more)
Participant partial (>75%) clearance - Pulsed dye laser (CRITICAL OUTCOME)											
24 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	9/12 (75%)	5/12 (41.7%)	RR 0.56 (0.26 to 1.17)	750 per 1000	330 fewer per 1000 (from 555 fewer to 127 more)
Withdrawal due to AE - Blue light (CRITICAL OUTCOME)											
24 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	1/12 (8.3%)	0/12 (0%)	RR 0.33 (0.01 to 7.45)	83 per 1000	56 fewer per 1000 (from 82 fewer to 537 more)
Withdrawal due to AE - Pulsed dye laser (CRITICAL OUTCOME)											
24 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	1/12 (8.3%)	0/12 (0%)	RR 0.33 (0.01 to 7.45)	83 per 1000	56 fewer per 1000 (from 82 fewer to 537 more)
Cosmetic outcome: improvement in global response - Blue light (IMPORTANT OUTCOME)											
23 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	8/11 (72.7%)	6/12 (50%)	RR 0.69 (0.35 to 1.35)	727 per 1000	225 fewer per 1000 (from 473 fewer to 255 more)
Cosmetic outcome: improvement in global response - Pulsed dye laser (IMPORTANT OUTCOME)											
23 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	8/11 (72.7%)	7/12 (58.3%)	RR 0.8 (0.44 to 1.46)	727 per 1000	145 fewer per 1000 (from 407 fewer to 335 more)
Cosmetic outcome: improvement in tactile roughness - Blue light (IMPORTANT OUTCOME)											
23 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	7/11 (63.6%)	8/12 (66.7%)	RR 1.05 (0.58 to 1.91)	636 per 1000	32 more per 1000 (from 267 fewer to 579 more)
Cosmetic outcome: improvement in tactile roughness - Pulsed dye laser (IMPORTANT OUTCOME)											
23 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	7/11 (63.6%)	6/12 (50%)	RR 0.79 (0.38 to 1.62)	636 per 1000	134 fewer per 1000 (from 395 fewer to 395 more)
Cosmetic outcome: improvement in mottled hyperpigmentation - Blue light (IMPORTANT OUTCOME)											
23 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	7/11 (63.6%)	4/12 (33.3%)	RR 0.52 (0.21 to 1.31)	636 per 1000	305 fewer per 1000 (from 503 fewer to 197 more)
Cosmetic outcome: improvement in mottled hyperpigmentation - Pulsed dye laser (IMPORTANT OUTCOME)											
23 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	7/11 (63.6%)	6/12 (50%)	RR 0.79 (0.38 to 1.62)	636 per 1000	134 fewer per 1000 (from 395 fewer to 395 more)

[1] Unclear randomization method and allocation concealment, no blinding, selective reporting

[2] study included participants with at least 4 AK

[3] CI crosses MID thereshold and line of no effect (uncertain whether there is any difference)

4.11.5 ALA-PDT vs. 5% imiquimod

Study and patient characteristics:
One intraindividual (split-patient) RCT[46] compared AL-PDT with 5% imiquimod in a sample of 30 participants with at least six AK lesions (mean number of AK lesions per participant: 8.5) and a mean age of 63.8 years. No studies including samples of participants with single AK lesions were eligible.
Interventions:
20% 5-ALA was applied to the lesions including 5 mm of normal surrounding skin. Incubation time was 4 hours with an occlusive dressing. Illumination was performed using red light (Light source: Waldmann PDT 1200, Wavelength (nm): 570-670, Energy fluence (J/cm²): 75, Intensities (mW/cm²): 75). Two treatments were performed with an interval of 15 days.
0.5g of 5% imiquimod cream was used once per day for eight hours overnight, at 3 times per week. Treatment was performed for four weeks. After a four weeks interval patients were evaluated. Patients without complete clearance of their lesions after this first course received a second treatment course.
Outcomes:
Eligible outcomes reported by the authors were participants' preference at month six, and the following minor adverse events during the study period: burning, pain, erythema, and oedema.
Results (see table below):
Participants preferred ALA-PDT over 5% imiquimod cream on a statistically significant level (RR: 2.50; 95%-CI: 1.33 - 4.70; GRADE: moderate quality). No statistically significant differences were seen with respect to the minor adverse event "erythema" (RR: 1.08; 95%-CI: 0.95 - 1.21; GRADE: moderate quality). Statistically significantly more minor adverse events occurred in the ALA-PDT treated area, with respect to "burning" (RR: 8.14; 95%-CI: 3.05 - 21.77; GRADE: moderate quality), "pain" (RR 19; 95%-CI: 4.00 - 90.34; GRADE: low quality), and "oedema" (RR: 9.50; 95%-CI: 2.44 - 37.00; GRADE: moderate quality).
Additional results and comments: None.

Question: Should ALA-PDT vs 5% imiquimod be used in patients with multiple AK lesions / field cancerization?
Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 5% imiquimod	With ALA-PDT		Risk with 5% imiquimod	Risk difference with ALA-PDT (95% CI)
Participants preference (CRITICAL OUTCOME)											
56 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ MODERATE[1] due to risk of bias	8/28 (28.6%)	20/28 (71.4%)	**RR 2.5** (1.33 to 4.7)	**286 per 1000**	**429 more per 1000** (from 94 more to 1000 more)
Minor AE: burning (IMPORTANT OUTCOME)											
56 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ MODERATE[1] due to risk of bias	3/28 (10.7%)	28/28 (100%)	**RR 8.14** (3.05 to 21.77)	**107 per 1000**	**765 more per 1000** (from 220 more to 1000 more)
Minor AE: pain (IMPORTANT OUTCOME)											
56 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕◯ LOW[1,2] due to risk of bias, imprecision	1/28 (3.6%)	28/28 (100%)	**RR 19** (4 to 90.34)	**36 per 1000**	**643 more per 1000** (from 107 more to 1000 more)
Minor AE: erythema (IMPORTANT OUTCOME)											
56 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ MODERATE[1] due to risk of bias	26/28 (92.9%)	28/28 (100%)	**RR 1.08** (0.95 to 1.21)	**929 per 1000**	**74 more per 1000** (from 46 fewer to 195 more)
Minor AE: oedema (IMPORTANT OUTCOME)											
56 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ MODERATE[1] due to risk of bias	2/28 (7.1%)	19/28 (67.9%)	**RR 9.5** (2.44 to 37)	**71 per 1000**	**607 more per 1000** (from 103 more to 1000 more)

[1] Unclear randomization method and allocation concealment, no blinding
[2] Wide CI

4.11.6 ALA-PDT vs. MAL-PDT

Study and patient characteristics:
Two RCTs[51, 56] compared 5-aminolaevulinic acid-photodynamic therapy (ALA-PDT) with methylaminolevulinate-photodynamic therapy (MAL-PDT). Dirschka et al.[51] included a sample of 495 participants (in the ALA- and MAL-PDT groups) with 4 to 8 mild to moderate AK lesions (mean AK lesions per person: 6.1 in the ALA-PDT group and 6.3 in the MAL-PDT group) and a mean age of 70.2 (ALA-group) and 71.0 years (MAL-group). Moloney and Collins[56] conducted an intraindividual (split-patient) study in a sample of 16 participants with a mean age of 71 years and a mean number of AK lesions within each treated field of 7.3 (ALA-PDT treated side) and 8.8 (MAL-PDT treated side). No studies including solely participants with single AK lesions were eligible.
Interventions:
ALA-PDT was used with a 10% ALA hydrochloride concentration (BF-200 ALA gel) in the study by Dirschka et al.[51] and a 20% concentration in the study by Moloney and Collins[56]. In both trials, MAL-PDT with a 16% cream concentration was used as comparator. Dirschka et al.[51] applied 1 or 2 treatments, the second treatment in case of remaining lesions 12 weeks after the first PDT with the following parameters: incubation: occlusive, light-tight dressing over cream for 3 hours; type of light: red light; light source: Aktilite CL 128, Omnilux PDT, PhotoDyn 750 505, and Waldmann PDT 1200L; wavelength (nm): 580 – 1400; energy fluence (J/cm²): 37 – 170. Moloney and Collins[56] applied only one treatment with the following parameters: application of cream: visible layer; incubation: occlusive dressing over cream for 3 (MAL) or 5 (ALA) hours; type of light: red light; light source: Waldmann PDT lamp MSR 1200; wavelength (nm): 580-740; energy fluence (J/cm²): 50; intensities (mW/cm²): 50; exposure time: 16 minutes 40 seconds.
Outcomes:
The interventions were compared with respect to the rate of complete clearance 12 weeks after PDT[51] or 1 month after the treatment[56] and the mean reduction in AK lesion counts 1 month after the treatment.[56] Dirschka et al.[51] additionally assessed the rate of participants with the cosmetic outcome rated as “good or very good” and “unsatisfactory / impaired”, the improvement in skin quality, and minor adverse events (burning, pain). Moloney and Collins[56] additionally assessed participants’ preference.
Results (see table below):
The study by Dirschka et al.[51] could demonstrate a statistically significant superiority of ALA-PDT when compared to MAL-PDT with respect to the rate of complete clearance (RR: 1.22; 95%-CI: 1.09 - 1.37; GRADE: low quality). However, the effect is of uncertain clinical importance due to the small effect size (see comment). The intraindividual study by Moloney and Collins[56] does not show a statistically significant difference between the interventions concerning complete clearance rates (these data could not be pooled together due to the inter- and intraindividual study design). No statistically significant difference was seen with respect to the mean reduction in lesion counts from baseline to one month after the treatment (mean difference: 0.60; 95%-CI: -1.28 - 2.48; GRADE: low quality). No statistically significant differences were seen with respect to minor adverse events and cosmetic outcomes: local skin reactions in general (RR: 1.01; 95%-CI: 0.92 - 1.10; GRADE: moderate quality); burning (RR: 0.95; 95%-CI: 0.89 - 1.02; GRADE: moderate quality); pain (RR: 0.95; 95%-CI: 0.85 - 1.06; GRADE: moderate quality); the rate of participants whose cosmetic outcome was rated as “good/very good” (RR: 0.96; 95%-CI: 0.78 - 1.17; GRADE: moderate quality); the rate of participants whose cosmetic outcome was rated as “unsatisfactory/impaired” (RR: 0.94; 95%-CI: 0.52 - 1.72; GRADE: low quality); and improvement in skin quality (RR: 1.00; 95%-CI: 0.99 - 1.01; GRADE: moderate quality). However, a statistically significant difference was seen with respect to the participants’ preference: participants from the split-patient trial preferred MAL-PDT over ALA-PDT (RR: 0.2; 95%-CI: 0.05 - 0.76; GRADE: moderate quality).
Additional results and comments:

Moloney and Collins[56] reported data on the rate of complete clearance: in the ALA-PDT group the rate was 6/15 and in the MAL-PDT group 7/15. This means that no statistically significant difference between the interventions was seen (RR: 0.86; 95%-CI: 0.38 to 1.95). For methodological reasons, data from intraindividual comparisons could not be included into GRADE profiles that similarly include data from interindividual comparisons. This also applies to data on pain during the treatment: Moloney and Collins[56] reported higher pain scores on a statistically significant level (paired Student's t-test) for the ALA-PDT treated side as compared to the MAL-PDT treated side at minute 12 and 16 during the treatment. The study by Moloney and Collins[56] had a sample size of 16 participants, not 30 as reported in the GRADE profile due to methodological reasons (see below).
The statistically significant difference with respect to the rate of complete clearance is of uncertain clinical importance due to the small effect size (confidence interval crosses the minimal important difference threshold line).

Question: Should ALA-PDT vs MAL-PDT be used in patients with single AK lesions and / or patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With MAL-PDT	With ALA-PDT		Risk with MAL-PDT / Risk difference with ALA-PDT (95% CI)
Participant complete clearance (CRITICAL OUTCOME)										
494 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	undetected	⨁⨁◯◯ LOW[1,2] due to indirectness, imprecision	158/246 (64.2%)	194/248 (78.2%)	**RR 1.22** (1.09 to 1.37)	**642 per 1000** / **141 more per 1000** (from 58 more to 238 more)
Mean reduction in lesion counts (CRITICAL OUTCOME; Better indicated by lower values)										
30 (1 study)	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⨁⨁◯◯ LOW[3,4] due to risk of bias, imprecision	15	15	-	The mean mean reduction in lesion counts in the intervention groups was **0.6 higher** (1.28 lower to 2.48 higher)
Local skin reaktion in general (IMPORTANT OUTCOME)										
495 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[1] due to indirectness	198/247 (80.2%)	200/248 (80.6%)	**RR 1.01** (0.92 to 1.1)	**802 per 1000** / **8 more per 1000** (from 64 fewer to 80 more)
Burning (IMPORTANT OUTCOME)										
495 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[1] due to indirectness	222/247 (89.9%)	212/248 (85.5%)	**RR 0.95** (0.89 to 1.02)	**899 per 1000** / **45 fewer per 1000** (from 99 fewer to 18 more)
Pain (IMPORTANT OUTCOME)										
495 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[1] due to indirectness	180/247 (72.9%)	172/248 (69.4%)	**RR 0.95** (0.85 to 1.06)	**729 per 1000** / **36 fewer per 1000** (from 109 fewer to 44 more)
Cosmetic outcome: good/ very good (IMPORTANT OUTCOME)										
494 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[1] due to indirectness	111/246 (45.1%)	107/248 (43.1%)	**RR 0.96** (0.78 to 1.17)	**451 per 1000** / **18 fewer per 1000** (from 99 fewer to 77 more)
Cosmetic outcome: unsatisfactory/impaired (IMPORTANT OUTCOME)										
495 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	undetected	⨁⨁◯◯ LOW[1,4] due to indirectness, imprecision	20/247 (8.1%)	19/248 (7.7%)	**RR 0.94** (0.52 to 1.72)	**81 per 1000** / **5 fewer per 1000** (from 39 fewer to 58 more)
Improvement in skin quality (IMPORTANT OUTCOME)										
495 (1 study)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[1] due to indirectness	247/247 (100%)	248/248 (100%)	**RR 1.00** (0.99 to 1.01)	**1000 per 1000** / **0 fewer per 1000** (from 10 fewer to 10 more)
Participant's preference (CRITICAL OUTCOME)										
30 (1 study)	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁◯ MODERATE[3] due to risk of bias	10/15 (66.7%)	2/15 (13.3%)	**RR 0.2** (0.05 to 0.76)	**667 per 1000** / **533 fewer per 1000** (from 160 fewer to 633 fewer)

[1] Study included patients with single und multiple lesions (4 to 8 AK lesions; mean: 6.1 and 6.1)
[2] CI crosses MID threshold (stat. sig. difference of uncertain clinical importance)
[3] Unclear randomization method and allocation concealment, selective reporting
[4] CI crosses MID thereshold and line of no effect (uncertain whether there is any difference)

4.11.7 Additional reasoning and recommendations

The weak recommendation for using ALA-PDT in immunosuppressed patients is based on indirect evidence from the efficacy data of MAL-PDT in immunosuppressed patients and clinical experience with respect to efficacy and tolerability. There is concern and debate about the possibility of an increased risk for the development of SCC in immunosuppressed patients after PDT due to a possible mutagenic potential; however, there are two papers showing no increase of the risk for SCC development after PDT.[57, 58]

Recommendation	Strength of recommendation	Percentage of agreement
We suggest using ALA-PDT in patients with single AK lesions.	↑	≥75%
We recommend using ALA-PDT in patients with multiple AK lesions or field cancerization.	↑↑	≥75%
We suggest using ALA-PDT in immunosuppressed patients with AK.	↑	≥90%

4.12 Methylaminolevulinate photodynamic therapy (MAL-PDT)

4.12.1 MAL-PDT vs. placebo-PDT in immunocompetent participants

Study and patient characteristics / Interventions / Outcomes:
Six RCTs[51, 59-63] compared Methylaminolevulinate (MAL)-photodynamic therapy (PDT) with placebo-PDT. Table 3 lists details on the study and participants' characteristics, the interventions used and outcomes of the studies. No studies including solely participants with single AK lesions were available.

Table 3: MAL-PDT vs. placebo-PDT - Study and participants' characteristics, intervention and outcomes

Study	N	Incl. criteria	Mean AK	Mean age (years)	Mode of MAL-PDT	Outcome
Dirschka 2012[51]	322	4 to 8 mild to moderate actinic keratoses, 1 lesion confirmed histologically	6.3 (MAL-PDT group) and 6.4 (placebo-PDT group)	71.0 (MAL-PDT group) and 71.5 (placebo-PDT group)	MAL-PDT with 16% cream concentration; 1 or 2 treatments, second treatment in case of remaining lesions 12 weeks after first PDT; interval between treatments: 12 weeks; incubation: occlusive, light-tight dressing over cream for 3 hours; type of light: red light; light source: Aktilite CL 128, Omnilux PDT, PhotoDyn 750 505, and Waldmann PDT 1200L; wavelength (nm): 580 – 1400; energy fluence (J/cm²): 37 - 170	Rate of complete clearance 12 weeks after PDT
Pariser 2003[60]	80	4 to 10 previously-untreated mild (slightly palpable, better felt than seen) to moderate (moderately thick, easily felt and seen) non-pigmented actinic keratoses, at least	6.2 (MAL-PDT group) and 6.4 (placebo-PDT group)	64 (MAL-PDT group) and 67 (placebo-PDT group)	MAL-PDT with 16% cream concentration; 2 treatments at an interval of 1 week; application of cream: 1 mm thick onto lesion and 5 mm of surrounding tissue; incubation with an occlusive dressing for 3 hours; type of light: red light; wavelength (nm): 570-670; energy fluence (J/cm²): 75;	Rate of complete clearance 12 weeks after PDT

		3 mm in diameter			intensities (mW/cm²): 50 to 200; exposure time: 8 min	
Pariser 2008[59]	100	4 to 10 lesions, untreated, unpigmented, non-hyperkeratotic, grade 1 or 2, at least 3 mm in diameter	Median: 8	66.1 (MAL-PDT group) and 66.7 (placebo-PDT group)	MAL-PDT with 16.8% cream concentration; 2 treatments at an interval of 1 week; application of cream: 1 mm thick onto lesion and 5 mm of surrounding tissue; incubation with an occlusive dressing for 3 hours; type of light: red light LED; light source: Aktilite CL 128; wavelength (nm): 630; energy fluence (J/cm²): 37; exposure time: 8 min	Rate of complete clearance 12 weeks after PDT
Photocure-Australian 2004[61]	11	Non-hyperkeratotic actinic keratoses	<4 AK lesions: 63% of pts.; 4-10 AK lesions: 31%; >10 AK lesions: 6%	No data	MAL-PDT with 16.8% cream concentration; 2 treatments at an interval of 1 week; application of cream: lesion and 5 mm of surrounding tissue; incubation with an occlusive dressing for 2.5 to 4 hours; type of light: red light; wavelength (nm): 570-670; energy fluence (J/cm²): 75	Rate of complete and partial clearance 12 weeks after PDT
Photocure-US 2004[62]	80	4 – 10 non-hyperkeratotic actinic keratoses	No data	No data	MAL-PDT with 16.8% cream concentration; 2 treatments at an interval of 1 week; application of cream: lesion and 5 mm of surrounding tissue; incubation with an occlusive dressing for 2.5 to 4 hours; type of light: red light; wavelength (nm): 570-670; energy fluence (J/cm²): 75	Rate of complete and partial clearance 12 weeks after PDT
Szeimies 2009[63]	115	4 to 10 previously untreated actinic keratoses, non-pigmented, non-hyperkeratotic, grade 1 or 2, ≥ 3 mm in diameter	Median: 7	69.5 (MAL-PDT group) and 67.0 (placebo-PDT group)	MAL-PDT with 16% cream concentration; 2 treatments at an interval of 1 week; application of cream: 1 mm thick onto lesion and 5 mm of surrounding tissue; incubation with an occlusive dressing for 3 hours; type of light: red light LED; light source: Aktilite CL 128; wavelength (nm): 630; energy fluence (J/cm²): 37; intensities: 56 to 83; exposure time: 9 min	Rate of complete clearance 12 weeks after PDT

Results (see table below):

MAL-PDT was statistically significantly superior to placebo-PDT with respect to the rate of complete clearance (RR: 4.22; 95%-CI: 3.19 - 5.59; GRADE: moderate quality) and partial clearance (RR: 3.28; 95%-CI: 1.73 - 6.23; GRADE: low quality).

Additional results and comments:

None.

Question: Should MAL-red light PDT vs placebo-red light PDT be used in patients with single AK lesions and/or patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo-red light PDT	With MAL-red light PDT		Risk with placebo-red light PDT	Risk difference with MAL-red light PDT (95% CI)
Participant complete clearance [1-2 treatments] (CRITICAL OUTCOME)											
804 (6 studies)	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⊟⊟⊟⊟ MODERATE[1] due to indirectness	43/280 (15.4%)	362/524 (69.1%)	**RR 4.22** (3.19 to 5.59)	**154 per 1000**	**494 more per 1000** (from 336 more to 705 more)
Participant partial (>75%) clearance (CRITICAL OUTCOME)											
191 (2 studies)	serious[2]	no serious inconsistency	serious[1]	no serious imprecision	undetected	⊟⊟⊟⊟ LOW[1,2] due to risk of bias, indirectness	16/61 (26.2%)	111/130 (85.4%)	**RR 3.28** (1.73 to 6.23)	**262 per 1000**	**598 more per 1000** (from 191 more to 1000 more)

[1] All studies included participants with single AK lesions and multiple AK lesions / field cancerization

[2] Unclear randomisation methods in both studies, no additional data on methodology was provided (data source= product insert)

4.12.2 MAL-PDT vs. placebo-PDT in immunosuppressed patients

Study and patient characteristics:

One intraindividual (split-patient) RCT[64] compared MAL-redlight PDT with placebo-red light PDT in a sample of immunosuppressed organ transplant recipients. Dragieva et al.[64] included 17 organ transplant recipients (13 kidney, 4 heart) with a mean number of 7.6 AK lesions. Mean age of the participants was 61 years.

Interventions:

MAL 160mg/g or placebo cream was applied to the lesional field and 5 mm of the surrounding tissue and incubated for 3 hours under an occlusive dressing. Two treatments with an interval of one week were applied. Type of light: visible non-coherent light; light source: Waldmann PDT 1200; wavelength (nm): 600-730; energy fluence (J/cm²): 75; intensity (mW/cm²): 80.

Outcomes:

Dragieva et al. reported the rate of complete clearance 16 weeks after the second PDT treatment.

Results (see table below):

MAL-PDT was statistically significantly more effective than placebo-PDT, concerning the rate of complete clearance (RR: 27.00; 95%-CI: 1.73 - 420.67; GRADE: low quality).

Additional results and comments:

None.

Question: Should MAL-red light PDT vs placebo-red light PDT be used in immunosuppressed patients with AK?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo-red light PDT	With MAL-red light PDT		Risk with Placebo-red light PDT	Risk difference with MAL-red light PDT (95% CI)
Participant complete clearance [2 treatments] (CRITICAL OUTCOME)											
34 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊟⊟⊟⊟ LOW[1,2] due to risk of bias, imprecision	0/17 (0%)	13/17 (76.5%)	**RR 27** (1.73 to 420.67)	**0 per 1000**	-

[1] unclear randomization method and allocation concealment, no blinding

[2] very wide CI

4.12.3 MAL-PDT vs. cryotherapy

For details on the study and participants' characteristics and the results see comparison 4.2.5 (cryotherapy vs. methylaminolevulinate-photodynamic therapy (MAL-PDT)).

Four RCTs compared methyl-aminolevulinic acid-photodynamic therapy (MAL-PDT) with cryotherapy.[16-19]
With respect to withdrawals due to AE, no statistically significant differences were seen (GRADE: very low quality), as well as with respect to the participant's rating of the cosmetic outcome as excellent or good (GRADE: low quality). For photosensitivity reaction, a lower rate was seen in the cryotherapy group, when compared to the MAL-PDT group (GRADE: very low quality). For the event 'cold exposure injury', a higher rate was seen in the cryotherapy group (GRADE: very low quality). An "excellent or good" cosmetic outcome as rated by the investigator was seen in a higher proportion of participants who were assigned to the MAL-PDT group (statistically significant difference of uncertain clinical importance due to the small effect size; GRADE: very low quality). Participants from the intraindividual split-patient trial preferred MAL-PDT over cryotherapy (GRADE: low quality) and a lower proportion of patients was satisfied with the cryotherapy (GRADE: very low quality).

4.12.4 MAL-PDT vs. 5% imiquimod

Study and patient characteristics:
Two RCTs[47, 48] compared Methylaminolevulinate-photodynamic therapy (MAL-PDT) with 5% imiquimod cream. The study by Serra-Guillen et al. (2011)[47] included a sample of 58 participants with at least six non-hyperkeratotic AK lesions in a 25 cm² area (no data on mean age and on the mean number of AK lesions per participant). The study from 2012[48] included a sample of 73 participants with the same inclusion criteria, mean age of the participants was 72.7 and 74.3 years and the mean number of AK lesions 9.0 and 9.4 in the MAL-PDT group and in the 5% imiquimod group, respectively. No studies including participants with single AK lesions were eligible.
Interventions:
MAL cream was applied over the whole treatment area and incubated for 3 hours. Illumination was performed with the following parameters: light source: Aktilite CL 128 model diode lamp; energy fluence (J/cm²): 37, from 5 cm distance; exposure time: 8 min. After the illumination fusidic acid cream was applied.
5% imiquimod cream was applied to the treatment area three times per week for eight hours over night and then washed off. The treatment was applied for four weeks.
Outcomes:
Satisfaction with the treatment (on a Likert-scale from 0 to 10, with the value of 8-10 grouped as "very satisfied") was assessed one month after the end of the treatment period.[47, 48] Serra-Guillen et al. (2012)[48] additionally assessed the rate of complete and partial clearance at the one month posttreatment visit.
Results (see table below):
There was no statistically significant difference between the interventions concerning efficacy: complete clearance (RR: 0.37; 95%-CI: 0.12 - 1.08; GRADE: low quality) and partial clearance rates (RR: 1.30; 95%-CI: 0.92 - 1.84; GRADE: low quality). A statistically significantly higher rate of participants was "very satisfied" with MAL-PDT than with 5% imiquimod (RR: 1.49; 95%-CI: 1.21 - 1.84; GRADE: moderate quality).
Additional results and comments:
None.

Question: Should MAL-PDT vs 5% imiquimod be used in patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 5% imiquimod	With MAL-PDT		Risk with 5% imiquimod	Risk difference with MAL-PDT (95% CI)
Participant's complete clearance at 1 month posttreatment (CRITICAL OUTCOME)											
73 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	9/33 (27.3%)	4/40 (10%)	RR 0.37 (0.12 to 1.08)	273 per 1000	172 fewer per 1000 (from 240 fewer to 22 more)
Participant's partial clearance at 1 month posttreatment (CRITICAL OUTCOME)											
73 (1 study)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	19/33 (57.6%)	30/40 (75%)	RR 1.3 (0.92 to 1.84)	576 per 1000	173 more per 1000 (from 46 fewer to 484 more)
Participant's satifaction (1 months after completion of treatment): very satisfied (CRITICAL OUTCOME)											
131 (2 studies)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ MODERATE[1] due to risk of bias	38/62 (61.3%)	63/69 (91.3%)	RR 1.49 (1.21 to 1.84)	613 per 1000	300 more per 1000 (from 129 more to 515 more)

[1] Unclear randomization method and allocation concealment, no blinding

[2] CI crosses MID thereshold and line of no effect (uncertain whether there is any difference)

4.12.5 MAL-PDT vs. ALA-PDT

For details on the study and participants' characteristics and the results see comparison 4.11.6 (ALA-PDT vs. MAL-PDT).

Two RCTs[51, 56] compared Methylaminolevulinate-photodynamic therapy (MAL-PDT) with 5-aminolaevulinic acid-photodynamic therapy (ALA-PDT). The study by Dirschka et al.[51] could demonstrate a statistically significant superiority of ALA-PDT when compared to MAL-PDT with respect to the rate of complete clearance (GRADE: low quality). However, the effect is of uncertain clinical importance due to the small effect size (see comment). The intraindividual study by Moloney and Collins[56] does not show a statistically significant difference between the interventions concerning complete clearance (these data could not be pooled together due to the inter- and intraindividual study design). No statistically significant difference was seen with respect to the mean reduction in lesion counts from baseline to one month after the treatment (GRADE: low quality). No statistically significant differences were seen with respect to minor adverse events and cosmetic outcomes: local skin reactions in general (GRADE: moderate quality); burning (GRADE: moderate quality); pain (GRADE: moderate quality); the rate of participants whose cosmetic outcome was rated as "good/very good" (GRADE: moderate quality); the rate of participants whose cosmetic outcome was rated as "unsatisfactory/impaired" (GRADE: low quality); and improvement in skin quality (GRADE: moderate quality). However, a statistically significant difference was seen with respect to the participants' preference: participants from the split-patient trial preferred MAL-PDT over ALA-PDT (GRADE: moderate quality).

Additional results and comments:

Moloney and Collins[56] reported data on the rate of complete clearance: in the ALA-PDT group the rate was 6/15 and in the MAL-PDT group 7/15. This means that no statistically significant difference between the interventions was seen (RR: 0.86; 95%-CI: 0.38 to 1.95). For methodological reasons, data from intraindividual comparisons could not be included into GRADE profiles that similarly include data from interindividual comparisons. This also applies to data on pain during the treatment: Moloney and Collins[56] reported higher pain scores on a statistically significant level (paired Student's t-test) for the ALA-PDT treated side as compared to the MAL-PDT treated side at minute 12 and 16 during the treatment.

The statistically significant difference with respect to the rate of complete clearance in the study by Dirschka et al.[51] is of uncertain clinical importance due to the small effect size (confidence interval crosses the minimal important difference threshold line).

4.12.6 Additional reasoning and recommendations

There is concern and debate about the possibility of an increased risk for the development of SCC in immunosuppressed patients after PDT due to a possible mutagenic potential; however, there are two papers showing no increase of the risk for SCC development after PDT.[57, 58]

Recommendation	Strength of recommendation	Percentage of agreement
We suggest using MAL-PDT in patients with single AK lesions.	↑	≥75%
We recommend using MAL-PDT in patients with multiple AK lesions or field cancerization.	↑↑	≥75%
We suggest using MAL-PDT in immunosuppressed patients with AK.	↑	≥75%

4.13 0.5% 5-fluorouracil + 10% salicylic acid (5-FU/SA)

4.13.1 0.5% 5-fluorouracil + 10% salicylic acid vs. 10% salicylic acid

Study and patient characteristics:
One RCT[12] compared 0.5% 5-fluorouracil in combination with 10% salicylic acid (5-FU/SA) with its vehicle in a sample of 285 participants with 4-10 AK lesions of grade I-II in an area of 25 cm² and a mean age of 71.9 (5-FU/SA group) and 72.3 years (vehicle group). Mean number of AK lesions were 5.8 (5-FU/SA group) and 5.5 (vehicle group. No studies including solely samples of participants with single or with multiple AK lesions / field cancerization were eligible.
Interventions:
0.5% 5-FU in combination with salicylic acid 10% solution was applied to the treatment field once daily until the AK lesions completely cleared or for a maximum of 12 weeks. If severe side effects occurred, the frequency of drug application could be reduced to three times per week.
Outcomes:
Stockfleth et al.[12] assessed the rate of complete clearance, the physicians' global assessment of the outcome as "good/very good" and the participant's overall assessment of the clinical improvement as "good/very good", eight weeks after the end of the treatment.
Results (see table below):
In the study conducted by Stockfleth et al.,[12] 0.5% 5-fluorouracil in combination with 10% salicylic acid was statistically significantly more effective than salicylic acid alone with respect to the rate of complete clearance (RR: 3.80; 95%-CI: 2.30 - 6.27; GRADE: low quality), the rate of physician's global assessment as "good/very good" (RR: 1.68; 95%-CI: 1.39 - 2.03; GRADE: low quality) and the rate of participant's global assessment of the clinical improvement as "good/very good" (RR: 1.40; 95%-CI: 1.20 - 1.62; GRADE: very low quality).
Additional results and comments:
The statistically significant differences with respect to the rate of physician's and participants' global assessment as "good/very good" are of uncertain clinical importance due to the small effect size (confidence interval crosses the minimal important difference threshold line).

Question: Should 0.5% 5-FU/ 10% salicylic acid vs vehicle (10% salicylic acid) be used in patients with single AK lesions and/or patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Vehicle (10% salicylic acid)	With 0.5% 5-FU/ 10% salicylic acid		Risk with Vehicle (10% salicylic acid)	Risk difference with 0.5% 5-FU/ 10% salicylic acid (95% CI)
Participant's complete clearance at 8 weeks posttreatment (CRITICAL OUTCOME)											
273 (1 study)	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⨁◯◯ LOW[1,2] due to risk of bias, indirectness	14/96 (14.6%)	98/177 (55.4%)	RR 3.8 (2.3 to 6.27)	146 per 1000	408 more per 1000 (from 190 more to 769 more)
Physicians's global assessment of outcome at 8 weeks posttreatment: very good/good (CRITICAL OUTCOME)											
268 (1 study)	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⨁◯◯ LOW[1,2] due to risk of bias, indirectness	51/93 (54.8%)	161/175 (92%)	RR 1.68 (1.39 to 2.03)	548 per 1000	373 more per 1000 (from 214 more to 565 more)
Participant's global improvement assessment at 8 weeks posttreatment: very good/good											
268 (1 study)	very serious[3]	no serious inconsistency	serious[2]	serious[4]	undetected	⨁◯◯◯ VERY LOW[2,3,4] due to risk of bias, indirectness, imprecision	62/93 (66.7%)	163/175 (93.1%)	RR 1.4 (1.2 to 1.62)	667 per 1000	267 more per 1000 (from 133 more to 413 more)

[1] unclear allocation concealment and blinding of personell and participants, incomplete and inconsistent (outcome)- data,

[2] Study included participants both with single and multiple AK lesions / field cancerization (mean: 5.5 and 5.8 AK lesions)

[3] unclear allocation concealment and blinding of personell and participants (subjective outcomes), incomplete and inconsistent (outcome)- data,

[4] CI crosses the MID threshould (stat. significant differences of uncertain clinical importance)

4.13.2 0.5% 5-fluorouracil + 10% SA vs. 3% diclofenac in 2.5% HA

Study and patient characteristics:

One RCT[12] compared 0.5% 5-fluorouracil in combination with 10% salicylic acid with 3% diclofenac in 2.5% hyaluronic acid in a sample of 372 participants with 4-10 AK lesions of grade I-II in an area of 25 cm² (mean 5.8 AK lesions per participant) and a mean age of 71.9 (5-FU/SA group) and 71.6 years (diclofenac group). No studies including solely samples of participants with single or with multiple AK lesions / field cancerization were eligible.

Interventions:

0.5% 5-FU in combination with salicylic acid 10% solution was applied to the treatment field once daily until the AK lesions completely cleared or for a maximum of 12 weeks. 3% diclofenac in hyaluronic acid was applied to the treatment area twice daily, equally until the AK lesions completely cleared or for a maximum of 12 weeks. If severe side effects occurred, the frequency of drug application could be reduced to three times per week (0.5% 5-FU in combination with salicylic acid 10% solution) or to once daily (3% diclofenac in hyaluronic acid).

Outcomes:

Stockfleth et al.[12] assessed the rate of complete clearance, the physicians' global assessment of the outcome as "good/very good" and the participant's overall assessment of the clinical improvement as "good/very good", eight weeks after the end of the treatment. Furthermore, application-site irritation and minor adverse events (treatment-emergent AE in total, infections and infestations, and administration-site reactions related to the treatment) were assessed during the period of the study.

Results (see table below):

Stockfleth et al.,[12] could demonstrate that 0.5% 5-fluorouracil in combination with 10% salicylic acid was statistically significantly more effective than diclofenac 3% in hyaluronic acid with respect to the rate of complete clearance (RR: 1.72; 95%-CI: 1.34 - 2.20; GRADE: low quality), the rate of participant's global assessment as "good/very good" (RR: 1.14; 95%-CI: 1.05 - 1.24; GRADE: very low quality) and the rate of physician's global assessment of the clinical improvement as "good/very good" (RR: 1.25; 95%-CI: 1.13 - 1.38; GRADE: very low quality). In the 0.5% 5-fluorouracil in combination with 10% salicylic acid group, a statistically significantly higher rate of minor adverse events with respect to application-site irritation (RR: 2.24; 95%-CI: 1.85 - 2.72; GRADE: low quality), treatment emergent adverse

events (RR: 1.24; 95%-CI: 1.14 - 1.35; GRADE: very low quality) and administration site reaction (RR: 1.47; 95%-CI: 1.30 - 1.65; GRADE: low quality) was seen. No statistically significant difference with respect to the rate of infections and infestations was seen (RR: 0.99; 95%-CI: 0.54 - 1.81; GRADE: very low quality).

Additional results and comments:

The statistically significant differences with respect to the rate of physician's and participant's global assessment as "good/very good" as well as with respect to the rate of treatment emergent adverse events are of uncertain clinical importance due to the small effect size (confidence interval crosses the minimal important difference threshold line).

Question: Should 0.5% 5-FU/ 10% salicylic acid vs 3% diclofenac in HA be used for patients with single AK lesions and/or patients with multiple AK lesions / field cancerization?

Bibliography: see description of study and patient characteristics.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 3% diclofenac in HA	With 0.5% 5-FU/ 10% salicylic acid		Risk with 3% diclofenac in HA	Risk difference with 0.5% 5-FU/ 10% salicylic acid (95% CI)
Participant's complete clearance at 8 weeks posttreatment (CRITICAL OUTCOME)											
360 (1 study)	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⨁◯◯ LOW[1,2] due to risk of bias, indirectness	59/183 (32.2%)	98/177 (55.4%)	**RR 1.72** (1.34 to 2.2)	**322 per 1000**	**232 more per 1000** (from 110 more to 387 more)
Physicians's global assessment of outcome at 8 weeks posttreatment: very good/good (CRITICAL OUTCOME)											
350 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	129/175 (73.7%)	161/175 (92%)	**RR 1.25** (1.13 to 1.38)	**737 per 1000**	**184 more per 1000** (from 96 more to 280 more)
Participant's global improvement assessment at 8 weeks posttreatment: very good/good (CRITICAL OUTCOME)											
349 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	142/174 (81.6%)	163/175 (93.1%)	**RR 1.14** (1.05 to 1.24)	**816 per 1000**	**114 more per 1000** (from 41 more to 196 more)
Application-site reaction: irritation (IMPORTANT OUTCOME)											
372 (1 study)	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⨁◯◯ LOW[1,2] due to risk of bias, indirectness	71/185 (38.4%)	161/187 (86.1%)	**RR 2.24** (1.85 to 2.72)	**384 per 1000**	**476 more per 1000** (from 326 more to 660 more)
Minor AE: treatment-emergent AE in total (IMPORTANT OUTCOME)											
372 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[3]	undetected	⨁◯◯◯ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	142/185 (76.8%)	178/187 (95.2%)	**RR 1.24** (1.14 to 1.35)	**768 per 1000**	**184 more per 1000** (from 107 more to 269 more)
Minor AE: infections and infestations (IMPORTANT OUTCOME)											
372 (1 study)	serious[1]	no serious inconsistency	serious[2]	serious[4]	undetected	⨁◯◯◯ VERY LOW[1,2,4] due to risk of bias, indirectness, imprecision	19/185 (10.3%)	19/187 (10.2%)	**RR 0.99** (0.54 to 1.81)	**103 per 1000**	**1 fewer per 1000** (from 47 fewer to 83 more)
Minor AE: administration-site reaction, related (irritation, inflammation, pruritus)) (IMPORTANT OUTCOME)											
372 (1 study)	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	undetected	⨁⨁◯◯ LOW[1,2] due to risk of bias, indirectness	116/185 (62.7%)	172/187 (92%)	**RR 1.47** (1.3 to 1.65)	**627 per 1000**	**295 more per 1000** (from 188 more to 408 more)

[1] unclear allocation concealment and blinding of personell and participants, incomplete and inconsistent (outcome)- data,

[2] Study included participants both with single and multiple AK lesions / field cancerization (mean: 5.5 and 5.8 AK lesions)

[3] CI crosses the MID threshould (stat. significant differences of uncertain clinical importance)

[4] CI crosses the MID threshould and line of no effect (uncertain whether there is any difference)

4.13.3 Additional reasoning and recommendations

Recommendation	**Strength of recommendation**	**Percentage of agreement**
We suggest using 0.5% 5-fluorouracil + 10% salicylic acid for discrete, hyperkeratotic lesions in patients with single AK lesions.*	↑	≥75%
We suggest using 0.5% 5-fluorouracil + 10% salicylic acid for	↑	≥90%

discrete, hyperkeratotic lesions in patients with multiple AK lesions or field cancerization.*		
We cannot make a recommendation with respect to 0.5% 5-fluorouracil + 10% salicylic acid for immunosuppressed patients.	0	≥75%
* To become effective, most of the treatments need to penetrate properly into the skin. Penetration can be hindered by strong hyperkeratosis and measures to remove the hyperkeratosis may be necessary. Due to the combination with salicylic acid, this treatment is particularly deemed appropriate for the treatment of discrete hyperkeratotic AK.		

5 Treatment-related recommendations (overview)

In the following chapter, an overview of the recommendations for the different patient subgroups is presented (Table 4, Table 5 and Table 6).

5.1 Recommendations for patients who have single AK lesions

Table 4: Recommendations for patients who have single AK lesions

Intervention	**Evidence / reasoning, see chapter (long version / results report)**	Strength of the recommendation	Percentage of agreement
For patients who have single AK lesions, we recommend using (↑↑) …			
Cryotherapy	8.2 / 3.2	↑↑	≥75%
For patients who have single AK lesions, we suggest using (↑) …			
curettage (discrete, hyperkeratotic lesions)	8.1 / 3.1	↑	≥90%
0.5% 5-fluorouracil	8.5 / 3.5	↑	≥75%
5% 5-fluorouracil	8.6 / 3.6	↑	≥50%[1]
0.5% 5-fluorouracil + 10% salicylic acid (discrete, hyperkeratotic lesions)[2]	8.13 / 3.13	↑	≥75%
3.75% imiquimod	8.8 / 3.8	↑	≥90%
5% imiquimod	8.9 / 3.9	↑	≥75%
ingenol mebutate 0.015% (lesions on the face or scalp) and ingenol mebutate 0.05% (lesions on the trunk or extremities)	8.10 / 3.10	↑	≥75%
ALA-PDT	8.11 / 3.11	↑	≥75%
MAL-PDT	8.12 / 3.12	↑	≥75%
We cannot make a recommendation (0) for patients who have single lesions with respect to …			
3% diclofenac in 2.5% hyaluronic acid gel	8.4 / 3.4	0	≥75%
2.5% imiquimod	8.7 / 3.7	0	≥90%
CO_2 laser and Er:YAG laser	8.3 / 3.3	0	≥75%

1 *Experts who did not agree voted for making a strong recommendation (↑↑) or no recommendation (0) for the use of 5% 5-fluorouracil in patients with single AK lesions.*

2 *To become effective, most of the treatments need to penetrate properly into the skin. Penetration can be hindered by strong hyperkeratosis and measures to remove the hyperkeratosis may be necessary. Due to the combination with salicylic acid, this treatment is particularly deemed appropriate for the treatment of discrete hyperkeratotic AK.*

5.2 Recommendations for multiple AK lesions / field cancerization

Table 5: Recommendations for patients who have multiple AK lesions or field cancerization

Intervention	Evidence / reasoning, see chapter (long version / results report)	Strength of the recommendation	Percentage of agreement
For patients who have multiple AK lesions / field cancerization, we recommend using (↑↑) …			
0.5% 5-fluorouracil	8.5 / 3.5	↑↑	≥50%[3]
3.75% imiquimod	8.8 / 3.8	↑↑	≥90%
ingenol mebutate 0.015% (lesions on the face or scalp) and ingenol mebutate 0.05% (lesions on the trunk or extremities)	8.10 / 3.10	↑↑	≥50%[4]
ALA-PDT	8.11 / 3.11	↑↑	≥75%
MAL-PDT	8.12 / 3.12	↑↑	≥75%
For patients who have multiple AK lesions / field cancerization, we suggest using (↑) …			
Cryotherapy (patients with multiple lesions, especially for multiple discrete lesions; not suitable for the treatment of field cancerization)	8.2 / 3.2	↑	≥90%
3% diclofenac in 2.5% hyaluronic acid gel	8.4 / 3.4	↑	≥75%
5% 5-fluorouracil	8.6 / 3.6	↑	≥50%[5]
0.5% 5-fluorouracil + 10% salicylic acid (discrete, hyperkeratotic lesions)[6]	8.13 / 3.13	↑	≥90%
5% imiquimod	8.9 / 3.9	↑	≥75%
2.5% imiquimod	8.7 / 3.7	↑	≥75%
CO_2 laser and Er:YAG laser	8.3 / 3.3	↑	≥50%[7]
We cannot make a recommendation (0) for patients who have multiple AK lesions / field cancerization with respect to …			
Curettage	8.1 / 3.1	0	≥90%

3 *Experts who did not agree voted for making a weak recommendation (↑) for the use of 0.5% 5-fluorouracil in patients with multiple lesions or field cancerization.*

4 *Experts who did not agree voted for making a weak recommendation (↑) for the use of imiquimod in patients with multiple lesions or field cancerization.*

5 *Experts who did not agree voted for making a strong recommendation (↑↑) for the use of 5% 5-fluorouracil in patients with multiple lesions or field cancerization.*

6 *To become effective, most of the treatments need to penetrate properly into the skin. Penetration can be hindered by strong hyperkeratosis and measures to remove the hyperkeratosis may be necessary. Due to the combination with salicylic acid, this treatment is particularly deemed appropriate for the treatment of discrete hyperkeratotic AK.*

7 *Experts who did not agree to this recommendation voted for making no recommendation (0) for the use of CO2 laser or Er:YAG laser in patients with multiple lesions or field cancerization.*

5.3 Recommendations for immunocompromized patients with AK

Table 6: Recommendations for immunocompromized patients who have AK

Recommendations for immunocompromized patients presenting with AK	**Evidence / reasoning: see chapter (long version / results report)**	Strength of the recommendation	Percentage of agreement
For immunosuppressed patients who have AK, we suggest using (↑) …			
Cryotherapy (especially for single lesions or multiple discrete lesions; not suitable for the treatment of field cancerization)	8.2 / 3.2	↑	≥75%
curettage (discrete, hyperkeratotic lesions)	8.1 / 3.1	↑	≥75%
5% fluorouracil	8.6 / 3.6	↑	≥75%
5% imiquimod[8]	8.9 / 3.9	↑	≥50%[9]
ALA-PDT	8.11 / 3.11	↑	≥90%
MAL-PDT	8.12 / 3.12	↑	≥75%
We cannot make a recommendation (0) for immunosuppressed patients who have AK with respect to …			
3% diclofenac in 2.5% hyaluronic acid gel	8.4 / 3.4	0	≥90%
0.5% 5-fluorouracil	8.5 / 3.5	0	≥75%
0.5% 5-fluorouracil + 10% salicylic acid	8.13 / 3.13	0	≥75%
2.5% imiquimod	8.7 / 3.7	0	≥90%
3.75% imiquimod	8.8 / 3.8	0	≥90%
ingenol mebutate	8.10 / 3.10	0	≥90%
For immunosuppressed patients who have AK, we suggest NOT using (↓) …			
CO_2 laser and Er:YAG laser	8.3 / 3.3	↓	≥75%

8 *For immunosuppression, different clinical situations may exist, e.g. iatrogenic medical immunosuppression after organ transplantation, iatrogenic medical immunosuppression because of autoimmune disorders, immunosuppression due to other reasons (hematologic disorders, AIDS etc). Depending on the underlying disease, special care has to be given to the selection of the treatment to avoid (auto-) immunstimulation that may lead to a worsening of the underlying condition.*

9 *Experts who did not agree voted for making a strong recommendation (↑↑) for the use of 5% imiquimod in immunosuppressed patients.*

6 Overview: Recommendations for the treatment of AK

		single AK lesions ≥ 1 and ≤ 5 palpable or visible AK lesions per field or affected body region	**multiple AK lesions** ≥ 6 distinguishable AK lesions in one body region or field	**field cancerization** ≥ 6 AK lesions in one body region or field, and contiguous areas of chronic actinic sun damage and hyperkeratosis	**Immunocompromised patients with AK** AK at any of the mentioned severity degrees and a concomitant condition of immunosuppression
		Sun protection in all patient subgroups!			
Strength of recommendation	↑↑	Cryotherapy	0.5% 5-FU 3.75% imiquimod Ingenol mebutate 0.015% / 0.05% MAL-PDT, ALA-PDT		-
	↑	Curettage* 0.5% 5-FU, 5% 5-FU 0.5% 5-FU + 10% SA* 3.75% imiquimod 5% imiquimod ingenol mebutate 0.015/0.05% ALA-PDT, MAL-PDT	Cryotherapy** 3% diclofenac in 2.5% HA 5% 5-FU 0.5% 5-FU + 10% SA* 5% imiquimod, 2.5% imiquimod CO2-laser, Er:YAG-laser		cryotherapy** curettage* 5% 5-FU 5% imiquimod*** ALA-PDT, MAL-PDT
	0	3% diclofenac in 2.5% HA 2.5% imiquimod CO2-laser, Er:YAG-laser	Curettage*		3% diclofenac in 2.5 % HA 0.5% 5-FU 0.5% 5-FU + 10% SA 2.5% imiquimod, 3.75% imiquimod Ingenol mebutate 0.015%/0.05%
	↓	-	-		CO2-laser, Er:YAG-laser

* discrete, hyperkeratotic AK lesions
** single or multiple discrete AK lesions, not for treatment of field cancerization
*** For immunosuppression, different clinical situations may exist, e.g. iatrogenic medical immunosuppression after organ transplantation, iatrogenic medical immunosuppression because of autoimmune disorders, immunosuppression due to other reasons (hematologic disorders, AIDS etc). Depending on the underlying disease, special care has to be given to the selection of the treatment to avoid (auto-) immunstimulation that may lead to a worsening of the underlying condition.

7 Limitations, implications and future directions

From the methodological point of view, there were limitations with respect to the evidence assessment as described by Gupta et al.:[6] data from intraindividual (split-patient) studies could not be pooled with data from interindividual studies due to statistical reasons. Therefore data from intraindividual studies were not included in the meta-analyses and reported separately. For continuous data such as the mean reduction in AK lesions counts, an analysis could only be performed, if studies reported mean values and standard deviation. No attempts were made to impute standard deviations from other comparisons. Without standard deviation, data were not included in the systematic review because the statistical significance of differences could not be calculated. This led to exclusion of data from several studies. Furthermore, tests for publication bias could not be performed due to the limited number of studies contributing to each comparison.

The consensus conference was performed as an online conference. Using a questionnaire, participants were asked for their experiences during the conference. One participant reported problems with the online access during a period of the conference, impeding his participation. No further relevant problems were reported.[65]

Due to possible efficacy and safety differences, patients with concomitant conditions of immunosuppression were assessed separately. This led to a very limited amount of available data for this patient subgroup. More trials assessing the efficacy and safety of interventions in immunosuppressed patients who have AK are needed. Similarly, data for patients with single AK lesions were very limited and the majority of recommendations for this population is therefore based on expert consensus and indirect evidence from data on patients with multiple AK lesions.

Participant's self-reported outcomes, such as the quality of life, are an increasingly significant concept of efficacy measures in dermatological studies.[66] The number of studies reporting on patient-reported outcomes that were included in this review was very limited. For further research within the field of AK treatment, patient-reported outcomes as part of the primary outcomes should be assessed. Particularly, an increased use of quality of life instruments – generic and/ or specific – is desirable. Recently, an instrument specific for patients affected by AK, the 'Actinic Keratosis Quality of Life Questonnaire (AKQoL)' has been developed.[67]

Furthermore, the need for research including long-term efficacy data must be emphasized. Efficacy outcomes included in the systematic literature assessment were limited to six months after treatment to ensure comparability. This time frame was chosen by the expert panel because of the limited number of studies assessing long-term efficacy (e.g. one or two year clearance rates). Studies assessing the long-term efficacy of the different interventions are highly desirable.

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8.1 Declarations of interests

Connolly, S. M.	
Employment	Mayo Clinic Arizona
Correia, O.	
Payment for lectures including service on speakers bureaus	Abbott/AbbVie, Àvene/Pierre Fabre, Leo, Galderma, Meda, MSD, Pfizer
Erdmann, R.	
Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	European Skin Cancer Foundation
Payment for writing or reviewing the manuscript	European Skin Cancer Foundation
Foley, P.	
Advisory Board membership	LEO, PhotoCure/Galderma, Janssen, Wyeth/Pfizer, Abbott/Abbvie, GSK/Stiefel, Amgen, Novartis, Eli Lilly
Consultancy	3M/iNova, Eli Lilly
Expert testimony	PhotoCure/Galderma
Grants/grants pending	Janssen, Abbott/Abbvie, Wyeth/Pfizer, Merck Serono, Amgen, Novartis
Payment for lectures including service on speakers bureaus	LEO, PhotoCure/Galderma, 3M/iNova, Janssen, Abbott/Abbvie, Wyeth/Pfizer, Schering-Plough/MSD, CSL
Payment for development of educational presentations	LEO, Janssen, GSK/Stiefel, Abbott/Abbvie, Galderma, 3M
Travel/accommodations/meeting expenses unrelated to activities listed	Leo, 3M, Roche
Gupta, A. K.	None
Jacobs, A.	
Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	European Skin Cancer Foundation
Payment for writing or reviewing the manuscript	European Skin Cancer Foundation
Kars, H.-J.	None
Kerl, H.	
Consultancy, consulting fee or honorarium	MEDA
Lim, H. W.	
Board membership	Skin of Color Society
Royalties	Editor of textbooks: - Clinical guides to sunscreens and photoprotection - Cancer of the skin - Photodermatology
Grants	Clinuvel, Estee Lauder, Ferndale

Consultancy, consulting fee or honorarium	Uriage, Estee Lauder, Sanofi, Ferndale, Johnson & Johnson
Martin, G.	
Consultancy, consulting fee or honorarium	DUSA, Medicis/Valeant, LEO
Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	DUSA, Medicis/Valeant, LEO
Provision of writing assistance, medicines, equipment, or administrative support	Medicis/Valeant, Pharmaderm/Nycomed
Board membership	DUSA (Medical Advisory Board, not Board of Company Directors)
Payment for lectures including service on speakers bureaus	DUSA, Medicis/Valeant, LEO
Travel/accommodation/meeting expenses unrelated to activities listed	DUSA, Medicis/Valeant, LEO
Nast, A.	
Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	European Skin Cancer Foundation
Payment for writing or reviewing the manuscript	European Skin Cancer Foundation
Grants/grants pending	Intendis, Galderma, Ipsen Pharma, Kythera, GlaxoSmithKline, Biogen
Payment for lectures including service on speakers bureaus	Pfizer, Biogen Idec, Synergy, Sinclair, Intendis, AbbVie, Janssen
Payment for development of educational presentations	AbbVie
Paquet, M.	
Employment	Mediprobe Research Inc
Pariser, D. M.	
Consultancy	Abbott Labs, Amgen, Astellas US, Asubio Pharm., Brickel Biotech, Celgene Corp., Dermira, DUSA, Galderma, Genentech, LEO Pharma US, Medicis Valeant, MelaSciences, Novartis, Ortho, Peplin, Pfizer, Photocure, Stiefel/GSK
Grants/grants pending	Abbott Labs, Amgen, Astellas US, Basliea, Celgene Corp., Dow Pharmaceutical, DUSA, ELI LILLY, Galderma, Johnson and Johnson, LEO Pharma US, Medicis Valeant, Novartis, NovoNordisk, Ortho, Peplin, Pfizer, Photocure, Stiefel/GSK
Rosumeck, S.	
Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	European Skin Cancer Foundation

Payment for writing or reviewing the manuscript	European Skin Cancer Foundation
Röwert-Huber, J.	None
Sahota, A.	
Support for travel to meetings for the study or other purposes	Leo Pharma, Galderma
Payment for lectures including service on speakers bureaus	Leo Pharma, Galderma
Sangueza, O. P.	None
Shumack, S.	
Payment for lectures including service on speakers bureaus	LeoPharma, Galderma, 3M
Sporbeck, B.	
Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	European Skin Cancer Foundation
Payment for writing or reviewing the manuscript	European Skin Cancer Foundation
Stockfleth, E.	
Consultancy, consulting fee or honorarium	Meda, Almirall, Galderma, Leo, Medicis
Grants/grants pending	Meda, Leo
Payment for lectures including service on speakers bureaus	Meda, Almirall, Galderma, Leo, Medicis
Payment for development of educational presentations	Meda, Almirall
Support for travel to meetings for the study or other purposes	Meda, Almirall, Galderma, Leo, Medicis
Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	Meda, Leo
Swanson, N. A.	
Consultancy	Leo Pharma, Genentech, Precision Pharma
Grants/grants pending	Leo Pharma, Genentech
Payment for lectures including service on speakers bureaus	Leo Pharma, Genentech
Torezan, L.	
Board membership	Leo Pharma
Consultancy	Galderma
Payment for lectures including service on speakers bureaus	Galderma
Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point	Galderma, Leo Pharma

committees, and the like	
Werner, R. N.	
Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	European Skin Cancer Foundation
Payment for writing or reviewing the manuscript	European Skin Cancer Foundation

Completed forms are available at the dEBM.

8.2 Excluded studies: reasons for exclusion

Table 7 shows the reasons for the exclusion of studies during the evaluation of the full texts for the systematic literature review. The table lists excluded studies that were included in the original Cochrane review and studies that were identified in the update search for the guidelines. Multiple reasons could apply to exclude studies. Therefore studies may be listed in various categories.

Table 7: Reasons for exclusion of studies during full-text evaluation

<table>
<tr>
<td>
<u>Studies that did not meet criteria concerning reported outcomes:</u>

Fariba 2006[68]
Haddad 2011[69]
Lebwohl 2012[9]
Persaud 2002[70]
Siller 2009[71]
Weinstock 2012[72]
Wiegell 2012[73]

</td>
<td>
<u>Studies that did not meet the inclusion criteria for interventions concerning treatment duration/frequency of application:</u>

Chen 2003[74]
Hanke 2010[75]
McEwan 1997[76]
Ostertag 2006[77]
Zeichner 2009[78]

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<td>
<u>Unacceptable or unclear randomization:</u>

Hadley 2012[118]
Hirata 2011[90]
Jeffes 2001[119]

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<td rowspan="6">
<u>Studies that did not meet the inclusion criteria for interventions concerning the intervention type:</u>

Akar 2001[79]
Alberts 2000[80]
Alirezai 1994[81]
Apalla 2011[82]
Azimi 2012[83]
Bercovitch 1987[84]
Chen 2012[85]
Deonizio 2011[86]
Fariba 2006[68]
Foote 2009[87]
Galitzer 2011[88]
Hauschild 2009[89]
Hirata 2011[90]
Huyke 2009[91]
Jorizzo 2006[92]
Jorizzo 2010[93]
Kang 2003[94]
Kulp-Shorten[95]
Misiewicz 1991[96]
Moloney 2010[97]
Moriarty 1982[98]
NCT00774787[99]
Olsen 1991[100]
Pflugfelder 2012[101]
Seckin 2009[102]
Serra-Guillen 2012[48]
Shaffelburg 2009[103]
Sotiriou 2012[104]
Surjana 2012[105]
Surjana 2012[106]
Szeimies 2008[107]
Tan 2007[108]
Tarstedt 2005[109]
Thompson 1993[110]
Togsverd-Bo 2012[111]
Tong 1996[112]
von Felbert 2010[113]
Wiegell 2011[114]
Wiegell 2009[115]
Wiegell 2008[116]
Willey 2012[117]

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<td>
<u>Studies that did not report numerical values or incomplete information for the inclusion in the metaanalyses:</u>

Damian 2011[120]
Persaud 2002[70]
Szeimies 2011[121]
Van der Geer 2009[122]

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<td>
<u>Publications that did not report original data:</u>

Author unknown 2011[123]
Author unknown 2012[124]
Anderson 2012[125]
Berman 2012[126]
Dirschka 2011[127]
Hauschild 2012[128]
Hollestein 2012[129]
Keating 2012[130]
Lee 2011[131]
Prado 2011[132]
Stockfleth 2011[133]
Surjana 2012[105]
Szeimies 2011[121]
Togsverd-Bo 2012[134]
Wiegell 2012[73]
Willey 2011[135]
Willey 2012[136]

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<tr>
<td>
<u>Studies without AK as inclusion criterion or unclear baseline characteristics:</u>

Almagro 2012[137]
Palm 2011[138]

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<td>
<u>Follow-up reports on included studies:</u>

Stockfleth 2012[139]

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</table>

Other reasons:

- Haddad 2011[69]: N per group: 3-5 patients
- Perrett 2007[140]: The treated lesion areas were not predefined and therefore not comparable. Treatment areas comprised either one individual lesion or multiple lesions; the smallest lesional area treated was 39 mm², the largest 5010 mm²
- Swanson, 2010[141]: conference abstract, data included in Lebwohl 2012[49]